

THE MAX MEDICAL JOURNAL

Volume III | Issue III

September 2026



ORIGINAL ARTICLES

REVIEW ARTICLES

PATH-BREAKING CASES

THE IMAGES

STUDENTS' CORNER



Restoring Hope Through Liver Transplantation: The Journey of 12 Children with Biliary Atresia from the Philippines

A journey of hope and healing brought twelve children with biliary atresia, a rare, progressive, and life-threatening liver disease affecting infants and young children, from the Philippines to Max Super Speciality Hospital, Saket, New Delhi, for specialised liver transplant care. Their travel and treatment were sponsored by the Mayor of Manila, Francisco "Isko Moreno" Domagoso, reaffirming a shared commitment to giving these children a second chance at life.

The journey began with an outreach outpatient department (OPD) conducted by Dr Vikram Kumar in the Philippines, where he evaluated several children and diagnosed them with biliary atresia. Following assessment, liver transplantation was recommended. In the majority of cases, the children's mothers came forward as living liver donors.

Under the leadership of Dr Subhash Gupta, Group Chairman, Centre for Liver and Biliary Sciences, along with the expertise of Dr Vikram Kumar and Dr Vipul Gautam, the children underwent comprehensive evaluation, advanced liver transplant treatment, and dedicated postoperative care. Following transplantation, they remained in the hospital for approximately one month for close monitoring, recovery, and continued postoperative care.

Throughout their treatment journey, the children and their families received compassionate, multidisciplinary care. Their journey reflects the trust that families across borders place in Max Healthcare and highlights the impact of specialised paediatric liver transplantation. The successful treatment of these children reinforces Max Healthcare's commitment to delivering world-class, compassionate, and patient-centred care.

Contents

Editorial

02–04

Original Articles

05–56

6	Feasibility of Early Laparoscopic Appendectomy in Appendicular Lump Patients: Experience from a Tertiary-Care Centre - Vikas Panwar, Vishal Lakhotia, Nikhil M Nagakumar, Aditi Sachdeva, Sourav Panda, Srishthi Rawat
14	Clinical Outcomes of Platelet-Rich Plasma in the First 100 Patients with Various Musculoskeletal Disorders: A Single-Centre Study - Aanchal Sharma, Aarzoo
24	Association Between Digital Sexual Exposure, Childhood Trauma, and Internet Addiction Among Adolescents: A Quantitative Study - Meher Kohli, Vanya Bindra
30	The Rise of Artificial Intelligence in Oncology: Opportunities, Challenges, and Future Directions - Khushboo Rastogi, Anusheel Munshi
36	Evolution of Guillain-Barré Syndrome: From Classical Descriptions to Modern Diagnostic and Therapeutic Concepts - Deepinder Kaur Maini, Satyan Nanda, Rajiv Anand, Varun Rehani, Atul Prasad, Pratik Kishore, Ankita Kumari, Prabhjeet Kaur Bedi
47	Enhanced Recovery and Early Functional Outcomes Following Simultaneous Bilateral Total Hip Arthroplasty: A Single-Surgeon Case Series - Sushant Niramohi, Chanddeep Singh, Shitij Kacker, SKS Marya

Review Articles

56–94

57	From Morphology to Molecularly Integrated Diagnosis: Contemporary Neuropathology Practice in Neuro-Oncology - Vaishali Suri, Ashwinee Kumar, Kirti Srivastava
66	Hippocampal Avoidance in Whole Brain Radiotherapy: Biological Basis, Clinical Evidence, and Future Perspectives - Gayatri Patil, Vansh Parekh, Kaustav Talapatra
71	Radiation Cancer Biology: Mechanisms of Carcinogenesis and Clinical Implications - Albert Paul Varghese, Anurag Ashok Luharia, Suhas Tiwaskar, Shreya Naik, Ishiqua Vinay Patil, Arif Hussain Malla, Sheikh Mohammed Irfan, Ginesh Job M, Kashmira Patil
75	Beyond the Pill – The Future of Lipid-Lowering Therapy: A 2026 Review of Novel Lipid-Lowering Agents - Aryan Arora, Monica Mahajan
91	Patient Satisfaction and Experience in Inpatient Care: A Systematic Review of Global Evidence - Ayuj Kaushik, Pragya, Shivam Sharma

Case Studies

95–167

96	Beyond the Scope: Laparoscopic Rescue of Jejunal Gallstone Ileus Following Failed Endoscopic Retrieval - Manmohan M Kamat, Divya Udaykumar, Sharvari Gorkar, Rohan KJ, Akhil Mishra, Gulamgous Shaikh, Kristina Matthew, Sainath Kuppa, Yashraj Thakur
100	Undifferentiated Small Round Cell Sarcoma of the Pelvic Space in an Infant: A Rare Case Report - Krishna Kant Singh
104	Bilateral Patellofemoral Arthroplasty for End-Stage Patellofemoral Osteoarthritis in a Young Adult with Ehlers-Danlos Syndrome and Lifelong Patellar Instability: A Case Report - Prateek Upadhyay, Harshavardhan Hegde, Nitiraj Oberoi, Rakesh Mattoo, Akshay Kumar Saxena, Ajay Dhanopeya
112	Zolpidem Intoxication Leading to Coma and a Rapid Flumazenil Awakening Response: A Definitive Antidote - Bhanu Pratap Singh, Mandeep Singh Gill, Vedvartya, Harjit Singh

116	Diagnostic Masquerade in Advanced Lymphoma: Angioimmunoblastic T-Cell Lymphoma Initially Mimicking Diffuse Large B-Cell Lymphoma - Kshirabdh Tanaya Panda, Sanjeev Kumar Sharma, Anamika Bakliwal, Anil Handoo, Pratyush Mishra, Rajan Duggal, Nivedita Patnaik
121	When the Node Fails and the Heart Follows: Anti-NF140 and Anti-GAD65 Autoimmune Nodopathy Presenting as Acute Quadriparesis with Takotsubo Cardiomyopathy and Type 2 Respiratory Failure - Prateek Bhanu, Rommel Tickoo, Shiveta Mattoo, Shubham Mishra, Sharanya Kohli, Anjali Mutreja, Manisha Agrawal
130	Multisystem Sarcoidosis Masquerading as Tuberculosis Despite Normal Serum Angiotensin-Converting Enzyme Levels: A Case Report - Nitin Rathod, Andrea Janice Fonseca, Snehal Sadanandan, Akshita Jain
136	Primary Vaginal Adenocarcinoma with Intestinal Differentiation: Diagnostic Complexity and Individualised Radiation Planning - Apoorva Singh, Garima Singh, Khushboo Rastogi, Nidhi Sharma, Varshu Goel, Annu Dalal, Anusheel Munshi
141	Endobronchial Watanabe Spigot Placement for a Tuberculosis-Associated Bronchopleural Fistula: A Stepwise Balloon Occlusion Technique - Sameer Arbat, Manoj Pethe, Nitin Wadaskar
147	Unmasking Steroid-Induced Psychosis in a Patient with Metastatic Spinal Tumour: A Clinical Challenge - Nitin Rathod, Andrea Janice Fonseca, Shweta Thadeshwar, Surbhi Padte
151	Rapid Neurological and Multiorgan Recovery After Two-Session Automated Red Cell Exchange for Fulminant Sickle Cell Crisis: A Case Report - Vipul Sharma, Siddhi Karale, Nidhi Mehta, Hemalata Arora
155	Endoscopic Intersphincteric Dissection: A Novel Sphincter-Preserving Technique for Ultra-Low Rectal Tumours - A Case Report - Gaurav Patil, Ankit Dalal, Amol Vodgaonkar, Prathvi Alva
159	Peripheral T-Cell Lymphoma Masquerading as Prolonged Pyrexia of Unknown Origin and Culminating in Carbapenem-Resistant <i>Acinetobacter baumannii</i> Septic Shock: A Case Report - Osheen Gera, Richa Nema, Adiba Rao, Akanksha Verma, Supriya Bali
163	Giant Cervicothoracic Schwannoma Involving the Brachial Plexus and Thoracic Inlet - Prem Kumar Ganesan, Narottam Khadaria, Dhruv Dinesh Jain, Anchal Singh

The Images

168–177

169	Inflammatory Pseudotumour of the Gallbladder Mimicking an Aggressive Malignant Process: Correlation of Magnetic Resonance Cholangiopancreatography, Triple-Phase Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, and Histopathology - Shubham Aggarwal, Mitusha Verma, Deepak Patkar
174	Cone-Beam Computed Tomography: The Evolution of Volumetric Imaging in Dentistry - Shreya Naik, Anurag Luharia, Gaurav Mishra, Suhas Tiwaskar, Albert Varghese, Vinay Tiwari

Students' Corner

178–186

179	Clinical Signs – The Forgotten Art (Part 3): Ten More Bedside Signs Every Clinician Should Master - Narinder Pal Singh, Vanraj N Padhiyar
-----	--

MIME Announcements

187–190

Office of Research

191–192

Scope of the Journal

193

Author Guidelines

194

Mirror, Mirror on the Wall: The Modern Toll of Looking Good



“

Each time that the media highlights a death in the gym or on the running track, it forgets the millions of lives saved by moderate exercise, and this gives our couch potato a reason for not exercising.”

— Dr. Monica Mahajan

Orthorexia nervosa (ON) is not an ailment of bones and joints. In Greek, ‘ortho’ means correct and ‘orexi’ means appetite. Steven Bratman coined this term in 1997, and it is mentioned in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. This is a gentleman who feels pride in eating healthy. He will spend hours researching food, looking up recipes and eliminating multiple food items from his diet. He feels obligated to vociferously opine about food, criticising and lecturing other guests about their food choices. If he consumes one piece of cake or pizza himself, it will make him feel guilty or ashamed. Ultimately, he becomes a malnourished, obsessive-compulsive social pariah with nutritional deficiencies. In contrast, there are party animals who have no self-control and just live to eat or drink.

There is another subset of individuals who strive to look like Adonis, the Greek symbol of male beauty, and some want to be like Narcissus, who had a beautiful face and fell in love with his own reflection. These people will pump iron for hours at a time in the gym, and their professional and personal lives take a back seat. It does not stop here. They take multiple gym supplements and strongly advocate their use. As per the World Health Organization (WHO), the recommendation is to engage in 150 minutes/week of moderate-intensity or 75 minutes per week of high-intensity aerobic exercise. Additionally, at least two days of strength training for various muscle groups should be performed. We all know that this will result in reduced cardiac morbidity and mortality, and the more one exercises, the better. The controversy and the topic of debate are the impact of the highest volume of exercise. This has led to the ‘Extreme Exercise Hypothesis’ or

a dose-response association between physical activity and its benefits being a U-shaped or reverse J-shaped curve. Epidemiological data suggest that the benefits of exercise tend to plateau or even decline in extreme fitness freaks, making them more vulnerable to fibrosis of the myocardium, increased coronary calcification and atrial fibrillation. High volumes of exercise may lose their benefits over the years, and the same has been documented in studies conducted in former endurance runners. Sudden cardiac death (SCD) in young athletes is due to inherited cardiac causes, including hypertrophic cardiomyopathy (HCM), right ventricular cardiomyopathy (RVCM) and coronary artery anomalies. In athletes older than 40 years, SCD is due to atherosclerotic cardiovascular disease (ASCVD). A Canadian study on athletes found only 74 cases of SCD against 18.5 million person-years of observation, or an incidence of 0.76 cases per 100,000 athletes per year. Another study from Australia has reported that most cases of SCD in the young population occur during sleep (28%) and rest (20%), and only very few during exercise (8%). Even if the coronary artery calcification scores are higher in athletes, it is good news since these calcified plaques are stable and less likely to rupture. As of now, the data supporting the extreme exercise hypothesis are not compelling enough. Each time that the media highlights a death in the gym or on the running track, it forgets the millions of lives saved by moderate exercise, and this gives our couch potato a reason for not exercising.

Professional bodybuilders indulge in high-volume and high-intensity strength training and ‘optimal’ nutrition, which should have resulted in longevity. Yet they are at high risk of dying prematurely.

In 2021, more than two dozen professional bodybuilders died of cardiac causes and made newspaper headlines for the wrong reason. Famous professionals who lost their lives early include 26-year-old International Fitness and Bodybuilding Federation (IFBB) professional Dallas McCarver, 31-year-old Austrian Andreas Munzer with sub-3% body fat, 46-year-old Mr. Olympia champion Shawn Rhoden, and the 33-year-old Algerian 'giant killer' Mohammed Benaziza. A study from the European Heart Journal has revealed that male bodybuilders who compete professionally have a fivefold rise in SCD compared to amateurs, and their average age at the time of death is 45 years. The study conducted by Dr. Marco Vecchiato, a sports physician from Italy, included 20,286 bodybuilders who had participated in at least one international bodybuilding competition between 2005 and 2020. There were 121 deaths reported. 15% of these were traumatic deaths due to car crashes, suicides, murders and drug overdoses, highlighting the mental issues, impulsiveness and self-destructive persona. Extreme body transformation comes at a cost, and the heart has to pay the price. While bodybuilding inculcates fitness and self-discipline, the extreme level of strength training, severe calorie restriction to lose weight suddenly, weight swings, performance-enhancing anabolic substances, and dehydration may be contributing. Anabolic-androgenic steroids (AAS), growth hormones, and thyroid hormones cause left ventricular hypertrophy, arrhythmias and "sludge blood" leading to clots. Weight cycling stresses the kidney as well. The usage of AAS has been estimated to be 54% – 76% among male and 10% – 40% among female bodybuilders. Rapid weight loss is achieved by intentional dehydration, thermal stress and diuretic abuse. This sport needs enhanced medical supervision, screening and counselling of these young men and women and a complete ban on performance boosters. Bodybuilding associations need a revamp with stricter anti-doping measures, media campaigns and health surveillance.

There are other bodybuilders, such as Arnold Schwarzenegger and Lou Ferrigno, who are alive and perhaps an exception to the rule. Schwarzenegger had undergone a Ross procedure to replace his bicuspid aortic valve with his native pulmonary valve. Subsequently, he underwent a pulmonary and aortic valve replacement on different occasions and finally a pacemaker implant. So, he has managed to defy the odds, and the Terminator star moved closer to becoming a 'machine'.

There is another generation that is striving towards chasing size-zero. This sculpted, starved, and supplemented beauty grew in this age of vanity. Her favourite toy was a Barbie doll, and her role model has been Kareena Kapoor. A

study published in the journal 'Developmental Psychology' found that 5- to 8-year-olds who played with Barbie lacked confidence in their own body types, skin tones and hair textures and earnestly desired to be as thin as her. Since its launch in 1959, Barbie has been embroiled in controversies because of its impossible-to-attain body proportions, accessories like a weighing scale permanently set at 110 pounds and a book titled 'How to Lose Weight' with the unreasonable advice: 'Don't eat'. In an effort towards realism, Mattel introduced the tall, petite and curvy Barbies in 2016, wherein curvy was perceived as 'fat'. The rest of the damage has been done by the fashion industry and the runway models. Most of them suffer from anorexia nervosa, bulimia nervosa or orthorexia nervosa. Hormonal imbalance, menstrual irregularities, infertility, premature osteoporosis, cardiac arrhythmias and chronic fatigue are common. There is laxative and substance abuse. Body dysmorphic disorder (BDD), anxiety and depression are rampant. Anthropometric analysis over seven consecutive fashion week seasons showed that all female models were grossly underweight, with body mass index (BMI) < 16 and severely malnourished. 92% of male models too were underweight. They did not seek help for eating disorders as they risked losing employment. Deaths due to starvation are increasing in the modelling industry. The consumer is being fooled by a false culture of beauty and body ideals of extreme thinness by models whose own lives and health are in the doldrums. French law bans employing models with a BMI less than 18, and Israel has a cut-off of BMI 18.5. While models are becoming thinner and thinner and the world population is becoming larger around the waistline, there is rising body dissatisfaction.

What does an average person do? As the wedding season approaches, more and more prospective brides rush to beauticians who dole out glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with a licence to kill. On 10th March 2026, a government advisory was issued by the Drug Controller General of India to stop misleading advertisements and disallow the use of these drugs without a prescription from an endocrinologist, internal medicine specialist or cardiologist. Orforglipron, an oral GLP-1 RA, and retatrutide, a triple agonist peptide, are new kids on the block in this armamentarium of weight loss drugs. The challenge is how to sustain the weight loss once you get off these expensive medications with potentially severe side effects. What do you do about the lean muscle loss? Are these a game changer for obesity management, or are they only quick-fix solutions? Can these ever be a substitute for diet and lifestyle modifications? Certainly not.

As we look for that prescription for perfection, we indulge in various diets from one meal a day

(OMAD) to intermittent fasting, high-protein and Mediterranean diets. We climb mountaintops, run marathons, work out endlessly or simply enjoy popcorn while we watch Netflix. In this world full of Laurels and Hardys, the challenge is in striking the right balance. In this age of diet, drudgery and drugs, the middle path makes more sense rather than extremism.

Advisory Board

Dr. Sandeep Budhiraja
Mr. Anas Abdul Wajid
Dr. Anil Handoo
Dr. Vinitaa Malhotra Jha
Mr. Mayank Mathur

Editor-in-Chief

Dr. Monica Mahajan

Board of Editors

Dr. Abhaya Indrayan
Dr. Abhinav Verma
Dr. Ajay Gupta
Dr. Anil Handoo
Dr. Ankit Bhatia
Dr. Anju Shukla
Dr. Bela Makhija
Dr. Deepak Bhasin
Dr. Ganesh Mani
Dr. Garvit Chitkara
Dr. Gyanendra Agarwal
Dr. Kaustav Talapatra
Dr. Man Mohan Mehendiratta
Dr. Meenu Walia
Dr. Mitusha Verma
Dr. Mukesh Rathore
Dr. Narinder Pal Singh

Dr. Monica Mahajan

Editor-in-chief,
The Max Medical Journal

DOI: <https://doi.org/10.62830/mmj3-03-editorialx>

Editorial Office

Dr. Saroj Sabath
Dr. Poorvee Mathur
Ms. Taruna Sharma
Ms. Oshita Taneja Narula
Dr. Ritika Pan Banerjee

International Editors

Dr. Eric Livingston
Dr. Mumtaz Patel

Dr. Pooja Gupta
Dr. Prem Kumar Ganesan
Dr. Prasoon Shamsheery
Dr. Puneet Arora
Dr. Punish Sadana
Dr. Rahul Arora
Dr. Rajesh Ahlawat
Dr. Ritesh Aggarwal
Dr. Shailesh Sahay
Dr. Suman Lal
Dr. Surveen Ghuman
Dr. Vandana Soni
Dr. Vinod Kumar Nigam
Dr. Vishal Ramteke
Dr. Vishwas Sharma
Dr. Vivek Bindal
Dr. Waseem Abbas



ORIGINAL ARTICLES

- | | | | |
|----|--|----|---|
| 6 | Feasibility of Early Laparoscopic Appendicectomy in Appendicular Lump Patients: Experience from a Tertiary-Care Centre - Vikas Panwar, Vishal Lakhotia, Nikhil M Nagakumar, Aditi Sachdeva, Sourav Panda, Sristhi Rawat | 30 | The Rise of Artificial Intelligence in Oncology: Opportunities, Challenges, and Future Directions - Khushboo Rastogi, Anusheel Munshi |
| 14 | Clinical Outcomes of Platelet-Rich Plasma in the First 100 Patients with Various Musculoskeletal Disorders: A Single-Centre Study - Aanchal Sharma, Aarzoo | 36 | Evolution of Guillain-Barré Syndrome: From Classical Descriptions to Modern Diagnostic and Therapeutic Concepts - Deepinder Kaur Maini, Satyan Nanda, Rajiv Anand, Varun Rehani, Atul Prasad, Pratik Kishore, Ankita Kumari, Prabhjeet Kaur Bedi |
| 24 | Association Between Digital Sexual Exposure, Childhood Trauma, and Internet Addiction Among Adolescents: A Quantitative Study - Meher Kohli, Vanya Bindra | 47 | Enhanced Recovery and Early Functional Outcomes Following Simultaneous Bilateral Total Hip Arthroplasty: A Single-Surgeon Case Series - Sushant Niramohi, Chandeeep Singh, Shitij Kacker, SKS Marya |

Feasibility of Early Laparoscopic Appendicectomy in Appendicular Lump Patients: Experience from a Tertiary-Care Centre

Vikas Panwar¹*, Vishal Lakhotia¹, Nikhil M Nagakumar¹, Aditi Sachdeva¹, Sourav Panda¹, Srishthi Rawat¹

¹Department of General Surgery and Robotics, Max Super Speciality Hospital, New Delhi

Correspondence:

Vikas Panwar

E-mail: drv16@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-2>

Abstract:

Management of appendicular lump remains controversial. Traditional conservative therapy often requires prolonged hospitalisation, interval appendicectomy, and carries risks of recurrence or missed alternative diagnoses. With advances in minimally invasive surgery, early laparoscopic appendicectomy (ELA) has emerged as a potential single-stage alternative. This retrospective cohort study evaluated the safety and feasibility of ELA in patients presenting with an appendicular lump. The study was conducted from December 2013 to February 2024 at a tertiary-care centre. Among 469 patients with acute appendicitis, 185 were identified with an appendicular lump based on clinical and radiological assessment. All patients underwent ELA within 24 hours using a standard three-port laparoscopic technique. Intraoperative findings, operative time, postoperative complications, length of stay, and histopathological outcomes were recorded, and all specimens underwent histopathological examination. Of 185 patients, 60% were male, with the most common age group being 20 – 40 years. Mean symptom duration was 5.36 days. Intraoperative findings included tip perforation in 62%, gangrene in 43%, localised abscess in 42%, and pyoperitoneum in 7.5%. Simple lumps were observed in 70% and complex lumps in 30% of cases. Mean operative time was 38 minutes (27 – 110 minutes). No patient required conversion to open surgery. Two patients required additional laparoscopic resections for extensive inflammatory involvement. Postoperative morbidity was low, with wound infection in 3%, wound dehiscence in 1%, paralytic ileus in 6%, and intra-abdominal abscess in 1.6%; no faecal fistula occurred. Mean hospital stay was three days (2 – 8 days). Histopathological examination confirmed acute appendicitis in all cases, with no alternative pathology identified. ELA for appendicular lump is safe, feasible, and effective in experienced hands. It provides low morbidity, acceptable operative duration, and short hospital stay, while avoiding the limitations of conservative management and interval surgery. ELA offers definitive single-admission treatment and may be considered a preferred approach in centres with established laparoscopic expertise.

Key words: Appendicular Lump, Appendiceal Phlegmon, Early Laparoscopic Appendicectomy, Complicated Appendicitis, Minimally Invasive Surgery, Interval Appendicectomy.

Introduction

Acute appendicitis remains one of the most common surgical emergencies worldwide, with a lifetime risk estimated between 7% – 8%.¹ Delay in diagnosis or treatment can lead to localised complications, one of which is the formation of an appendicular lump or appendiceal phlegmon. This condition is seen in approximately 2% – 6% of patients with acute appendicitis and represents an inflammatory mass in which the appendix is surrounded by omentum and adjacent bowel loops, in an attempt to contain the infection.^{2,3}

Traditionally, appendicular lump has been managed conservatively using the classical Ochsner-Sherren regimen. This involves bowel rest, intravenous fluids, and broad-spectrum antibiotics, often followed by an interval appendicectomy 6 – 8 weeks later once the acute inflammation has subsided.⁴ The rationale for this approach is to avoid the technical difficulties and complications associated with operating in an inflamed field, where friable tissues, dense adhesions, and distorted anatomy increase the risk of inadvertent bowel or vascular injury.⁵

Despite these perceived advantages, conservative management has notable limitations. Prolonged hospitalisation, recurrent appendicitis during the waiting period, and the need for a second hospital admission for interval surgery add to patient morbidity and healthcare costs.^{6,7} Furthermore, studies have shown that recurrence rates after conservative management may be as high as 10% – 20%,⁸ and not all patients comply with the recommended follow-up for interval appendicectomy.⁹

With improvements in perioperative care, anaesthesia, and minimally invasive surgery, early laparoscopic appendicectomy (ELA) has been proposed as an alternative. Laparoscopy provides excellent visualisation of the abdominal cavity, allows definitive treatment in a single admission, and facilitates drainage of any localised abscesses when present.¹⁰ Moreover, it enables diagnostic confirmation and exclusion of alternative pathologies such as Crohn's disease or neoplasms, which may masquerade as an appendicular mass.¹¹

Several randomised controlled trials and meta-analyses have demonstrated that early appendicectomy, particularly by the laparoscopic approach, is both feasible and safe in experienced hands.^{12,13} Early surgery has been associated with reduced recurrence, avoidance of a second admission, and shorter total duration of hospital stay when compared with conservative treatment followed by interval appendicectomy.¹⁴ However, concerns remain regarding longer operative time, higher technical difficulty, and the potential risk of postoperative intra-abdominal abscess formation.¹⁵

Given these ongoing controversies, the feasibility and safety of ELA in appendicular lump continues to be debated, particularly in resource-limited settings or in centres with limited laparoscopic expertise. This study was therefore undertaken to evaluate the feasibility, outcomes, and potential advantages of ELA in patients presenting with an appendicular lump in a tertiary-care hospital that has all facilities and excellent expertise of surgeons in the field of laparoscopy. ELA in our study means appendicectomy performed within 24 hours of hospital admission.

This study aimed to determine whether early appendicectomy is a safe alternative to conservative management in patients with appendicular mass.

Materials and Methods

The study was conducted from December 2013 to February 2024 in Max Super Speciality Hospital, Saket, New Delhi, India. It was a retrospective cohort study. A total of 469 patients were diagnosed with acute appendicitis. All these patients were planned for ELA. Out of these, 185 patients were diagnosed with appendicular lump secondary to appendicitis.

Patients were diagnosed with an appendicular lump based on clinical examination. Radiology was done to confirm the findings of clinical examination and to rule out other causes of right iliac fossa (RIF) lump. Upon admission, routine blood investigations and ultrasound examinations were done for all patients. In a few cases where ultrasound was unable to visualise the pathology in the RIF, a contrast-enhanced computed tomography (CT) scan was done. Injection ceftriaxone 1 g BD and metronidazole 500 mg TDS were given intravenously to all patients after admission.

After all routine tests were completed, patients were shifted to the theatre for ELA. The procedure was performed via three ports: an infraumbilical 5 mm port the camera and two working ports in the left iliac fossa (5 mm) and suprapubic (10 mm). Intraoperative findings were noted. The specimen was removed through the suprapubic port of varied sizes. All patients with an appendicular lump were included in the study.

Any lump in the right iliac region other than an appendicular lump, e.g., ileocecal tuberculosis, carcinoma of the caecum, right-sided ovarian cyst, and malignancy, was excluded. Unfit patients or patients refusing to give consent to take part in the study were excluded. All postoperative specimens were sent for histopathological examination to rule out other causes of appendicular lump.

Results

The study included 185 patients, out of which 111 (60%) were male and 74 (40%) were female. The most common age group diagnosed with appendicular lump was found to be between 20 – 40 years, as shown in Figure 1.

Upon clinical examination, tenderness in RIF was seen in 145 patients (78%) and rebound tenderness in 57

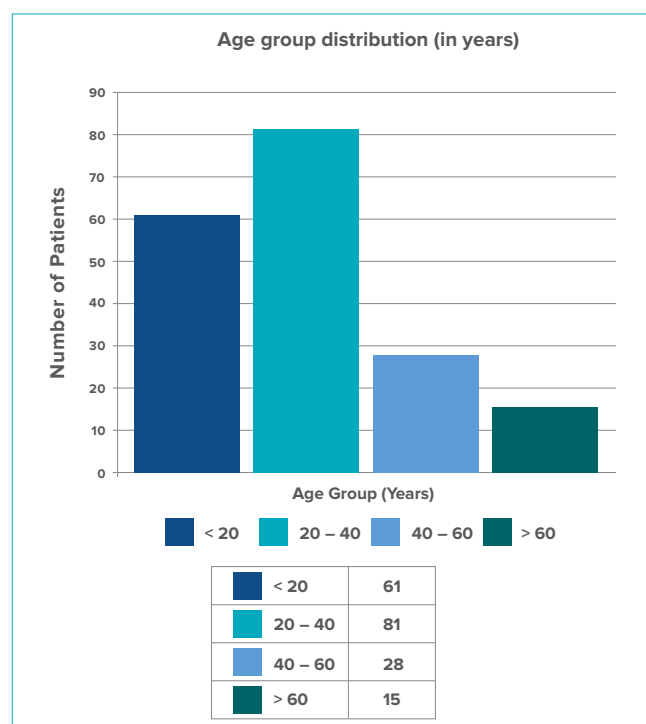


Figure 1: Appendicular lump age distribution (In years).

All patients presented with pain in the right lower abdomen; 122 had anorexia, and 111 had nausea and vomiting. The minimum duration of symptoms was three days, maximum was 8 days, with an average duration of 5.36 days (Figure 2). Most patients with an appendicular lump had 5 days duration of onset of symptoms (Figures 3 and 4).

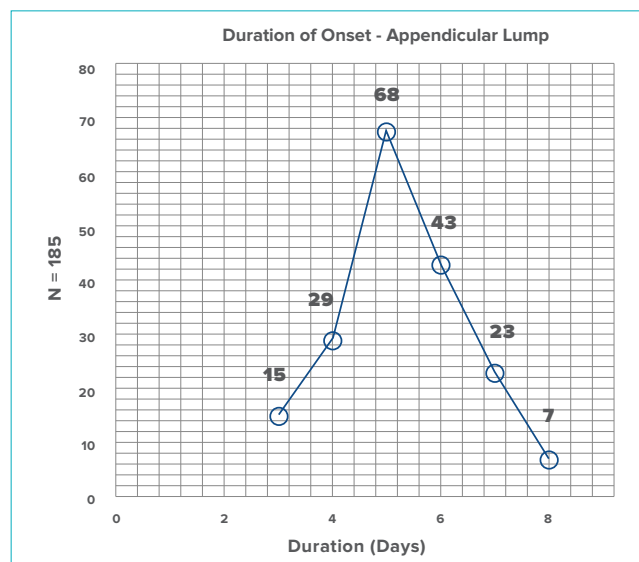


Figure 2: Appendicular lump duration (in days).



Figure 3: Coronal computed tomography (CT) scan with an arrow showing appendicitis with an appendicular lump.

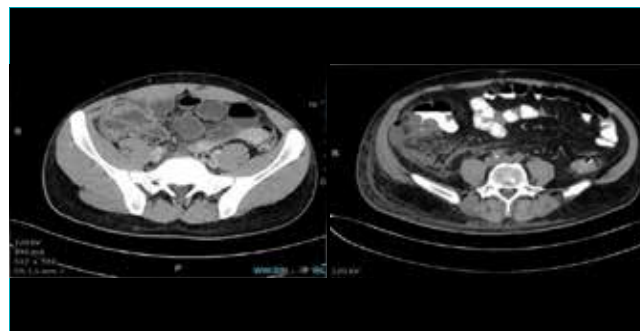


Figure 4: Axial contrast-enhanced computed tomography (CT) scan demonstrating an appendicular lump.

(31%) patients. Laboratory tests showed total leucocyte count (TLC) > 12,000 in 143 and < 12,000 in 42 patients.

Intraoperatively (Figure 5), gangrenous appendix was seen in 81 (43%), appendicular tip perforation in 115 (62%), appendicular abscess in 79 (42%), localised pus in 83 (44%) and pyoperitoneum in 14 (7.5%). Autolysis of the appendix was noted in 2 (1.08%) cases for which a drain was placed in the right paracolic gutter and pelvis (Figure 6). A simple appendicular lump in which the appendix was adhered to omentum was present in 130 patients (70%), while a complex appendicular lump in which the appendix was adhered to small bowel, omentum, mesentery, and colon was seen in 55 patients (30%). Dense adhesions were present in 37 patients (20%).



Figure 5: Laparoscopic view of an appendicular lump.



Figure 6: Laparoscopic view showing a perforated appendix with pus flakes over the surrounding structures.

Average operative time was 38 minutes, with a minimum time taken of 27 minutes and a maximum of 110 minutes. With diagnostic laparoscopy, all areas were inspected, any collection or pus was aspirated, and a thorough peritoneal lavage with lukewarm normal saline was given. Two catgut loops were used for appendicular base ligation in 111 (60%) cases, an Endo-GIA stapler

(Figures 7 and 8) was used in 65 (35%) cases, and Vicryl suturing was performed in 9 (5%) cases.



Figure 7: Stapled laparoscopic appendicectomy performed for a wide and friable appendiceal base.



Figure 8: Harmonic scalpel used for adhesiolysis during laparoscopic appendicectomy in a dense appendicular lump.

In 161 (87%) patients, the specimen was removed in a glove Endobag. For specimen removal, different sizes of suprapubic port were used: 10 mm in 13 (8%), 12 mm in 133 (83%), and 15 mm in 15 (9%) cases. Minimum length of hospital stay was two days, maximum was 8 days, with an average length of hospital stay of three days.

No patients were converted to open surgery. One patient had an appendicular abscess with the sigmoid colon forming a part of the wall of the abscess cavity, making its wall friable and leading to sigmoid perforation, for which the patient underwent laparoscopic sigmoid resection and anastomosis using a trans-anal circular stapler and had a prolonged hospital stay of 8 days.

Postoperative complications

Wound site infection was seen in 6 (3%) patients, wound dehiscence in 2 (1%). In these patients, sutures were removed, and pus was drained, followed by daily dressing. Patients were treated on an outpatient basis with oral antibiotics based on culture and sensitivity. 11 (6%) patients developed paralytic ileus postoperatively

and were kept nil per oral; a Ryle's tube was inserted, and crystalloids were started to maintain hydration. These patients responded well to conservative management. Intra-abdominal abscess developed in 3 (1.6%) patients, in which ultrasound-guided pigtail was inserted and the pus drained was sent for culture and sensitivity. They were initially started on empirical antibiotics, which were later modified according to the results of culture and sensitivity. No patient developed faecal fistula.

Discussion

Operative management for appendicular lumps has been a topic of debate amongst surgeons, with most surgeons managing it conservatively. However, Pandey *et al.*¹⁶ stated that 10% – 20% of cases do not improve with conservative treatment, which might result in gangrene or perforation, a localised abscess, and widespread peritonitis that necessitates immediate exploratory laparotomy. Conservative management includes charting the lump size, monitoring vitals, administering antibiotics, fluids and analgesics. One of the major drawbacks of the initial conservative strategy is that many patients do not follow up with surgeons once their abdominal pain is resolved. An additional downside to opting for conservative treatment lies in the potential for incorrect diagnosis, occurring in about 15% of cases, where conditions like ileocecal tuberculosis, intussusception, bowel malignancy, etc can be wrongly managed non-operatively, which can greatly worsen a patient's health.¹⁷

An appendicular lump is difficult to palpate clinically in patients who are obese or have abdominal rigidity. In such cases, radiology helps us to know about the lump.

In our study of 185 patients with appendicular lumps, we observed a male predominance (60%), and the most affected age group was 20 – 40 years. This demographic profile is similar to that described by Bhangu *et al.*¹⁸ and Khan *et al.*,¹⁹ who also noted that appendicitis was frequent in younger males. The universal symptom of right lower abdominal pain, along with anorexia (66%) and nausea and vomiting (60%), parallels the clinical features reported by Andersson²⁰ and Raja *et al.*,²¹ who highlighted these as reliable indicators of acute appendicitis.

The mean duration of symptoms observed in our study was 5.3 days, reflecting delayed presentation. Such delays are clinically important, as prolonged inflammation increases the risk of perforation and abscess formation. Bickell *et al.*²² demonstrated that the risk of rupture increases significantly with time, while Ditillo *et al.*²³ reported higher complication rates in patients operated after 48 hours of symptom onset. In our series, tip perforation was seen in 62%, gangrenous appendix in 43%, localised pus in nearly 44% and pyoperitoneum in 7.5%. These findings are consistent with Shindholimath *et al.*,²⁴ who reported a high incidence of complicated pathology among patients presenting after 4 – 5 days.

Notably, in our series, no patient required conversion to open surgery. One patient required an extended laparoscopic procedure — sigmoid resection and anastomosis using a trans-anal stapler — due to complex inflammatory involvement and sigmoid perforation. In cases with dense adhesions or severely inflamed tissue, the harmonic scalpel facilitated precise dissection with effective haemostasis and reduced thermal injury, allowing safer separation of the appendix from surrounding structures. Similarly, the Endo-GIA stapler provided a reliable method for securing the appendiceal base, particularly in patients with perforated or friable caecal tissue, thereby minimising the risk of stump-related complications and reducing operative time compared with intracorporeal suturing. The availability of 4K ultra-high-definition monitors further enhanced visualisation by improving depth perception and tissue differentiation, which is particularly valuable in distorted anatomy associated with appendicular lumps. Collectively, these technological advantages supported the safe completion of all procedures laparoscopically and may partially explain the low conversion and complication rates in our cohort. Similar successful laparoscopic resections for complicated appendicular pathology have been documented by Kim *et al.*²⁵ and Al-Khayat *et al.*,²⁶ supporting the growing role of laparoscopy even in complex scenarios. The mean operative time was 38 minutes. Güler *et al.*²⁷ similarly reported a low conversion rate (3.4%) with an average operative duration of 60 minutes in complicated appendicitis. Tarar *et al.*²⁸ also found that ELA in appendicular lump is safe, with comparable operative times and shorter hospital

stays compared to conservative management. Our results therefore support the growing consensus that laparoscopy is technically safe even in the presence of a mass. Sadaf *et al.*²⁹ reported a 19.8% conversion rate and documented that converted cases required significantly longer operative times (mean = 91.6 min) compared with completed laparoscopic procedures (= 61.7 min). These studies highlight that case-mix (disease severity, abscesses, severity of adhesions) and timing of presentation are major determinants of both conversion risk and operative duration, and they help explain why conversion rates and operative times vary widely between centres.

The postoperative complication rate in our series was low, with wound infection (3%), wound dehiscence (1%), paralytic ileus (6%), and intra-abdominal abscess (1.6%). Comparable results were reported by Das *et al.*,³⁰ who found wound infection in 4.5% and intra-abdominal abscess in 2% of cases, which were managed laparoscopically.

Similarly, Zani *et al.*³¹ observed intra-abdominal abscess in 2% – 5% of patients following laparoscopic appendicectomy, while Mao *et al.*³² identified contamination severity and operative difficulty as predictors of abscess formation. Notably, no faecal fistula occurred in our series, while Sahoo *et al.*³³ described fistula formation in 2% of complicated cases.

Hospital stays in our patients averaged three days, which is shorter than the mean stay of 6 – 7 days commonly reported in conservatively managed patients

undergoing interval appendicectomy.^{12,34} Blakely *et al.*¹² demonstrated that early appendicectomy reduced hospital stay and readmissions in perforated appendicitis, while Andersson and Petzold³⁴ highlighted the risk of recurrent symptoms and prolonged treatment with conservative strategies. Our findings of short hospital stay align with Simillis *et al.*,³⁵ who concluded in a meta-analysis that early surgery reduced overall treatment duration compared to staged approaches.

In their study, Peter and colleagues¹⁵ noted that individuals receiving non-surgical care had an average of 3.5 CT scans each, creating a significant financial strain and raising considerable concerns about radiation exposure.

Overall, our results confirm that laparoscopic appendicectomy for appendicular lump is safe, effective and associated with low morbidity in experienced hands. These outcomes are consistent with recent systematic reviews and the World Society of Emergency Surgery (WSES) Jerusalem guidelines, which recommend laparoscopy as the preferred approach for complicated appendicitis in centres with appropriate expertise.³⁶ Early laparoscopy offers the dual benefits of diagnostic confirmation and definitive treatment, thereby avoiding prolonged conservative therapy and interval surgery. Nonetheless, patient selection and surgical expertise remain critical, and further multicentre trials are needed to strengthen the evidence base.

Conclusion

Early laparoscopic management of appendicular lump is safe, feasible, and effective when performed by experienced surgeons. In our study, the procedure was associated with low conversion rates, acceptable operative times, minimal postoperative morbidity, and a short hospital stay. Compared with published literature that reports higher conversion rates and prolonged operative durations in complicated cases, our findings highlight the advantages of early laparoscopic intervention. This approach not only provides definitive treatment in a single admission but also reduces the risk of recurrent symptoms, increased radiation exposure and avoids the morbidity of interval appendicectomy. Wider adoption of laparoscopic appendicectomy in appendicular lumps, particularly in resource-limited settings, can improve patient outcomes provided careful patient selection and surgical expertise are ensured.

Vikas Panwar, Vishal Lakhota, Nikhil M Nagakumar, Aditi Sachdeva, Sourav Panda, Srishthi Rawat. Feasibility of Early Laparoscopic Appendicectomy in Appendicular Lump Patients: Experience from a Tertiary-Care Centre. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-2>

References

1. Addiss DG, Shaffer N, Fowler BS, *et al.* The epidemiology of appendicitis and appendicectomy in the United States. *Am J Epidemiol.* 1990;132(5):910–25.
2. Buckius MT, McGrath B, Monk J, *et al.* Changing epidemiology of acute appendicitis in the United States: study period 1993–2008. *J Surg Res.* 2012;175(2):185–90.
3. Yang Z, Sun F, Ai S, *et al.* Meta-analysis of studies comparing conservative treatment with antibiotics and appendicectomy for acute appendicitis in the adult. *BMC Surg.* 2019;14;19(1):110.
4. Ochsner AJ. The Cause of Diffuse Peritonitis Complicating Appendicitis and Its Prevention: Chairman's Address, Delivered Before the Section on Surgery and Anatomy, at the Fifty-Second Annual Meeting of the AMA, at St. Paul, Minn., June 4–7. *JAMA.* 1901;36(25):1747–54.
5. Bagi P, Dueholm S. Nonoperative management of the appendiceal mass. *Surgery.* 1987;101(5):602–5.
6. Corfield L. Interval appendicectomy after appendiceal mass or abscess in adults: what is “best practice”? *Surgery today.* 2007;37(1):1–4.
7. Tekin AH, Kurtoğlu HC, Can I, *et al.* Routine interval appendicectomy is unnecessary after conservative treatment of appendiceal mass. *Colorectal Disease.* 2008;10(5):465–8.
8. Kumar S, Jain S. Treatment of appendiceal mass: prospective, randomized clinical trial. *Indian J Gastroenterol.* 2004;23(5):165–7.
9. Oliak D, Yamini D, Udani VM, *et al.* Nonoperative management of perforated appendicitis without periappendiceal mass. *Arch Surg.* 2000;135(2):196–200.
10. Shah WJ, Fahiem UI Hassan M, Bhat NA, *et al.* Laparoscopic Appendicectomy for Early Appendicular Lump in Children: A Single-Institution Experience. *Cureus.* 2026;18(2):e103634.
11. Andersson RE. The role of laparoscopy in the management of appendicitis. *Curr Opin Infect Dis.* 2010;23(2):190–6.
12. Blakely ML, Williams R, Dassinger MS, *et al.* Early vs interval appendicectomy for children with perforated appendicitis. *Arch Surg.* 2011;146(6):660–5.
13. Mentula P, Leppäniemi A. Laparoscopic surgery in complicated appendicitis: meta-analysis of randomized controlled trials. *Surg Endosc.* 2014;28(2):473–80.
14. Zhou S, Cheng Y, Cheng N, *et al.* Early versus delayed appendicectomy for appendiceal phlegmon or abscess. *Cochrane Database Syst Rev.* 2024;5(5):CD011670.
15. St Peter SD, Aguayo P, Fraser JD, *et al.* Initial laparoscopic appendicectomy versus initial nonoperative management and interval appendicectomy for perforated appendicitis with abscess: a prospective, randomized trial. *J Pediatr Surg.* 2010;45(1):236–40.
16. Pandey CP, Kesharwani RC, Chauhan CGS, *et al.* Management of Appendicular Lump: Early exploration Vs conservative management. *Int J Med Sci Public Health.* 2013;2(4):1046–9.
17. Sanapathi PSP, Bhattacharya D, Amori BJ. Early laparoscopic appendicectomy for appendicular mass. *Surg Endosc.* 2002;16(12):1783e5.
18. Bhangu A, Søreide K, Di Saverio S, *et al.* Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet.* 2015;386(10000):1278–87.
19. Khan S. The pattern of acute appendicitis in a developing country: clinical findings, management, and complications. *Ann Afr Med.* 2010;9(4):213–18.
20. Andersson RE. Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg.* 2004;91(1):28–37.
21. Raja AS, Wright C, Sodickson AD, *et al.* Negative appendicectomy rate in the era of CT: an 18-year perspective. *Radiology.* 2010;256(2):460–5.
22. Bickell NA, Aufses AH, Rojas M, *et al.* How time affects the risk of rupture in appendicitis. *J Am Coll Surg.* 2006;202(3):401–6.
23. Ditillo MF, Dziura JD, Rabinovici R. Is it safe to delay appendicectomy in adults with acute appendicitis? *Ann Surg.* 2006;244(5):656–60.
24. Shindholimath VV, Seema S, Patil NS, *et al.* Laparoscopic management of appendicular mass. *J Min Access Surg.* 2011;7(2):54–7.

25. Kim MJ, Fleming FJ, Gunzler D, *et al.* Laparoscopic right hemicolectomy for inflammatory appendiceal mass: Is it safe and feasible? *Surgical Endoscopy*. 2013;27(10):3628–34.
26. Al-Khayat H, Al-Khayat H, Abu-Zidan FM. Laparoscopic management of appendicular mass. *Surgical Endoscopy*. 2007;21(6):925–8.
27. Güller Y, Bıçakcı Ü, Özdemir A, *et al.* Laparoscopic versus open appendectomy in complicated appendicitis: outcomes and complications. *JSLS*. 2020;24(1):e2019.00056.
28. Tarar B, Batool S, Majeed S, *et al.* Comparison Between Early Appendectomy vs. Conservative Management in Cases of Appendicular Mass. *Cureus*. 2023;15(4):e37986.
29. Sadaf F, Asif M, Iqbal A, *et al.* Conversion Rates and Outcomes of Laparoscopic Appendectomy in Complicated Appendicitis: A Retrospective Study. *Cureus*. 2025;17(8):e90411.
30. Das BB, Haldar S, Nath S. Conservative management versus early appendectomy in appendicular mass: a retrospective analysis. *Int Surg J*. 2022;9(2):257–62.
31. Zani A, Teague WJ, Clarke SA, *et al.* Can the laparoscopic approach reduce the incidence of intraabdominal abscess after appendectomy in children? *J Pediatr Surg*. 2007;42(6):875–80.
32. Mao BP, Liu Y, Zhang Z, *et al.* Risk factors for developing intra-abdominal abscess after appendectomy. *Langenbecks Arch Surg*. 2024;409(2):523–31.
33. Sahoo MR, Biswal R. Fecal fistula following appendectomy: an analysis of risk factors and management. *Indian J Surg*. 2013;75(5):365–68.
34. Andersson RE, Petzold MG. Nonsurgical treatment of appendiceal abscess or phlegmon: a systematic review and meta-analysis. *Ann Surg*. 2007;246(5):741–48.
35. Simillis C, Symeonides P, Shorthouse AJ, *et al.* A meta-analysis comparing conservative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon). *Surgery*. 2010;147(6):818–29.
36. Di Saverio S, Podda M, De Simone B, *et al.* Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg*. 2020;15:27.

Clinical Outcomes of Platelet-Rich Plasma in the First 100 Patients with Various Musculoskeletal Disorders: A Single-Centre Study

Aanchal Sharma¹, Aarzoo¹

¹Department of Pain and Palliative Medicine, BLK-Max Super Speciality Hospital, Delhi

Correspondence:

Aanchal Sharma

E-mail: aanchalsharma253@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-3>

Abstract:

Platelet-rich plasma (PRP) is an autologous biological therapy enriched with platelets and growth factors that promote tissue healing, angiogenesis, extracellular matrix synthesis, and modulation of inflammation. Although PRP has gained increasing acceptance in the management of musculoskeletal disorders, evidence evaluating its effectiveness across multiple pathologies in routine clinical practice remains limited. This retrospective study evaluated the clinical outcomes of PRP therapy in 100 patients aged 11 – 80 years who underwent treatment for various musculoskeletal disorders at a tertiary-care Pain Medicine Department between November 2023 and March 2026. Pain was assessed using the Numeric Rating Scale (NRS), while patients with knee osteoarthritis (OA) were additionally evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Of the 100 patients, 54 were male and 46 were female. Knee OA was the most common indication (36%), followed by supraspinatus tendinopathy, subacromial-subdeltoid (SASD) bursitis, peroneal tendinopathy, superior labrum anterior to posterior (SLAP) tears, anterior talofibular ligament injuries, hamstring tendinopathy, acromioclavicular joint arthropathy, and lumbar facet arthropathy. Patients with knee OA demonstrated progressive improvement following serial PRP injections, with the number achieving $\geq 70\%$ pain relief increasing from 22 after the first session to 28 after the third session, accompanied by significant improvements in WOMAC scores. Favourable clinical outcomes were also observed in patients with chondromalacia patella, meniscal injuries, anterior cruciate ligament tears, shoulder disorders, epicondylitis, bursitis, hip, foot and ankle disorders, lumbar facet arthropathy, and carpometacarpal joint OA. Younger patients generally demonstrated slightly greater pain relief than older patients, although substantial improvement was observed across all age groups. Overall, PRP therapy was associated with significant pain reduction and functional improvement across a broad spectrum of musculoskeletal disorders, supporting its role as a valuable minimally invasive treatment option. However, larger prospective controlled studies with longer follow-up are required to confirm these findings and establish condition-specific treatment recommendations.

Key words: Platelet-Rich Plasma (PRP), Musculoskeletal Disorders, Knee Osteoarthritis, Tendinopathy, Regenerative Medicine, Pain Relief, Functional Outcomes.

Introduction

Platelet-rich plasma (PRP) has emerged as one of the most widely investigated biological therapies in regenerative medicine and musculoskeletal practice. PRP is an autologous blood-derived product containing a higher platelet concentration and serves as a reservoir of numerous growth factors and cytokines involved in tissue repair and regeneration. These bioactive molecules, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF), are released following platelet activation and play important roles in angiogenesis, extracellular matrix synthesis, cell proliferation, and modulation of inflammation.^{1,2} In tendon injuries, PRP enhances tenocyte proliferation and tendon healing.³ Additionally, in knee osteoarthritis (OA), PRP has emerged as a promising regenerative therapy with potential for cartilage healing.⁴

The growing interest in PRP therapy is driven by the increasing prevalence of chronic musculoskeletal disorders and limitations associated with conventional treatment modalities. Although pharmacological therapies, corticosteroid injections, physiotherapy, and surgical interventions remain important treatment options, many patients continue to experience recurrent symptoms or incomplete recovery. Consequently, biologic therapies aimed at enhancing the intrinsic healing response have gained substantial attention.^{1,5}

The therapeutic rationale of PRP is based on the concept of delivering a concentrated source of platelets and growth factors directly to the site of tissue injury. PRP has been shown to exert anti-inflammatory effects by modulating cyclooxygenase pathways and reducing the production of inflammatory mediators, which may contribute to pain reduction and functional improvement.³

Most available studies focus on a single pathology, limiting the understanding of PRP effectiveness across different musculoskeletal disorders.^{1,2} However, real-world data evaluating the effectiveness of PRP across multiple musculoskeletal pathologies within a single clinical setting remain limited.

Therefore, the present study aimed to evaluate the clinical effectiveness of PRP therapy. The study also aimed to assess pain relief and functional improvement following

PRP therapy in 100 patients with various musculoskeletal conditions involving pathologies of the knee, shoulder, hip, ankle, elbow, bursae, thumb, and spine.

Methodology

This retrospective study was conducted at the BLK-Max Pain Medicine Department, a tertiary-care referral centre. A total of 100 patients aged 11 – 80 years who underwent PRP intervention for various musculoskeletal pathologies from November 2023 to March 2026 were included in this study. The primary objective of the study was to examine the effect of PRP across various pathologies, and the secondary objective was to examine its effect in various age groups. Numeric Rating Scale (NRS) scores were recorded pre- and post-procedure for all pathologies. Additionally, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores before the first session and at 1 and 6 months after the first session were recorded. According to the institutional protocol for knee OA, only patients with Kellgren-Lawrence (KL) grade I, II, and III knee OA were included in the study. Patients with KL grade IV OA were considered unsuitable for PRP therapy and were referred for total knee replacement surgery. All patients were planned to receive three sessions of PRP therapy. The first two sessions were performed 4 weeks apart, and the third was performed at the eleventh month. For other knee pathologies, two PRP injections were routinely administered 4 weeks apart. For pathologies involving the ankle, foot, elbow, lumbar facet joints, carpometacarpal (CMC) joint, hip, shoulder, and bursitis, a single PRP session was initially planned according to the institutional protocol. However, if pain relief after the first session was less than 50%, a second PRP session was administered. All PRP procedures were performed under image guidance using ultrasonography (USG), fluoroscopy, or a hybrid technique (combined USG and fluoroscopy), depending on the pathology and anatomical site. All interventions were performed by a single pain physician with formal training and expertise in Pain Medicine, ensuring procedural consistency throughout the study.

NRS score: A simple pain assessment tool in which patients rate their pain intensity on a scale from 0 (no pain) to 10 (worst imaginable pain).

WOMAC score: A patient-reported outcome measure consisting of 24 items divided into three subscales of pain (Table 1).

Domain	Questions
Pain (5 questions)	Walking on a flat surface
	Going up or down stairs
	At night while in bed
	Sitting or lying
	Standing upright
Stiffness (2 items)	After first waking
	Later in the day
Physical function (17 items)	Descending stairs
	Ascending stairs
	Rising from sitting
	Standing
	Bending to the floor
	Walking on a flat surface
	Getting in/out of a car
	Going shopping
	Putting on socks/stockings
	Taking off socks/stockings
	Lying in bed
	Getting in/out of the bath
	Sitting
	Getting on/off the toilet
	Heavy domestic duties
	Light domestic duties
	Rising from bed

Table 1: Questionnaire for the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, showing the domains and individual items used for assessment of pain, stiffness, and physical function in patients with knee osteoarthritis.

It is scored on a 5-point Likert scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = extreme. A score of 0% indicates no symptoms, whereas 100% represents maximum pain, stiffness, and functional limitation.

Preparation of PRP

PRP was prepared by collecting venous blood from the patient under aseptic precautions. To prevent clotting during the process, blood was drawn into a 20 mL syringe containing 2 mL (2000 IU) of heparin. The collected sample was then transferred into a PRP kit for further processing. The following steps were followed to prepare PRP:

1. Pre-cooling

The centrifuge was switched on, and the system check was verified. A pre-cooling cycle was performed to stabilise the sample environment using the following Remi protocol parameters:

- Speed: 2500 rpm
- Time: 5 minutes
- Temperature: +18°C

The load tubes were carefully balanced in the rotor, and the lid was securely closed before starting the cycle.

2. Separation

Following the initial phase, blood was centrifuged using a Remi device according to the following specific parameters:

- Speed: 2700 – 2800 rpm
- Time: 12 minutes
- Temperature: +18°C

This process stratified whole blood into three distinct density layers: high-density red blood cells settled at the bottom, a thin buffy coat containing platelets and white blood cells formed in the middle, and platelet-poor plasma remained at the top. The plasma and buffy coat layers were then carefully extracted, ensuring that the underlying red blood cell layer was not disturbed.

3. Concentration

Once this step was completed, a concentration step was performed to further refine the preparation.

- Speed: 3200 rpm
- Time: 6 minutes
- Temperature: +18°C

This resulted in an optimal concentration of platelets in the final product, which was usually obtained in a volume of approximately 10 mL.

Results

The results are organised into demographic characteristics, distribution of musculoskeletal pathologies, effects across various age groups, and pathology-specific clinical outcomes following PRP

therapy. Table 2 presents the demographic profile of the study population, Table 3 summarises the various musculoskeletal disorders included in the study, and Figure 1 illustrates their distribution by body region involvement. The subsequent sections describe the clinical outcomes observed across different age groups and individual pathologies following PRP therapy.

A total of 100 patients were included in the study, with the highest number of participants belonging to the 51 – 60 and 61 – 70 years age groups (20 patients each), while the 71 – 80 years age group had the fewest participants (7 patients), as shown in Table 4.

Age group (years)	Female	Male	Total
11 – 20	0	10	10
21 – 30	2	8	10
31 – 40	8	7	15
41 – 50	8	10	18
51 – 60	11	9	20
61 – 70	13	7	20
71 – 80	4	3	7
Total	46	54	100

Table 2: Demographic data showing the age group and number of patients included in our study.

Diagnosis	Number of cases
Knee	
Knee osteoarthritis	36
Chondromalacia patella	2
Patellar tendinopathy	2
Anterior cruciate ligament tear	2
Meniscus injury	2
Osgood-Schlatter disease	1
Shoulder	
Superior labrum anterior to posterior (SLAP) tear	5
Supraspinatus tendinopathy	9
Acromioclavicular joint arthropathy	4
Biceps tendinopathy	1
Triceps tendon tear	1
Elbow	
Lateral epicondylitis	2
Medial epicondylitis	2

Diagnosis	Number of cases
Hip	
Hamstring tendinopathy	3
Gluteus medius tear	1
Biceps femoris tendon sprain	1
Ankle	
Anterior talofibular ligament injury	4
Haglund deformity	2
Posterior tibialis tendon tear	1
Plantar fasciitis	1
Peroneal tendinopathy	5
Bursitis	
Subacromial-subdeltoid bursitis	6
Olecranon bursitis	1
Ischial bursitis	2
Other	
Lumbar facet arthropathy	3
Carpometacarpal joint osteoarthritis	1
Grand Total	100

Table 3: Total number of pathologies and patients for each pathology.

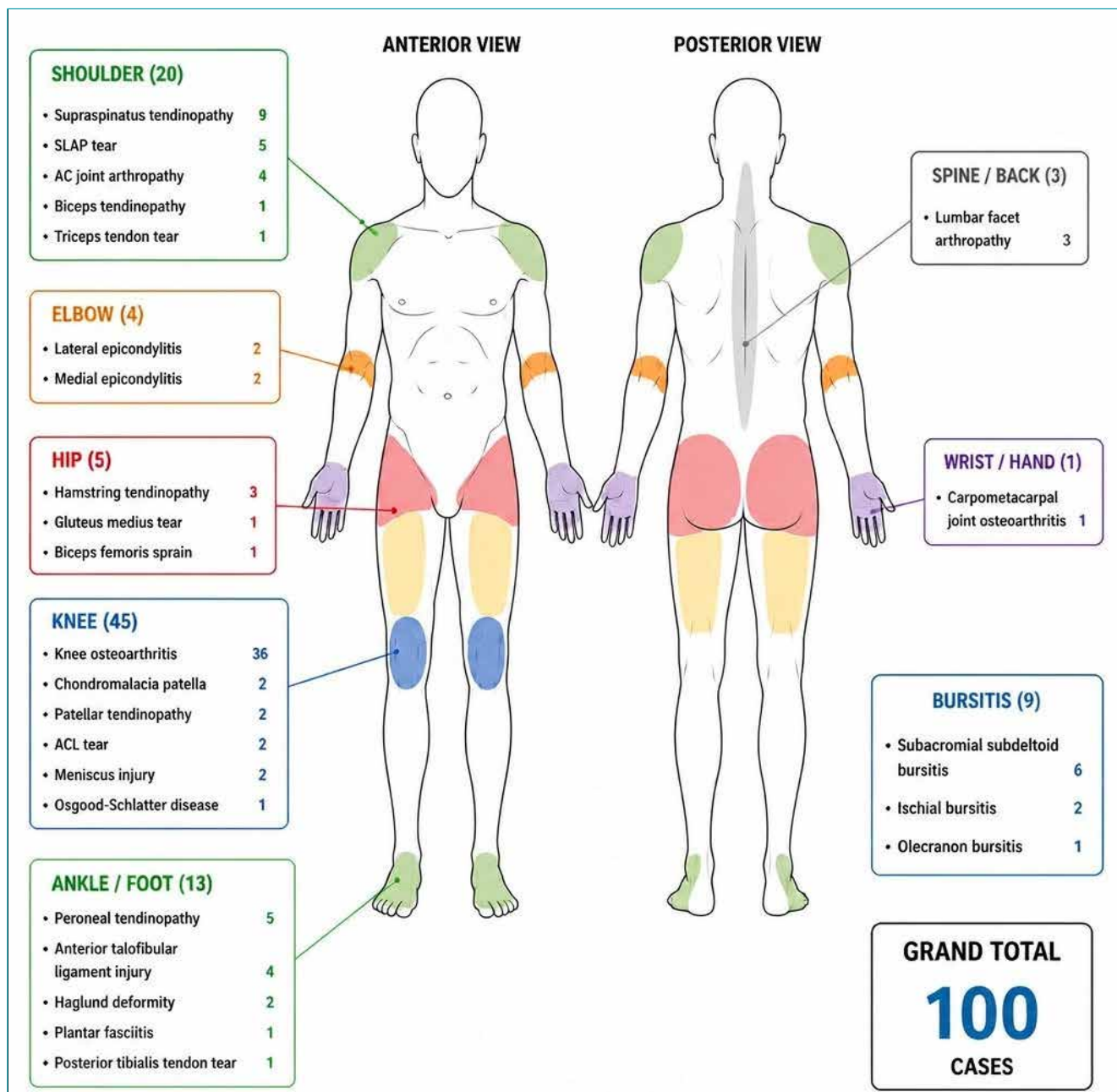


Figure 1: Distribution of diagnosis by body region (100 cases).

Age group (Years)	Number of patients (N = 100)	Mean pain relief at 1 month after completion of treatment (%)
11 – 20	10	86.90
21 – 30	10	85.70
31 – 40	15	83.40
41 – 50	18	82.60
51 – 60	20	80.90
61 – 70	20	79.80
71 – 80	7	78.10
Total	100	—

Table 4: Pain relief across different age groups.

Knee OA

A total of 36 patients ranging from 34 – 78 years of age with knee OA were included in the study.

Response after PRP sessions

The distribution of pain relief following successive PRP sessions in patients with knee OA is shown in Figure 2.

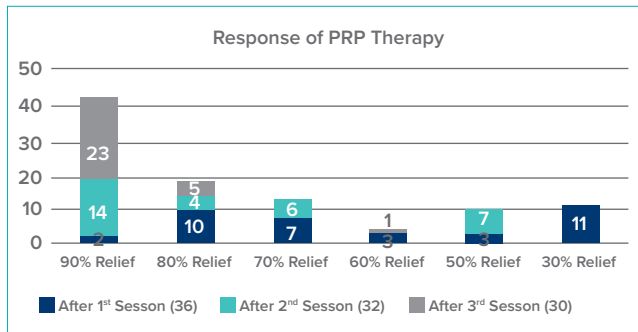


Figure 2: Pain relief following platelet-rich plasma (PRP) therapy in patients with osteoarthritic knee pathologies.

The proportion of patients achieving $\geq 80\%$ pain relief increased from 33.4% after the first session to 56.3% after the second session and 93.4% after the third session, demonstrating the cumulative therapeutic benefit of repeated PRP injections.

WOMAC scores among patients with knee OA

Before the procedure, most patients had poor WOMAC scores, with 16 (45.7%) patients scoring > 76 and 15 (42.9%) patients scoring between 51% and 75%. Only four (11.4%) patients had WOMAC scores below 50%.

Following the procedure, at the 1-month follow-up, there was a marked shift toward lower WOMAC score categories. The number of patients in the 0% – 25% category increased from one (2.9%) to 12 (34.3%), and those in the 26% – 50% category increased from three (8.6%) to 13 (37.1%). Conversely, the proportion of patients with higher WOMAC scores decreased substantially, with the 51% – 75% category decreasing from 15 (42.9%) to six (17.1%) and the > 76 % category decreasing from 16 (45.7%) to four (11.4%). At the 6-month follow-up, 31 patients were available for assessment. The majority of patients, 24 (77.4%), had WOMAC scores in the 0% – 25% category, indicating marked improvement in pain, stiffness, and functional status. Four patients (12.9%) had scores between 26 and 50%, whereas only one patient (3.2%) remained in the 51% – 75% category. Two patients (6.5%) had WOMAC scores of > 76 %.

Compared with the pre-procedure distribution, there was a clear shift towards lower WOMAC score categories at 1 and 6 months, demonstrating sustained clinical improvement and better functional outcomes following the procedure.

Other knee pathologies

Nine patients were aged 14 – 42 years and had other knee pathologies, including medial meniscus injury (two patients), anterior cruciate ligament (ACL) tear (two patients), patellar tendinopathy (two patients), chondromalacia patella (two patients), and Osgood-Schlatter disease (one patient) (Table 5).

Pathology	Number of patients	Number of sessions	Relief in pain at 1 month (Based on reduction in NRS score)
Medial meniscus injury	2	1	80%
Anterior cruciate ligament tear	2	1	80%
Patellar tendinopathy	2	1	70%
Chondromalacia patella	2	2	90%
Osgood-Schlatter disease	1	2	90%

Table 5: Pain relief following PRP therapy in patients with non-osteoarthritic knee pathologies. **Abbreviations:** NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma.

Hip pathologies

This group included five patients aged 21 – 62 years of age with various pathologies, such as hamstring tendinopathy (three patients), gluteus medius tear (one patient), and biceps femoris tendon sprain (one patient) (Table 6).

Pathology	Number of patients	Relief in pain at 1 week (Based on reduction in NRS score)	Relief in pain at 1 month (Based on reduction in NRS score)
Hamstring tendinopathy	2	30%	Lost to follow-up
	1	50%	70%
Bicep femoris tear	1	50%	70%
Gluteus medius tear	1	50%	70%

Table 6: Pain relief following PRP therapy in patients with hip pathologies.

Abbreviations: NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma.

Ankle and foot pathologies

A total of 13 patients aged 12 – 70 years with various ankle and foot pathologies like anterior talofibular ligament (ATFL) tear (four patients), peroneal tendinopathy (five patients), plantar fasciitis (one patient), Haglund deformity (two patients), and posterior tibialis tendon tear (one patient) were included (Table 7).

Pathology	Number of patients	Relief in pain at 1 week (Based on reduction in NRS score)	Relief in pain at 1 month (Based on reduction in NRS score)
ATFL injuries	3	70%	70%
	1	10%	10%
Peroneal tendinitis	1	60%	70%
	3	70%	70%
	1	10%	10%
Haglund deformity	1	50%	80%
	1	80%	80%
Plantar fasciitis	1	70%	70%
Tibialis posterior tendon (partial tear)	1	40%	80%

Table 7: Pain relief following PRP therapy in patients with ankle and foot pathologies.

Abbreviations: ATFL: Anterior Talofibular Ligament Tear; NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma.

Elbow pathologies

Four patients between 40 and 55 years of age were included. Two patients had medial epicondylitis, and two had lateral epicondylitis (Table 8).

Pathology	Number of patients	Number of sessions	Relief in pain at 1 month (Based on reduction in NRS score)
Medial epicondylitis	1	1	70%
	1	2	70%
Lateral epicondylitis	2	1	70%

Table 8: Pain relief following PRP therapy in patients with elbow pathologies.

Abbreviations: NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma.

Bursitis

A total of nine patients between 14 – 69 years of age were included, comprising six patients with SASD bursitis, one patient with olecranon bursitis, and two patients with ischial bursitis (Table 9).

Pathology	Number of patients	Number of sessions	Relief in pain at 1 month (Based on reduction in NRS score)
SASD bursitis	3	1	70%
	3	1	90%
Olecranon bursitis	1	1	90%
Ischial bursitis	1	1	90%
	1	2	60%

Table 9: Pain relief following PRP therapy in patients with bursitis. **Abbreviations:** NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma; SASD: Subacromial-Subdeltoid.

Shoulder joint pathologies

Patients with shoulder joint pathologies were aged 33 – 65 years. A total of four patients had acromioclavicular joint arthropathy (Table 10).

Pathology	Number of patients	Relief in pain at 1 week (Based on reduction in NRS score)	Relief in pain at 1 month (Based on reduction in NRS score)
Acromioclavicular joint arthropathy	2	80%	80%
	1	20%	70%
	1	70%	70%

Table 10: Pain relief following PRP therapy in patients with acromioclavicular joint arthropathy. **Abbreviations:** NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma.

Other shoulder pathologies

For other shoulder pathologies, patients aged 18 – 69 years included those with supraspinatus tear and tendinopathy (nine patients), triceps tendon tear (one patient), bicipital tendinopathy (one patient), and SLAP tear (five patients) (Table 11).

Pathology	Number of patients	Number of sessions	Relief in pain at 1 month (Based on reduction in NRS score)
Supraspinatus tear and tendinopathy	7	1	90%
	2	2	70%
Triceps tendon tear	1	1	90%
SLAP tear	3	2	70%
	2	1	80%
Bicipital tendinopathy	1	2	60%

Table 11: Pain relief following PRP therapy in patients with other shoulder pathologies.

Abbreviations: NRS: Numeric Rating Scale; PRP: Platelet-Rich Plasma; SLAP: Superior Labrum Anterior to Posterior.

Lumbar facet arthropathy

Three patients aged 35 – 49 years experienced 70% – 80% pain reduction, with sustained improvement observed at both 1-week and 1-month follow-up evaluations.

CMC joint OA

A 53-year-old patient reported 90% pain relief at both 1-week and 1-month follow-up visits.

Discussion

The present study evaluated the effectiveness of PRP therapy in 100 patients with a broad spectrum of musculoskeletal disorders. Overall, favourable clinical outcomes were observed across multiple pathologies, with particularly encouraging results in knee OA, shoulder disorders, tendinopathy, ligament injuries, and bursitis. These findings support the growing body of evidence suggesting that PRP is an effective regenerative treatment modality capable of promoting tissue healing and improving clinical outcomes through the release of growth factors and bioactive mediators involved in tissue repair, angiogenesis, extracellular matrix synthesis, and modulation of inflammation.^{1–3,5}

Mean pain relief was generally high across all age groups, ranging from 78.10% to 86.90%. The highest mean pain relief was observed in the 11 – 20 years group (86.90%), followed by the 21 – 30 years (85.70%) and 31 – 40 years (83.40%) age groups. Pain relief showed a gradual decline with increasing age, with the lowest mean pain relief observed in the 71 – 80 years group (78.10%). Chowdhary *et al.*⁶ concluded that age is a key determinant of PRP efficacy in OA, with PRP from younger individuals demonstrating greater cartilage regenerative potential than PRP from older individuals.

Knee OA was the most common pathology in the present study. Progressive clinical improvement was observed following serial PRP injections, with an increasing number of patients reporting substantial pain relief after subsequent treatments. In addition, post-treatment WOMAC scores demonstrated marked improvements in stiffness and functional ability compared with baseline scores. Das D *et al.*⁴ postulated that the observed clinical improvement following PRP therapy may be attributed to an increase in articular cartilage thickness. These structural changes were further supported by magnetic resonance imaging (MRI) findings.

These findings are consistent with those reported by Shen *et al.*,⁷ who demonstrated significant improvements in pain and physical function following PRP therapy in patients with knee OA. Similarly, Huang *et al.*⁸ observed favourable clinical outcomes following intra-articular PRP injection in early OA. Vilchez-Cavazos *et al.*⁹ further reported that multiple PRP injections provided superior clinical outcomes compared with a single injection, supporting the progressive improvement observed in the present study.

Apart from OA, other knee pathologies included medial meniscus injuries, anterior cruciate ligament tears, patellar tendinopathy, chondromalacia patella, and Osgood-Schlatter disease. Favourable clinical improvement was observed in all these conditions, particularly in patients with chondromalacia patella and Osgood-Schlatter disease. These findings suggest that PRP may be beneficial for selected non-osteoarthritic knee disorders. Collins *et al.*¹ highlighted the role of PRP-derived growth factors in stimulating cartilage and tendon healing, while Filardo *et al.*¹⁰ reported favourable outcomes following PRP treatment in degenerative cartilage lesions such as chondromalacia patellae and chondropathy.

Shoulder disorders constituted another major subgroup and included supraspinatus tendinopathy and tears, SLAP tears, acromioclavicular joint arthropathy, triceps tendon tears, and bicipital tendinopathy. The majority of these patients demonstrated favourable clinical outcomes. Most patients with supraspinatus pathology experienced significant symptomatic relief. These findings are in agreement with those reported by Rosso *et al.*,¹¹ who concluded that PRP appears particularly beneficial for rotator cuff disorders. Similarly, Blanchard *et al.*¹² reported significant improvements in pain, range of motion, and shoulder function following PRP therapy in patients with rotator cuff pathologies.

Among foot and ankle disorders, the study included patients with ATFL injuries, peroneal tendinopathy, Haglund deformity, plantar fasciitis, and partial posterior tibialis tendon tears. Clinical improvement was observed in most patients, although a small number demonstrated a limited response. Similarly, Kothari *et al.*¹³ observed significant reductions in pain and improvements in functional outcomes among patients with chronic plantar fasciitis treated with PRP. Vannini *et al.*¹⁴ also reported encouraging results with PRP in various foot and ankle disorders, supporting the findings of the present study.

Hip-related disorders included patients with hamstring tendinopathy, gluteus medius tear, and biceps femoris tendon

injury. Although two patients with hamstring tendinopathy were lost to follow-up, the patients who completed the follow-up demonstrated progressive symptomatic improvement. Similar findings have been reported by Fitzpatrick *et al.*,¹⁵ who demonstrated sustained improvements in pain and function in patients with chronic gluteal tendinopathy treated with PRP. The favourable outcomes observed in the present study may be attributed to the regenerative and anti-inflammatory effects of PRP on chronically degenerated tendon tissue.²

The present study also included patients with medial and lateral epicondylitis. All patients demonstrated favourable clinical outcomes following treatment. These findings are consistent with those reported by Mishra and Pavelko,¹⁶ who demonstrated significant long-term clinical improvement in patients with chronic epicondylitis treated with PRP. PRP is believed to promote tendon healing by stimulating fibroblast proliferation, collagen synthesis, and tissue remodelling.

The bursitis cases included patients with SASD, olecranon, and ischial bursitis. Most patients demonstrated substantial improvements in symptoms during follow-up. Although published evidence regarding the use of PRP in bursitis remains limited, its anti-inflammatory and regenerative properties may contribute to the reduction in symptoms and restoration of normal tissue function.

The present study also included patients with lumbar facet arthropathy and CMC joint OA. Favourable clinical outcomes were observed in these patients after PRP therapy. Although the sample size was small, these findings suggest a potential role for PRP in selected degenerative spinal and small joint disorders. Similar findings have been reported by Wu *et al.*,¹⁷ who demonstrated encouraging outcomes following PRP treatment for lumbar facet joint syndrome.

Conclusion

In this retrospective review of the initial 100 patients who underwent PRP therapy for diverse musculoskeletal disorders, significant reductions in pain and marked improvements in function were observed across various conditions. The most notable benefits were observed in patients with knee OA, chondromalacia patella, Osgood-Schlatter disease, triceps tendon tears, olecranon bursitis, and CMC joint OA. Additionally, the majority of patients with shoulder, hip, elbow, foot, and ankle disorders experienced meaningful clinical improvement. Multiple PRP injections for knee OA led to sustained progress in pain relief and WOMAC scores, indicating a cumulative therapeutic effect with repeated treatment. Overall, the data suggest that younger patients experienced slightly greater pain relief than older patients, although all age groups demonstrated substantial clinical improvement after PRP therapy.

A comparatively less favourable therapeutic response was observed in a small subset of patients with ATFL injury and peroneal tendinopathy. Although most patients in both groups experienced approximately 70% pain relief following PRP therapy, one patient in each group demonstrated minimal improvement (10% pain relief). Notably, these patients had coexisting musculoskeletal pathologies, including subtalar arthritis in the patient with ATFL injury and concomitant plantar fasciitis with Achilles tendinopathy in the patient with peroneal tendinopathy, which may have contributed to their suboptimal clinical response.

The principal limitations of this study include its retrospective nature, lack of a control group, the small number of patients within several pathology subgroups, and shorter follow-up durations in certain groups. Nevertheless, the data suggest that PRP is a promising, minimally invasive therapeutic option for treating musculoskeletal disorders. To confirm these results and develop condition-specific treatment guidelines, future prospective controlled trials with larger patient cohorts and extended follow-up periods are essential.

Aanchal Sharma, Aarzoo. Clinical Outcomes of Platelet-Rich Plasma in the First 100 Patients with Various Musculoskeletal Disorders: A Single-Centre Study. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-3>

References

1. Collins T, Alexander D, Barkatali B. Platelet-rich plasma: a narrative review. *EFORT Open Rev.* 2021;6(4):225–35.
2. Wang JHC. Can PRP effectively treat injured tendons? *Muscles Ligaments Tendons J.* 2014;4(1):35–7.
3. Wang JHC, Zhang N. The role of platelet-rich plasma in tendon healing. *Muscles Ligaments Tendons J.* 2014;4(1):3–6.
4. Das D, Sarker S, Roy A, *et al.* Assessment of MRI changes on articular cartilages after intra-articular injection of platelet-rich plasma in knee osteoarthritis: An interventional study. *J Clin Diagn Res.* 2025;19(3).
5. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol.* 2013;9(12):721–30.
6. Chowdhary K, Kanke M, Dyer C, *et al.* Aging affects the efficacy of platelet-rich plasma treatment for osteoarthritis. *Cells.* 2022;11(24):4014.
7. Shen L, Yuan T, Chen S, *et al.* The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. *J Orthop Surg Res.* 2017;12(1):16.
8. Huang PH, Wang CJ, Chou WY, *et al.* Short-term clinical results of intra-articular platelet-rich plasma injections for early osteoarthritis of the knee. *Int J Surg.* 2017;42:117–22.
9. Vilchez-Cavazos F, Millan-Alanis JM, Blazquez-Saldana J, *et al.* Comparison of the clinical effectiveness of single versus multiple injections of platelet-rich plasma in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Orthop J Sports Med.* 2019;7(12):2325967119887116.
10. Filardo G, Di Matteo B, Di Martino A, *et al.* Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(4):528–35.
11. Rosso C, Morrey ME, Schär MO, *et al.* The role of platelet-rich plasma in shoulder pathologies: a critical review of the literature. *EFORT Open Rev.* 2023;8(4):213–22.
12. Blanchard E, Harvi J, Vasudevan J, *et al.* Platelet-rich plasma for adhesive capsulitis: a systematic review. *Cureus.* 2023;15(10):e46580.
13. Kothari U, Shah S, Pancholi D, *et al.* Efficacy and safety of platelet-rich plasma injection for chronic plantar fasciitis: a prospective study on functional restoration and pain relief. *Cureus.* 2024;16(1):e52414.
14. Vannini F, Di Matteo B, Filardo G, *et al.* Platelet-rich plasma for foot and ankle pathologies: a systematic review. *Foot Ankle Surg.* 2014;20(1):2–9.
15. Fitzpatrick J, Bulsara M, O'Donnell J, *et al.* The effectiveness of platelet-rich plasma injections in gluteal tendinopathy: a randomized controlled trial. *Am J Sports Med.* 2018;46(4):933–9.
16. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med.* 2006;34(11):1774–8.
17. Wu J, Zhou J, Liu C, *et al.* A prospective study comparing platelet-rich plasma and local anesthetic for lumbar facet joint syndrome. *Pain Pract.* 2017;17(7):914–24.

Association Between Digital Sexual Exposure, Childhood Trauma, and Internet Addiction Among Adolescents: A Quantitative Study

Meher Kohli¹, Vanya Bindra²

¹Department of Applied Psychology, Ramanujan College, Delhi University

²Department of Psychology, Mata Sundri College for Women, Delhi University

Correspondence:

Meher Kohli

E-mail: meherkohli0@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-4>

Abstract:

Child sexual exploitation material (CSEM), online grooming, sextortion, and exposure to pornography are serious risks to children on the internet. Digital sexual abuse remains a severe psychological threat, even with the legal framework of the Protection of Children from Sexual Offences (POCSO) Act, 2012, and the Information Technology (IT) Act, 2000, in place. Exposure to sexualised images during early years may lead to distortions in sexual perceptions, compulsive behaviours, and sensitivity to anxiety, trauma, and other mental health issues. This study aimed to measure the prevalence, risk factors, and relationship between digital sexual exposure and internet-related compulsive behaviours, as well as attitudes towards legal and artificial intelligence (AI) assistant protective measures. This quantitative study was designed to investigate the psychological effects of exposure to pornography in adolescents, based on the use of Likert scales: the Internet Addiction Test and EMERGE-Gender Empowerment Measures Repository, focusing on childhood trauma. The data were analysed for correlations among frequency and type of exposure, patterns of internet use, and psychological outcomes. The study enrolled 50 adolescents (13 – 17 years) with at least 2 hours of daily exposure. Increased exposure to online sexual content is likely associated with higher psychological distress and greater compulsive internet use. There are very few quantitative studies in India that cover the psychological effects of digital sexual exposure, establish a connection with internet addiction, and connect them to legal and technological protection methods. The results show a positive relationship between childhood maltreatment and internet addiction, with emotional and physical neglect having the strongest relationship.

Key words: Protection of Children from Sexual Offences (POCSO) Act, Digital abuse, Information Technology Act, Psychological Effects, Online Addiction, Quantitative Research, Sexual Exposure, Adolescents.

Introduction

With the rapid development of digital technology, the environment in which children and adolescents develop has changed significantly.¹ Globally, over 82% of young people aged 15 – 24 years use the internet, making them the most connected age group. Early exposure

to smartphones, social media, and the internet at a tender age has exposed them to a global digital culture where they can converse with and learn, while putting themselves in great danger, leading to obsessive internet use, exposure to pornography at an early age, and distorted attitudes towards sex and consent.¹

Studies estimate that 10% – 30% of adolescents experience problematic internet use, while 40% – 70% report exposure to online sexually explicit content before the age of 18 years.¹ Adolescence is a particularly vulnerable developmental stage, characterised by identity formation, emotional control, and relationship-building.² Exposure to unrealistic notions about intimacy and gender norms on the internet may have long-term effects on self-esteem, trust, and relational well-being due to the psychological theories that behaviours are learned through observation and experience.² The spread of sexually explicit content is causing these apprehensions by desensitising to objectification and power relations and by activating the brain reward system through repetitive exposure, enhancing compulsive consumption habits that impact both academic success and mood.^{1,2}

In addition to these psychological risks, adolescents face an increasing risk of online abuse due to online grooming, sextortion, cyberbullying, and exposure to child sexual exploitation material (CSEM).^{3,4} Although there are laws protecting children's rights, such as the Protection of Children from Sexual Offences (POCSO) Act (2012), the Information Technology (IT) Act (2000), and the Juvenile Justice Act (2015), enforcement of these in the digital space remains challenging due to its anonymity, global connectivity, and rapid dissemination of information.^{3–5} Consequently, legal interventions are often more reactive than preventive. Besides exposing adolescents to harmful material, this may have psychological consequences, including trauma, anxiety, emotional dysregulation, and identity uncertainty.^{6–8}

Although these issues have received increasing attention, there remains a significant gap in the research examining the interdependent relationship between childhood trauma, exposure to digital material, and problematic internet use within the Indian sociocultural context.^{9,10} The existing laws primarily focus on punitive and protective processes.^{3–5} However, they pay limited attention to the psychological component of online vulnerability, particularly the long-term consequences of traumatic experiences and the emotional neglect of online behaviour.^{7,10} Furthermore, although internet addiction and exposure to harmful content have been studied independently or in a combination with other interventions, the relationship between early negative

experiences and exposure to the digital environment in the context of determining maladaptive coping strategies remains unclear.^{6,9,10} This knowledge gap is further compounded by stigma, lack of digital literacy, underreporting of cases of abuse, and lack of access to psychological support systems only complicate this disparity.^{3,5} Additionally, cultural taboos surrounding discussions of sexuality often compel adolescents to rely on online sources as their primary source of information, potentially reinforcing false assumptions and maladaptive behaviours.² Ethical concerns surrounding the increasing use of artificial intelligence (AI) to detect and monitor harmful online content including privacy, surveillance, and psychological well-being, have not been discussed.^{3,4} Consequently, the lack of an integrated framework required to connect the legal, psychological, and technological viewpoints leaves a gap in research and practice, making the current approaches to the protection of children in the digital age less effective.^{3–5}

In this regard, the present study aims to address these loopholes by examining the correlation between problematic internet use and childhood trauma, and integrating the results into comprehensive legal and digital interventions.^{9,10} The rationale behind the study is that the problem of digital vulnerability is psychologically rooted in early trauma, rather than being a mere reality of technology.^{6,7,10} This research will help gain a deeper understanding of the dangers that the online environment presents to adolescents by analysing how these factors affect internet usage behaviours.¹⁰

In addition to focusing on risk assessment, it emphasises the significance of trauma-informed and preventive approaches, such as early psychological intervention, consent education, and digital literacy. Furthermore, it emphasises the need for the inclusion of mental health services within legislation, such as the POCSO Act, to provide protection and rehabilitation.³ The role of families, schools, and legislators in promoting safe online behaviours through digital literacy, emotional support, and access to resources is also addressed.^{5,7} Lastly, the study indicates that, to make the internet a safer and more empowering environment for children and adolescents, a multidisciplinary strategy must be employed that includes psychological sensitivity, legal protection, and mindful use of technology.^{3–5}

Accordingly, the objective of the present study was to explore the relationship between exposure to pornographic content on the internet and its psychological effects on adolescents, as well as to measure the correlation between exposure to digital sexual material and adolescents' emotional state and compulsive internet use.

Methodology

A cross-sectional research design was used, and the study investigated the relationship between childhood trauma, exposure to online sexual material, and problematic internet use. This design helped measure the strength and direction of the associations between the variables.

Tools used

Internet Addiction Test (IAT): This is a 20-item questionnaire on a 5-point Likert scale, developed by Kimberly Young (1998). It helps evaluate behavioural, cognitive, and emotional aspects to internet use, including preoccupation and compulsivity.

EMERGE Childhood Trauma Questionnaire-Short Form (EMERGE CTQ-SF): This instrument evaluates childhood abuse and neglect in emotional, physical, and sexual aspects (EMERGE, 2020).

Participants and sampling

In this study, a sample of 50 adolescents aged 13 – 17 years was included. Participants were selected using purposive sampling to ensure that the sample was relevant to the research objectives. Ethical guidelines, including informed consent and parental consent, were considered.

Procedure

The participants were evaluated in a controlled environment. Demographic information such as age, gender, and years of internet use was collected, and the CTQ-SF and IAT were administered.

The CTQ-SF consists of 28 items, including 25 clinical and three validity items. It measures five areas of trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, rated on a 5-point Likert scale (1 = never true to 5 = very often true). Subscale scores (range: 5 – 25) were calculated

by adding all items within each domain, and the total clinical score (range: 25 – 125) was obtained by adding all domains. Under-reporting or minimisation was identified with the help of the validity items.

The IAT consists of 20 items with scores ranging from 0 to 100, with each item rated between 0 (not applicable) and 5 (always). Higher scores indicate higher levels of internet addiction, ranging from normal (0 – 30), mild (31 – 49), moderate (50 – 79), and severe (80 – 100).

All responses to the questionnaires were collected anonymously. The data were screened for missing values and outliers, and positively worded CTQ items were reverse-scored. Subscale and total scores were then computed.

Results

The relationship between childhood trauma (CTQ total and subscales) and IAT scores was investigated using Pearson's product-moment correlation (Table 1). The results showed a significant positive relationship between overall childhood trauma and problematic internet use ($r = 0.83$), indicating that higher levels of trauma were correlated with higher levels of problematic internet use.

Variable (CTQ subscales)	Correlation with IAT (r-value)	Interpretation
CTQ total	0.83	Strong positive correlation
Emotional neglect	0.75	High positive correlation
Physical neglect	0.75	High positive correlation
Emotional abuse	0.73	Moderate to high correlation
Sexual abuse	0.73	Moderate to high correlation
Physical abuse	0.67	Moderate positive correlation

Table 1: Correlation between childhood trauma and internet addiction.

Abbreviations: CTQ: Childhood Trauma Questionnaire; IAT: Internet Addiction Test.

Additional analysis revealed significant positive correlations between all subscales of childhood maltreatment, indicating that various types of childhood maltreatment are associated with increased internet addiction.

Additional findings: Interpretation of results

- A strong relationship was observed between emotional and physical neglect and internet addiction, highlighting the role of neglect in excessive internet use.
- All types of trauma were significantly positively correlated, indicating that different types of abuse and neglect are positively correlated with maladaptive digital behaviour.
- The correlations between subscales indicate that internet addiction may be viewed as a coping strategy for different types of childhood adversity.

Taken together, these findings corroborate the hypothesis that greater exposure to childhood trauma is positively associated with increased problematic internet use among adolescents.

Discussion

This study aimed to investigate the connection between childhood trauma and problematic internet use in adolescents.^{9,10} The results showed a strong, significant positive correlation between total CTQ-SF scores and IAT scores ($r = 0.83$), indicating that higher levels of childhood maltreatment are positively associated with higher IAT scores.^{11,12} Emotional neglect ($r = 0.75$) and physical neglect ($r = 0.75$) were the strongest subtypes of trauma, followed by emotional abuse ($r = 0.73$), sexual abuse ($r = 0.73$), and physical abuse ($r = 0.67$).¹¹ These findings indicate that experiences of emotional neglect may drive adolescents to overuse the internet as a form of coping.^{7,8}

The findings of this study are consistent with previous studies, which have indicated a relationship between negative childhood experiences and behavioural addictions.^{7,9,10} As illustrated by Wang *et al.* (2023) and Tang *et al.* (2024), there are significant positive relationships between childhood trauma and internet addiction, with correlation coefficients ranging from moderate to high levels.^{9,10} Similarly, Hu *et al.* (2022) found that emotional neglect and family dysfunction were strong predictors of problematic internet use, highlighting their disruptive effects on the processes of emotional regulation and attachment.⁷ The high correlation between CTQ-SF and IAT scores ($r = 0.83$) in the present study further supports this evidence,

indicating an exceptionally strong relationship between childhood trauma and problematic internet usage among adolescents.^{7,9,10}

Adolescents who have experienced trauma, particularly neglect, may find emotional relief and validation on the internet.^{7,8} This is consistent with the previous findings by Guo *et al.* (2023) and Sheng *et al.* (2022), who identified depression, anxiety, loneliness, and emotional dysregulation as the mediating factors between childhood trauma and internet addiction.^{6,10} The high correlations found in the current study support the notion that problematic internet use may serve as a compensatory mechanism to deal with unmet emotional needs.^{6–8}

The social learning theory suggests that repeated exposure to exploitative material may lead to the internalisation of distorted sexual scripts and maladaptive behavioural patterns, leading to emotional dysregulation, guilt, and compulsive use of the internet.² Such trends contribute over time to desensitisation, hypersexuality, and trauma-like symptoms such as anxiety and depression.^{2,6,8} These processes provide a psychological explanation for the strong relationship between trauma and internet dependency.^{2,10}

The results of the study indicate the increased susceptibility of adolescents online.^{3,4} Poor digital literacy, peer influence, and easy access to explicit online material increase the risk of unwanted exposure to harmful internet activity, i.e., grooming, sextortion, and CSEM.^{3,4} Although legislation such as the POCSO Act, 2012 and the IT Act, 2000, has been enacted to address these concerns, their effectiveness is often limited due to underreporting, stigma, and the absence of psychological support.^{3,4} These results imply that traumatised adolescents may be particularly vulnerable because of emotional vulnerability and increased virtual peer interactions.^{6–8}

The internet is a double-edged sword, serving both as a coping mechanism and a source of vulnerability for adolescents.^{7,10} Online environments are perceived to be safer and more manageable than offline environments, particularly by adolescents experiencing neglect or abuse.^{7,8} Nevertheless, this dependency may reinforce avoidant behaviours and result in compulsive internet use.^{9,10} This trend is especially applicable to the Indian

context, where rapid digital growth has not been accompanied by adequate digital literacy or parental control.^{3–5}

The results indicate that dealing with childhood trauma is crucial for promoting healthy internet use.^{9,12} Interventions focused solely on reducing screen time may not be effective unless the underlying emotional distress is addressed.^{6–8} Trauma-informed care that enhances emotional resilience, self-regulation, and supportive family environments is likely to be more effective in reducing problematic internet use.^{7,8}

Moreover, the integration of trauma screening instruments, such as the CTQ-SF, into school counselling, child welfare, and juvenile justice systems may facilitate the early detection of at-risk adolescents.^{5,11} This can inform interventions and prevention measures, especially as legal frameworks increasingly address the digital manifestations of exploitation.^{3–5} Understanding the psychological antecedents of risky online behaviour is important for both mental health professionals and policymakers.^{6,7,10}

However, this study has certain limitations, such as the cross-sectional research design, which does not provide any causal interpretations. The use of self-reported measures may result in recall bias or underreporting, especially since trauma is a sensitive subject.^{11,12} In addition, the small sample size limits the generalisability of the results. Future research should adopt a longitudinal research design to investigate cause-and-effect relationships and examine protective factors such as parental attachment, digital literacy, and social support.^{7,8,10}

Finally, the present research confirms a strong correlation between childhood trauma and problematic internet use, where there is a very high correlation ($r = 0.83$).^{11,12} By contextualising the findings within the existing literature, this research highlights the importance of trauma-informed, psychologically based strategies for digital safety.^{6–8,10} Combining mental health programmes with digital literacy programmes is important for reducing internet addiction and protecting adolescents against internet threats.^{3,5,7}

Conclusion

The primary finding of this study is a strong positive correlation between overall trauma and internet addiction ($r = 0.83$). Specifically, emotional and physical neglect were the strongest predictors of excessive and maladaptive digital behaviour. This study demonstrates that internet addiction is not merely behavioural in nature but is also rooted in emotional distress, with adolescents potentially using the internet as an escape mechanism, validation, and coping with unmet psychological needs. Overall, the findings suggest that childhood trauma, emotional dysregulation, and digital vulnerability are interrelated and increase the risk of compulsive internet use and harmful online experiences. Although legal frameworks, such as the POCSO Act (2012), are crucial in combating digital exploitation, their effectiveness could be enhanced through the integration of psychological understanding and support systems. Interventions must go beyond the regulation of screen time and adopt a more holistic and trauma-informed strategy, including early detection, digital literacy, and supportive family and school environments. Overall, understanding the psychological foundations of digital vulnerability is key to ensuring improved health by engaging in healthier digital practices and developing safer digital environments in which adolescents can enjoy improved health.

Meher Kohli, Vanya Bindra. Association Between Digital Sexual Exposure, Childhood Trauma, and Internet Addiction Among Adolescents: A Quantitative Study. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-4>

References

1. Young KS. Internet addiction: The emergence of a new clinical disorder. *Cyberpsychol Behav Soc Netw*. 1998;1(3):237–44.
2. Bandura A, Walters RH. Social learning theory. Englewood Cliffs, NJ: Prentice-hall; 1977.
3. Government of India. The Protection of Children from Sexual Offences Act, 2012. Available at: <https://www.indiacode.nic.in/bitstream/123456789/2079/1/AA2012-32.pdf>. Accessed on: 9th July 2026.
4. Government of India. The Information Technology Act, 2000. Available at: https://www.indiacode.nic.in/bitstream/123456789/13116/1/it_act_2000_updated.pdf. Accessed on: 9th July 2026.
5. Government of India. The Juvenile Justice (Care and Protection of Children) Act, 2015. Available at: <https://www.indiacode.nic.in/bitstream/123456789/2148/1/a2016-2.pdf>. Accessed on: 9th July 2026.
6. Hua Y, Wang W, Shi J, *et al*. Childhood trauma and internet addiction among Chinese adolescents: The mediating role of coping styles. *Curr Psychol*. 2023;42(19):16507–17.
7. Gioia F, Rega V, Boursier V, *et al*. Problematic internet use and emotional dysregulation among young people: A literature review. *Clin Neuropsychiatry*. 2021;18(1):41–54.
8. Wang Y, Zeng Y. Relationship between loneliness and internet addiction: a meta-analysis. *BMC Public Health*. 2024;24(1):858.
9. Tang H, Li Y, Dong W, *et al*. The relationship between childhood trauma and internet addiction in adolescents: A meta-analysis. *K Behav Addict*. 2024;9;13(1):36–50.
10. Wang X, Li D, Li S. Childhood trauma and problematic internet use: A meta-analysis based on students in mainland China. *Front Psychol*. 2023;14:1115129.
11. Raj A, Dey A, Rao N, *et al*. The EMERGE framework to measure empowerment for health and development. *Soc Sci Med*. 2024;351(Suppl 1):116879.
12. Young KS. Caught in the net: How to recognize the signs of internet addiction and a winning strategy for recovery. John Wiley & Sons. 1998.

The Rise of Artificial Intelligence in Oncology: Opportunities, Challenges, and Future Directions

Khushboo Rastogi^{1*}, Anusheel Munshi¹

¹Department of Radiation Oncology, BLK-Max Super Speciality Hospital, Delhi

Correspondence:

Khushboo Rastogi

E-mail: drkhush.r13@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-20>

Abstract:

Artificial intelligence (AI) is rapidly transforming oncology by supporting clinical decision-making across the entire cancer care continuum, with radiation oncology emerging as one of the leading specialties in its clinical adoption due to its inherently digital workflow. This narrative review summarises the current evidence on AI applications in oncology, with particular emphasis on radiation oncology, highlighting recent advances in machine learning, deep learning, large language models (LLMs), and multimodal AI, while also discussing the challenges and future directions for clinical implementation. AI has demonstrated significant potential in cancer screening, imaging, pathology, genomics, treatment selection, and outcome prediction. Within radiation oncology, it enhances auto-segmentation, treatment planning, image guidance, adaptive radiotherapy, radiomics, and quality assurance (QA), improving workflow efficiency, consistency, and treatment precision. Emerging technologies such as multimodal AI, LLMs, federated learning, and digital twins are expected to further accelerate the development of precision oncology. However, widespread clinical implementation continues to face challenges, including limited external validation, algorithmic bias, poor model interpretability, and ethical and regulatory concerns. Overall, AI is becoming an integral component of modern oncology, particularly radiation oncology, and its successful integration into routine clinical practice will require robust validation, transparent governance, equitable implementation, and continued clinician oversight to ensure safe, effective, and patient-centred cancer care.

Key words: Artificial Intelligence, Oncology, Radiation Oncology, Machine Learning, Deep Learning, Radiotherapy, Precision Oncology.

Introduction

Modern oncology generates enormous volumes of clinical data, including imaging studies, digital pathology slides, genomic sequencing, laboratory investigations, and electronic medical records (EMRs). Integrating these diverse datasets into timely clinical decisions is increasingly difficult using conventional approaches. Artificial intelligence (AI) has emerged as a powerful tool for analysing complex medical data, recognising clinically relevant patterns, and assisting clinicians in diagnosis, treatment planning, and outcome prediction.¹ Rapid advances in computing power, together with widespread

digitisation of radiology, pathology, and genomics, have accelerated AI development in oncology.² Together, these changes have given AI access to both the data and computing power needed to assist clinicians in near real time.

The Expanding Scope of AI Across Oncology

Screening and early detection

Among the various applications of AI in oncology, cancer screening has shown the strongest clinical evidence to date (Figure 1). Deep learning algorithms have demonstrated diagnostic performance comparable to that

of expert radiologists in mammographic screening while improving workflow efficiency. Beyond lesion detection, AI can estimate individualised breast cancer risk, thereby enabling personalised screening strategies, such as the selective use of breast magnetic resonance imaging (MRI) in high-risk women. The ongoing Swedish ScreenTrustMRI trial is evaluating this risk-adapted approach.³

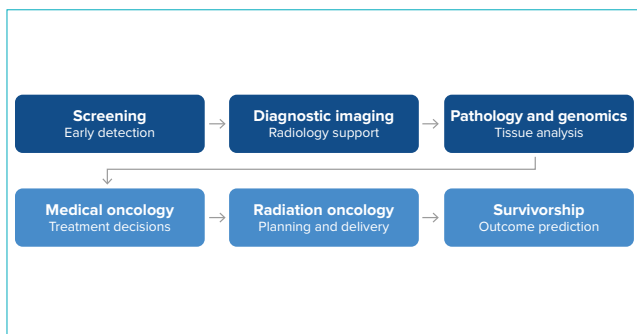


Figure 1: The expanding scope of artificial intelligence (AI) across the oncology care continuum, from population screening to survivorship.

AI has also shown promising results in lung cancer screening using low-dose computed tomography (CT) scans, automated polyp detection during colonoscopy, prostate cancer diagnosis, and smartphone-based skin cancer assessment.⁴ Although these systems generally demonstrate high sensitivity, concerns remain regarding false-positive rates and reduced accuracy in underrepresented populations, particularly among individuals with darker skin tones, highlighting the importance of diverse training datasets.⁵

Diagnostic imaging and radiology

Diagnostic imaging was one of the first areas in oncology to incorporate AI into routine clinical practice. AI algorithms assist in detecting lesions, characterising tumours, assessing disease extent, and monitoring treatment response across CT, MRI, and positron emission tomography (PET) imaging. Their primary role is to enhance reporting efficiency while maintaining diagnostic accuracy. Radiomics further extends these capabilities by extracting quantitative imaging features that are not appreciable by visual inspection. These imaging biomarkers may reflect the underlying tumour biology and help predict treatment response, prognosis, and survival. AI is also improving image acquisition by enabling faster reconstruction and noise reduction, allowing shorter scan times and, in selected settings, lower radiation exposure without compromising image quality.⁶

Digital pathology and genomics

The increasing adoption of digital pathology has created new opportunities for AI-assisted diagnosis in this field. AI algorithms can support pathologists in tumour grading, mitotic counting, and detecting lymph node metastases. Studies have also found that AI models can detect certain molecular features, including microsatellite instability (MSI) and specific gene mutations, directly from pathology images, which could eventually reduce the need for additional molecular testing in selected patients. Emerging multimodal foundation models integrate pathology, imaging, genomic, and clinical information to provide a comprehensive assessment of tumour biology.⁷ AI has also become increasingly valuable in genomic analysis by interpreting large volumes of data produced by next-generation sequencing (NGS), identifying clinically relevant

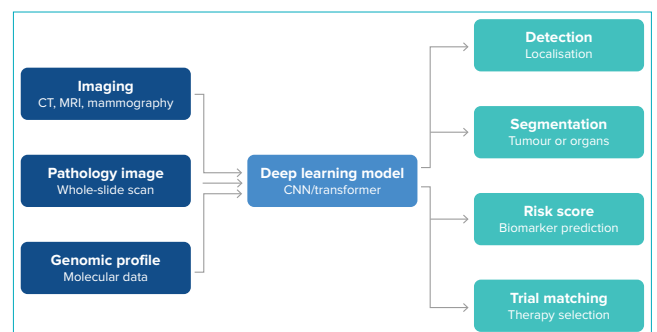


Figure 2: Multimodal AI pipeline for cancer detection, segmentation, risk stratification, and treatment selection. **Abbreviations:** AI: Artificial Intelligence; CNN: Convolutional Neural Network; CT: Computed Tomography; MRI: Magnetic Resonance Imaging.

genetic alterations, matching patients to targeted therapies, and facilitating enrolment in suitable clinical trials (Figure 2).⁸

Medical oncology: Treatment selection and drug discovery

In medical oncology, AI is increasingly being used to support treatment decisions by integrating a patient's clinical history, imaging, pathology, and genomic profile into a unified clinical framework. Such systems can facilitate the identification of appropriate treatment options and streamline multidisciplinary tumour board discussions, thereby reducing the time required to organise complex patient information.^{4,9}

Large language models (LLMs) are emerging as practical clinical tools capable of extracting relevant information

from EMRs, generating patient-friendly consultation summaries, and identifying patients eligible for clinical trials.¹⁰ AI also plays a crucial role in drug discovery by identifying therapeutic targets, predicting effective drug combinations, and prioritising compounds for laboratory and clinical testing, potentially reducing both development time and cost.¹¹

Outcome prediction and survivorship

Beyond diagnosis and treatment planning, AI is increasingly used to predict clinical outcomes. By analysing longitudinal clinical and real-world datasets, AI models can estimate recurrence risk, predict treatment response, and identify patients at greater risk of treatment-related toxicity. Such information may help personalise follow-up strategies and enable earlier supportive interventions.¹² AI applications are also being explored in supportive and palliative oncology, including symptom monitoring, early identification of patients requiring supportive care, and improving clinician-patient communication. Although these applications remain less mature than diagnostic or treatment-planning tools, they represent an important area of future development.¹³

AI in Radiation Oncology

Radiation oncology is the speciality in which AI has found the widest clinical application. The speciality is inherently digital, relying heavily on imaging, computerised treatment planning, and image-guided treatment delivery, generating large volumes of structured data throughout the radiotherapy workflow.¹⁴ Therefore, AI has become increasingly embedded in routine practice, supporting contouring, treatment planning, image guidance, adaptive radiotherapy, and quality assurance (QA). Rather than replacing clinicians, AI primarily automates repetitive tasks, improves workflow efficiency, and reduces interobserver

variability while preserving physician oversight and clinical judgement (Figure 3).^{14,15}

Auto-segmentation of targets and organs at risk (OAR)

Outlining or “contouring” the tumour (or target) and nearby normal structures (or OAR) is one of the most time-consuming steps in radiotherapy planning and a major source of interobserver variability. Differences in clinicians’ contouring can significantly influence dose distribution and treatment outcomes, particularly in anatomically complex sites such as the head and neck. To address this challenge, deep learning-based auto-segmentation has been incorporated into most modern treatment planning systems (TPS), substantially reducing contouring time while improving consistency, especially for OARs.¹⁵ Automatic delineation of tumour volumes remains challenging because of variations in tumour shape, size, and imaging characteristics. Consequently, AI-generated contours require careful review and editing by clinicians before treatment planning.

AI-assisted treatment planning

Treatment planning is another area where AI has demonstrated significant clinical benefits. Knowledge-based planning and deep learning algorithms can automatically generate radiotherapy plans that satisfy predefined tumour coverage and OAR dose limits with minimal manual intervention. These approaches shorten planning time, reduce variability between planners, and improve workflow efficiency.¹⁶ An example of such an AI-based integrated workflow was reported recently in a case of prostate cancer, where plan quality was comparable to that produced by experienced dosimetrists.

Image guidance and adaptive radiotherapy (ART)

ART aims to account for anatomical changes that occur during treatment, including tumour regression, weight loss, and organ motion. Conventional adaptive workflows are resource-intensive because they require repeated image registration, contour modification, and treatment re-planning. AI is making ART increasingly feasible by automating these processes. Deep learning algorithms can rapidly perform image registration, identify clinically significant anatomical changes, and generate updated contours, allowing treatment plans to be modified within clinically acceptable time frames.¹⁶ These advances are facilitating the transition of ART

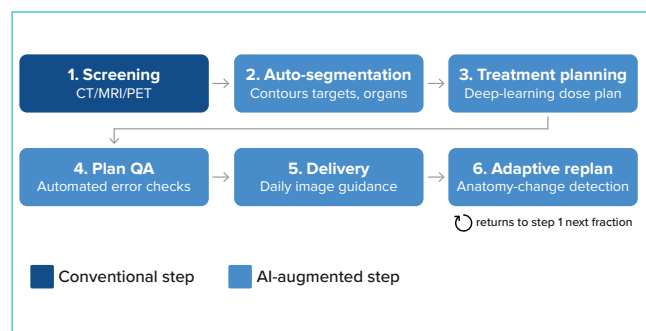


Figure 3: Extent of AI integration across the modern radiotherapy workflow.

Abbreviations: AI: Artificial Intelligence; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; QA: Quality Assurance.

from a specialised research technique to a practical component of routine clinical care.

Outcome prediction and radiomics in radiation oncology

Beyond treatment planning, AI is increasingly used to predict clinical outcomes. Quantitative radiomic features extracted from planned CT scans can be combined with clinical, pathological, and treatment data to predict tumour control, the likelihood of radiation-induced toxicity, and overall survival. Such models may eventually support personalised radiotherapy, including patient-specific dose prescriptions and fractionation schedules. Another area of active research is explainable AI (XAI), which seeks to improve transparency by identifying the factors that influence AI-generated predictions. Improved interpretability may increase clinician confidence when AI is used to support complex treatment decisions, such as the selection of surgery or radiotherapy for patients with early-stage non-small cell lung cancer.¹⁷

Workflow efficiency and QA

AI is increasingly being used for routine quality checks in radiation oncology, including the automatic verification of completed treatment plans, error detection, treatment delivery monitoring, and identification of deviations requiring clinician review. The use of AI applications for these tasks can minimise the need for repetitive manual checks while improving process efficiency and patient safety. Such monitoring is crucial because the performance of an AI tool can vary depending on the hospital, imaging equipment, or patient population in which it is being used. Commercial auto-segmentation tools, for example, often demonstrate reduced accuracy when applied outside the datasets on which they were originally developed.¹⁷ Consequently, routine clinical validation and ongoing performance evaluation are critical before widespread implementation.

Challenges to Clinical Implementation

Data quality, representational and algorithmic bias

Despite remarkable advances, several challenges continue to limit the widespread adoption of AI in oncology (Figure 4) (Table 1). A major concern is the quality and representativeness of the training data. Many AI models are developed using datasets from a limited number of institutions, imaging platforms, or patient populations, which may reduce their performance when applied to different healthcare settings.¹⁸ Limited representation of diverse

ethnic and demographic groups further increases the risk of algorithmic bias and unequal clinical performance. Federated learning, which enables multiple institutions to collaboratively train AI models without sharing patient

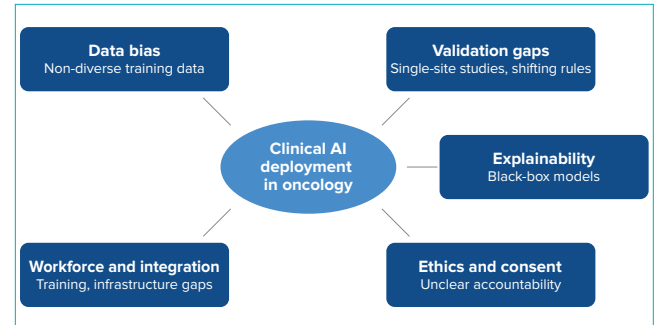


Figure 4: Key barriers to the routine and equitable implementation of artificial intelligence (AI) in oncology.

Strengths	Weakness	Opportunities	Threats
Strong evidence for screening	Often single-site validation	Federated privacy-preserving techniques	Non-diverse data risk bias
Mature integration in radiation oncology	Segmentation tools underperform outside their original settings	Treatment planning using digital twins	Regulatory frameworks lag behind evolving models
Reduces variability and workload	"Black-box" limits interpretability and clinical trust	LLMs reduce administrative burden	Unclear accountability for AI-linked errors
Boost precision oncology matching	Target delineation still needs manual clinician refinement	XAI improves trust	LMIC access gaps may widen disparities

Table 1: SWOT analysis of the role of AI in oncology. **Abbreviations:** AI: Artificial Intelligence; LLMs: Large Language Models; LMIC: Low- and Middle-Income Countries; XAI: Explainable AI.

data, offers a promising strategy for improving model generalisability while preserving data privacy.¹⁹

Validation, generalisability, and regulatory oversight

Despite these encouraging results, an important limitation is the lack of robust external validation. Many AI systems have

demonstrated excellent performance in retrospective or single-institution studies but remain insufficiently evaluated in prospective multicentre clinical settings. Before routine implementation, AI tools must demonstrate consistent performance across diverse patient populations, imaging protocols, and healthcare environments. Regulatory oversight is also evolving to address continuously learning AI systems. In the United States, many clinical AI applications are regulated as software as a medical device (SaMD), while the European Union AI Act provides a dedicated framework for AI governance in healthcare.²⁰

Explainability and clinical trust

Model interpretability remains a challenge. Although deep learning algorithms often achieve high diagnostic accuracy, many function as “black boxes”, providing predictions without explaining how decisions are made. This lack of transparency may reduce clinician confidence, particularly in high-stakes oncological decision-making. XAI seeks to address this issue by identifying the variables influencing model predictions, thereby improving trust and facilitating clinical adoption.²¹

Ethical, legal, and informed consent considerations

Ethical and legal concerns also require careful consideration when implementing AI in clinical practice. Questions regarding accountability, patient consent, data privacy, and responsibility for AI-assisted decisions remain unresolved. A recent systematic review highlighted persistent concerns

regarding transparency, informed consent, and unclear liability when AI contributes to clinical decision-making.²²

Integration, workforce, and health system readiness

The success of an AI tool depends not only on its technical performance but also on workforce training, digital infrastructure, and integration into existing clinical workflows. These challenges are particularly relevant in low- and middle-income countries (LMICs), where limited resources could widen disparities in cancer care if AI technologies are not implemented equitably.^{7,18}

Future Directions

The next generation of AI in oncology will increasingly rely on multimodal foundation models capable of integrating radiology, pathology, genomics, clinical records, and laboratory data into unified predictive models.⁹ Such systems may improve diagnosis, treatment selection, and prognostication by providing a more comprehensive understanding of tumour biology than that provided by individual data sources alone. Privacy-preserving approaches, such as federated learning, differential privacy, and secure multiparty computation, are expected to facilitate collaboration between institutions while protecting patient confidentiality.¹⁹ Another emerging concept is the “digital twin” — a dynamic virtual representation of an individual patient that continuously incorporates imaging, pathological, genomic, and clinical information to simulate disease progression and predict treatment response.²³

Conclusion

AI is steadily transitioning from a research tool to an integral component of routine oncology practice. Its applications now span cancer screening, diagnostic imaging, pathology, genomics, treatment selection, and survivorship, with radiation oncology representing one of the most mature examples of successful clinical implementation of AI. AI-assisted contouring, treatment planning, and workflow optimisation have already improved efficiency and consistency, whereas adaptive radiotherapy, radiomics, and predictive models continue to evolve.

Despite these advances, AI should be viewed as a clinical decision support tool rather than a replacement for oncologists. Broader adoption will require diverse and representative datasets, rigorous multicentre validation, transparent and explainable algorithms, robust regulatory oversight, and ongoing post-deployment monitoring of these systems. With responsible development and equitable implementation, AI has the potential to enhance precision oncology, optimise radiotherapy workflows, and ultimately improve patient outcomes, while allowing clinicians to devote more time to individualised patient care.

Khushboo Rastogi, Anusheel Munshi. The Rise of Artificial Intelligence in Oncology: Opportunities, Challenges, and Future Directions. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-20>

References

1. Roy A, Bhoyar A, Ahirwar A, et al. Artificial intelligence in oncology: Current status and possibilities. *Med Int (Lond)*. 2026;6(2):20.
2. Tiwari A, Mishra S, Kuo TR. Current AI technologies in cancer diagnostics and treatment. *Mol cancer*. 2025;24(1):159.
3. Salim M, Liu Y, Sorkhei M, et al. AI-based selection of individuals for supplemental MRI in population-based breast cancer screening: the randomized ScreenTrustMRI trial. *Nat med*. 2024;30(9):2623–30.
4. Alaca EC, Aránguiz C, Bracchiglione J, et al. Applications of Artificial Intelligence in clinical decision-making and technical support in Oncology: A Scoping Review protocol. *medRxiv*. 2025;2025–05.
5. Chuchu N, Takwoingi Y, Dinnes J, et al. Smartphone applications for triaging adults with skin lesions that are suspicious for melanoma. *Cochrane Database Syst Rev*. 2018;12(12):CD013192.
6. Huang J, Xiang Y, Gan S, et al. Application of artificial intelligence in medical imaging for tumor diagnosis and treatment: a comprehensive approach. *Discov Oncol*. 2025;16(1):1625.
7. Ruelle T, Grinda T, Del Mastro L, et al. How artificial intelligence applied to digital pathology could guide treatment personalization in breast cancer. *ESMO Real World Data and Digit Oncol*. 2026;11:100662.
8. Athanasopoulou K, Michalopoulou VI, Scorilas A, et al. Integrating artificial intelligence in next-generation sequencing: advances, challenges, and future directions. *Curr Issues Mol Biol*. 2025;47(6):470.
9. Parkinson G, Patel R, Bergstrom C, et al. Artificial Intelligence in Oncology: Clinical Applications, Challenges, and Opportunities. *Am Soc Clin Oncol Educ Book*. 2026;46(3):e520716.
10. Griot M, Vanderdonckt J, Yuksel D. Implementation of large language models in electronic health records. *PLOS Digit Health*. 2025;4(12):e0001141.
11. Blanco-Gonzalez A, Cabezon A, Seco-Gonzalez A, et al. The role of AI in drug discovery: challenges, opportunities, and strategies. *Pharmaceuticals (Basel)*. 2023;16(6):891.
12. Moglia V, Johnson O, Cook G, et al. Artificial intelligence methods applied to longitudinal data from electronic health records for prediction of cancer: A scoping review. *BMC Med Res Methodol*. 2025;25(1):24.
13. Gonçalves F, Gaudencio M, Nunes SB, et al. Impact of Artificial Intelligence on the Care of Terminally Ill Patients. *Healthcare (Basel)*. 2026;14(5):602.
14. AI in radiotherapy planning and workflow optimisation. Available at: <https://oncodaily.com/oncolibrary/radiotherapy/ai-in-radiotherapy>. Accessed on: 5th July 2026.
15. Rong Y, Chen Q, Fu Y, et al. NRG oncology assessment of artificial intelligence deep learning–based auto-segmentation for radiation therapy: current developments, clinical considerations, and future directions. *Int J Radiat Oncol Biol Phys*. 2024;119(1):261–80.
16. Jia X, Rong Y, Wu Q, et al. NRG oncology assessment of artificial intelligence for automatic treatment planning in radiation therapy clinical trials: present and future. *Int J Radiat Oncol Biol Phys*. 2025;123(1):282–95.
17. Alkhanbouli R, Matar Abdulla Almadhaani H, Alhosani F, et al. The role of explainable artificial intelligence in disease prediction: a systematic literature review and future research directions. *BMC Med Inform Decis Mak*. 2025;25(1):110.
18. Sabet CJ, Tamirisa K, Bitterman DS, et al. Regulating medical AI before midnight strikes: Addressing bias, data fidelity, and implementation challenges. *PLOS Digit Health*. 2025;4(8):e0000986.
19. Srivastav AK, Singh A, Singh S, et al. Revolutionizing oncology through AI: addressing cancer disparities by improving screening, treatment, and survival outcomes via integration of social determinants of health. *Cancers*. 2025;17(17):2866.
20. Cheng CH, Shi SS. Artificial intelligence in cancer: applications, challenges, and future perspectives. *Mol Cancer*. 2025;24(1):274.
21. AI Medical Devices: 2025 Status, Regulation & Challenges. Available at: <https://intuitionlabs.ai/articles/ai-medical-devices-regulation-2025>. Accessed on: 5th July 2026.
22. Hettikankanamage N, Shafiabady N, Chateur F, et al. eXplainable artificial intelligence (XAI): a systematic review for unveiling the black box models and their relevance to biomedical imaging and sensing. *Sensors*. 2025;25(21):6649.
23. Froicu EM, Creangă-Murariu I, Afrăsânie VA, et al. Artificial intelligence and decision-making in oncology: A review of ethical, legal, and informed consent challenges. *Curr Oncol Rep*. 2025;27(8):1002–12.

Evolution of Guillain-Barré Syndrome: From Classical Descriptions to Modern Diagnostic and Therapeutic Concepts

Deepinder Kaur Maini^{1*}, Satyan Nanda², Rajiv Anand¹, Varun Rehani¹, Atul Prasad¹, Pratik Kishore¹, Ankita Kumari¹, Prabhjeet Kaur Bedi¹

¹Department of Neurology, BLK-Max Super Speciality Hospital, Delhi

²Department of Neurology, Yatharth Hospital, Noida

Correspondence:

Deepinder Kaur Maini

E-mail: Deepinder.Kaur@blkhospital.com

DOI: <https://doi.org/10.62830/mmj3-03-1>

Abstract:

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with considerable clinical, electrophysiological, and immunological heterogeneity. Over the years, the understanding of GBS has evolved beyond the classical post-infectious demyelinating presentation to include axonal forms, nodopathies, anti-ganglioside antibody-associated syndromes, regional variants, and central nervous system-peripheral nervous system (CNS-PNS) overlap syndromes. Advances in serial nerve conduction studies and electrodiagnostic criteria have improved recognition and classification of atypical presentations, including reversible conduction failure. Parallel developments in clinical assessment and prognostic tools, particularly the Hughes disability score and the Erasmus GBS Respiratory Insufficiency Score (EGRIS), Erasmus GBS Outcome Score (EGOS), and modified EGOS (mEGOS), have strengthened prediction of respiratory compromise and functional recovery. Current management remains centred on intravenous immunoglobulin and plasma exchange, while targeted therapies including monoclonal antibodies are being investigated in clinical trials. Despite these advances, early diagnosis, accurate subclassification, and prognostication remain challenging, underscoring the need for a more individualised approach to management and continued exploration of disease-specific therapeutic strategies.

Key words: Guillain-Barré Syndrome (GBS), Clinical Variants, Anti-Ganglioside Antibody Syndromes (AGAS), Electrodiagnostic Evolution, Prognostic Assessment, Erasmus GBS Respiratory Insufficiency Score (EGRIS), Erasmus GBS Outcome Score (EGOS), Immunotherapy.

Introduction

Guillain-Barré syndrome (GBS) is a serious neurological disorder characterised by acute weakness that may advance to flaccid paralysis and, in severe cases, result in life-threatening respiratory distress. Arising from a complex interaction between the immune system and the peripheral nervous system (PNS), this condition leads to immune-mediated injury of the myelin sheath or the axon.¹

History

In 1916, Georges Guillain, Jean Alexandre Barré, and André Strohl described GBS by reporting two cases of flaccid paralysis, with albuminocytological dissociation (ACD) in cerebrospinal fluid (CSF). The presence of ACD helped distinguish GBS from poliomyelitis. Acute flaccid paralysis was first described in 1859 by Jean Baptiste Octave Landry as sensory formication, ascending weakness after fever, malaise and pain, progressing

to quadriparesis and respiratory failure, often causing death within three weeks in a few cases.²

Epidemiology

The incidence of GBS is 0.84 – 1.91/100,000/year worldwide. Epidemiologically, the variation in the incidence and prevalence of GBS can be related to variation in the climate, genetic susceptibility, and infection rates across the globe. Methodological differences between studies, and lack of robust, systematic population-based studies in certain countries can also be considered as a factor for this variation. Most studies on incidence are performed in high-income countries, indicating data bias. There is higher incidence amongst males than females (1.5:1).³

Aetiology

Two-thirds of patients report symptoms of infection within four weeks preceding GBS onset. Populations in low- and middle-income countries are prone to outbreaks of infections due to poor hygiene and sanitation, and exposure to pathogens, which may trigger GBS.^{1,4}

Upper respiratory tract infection (URTI) is the leading antecedent infection among GBS patients in Europe, North America, South America, and parts of Asia (22% – 53%), while it is higher in paediatric GBS (50% – 70%). In India and Bangladesh, acute gastroenteritis (AGE) is most common (36% – 47%). Worldwide, the most common antecedent infections include *Campylobacter jejuni*, cytomegalovirus (CMV), Epstein-Barr virus (EBV), *Mycoplasma pneumoniae*, hepatitis E virus, and Zika virus. There was reportedly an eight-fold increase in GBS numbers after an influenza vaccination drive was undertaken during the 1976 national programme against swine flu. The outbreak of coronavirus disease 2019 (COVID-19) showed a surge of GBS in 2020, among other neurological conditions (stroke, Bell's palsy, and anosmia).^{1,4}

Seasonal Variation

Seasonal variation of GBS also varies by geographical area. According to a meta-analysis, GBS incidence increases in winter (January to March) in Western, Middle Eastern, and East Asian countries, whereas in the Indian Subcontinent and Latin America a decreased incidence is witnessed during January to March.^{5,6}

Clinical Features and Variants

Guillain identified multiple clinical patterns of GBS by 1939 and proposed a classification encompassing four forms: the lower form, spinal form, midbrain form, and polyradiculoneuropathy associated with impaired consciousness. In 1986, Allan Ropper described a descending variant characterised by rapid involvement of the oropharyngeal, neck, and shoulder muscles, closely resembling botulism. Later, in 1994, he further expanded the spectrum by documenting additional presentations, including paraplegic variants, facial diplegia, and distal sensory disturbances.^{2,5}

Overall, the clinical variants of GBS are determined by the type of nerve fibres affected (motor, sensory, mixed sensorimotor, or autonomic), the predominant pattern of nerve injury (demyelinating versus axonal), and whether alterations in consciousness are present. This classification of GBS is important for assessing its pathogenesis, severity, and prognosis, which differ across subtypes.^{1,5}

A patient with GBS can present with paraesthesia, pain, or radicular leg pain in the initial stage. The most common presentation is an ascending flaccid, areflexic quadriparesis, which may or may not involve cranial nerves (III – ophthalmoplegia, ptosis; VII – facial diplegia; IX, XI – dysarthria, dysphagia; X – cardiac arrhythmias), autonomic dysfunction (hypertension, tachycardia) and less commonly, sensory involvement with small fibre (dysesthesias, paraesthesias) or large fibre (loss of vibration and position sense) neuropathy. Respiratory failure requiring ventilatory support occurs in up to one-third of patients. Children can present with atypical clinical features, such as poorly localised pain, irritability, meningism, refusal to bear weight, or an unsteady gait with normal to exaggerated reflexes.^{1,5}

Demyelination disrupts baroreflex and vagal activity, leading to dysautonomia with fluctuating blood pressure. Sympathetic nerve overdrive and impaired afferent input from atrial receptors could worsen blood pressure (BP). Patients may develop tachycardia, labile BP, orthostatic hypotension, arrhythmias, pulmonary oedema, and sweating changes from dysautonomia. Bladder involvement occurs in under 5% of cases, sometimes mimicking spinal cord disease.¹

Clinical features in most of the GBS patients are well defined in Table 1.

Subtype	Pattern of limb weakness	Sensory involvement	Cranial nerve involvement	CNS involvement	Serial nerve conduction	Common antibodies
AIDP (Classic demyelinating GBS)	Upper and lower limbs	Yes	Yes	No	Demyelinating	Usually none
AMAN	Upper and lower limbs	No	Yes	No	Axonal motor	GM1, GD1a
AMSAN	Upper and lower limbs	Yes	Yes	No	Axonal motor and sensory	GM1, GD1a
Pure motor GBS	Upper and lower limbs	No	Yes	No	Axonal/RCF	GM1, GD1a
Pure sensory GBS	None	Yes	No	No	Abnormal SNAPs	GD1b
Sensory ataxic GBS	None	Yes (proprioceptive)	Rare	No	Sensory axonal	GD1b
Paraparetic GBS	Lower limbs	Yes	No	No	Axonal or demyelinating	GM1, GD1b
PCB	Proximal upper limbs	Supportive	Bulbar	No	Often axonal	GT1a, GQ1b
Classic BBE	None	Supportive	Oculomotor	Yes	Axonal	GQ1b, GT1a
Acute ataxic hypersomnolence	None	Ataxia	Variable	Yes	Normal	GQ1b

Table 1: Clinical presentation in variants of GBS.

Source: Wakerley BR, *et al. Lancet Neurology.* 2014;13(12):1224–34.⁵

Abbreviations: AMAN: Acute Motor Axonal Neuropathy; AMSAN: Acute Motor and Sensory Axonal Neuropathy; AIDP: Acute Inflammatory Demyelinating Polyradiculoneuropathy; BBE: Bickerstaff Brainstem Encephalitis; CNS: Central Nervous System; GBS: Guillain-Barré Syndrome; PCB: Pharyngeal-Cervical-Brachial; RCF: Reversible Conduction Failure; SNAPs: Sensory Nerve Action Potentials.

Acute inflammatory demyelinating polyneuropathy (AIDP)

Weakness begins in proximal muscles, causing difficulty in climbing stairs and getting out of a chair, mostly within 1 – 2 days after the onset of paraesthesia. Severe back pain and paraesthesia gradually spread over the limbs and move proximally. However, sensory modalities remain normal or mildly impaired. In 50% of cases, facial and oropharyngeal muscles are affected, which can also be the first clinical presentation.^{1,5}

Acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN)

Axonal variants of GBS, including AMAN and AMSAN, are characterised by immune-mediated axonal injury and exhibit clinical features distinct from demyelinating forms. Weakness is often of distal limb onset, rapidly progressive, frequently severe at onset, and may

occur with minimal or absent sensory symptoms in AMAN, whereas AMSAN is associated with prominent sensory involvement and profound disability. Cranial nerve involvement and respiratory failure are common, particularly in severe cases.^{1,5}

Across the GBS spectrum, numerous atypical and less common presentations highlight the diverse clinical expressions. The recently recognised anti-ganglioside antibody syndromes (AGAS) encompass features of both peripheral and central nervous system (CNS) involvement. Variants under AGAS include Miller Fisher syndrome (MFS), pure paraparesis, the pharyngeal-cervical-brachial (PCB) variant, bilateral facial variant, bilateral lumbar polyradiculopathy, and Bickerstaff brainstem encephalitis (BBE), which are more difficult to recognise.⁵

Miller Fisher syndrome (MFS)

MFS, reported in 1956, is characterised by a triad of symptoms: ophthalmoplegia, ataxia, and areflexia, often preceded by URTI or AGE and affecting cranial nerves; antibodies against GQ1b are implicated. There are two variants of MFS:⁵

1. MFS plus – having BBE (CNS signs), GBS (motor weakness of limbs and respiratory muscles) with ophthalmoplegia
2. MFS minus – with ophthalmoplegia and ataxia

Bickerstaff brainstem encephalitis (BBE)

BBE is potentially life-threatening, with brainstem and peripheral nerve involvement; altered sensorium, hypersomnolence, areflexia, ophthalmoplegia, and ataxia reflect a mixture of CNS and PNS involvement. Paediatric cases may show hyperreflexia and cerebellar signs.⁵ These variants, each defined by distinct clinical and pathophysiological characteristics, reflect the marked heterogeneity of GBS and often complicate timely diagnosis.⁵

PCB variant

The PCB variant is a localised form, characterised by rapidly progressive weakness involving the oropharyngeal, neck, and upper limb muscles, with relative sparing of the lower limbs. Patients typically present with dysphagia, dysarthria, neck flexor weakness, and proximal upper limb weakness, often associated with areflexia or hyporeflexia in the upper extremities. Because of prominent bulbar involvement, this variant may mimic brainstem stroke, myasthenia gravis, or botulism. PCB is considered part of the anti-ganglioside antibody spectrum and is frequently associated with anti-GT1a antibodies, with occasional overlap with MFS or BBE. Early recognition is important, as bulbar and respiratory compromise may occur despite limited lower limb involvement.⁵

Paraparetic (Paraplegic) variant

The paraparetic variant is an uncommon regional form in which weakness is confined predominantly to the lower limbs, producing acute flaccid paraparesis with reduced or absent deep tendon reflexes in the legs. Sensory symptoms such as distal paraesthesia, radicular pain, or mild sensory loss may accompany the motor deficit, while upper limb, cranial nerve, and respiratory

muscle involvement are minimal or absent. Because of its restricted lower limb presentation, this variant may be mistaken for acute transverse myelitis, cauda equina syndrome, spinal cord compression, or other causes of acute paraplegia. Cerebrospinal fluid and electrophysiological findings, together with exclusion of spinal cord pathology, help establish the diagnosis.⁵

Pathophysiology

Nerve oedema, perivenular lymphocytic infiltrates, and macrophage-mediated demyelination are hallmarks of the pathology of GBS. In AIDP, the most common variant, segmental demyelination occurs with T-cell infiltration and macrophages. Inflammatory mediators localise to nerve roots and induce damage via macrophage activation and an increase in pro-inflammatory chemokines and cytokines (including tumour necrosis factor [TNF]- α and interleukin [IL]-1). There is a breakdown of the blood-nerve barrier and macrophage-associated demyelination. CSF in GBS shows increased concentrations of pro-inflammatory cytokines such as IL-8 and IL-1 and chemokines; upregulation of interferon (IFN)- γ , TNF- α and T helper-17 (Th17) correlates with maximum clinical severity, while increases in anti-inflammatory cytokines (IL-4, IL-10 and TGF- β) correlate with recovery.¹⁷

Axonal variants are linked to antibodies against ganglioside moieties (GM1, GD1a, GD1b, GQ1b), often preceded by *Campylobacter jejuni* infection; antibodies against GM2 moieties have been linked to CMV. Molecular mimicry between microbial and neuronal antigens activates humoral immunity against host nerves, a phenomenon seen in experimental models.¹⁷

In MFS, the primary target is GQ1b ganglioside, which is highly expressed in the oculomotor nerves, muscle spindles, and large-diameter sensory neurons. Binding of anti-GQ1b immunoglobulin G (IgG) antibodies activates complement and disrupts nerve terminal and paranodal function. Ataxia in MFS is believed to result largely from involvement of muscle spindle afferents rather than primary cerebellar dysfunction.^{5,7}

BBE shares a similar immunological basis and is also strongly associated with anti-GQ1b antibodies, but the pathological process extends beyond the peripheral nerves to involve the brainstem reticular formation and central pathways. This explains the presence of ophthalmoplegia, ataxia, and impaired consciousness

or pyramidal signs, which distinguish BBE from classical MFS. Thus, MFS and BBE are best viewed as overlapping disorders in which the site and extent of anti-ganglioside antibody-mediated injury determine the clinical phenotype.^{5,7}

Diagnosis

Diagnosis of GBS is clinical; symptoms usually progress within days to weeks. Ascending paralysis with symmetrical weakness is the hallmark of GBS. Legs are typically more involved than arms. Most patients develop initial weakness in the legs, subsequently ascending to the arms. Approximately 32% of cases have reported combined leg and arm weakness at onset, and 56% showed either proximal or distal leg weakness that later spread upward. Around 12% experience early weakness beginning in the arms. Muscle weakness is typically symmetrical, accompanied by reduced or absent deep tendon reflexes (DTRs) within the first few days, although in some cases areflexia may not become evident until about a week later.^{1,8}

Areflexia is part of the clinical diagnostic criteria. However, preserved or even exaggerated reflexes have been reported in some GBS patients, particularly after *C. jejuni* infection with anti-GM1 antibodies. In such cases, history, electrodiagnosis, CSF, and neuroimaging together improve diagnostic accuracy.^{1,8} The clinical course of GBS can be divided into 3 phases:¹

1. Initial phase: Definite symptom (a sensory symptom in the form of tingling or motor weakness preceding the sensory symptom) develops.
2. Plateau/nadir phase: Usually lasting for several days to two weeks, the patient reaches the maximum deficits, with no further deterioration of symptoms.
3. Recovery phase: Begins 2 – 4 weeks after the plateau phase and may extend over 6 months or longer. Patients with severe disease may require two years to recover, which may be incomplete.

Nadir of weakness is reached within 2 weeks in 50% of cases and in 90% by four weeks. Weakness ranges from mild to severe flaccid paralysis, and up to 30% of patients might experience respiratory distress within the first few days of onset. In patients with fulminant GBS, disease progresses, leading to respiratory involvement within seven days. Others deteriorate slowly over several weeks, sometimes retaining ambulation. Symptoms worsening beyond four weeks are suggestive of subacute inflammatory demyelinating polyradiculopathy.^{1,8}

Diagnostic Criteria

In 1960, Osler and Sidell proposed that GBS risked becoming a vague term and proposed a strict definition of 12 diagnostic criteria. The frequently used National Institute of Neurological Disorders and Stroke (NINDS) criteria, developed in 1981 and revised in 1990 by Asbury and Cornblath, standardised diagnosis for research and clinical use. An ad hoc NINDS committee designed a scale for use by both neurologists and non-neurologists. Later, the Brighton Collaboration consensus criteria (2011), Wakerley and Yuki (2015), and the consensus guidelines by Leonhard (2019) were developed. Sensitivity of the Brighton Criteria correlated with the levels of criteria 1, 2, and 3, with 72%, 96% and 98%, respectively. An Indian study showed that level 3 of the Brighton Criteria detected 86% of the GBS cases, whereas level 2 detected 84% and level 1 detected 62% of the cases, supporting patient risk stratification, early diagnosis, and treatment guidance, even in resource-limited clinical settings.⁸

Electrodiagnosis (EDx)

There are various electrodiagnostic criteria defined to understand the axonal and demyelinating variants of GBS.^{9–12}

Many investigations have dissected the correlates of nerve conduction studies (NCS) and nerve diseases, including Dyck and Lambert at Mayo Clinic, Buchthal and Behse in Copenhagen, Gilliat, Cragg and Thomas, and McDonald from England. In 1983, criteria for demyelination were summarised by Kelly (Table 2).^{9–12}

Criteria	Main demyelinating cut-offs	Axonal definition	Strengths	Limitations
Albers and Kelly, 1985	Motor conduction velocity < 70% LLN; distal latency > 150% ULN; F-wave latency > 120% ULN; CB ≥ 50% CMAP drop	Reduced CMAP amplitudes without demyelinating features	First standardised EDx system for GBS	Overestimates demyelination; low specificity; rarely used today
Ho <i>et al.</i> , 1995	Motor conduction velocity < 80% LLN; distal latency > 125% ULN; F-wave > 120% ULN or absent; CB ≥ 50% CMAP drop	CMAP reduction with preserved conduction velocity	Improved differentiation compared with Albers	Still less accurate in early GBS (< 7 days)
Hadden <i>et al.</i> , 1998	Motor conduction velocity < 80% LLN (sensory < 70%); distal latency > 150% ULN; F-wave > 120% ULN or absent in ≥ 2 nerves; CB ≥ 50% CMAP drop with < 30% area reduction; temporal dispersion > 30%	CMAP < 80% LLN without demyelination	Widely used; “gold standard” in clinical trials; high specificity	May miss early GBS (requires ≥ 2 abnormal nerves)
Uncini and Kuwabara (Serial NCS), 2012	Same as Hadden cut-offs but emphasises serial reassessment: repeat NCS at 1 – 2 weeks; distinguishes reversible conduction failure (RCF) from demyelination	Persistent CMAP reduction without demyelinating features	Clarifies AMAN vs AIDP; prevents misclassification; highlights RCF	Requires serial NCS; less practical in some clinical settings
Rajabally <i>et al.</i> , 2015	Motor conduction velocity < 90% LLN in ≥ 2 nerves; distal latency > 125% ULN in ≥ 2 nerves; F-wave > 120% ULN or absent; CB ≥ 50% drop in ≥ 1 nerve; temporal dispersion > 30%	CMAP < 80% LLN	More sensitive; better for early GBS; simpler to apply	Slightly less specific than Hadden
Yadegari <i>et al.</i> , 2014	Similar to Hadden criteria but emphasises earlier detection of demyelination and careful evaluation of CB and temporal dispersion	Axonal GBS defined by low CMAP amplitudes without demyelinating features	Improves early subtype classification; useful in research settings	Less widely adopted; requires careful interpretation
Rath <i>et al.</i> , 2020	Integrates conventional demyelinating criteria with serial NCS and clinical correlation	Persistent CMAP reduction with absence of demyelinating features on follow-up NCS	Helps distinguish true axonal degeneration from RCF	Requires serial studies and follow-up electrophysiology

Table 2: Evolution of electrodiagnostic criteria of GBS.

Source: Generated from secondary literature.^{9–12}

Abbreviations: AIDP: Acute Inflammatory Demyelinating Polyradiculoneuropathy; AMAN: Acute Motor Axonal Neuropathy; CB: Conduction Block; CMAP: Compound Muscle Action Potential; EDx: Electrodiagnosis; GBS: Guillain-Barré Syndrome; LLN: Lower Limit of Normal; NCS: Nerve Conduction Study; RCF: Reversible Conduction Failure; ULN: Upper Limit of Normal.

Reversible conduction failure (RCF) is seen in axonal variants of GBS, known as axonal motor neuropathy with conduction block (AMNCB). It involves IgG deposition at the nodes of Ranvier, precisely at the axolemma, followed by complement activation with the formation of the membrane attack complex (MAC). A patient's conduction velocity is reduced when conduction block (CB) is maximal and recovers when the CB disappears.^{7,10}

Outcome and Prognostic scores

GBS is treatable, and most patients experience substantial recovery. About 80% of patients regain independent ambulation and roughly 50% return to their pre-illness functional status within a year. However, up to 10% require prolonged mechanical ventilation, and about 3% – 7% of patients die from complications such as sepsis, respiratory failure, or cardiac arrest.^{1,13}

Poorer outcomes are associated with factors such as older age, rapid symptom progression, need for ventilatory support, antecedent diarrhoeal illness, and severe electrophysiological abnormalities on NCS. Early predictors of respiratory failure identified several markers of poor prognosis, including a rapid onset of symptoms to admission within seven days, inability to cough, stand, or lift the head or elbows. These factors contributed to the development of the Erasmus GBS Respiratory Insufficiency Score (EGRIS), a validated tool for predicting the need for mechanical ventilation.^{1,13–15}

The Erasmus GBS Outcome Score (EGOS), ranging from 0 to 7, was developed using age, preceding diarrhoea, and Medical Research Council (MRC) sum scores at admission and Day 7. These factors independently predicted the ability to walk at four weeks, three months, and six months. Lower scores (EGOS 1 – 3) indicated a higher likelihood of walking independently at three months, while EGOS 3.5 – 4.5 were associated with a 7% mean risk. An EGOS of 5 indicated a mean risk of 27%, while scores of 5.5 – 7 were associated with a 52% mean risk of inability to walk independently. The modified EGOS (mEGOS) is a validated model predicting outcomes within the first six months of GBS onset and is useful for clinical trials and optimising individualised

treatment planning. Validated in over 1,500 patients (aged ≥ 6 years), mEGOS accurately predicts unaided walking at four and 26 weeks.^{13–15}

Recurrent GBS

GBS is usually monophasic, but 2% – 5% of patients experience recurrence. Recurrent GBS, defined in 1992 as two or more acute episodes of acute idiopathic demyelinating polyneuropathy with appropriate recovery intervals, presents similarly to the initial attack despite differing in antecedent infections, suggesting possible immunological or genetic host factor susceptibility. According to the NINDS criteria, recurrence is recognised when two or more episodes occur with a minimum interval of ≥ 4 months between attacks if the patient does not achieve full recovery (GBS disability score ≥ 2), or ≥ 2 months if recovery is complete or near complete (GBS score ≥ 1).^{16,17}

Recurrent cases tend to occur in younger patients, often with MFS and milder prognosis. Markedly elevated CSF protein, exceeding 450 mg/L, is typical in recurrent GBS and is reported to be as high as 2480 mg/L on average, with absence of leucocytosis, consistent with ACD. NCS commonly demonstrate demyelinating polyneuropathy with CB or temporal dispersion during acute episodes.^{16,17}

Recurrent GBS typically recurs after six years (range 3.3 – 9.7), with male predominance over females (3:1). Degree of disability is similar across first and recurrent episodes, with AIDP being the commonest GBS variant reported (23.1% of patients). Recurrent GBS occurs at younger ages, with its mean duration being longer (134 days) relative to monophasic GBS and shows a shorter clinical onset-to-nadir. Relapses persist in 6% of patients over decades, with no decrease in recurrence tendency. Gastrointestinal and respiratory infections often precede recurrent GBS, with similar course and outcomes in the first and second courses of GBS.^{16,17}

A study found that following the influenza and flu vaccinations in GBS patients, 4% experienced recurrence; some had both GBS and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and recurrent GBS, suggesting genetic predisposition.^{16,17}

Treatment-Related Fluctuations (TRF), and Acute-Onset CIDP (aCIDP)

Recurrent GBS must be differentiated from (i) aCIDP, in which patients experience a chronic course after the nadir of the first episode is reached at 8 weeks, and from (ii) TRF, where initial improvement in GBS scale by 1 grade and in MRC sum score of more than 5 points post-immunotherapy is followed by worsening within two months of disease onset. Worsening after treatment for more than one week, followed by worsening of Hughes Disability Scale (HDS) by more than one or MRC sum score > 5, can also be considered as TRF.¹⁸

Mortality in GBS

The mortality rate of GBS is 3% – 13%. Around 20% of patients died during the acute progressive phase, 13% during the plateau phase, and 67% during the recovery phase when neurological recovery had occurred. A study showed that 73% were admitted to the Intensive Care Unit (ICU), of whom 47% died. Risk factors for death include age at entry and delay from onset of weakness to admission, with the most frequent causes being pneumonia, cardiac arrest, respiratory failure, and autonomic dysfunction.^{1,8}

In a 2001 – 2012 study covering Singapore, Japan, Malaysia, and Hong Kong, 16 of the 261 GBS patients died due to myocardial infarction and respiratory infections, mostly in the plateau phase (63%), followed by the progressive phase (25%) and the recovery phase (12%), with 56% of patients requiring ventilation, despite 94% receiving treatment.^{1,8}

Medical Management

Although GBS is generally a self-remitting disease, immunomodulatory therapies such as intravenous immunoglobulin (IVIG) and plasma exchange (PE) accelerate disease stabilisation, often shortening the time to nadir to approximately two weeks and reducing overall recovery time.^{8,19–21}

Indications for initiating immunotherapy include a HDS score ≥ 3 (inability to walk 10 m without support), severe bulbar involvement with risk of aspiration, severe ataxia, BBE, and severe autonomic dysfunction manifesting as labile hypertension or cardiac arrhythmias.⁸

Role of PE

PE was first reported as an effective GBS treatment by Brettle and colleagues in 1978. The standard procedure involves removal of approximately 3 – 6 litres of plasma, which is replaced with albumin or fresh frozen plasma, exchanging 35 – 50 mL/kg of plasma over 10 – 14 days. Given the high prevalence of autonomic dysfunction and the risk of haemodynamic instability in GBS, 5% albumin is generally recommended as the replacement fluid, unless the patient has active bleeding, coagulopathy, or is expected to undergo invasive procedures shortly after PE. Although albumin and fresh frozen plasma are equally effective, the latter carries a potential risk of viral transmission.^{8,19}

PE works therapeutically by removing circulating humoral factors such as autoantibodies, immune complexes, cytokines, and complement components. This exchange reduces hypercytokinaemia, decreases leucocyte degranulation, and inhibits macrophage activation and phagocytosis when initiated early. During initial therapy, serum immunoglobulin levels fall by 40% – 60%, so at least two sessions are recommended even for mild GBS. Contraindications include severe dysautonomia, septicaemia, hypotension, allergies (to albumin or fresh frozen plasma, and heparin allergy), while adverse effects include hypotension, septicaemia, hypocalcaemia, coagulation abnormalities, pneumothorax, and haematoma.^{8,19}

Role of IVIG

In 1988, IVIG was first reported as a GBS treatment by Kleyweg and colleagues. IVIG is a preparation of pooled polyclonal IgG derived from thousands of blood donors and contains IgA, monomeric IgG, and stabilising agents such as sorbitol, glycine, sucrose, or L-proline, which may initiate adverse effects including headache, nausea, and fever. IVIG is considered safer in pregnancy and for children.^{8,20}

Its mechanisms of action include B-cell modulation, anti-inflammatory effects mediated by IgG glycosylation, modulation of pro-inflammatory and inflammatory cytokines, inhibition of complement activation, and binding to Fc receptors.^{8,20}

The standard adult dose of IVIG is 0.4 g/kg/day for five consecutive days. For children, a total dose of 2 g/kg

administered over two to three days is recommended. Infusion is initiated at a slow rate (0.3 – 0.5 mL/kg/hour) and gradually increased every 15 – 30 minutes as tolerated, up to a maximum of 6 – 8 mL/kg/hour. Contraindications to IVIG include congenital IgA deficiency, severe renal dysfunction, and congestive heart failure. Adverse effects include headache, nausea, fatigue, aseptic meningitis, hyperviscosity-related thrombotic events, skin rashes (palmar eczema), and renal dysfunction. Many of these adverse effects can be mitigated by slower infusion rates.^{8,20}

IVIG has practical advantages over PE, including shorter treatment, better tolerability, and easier availability. PE is most effective within seven days of symptom onset, while IVIG works best within two weeks. According to the Cochrane review (2014), IVIG and PE are similar with respect to improvement by one or more disability grades at four weeks, death or disability at 12 months, treatment-related fluctuations, adverse events, or treatment discontinuation. Both therapies have comparable efficacy in hastening recovery in GBS.^{19–21}

The efficacy of IVIG for treating MFS and BBE is not firmly established. In MFS, immunotherapy, particularly PE, may be considered in patients with respiratory involvement or progression to bulbar or limb weakness. In BBE, PE is often offered due to the severity of symptoms, despite limited evidence supporting its efficacy.^{5,8}

Evidence from trials on the role and benefits of repeat IVIG is inconsistent and suggests an increased risk of thromboembolism and renal dysfunction. Low serum IgG resulting from sepsis or severe inflammation-related increased IgG catabolism can occur; patients maintaining an increase in serum IgG ≥ 7.3 g/L IgG at two weeks show better clinical outcomes. PE initiated after IVIG in refractory disease may benefit patients relative to a second IVIG course.^{8,21}

For patients who worsen after initial immunomodulatory therapy, options include a second course of IVIG or alternatives like the zipper method.^{8,21}

Zipper method

The zipper method is an emerging therapy for severe GBS based on sequential immunomodulation targeting both autoantibodies and complement activation. The zipper method may be particularly beneficial in severe axonal forms of GBS, as evidenced by a study by Ozlem and colleagues (2021), conducted during the COVID-19 pandemic. The study

showed earlier weaning from mechanical ventilation and reduced duration of hospitalisation.⁸

It is based on the principle of using alternating IVIG and PE to target autoantibodies and complement. IVIG or PE alone may be insufficient to eliminate both cellular and humoral immune responses, and thus both are administered alternatively, with treatment repeated up to five cycles. PE may cause antibody rebound, which may be reduced by subsequent IVIG.⁸

Role of corticosteroids

Corticosteroids, including methylprednisolone, are not recommended in the treatment of GBS. Case-control studies comparing IVIG with steroids and steroid-sparing immunosuppressive agents combined with PE have shown no benefit. Steroids are thought to interfere with macrophage scavenging function, potentially delaying neuronal recovery, and are therefore associated with poorer outcomes.¹⁹

Symptomatic treatment

Symptomatic management remains a cornerstone of care. Endotracheal intubation is indicated when forced vital capacity falls below 15 mL/kg, single breath count (SBC) is < 20 , or negative inspiratory force is less than 60 cm H₂O. Extubation is considered when the patient demonstrates an effective cough reflex and an MRC grade of at least 3 in neck flexors and shoulder abductors.⁸

IVIG is effective in managing dysautonomia, while symptomatic treatment includes beta-blockers for tachycardia, atropine for bradycardia, antihypertensive agents for hypertension, vasopressors for hypotension, and targeted management of pain, dysphagia, bowel and bladder dysfunction, electrolyte imbalance, and respiratory complications.⁸

Supportive care in the acute phase includes deep vein thrombosis (DVT) prophylaxis, anticoagulation in immobilised patients, and empiric antibiotics when infection is suspected, followed by targeted therapy based on culture results.⁸

Long-term management

Long-term care involves tracheostomy, percutaneous endoscopic gastrostomy for severe dysphagia, nutritional support, pressure-ulcer prevention, and structured rehabilitation through physiotherapy to promote recovery and early ambulation and prevent secondary complications.⁸

In patients who fail immunomodulatory therapies, immunosuppressive treatment may be considered. Rituximab, a monoclonal antibody targeting CD20 and suppressing B-cell-mediated immune responses, has been used in selected patients with suspected neuropathy, refractory disease, MFS with severe ataxia, and AMAN with CB.²²

The conundrum while treating GBS

1. The second induction dose of IVIG is not effective in the management of GBS patients who did not respond to initial IVIG.^{8,21}
2. Patients unresponsive or refractory to the primary course of IVIG should be given PE. There is evidence of an IVIG-resistant subtype of GBS.^{8,21}
3. Treatment dilemmas in GBS persist. There is no indication to treat children with GBS differently from adults. IVIG seems to be effective in children with GBS, with level 2 evidence. It is preferred over PE because it is easier to administer and possibly better tolerated in smaller children, with level 3 evidence.^{8,20}

Newer therapeutic strategies for GBS primarily target complement activation or accelerate the clearance of pathogenic IgG, reflecting the substantial proportion of patients who experience incomplete recovery despite IVIG or PE. Complement inhibition is currently the most advanced mechanism-based approach. However, the Phase III trial of the terminal complement C5 inhibitor eculizumab did not demonstrate a significant improvement in functional recovery when added to IVIG, despite effective complement suppression and an acceptable safety profile; therefore, eculizumab is not recommended as routine treatment for GBS. In contrast, the C1q inhibitor ANX005 (tanruprubar), which blocks initiation of the

classical complement pathway, demonstrated acceptable tolerability, rapid target engagement, reductions in serum neurofilament light chain and exploratory improvements in disability and muscle strength in a randomised Phase I study. Subsequent Phase III findings have strengthened the evidence for its clinical efficacy, although regulatory evaluation and further peer-reviewed confirmation remain important. FcRn inhibition represents another emerging approach: efgartigimod promotes lysosomal degradation of IgG by preventing its recycling through the neonatal Fc receptor. Preliminary case reports and small case series have described rapid neurological improvement, including recovery of independent walking, while a Phase II clinical trial is evaluating its efficacy and safety in GBS. Other investigational approaches include imlifidase-mediated IgG cleavage and therapies directed against cytokines or specific immune-cell populations; nevertheless, none of these newer targeted agents is currently established as an approved standard treatment for GBS.^{22–25}

Declarations

Conflict of interest: The authors declare that they have no financial or non-financial conflicts of interest relevant to the content of this article.

Funding: No specific funding was received from any public, commercial, or not-for-profit funding agency for the preparation of this article.

Author disclosures: All authors declare that they have no relevant financial relationships, consultancy roles, honoraria, stock ownership, patents, advisory-board memberships, or other personal or institutional relationships that could have influenced the work reported in this manuscript.

Conclusion

GBS represents a spectrum of immune-mediated polyradiculoneuropathies rather than a single uniform disorder. Recognition of atypical variants, use of serial electrodiagnostic assessment, and early identification of respiratory and autonomic risk factors are critical to avoid diagnostic delay and guide treatment. Despite generally favourable outcomes, severe axonal disease, fulminant progression, and treatment-refractory cases remain major contributors to morbidity and mortality, underscoring the need for early stratification and individualised management.

Deepinder Kaur Maini, Satyan Nanda, Rajiv Anand, Varun Rehani, Atul Prasad, Pratik Kishore, Ankita Kumari, Prabhjeet Kaur Bedi. Evolution of Guillain-Barré Syndrome: From Classical Descriptions to Modern Diagnostic and Therapeutic Concepts. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-1>

References

- van den Berg B, Walgaard C, Drenthen J, et al. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nat Rev Neurol*. 2014;10:469–82.
- Hughes RAC, Cornblath DR, Willison HJ. Guillain-Barré syndrome in the 100 years since its description by Guillain, Barré and Strohl. *Brain*. 2016;139(11):3041–7.
- Hughes RAC, Rees JH. Clinical and epidemiologic features of Guillain-Barré syndrome. *J Infect Dis*. 1997;176 Suppl 2:S92–8.
- Dutta D, Debnath M, Nagappa M, et al. Antecedent infections in Guillain-Barré syndrome patients from south India. *J Peripher Nerv Syst*. 2021;26:298–306.
- Wakerley BR, Uncini A, Yuki N. Guillain-Barré and Miller Fisher syndromes-new diagnostic classification. *Nat Rev Neurol*. 2014;10:537–44.
- Webb AJS, Brain SAE, Wood R, et al. Seasonal variation in Guillain-Barré syndrome: a systematic review, meta-analysis and Oxfordshire cohort study. *J Neurol Neurosurg Psychiatry*. 2015;86:1196–201.
- Goodfellow JA, Willison HJ. Guillain-Barré syndrome: a century of progress. *Nat Rev Neurol*. 2016;12:723–31.
- Leonhard SE, Mandarakas MR, Gondim FAA, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. *Nat Rev Neurol*. 2019;15:671–83.
- Hadden RDM, Cornblath DR, Hughes RAC, et al. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. *Ann Neurol*. 1998;44:780–8.
- Uncini A, Kuwabara S. The electrodiagnosis of Guillain-Barré syndrome subtypes: where do we stand? *Clin Neurophysiol*. 2018;129(12):2586–93.
- Rajabally YA, Durand MC, Mitchell J, et al. Electrophysiological diagnosis of Guillain-Barré syndrome subtype: could a single study suffice? *J Neurol Neurosurg Psychiatry*. 2015;86:115–9.
- Mani AM, Prabhakar AT, Alexander PT, et al. Utility of serial nerve conduction studies in the electrodiagnosis of Guillain-Barré syndrome. *Neurol India*. 2021;69:369–75.
- Yao J, Zhou R, Liu Y, et al. Predicting of mechanical ventilation and outcomes by using models and biomarker in Guillain-Barré syndrome. *Neurol Ther*. 2023;12(6):2121–32.
- Luijten LWG, Doets AY, Arends S, et al. Modified Erasmus GBS Respiratory Insufficiency Score: a simplified clinical tool to predict the risk of mechanical ventilation in Guillain-Barré syndrome. *J Neurol Neurosurg Psychiatry*. 2023;94:300–8.
- Busl KM, Fried HI, Muehlschlegel S, et al. Guidelines for neuroprognostication in adults with Guillain-Barré syndrome. *Neurocrit Care*. 2023;38:564–83.
- Inan B, Bekircan-Kurt CE, Demirci M, et al. Differentiating recurrent Guillain-Barré syndrome and acute-onset chronic inflammatory polyneuropathy: literature review. *Acta Neurol Belg*. 2024;124:1467–75.
- Notturmo F, Kokubun N, Sekiguchi Y, et al. Demyelinating Guillain-Barré syndrome recurs more frequently than axonal subtypes. *J Neurol Sci*. 2016;365:132–6.
- Ruts L, Drenthen J, Jacobs BC, et al. Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome. *Neurology*. 2010;74:1680–6.
- Hughes RAC, Swan AV, Raphaël JC, et al. Immunotherapy for Guillain-Barré syndrome: a systematic review. *Brain*. 2007;130(Pt 9):2245–57.
- Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev*. 2014;(9):CD002063.
- Zaki HA, Iftikhar H, Najam M, et al. Plasma exchange (PE) versus intravenous immunoglobulin (IVIG) for the treatment of Guillain-Barré syndrome (GBS) in patients with severe symptoms: a systematic review and meta-analysis. *eNeurological Sci*. 2023;31:100468.
- Rajabally YA. Immunoglobulin and monoclonal antibody therapies in Guillain-Barré syndrome. *Neurotherapeutics*. 2022;19:885–96.
- Kuwabara S, Kusunoki S, Kuwahara M, et al. Efficacy and safety of eculizumab in Guillain-Barré syndrome: a phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial. *J Peripher Nerv Syst*. 2024;29:339–49.
- Mohammad QD, Islam Z, Papri N, et al. Results from a phase 1 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of ANX005, a C1q inhibitor, in patients with Guillain-Barré syndrome. *J Peripher Nerv Syst*. 2025;30(1):e70009.
- Zhang H, Ma J, Feng Y, et al. Efgartigimod in the treatment of Guillain-Barré syndrome. *J Neurol*. 2024;271:3506–11.

Enhanced Recovery and Early Functional Outcomes Following Simultaneous Bilateral Total Hip Arthroplasty: A Single-Surgeon Case Series

Sushant Niramohi¹, Chandeeep Singh¹, Shitij Kacker¹, SKS Marya¹

¹Department of Orthopaedic Surgery, Max Healthcare Institute, New Delhi

Correspondence:

Chandeeep Singh

E-mail: Chandeeep@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-30>

Abstract:

Simultaneous bilateral total hip arthroplasty (THA) remains controversial because of concerns regarding perioperative physiological stress, blood loss, and postoperative complications; however, advances in patient selection, perioperative optimisation, blood conservation, anaesthesia, and enhanced recovery have supported its use in appropriately selected patients. This prospective observational case series evaluated the perioperative, functional, and early radiological outcomes of simultaneous bilateral THA performed by a single experienced surgeon at a tertiary-care arthroplasty centre between January 2025 and April 2026. Sixteen consecutive patients underwent simultaneous bilateral THA following comprehensive medical and anaesthetic assessment and counselling regarding simultaneous and staged procedures. Demographic characteristics, operative time, estimated blood loss, postoperative haemoglobin change, transfusion requirements, time to mobilisation, hospital stay, Harris Hip Score (HHS), and radiological outcomes were assessed. A standardised perioperative pathway incorporating tranexamic acid, multimodal analgesia, thromboprophylaxis, and early mobilisation was used. The mean age was 44.8 ± 15.1 years, with 12 (75.0%) males and 4 (25.0%) females; 11 patients (68.8%) underwent THA for avascular necrosis and 5 (31.2%) for secondary osteoarthritis. The mean operative time was 103.9 ± 11.3 minutes, estimated blood loss was 307.8 ± 61.3 mL, and postoperative haemoglobin decrease was 1.45 ± 0.38 g/dL. One patient (6.3%) required one unit of allogeneic blood transfusion. Mean time to mobilisation was 1.2 ± 0.4 days and hospital stay was 5.1 ± 0.5 days. Mean HHS improved significantly from 43.4 ± 5.0 preoperatively to 89.1 ± 3.0 at a mean follow-up of 8.2 ± 2.1 months, representing a mean improvement of 45.6 points (95% CI, 41.4 – 49.8; $p < 0.001$), with all patients achieving good-to-excellent functional outcomes. Radiographs demonstrated satisfactory component positioning and stable fixation, with limb-length restoration within 5 mm in 15 patients (93.8%). No deep infection, dislocation, symptomatic venous thromboembolism, perioperative mortality, or revision surgery occurred during follow-up. In this small prospective case series of carefully selected patients, simultaneous bilateral THA was associated with substantial early functional improvement, early mobilisation, low transfusion requirements, and favourable short-term radiological outcomes, supporting its feasibility when appropriate patient selection, multidisciplinary perioperative optimisation, and experienced surgical care are available. Larger comparative studies with longer follow-up are required to establish optimal patient selection and the long-term durability and comparative safety of this approach.

Key words: Simultaneous Bilateral Total Hip Arthroplasty, Enhanced Recovery, Harris Hip Score, Blood Conservation, Avascular Necrosis, Perioperative Outcomes.

Introduction

Bilateral hip involvement is commonly encountered in various pathological conditions, including avascular necrosis (AVN) of the femoral head and inflammatory arthropathies, such as rheumatoid arthritis, ankylosing spondylitis, and advanced bilateral osteoarthritis (OA). These patients frequently present with severe, debilitating pain, markedly restricted mobility, significant gait abnormalities, and a substantially compromised quality of life. The social and economic burden of bilateral hip disease is considerable, as affected individuals often experience limitations in their occupation, independence, and psychosocial well-being. Traditionally, bilateral hip arthroplasties have been performed as staged procedures at variable intervals.¹ However, the logistical challenges, cumulative hospitalisation, repeated anaesthesia exposure, and prolonged total rehabilitation time associated with the two-stage approach have increasingly led clinicians to consider simultaneous bilateral total hip arthroplasty (THA) as a viable alternative in carefully selected patients.

Simultaneous bilateral THA offers several potential theoretical and practical benefits. These include single-stage exposure to anaesthesia, reduced cumulative hospitalisation duration, lower overall treatment cost due to a single admission and rehabilitation programme, shorter total rehabilitation period, avoidance of prolonged musculoskeletal imbalance during the interval between staged procedures, and earlier restoration of symmetrical gait mechanics and lower limb function. Furthermore, single-stage bilateral procedures eliminate the psychological burden and socioeconomic disruption associated with awaiting a second surgical intervention. These advantages are particularly compelling in younger, active patients with bilateral AVN who wish to return to a productive life expeditiously.

Despite these appealing theoretical benefits, legitimate concerns persist among orthopaedic surgeons and anaesthesiologists regarding the safety profiles of simultaneous bilateral procedures. These concerns include potentially increased operative blood loss, prolonged surgical duration leading to greater physiological stress, increased cardiopulmonary demands during the perioperative period, higher rates of serious thromboembolic events, and the risk of bilateral fat embolism syndrome. Early reports in the orthopaedic literature documented increased morbidity and mortality with single-stage bilateral THA, which appropriately

generated significant apprehension within surgical communities worldwide. However, subsequent decades have witnessed remarkable advances in anaesthesia techniques, including neuraxial and multimodal analgesic approaches, perioperative optimisation protocols, evidence-based enhanced recovery after surgery (ERAS) pathways, modern blood conservation strategies utilising tranexamic acid and sophisticated transfusion protocols, and improved perioperative monitoring capabilities, including goal-directed fluid therapy and haemodynamic optimisation.

Several contemporary studies, including meta-analyses and systematic reviews, have demonstrated encouraging and comparable outcomes for simultaneous bilateral THA in appropriately selected patients when performed within modern perioperative care frameworks.^{2–4} Accumulating evidence suggests that with rigorous patient selection, meticulous preoperative fitness assessment, standardised surgical and perioperative protocols, and vigilant postoperative monitoring, the safety profile of simultaneous bilateral THA can be comparable to that of unilateral or staged procedures. This study aimed to evaluate the perioperative safety profile, functional outcomes, radiological results, and early rehabilitation characteristics of patients undergoing simultaneous bilateral THA at a high-volume tertiary-care arthroplasty unit utilising standardised contemporary perioperative protocols.

Materials and Methods

Study design and ethical considerations

A prospective observational case series was conducted at the Max Healthcare Institute, a tertiary-care multispeciality centre in New Delhi, India, between January 2025 and April 2026. The study was approved by the Institutional Ethics Committee, and all participants provided written informed consent prior to their enrolment. This study was conducted in accordance with the principles of the Declaration of Helsinki. All patient data were maintained confidentially and de-identified prior to the analysis. This study conformed to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for case series reporting.

Patient selection

Sixteen consecutive patients with symptomatic bilateral end-stage hip disease who were scheduled to undergo

simultaneous bilateral THA were prospectively enrolled in this study. The decision for bilateral simultaneous surgery was made following a comprehensive multidisciplinary evaluation, including orthopaedic consultation, detailed preoperative medical fitness assessment by the Internal Medicine and Anaesthesiology teams, and careful patient counselling regarding the risks, benefits, and alternatives, including staged procedures. Patient selection was individualised and based on a thorough evaluation of physiological fitness, disease severity, patient preference, and logistical considerations.

The inclusion criteria were as follows: bilateral symptomatic hip arthritis or femoral head osteonecrosis confirmed by clinical examination and radiological imaging, severe functional limitation substantially affecting activities of daily living and quality of life, documented medical fitness for single-stage bilateral surgery based on cardiorespiratory assessment and laboratory parameters, and age greater than 18 years.

The exclusion criteria comprised active local or systemic infection, severe uncontrolled cardiopulmonary disease precluding prolonged surgery and immediate postoperative mobilisation, American Society of Anesthesiologists (ASA) physical status classification grade IV or higher, and revision hip arthroplasty cases or patients with prior hip surgery.

Preoperative assessment

All patients underwent comprehensive preoperative evaluation, including detailed clinical history and physical examination, plain radiographs of bilateral hips in anteroposterior and frog-leg lateral projections to assess disease severity and templating, routine haematological and biochemical investigations, blood grouping and crossmatching, electrocardiography, and chest radiography. Patients aged > 50 years or those with cardiovascular risk factors underwent echocardiography and cardiology clearance. Preoperative functional status was quantified using the Harris Hip Score (HHS) by a trained physiotherapist who was unaware of the surgical plan. Digital templating was performed in all cases to anticipate implant sizing, ensure adequate restoration of limb length and offset, and optimise component positioning.

Surgical technique

All procedures were performed by a single experienced arthroplasty surgeon using a standardised operative

protocol. Patients were positioned in the lateral decubitus position. Spinal anaesthesia was used whenever feasible, while general anaesthesia was administered in selected patients, particularly those with ankylosing spondylitis in whom neuraxial anaesthesia was not feasible. Prophylactic intravenous cefuroxime (1.5 g) was administered within 60 min before skin incision. A standardised direct lateral (Hardinge) approach was used, with meticulous handling and subsequent anatomical repair of the abductor mechanism. Following exposure and capsulotomy, the femoral neck was osteotomised according to the preoperative template and the femoral head removed. The acetabulum was sequentially reamed and prepared, with component orientation guided by preoperative templating and intraoperative anatomical landmarks. Cementless acetabular components were inserted with a target inclination of 35° – 45° and anteversion of 15° – 25°. The femoral canal was sequentially broached to achieve appropriate component size, axial alignment, version, limb length, and offset. Trial reduction was performed to assess stability, soft-tissue tension, component position, and restoration of limb length before definitive implantation. Cementless femoral and acetabular components (DePuy Synthes, Warsaw, IN, USA) were then implanted according to the final trial and intraoperative assessment. The first hip was completed before repositioning and sterile redraping for preparation of the contralateral hip on the same operating table. Following definitive implantation, the operative field was thoroughly irrigated, meticulous haemostasis was achieved, and the capsule and abductor mechanism were anatomically repaired. Layered wound closure was performed with absorbable sutures and subcuticular skin closure. Estimated blood loss (EBL) was determined by the anaesthesia and surgical teams using suction-canister volume, sponge assessment, and intraoperative visual estimation.

Perioperative protocol

A standardised enhanced recovery protocol was implemented for all patients. Intravenous tranexamic acid was administered at a dose of 1 g at skin incision and 1 g at wound closure to minimise perioperative blood loss. Mechanical thromboprophylaxis with intermittent pneumatic compression devices was applied intraoperatively and continued throughout hospitalisation. Chemical thromboprophylaxis with enoxaparin 40 mg subcutaneously was initiated 12 h postoperatively and continued for 21 days. Multimodal analgesia comprising regular

paracetamol and non-steroidal anti-inflammatory drugs were not contraindicated, with judicious opioid analgesia used as rescue therapy. Intravenous fluid therapy was guided by intraoperative and postoperative haemodynamic parameters. Early physiotherapy was initiated on postoperative Day 1, including active ankle-pump exercises, quadriceps strengthening, and progressive mobilisation with walker support as tolerated. Nutritional optimisation and early oral intake were encouraged, with prophylactic proton-pump inhibitor therapy administered during hospitalisation.

Outcome measures

The primary outcome measures included perioperative parameters (operative duration, EBL, haemoglobin drop from preoperative to postoperative Day 1, and allogeneic transfusion requirement), postoperative recovery parameters (time to first mobilisation and duration of hospital stay), functional outcomes assessed using the HHS preoperatively and at the latest follow-up, radiographic assessment of implant positioning and fixation, and perioperative complications, including surgical site infection, venous thromboembolism, dislocation, neurovascular injury, and mortality. Operative time was recorded from the skin incision to the final dressing application, encompassing both hips. Haemoglobin levels were measured on admission and on postoperative Day 1. Radiographic evaluation was performed at discharge, six weeks, three months, and at the latest follow-up. Acetabular cup inclination was assessed on standardised anteroposterior pelvic radiographs. Component orientation was assessed using the predefined radiographic protocol. Stem alignment and limb length restoration were assessed by comparing the preoperative and postoperative radiographs.

Statistical analysis

Preoperative and postoperative HHS were compared using the paired Student's t-test for normally distributed paired differences. The mean change in HHS was reported with a 95% confidence interval. Statistical significance was set at $p < 0.05$. Missing data were handled using case-wise deletion. No formal power calculation was performed, given the observational case series design.

Results

Demographic and baseline characteristics

The study cohort comprised 16 consecutive patients who underwent simultaneous bilateral THA. The demographic

and baseline characteristics of the study population are presented in Table 1. The mean age at the time of surgery was 44.8 ± 15.1 years (median 42.0 years, range 21 – 73 years). The cohort included 12 male (75.0%) and 4 female (25.0%) patients. The most common underlying diagnosis was AVN of the femoral head, which was present in 11 patients (68.8%), followed by secondary OA in 5 patients (31.2%). The aetiology of AVN was idiopathic in 6 patients, steroid-induced in 3 patients, and alcohol-related in 2 patients. Patients with secondary OA had pre-existing unilateral hip conditions that progressed to bilateral involvement with concomitant degenerative changes on the contralateral side over time. The mean body mass index (BMI) was 25.4 ± 3.2 kg/m². The mean duration of symptoms prior to surgery was 4.8 ± 2.6 years. Most patients (87.5%) were ASA grade II, and 12.5% were ASA grade III. Eight patients (50.0%) were operated on at the Saket facility and 8 (50.0%) at the Gurgaon facility.

Parameter	Value (N = 16)
Total number of patients	16
Age (years), mean $\pm$ SD	44.8 ± 15.1
Age range (years)	21 – 73
Male/Female, n (%)	12 (75.0)/4 (25.0)
Body mass index (kg/m ²), mean $\pm$ SD	25.4 ± 3.2
Diagnosis, n (%)	
Avascular necrosis	11 (68.8)
Secondary OA	5 (31.2)
ASA grade, n (%)	
Grade II	14 (87.5)
Grade III	2 (12.5)
Location, n (%)	
Saket	8 (50.0)
Gurgaon	8 (50.0)
Mean follow-up duration (months)	8.2 ± 2.1



Table 1: Demographic and baseline characteristics of the study population.

Abbreviations: ASA: American Society of Anesthesiologists; OA: Osteoarthritis.

Patient-wise clinical data

Detailed patient demographic, perioperative, and functional data are presented in Table 2. The ages of the individuals ranged from 21 to 73 years, reflecting a predominantly young cohort with AVN. All patients underwent surgery using the lateral Hardinge approach with cementless DePuy Synthes implants. None of the 16 patients required postoperative Intensive Care Unit (ICU) admission.

Sr. No.	Diagnosis	ICU stay	Hospital stay	Operative time (min)	EBL (mL)	Preoperative HHS	Postoperative HHS
1	AVN Hip	Nil	5 days	95	280	44	91
2	AVN Hip	Nil	5 days	102	290	40	90
3	AVN Hip	Nil	5 days	98	270	38	91
4	AVN Hip	Nil	5 days	92	250	42	93
5	AVN Hip	Nil	5 days	88	240	35	94
6	Secondary OA	Nil	5 days	115	360	48	87
7	AVN Hip	Nil	5 days	105	310	44	89
8	AVN Hip	Nil	5 days	108	300	41	88
9	AVN Hip	Nil	5 days	90	235	36	93
10	AVN Hip	Nil	5 days	96	265	40	91
11	AVN Hip	Nil	5 days	100	280	46	86
12	AVN Hip	Nil	5 days	99	275	43	90
13	Secondary OA	Nil	5 days	120	410	50	85
14	Secondary OA	Nil	7 days	125	440	52	84
15	Secondary OA	Nil	5 days	118	380	49	86
16	Secondary OA	Nil	5 days	112	340	47	87

Table 2: Patient-wise demographic, perioperative, and functional outcome data.

Abbreviations: AVN: Avascular Necrosis; EBL: Estimated Blood Loss; HHS: Harris Hip Score; ICU: Intensive Care Unit; OA: Osteoarthritis.

Perioperative outcomes

The perioperative outcomes of the study cohort are summarised in Table 3. The mean operative time for the bilateral procedure was 103.9 ± 11.3 minutes (range, 88 – 125). The mean hospital stay was 5.1 ± 0.5 days (range, 5 – 7); 15 patients were discharged within 5 days, and 1 patient was discharged on postoperative Day 7.

Parameter	Value (N = 16)
Operative time (min), mean $\pm$ SD	103.9 ± 11.3
Range (min)	88 – 125
Estimated blood loss (mL), mean $\pm$ SD	307.8 ± 61.3
Range (mL)	235 – 440
Haemoglobin drop (g/dL), mean $\pm$ SD	1.45 ± 0.38
Range (g/dL)	1.0 – 2.1
Transfusion required, n (%)	1 (6.3)
Mean units transfused	1.0
Time to mobilisation (days), mean $\pm$ SD	1.2 ± 0.4
Range (days)	1.0 – 2.0
Duration of hospital stay (days), mean $\pm$ SD	5.1 ± 0.5
Range (days)	5 – 7

Table 3: Perioperative outcomes.

Functional outcomes

The functional outcomes of the study cohort are summarised in Table 4. The mean preoperative HHS was 43.4 ± 5.0 (range, 35 – 52). All 16 patients (100%) achieved good-to-excellent functional outcomes (HHS $\geq$ 80).

Parameter	Value (N = 16)
Preoperative Harris Hip Score (HHS), mean $\pm$ SD	43.4 ± 5.0
95% CI for mean improvement	41.4 – 49.8
Postoperative HHS, mean $\pm$ SD	89.1 ± 3.0
Mean improvement in HHS	45.6
Median improvement	47.0
Range of improvement	32 – 59
P-value (paired t-test)	< 0.001
Patients achieving good-to-excellent outcome (HHS $\geq$ 80), n (%)	16 (100)

Table 4: Summary of functional outcomes.

Radiological outcomes

Postoperative plain radiographs of the pelvis and hips were evaluated for all patients at discharge, six weeks, three months, and at the latest follow-up. Radiographic evaluation demonstrated a satisfactory acetabular cup inclination (mean $40.2^\circ \pm 3.8^\circ$, range $36^\circ - 46^\circ$) within the predefined target range in all patients. The femoral stem alignment was neutral in 14 patients (87.5%), slightly valgus in 1 patient (6.25%), and slightly varus in 1 patient (6.25%). Neither deviation was clinically significant, and both patients with slight stem malalignment demonstrated excellent functional outcomes without evidence of subsidence. Stable biological fixation was evident in all patients, with no radiolucent lines surrounding the acetabular or femoral components. Limb length restoration within 5 mm of the contralateral side was achieved in 15 patients (93.8%). One patient (6.25%) had a limb-length discrepancy of 7 mm, which was well tolerated clinically without the need for a shoe raise intervention. No evidence of component migration, subsidence, osteolysis, heterotopic ossification, or loosening was observed during the follow-up period.

Representative radiographic images

Preoperative and postoperative anteroposterior pelvic radiographs of three representative patients from the cohort are presented in Figures 1 – 3, illustrating the implant systems used in each case.

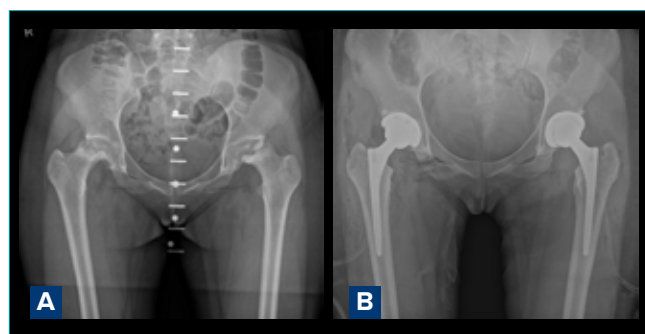


Figure 1A and B: Anteroposterior pelvic radiographs of Patient 1 showing bilateral cementless total hip arthroplasty using Corail femoral stems and Pinnacle acetabular components: **A.** Preoperative; **B.** Postoperative.

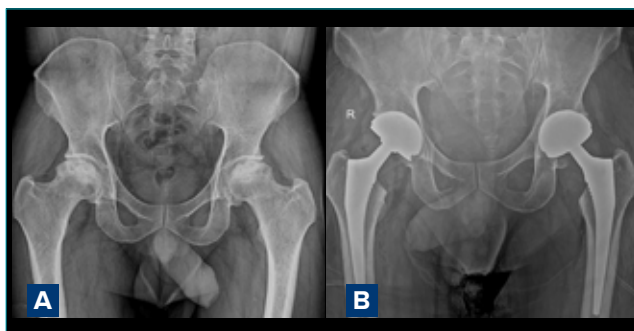


Figure 2A and B: Anteroposterior pelvic radiographs of Patient 2 showing bilateral cementless total hip arthroplasty using Corail femoral stems and the Pinnacle dual-mobility acetabular system: **A.** Preoperative; **B.** Postoperative.

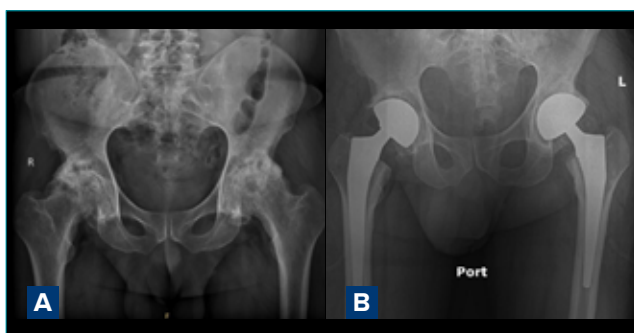


Figure 3A and B: Anteroposterior pelvic radiographs of Patient 3 showing bilateral cementless total hip arthroplasty using Corail femoral stems and the Bimentum dual-mobility acetabular system: **A.** Preoperative; **B.** Postoperative.

Complications

No major perioperative complications were observed during follow-up. Specifically, there were no cases of deep periprosthetic infection, hip dislocation, pulmonary embolism, symptomatic deep vein thrombosis, perioperative mortality, or the need for revision surgery during the follow-up period. Two minor perioperative events were observed. One patient (Patient 13, age 64 years, secondary OA) experienced transient intraoperative hypotension during preparation of the second hip, which responded promptly to fluid bolus administration and slight reduction in anaesthetic depth; haemodynamics stabilised without the need for vasopressor support, and the procedure was completed without further events. The same patient received one unit of allogeneic transfusion postoperatively, as detailed above. Another patient (Patient 14, age 73 years, secondary OA) reported mild anterior thigh pain during the second postoperative week, which was attributed to tensor fasciae latae irritation related to the lateral approach of the surgery. This symptom

responded well to targeted physiotherapy, analgesics, and activity modification and resolved completely within four weeks without functional limitation.

Discussion

This prospective observational case series suggests that simultaneous bilateral THA, when performed under standardised perioperative and enhanced recovery protocols in carefully selected patients, can be associated with favourable early functional and perioperative outcomes. Our results showed substantial improvement in HHS across all 16 patients, early mobilisation within one to two days postoperatively, low transfusion requirements, and no observed major complications. These findings are consistent with contemporary literature supporting the feasibility of simultaneous bilateral procedures in appropriately selected patients.

Historically, simultaneous bilateral THA has been viewed with considerable scepticism because of early reports documenting increased morbidity and mortality. Ritter *et al.*¹ documented promising early results with bilateral procedures during a single hospitalisation, although their patient selection was highly restrictive. Subsequent studies by Woolson *et al.* and Schwarzkopf *et al.*^{2,3} provided mixed results, with some demonstrating acceptable outcomes, while others raised concerns about blood loss and cardiopulmonary stress. The landmark study by Ramezani *et al.*⁴ analysed the outcomes of 1,155 simultaneous bilateral THAs and contributed significantly to the evolving understanding by demonstrating that with modern perioperative care, simultaneous procedures could be performed safely with favourable outcomes reported in appropriately selected patients.

The contemporary evidence base supports the feasibility of simultaneous bilateral THA in appropriately selected patients. The systematic review and meta-analysis by Peng *et al.*⁵ comparing simultaneous versus staged bilateral THA reported no significant difference in serious complications, mortality, or functional outcomes, while simultaneous procedures offered advantages in total hospitalisation and rehabilitation. Similarly, Tsiridis *et al.*⁶ reported that simultaneous bilateral THA was not associated with increased 30-day or 90-day mortality compared with staged procedures, although a modestly increased risk of blood transfusion was observed. Both reviews emphasised the importance of patient selection

and institutional experience. Parvizi *et al.*⁷ also compared one-stage and two-stage bilateral THA, further contributing to the evidence base for simultaneous procedures.

Blood management is an important consideration in simultaneous bilateral THA. In our study, the mean EBL was 307.8 mL, and the mean haemoglobin drop was 1.45 g/dL, with a transfusion rate of 6.3%. These outcomes may reflect the use of contemporary blood-conservation strategies, including intravenous tranexamic acid, meticulous haemostasis, and standardised perioperative care. Wu *et al.*⁸ reported that tranexamic acid reduces blood loss and transfusion requirements in bilateral THA without increasing thromboembolic risk. The use of spinal anaesthesia in most patients, with general anaesthesia in selected cases where neuraxial anaesthesia was not feasible, together with goal-directed fluid therapy, supported perioperative management in our cohort.

The functional outcomes of our study were particularly encouraging. The mean postoperative HHS was 89.1 at a mean follow-up of 8.2 months, which was consistent with favourable functional outcomes reported in contemporary literature. Kim *et al.*,⁹ in their early series of simultaneous bilateral THA, reported comparable functional scores. The absence of a documented limb-length discrepancy beyond 7 mm in any patient is noteworthy, as symmetrical limb-length restoration is a potential advantage of simultaneous over staged bilateral surgery. Patients undergoing staged procedures may experience an interval of limb-length asymmetry between surgeries; however, the present study was not designed to compare these effects directly.

The ERAS pathway was an important component of the perioperative management in our cohort. Contemporary ERAS literature supports multimodal perioperative optimisation, including patient education, multimodal analgesia, early mobilisation, and standardised discharge criteria.¹⁰ Our mean hospital stay of 5.1 days was longer than that reported by some Western ERAS programmes, but all patients were mobilised by postoperative Day 2 and 15 of 16 patients were discharged within five days.

The broader literature has also described indications, implications, and outcomes of simultaneous bilateral THA,¹¹ compared one-stage bilateral THA with unilateral THA,¹² examined perioperative complications in arthroplasty,¹³ and outlined established principles of hip arthroplasty.¹⁴

This study has several limitations. First, the observational case-series design without a control group precluded direct comparison with staged bilateral or unilateral THA. Second, the small sample size of 16 patients limits generalisability and the ability to detect uncommon complications. Third, the mean follow-up of 8.2 months is insufficient to evaluate long-term implant survivorship, wear, or late

complications such as aseptic loosening and periprosthetic fracture. Fourth, all procedures were performed by a single experienced surgeon at a high-volume arthroplasty centre, limiting generalisability to lower-volume settings or less experienced teams. These limitations should be considered when interpreting the favourable early outcomes observed in this series.

Conclusion

Simultaneous bilateral THA may be a feasible treatment option for carefully selected patients with bilateral end-stage hip disease. In this prospective case series, the procedure was associated with substantial functional improvement, early mobilisation, low transfusion requirements, and favourable short-term radiological outcomes. These findings support the use of simultaneous bilateral THA within an experienced multidisciplinary arthroplasty programme, while larger comparative studies with longer follow-up are needed to define optimal patient selection and establish comparative safety and long-term implant outcomes.

Sushant Niramohi, Chandeeep Singh, Shitij Kacker, SKS Marya. Enhanced Recovery and Early Functional Outcomes Following Simultaneous Bilateral Total Hip Arthroplasty: A Single-Surgeon Case Series. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-30>

References

- Ritter MA, Stringer EA. Bilateral total hip arthroplasty: a single procedure. *Clin Orthop Relat Res*. 1980;(149):185–90.
- Woolson ST, Hartford JM, Sawyer A. Results of a method of leg-length equalization for patients undergoing primary total hip replacement. *J Arthroplasty*. 1999;14(2):159–64.
- Schwarzkopf R, Olivieri P, Jaffe WL. Simultaneous bilateral total hip arthroplasty with hydroxyapatite-coated implants: a 20-year follow-up. *J Arthroplasty*. 2012;27(7):1364–9.
- Ramezani A, Ghaseminejad Raeini A, Sharafi A, *et al*. Simultaneous versus staged bilateral total hip arthroplasty: a systematic review and meta-analysis. *J Orthop Surg Res*. 2022;17(1):392.
- Peng L, Peterson B, Singh A, *et al*. Simultaneous or Staged Bilateral Total Hip Arthroplasty: An Analysis of 82,897 Patients. *J Am Acad Orthop Surg Glob Res Rev*. 2025;9(10):e25.00046.
- Tsiridis E, Pavlou G, Charity J, *et al*. The safety and efficacy of bilateral simultaneous total hip replacement: an analysis of 2063 cases. *J Bone Joint Surg Br*. 2008;90(8):1005–12.
- Parvizi J, Tarity TD, Sheikh E, *et al*. Bilateral total hip arthroplasty: one-stage versus two-stage procedures. *Clin Orthop Relat Res*. 2006;453:137–41.
- Wu Y, Yang T, Zeng Y, *et al*. Tranexamic acid reduces blood loss and transfusion requirements in primary simultaneous bilateral total knee arthroplasty: a meta-analysis of randomized controlled trials. *Blood Coagul Fibrinolysis*. 2017;28(7):501–8.
- Kim YH, Kim JS, Cho SH. Early results of simultaneous bilateral total hip arthroplasty. *J Bone Joint Surg Am*. 1996;78(6):841–7.
- Lee DH, Kim JW, Kim CH. The Effect of Enhanced Recovery after Surgery Protocol in Orthopedic Hip Surgery: A Systematic Review and Meta-Analysis. *Clin Orthop Surg*. 2025;17(3):389–99.
- Razzaghof M, Ardakani MV, Poursalehian M, *et al*. Simultaneous Bilateral Total hip Arthroplasty in Patients With Juvenile Idiopathic Arthritis via Direct Anterior Approach: Long-Term Outcomes. *Arthroplast Today*. 2024;30:101557.

12. Parvizi J, Pour AE, Peak EL, *et al.* One-stage bilateral total hip arthroplasty compared with unilateral total hip arthroplasty: a prospective study. *J Arthroplasty*. 2006;21(6 Suppl 2):26–31.
13. Alfonso DT, Toussaint RJ, Alfonso BD, *et al.* Nonsurgical complications after total hip and knee arthroplasty. *Am J Orthop (Belle Mead NJ)*. 2006;35(11):503–10.
14. Harkess JW, Crockarell JR. Arthroplasty of the hip. In: Azar FM, Canale ST, Beaty JH, eds. *Campbell's Operative Orthopaedics*. 14th Edition. Philadelphia, PA: Elsevier; 2021. p. 267–401.



REVIEW ARTICLES

- | | | | |
|----|---|----|--|
| 57 | From Morphology to Molecularly Integrated Diagnosis: Contemporary Neuropathology Practice in Neuro-Oncology - Vaishali Suri, Ashwinee Kumar, Kirti Srivastava | 75 | Beyond the Pill – The Future of Lipid-Lowering Therapy: A 2026 Review of Novel Lipid-Lowering Agents - Aryan Arora, Monica Mahajan |
| 66 | Hippocampal Avoidance in Whole Brain Radiotherapy: Biological Basis, Clinical Evidence, and Future Perspectives - Gayatri Patil, Vansh Parekh, Kaustav Talapatra | 91 | Patient Satisfaction and Experience in Inpatient Care: A Systematic Review of Global Evidence - Ayuj Kaushik, Pragya, Shivam Sharma |
| 71 | Radiation Cancer Biology: Mechanisms of Carcinogenesis and Clinical Implications - Albert Paul Varghese, Anurag Ashok Luharia, Suhas Tiwaskar, Shreya Naik, Ishiqua Vinay Patil, Arif Hussain Malla, Sheikh Mohammed Irfan, Ginesh Job M, Kashmira Patil | | |

From Morphology to Molecularly Integrated Diagnosis: Contemporary Neuropathology Practice in Neuro-Oncology

Vaishali Suri^{1*}, Ashwinee Kumar¹, Kirti Srivastava¹

¹Neuropathology Laboratory, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi

Correspondence:

Vaishali Suri

E-mail: surivaishali@yahoo.co.in

DOI: <https://doi.org/10.62830/mmj3-03-5>

Abstract:

The practice of neuropathology in neuro-oncology has undergone a fundamental transformation. For much of the twentieth century, central nervous system (CNS) tumours were classified predominantly according to their microscopic resemblance to presumed cells of origin, architectural patterns, and histological features of malignancy. Although histopathology remains indispensable, the identification of recurrent genetic and epigenetic alterations has demonstrated that morphologically similar tumours may represent biologically distinct diseases, while tumours with variable histology may share a common molecular identity. The fifth edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System, published in 2021, consolidated this transition by making molecular alterations essential diagnostic criteria for numerous tumour types. The contemporary neuropathology report is therefore an integrated diagnosis incorporating morphology, immunophenotype, molecular findings and CNS WHO grade. The present review discusses the continuing role of conventional histology and immunohistochemistry (IHC) and examines the applications, advantages and limitations of targeted platforms such as fluorescence in situ hybridisation (FISH), Sanger sequencing and reverse transcription polymerase chain reaction (RT-PCR). It further outlines the expanding role of next-generation sequencing (NGS) and genome-wide deoxyribonucleic acid (DNA) methylation profiling in CNS tumour classification. A rational, tiered approach combining morphology with appropriately selected molecular platforms offers the most practical route towards accurate, reproducible and clinically relevant diagnosis, particularly in settings where access to comprehensive genomic testing remains limited.

Key words: Neuropathology, Neuro-Oncology, Integrated Diagnosis, Central Nervous System (CNS) Tumours, Next-Generation Sequencing, Deoxyribonucleic Acid (DNA) Methylation Profiling, World Health Organization (WHO) CNS5.

Introduction

Neuropathological diagnosis has traditionally been rooted in morphology. For decades, central nervous system (CNS) tumours were classified according to cellular appearance, growth pattern, anatomical location, mitotic activity, microvascular proliferation and necrosis. The neuropathologist attempted to identify the presumed line of differentiation of a tumour and subsequently assign a histological grade. This approach provided the foundation for the early World Health

Organization (WHO) classifications and continues to underpin daily diagnostic practice.¹

Nevertheless, morphology-based classification had important limitations. Considerable interobserver variation existed in the diagnosis and grading of several tumour groups, particularly diffuse gliomas, embryonal tumours and ependymal neoplasms.² More importantly, morphologically similar tumours may exhibit markedly different biological behaviour, treatment response and prognosis. Conversely, tumours with diverse histological appearances may belong to the same biological group.

Over the last two decades, genomic and epigenomic studies have identified recurrent alterations that define biologically coherent tumour groups. The introduction of isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion into routine glioma diagnosis was among the earliest and most influential examples.³ Molecular alterations are now used not merely as ancillary findings, but as essential diagnostic criteria that establish tumour type, determine CNS WHO grade, define prognostic groups and increasingly guide targeted therapy. The contemporary discipline has therefore evolved from conventional histopathology to integrated histomolecular neuropathology.

The 2021 WHO Classification: Establishing the Integrated Diagnosis

The 2016 revised fourth edition of the WHO classification formally incorporated molecular findings into the definition of selected diffuse gliomas.³ The 2021 fifth edition, WHO CNS5, expanded this principle across a much broader spectrum of CNS tumours.^{1–5} Molecular parameters now constitute essential diagnostic criteria for numerous adult and paediatric gliomas, ependymomas, embryonal tumours and other CNS neoplasms. WHO CNS5 further distinguishes adult-type from paediatric-type diffuse gliomas, recognising that histologically similar tumours arising in different age groups may harbour distinct molecular drivers and biological behaviour.

The adult-type diffuse glioma category is now restricted to three principal tumour types:

- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant and 1p/19q-codeleted
- Glioblastoma, IDH-wildtype

The name “oligodendroglioma” can therefore no longer be assigned solely on the basis of rounded nuclei, perinuclear clearing and branching vasculature. Demonstration of both an IDH mutation and whole-arm 1p/19q codeletion is required. Similarly, adult diffuse astrocytomas carrying an IDH mutation are classified under the single tumour type astrocytoma, IDH-mutant, with CNS WHO grades 2, 3 or 4. The older term “glioblastoma, IDH-mutant” has been removed; such tumours are now classified as astrocytoma, IDH-mutant, CNS WHO grade 4.¹

WHO CNS5 also incorporates molecular alterations into tumour grading. For example, homozygous deletion

of CDKN2A/B assigns CNS WHO grade 4 to an IDH-mutant astrocytoma even in the absence of necrosis or microvascular proliferation.⁶ Conversely, selected adult diffuse IDH-wildtype astrocytic tumours may be classified as glioblastoma on the basis of defining molecular alterations despite lacking conventional histological features of grade 4 disease. Recent recommendations by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW), however, emphasise caution when interpreting isolated molecular findings, particularly telomerase reverse transcriptase (TERT) promoter mutation alone and IDH-wildtype tumours occurring in younger patients.⁷

Integrated and Layered Reporting

The integrated diagnosis represents the synthesis of all tissue-based information rather than the result of any single investigation. A layered report allows the clinician to understand how the final diagnosis was derived.⁸

A typical format is:

- Integrated diagnosis: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2
- Histological classification: Diffuse glioma with oligodendroglial morphology
- CNS WHO grade: 2
- Molecular information: IDH1 mutation present; ATRX retained; whole-arm 1p/19q codeletion demonstrated

The integrated diagnosis should guide clinical management, whereas the underlying layers preserve the morphological and molecular evidence. The suffix NOS (not otherwise specified) is used when essential testing has not been performed, is unavailable or has failed. NEC (not elsewhere classified) is used when an adequate work-up has been completed but the findings do not conform to a recognised WHO tumour type.^{1,8}

Diagnostic Platforms in Contemporary Neuropathology

The selection of ancillary tests should be guided by the differential diagnosis and by the diagnostic value each platform adds to the integrated diagnosis.⁹ The principal diagnostic modalities currently used in contemporary neuropathology, spanning conventional histology to genome-wide molecular profiling, are summarised in Figure 1.

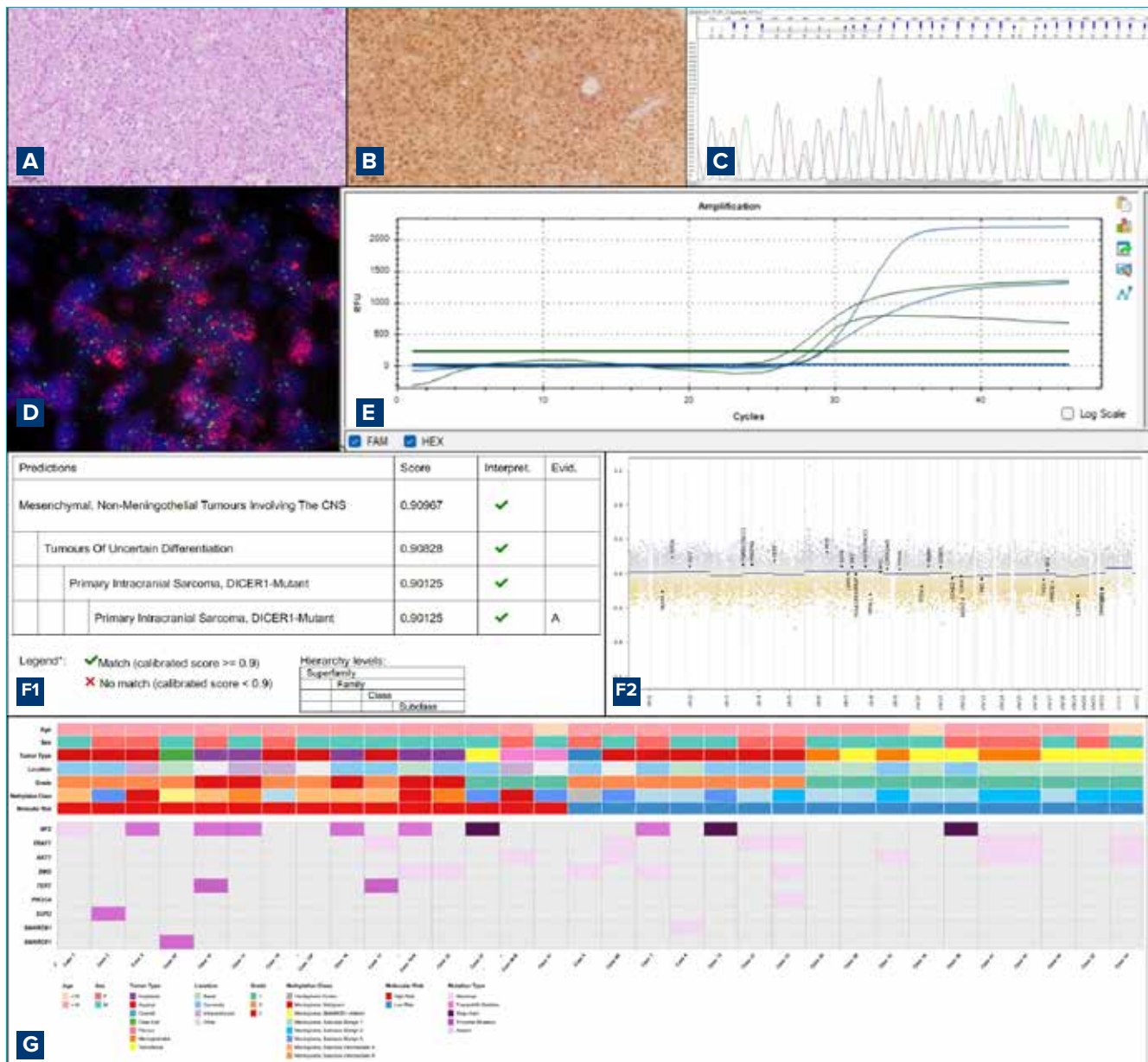


Figure 1A – G: Representative diagnostic modalities in contemporary neuropathology practice, spanning conventional histology to genome-wide molecular platforms. Each panel is derived from a different, de-identified representative case selected solely to illustrate the corresponding platform and should not be interpreted as a single patient's diagnostic work-up. **A.** Haematoxylin and eosin (H&E) stained section of oligodendroglioma, demonstrating the diffuse glioma architecture on which morphological diagnosis was traditionally based; **B.** Immunohistochemistry showing isocitrate dehydrogenase 1 (IDH1) R132H positivity, the most widely used surrogate marker for the common canonical IDH1 mutation in diffuse gliomas; **C.** Sanger sequencing chromatogram demonstrating a non-canonical IDH1 R132C mutation, illustrating the continued role of targeted sequencing in detecting alterations not captured by mutation-specific immunohistochemistry; **D.** Fluorescence in situ hybridisation (FISH) demonstrating epidermal growth factor receptor (EGFR) amplification, one of the copy-number alterations routinely assessed by this platform in diffuse gliomas; **E.** Methylation-specific polymerase chain reaction (MSP) amplification plot showing FAM and HEX fluorophore channels, demonstrating a methylated O⁶-methylguanine-DNA methyltransferase (MGMT) promoter status, a biomarker with established relevance to alkylating chemotherapy response in gliomas; **F1 – F2:** Genome-wide deoxyribonucleic acid (DNA) methylation profiling (Central nervous system [CNS] Tumor Methylation Classifier v12.8, Heidelberg/DKFZ-Epignostix platform) of a representative case: **F1.** Hierarchical classification output showing assignment to the methylation class "Primary Intracranial Sarcoma, DICER1-Mutant," with a calibrated score of 0.90 at the subclass level (Evidence Level A), **F2.** Corresponding copy number variation profile (conumee2) across chromosomes 1 – 22 and X/Y, annotated with CNS tumour-relevant gene loci, showing a relatively flat genomic profile without high-level focal amplification or deletion; **G.** Next-generation sequencing (NGS)-derived oncoprint of a meningioma cohort, integrating clinical annotations (age, sex, tumour type, location, CNS World Health Organization [WHO] grade, methylation class, molecular risk group) with mutation status across genes recurrently altered in meningioma, including NF2, TRAF7, AKT1, SMO, TERT promoter, PIK3CA, SUFU, SMARCB1, and SMARCE1, illustrating the capacity of multi-gene panels to capture diagnostic, prognostic, and molecularly-defined subgroup information simultaneously.

1. Haematoxylin and eosin (H&E) histology

H&E examination remains the starting point of every CNS tumour diagnosis. It establishes whether the tissue is lesional, assesses adequacy and viability, identifies the relationship of the tumour to the surrounding brain and defines its fundamental architectural and cytological pattern. Infiltration, cellularity, mitotic activity, microvascular proliferation and necrosis continue to provide essential diagnostic and grading information. Some tumours with highly characteristic morphology can often be diagnosed with limited ancillary testing. A conventional schwannoma showing Antoni A and Antoni B areas, Verocay bodies, hyalinised vessels and appropriate clinical localisation is a typical example. Similarly, many conventional meningiomas and certain circumscribed glial or neuronal tumours can be strongly suspected on morphology.

However, an H&E diagnosis should not be considered equivalent to an integrated diagnosis when molecular findings are essential to the tumour definition. Morphology is particularly unreliable when distinguishing:

- Astrocytoma from oligodendroglioma
- Adult-type from paediatric-type diffuse glioma
- Morphological mimics of ependymoma
- Embryonal tumours with overlapping small-round-cell morphology
- Histologically unusual or treatment-altered tumours

Thus, H&E has not lost importance; rather, its role has evolved from being the sole determinant to serving as the morphological framework that directs ancillary testing and validates molecular results.¹

2. Immunohistochemistry (IHC)

IHC remains the most accessible bridge between morphology and molecular pathology. It assists in establishing lineage, excluding mimics and detecting the protein consequences of selected genetic alterations.

Frequently used molecular surrogate markers include:

- IDH1 R132H for the most common IDH1 mutation
- ATRX loss as evidence of ATRX mutation

- p53 overexpression as a surrogate marker for TP53 mutation
- H3 K27M and loss of H3K27me3 in appropriate midline tumours
- H3 G34R/V in diffuse hemispheric gliomas
- BRAF V600E in selected glial and glioneuronal tumours
- INI1/SMARCB1 and BRG1/SMARCA4 in rhabdoid tumours
- L1CAM, p65 in selected ependymal differentials

IHC is rapid, economical, preserves tissue and can be implemented in laboratories lacking advanced molecular platforms. It is especially valuable as a first-line screening strategy. Its limitations must nevertheless be recognised. A mutation-specific antibody detects only the alteration against which it was developed; negative IDH1 R132H staining, for example, does not exclude a non-canonical IDH1 or IDH2 mutation.¹⁰ Abnormal staining may also be focal, technically suboptimal or difficult to interpret in small biopsies. IHC should therefore be regarded as a powerful surrogate assay rather than a universal substitute for sequencing.

3. Fluorescence in situ hybridisation (FISH)

FISH detects defined chromosomal copy-number abnormalities or rearrangements within individual nuclei. It is particularly useful in formalin-fixed, paraffin-embedded (FFPE) tissue and permits correlation of an abnormal signal with tumour morphology.

Common neuro-oncology applications include:

- Assessment of 1p and 19q deletion
- Epidermal growth factor receptor (EGFR) amplification
- CDKN2A/B homozygous deletion
- MYC or MYCN amplification
- Selected gene rearrangements or copy-number alterations

FISH is relatively rapid and is well suited for detecting predefined chromosomal alterations, such as specific deletions, amplifications and gene rearrangements. However, it is intrinsically low-plex and only detects

the locus interrogated by the probe. In assessment of 1p/19q status, conventional locus-specific FISH may detect partial deletions and cannot always establish the whole-arm codeletion required for oligodendroglioma.¹ Results must therefore be interpreted with morphology, IDH status and the technical characteristics of the probes used. Chromosomal microarray, methylation-derived copy-number profiling or appropriately designed next-generation sequencing (NGS) approaches may provide more comprehensive copy-number information.

4. Sanger sequencing

Sanger sequencing remains valuable for the targeted analysis of recurrent mutational hotspots. In neuropathology practice, it may be used to detect non-canonical alterations in IDH1 and IDH2, as well as mutations involving histone H3 genes, BRAF, and the TERT promoter, provided that the assay has been appropriately validated. Its principal advantages are technical familiarity, comparatively straightforward interpretation and suitability for single-gene testing. However, it has limited sensitivity in samples with low tumour content and generally requires a higher mutant allele fraction than contemporary deep-sequencing platforms. It is also inefficient when several genes or exons need to be tested sequentially. Sanger sequencing therefore remains useful for analysing predefined mutational hotspots, although it is increasingly being replaced by targeted NGS in laboratories with sufficient case volume, infrastructure and resources.

5. Polymerase chain reaction (PCR) and reverse transcription PCR (RT-PCR)

PCR-based assays provide rapid and cost-effective detection of predefined molecular alterations in CNS tumours. Mutation-specific approaches, including allele-specific and real-time PCR, may be used to identify recurrent hotspot mutations when the exact alteration is known. Methylation-specific PCR is widely used to assess O⁶-methylguanine-DNA methyltransferase (MGMT) promoter methylation in diffuse gliomas.¹¹ RT-PCR uses ribonucleic acid (RNA) as the template and is useful for detecting known expressed fusion transcripts, such as KIAA1549::BRAF, when the fusion partners and common breakpoints are predefined.¹² However, these targeted assays may not detect uncommon mutations, novel fusion partners or unexpected breakpoints; broader DNA- or RNA-based NGS is preferable when multiple or previously undefined alterations need to be evaluated.

6. Next-generation sequencing (NGS)

NGS has become the principal high-throughput genomic platform in contemporary neuro-oncology. Unlike sequential single-gene testing, a well-designed panel can interrogate numerous genes simultaneously while conserving limited tumour tissue.¹³

DNA-based NGS may identify:

- Single-nucleotide variants
- Small insertions and deletions
- Selected copy-number alterations
- Tumour mutational burden or mismatch-repair-related alterations in appropriately validated assays

RNA-based NGS is particularly useful for:

- Fusion detection
- Identification of unexpected fusion partners
- Confirmation that a rearrangement produces an expressed transcript
- Selected transcriptomic or expression-based classifications

NGS is particularly valuable in paediatric and young-adult CNS tumours, where kinase fusions and uncommon driver alterations are relatively frequent. It enables simultaneous detection of diagnostic, prognostic and potentially actionable alterations while conserving limited tissue.¹³ However, NGS requires specialised laboratory infrastructure, validated bioinformatic pipelines and trained molecular scientists for data analysis and interpretation. In many laboratories, samples must be processed in batches to remain cost-effective, which makes single-sample testing impractical and increases turnaround time. Its performance is also influenced by tumour content, nucleic acid quality, sequencing depth and panel design. Consequently, a negative result may reflect inadequate assay coverage rather than true absence of the alteration. NGS findings must therefore be interpreted together with morphology, IHC and clinical-radiological information.

7. DNA methylation profiling

Genome-wide DNA methylation profiling has emerged as a powerful tool for CNS tumour classification. CNS tumours exhibit reproducible epigenetic signatures that

reflect their lineage, cell of origin and underlying molecular alterations. These genome-wide methylation data are analysed using a validated reference classifier, which assigns the tumour to the most closely corresponding recognised methylation class.

Methylation profiling is especially useful when:

- Morphology and immunophenotype are discordant
- The differential diagnosis includes several molecularly distinct entities
- The tumour has unusual or ambiguous histology
- Further subclassification has prognostic significance
- A WHO tumour type is primarily or most reliably defined by methylation class
- Tissue is limited and simultaneous classification and copy-number analysis are desirable

The original Heidelberg classifier demonstrated that methylation-based analysis could alter the diagnosis in a meaningful proportion of prospectively assessed CNS tumours.¹⁴ Methylation arrays also generate copy-number profiles, potentially identifying alterations such as chromosomal gains and losses, amplifications and homozygous deletions from the same assay. This technology is particularly valuable in ependymal, embryonal and paediatric glial tumours and in entities such as high-grade astrocytoma with piloid features. However, methylation profiling is not an autonomous diagnostic authority. A high classifier score must still be reconciled with histology, location, age, imaging and other molecular findings. Low tumour content, poor-quality DNA, classifier-version limitations or absence of a tumour class from the reference set may lead to

low-confidence or misleading results. Current cIMPACT-NOW guidance specifically recommends that methylation results be reported within an integrated, layered diagnostic framework and reviewed by a neuropathologist familiar with the platform.¹⁵

A Practical Tiered Diagnostic Workflow

A contemporary neuropathology laboratory does not need to perform every available test on every CNS tumour; the diagnostic approach should be guided by the differential diagnosis, patient age, anatomical site, radiological findings, morphology and clinical relevance (Table 1).⁹ H&E examination and a core IHC panel form the first tier, defining the broad tumour family, establishing lineage and screening for common defining alterations. Targeted assays such as FISH, Sanger sequencing, mutation-specific PCR or RT-PCR may then be used to assess specific abnormalities, including 1p/19q codeletion, non-canonical IDH1 or IDH2 mutations and recurrent gene fusions. DNA- and RNA-based NGS should be considered when multiple alterations require simultaneous evaluation, tissue is limited, targeted tests are inconclusive or potentially actionable alterations are being investigated. Genome-wide methylation profiling is particularly valuable in diagnostically unresolved or discordant cases and in tumour groups for which methylation class has defining or major subclassifying significance. This tiered approach is especially practical in resource-constrained settings, where morphology, validated IHC surrogates and selected targeted assays can resolve many routine cases, while advanced platforms are reserved for situations in which they are likely to alter the diagnosis, grade or clinical management. The objective is not maximal testing, but the minimum sufficient testing required to establish a reliable integrated diagnosis.

Platform	Best suited for	Principal strength	Major limitation
H&E	Architecture, cytology, infiltration and grading features	Rapid overview of the entire lesion	Cannot define many modern tumour types alone
IHC	Lineage and molecular-surrogate testing	Accessible, economical, tissue-sparing	Surrogate markers may be incomplete or technically variable
FISH	Specific deletions, amplifications or rearrangements	Works well on FFPE and individual nuclei	Targeted; limited genomic coverage
Sanger sequencing	Known hotspot mutations	Straightforward targeted testing	Low throughput and relatively limited sensitivity
RT-PCR	Known fusion transcripts	Sensitive and economical	Requires good RNA and prior knowledge of breakpoints
DNA/RNA NGS	Multi-gene and fusion analysis	Comprehensive and tissue-efficient	Cost, bioinformatics and interpretation requirements
Methylation profiling	Tumour classification and copy-number profiling	Objective genome-wide classification	Reference-dependent; must be integrated with other findings

Table 1: Comparative role of the major platforms.

Abbreviations: CNS: Central Nervous System; DNA: Deoxyribonucleic Acid; FFPE: Formalin-Fixed, Paraffin-Embedded; FISH: Fluorescence in Situ Hybridisation; H&E: Haematoxylin and Eosin; IHC: Immunohistochemistry; NGS: Next-Generation Sequencing; PCR: Polymerase Chain Reaction; RNA: Ribonucleic Acid; RT-PCR: Reverse Transcription Polymerase Chain Reaction; WHO: World Health Organization.

Challenges in the Molecular Era

The molecular transformation of neuropathology has created several practical challenges. Tissue obtained from stereotactic biopsies may be extremely limited, making pre-analytical planning and tissue stewardship essential. Formalin fixation, decalcification and prolonged block storage may compromise DNA and RNA quality. Molecular tests must be analytically validated, and laboratories must participate in appropriate quality-assurance programmes. Access and affordability remain major concerns. The molecular requirements of WHO CNS5 may be difficult to implement uniformly, particularly in low- and middle-income countries.⁵ This can lead to increased use of NOS diagnoses, delayed reporting and inequity in access to precise tumour classification. Regional referral networks, shared molecular platforms, validated IHC-based algorithms and centralised methylation or NGS services may offer pragmatic solutions. Another challenge is that tumour classification is no longer static. Molecularly defined groups continue to be divided, merged or refined as larger datasets become available. cIMPACT-NOW provides interim recommendations between WHO editions; its recent updates on methylation profiling and IDH- and H3-wildtype diffuse gliomas demonstrate

that interpretation continues to evolve even after WHO CNS5.^{7,15}

Future Directions

Future neuropathology practice is likely to evolve towards broader multi-omic integration. Combined assessment of sequence alterations, gene fusions, copy-number changes, methylation, transcriptomic profiles and, potentially, proteomic features may improve tumour classification and risk stratification. Long-read sequencing may resolve complex structural alterations, while liquid biopsy and cerebrospinal-fluid analysis may allow molecular assessment when tissue is inaccessible or during disease monitoring.^{16,17} Digital pathology and artificial intelligence may assist in tumour detection, grading, quantification and prediction of molecular alterations from histological images.¹⁸ These approaches are expected to function as decision-support systems rather than replace the neuropathologist. The central responsibility will remain the reconciliation of morphology, molecular data, imaging and clinical context into a biologically coherent diagnosis. The future neuropathologist will therefore require competence not only in microscopy but also in molecular assay selection, quality control, bioinformatic interpretation and communication of clinically meaningful results.

Conclusion

The future of neuro-oncology diagnostics will be determined not by the availability of the largest number of molecular tests, but by their appropriate selection, validation and interpretation. Neuropathology laboratories must therefore develop practical diagnostic algorithms that preserve tissue, minimise unnecessary testing and deliver clinically relevant results within an acceptable turnaround time. Regional referral networks, shared high-throughput platforms and robust quality-assurance systems will be essential to extend molecularly informed diagnosis beyond a limited number of specialised centres.

As classification systems continue to evolve, the neuropathologist will remain central to neuro-oncology practice, not merely as an interpreter of morphology but as the specialist who determines which molecular test is required, resolves discordant findings and converts complex data into an actionable diagnosis. The next phase of progress must focus on making integrated diagnosis reproducible, affordable and accessible, so that advances in molecular classification translate into better care for every patient with a CNS tumour.

Vaishali Suri, Ashwinee Kumar, Kirti Srivastava. From Morphology to Molecularly Integrated Diagnosis: Contemporary Neuropathology Practice in Neuro-Oncology. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-5>

References

- Louis DN, Perry A, Wesseling P, *et al.* The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021;23(8):1231–51.
- van den Bent MJ. Interobserver variation of the histopathological diagnosis in clinical trials on glioma: a clinician's perspective. *Acta Neuropathol.* 2010;120(3): 297–304.
- Louis DN, Perry A, Reifenberger G, *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(6):803–20.
- Yan H, Parsons DW, Jin G, *et al.* IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 2009;360(8):765–73.
- WHO Classification of Tumours Editorial Board. Central nervous system tumours. 5th Edition. Lyon: International Agency for Research on Cancer; 2021.
- Shirahata M, Ono T, Stichel D, *et al.* Novel, improved grading system(s) for IDH-mutant astrocytic gliomas. *Acta Neuropathol.* 2018;136(1):153–66.
- Brat DJ, Aldape K, Colman H, *et al.* cIMPACT-NOW update 5: recommendations for grading of diffuse gliomas. *Acta Neuropathol.* 2020;139(3):603–8.
- Louis DN, Perry A, Burger P, *et al.* International Society Of Neuropathology–Haarlem consensus guidelines for nervous system tumor classification and grading. *Brain Pathol.* 2014;24(5):429–35.
- Sahm F, Brandner S, Bertero L, *et al.* Molecular diagnostic tools for the World Health Organization (WHO) 2021 classification of gliomas, glioneuronal and neuronal tumors; an EANO guideline. *Neuro Oncol.* 2023;25(10):1731–49.
- Reuss DE, Sahm F, Schrimpf D, *et al.* ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an integrated diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. *Acta Neuropathol.* 2015;129(1):133–46.
- Hegi ME, Diserens AC, Gorlia T, *et al.* MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997–1003.
- Jones DTW, Kocalkowski S, Liu L, *et al.* Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. *Cancer Res.* 2008;68(21):8673–7.
- Sahm F, Schrimpf D, Jones DTW, *et al.* Next-generation sequencing in routine brain tumor diagnostics enables an integrated diagnosis and identifies actionable targets. *Acta Neuropathol.* 2016;131(6):903–10.
- Capper D, Jones DTW, Sill M, *et al.* DNA methylation-based classification of central nervous system tumours. *Nature.* 2018;555(7697):469–74.

15. Louis DN, Wesseling P, Aldape K, *et al.* cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. *Brain Pathol.* 2020;30(4):844–56.
16. Roberts HE, Lopopolo M, Pagnamenta AT, *et al.* Short and long-read genome sequencing methodologies for somatic variant detection; genomic analysis of a patient with diffuse large B-cell lymphoma. *Sci Rep.* 2021;11(1):6408.
17. Miller AM, Shah RH, Pentsova EI, *et al.* Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. *Nature.* 2019;565:654–8.
18. Hollon TC, Jiang C, Chowdury A, *et al.* Artificial-intelligence-based molecular classification of diffuse gliomas using rapid, label-free optical imaging. *Nature Medicine.* 2023;29:828–32.

Hippocampal Avoidance in Whole Brain Radiotherapy: Biological Basis, Clinical Evidence, and Future Perspectives

Gayatri Patil¹, Vansh Parekh¹, Kaustav Talapatra^{1*}

¹Department of Radiation Oncology, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

Correspondence:

Kaustav Talapatra

E-mail: kaustee@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-6>

Abstract:

Radiotherapy continues to be an important aspect of the management of primary and secondary brain tumours. Despite improvements in intracranial disease control and survival outcomes, radiation-induced neurocognitive impairment continues to pose a problem. The hippocampus plays a crucial role in memory formation and learning, and it has been identified as a critical organ at risk owing to its sensitivity to radiotherapy. The development of advanced radiotherapy techniques has enabled selective sparing of the hippocampus during whole brain radiotherapy (WBRT), leading to better neurocognitive outcomes while maintaining tumour control. This review discusses the anatomical and biological importance of the hippocampus, the rationale for hippocampal avoidance, clinical evidence supporting hippocampal-sparing approaches, patient selection criteria, dosimetric considerations, and future directions in the field of WBRT.

Key words: Hippocampus, Whole Brain Radiotherapy (WBRT), Neurocognitive Function, Brain Metastases, Hippocampal Avoidance, Memory Preservation.

Introduction

The hippocampus is located bilaterally within the medial temporal lobes and is an integral component of the limbic system. The left hippocampus plays a crucial role in the encoding and retrieval of verbal and declarative memories, whereas the right hippocampus is primarily associated with visuospatial processing, topographical memory and non-verbal encoding.^{1,2}

Radiotherapy is widely used in the treatment of primary and secondary brain tumours. It is effective in controlling intracranial disease, but it is also associated with significant late toxicities that affect neurocognitive function, including memory impairment and difficulties in delayed recall, which can significantly affect quality of life (QOL).^{1,3}

With advancements in radiotherapy techniques and a growing understanding of the relationship between

radiation exposure and hippocampal function impairment, hippocampal avoidance techniques have been developed to mitigate cognitive decline while maintaining adequate target coverage.

Clinical Significance of Whole Brain Radiotherapy (WBRT)

Brain metastases occur in approximately 70,000 – 200,000 patients per year.⁴ WBRT has historically been the standard of care for the management of brain metastases, particularly in patients with multiple lesions or widespread disease for whom focal therapies like stereotactic radiosurgery (SRS) or surgery are impractical.⁵ The clinical significance of cranial radiotherapy is multifaceted, serving as a cornerstone for both definitive and prophylactic management of intracranial disease by addressing both macroscopic and microscopic disease.

It provides significant clinical benefit, manifested by symptomatic relief, improved intracranial control, and prolonged survival compared with supportive care alone in appropriately selected patients.⁶ WBRT has also been utilised in prophylactic cranial irradiation (PCI) and certain diffuse intracranial malignancies.^{1,3} PCI is the standard of care for small cell lung cancer (SCLC), reducing intracranial relapse and improving survival. However, in haematological malignancies, the paradigm has increasingly shifted toward intensive systemic and intrathecal therapy to mitigate the profound long-term neurotoxicity associated with cranial irradiation.

Despite its therapeutic benefits, WBRT is associated with significant neurocognitive sequelae. It has been shown that WBRT is associated with substantial neurocognitive decline, with 35% – 52% of the cohort demonstrating a ≥ 3 -standard deviation (SD) reduction in test scores at the 3 – 6 months follow-up.¹ As advances in systemic therapies have prolonged survival among patients with metastatic cancer, preserving cognitive function has become increasingly important.¹

Biological Rationale for Hippocampal Sparing

The biological rationale for hippocampal avoidance is grounded in the hippocampus's essential role in memory consolidation, learning, and spatial navigation,^{1,2} functions supported by a highly specialised neural circuitry with persistent synaptic plasticity and ongoing adult neurogenesis in the dentate gyrus. The subgranular zone of the dentate gyrus contains neural stem and progenitor cells that are particularly vulnerable to injury. Ionising radiation may impair hippocampal function through direct DNA damage, oxidative stress, neuroinflammation, and microvascular injury,^{1,2,7} culminating in neuronal loss, altered synaptic integrity, and chronic hypoperfusion. In addition, radiation suppresses hippocampal neurogenesis, thereby compromising the generation of new neurons required for memory processing and cognitive resilience. These distinct pathways of hippocampal injury require a combined approach of hippocampal avoidance WBRT (HA-WBRT) and pharmacological neuroprotection with memantine.^{3,8}

Hippocampal avoidance is feasible because the hippocampal and perihippocampal regions represent relatively low-risk sites for metastatic involvement, whereas the bulk of subclinical disease resides in the

remaining cerebral parenchyma. The reported incidences of hippocampal and perihippocampal metastases are low, at 4.4% (0% – 27%) and 9.2% (3% – 21%), respectively, supporting a minimal risk of geographic miss and local under-treatment. The total number of brain metastases was the primary risk factor identified for hippocampal involvement.^{9,10}

The prophylactic administration of memantine serves as a vital pharmacological adjunct to dosimetric hippocampal sparing, effectively minimising the mechanisms underlying radiation-associated cognitive impairment. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, limits pathological calcium influx and reduces excitotoxic injury. This neuroprotective mechanism provides the biological rationale for combining memantine with HA-WBRT, thereby reducing the probability of cognitive failure at 24 weeks by 11.1% (53.8% vs. 64.9%) and lowering the hazard of cognitive decline by 22% (hazard ratio [HR] 0.78).³

Clinical Evidence Supporting HA-WBRT

Early clinical investigations

Early retrospective studies demonstrated that brain metastases rarely occur within the hippocampus or its immediate vicinity. These findings formed the foundation for exploring hippocampal avoidance strategies in clinical practice. Subsequently, prospective investigations evaluated the feasibility of reducing hippocampal dose during WBRT. These studies established that modern planning techniques could successfully spare the hippocampus without compromising target coverage.

Radiation Therapy Oncology Group (RTOG) 0933 trial

The Phase II RTOG 0933 trial established the clinical utility of HA-WBRT as a neuroprotective strategy for patients with brain metastases. By using intensity-modulated radiotherapy (IMRT) to restrict the dose to the hippocampal neural stem-cell niche, this multi-institutional study demonstrated a substantial mitigation of neurocognitive toxicity, with a mean relative decline in Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR) scores of only 7.0% at 4 months, significantly lower than the 30% decline documented in historical cohorts ($P < 0.001$). Beyond memory preservation, HA-WBRT maintained patient-reported QOL and exhibited a favourable safety profile with minimal grade 3 or higher adverse events. By

characterising the hippocampus as a critical organ at risk (OAR) and demonstrating the feasibility of dose-sparing without compromising oncological efficacy, RTOG 0933 provided the foundational evidence that facilitated the adoption of HA-WBRT as the current standard of care for patients with brain metastases.¹¹

NRG-CC001 trial

The NRG-CC001 Phase III randomised trial further strengthened the evidence supporting hippocampal avoidance. Patients were randomised to receive either standard WBRT plus memantine or HA-WBRT plus memantine. Results demonstrated a significantly lower risk of cognitive failure in the hippocampal avoidance group (adjusted HR 0.74; $P = 0.02$). Specifically, HA-WBRT demonstrated superior preservation of executive function and memory at 4 and 6 months, alongside reduced patient-reported fatigue and neurological symptom interference, without compromising overall survival or intracranial progression-free survival. These findings establish HA-WBRT plus memantine as the current standard of care for patients with good performance status and no metastases within the hippocampal avoidance region, effectively balancing intracranial disease control with the mitigation of treatment-associated cognitive toxicity.⁸ The key findings of both these trials are summarised in Table 1.

These findings established HA-WBRT combined with memantine as the preferred standard of care for eligible patients requiring WBRT.

Clinical Prerequisites for HA-WBRT and Patient Selection

Patient selection for HA-WBRT requires a careful evaluation of prognosis and distribution of intracranial disease. According to current clinical consensus, based on Phase III evidence, HA-WBRT should be offered to

patients with a good performance status and adequate life expectancy to obtain meaningful neurocognitive benefit. Absolute contraindications for hippocampal sparing include metastases within the hippocampal avoidance region — typically defined as the hippocampus plus a 5 mm margin because these lesions preclude the delivery of a therapeutic dose to the tumour site.^{2,8} The success of HA-WBRT depends on the availability of advanced radiotherapy infrastructure. Although choosing clinical candidates depends on prognostic factors and tumour distribution, the logistical feasibility of HA-WBRT depends on the presence of high-precision planning and delivery technology.

Hippocampal Delineation

Precise contouring of the hippocampus is critical. Magnetic resonance imaging (MRI) fusion with planning computed tomography (CT) scans enhances visualisation and improves contour accuracy. Standardised contouring atlases have been developed to reduce inter-observer variability. In accordance with established consensus guidelines, the hippocampus is delineated on T1-weighted MRI sequences. The hippocampus begins at the level where the temporal horn is most clearly visualised and is delineated as a distinct grey matter structure situated within the medial aspect of the ventricular curvature. Inferiorly, the hippocampus reaches its caudal extent at the level of the pons and pituitary gland. At this level, where the anatomical distinction between the hippocampus and the amygdala becomes indistinct, its boundaries are extrapolated from more superior cross-sections. Superiorly, the hippocampus is contoured as a defined strip of grey matter bordered by cerebrospinal fluid within the lateral ventricle and the ambient cistern, with the cranial terminus identified at the level of the splenium of the corpus callosum.¹² This structured

Study	Sample size (N)	Primary end point	Cognitive outcome	Oncological safety	Clinical impact
RTOG 0933 ¹¹	113	Mean relative decline in memory at 4 months	7% decline (vs. 30% historic)	Non-inferior (retrospective data)	Demonstrated feasibility and memory preservation
NRG Oncology CC001 ⁸	518	Time to neurocognitive failure	26% reduction in risk of cognitive failure	Non-inferior (prospective randomised)	Established as a standard of care approach

Table 1: Summary of clinical outcomes: RTOG 0933 vs. NRG Oncology CC001.

Abbreviation: RTOG: Radiation Therapy Oncology Group.

approach ensures anatomical consistency and minimises inter-observer variability in target volume delineation. A hippocampal avoidance zone is generated by expanding the hippocampal contour by 5 mm volumetrically. This region serves as the primary avoidance structure during optimisation.⁸

Dosimetric Considerations

The delivery of HA-WBRT necessitates high-precision dose-modulation techniques to achieve the steep dose gradients required for effective hippocampal sparing. Currently, this is clinically achieved using IMRT or volumetric modulated arc therapy (VMAT), which can be delivered via conventional linear accelerator (LINAC) platforms or helical tomotherapy units. More recently, intensity-modulated proton therapy (IMPT) has been investigated as an alternative, demonstrating superior dosimetric profiles characterised by enhanced conformity and sparing of healthy brain parenchyma compared with photon-based IMRT or tomotherapy approaches.^{1,2}

Current guidelines recommend hippocampal dose constraints during HA-WBRT to preserve hippocampal function during the standard regimen of 30 Gy in 10 fractions. The mean hippocampal dose (D_{mean}) should be ≤ 9 Gy, with a maximum allowable dose ($D_{0.03\text{cc}}$) of ≤ 16 Gy, permitting minor variations up to 10 Gy and 17 Gy, respectively.^{7,11} It is important to adhere to these strict constraints to maximise the clinical efficacy of HA-WBRT. Studies have shown that HA-WBRT combined

with memantine provides statistically significant preservation of neurocognitive function and reduction in patient-reported symptoms.¹¹ Compliance with these dosimetric parameters is of paramount importance in reducing neurocognitive decline without compromising intracranial disease outcomes. In addition to hippocampal sparing, treatment planning requires a careful balance between restricting lens doses to $\leq 3 - 5$ Gy to reduce the risk of cataract and managing the maximum dose ($D_{\text{max}} \leq 34$ Gy) delivered to healthy brain tissue.¹³

Future Directions

Ongoing investigations into the role of SRS for multiple brain metastases necessitate a strategic repositioning of HA-WBRT, limiting its application to clinical scenarios where the intracranial disease burden renders focal therapy technically infeasible. Concurrently, the emerging paradigm of "memory-avoidance" WBRT (MA-WBRT) represents a technical evolution, expanding the avoidance volume from the hippocampus to include the fornix, amygdala, and corpus callosum to better preserve interconnected cognitive networks.¹⁴ Current research is actively investigating targeted anti-inflammatory and oxidative stress modulators to further enhance neuroprotection; however, these agents remain largely investigational and have not yet been integrated into the standard clinical management paradigm.

Conclusion

The integration of HA-WBRT with memantine represents a paradigm shift towards neuro-preservative oncology. Supported by robust Phase II and III evidence, this combined approach effectively mitigates treatment-associated cognitive decline without compromising intracranial control. As focal stereotactic approaches increasingly manage limited disease, HA-WBRT remains essential for patients with extensive intracranial disease burden. As survival outcomes improve, preserving neurocognitive integrity is important, demanding a continued commitment to precision radiotherapy to ensure both long-term disease control and the preservation of QOL for survivors of brain metastases.

Gayatri Patil, Vansh Parekh, Kaustav Talapatra. Hippocampal Avoidance in Whole Brain Radiotherapy: Biological Basis, Clinical Evidence, and Future Perspectives. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-6>

References

1. Brown PD, Ahluwalia MS, Khan OH, *et al.* Whole-brain radiotherapy for brain metastases: evolution or revolution? *J Clin Oncol.* 2018;36(5):483–91.
2. Liu R, Gong G, Meng K, *et al.* Hippocampal sparing in whole-brain radiotherapy for brain metastases: controversy, technology and the future. *Front Oncol.* 2024;14:1342669.
3. Brown PD, Pugh S, Laack NN, *et al.* Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* 2013;15(10):1429–37.
4. Brain Tumour Facts. National Brain Tumour Society. Available at: <https://braintumour.org/brain-tumours/about-brain-tumours/brain-tumour-facts/>. Accessed on: 29th June 2026.
5. Koo J, Roh TH, Lee SR, *et al.* Whole-brain radiotherapy vs. localized radiotherapy after resection of brain metastases in the era of targeted therapy: a retrospective study. *Cancers.* 2021;13(18):4711.
6. Alare K, Bakwa ND, Nwachukwu IO, *et al.* Whole brain radiotherapy for brain metastases in Nigeria: a systematic review. *Front Public Health.* 2026;14:1868865.
7. Goda JS, Dutta D, Krishna U, *et al.* Hippocampal radiotherapy dose constraints for predicting long-term neurocognitive outcomes: mature data from a prospective trial in young patients with brain tumors. *Neuro Oncol.* 2020;22(11):1677–85.
8. Brown PD, Gondi V, Pugh S, *et al.* Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. *J Clin Oncol.* 2020;38(10):1019–29.
9. Wiegrefe S, Sarria GR, Layer JP, *et al.* Incidence of hippocampal and perihippocampal brain metastases and impact on hippocampal-avoiding radiotherapy: A systematic review and meta-analysis. *Radiother Oncol.* 2024;197:110331.
10. Leskinen S, Shah HA, Yaffe B, *et al.* Hippocampal avoidance in whole brain radiotherapy and prophylactic cranial irradiation: a systematic review and meta-analysis. *J Neurooncol.* 2023;163(3):515–27.
11. Gondi V, Pugh SL, Tome WA, *et al.* Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* 2014;32(34):3810–6.
12. Chera BS, Amdur RJ, Patel P, *et al.* A radiation oncologist's guide to contouring the hippocampus. *Am J Clin Oncol.* 2009;32(1):20–2.
13. Gondi V, Tolakanahalli R, Mehta MP, *et al.* Hippocampal-sparing whole-brain radiotherapy: a “how-to” technique using helical tomotherapy and linear accelerator–based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;78(4):1244–52.
14. Palmer JD, Dawson E, Dibs K, *et al.* An Initial Report of Memory Avoidance Whole Brain Radiotherapy to Treat Brain Metastases: A Prospective Phase 2 Trial. *Int J Radiat Oncol Biol Phys.* 2025;123(1):S35–6.

Radiation Cancer Biology: Mechanisms of Carcinogenesis and Clinical Implications

Albert Paul Varghese^{1*}, Anurag Ashok Luharia², Suhas Tiwaskar², Shreya Naik¹, Ishiqua Vinay Patil³, Arif Hussain Malla¹, Sheikh Mohammed Irfan⁴, Ginesh Job M⁵, Kashmira Patil⁶

¹Department of Radiology, Max Institute of Allied and Paramedical Education (MIAPE), Rohini, Delhi

²Department of Radiology, Datta Meghe Institute of Higher Education & Research

³Department of Hospital Administration, Datta Meghe Institute of Higher Education & Research

⁴Department of Anaesthesia Technology, Jamia Hamdard University

⁵Department of Biomedical Trainer, Medtronic India PVT

⁶Department of Family Medicine, Artemis Hospitals, Gurugram

Correspondence:

Albert Paul Varghese

E-mail: Albert.Varghese@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-7>

Abstract:

Ionising radiation is widely used in diagnostic imaging and cancer therapy; however, it is also a recognised environmental carcinogen. The biological effects of radiation at the molecular and cellular levels form the basis for both tumour eradication and radiation-induced malignancies. This review summarises current understanding of radiation-induced deoxyribonucleic acid (DNA) damage, cellular stress responses, genomic instability, dose-response relationships, and individual radiosensitivity. Recent advances in identifying both radiation-associated mutational signatures as well as in precision radiotherapy approaches are highlighted. Clinical implications for radiotherapy practice and radiation protection are discussed, emphasising the importance of optimising therapeutic benefit while minimising long-term cancer risk.

Key words: Ionising Radiation, Carcinogenesis, Deoxyribonucleic Acid (DNA) Damage, Genomic Instability, Radiotherapy, Radiation Protection, Mutational Signatures.

Introduction

Exposure to ionising radiation often occurs in medical, occupational, environmental, and natural settings. In oncology, radiation is indispensable for tumour control, yet epidemiological and experimental evidence demonstrates that radiation can induce cancer in normal tissues. Radiation cancer biology encompasses the molecular and cellular mechanisms responsible for malignant transformation following exposure, including deoxyribonucleic acid (DNA) damage, repair fidelity, oxidative stress, and long-term genomic instability.

Understanding these mechanisms is critical for improving radiotherapy outcomes, refining radiation protection policies, and guiding emerging strategies

such as radiogenomics and precision radiation medicine. This review provides a contemporary overview of radiation-induced carcinogenesis and its clinical relevance.¹

Mechanisms of Radiation-Induced DNA Damage

Ionising radiation induces DNA damage through both direct and indirect mechanisms, ultimately compromising genomic integrity and cellular homeostasis. The direct mechanism involves the deposition of energy directly onto DNA molecules, resulting in ionisation or excitation of nucleic acids. This energy transfer can break the covalent bonds within the DNA backbone or alter nucleotide bases, leading to structural disruption of the double helix.²

However, in biological systems, the indirect effect predominates, particularly in low-linear energy transfer (LET) radiations, such as X-rays and gamma rays. Since approximately 70% of the cell is composed of water, ionising radiation primarily interacts with water molecules, causing radiolysis of water. This process generates highly reactive free radicals, including hydroxyl radicals (OH), hydrogen radicals (H), and superoxide anions (O₂⁻). Among these, hydroxyl radicals are the most damaging due to their high reactivity and short diffusion distance. These reactive oxygen species (ROS) attack DNA bases and the sugar-phosphate backbone, producing a broad spectrum of lesions.²

The types of DNA damage induced by ionising radiation include:²

- Single-strand breaks (SSBs)
- Double-strand breaks (DSBs)
- DNA-protein crosslinks
- Interstrand crosslinks
- Clustered DNA lesions (locally multiply damaged sites)

Among these, DSBs are considered the most biologically critical lesions. DSBs involve simultaneous breaks in both strands of the DNA helix and can severely disrupt chromosomal integrity. If not accurately repaired, DSBs may lead to chromosomal aberrations such as deletions, inversions, translocations, and amplifications. The two primary repair pathways involved are:

1. Non-homologous end joining (NHEJ): A rapid but error-prone repair mechanism.
2. Homologous recombination (HR): A high-fidelity repair pathway active during the S and G2 phases of the cell cycle.

Misrepair through NHEJ can result in oncogenic mutations and genomic instability, thereby contributing to carcinogenesis. In addition to direct mutagenesis, radiation-induced DNA damage activates complex cellular signalling cascades involving key proteins such as ataxia-telangiectasia mutated (ATM), ataxia telangiectasia and Rad3-related (ATR), and p53, which regulate cell cycle arrest, DNA repair, senescence, or apoptosis.²

High-LET radiation (such as alpha particles, neutrons, and heavy ion beams) produces denser ionisation tracks and more complex, clustered DNA damage compared with low-LET radiation. Clustered lesions are particularly challenging for the cell to repair and significantly increase the probability of mutation and cell death.²

Recent advances in genomic sequencing technologies have provided deeper insight into the long-term consequences of radiation exposure. Studies have identified distinct mutational signatures in radiation-associated tumours. These signatures often include:²

- Large-scale deletions
- Complex chromosomal rearrangements
- Balanced and unbalanced translocations
- Increased small insertion-deletion mutations

Such genomic patterns are now being investigated as potential molecular biomarkers of prior radiation exposure. These mutational signatures help differentiate radiation-induced malignancies from sporadic cancers and enhance our understanding of radiation-related carcinogenesis. Furthermore, integrative genomic analyses suggest that radiation exposure may accelerate clonal evolution, promoting the expansion of mutated cell populations over time.³

Overall, radiation-induced DNA damage represents a multifaceted biological process involving physicochemical interactions, molecular repair pathways, and long-term genomic alterations. Understanding these mechanisms is essential for improving radiation protection strategies, refining radiotherapy protocols, and developing targeted interventions to mitigate radiation-associated cancer risk.

Cellular Responses to Radiation

Cells respond to radiation-induced DNA damage through activation of the DNA damage response network. Key kinases such as ATM and ATR initiate signalling cascades that regulate cell-cycle arrest, DNA repair, and apoptosis via downstream effectors including p53.

Multiple DNA repair pathways operate depending on lesion type, including base excision repair, nucleotide excision repair, homologous recombination, and non-homologous end joining. Accurate repair promotes cell survival, whereas faulty repair can generate mutations and chromosomal instability.

When damage is extensive, cells may undergo apoptosis, senescence, or mitotic catastrophe. Failure of these protective mechanisms increases the probability of malignant transformation.³

Radiation-Induced Carcinogenesis and Genomic Instability

Radiation acts primarily as a tumour initiator by inducing genetic and epigenetic alterations that disrupt growth regulation. Persistent oxidative stress and inflammation can promote clonal expansion of mutated cells, facilitating tumour progression.

Radiation exposure can also induce delayed genomic instability in descendant cells, manifested as chromosomal aberrations, micronuclei formation, and increased mutation rates long after the initial insult. In addition, bystander effects allow non-irradiated neighbouring cells to exhibit DNA damage responses through intercellular signalling, extending the biological impact beyond directly exposed tissues.

Dose-Response Relationships and Risk Models

Cancer induction by radiation is categorised as a stochastic effect, in which the probability but not the severity of cancer increases with dose. Radiation protection frameworks generally rely on the linear no-threshold model, which assumes that even very low doses confer some risk. Although this model remains controversial at low doses, it continues to guide regulatory standards and occupational safety practices.²

Individual Radiosensitivity and Radiogenomics

Inter-individual variability in radiation response is influenced by genetic polymorphisms and mutations in DNA repair and cell-cycle genes such as TP53, ATM, and breast cancer gene 1 and 2 (BRCA1/2). The emerging field of radiogenomics seeks to integrate genomic data into treatment planning, enabling personalisation of radiation dose, and fractionation to reduce toxicity and secondary cancer risk while maintaining tumour control.^{2,4,5}

Clinical Implications

Radiotherapy and secondary malignancies

Modern radiotherapy techniques, including intensity-modulated radiotherapy, image-guided radiotherapy, proton therapy, and ultra-high dose-rate FLASH radiotherapy, aim to maximise tumouricidal effects while sparing surrounding normal tissues. Nevertheless, long-term cancer survivors may develop radiation-induced secondary malignancies decades after treatment, particularly in tissues receiving low or moderate scattered doses.^{6–8}

Radiation protection in medical practice

Healthcare workers exposed to chronic low-dose radiation, such as interventional radiologists and cardiologists demonstrate biomarkers of DNA damage and may carry increased long-term cancer risk. Strict adherence to justification, optimisation following the as low as reasonably achievable (ALARA) principle, and dose limitation is essential in both diagnostic and therapeutic settings.^{9,10}

Conclusion

Radiation cancer biology involves a complex interplay between DNA damage, cellular stress responses, genomic instability, and host susceptibility. While radiation remains a cornerstone of cancer management, its carcinogenic potential necessitates continual refinement of treatment strategies and protective measures. Advances in molecular biology, mutational signature analysis, and radiogenomics are expected to further personalise radiation use and mitigate long-term risks.

Albert Paul Varghese, Anurag Ashok Luharia, Suhas Tiwaskar, Shreya Naik, Ishiqua Vinay Patil, Arif Hussain Malla, Sheikh Mohammed Irfan, Ginesh Job M, Kashmira Patil. Radiation Cancer Biology: Mechanisms of Carcinogenesis and Clinical Implications. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-7>

References

1. Daino K, Tsuruoka C, Ishikawa A, et al. Mutational signatures in radiation-induced cancer: experimental animal and human studies. *Biology*. 2025;14(9):1142.
2. Wei W, Ren Y, Lan J, et al. Ionizing radiation: molecular mechanisms, biological effects, and therapeutic targets. *Mol Biomed*. 2026;7(1):3.
3. Hu Z, Chen Y, Yang S, et al. Radiation-induced biological effects: molecular and cellular mechanisms and applications to cancer therapy. *Mol Clin Oncol*. 2025;23;6(12):e70478.
4. Maris EL, Klaassen J, Hazenberg CEVB, et al. Radiation-induced DNA damage and cancer risk in endovascular operators: a systematic review. *J Vasc Surg*. 2025;82(6):2283–97.
5. Battestini M, Missiaggia M, Bolzoni S, et al. Multiscale radiation biophysical modeling of cell survival at ultra-high dose rate. arXiv:2412.16322. 2024;1–15.
6. Yusufaly T, Abdollahi H, Saboury B, et al. Quantitative and computational radiobiology for precision radiopharmaceutical therapies. *PET Clin*. 2026;21(1):133–42.
7. Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 8th Edition. Philadelphia: Wolters Kluwer; 2019.
8. Tubiana M, Aurengo A, Averbeck D, et al. The debate on the use of linear no-threshold for assessing the effects of low doses. *J Radiol Prot*. 2006;26(3):317–24.
9. Little MP, Azizova TV, Bazyka D, et al. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. *Environ Health Perspect*. 2012;120(11):1503–11.
10. UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 2020/2021. Volume I-Report to the General Assembly. Scientific Annex A: Evaluation of medical exposure to ionizing radiation. 2021. Available at: https://www.unscear.org/unscear/en/publications/2020_2021_1.html. Accessed on: 20th March 2026.

Beyond the Pill – The Future of Lipid-Lowering Therapy: A 2026 Review of Novel Lipid-Lowering Agents

Aryan Arora^{1*}, Monica Mahajan¹

¹Department of Internal Medicine, Max Super Speciality Hospital, Saket, Delhi

Correspondence:

Aryan Arora

E-mail: draryan.arorapg96@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-8>

Abstract:

Despite the success of statins, many patients with dyslipidaemia continue to have residual cardiovascular risk because of persistent low-density lipoprotein cholesterol (LDL-C) elevation, statin intolerance, hypertriglyceridaemia, or elevated lipoprotein(a) [Lp(a)]. Recent advances in molecular biology have led to the development of targeted lipid-lowering therapies, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, adenosine triphosphate-citrate lyase (ACL) inhibitors, apolipoprotein C-III (ApoC-III) inhibitors, angiopoietin-like protein 3 (ANGPTL3) inhibitors, Lp(a)-lowering agents, and gene-editing technologies. This review summarises the mechanisms of action, landmark clinical trials, lipid-lowering efficacy, safety, and current clinical applications of these novel agents, with emphasis on therapies introduced since 2018. Collectively, these agents have expanded treatment options for patients with familial dyslipidaemia, severe hypertriglyceridaemia, and persistent residual cardiovascular risk while paving the way for precision medicine. As ongoing cardiovascular outcome studies and gene-editing technologies mature, these advances are expected to reshape the future of dyslipidaemia management and cardiovascular prevention.

Key words: Dyslipidaemia, Atherosclerotic Cardiovascular Disease (ASCVD), Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors, Inclisiran, ApoC-III, Angiopoietin-Like Protein 3 (ANGPTL3), Lipoprotein(a), Gene-Editing, Precision Medicine.

Introduction¹⁻³

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide, with dyslipidaemia being one of its most important modifiable risk factors. Elevated low-density lipoprotein cholesterol (LDL-C) plays a central role in the initiation and progression of atherosclerosis, making LDL-C reduction the cornerstone of cardiovascular risk prevention. Over the past three decades, statins have revolutionised dyslipidaemia management, significantly reducing cardiovascular events and mortality. The subsequent introduction of ezetimibe, fibrates, bile acid sequestrants, and omega-3 fatty acids further

expanded therapeutic options for selected patient populations.

Despite these advances, a substantial residual cardiovascular risk persists. Many high-risk patients fail to achieve recommended LDL-C targets despite maximally tolerated lipid-lowering therapy, while others are unable to tolerate intensive statin treatment. In addition, conventional therapies have limited effects on important contributors to residual lipid risk, including elevated lipoprotein(a) [Lp(a)], remnant cholesterol, and severe hypertriglyceridaemia. These unmet clinical needs have driven the search for therapies targeting novel pathways involved in lipid metabolism.

Recent advances in molecular biology and lipid metabolism have transformed the therapeutic landscape of dyslipidaemia. Novel targets such as proprotein convertase subtilisin/kexin type 9 (PCSK9), adenosine triphosphate-citrate lyase (ACL), angiopoietin-like protein 3 (ANGPTL3), apolipoprotein C-III (ApoC-III), and Lp(a) have led to the development of innovative therapies, including monoclonal antibodies, small interfering ribonucleic acid (siRNA), antisense oligonucleotides (ASOs), and oral small-molecule inhibitors. These agents provide potent lipid-lowering through highly specific mechanisms and have expanded treatment options for patients with familial hypercholesterolaemia, statin intolerance, severe hypertriglyceridaemia, and established ASCVD.

The period since 2018 has marked a new era in lipid-lowering pharmacotherapy, with several novel agents receiving regulatory approval and demonstrating significant lipid-lowering efficacy and cardiovascular benefit in large randomised clinical trials.

The recent development of oral PCSK9 inhibitors further represents an important milestone, offering the potential advantages of potent LDL-C reduction with the convenience of oral administration.

This review focuses on the novel lipid-lowering agents approved or introduced into clinical practice since 2018. We summarise their mechanisms of action, pharmacological properties, dosing strategies, landmark clinical trials, efficacy, safety, and emerging role in contemporary dyslipidaemia management,

highlighting how these therapies are reshaping the future of precision cardiovascular prevention.

Evolution of Lipid-Lowering Therapy⁴

Lipid-lowering therapy has evolved from conventional agents to highly targeted therapies driven by advances in molecular biology and human genetics. The introduction of statins in the late 1980s revolutionised dyslipidaemia management, followed by ezetimibe, fibrates, bile acid sequestrants, niacin, and omega-3 fatty acids, which broadened treatment options for specific lipid abnormalities.

Despite these advances, many high-risk patients continued to have residual cardiovascular risk and failed to achieve recommended LDL-C targets, highlighting the need for novel therapeutic approaches. The discovery of the PCSK9 pathway marked a major breakthrough, leading to monoclonal antibodies and later siRNA-based therapies capable of producing profound and sustained LDL-C reduction.

Since 2018, the field has expanded rapidly with the introduction of ACL inhibitors, oral PCSK9 inhibitors, and emerging therapies targeting ANGPTL3, ApoC-III, and Lp(a) as shown in Figure 1.

These innovations have ushered in an era of precision lipid management, where therapy is tailored to individual lipid profiles, genetic disorders, and cardiovascular risk.

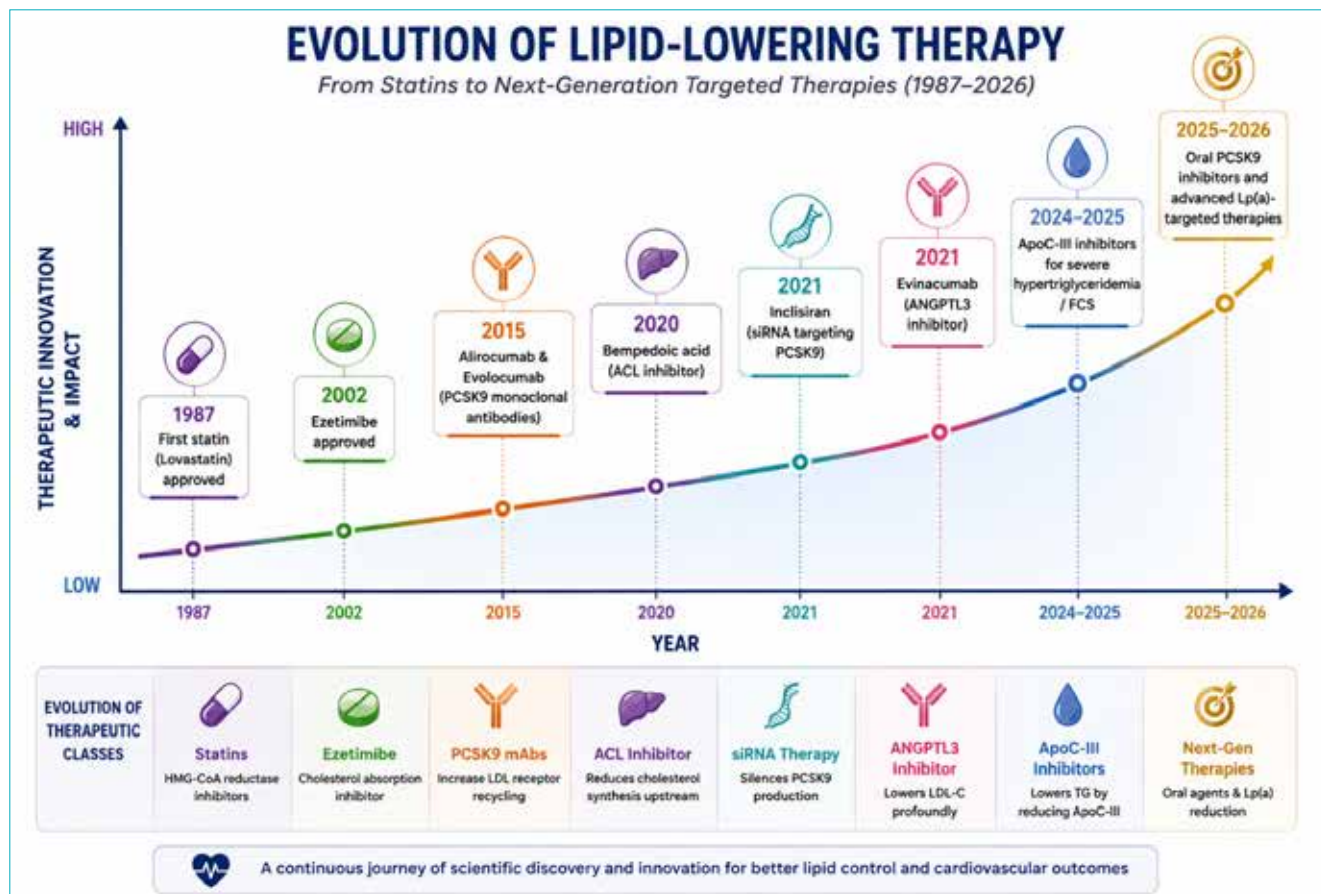


Figure 1: Evolution of lipid-lowering therapy – From statins to precision ribonucleic acid (RNA)-targeted therapeutics (1987 – 2026).
Abbreviations: ACL: Adenosine Triphosphate-Citrate Lyase; ANGPTL3: Angiopoietin-Like Protein 3; ApoC-III: Apolipoprotein C-III; FCS: Familial Chylomicronaemia Syndrome; LDL-C: Low-Density Lipoprotein Cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; siRNA: Small Interfering Ribonucleic Acid.

Overall Classification of Anti-Dyslipidaemic Agents

The expanding armamentarium of lipid-lowering therapies acts through diverse molecular pathways, enabling targeted management of specific lipid abnormalities and cardiovascular risk.

A. Drugs decreasing absorption of lipids

Intestinal cholesterol absorption represents the first therapeutic target in lipid management. Drugs acting at this level reduce the entry of dietary and biliary cholesterol into the circulation by inhibiting cholesterol transport, esterification, or enterohepatic bile acid recycling, thereby lowering hepatic cholesterol stores and promoting LDL receptor-mediated clearance of circulating LDL-C, as shown in Figure 2.

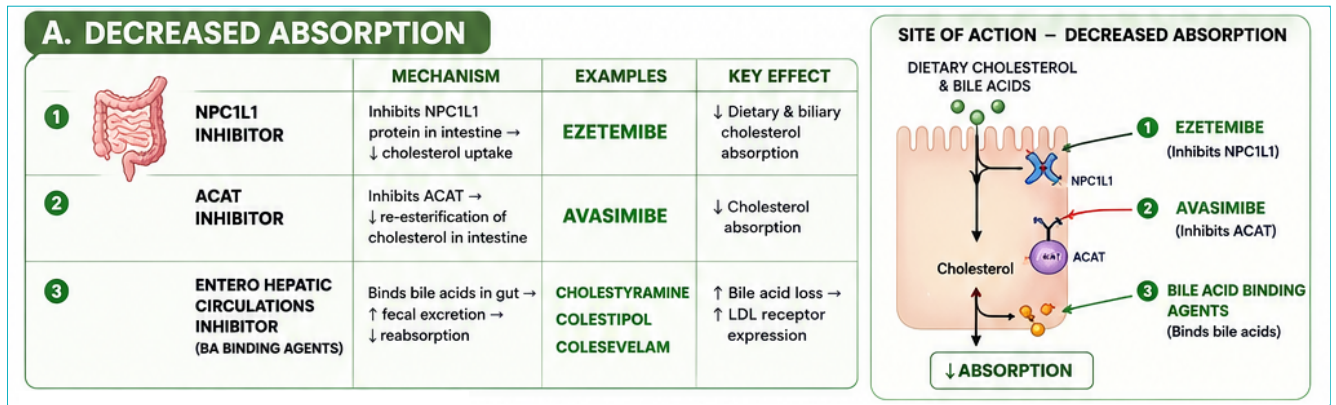


Figure 2: Drugs decreasing absorption of lipids.

Abbreviations: ACAT: Acyl-Coenzyme A:Cholesterol Acyltransferase; BA: Bile Acid; LDL: Low-Density Lipoprotein; NPC1L1: Niemann-Pick C1-Like 1.

B. Drugs decreasing synthesis of lipids

Reducing hepatic lipoprotein synthesis is a fundamental strategy in the management of dyslipidaemia. In addition to statins, several newer therapies target specific molecular pathways involved in the production

of cholesterol, very low-density lipoprotein (VLDL), triglycerides, and Lp(a), offering effective treatment options for patients with refractory or genetically determined lipid disorders, as shown in Figure 3.

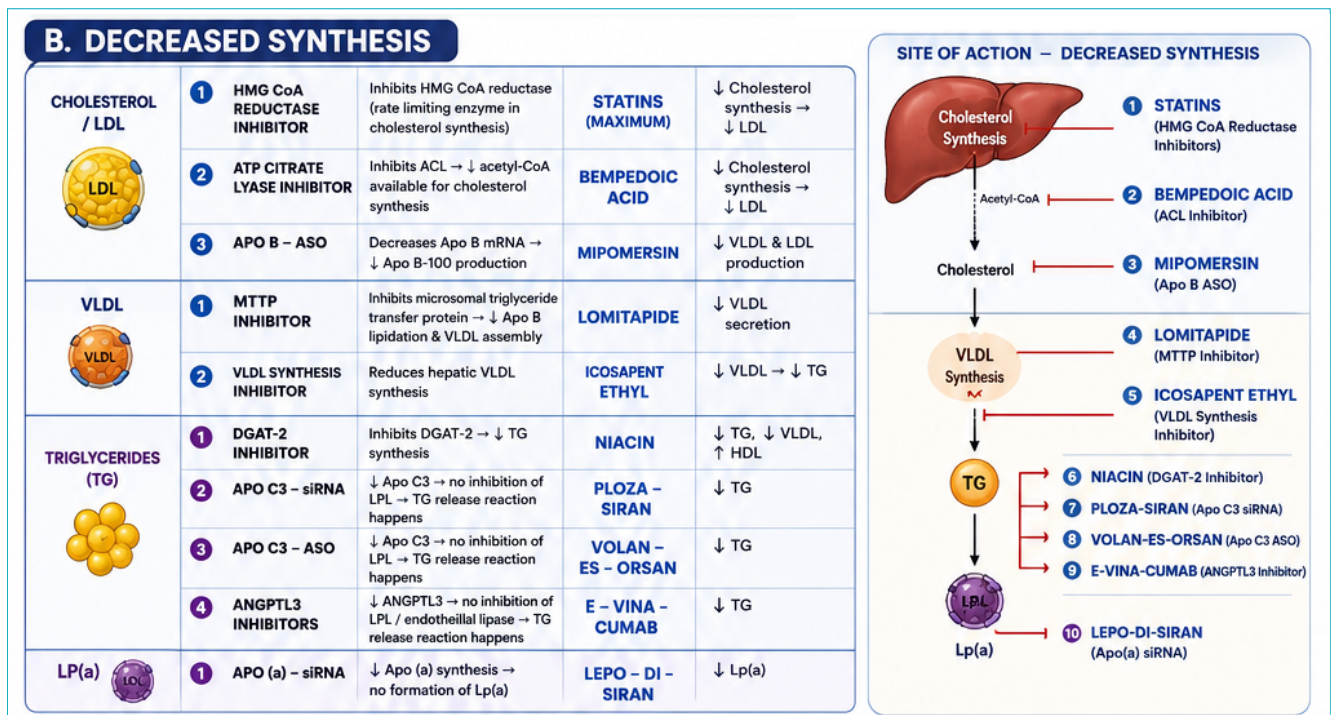


Figure 3: Drugs decreasing synthesis of lipids.

Abbreviations: ACL: ATP Citrate Lyase; ANGPTL3: Angiopoietin-Like Protein 3; Apo: Apolipoprotein; Apo B: Apolipoprotein B; Apo B-100: Apolipoprotein B-100; Apo C3: Apolipoprotein C3; ASO: Antisense Oligonucleotide; ATP: Adenosine Triphosphate; CoA: Coenzyme A; DGAT-2: Diacylglycerol Acyltransferase 2; HDL: High-Density Lipoprotein; HMG CoA: 3-Hydroxy-3-Methylglutaryl Coenzyme A; LDL: Low-Density Lipoprotein; Lp(a): Lipoprotein(a); LPL: Lipoprotein Lipase; mRNA: Messenger Ribonucleic Acid; MTTP: Microsomal Triglyceride Transfer Protein; siRNA: Small Interfering Ribonucleic Acid; TG: Triglycerides; VLDL: Very Low-Density Lipoprotein.

C. Drugs causing increased removal of lipids from blood

Increasing the clearance of circulating lipoproteins is a key therapeutic strategy in the management of dyslipidaemia. This is achieved by enhancing hepatic LDL receptor recycling through PCSK9 inhibition to lower LDL-C, or by stimulating lipoprotein lipase (LPL) activity with peroxisome proliferator-activated receptor alpha (PPAR- α) agonists to accelerate the clearance of triglyceride-rich lipoproteins. Recent therapies, including monoclonal antibodies, siRNA, and oral PCSK9 inhibitors, have further improved the efficacy and durability of lipid-lowering, as shown in Figure 4.

Individual New Drug Classes

A. PCSK9 inhibition-based therapies (Monoclonal antibodies and siRNA)^{3,5}

PCSK9 inhibitors represent one of the most important advances in lipid-lowering pharmacotherapy over the past decade. PCSK9 is a hepatic serine protease that promotes lysosomal degradation of LDL receptors, thereby reducing hepatic LDL receptor recycling and increasing circulating LDL-C. Therapeutic inhibition of PCSK9 increases the number of functional LDL

receptors on hepatocytes, resulting in enhanced clearance of LDL-C and substantial reductions in cardiovascular risk. Currently, three approaches to PCSK9 inhibition are available: monoclonal antibodies, siRNA, and oral PCSK9 inhibitors.

1. Monoclonal antibodies (Alirocumab and evolocumab)^{6,7}

Mechanism of action: Alirocumab and evolocumab are fully human monoclonal antibodies that bind circulating PCSK9, preventing its interaction with LDL receptors. This preserves LDL receptor recycling, increases hepatic uptake of LDL particles, and produces profound reductions in circulating LDL-C levels.

Pivotal clinical trials: The efficacy and cardiovascular benefits of monoclonal antibody therapy were established by the FOURIER trial, which demonstrated that evolocumab reduced LDL-C by approximately 59% and significantly lowered major adverse cardiovascular events in patients with established ASCVD receiving statin therapy. Similarly, the ODYSSEY OUTCOMES trial showed that alirocumab significantly reduced recurrent cardiovascular events in patients following acute coronary syndrome.^{6,7}

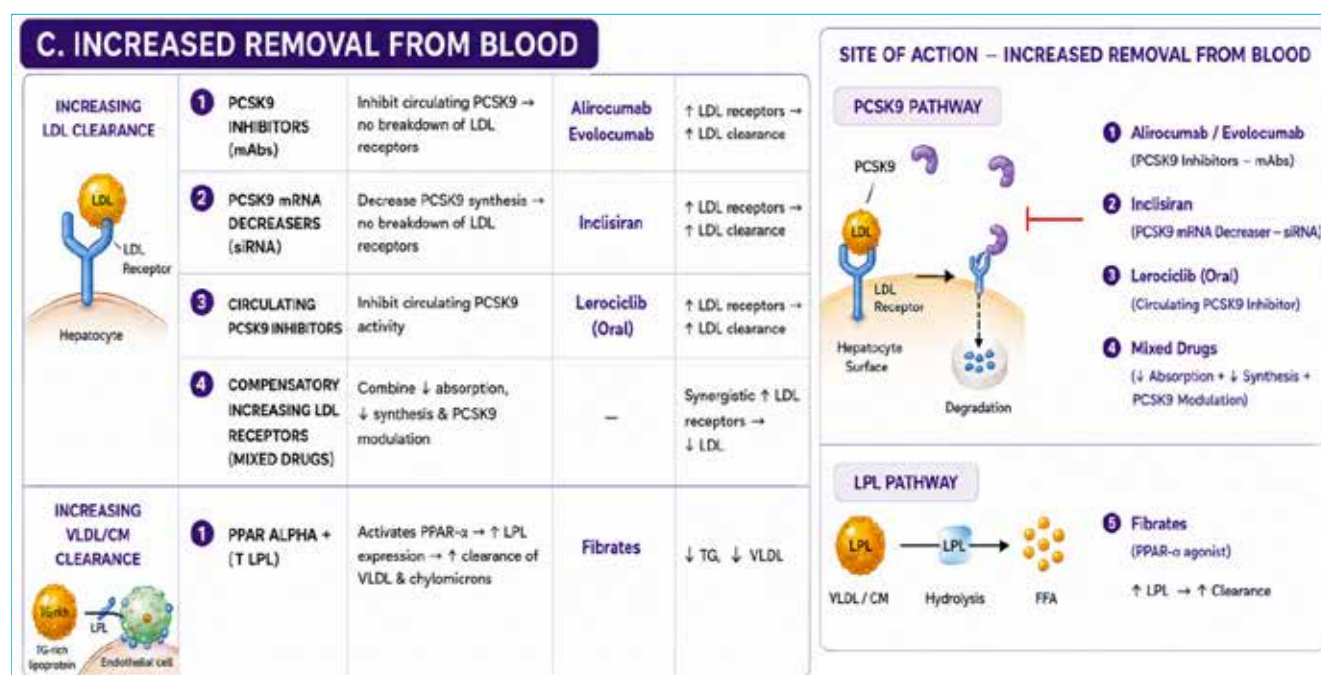


Figure 4: Drugs causing increased removal of lipids from blood.

Abbreviations: CM: Chylomicrons; FFA: Free Fatty Acids; LDL: Low-Density Lipoprotein; LPL: Lipoprotein Lipase; mAbs: Monoclonal Antibodies; mRNA: Messenger Ribonucleic Acid; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; PPAR- α : Peroxisome Proliferator-Activated Receptor Alpha; siRNA: Small Interfering Ribonucleic Acid; TG: Triglycerides; VLDL: Very Low-Density Lipoprotein.

Primary lipid-lowering effects: Monoclonal antibodies reduce LDL-C by approximately 50% – 65%, while also lowering apolipoprotein B (Apo B) by 40% – 50%, non-high-density lipoprotein (non-HDL) cholesterol by 45% – 55%, triglycerides by 10% – 20%, and Lp(a) by 20% – 30%.

Indications and uses: These agents are indicated as add-on therapy to maximally tolerated statins, with or without ezetimibe, in patients with established ASCVD or familial hypercholesterolaemia requiring further LDL-C reduction. They are also valuable in selected patients with statin intolerance and homozygous familial hypercholesterolaemia.

Dose: Alirocumab is administered subcutaneously at a dose of 75 mg every two weeks, which may be increased to 150 mg every two weeks if additional LDL-C reduction is required. Evolocumab is administered as 140 mg every two weeks or 420 mg once monthly by subcutaneous injection.

Side effects: Monoclonal antibodies are generally well tolerated. The most common adverse effects include injection-site reactions, nasopharyngitis, upper respiratory tract infections, influenza-like illness, arthralgia, and myalgia.

Important points: Monoclonal antibodies are currently the only PCSK9-targeted therapies with robust evidence demonstrating reductions in major adverse cardiovascular events. Their principal limitations are high cost and the need for long-term subcutaneous administration.

2. siRNA (Inclisiran)^{8,9}

Mechanism of action: Inclisiran is an N-acetylgalactosamine (GalNAc)-conjugated siRNA that selectively targets hepatocytes, where it degrades PCSK9 messenger RNA (mRNA) through the RNA-induced silencing complex (RISC). This suppresses hepatic PCSK9 synthesis, enhances LDL receptor recycling, and produces sustained LDL-C reduction.

Pivotal clinical trials: The ORION-9, ORION-10, and ORION-11 trials demonstrated sustained reductions in LDL-C of approximately 50% in patients with heterozygous familial hypercholesterolaemia and ASCVD receiving maximally tolerated lipid-lowering therapy. Cardiovascular outcome trials, including

ORION-4 and VICTORION-2 PREVENT, are currently ongoing.^{8,9}

Primary lipid-lowering effects: Inclisiran lowers LDL-C by approximately 45% – 52%, with additional reductions in Apo B, non-HDL cholesterol, and Lp(a), while producing modest reductions in triglycerides.

Indications and uses: Inclisiran is approved as an adjunct to diet and maximally tolerated statin therapy in adults with primary hypercholesterolaemia or heterozygous familial hypercholesterolaemia requiring additional LDL-C reduction. It is particularly advantageous in patients requiring long-term lipid control with infrequent dosing.

Dose: Inclisiran is administered as a 284 mg subcutaneous injection on Day 1, at Month 3, and every six months thereafter.

Side effects: Injection-site reactions are the most frequently reported adverse effect. Other adverse events, including arthralgia, bronchitis, diarrhoea, and urinary tract infections, are generally mild and infrequent.

Important points: The major advantage of inclisiran is its twice-yearly maintenance dosing, which may improve long-term adherence. Although LDL-C lowering is well established, cardiovascular outcome data are still awaited.

3. Oral PCSK9 inhibitor (Enlincitide)¹⁰

Mechanism of action: Enlincitide is the first orally administered macrocyclic peptide PCSK9 inhibitor. It binds circulating PCSK9 with high affinity, preventing its interaction with LDL receptors and thereby increasing LDL receptor recycling and hepatic LDL clearance.

Pivotal clinical trials: The efficacy and safety of enlincitide have been demonstrated in the CORALreef clinical trial programme, which has shown substantial LDL-C reductions with favourable tolerability. Long-term cardiovascular outcome studies are currently underway.

Primary lipid-lowering effects: Enlincitide produces LDL-C reductions of approximately 50% – 60%, while also lowering Apo B, non-HDL cholesterol, and Lp(a), with minimal effects on triglycerides.

Indications and uses: Enlicitide is approved as an adjunct to diet and maximally tolerated statin therapy in adults with primary hypercholesterolaemia who require additional LDL-C lowering, particularly those who prefer an oral alternative to injectable therapy.

Dose: The recommended dose is 20 mg orally once daily and should be taken on an empty stomach to optimise absorption.

Side effects: The most commonly reported adverse effects include nasopharyngitis, headache, diarrhoea, upper respiratory tract infections, and mild gastrointestinal symptoms.

Important points: Enlicitide is the first oral PCSK9 inhibitor and represents a major advance in lipid-lowering therapy by combining the efficacy of PCSK9 inhibition with the convenience of oral administration. Long-term cardiovascular outcome data are awaited to define its role alongside injectable PCSK9-targeted therapies.

B. ApoC-III-lowering therapies³

ApoC-III is a key regulator of triglyceride metabolism that inhibits LPL-mediated hydrolysis of triglyceride-rich lipoproteins and delays their hepatic clearance. Elevated ApoC-III levels contribute to severe hypertriglyceridaemia, familial chylomicronaemia syndrome (FCS), multifactorial chylomicronaemia syndrome (MCS), and an increased risk of acute pancreatitis. Therapeutic inhibition of ApoC-III has emerged as a promising strategy for reducing triglycerides and remnant lipoproteins. Two major approaches are currently under development or clinical use: ASOs and siRNA.

1. ASO (Olezarsen)¹¹

Mechanism of action: Olezarsen is a GalNAc-conjugated ASO that selectively targets hepatocytes and binds to APOC3 mRNA, promoting its degradation through RNase H1. This reduces hepatic ApoC-III synthesis, enhances LPL activity, accelerates the clearance of triglyceride-rich lipoproteins, and markedly lowers plasma triglyceride levels.

Pivotal clinical trials: The efficacy and safety of olezarsen were demonstrated in the BALANCE trial, which showed significant triglyceride reduction in patients with familial chylomicronaemia syndrome. Earlier Phase II studies also

demonstrated substantial reductions in triglycerides and ApoC-III levels with an improved safety profile compared with the first-generation ASO, volanesorsen.

Primary lipid-lowering effects: Olezarsen reduces triglycerides by approximately 50% – 70% and ApoC-III by 70% – 90%, with modest reductions in non-HDL cholesterol and remnant lipoproteins. It has minimal effects on LDL-C.

Indications and uses: Olezarsen is approved for adults with FCS to reduce triglyceride levels and lower the risk of recurrent acute pancreatitis. It is also being investigated in patients with severe hypertriglyceridaemia and MCS.

Dose: Olezarsen is administered as a subcutaneous injection, with dosing based on the approved regimen (typically 80 mg monthly or 50 mg every four weeks, depending on the indication and regulatory approval).

Side effects: The most common adverse effects include injection-site reactions, mild influenza-like symptoms, arthralgia, and transient elevations in liver enzymes. Unlike volanesorsen, clinically significant thrombocytopenia is uncommon.

Important points: Olezarsen is a second-generation GalNAc-conjugated ASO with improved hepatocyte targeting and a superior safety profile compared with earlier ApoC-III inhibitors. It represents an important advance in the management of severe hypertriglyceridaemia and FCS.

2. siRNA (Plozasiran)¹²

Mechanism of action: Plozasiran is a GalNAc-conjugated siRNA that selectively targets hepatocytes and degrades APOC3 mRNA through the RISC. This suppresses hepatic ApoC-III production, enhances LPL activity, promotes clearance of triglyceride-rich lipoproteins, and produces sustained triglyceride lowering.

Pivotal clinical trials: The SHASTA-2 trial demonstrated marked reductions in triglyceride levels in patients with FCS, while the MUIR study showed similar efficacy in patients with severe hypertriglyceridaemia. These studies also demonstrated reductions in pancreatitis episodes and favourable tolerability.

Primary lipid-lowering effects: Plozasiran reduces triglycerides by approximately 70% – 80% and ApoC-III by 80% – 90%, with additional reductions in remnant

cholesterol and modest decreases in non-HDL cholesterol. LDL-C is generally unchanged or may increase slightly because of enhanced lipolysis.

Indications and uses: Plozasiran is indicated for patients with FCS and is being evaluated for severe hypertriglyceridaemia and MCS.

Dose: Plozasiran is administered as a subcutaneous injection every 3 – 6 months, depending on the dosing regimen evaluated in clinical trials.

Side effects: Plozasiran is generally well tolerated, with mild injection-site reactions, nasopharyngitis, headache, and upper respiratory tract infections being the most commonly reported adverse effects.

Important points: Plozasiran provides prolonged triglyceride lowering with infrequent dosing and has shown promising reductions in pancreatitis risk. Compared with ASOs, siRNA therapy offers a longer duration of action and may improve treatment adherence, although long-term cardiovascular outcome studies are still awaited.

C. ANGPTL3 inhibitors^{3,13}

ANGPTL3 is a liver-derived glycoprotein that inhibits both LPL and endothelial lipase, thereby impairing the metabolism of triglyceride-rich lipoproteins and LDLs. Individuals with loss-of-function mutations in the ANGPTL3 gene have markedly reduced plasma levels of LDL-C, triglycerides, and HDL-C, with a significantly lower risk of ASCVD. These observations have led to the development of ANGPTL3-targeted therapies, particularly for patients with severe or refractory hypercholesterolaemia.

1. Monoclonal antibody (Evinacumab)

Mechanism of action: Evinacumab is a fully human monoclonal antibody that binds and neutralises circulating ANGPTL3, thereby relieving inhibition of LPL and endothelial lipase. This enhances the clearance of triglyceride-rich lipoproteins and LDL particles, producing significant reductions in LDL-C, triglycerides, and other atherogenic lipoproteins. Unlike PCSK9 inhibitors, evinacumab lowers LDL-C through a mechanism that is largely independent of LDL receptor activity, making it particularly effective in patients with homozygous familial hypercholesterolaemia (HoFH).

Pivotal clinical trials: The efficacy of evinacumab was established in the ELIPSE HoFH trial, which demonstrated a 47% reduction in LDL-C compared with placebo in patients with HoFH despite maximally tolerated lipid-lowering therapy. Additional studies have confirmed its sustained lipid-lowering efficacy and favourable safety profile in patients with severe hypercholesterolaemia.¹³

Primary lipid-lowering effects: Evinacumab reduces LDL-C by approximately 45% – 50%, triglycerides by 40% – 60%, and also lowers non-HDL cholesterol and ApoB. HDL-C may decrease modestly because of enhanced endothelial lipase activity.

Indications and uses: Evinacumab is approved as an adjunct to other lipid-lowering therapies for adults and children aged 5 years and older with HoFH. It is particularly beneficial in patients with minimal or absent LDL receptor function who respond poorly to statins and PCSK9 inhibitors.

Dose: Evinacumab is administered as an intravenous infusion of 15 mg/kg every four weeks.

Side effects: The most common adverse effects include nasopharyngitis, influenza-like illness, dizziness, fatigue, nausea, infusion-related reactions, and mild upper respiratory tract infections. It is generally well tolerated, with serious adverse events being uncommon.

Important points: Evinacumab is the first ANGPTL3 inhibitor approved for clinical use and is unique in lowering LDL-C independently of LDL receptor function. This distinguishes it from statins and PCSK9 inhibitors and makes it an important therapeutic option for patients with homozygous familial hypercholesterolaemia who have limited treatment alternatives. Ongoing studies are evaluating its potential role in broader populations with refractory hypercholesterolaemia and severe mixed dyslipidaemia.

D. Lp(a)-lowering therapies¹⁴

Lp(a) is an LDL-like lipoprotein in which ApoB-100 is covalently linked to apolipoprotein(a). Elevated Lp(a) is a genetically determined and independent risk factor for ASCVD and calcific aortic valve stenosis. Conventional lipid-lowering therapies have little or no effect on Lp(a), creating a major unmet therapeutic need. Recent advances in RNA-based therapeutics have led to the development of ASOs and siRNA therapies that

specifically target hepatic LPA gene expression and achieve profound reductions in circulating Lp(a).

1. ASO (Pelacarsen)¹⁵

Mechanism of action: Pelacarsen is a GalNAc-conjugated ASO that selectively targets hepatocytes and binds to LPA mRNA, promoting its degradation through RNase H1. This suppresses hepatic synthesis of apolipoprotein(a), resulting in marked reductions in circulating Lp(a) levels.

Pivotal clinical trials: The efficacy of pelacarsen was demonstrated in a Phase II dose-ranging trial, which showed dose-dependent reductions in Lp(a) of up to 80%. Its effect on cardiovascular outcomes is currently being evaluated in the ongoing Lp(a) HORIZON Phase III trial.

Primary lipid-lowering effects: Pelacarsen reduces Lp(a) by approximately 70% – 80%, with minimal effects on LDL-C, HDL-C, and triglycerides.

Indications and uses: Pelacarsen is currently under investigation for patients with established ASCVD and elevated Lp(a) who remain at high cardiovascular risk despite optimal lipid-lowering therapy.

Dose: Pelacarsen is administered as a subcutaneous injection, with dosing schedules evaluated in clinical trials ranging from monthly to every 4 weeks.

Side effects: The most commonly reported adverse effects include injection-site reactions, influenza-like symptoms, and mild elevations in liver enzymes. Overall, the drug has demonstrated a favourable safety profile.

Important points: Pelacarsen is the most advanced ASO targeting Lp(a) and is the first agent specifically developed to determine whether selective Lp(a) reduction translates into improved cardiovascular outcomes.

2. siRNA (Olpasiran, Lepodisiran, Zerlasiran)^{16,17}

Mechanism of action: Olpasiran, lepodisiran, and zerlasiran are GalNAc-conjugated siRNAs that selectively target hepatocytes and degrade LPA mRNA through the RISC. This suppresses hepatic production of

apolipoprotein(a), leading to profound and sustained reductions in circulating Lp(a) levels.

Pivotal clinical trials: Olpasiran demonstrated reductions in Lp(a) exceeding 95% in the OCEAN(a)-DOSE trial and is currently being evaluated in the Phase III OCEAN(a)-Outcomes trial. Lepodisiran produced sustained Lp(a) reductions of over 90% for up to one year following a single dose in the ALPACA Phase II study. Zerlasiran has also shown robust Lp(a)-lowering in early-phase clinical trials and is undergoing further evaluation.

Primary lipid-lowering effects: These siRNA therapies reduce Lp(a) by approximately 90% – 98%, with little or no effect on LDL-C, HDL-C, or triglycerides.

Indications and uses: These agents are being developed for patients with elevated Lp(a) and established ASCVD or those at high cardiovascular risk, particularly when residual risk persists despite optimal LDL-C lowering.

Dose: Olpasiran, lepodisiran, and zerlasiran are administered by subcutaneous injection, with dosing intervals ranging from every 3 to 6 months, depending on the agent and clinical trial protocol.

Side effects: The most frequently reported adverse effects are mild injection-site reactions, nasopharyngitis, headache, and influenza-like symptoms. Serious adverse events have been uncommon in clinical studies.

Important points: siRNA therapies produce the most profound and durable reductions in Lp(a) reported to date, with the potential for dosing only two to four times per year. Although lipid-lowering efficacy is well established, ongoing cardiovascular outcome trials will determine whether selective Lp(a) reduction translates into meaningful reductions in cardiovascular events.

Combined Comparison Table (Table 1)

Drug/Class	Molecular Target	Technology	Dose & Route	Primary Lipid Effect	Approximate Lipid Reduction	Major Clinical Trial(s)	Current Clinical Status / Major Indication
 Alirocumab / Evolocumab	PCSK9	Monoclonal antibody	SC; Alirocumab 75–150 mg Q2W or 300 mg monthly; Evolocumab 140 mg Q2W or 420 mg monthly	↓ LDL-C	50–65% LDL-C	FOURIER, ODYSSEY OUTCOMES	Approved; ASCVD, HeFH, HoFH
 Inclisiran	PCSK9 mRNA	siRNA	SC 284 mg on Day 1, Month 3, then every 6 months	↓ LDL-C	45–52% LDL-C	ORION-9, ORION-10, ORION-11	Approved; ASCVD, HeFH
 Evinacumab	PCSK9	Oral macrocyclic peptide	20 mg orally once daily	↓ LDL-C	50–60% LDL-C	CORALreef Program	Emerging oral PCSK9 inhibitor
 Bempedoic Acid	ATP-citrate lyase (ACL)	Small molecule	180 mg orally once daily	↓ LDL-C	18–25% LDL-C	CLEAR Harmony, CLEAR Wisdom, CLEAR Outcomes	Approved; ASCVD, HeFH, Statin intolerance
 Evinacumab	ANGPTL3	Monoclonal antibody	IV 15 mg/kg every 4 weeks	↓ LDL-C & TG	45–50% LDL-C; 40–60% TG	ELIPSE HoFH	Approved; HoFH
 Olezarsen	ApoC-III mRNA	ASO	SC 80 mg monthly (or approved regimen)	↓ Triglycerides	50–70% TG	BALANCE	Approved; Familial chylomicronemia syndrome
 Plazasiran	ApoC-III mRNA	siRNA	SC every 3–6 months	↓ Triglycerides	70–80% TG	SHASTA-2, MUIR	Investigational; FCS & severe hypertriglyceridemia
 Polocarsen	LPA mRNA	ASO	SC monthly (investigational regimen)	↓ Lipoprotein(a)	70–80% Lp(a)	Lp(a) HORIZON	Phase III
 Olpasiran	LPA mRNA	siRNA	SC every 3–6 months	↓ Lipoprotein(a)	90–98% Lp(a)	OCEAN(a)-DOSE, OCEAN(a)-Outcomes	Phase III
 Lepodisiran	LPA mRNA	siRNA	SC every 5–12 months*	↓ Lipoprotein(a)	>90% Lp(a)	ALPACA	Phase II
 Zerlasiran	LPA mRNA	siRNA	SC every 3–6 months*	↓ Lipoprotein(a)	~90% Lp(a)	Early-phase studies	Phase II

* Dosing interval under investigation and may be extended based on clinical trial outcomes.

Table 1: Combined comparison table of new anti-dyslipidaemic drugs.

Abbreviations: ACL: ATP Citrate Lyase; ANGPTL3: Angiopoietin-Like Protein 3; ApoC-III: Apolipoprotein C-III; ASCVD: Atherosclerotic Cardiovascular Disease; ASO: Antisense Oligonucleotide; ATP: Adenosine Triphosphate; FCS: Familial Chylomicronaemia Syndrome; HeFH: Heterozygous Familial Hypercholesterolaemia; HoFH: Homozygous Familial Hypercholesterolaemia; IV: Intravenous; LDL-C: Low-Density Lipoprotein Cholesterol; LPA: Lipoprotein(a); mRNA: Messenger Ribonucleic Acid; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; Q2W: Every 2 Weeks; SC: Subcutaneous; siRNA: Small Interfering Ribonucleic Acid; TG: Triglycerides.

Gene-Editing Therapies¹⁸

Gene-editing represents the next frontier in lipid-lowering therapy, offering the potential for a one-time, lifelong treatment by permanently modifying genes involved in lipid metabolism. Unlike conventional therapies that require continuous administration, gene-editing utilises technologies such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 and base-editing to selectively disrupt or modify disease-causing genes within hepatocytes. Current research has primarily focused on PCSK9, ANGPTL3, and LPA, with the aim of achieving sustained reductions in LDL-C, triglycerides, and Lp(a). Although these therapies remain investigational, early clinical studies have demonstrated promising efficacy with the potential to transform the management of inherited and refractory dyslipidaemias.

PCSK9 gene-editing: VERVE-101 and VERVE-102

Mechanism of action: VERVE-101 and VERVE-102 are in vivo CRISPR base-editing therapies designed to permanently inactivate the PCSK9 gene in hepatocytes. Delivered via lipid nanoparticles, the editing machinery introduces a single base-pair change in the PCSK9 gene, resulting in durable suppression of PCSK9 production, increased LDL receptor recycling, and sustained reductions in circulating LDL-C after a single intravenous infusion.

Pivotal clinical trials: The Heart-1 trial is evaluating the safety and efficacy of VERVE-101 in patients with heterozygous familial hypercholesterolaemia and premature ASCVD. VERVE-102, a next-generation base-editing therapy with an improved lipid nanoparticle delivery system, is also undergoing early-phase clinical evaluation.¹⁸

Primary lipid-lowering effects: Early clinical data have demonstrated LDL-C reductions of approximately 40% – 55% and PCSK9 reductions exceeding 80% following a single treatment.

Indications and uses: These therapies are being investigated in patients with heterozygous familial hypercholesterolaemia and premature ASCVD who require durable LDL-C lowering despite maximally tolerated conventional therapy.

Dose: VERVE-101 and VERVE-102 are administered as a single intravenous infusion, with dose escalation currently being evaluated in clinical trials.

Side effects: Reported adverse effects include transient infusion-related reactions and mild elevations in liver enzymes. Long-term safety, durability, and off-target editing remain under active investigation.

Important points: Gene-editing offers the possibility of lifelong LDL-C reduction following a single treatment, representing a paradigm shift in lipid management. However, these therapies remain investigational, and long-term efficacy and safety data are awaited before routine clinical use.

Among the next most promising targets are ANGPTL3 and the LPA gene, both of which play key roles in atherogenic lipoprotein metabolism. Experimental

ANGPTL3 gene-editing therapies permanently disrupt hepatic ANGPTL3 expression, thereby enhancing LPL activity and promoting the clearance of triglyceride-rich lipoproteins and LDL particles. Preclinical studies have demonstrated marked reductions in LDL-C, triglycerides, and ApoB, and these therapies are being developed for patients with familial hypercholesterolaemia, severe mixed dyslipidaemia, and refractory hypertriglyceridaemia. Similarly, LPA gene-editing strategies aim to permanently suppress hepatic apolipoprotein(a) synthesis, resulting in sustained and potentially near-complete reductions in circulating Lp(a) levels following a single treatment. These therapies are primarily intended for individuals with markedly elevated Lp(a) and persistent residual cardiovascular risk despite optimal lipid-lowering therapy. Although both approaches remain in the preclinical or early clinical development stage, they hold considerable promise as one-time, disease-modifying therapies capable of transforming the management of inherited dyslipidaemias and reducing lifelong cardiovascular risk.

Other Drugs – A Comparison Table^{3,19,20}

The principal characteristics of selected novel lipid-lowering agents, including their mechanisms of action, pivotal clinical trials, lipid-modifying effects, approved indications, dosing, adverse effects, and key clinical considerations, are summarised in Table 2.

Parameter	Bempedoic Acid	Icosapent Ethyl (IPE)	Mipomersen	Lomitapide
 Mechanism of Action	ACL inhibitor → ↓ cholesterol synthesis → ↑ LDL receptors → ↓ LDL-C	EPA derivative → ↓ VLDL synthesis, ↑ TG clearance; anti-inflammatory & plaque-stabilizing	ApoB-100 antisense oligonucleotide (ASO) → ↓ ApoB synthesis → ↓ VLDL & LDL production	MTP inhibitor → prevents assembly & secretion of ApoB-containing lipoproteins → ↓ VLDL & LDL production
 Key Trials	CLEAR Harmony, CLEAR Wisdom, CLEAR Outcomes	REDUCE-IT, EVAPORATE	ISIS 301012, Phase III HoFH	LOWER, Phase III HoFH
 Primary Lipid Effect	↓ LDL-C 18–25% (up to 38% with ezetimibe)	↓ TG 20–30%; proven CV event reduction	↓ LDL-C 25–40%, ↓ ApoB, ↓ Lp(a)	↓ LDL-C 40–50%, ↓ TG 30–45%, ↓ ApoB 40–50%
 Indications	ASCVD, HeFH, statin intolerance	ASCVD or diabetes with TG ≥150 mg/dL	Homozygous familial hypercholesterolemia (HoFH)	Homozygous familial hypercholesterolemia (HoFH)
 Dose	180 mg orally once daily	2 g orally twice daily (with meals)	200 mg subcutaneously once weekly	5–60 mg orally once daily (titrated)
 Major Adverse Effects	Hyperuricemia, gout, ↑ LFTs, rare tendon rupture	Arthralgia, AF, edema, GI discomfort, ↑ bleeding risk	Injection-site reactions, ↑ LFTs, hepatic steatosis	GI intolerance, hepatic steatosis, ↑ LFTs, vitamin deficiency
 Key Point	Liver-selective; useful in statin intolerance; proven CV benefit	REDUCE-IT showed 25% reduction in major CV events	Requires liver function monitoring	Requires low-fat diet, vitamin supplementation & liver monitoring

Table 2: Comparing other drugs.

Abbreviations: ACL: ATP Citrate Lyase; ApoB: Apolipoprotein B; ApoB-100: Apolipoprotein B-100; ASCVD: Atherosclerotic Cardiovascular Disease; ASO: Antisense Oligonucleotide; ATP: Adenosine Triphosphate; CV: Cardiovascular; EPA: Eicosapentaenoic Acid; GI: Gastrointestinal; HeFH: Heterozygous Familial Hypercholesterolaemia; HoFH: Homozygous Familial Hypercholesterolaemia; IPE: Icosapent Ethyl; LDL: Low-Density Lipoprotein; LDL-C: Low-Density Lipoprotein Cholesterol; LFTs: Liver Function Tests; Lp(a): Lipoprotein(a); MTP: Microsomal Triglyceride Transfer Protein; TG: Triglycerides; VLDL: Very Low-Density Lipoprotein.

Emerging Lipid-Lowering Therapies with Limited Clinical Evidence³

Several novel lipid-lowering agents targeting alternative metabolic pathways are currently under investigation or have limited clinical use. Although these therapies have demonstrated promising lipid-modifying effects in early studies or rare lipid disorders, their role in routine dyslipidaemia management remains uncertain because of limited long-term efficacy, safety, or cardiovascular outcome data.

1. Diacylglycerol acyltransferase-1 (DGAT-1) inhibitor (Pradigastat)

Mechanism of action: Pradigastat is a selective DGAT-1 inhibitor that reduces intestinal triglyceride synthesis and chylomicron formation, thereby lowering circulating triglyceride levels.

Clinical use: It has been investigated primarily in patients with FCS to reduce severe hypertriglyceridaemia and pancreatitis risk.

Important points: Although early studies demonstrated significant triglyceride reduction, gastrointestinal

intolerance has limited its clinical development and routine use.

2. DGAT inhibitor (Ervogastat)

Mechanism of action: Ervogastat is a selective DGAT-2 inhibitor that decreases hepatic triglyceride synthesis and VLDL production.

Clinical use: It is currently being evaluated for metabolic dysfunction-associated steatohepatitis (MASH) with associated dyslipidaemia and hypertriglyceridaemia.

Important points: Unlike DGAT-1 inhibitors, ervogastat has demonstrated a more favourable gastrointestinal safety profile. However, its long-term cardiovascular benefits remain to be established.

3. Recombinant leptin (Metreleptin)

Mechanism of action: Metreleptin is a recombinant human leptin analogue that restores leptin deficiency, improving insulin sensitivity, hepatic steatosis, and lipid metabolism.

Clinical use: It is approved for the treatment of generalised lipodystrophy, where it significantly

improves severe hypertriglyceridaemia and associated metabolic abnormalities.

Important points: Its use is restricted to patients with leptin deficiency due to lipodystrophy. Treatment requires careful monitoring because of the potential risk of anti-leptin antibodies and T-cell lymphoma.

4. Cholesteryl ester transfer protein (CETP) inhibitors (Anacetrapib and Obicetrapib)

Mechanism of action: CETP inhibitors increase HDL cholesterol while reducing LDL-C by inhibiting the transfer of cholesteryl esters from HDL to ApoB-containing lipoproteins.

Clinical use: Earlier CETP inhibitors showed inconsistent cardiovascular benefits, limiting their clinical adoption. Newer agents, particularly obicetrapib, have demonstrated substantial LDL-C lowering and are undergoing evaluation for cardiovascular outcomes.

Important points: The renewed interest in CETP inhibition is driven by newer molecules with improved

efficacy and safety profiles. However, their definitive role in routine dyslipidaemia management awaits results from ongoing outcome trials such as PREVAIL.

An Integrated Practical Clinical Approach^{4,21}

Despite the availability of multiple novel lipid-lowering agents, selecting the most appropriate therapy can be challenging because treatment should be guided by the patient's predominant lipid abnormality, cardiovascular risk, and underlying clinical condition. The following algorithm, as shown in Figure 5, summarises a practical, evidence-based approach to the contemporary management of dyslipidaemia, integrating current guideline-directed therapy with recently approved and emerging lipid-lowering agents. It highlights the sequential escalation of treatment and provides a phenotype-based strategy for selecting targeted therapies in routine clinical practice.

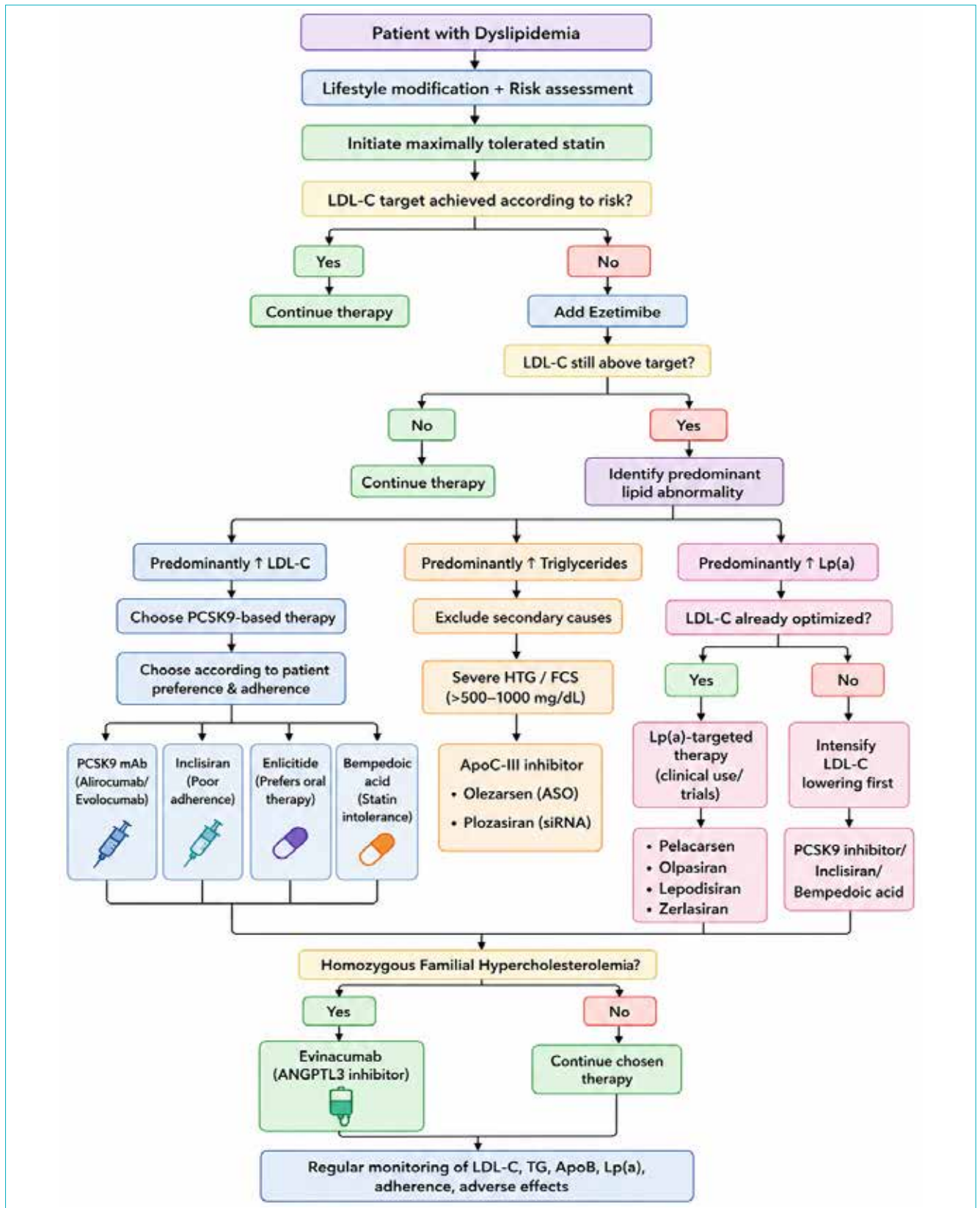


Figure 5: Practical clinical approach to the contemporary management of dyslipidaemia incorporating conventional, novel, and emerging lipid-lowering therapies.

Abbreviations: ANGPTL3: Angiopoietin-Like Protein 3; ApoB: Apolipoprotein B; ApoC-III: Apolipoprotein C-III; ASO: Antisense Oligonucleotide; FCS: Familial Chylomicronaemia Syndrome; HTG: Hypertriglyceridaemia; LDL-C: Low-Density Lipoprotein Cholesterol; Lp(a): Lipoprotein(a); mAb: Monoclonal Antibody; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; siRNA: Small Interfering Ribonucleic Acid; TG: Triglycerides.

Disclosures

Images in this article have been created by Dr. Aryan Arora with the help of artificial intelligence (AI) – All copyright reserved.

Conclusion^{22,23}

The therapeutic landscape of dyslipidaemia continues to evolve with several promising agents currently in the pipeline. Next-generation oral PCSK9 inhibitors, obicetrapib, longer-acting RNA-based therapies, combination siRNA platforms, and PCSK9 vaccines aim to improve efficacy, convenience, and long-term adherence. In parallel, advances in prime gene-editing technologies, DGAT inhibitors, and artificial intelligence (AI)-guided precision medicine have the potential to further personalise lipid management and address residual cardiovascular risk.

Overall, the management of dyslipidaemia has evolved from conventional LDL-C lowering to mechanism-based, target-specific therapies. Novel agents targeting PCSK9, ApoC-III, ANGPTL3, and Lp(a) have significantly expanded treatment options, particularly for patients with familial dyslipidaemias, severe hypertriglyceridaemia, and persistent residual cardiovascular risk. As ongoing cardiovascular outcome trials mature and newer therapies become clinically available, treatment strategies are expected to become increasingly individualised.

The future of dyslipidaemia management lies in precision medicine, where therapy is tailored according to the patient's lipid phenotype, genetic profile, and cardiovascular risk. Continued advances in molecular therapeutics may ultimately shift clinical practice from lifelong lipid-lowering therapy towards long-acting, personalised, and potentially disease-modifying interventions, with the overarching goal of maximising cardiovascular risk reduction and improving long-term patient outcomes.

Aryan Arora, Monica Mahajan. Beyond the Pill – The Future of Lipid-Lowering Therapy: A 2026 Review of Novel Lipid-Lowering Agents. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-8>

References

1. Ference BA, Ginsberg HN, Graham I, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J.* 2017;38(32):2459–72.
2. Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41(1):111–88.
3. Huang JXF, Yousaf A, Moon J, *et al.* Recent Advances in the Management of Dyslipidemia: A Systematic Review. *Cureus.* 2025;17(3):e81034.
4. Rallidis LS. The changing landscape of lipid-lowering therapy after the new ESC/EAS guidelines for the management of dyslipidaemias: Launching the era of triple hypolipidaemic therapy in very high risk patients. *Atherosclerosis.* 2020;292:231–3.
5. Seidah NG, Awan Z, Chrétien M, *et al.* PCSK9: a key modulator of cardiovascular health. *Circ Res.* 2014;114(6):1022–36.
6. Sabatine MS, Giugliano RP, Keech AC, *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med.* 2017;376(18):1713–22.
7. Schwartz GG, Steg PG, Szarek M, *et al.* Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med.* 2018;379(22):2097–107.
8. Ray KK, Wright RS, Kallend D, *et al.* Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med.* 2020;382(16):1507–19.
9. Raal FJ, Kallend D, Ray KK, *et al.* Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N Engl J Med.* 2020;382(16):1520–30.

10. Navar AM, Mikhailova E, Catapano AL, *et al.* A Placebo-Controlled Trial of the Oral PCSK9 Inhibitor Enlicitide. *N Engl J Med.* 2026;394(6):529–39.
11. Joshy J, Javed A, Kumar Singh M, *et al.* Olezarsen: A Next-Generation Antisense Therapy for Hypertriglyceridemia and Familial Chylomicronemia Syndrome. *Cureus.* 2025;17(11):e96715.
12. Watts GF, Rosenson RS, Hegele RA, *et al.* Plazasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. *N Engl J Med.* 2025;392(2):127–37.
13. Raal FJ, Rosenson RS, Reeskamp LF, *et al.* Evinacumab for Homozygous Familial Hypercholesterolemia. *N Engl J Med.* 2020;383(8):711–20.
14. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol.* 2017;69(6):692–711.
15. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, *et al.* Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. *N Engl J Med.* 2020;382(3):244–55.
16. O'Donoghue ML, Rosenson RS, Gencer B, *et al.* Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease. *N Engl J Med.* 2022;387(20):1855–64.
17. Nissen SE, Ni W, Shen X, *et al.* Lepodisiran - A Long-Duration Small Interfering RNA Targeting Lipoprotein(a). *N Engl J Med.* 2025;392(17):1673–83.
18. Vafai SB, Täubel J, Ashdown T, *et al.* In Vivo Base Editing of PCSK9 with VERVE-102 for Hypercholesterolemia. *N Engl J Med.* Published online May 25, 2026.
19. Cannon CP, Blazing MA, Giugliano RP, *et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372(25):2387–97.
20. Nissen SE, Lincoff AM, Brennan D, *et al.* Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *N Engl J Med.* 2023;388(15):1353–64.
21. Blumenthal RS, Morris PB, Gaudino M, *et al.* 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2026;87(19):2624–757.
22. Komiyama M, Wada H, Dan GA, *et al.* Lipid-lowering therapy: Evidence and future perspective. *JRSM Cardiovasc Dis.* 2026;15:20480040261435032.
23. Ference BA, Graham I, Tokgozoglu L, *et al.* Impact of Lipids on Cardiovascular Health: JACC Health Promotion Series. *J Am Coll Cardiol.* 2018;72(10):1141–56.

Patient Satisfaction and Experience in Inpatient Care: A Systematic Review of Global Evidence

Ayuj Kaushik^{1*}, Pragya, Shivam Sharma¹

¹Department of Clinical Research, Max Super Speciality Hospital, Saket, New Delhi

Correspondence:

Ayuj Kaushik

E-mail: ayuj.kaushik@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-10b>

Abstract:

Patient satisfaction in inpatient care is a crucial dimension of healthcare quality, impacting outcomes and service efficiency. A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, sourcing articles from PubMed, Scopus, Web of Science, Embase, and Google Scholar (2010 – 2023). Overall, 78 studies were analysed. Key satisfaction drivers included provider communication, staff responsiveness, and the hospital environment. Variations in satisfaction were linked to geography, cultural factors, and institutional practices. Recommendations focus on communication training and patient engagement.

Key words: Patient Satisfaction, Inpatient Care, Hospital Experience, Quality of Care, Global Healthcare, Patient-Reported Experience Measures (PREMs).

Introduction

Patient satisfaction has emerged as a critical marker of healthcare quality, particularly in inpatient settings where individuals are highly dependent on medical services. Beyond clinical outcomes, satisfaction levels reflect the overall effectiveness of health systems and are directly associated with adherence to treatment, reduced hospital readmissions, and enhanced patient safety and outcomes.^{1,2} Research has demonstrated that factors such as effective communication, staff responsiveness, the hospital environment, and shared decision-making significantly influence the patient experience.^{3,4} Additionally, tools such as the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) and patient-reported experience measures (PREMs) have standardised the assessment of satisfaction across different healthcare systems, enabling meaningful comparisons and improvement strategies.^{5,6}

Global studies suggest that satisfaction is shaped by institutional infrastructure, cultural context, and socioeconomic status.^{7,8} In some settings, even when resources are limited, patient satisfaction scores remain high due to compassionate care and culturally competent service delivery.^{9,10} Therefore, a deeper understanding of global trends is essential to align healthcare delivery with patient expectations and promote equity.

This systematic review aims to synthesise international literature on inpatient satisfaction and patient experience to inform policy and clinical practice reforms. By identifying the core drivers and variations in satisfaction across healthcare systems, the review provides a foundation for promoting patient-centred care globally.^{11–15}

Aim and Objectives

Aim

To systematically review and synthesise global evidence on patient satisfaction and experience in inpatient hospital care.

Objectives

- To identify the key factors influencing patient satisfaction in hospital inpatient settings
- To explore patient-reported experiences across diverse healthcare systems and cultural contexts
- To examine trends and disparities in inpatient satisfaction based on demographic and institutional variables
- To propose recommendations for improving patient-centred care based on global best practices

Methodology

Study design

Systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data sources

Electronic databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched for peer-reviewed articles published between January 2010 and December 2023.

Search terms

"patient satisfaction," "inpatient experience," "hospital care," "healthcare quality," "PREMs," and "patient-centred care."

Inclusion criteria

- Studies published in English
- Studies focusing on adult inpatients
- Studies using quantitative or qualitative measures of patient satisfaction and patient experience
- Studies conducted in hospital settings

Exclusion criteria

- Outpatient or community-based studies
- Editorials, commentaries, and conference abstracts
- Studies not providing primary data or clear methodologies

Data extraction and analysis

A standardised data extraction form was used to collect information on study characteristics, patient population, satisfaction dimensions, tools used,

and major findings. Thematic synthesis was used for qualitative findings, and quantitative data were summarised using descriptive statistics.

Results

Study selection

A total of 3,216 articles were identified through database searches. After removing duplicates and screening titles/abstracts, 245 full-text articles were assessed. Finally, 78 studies met the inclusion criteria (Table 1).

Region	Number of studies	Percentage (%)
North America	20	25.6
Europe	18	23.1
Asia	16	20.5
Africa	10	12.8
South America	8	10.3
Oceania	6	7.7



Table 1: Geographic distribution of studies.

Common themes identified

- **Communication with healthcare providers:** Patients consistently valued clear, respectful, and empathetic communication. Satisfaction scores were significantly higher when patients felt heard and understood.
- **Responsiveness of hospital staff:** Delayed responses to patient needs, particularly for pain management and assistance with mobility, were a common complaint.
- **Cleanliness and comfort of hospital environment:** Cleanliness of wards and adequacy of facilities contributed significantly to overall satisfaction.
- **Involvement in care decisions:** Patients expressed greater satisfaction when involved in care planning and treatment decisions.
- **Cultural and linguistic considerations:** Studies from multicultural settings highlighted the importance of language-appropriate services and culturally sensitive care.

Quantitative analysis revealed that patients rated their satisfaction with hospital care across five core domains. The highest mean satisfaction score was observed for communication (8.3), followed by environment and facilities (8.1), participation in decision-making (7.9), and staff responsiveness (7.6), with an overall satisfaction score of 8.0 (Table 2).

Domain	Mean satisfaction score (out of 10)
Communication	8.3
Staff responsiveness	7.6
Environment and facilities	8.1
Participation in decision-making	7.9
Overall satisfaction	8.0

Table 2: Quantitative findings.

Figure 1 illustrates global trends in inpatient satisfaction from 2010 to 2023, highlighting improvements over time, especially in domains linked to personalised care and patient engagement. However, regional disparities were evident, with lower satisfaction scores reported among older adults, individuals with lower education levels, and non-native language speakers. These findings suggest that while advancements have been made, targeted improvements are necessary to address inequities and enhance patient-centred care across healthcare systems.

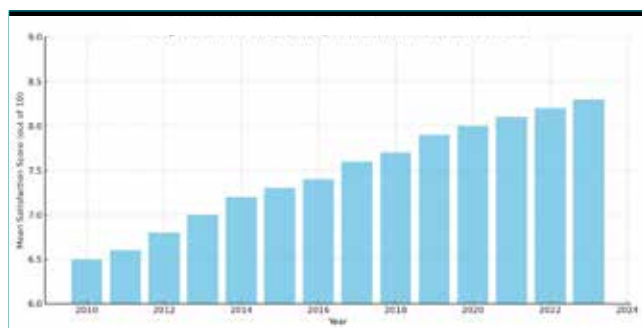


Figure 1: Global trends in inpatient satisfaction (2010 – 2023).

Discussion

This systematic review underscores the multifactorial nature of patient satisfaction in inpatient care. A consistent finding across the literature was the central role of healthcare provider-patient communication in shaping positive experiences.¹ Studies from both high- and low-income countries indicated that when patients felt listened to and respected, overall satisfaction increased, even when other aspects of care were suboptimal.² Responsiveness to patient needs, particularly regarding pain management and assistance with activities of daily living, was another key determinant.⁴

Disparities in satisfaction were observed across regions and demographic groups. Older adults, individuals with lower educational attainment, and non-native language speakers often reported lower satisfaction due to barriers in communication and limited engagement in care decisions. Gender also emerged as an influencing factor, particularly in patriarchal settings where women's autonomy in medical decisions was constrained.^{8,14}

A particularly notable theme was the mismatch between technical care quality and patients' perceived experience. Hospitals with advanced medical services were sometimes rated poorly for patient satisfaction due to deficits in empathy or poor environmental conditions.^{5,10} This illustrates the necessity of integrating emotional and environmental considerations into hospital care strategies.

Policy implications from this review are profound. Incorporating PREMs into national and institutional quality frameworks can generate actionable insights for service improvement.⁶ Staff training in empathetic communication and cultural competence, along with facility enhancements and better staffing ratios, was commonly recommended as a strategy. Importantly, several studies advocated involving patients as active partners in care planning and quality assessment, reinforcing the movement toward participatory healthcare systems.

Improving inpatient satisfaction requires a holistic approach that transcends biomedical care. Emphasising dignity, empathy, and responsiveness, alongside clinical effectiveness, is essential for building trust and achieving better health outcomes.

Conclusion

This systematic review provides global evidence that patient satisfaction and experience in inpatient care are critical indicators of healthcare quality. Effective communication, staff responsiveness, clean environments, and patient involvement in care are key drivers of positive experiences. While structural improvements are important, the human dimensions of empathy, respect, and responsiveness play a pivotal role in shaping perceptions of care. Policymakers, hospital administrators, and healthcare providers should consider patient-reported experiences as essential feedback for service improvement. Future research should explore longitudinal changes in patient satisfaction and develop culturally adaptable tools for global application.

Ayuj Kaushik, Pragya, Shivam Sharma. Patient Satisfaction and Experience in Inpatient Care: A Systematic Review of Global Evidence. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-10b>

References

1. Doyle C, Lennox L, Bell D. A systematic review of evidence on the links between patient experience and clinical safety and effectiveness. *BMJ Open*. 2013;3(1):e001570.
2. Manary MP, Boulding W, Staelin R, *et al*. The patient experience and health outcomes. *N Engl J Med*. 2013;368(3):201–3.
3. Wolf JA, Niederhauser V, Marshburn D, *et al*. Defining patient experience. *Patient Exp J*. 2014;1(1):7–19.
4. Isaac T, Zaslavsky AM, Cleary PD, *et al*. The relationship between patients' perception of care and measures of hospital quality and safety. *Health Serv Res*. 2010;45(4):1024–40.
5. Jenkinson C, Coulter A, Bruster S. The Picker Patient Experience Questionnaire: development and validation using data from in-patient surveys in five countries. *Int J Qual Health Care*. 2002;14(5):353–8.
6. Beattie M, Murphy DJ, Atherton I, *et al*. Instruments to measure patient experience of healthcare quality in hospitals: a systematic review. *Syst Rev*. 2015;4:97.
7. Arah OA, Westert GP, Hurst J, *et al*. A conceptual framework for the OECD Health Care Quality Indicators Project. *Int J Qual Health Care*. 2006;18(Suppl 1):5–13.
8. Anhang Price R, Elliott MN, Zaslavsky AM, *et al*. Examining the role of patient experience surveys in measuring health care quality. *Med Care Res Rev*. 2014;71(5):522–54.
9. Coulter A, Fitzpatrick R, Cornwell J. Measures of patients' experience in hospital: purpose, methods and uses. London: The King's Fund; 2009.
10. Hudak PL, Wright JG. The characteristics of patient satisfaction measures. *Spine (Phila Pa 1976)*. 2000;25(24):3167–77.
11. Cleary PD. The increasing importance of patient surveys. *BMJ*. 1999;319(7212):720–1.
12. LaVela SL, Gallan AS. Evaluation and measurement of patient experience. *Patient Exp J*. 2014;1(1):28–36.
13. Sitzia J, Wood N. Patient satisfaction: a review of issues and concepts. *Soc Sci Med*. 1997;45(12):1829–43.
14. Pomey MP, Ghadiri DP, Karazivan P, *et al*. Patients as partners: a qualitative study of patients' engagement in their health care. *PLoS One*. 2015;10(4):e0122499.
15. Coulter A. Patient engagement—what works? *J Ambul Care Manage*. 2012;35(2):80–9.



CASE STUDIES

98	Beyond the Scope: Laparoscopic Rescue of Jejunal Gallstone Ileus Following Failed Endoscopic Retrieval - Manmohan M Kamat, Divya Udaykumar, Sharvari Gorkar, Rohan KJ, Akhil Mishra, Gulamgous Shaikh, Kristina Matthew, Sainath Kuppa, Yashraj Thakur	136	Primary Vaginal Adenocarcinoma with Intestinal Differentiation: Diagnostic Complexity and Individualised Radiation Planning - Apoorva Singh, Garima Singh, Khushboo Rastogi, Nidhi Sharma, Varshu Goel, Annu Dalal, Anusheel Munshi
100	Undifferentiated Small Round Cell Sarcoma of the Pelvic Space in an Infant: A Rare Case Report - Krishna Kant Singh	141	Endobronchial Watanabe Spigot Placement for a Tuberculosis-Associated Bronchopleural Fistula: A Stepwise Balloon Occlusion Technique - Sameer Arbat, Manoj Pethe, Nitin Wadaskar
104	Bilateral Patellofemoral Arthroplasty for End-Stage Patellofemoral Osteoarthritis in a Young Adult with Ehlers-Danlos Syndrome and Lifelong Patellar Instability: A Case Report - Prateek Upadhyay, Harshavardhan Hegde, Nitiraj Oberoi, Rakesh Mattoo, Akshay Kumar Saxena, Ajay Dhanopeya	147	Unmasking Steroid-Induced Psychosis in a Patient with Metastatic Spinal Tumour: A Clinical Challenge - Nitin Rathod, Andrea Janice Fonseca, Shweta Thadeshwar, Surbhi Padte
112	Zolpidem Intoxication Leading to Coma and a Rapid Flumazenil Awakening Response: A Definitive Antidote - Bhanu Pratap Singh, Mandeep Singh Gill, Vedvartya, Harjit Singh	151	Rapid Neurological and Multiorgan Recovery After Two-Session Automated Red Cell Exchange for Fulminant Sickle Cell Crisis: A Case Report - Vipul Sharma, Siddhi Karale, Nidhi Mehta, Hemalata Arora
116	Diagnostic Masquerade in Advanced Lymphoma: Angioimmunoblastic T-Cell Lymphoma Initially Mimicking Diffuse Large B-Cell Lymphoma - Kshirabdh Tanaya Panda, Sanjeev Kumar Sharma, Anamika Bakliwal, Anil Handoo, Pratyush Mishra, Rajan Duggal, Nivedita Patnaik	155	Endoscopic Intersphincteric Dissection: A Novel Sphincter-Preserving Technique for Ultra-Low Rectal Tumours - A Case Report - Gaurav Patil, Ankit Dalal, Amol Vodgaonkar, Prathvi Alva
121	When the Node Fails and the Heart Follows: Anti-NF140 and Anti-GAD65 Autoimmune Nodopathy Presenting as Acute Quadriplegia with Takotsubo Cardiomyopathy and Type 2 Respiratory Failure - Prateek Bhanu, Rommel Tickoo, Shiveta Mattoo, Shubham Mishra, Sharanya Kohli, Anjali Mutreja, Manisha Agrawal	159	Peripheral T-Cell Lymphoma Masquerading as Prolonged Pyrexia of Unknown Origin and Culminating in Carbapenem-Resistant <i>Acinetobacter baumannii</i> Septic Shock: A Case Report - Osheen Gera, Richa Nema, Adiba Rao, Akanksha Verma, Supriya Bali
130	Multisystem Sarcoidosis Masquerading as Tuberculosis Despite Normal Serum Angiotensin-Converting Enzyme Levels: A Case Report - Nitin Rathod, Andrea Janice Fonseca, Snehal Sadanandan, Akshita Jain	163	Giant Cervicothoracic Schwannoma Involving the Brachial Plexus and Thoracic Inlet - Prem Kumar Ganesan, Narottam Khadaria, Dhruv Dinesh Jain, Anchal Singh

Beyond the Scope: Laparoscopic Rescue of Jejunal Gallstone Ileus Following Failed Endoscopic Retrieval

Manmohan M Kamat^{1*}, Divya Udaykumar¹, Sharvari Gorkar¹, Rohan KJ¹, Akhil Mishra¹, Gulamgous Shaikh¹, Kristina Matthew¹, Sainath Kuppa¹, Yashraj Thakur¹

¹Department of General Surgery, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

Correspondence:

Manmohan M Kamat

E-mail: drmmkamat@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-12>

Abstract:

Gallstone ileus (GSI) is an infrequent yet significant aetiology of mechanical small bowel obstruction, accounting for 1% – 4% of cases overall and up to 25% in the geriatric population. It results from the migration of a large biliary calculus into the intestinal tract via a bilioenteric fistula, most commonly cholecystoduodenal. Despite its rarity, the condition carries high morbidity and mortality in elderly patients due to delayed diagnosis and significant physiological fragility. We present the case of a 75-year-old female with a complex medical history, including type 2 diabetes mellitus (T2DM), hypertension (HTN), and stage III chronic kidney disease (CKD), who presented with acute proximal small bowel obstruction. Radiographic imaging revealed Rigler's triad, with a 4.1 cm enterolith impacted in the proximal jejunum. A minimally invasive "step-up" approach was initiated with an attempted endoscopic retrieval; however, this was unsuccessful due to the stone's dimensions and the inability to navigate the scope beyond the impaction. The patient subsequently underwent a laparoscopic enterolithotomy. A transverse enterotomy was performed for stone extraction, followed by a primary transverse repair. To minimise operative time and surgical stress in the setting of her comorbidities, the bilioenteric fistula was not addressed, and no cholecystectomy was performed. The patient had an uneventful recovery and was discharged on postoperative Day 4. This case was selected to demonstrate the safety and efficacy of a sequential management strategy — transitioning from endoscopic to laparoscopic intervention — for proximal GSI. It highlights that in high-risk geriatric patients with multiple comorbidities, laparoscopic enterolithotomy alone serves as a definitive and less morbid treatment compared to extensive one-stage biliary reconstruction, facilitating rapid recovery and minimising preoperative complications.

Key words: Gallstone Ileus, Laparoscopy, Enterolithotomy, Geriatric Surgery, Step-Up Approach.

Introduction

Gallstone ileus (GSI) is a rare and complex form of mechanical bowel obstruction caused by the impaction of a biliary calculus within the intestinal lumen, typically after migrating through a cholecystoenteric fistula.^{1,2} While it accounts for only 1% – 4% of all mechanical small bowel obstructions in the general population, its

incidence rises to nearly 25% in patients aged 65 and older, predominantly affecting elderly females.^{2–4} The classic diagnostic hallmark, "Rigler's Triad" — consisting of pneumobilia, ectopic gallstone, and mechanical bowel obstruction — is most reliably identified via computed tomography (CT), which remains the gold standard for preoperative planning.^{1,4,5}

The optimal surgical management of GSI remains a subject of significant debate. Surgeons must choose between a simple enterolithotomy alone or a more extensive one-stage procedure involving enterolithotomy, cholecystectomy, and fistula repair.^{3,6} In high-risk geriatric patients with multiple comorbidities, enterolithotomy alone is often favoured to minimise operative time and reduce the high perioperative mortality rates associated with more invasive biliary reconstructions.^{2,4,6} Furthermore, the evolution of minimally invasive surgery has introduced laparoscopic and laparoscopic-assisted enterolithotomy as safe alternatives that offer reduced postoperative pain and shorter hospital stays compared to traditional open surgery.^{5,7,8}

While endoscopic intervention may be considered for proximal stones, it frequently fails when the calculus is large or tightly impacted.⁹ We present a case of a 75-year-old female with morbid comorbidities, including type 2 diabetes mellitus (T2DM) and stage III chronic kidney disease (CKD), who presented with a 4.1 cm jejunal GSI. This case illustrates the successful transition to laparoscopic enterolithotomy following failed endoscopic management, advocating for a "step-up" minimally invasive approach in fragile geriatric populations.¹⁰

Case Report

A 75-year-old female presented with a history of acute abdominal pain, vomiting, and distension. Her medical history was significant for longstanding T2DM, hypertension (HTN), and CKD.

Diagnostic findings

- **Abdominal X-ray:** Multiple air-fluid levels suggestive of obstruction.
- **Contrast-enhanced CT:** Revealed proximal jejunal dilatation (3.5 × 3.6 cm) caused by an impacted 4.1 × 2.6 cm enterolith.
- **Biliary findings:** Pneumobilia was present, and a 9.5 mm fistula was identified between the gallbladder fundus and the first part of the duodenum.

Given the proximal location of the stone, an initial upper gastrointestinal enteroscopy was attempted.

A large enterolith was visualised, but extraction was unsuccessful as the scope could not navigate beyond the point of impaction.

Surgical procedure

Following the failed endoscopic attempt, a laparoscopic approach was initiated (Figure 1).

1. **Exploration:** Dilated jejunal loops were traced to the site of the transition zone.
2. **Enterotomy:** A transverse enterotomy was performed proximal to the stone (Figure 2).
3. **Extraction:** The 4.1 cm gallstone was successfully removed (Figure 3).
4. **Strategy:** No bowel resection was required (Figure 4). Considering the patient's age and comorbidities (T2DM, HTN, and CKD), the bilioenteric fistula was not addressed to minimise operative time and surgical stress (Figure 5).



Figure 1: Markedly dilated proximal jejunal loop containing a large, impacted intraluminal mass causing mechanical intestinal obstruction.

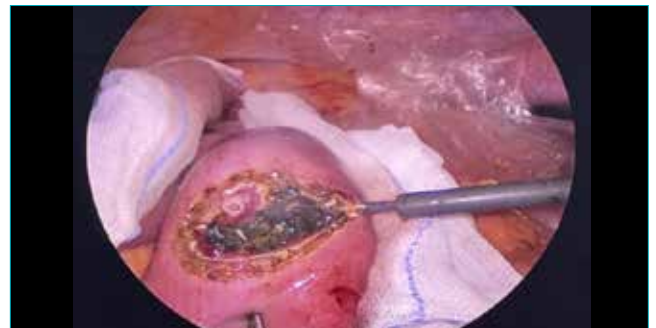


Figure 2: Transverse enterotomy performed on the antimesenteric border of the significantly dilated proximal jejunum.



Figure 3: Intraoperative view showing the extraction of the large gallstone placed in a bag.

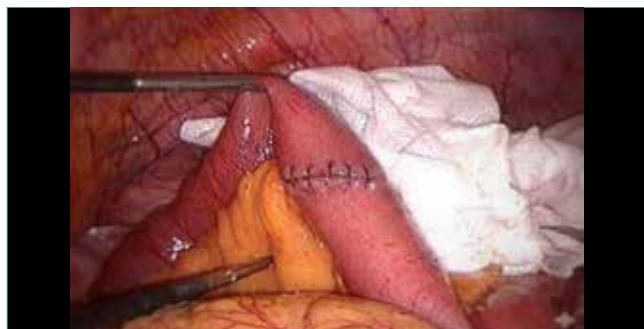


Figure 4: Transverse enterotomy.

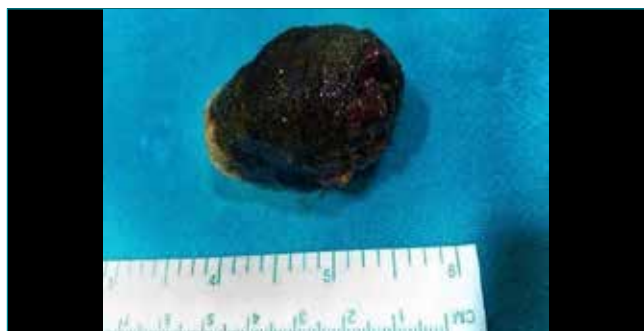


Figure 5: Retrieved ~ 4 cm gallstone, faceted morphology alongside a surgical scale for correlation.

Discussion

1. Prevalence and pathophysiology

GSI remains a rare but critical surgical entity. As noted in the classic literature, the condition is typically the result of a large stone eroding through the gallbladder wall into an adjacent viscus — most frequently the duodenum.¹ This process is usually preceded by chronic inflammation and adhesions.¹ In the geriatric population, GSI predominantly affects females, with a reported ratio of approximately 3.5:1 to 4.5:1.^{3,4}

2. The diagnostic gold standard

The diagnosis of GSI is historically challenging due to its non-specific clinical presentation. However,

the identification of Rigler's Triad remains the pathognomonic radiological hallmark.¹ Modern imaging, specifically CT, has revolutionised diagnosis with a sensitivity exceeding 93%.⁴ CT is essential for identifying the exact site of impaction and measuring stone size, which in our case was a significant 4.1 cm. Furthermore, CT helps in visualising the bilioenteric fistula, which occurs in approximately 0.3% – 0.5% of patients with cholelithiasis.⁵

3. Management controversy: One-stage vs. enterolithotomy alone

The optimal surgical management of GSI remains controversial, with ongoing debate regarding whether patients should undergo a one-stage procedure comprising enterolithotomy, cholecystectomy, and bilioenteric fistula repair, or a simpler enterolithotomy alone to relieve the intestinal obstruction.^{3,6}

- **Enterolithotomy alone:** This is increasingly viewed as the procedure of choice for high-risk patients. Data suggest it is associated with a lower mortality rate (~ 11.7%) compared to more extensive procedures.² In patients with a high American Society of Anesthesiologists (ASA) score (III or IV) and significant comorbidities such as T2DM, HTN, and CKD, enterolithotomy alone minimises operative time and physiological stress.^{4,6}
- **One-stage procedure:** While definitive, this approach carries a higher mortality risk (~ 16.9%) due to increased operative complexity in an acutely inflamed field.^{2,3} Furthermore, one-stage repairs significantly increase operative time — often doubling it — compared to simple enterolithotomy.⁶
- **Spontaneous closure:** Long-term follow-up indicates that up to 50% of cholecystoduodenal fistulas close spontaneously after the obstructing stone is removed, and only about 10% of patients require subsequent biliary surgery for recurrent symptoms.³

4. Failed endoscopic management and laparoscopic shift

While endoscopic retrieval or lithotripsy is a valid "step-up" measure for stones in the duodenum or proximal jejunum, it frequently fails when stones are larger than 3 – 4 cm or are tightly impacted.⁹ In our

case, the 4.1 cm stone and the inability to navigate the scope beyond the impaction necessitated a shift to surgical intervention.

Laparoscopic enterolithotomy is emerging as the modern "gold standard" for minimally invasive management.⁸ Comparative studies show that the laparoscopic approach is not only feasible but results in fewer major complications and a shorter hospital stay compared to open surgery.⁷ For the emergency general surgeon, a laparoscopic-assisted approach — where the bowel loop is exteriorised through a small incision — offers a reasonable middle ground, reducing

the trauma of a full laparotomy while bypassing the technical difficulty of intracorporeal suturing in the presence of dilated bowel.¹⁰

Our patient's outcome aligns with findings that a totally laparoscopic enterolithotomy is safe and effective in stable patients, allowing for rapid normalisation of kidney function and early discharge.⁶ By choosing enterolithotomy with primary repair and forgoing cholecystectomy, we minimised the risk of biliary complications and prolonged anaesthesia in a patient with limited physiological reserve.^{7,9}

Conclusion

In morbid geriatric patients with multiple comorbidities, a stepwise approach beginning with a minimally invasive attempt is ideal. When endoscopy fails, laparoscopic enterolithotomy alone stands as the most evidence-based, safe, and definitive treatment, as it addresses the acute obstruction while avoiding the high morbidity of a one-stage biliary repair.^{2,5,8}

Manmohan M Kamat, Divya Udaykumar, Sharvari Gorkar, Rohan KJ, Akhil Mishra, Gulamgous Shaikh, Kristina Matthew, Sainath Kuppa, Yashraj Thakur. Beyond the Scope: Laparoscopic Rescue of Jejunal Gallstone Ileus Following Failed Endoscopic Retrieval. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-12>

References

1. Rigler LG, Borman CN, Noble JF. Gallstone obstruction: pathogenesis and roentgen manifestations. *JAMA*. 1941;117(21):1753–9.
2. Halabi WJ, Kang CY, Ketana N, et al. Surgery for gallstone ileus: a nationwide comparison of trends and outcomes. *Ann Surg*. 2014;259(2):329–35.
3. Tan YM, Wong WK, Ooi LL. A comparison of two surgical strategies for the emergency treatment of gallstone ileus. *Singapore Med J*. 2004;45(2):69–72.
4. Ayantunde AA, Agrawal A. Gallstone ileus: diagnosis and management. *World J Surg*. 2007;31(6):1294–9.
5. Orellana M, Vegas L, Cáceres A, et al. Laparoscopic management of gallstone ileus: a case report and literature review. *Int J Surg Case Rep*. 2021;85:106171.
6. Riaz N, Khan MR, Tayeb M. Gallstone ileus: retrospective review of a single centre's experience using two surgical procedures. *Singapore Med J*. 2008;49(8):624–6.
7. Moberg AC, Montgomery A. Laparoscopically assisted or open enterolithotomy for gallstone ileus. *Br J Surg*. 2007;94(1):53–7.
8. Zygomalas A, Karamanakos S, Kehagias I. Totally laparoscopic management of gallstone ileus—technical report and review of the literature. *J Laparoendosc Adv Surg Tech A*. 2012;22(3):265–8.
9. Jakubauskas M, Luksaite R, Sileikis A, et al. Gallstone ileus: management and clinical outcomes. *Medicina (Kaunas)*. 2019;55(9):598.
10. Angamuthu N, Alagaratnam S, D'Souza R, et al. Laparoscopic assisted enterolithotomy: a viable option in the management of gallstone ileus. *Br J Surg*. 2021;108(Suppl 6):zab259-605.

Undifferentiated Small Round Cell Sarcoma of the Pelvic Space in an Infant: A Rare Case Report

Krishna Kant Singh^{*}

^{*}Department of Haemato-Oncology and Bone Marrow Transplantation, BLK-Max Super Speciality Hospital, New Delhi

Correspondence:

Krishna Kant Singh

E-mail: drkrishnakant06@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-13>

Abstract:

Undifferentiated small round cell sarcomas (USRCS) are rare high-grade malignancies, which are even more exceptional when arising in the retroperitoneal space in infancy, with fewer than 100 such cases documented worldwide. We report a 4-month-old infant who presented with an incidentally detected lower abdominal mass. Imaging, histopathology, and immunohistochemistry (IHC) established a diagnosis of USRCS. The patient was managed with multimodal therapy comprising neoadjuvant vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) chemotherapy, surgical excision with right pelvic lymph node dissection, adjuvant radiotherapy, and further chemotherapy. This case underscores the rarity of pelvic USRCS in infancy, the diagnostic complexity posed by coexisting conditions, and the necessity of a multimodal diagnostic and therapeutic approach.

Key words: Undifferentiated Small Round Cell Sarcoma (USRCS), Retroperitoneal, Infant, Immunohistochemistry (IHC), Multimodal Therapy, VDC/IE Chemotherapy.

Introduction

Undifferentiated small round cell sarcomas (USRCS) represent a heterogeneous group of malignant tumours of uncertain histogenesis that predominantly arise in bones but rarely in soft tissues.¹ Extraskelatal USRCSs have been reported across diverse anatomical sites, including the head and neck, skin, breast, lung, bone, and deep abdominal wall.^{2–5} However, USRCS arising in the retroperitoneal space is exceedingly rare, with fewer than 100 cases documented in the literature since its first description in 1981.^{6–10}

Occurrence in an infant further adds to the diagnostic and therapeutic complexity of this entity. Herein, we present a rare case of pelvic USRCS in a 4-month-old

infant, discuss the diagnostic workup, and review the relevant literature.

Case Report

Clinical history and physical examination

A 4-month-old infant was brought to our department following incidental detection of a lower abdominal mass. The mass was not associated with any bowel or bladder symptoms. The child had a notable history of developing swelling of the left thigh at 1 month of age following vaccination. This was subsequently diagnosed as a tuberculous abscess, and antitubercular therapy (ATT) was commenced in May 2025. The patient also had bilateral polydactyly of all four limbs, with accessory fingers of both hands having been amputated. On physical examination, a 7 × 7 cm mass was palpable in the hypogastric region.

The mass was hard in consistency and was not adherent to the overlying skin.

Investigations

Imaging studies:

- Ultrasonography (USG) of the abdomen revealed a well-defined soft tissue lesion measuring approximately $6.57 \times 5.81 \times 5.93$ cm in the pelvis, with imaging features suggestive of a neoplastic aetiology.
- Contrast-enhanced computed tomography (CECT) of the abdomen demonstrated a large, heterogeneously enhancing mass lesion with multiple vascular channels in the lower abdomen. The mass compressed and displaced the urinary bladder to the left and compressed the rectosigmoid colon, resulting in dilatation of the large bowel loops.
- Whole-body positron emission tomography-computed tomography (PET-CT) identified a fluorodeoxyglucose (FDG)-avid, heterogeneous soft tissue mass measuring $5.6 \times 6.7 \times 6.8$ cm (maximum standardised uptake value [SUV_{max}] of 3.5) in the pelvic cavity, extending into the lower abdominal cavity. The mass abutted the right lateral pelvic wall and the right iliopsoas and extended anteriorly to the anterior abdominal wall. No distant metastases were identified.

Serum tumour markers:

- Alpha-fetoprotein (AFP) (6th June 2025): 40 ng/mL
- Lactate dehydrogenase (LDH): 264 U/L

Histopathology:

A USG-guided biopsy of the abdominal mass showed a malignant round blue cell tumour on morphology.

Immunohistochemistry (IHC):

- Positive markers: Vimentin (strong, diffuse), cytokeratin (dot-like), cyclin D1 (focal, weak), transducin-like enhancer of split 1 (TLE1) (focal, weak)
- Negative markers: Cluster of differentiation 45 (CD45), Wilms' tumour gene 1 (WT1), synaptophysin, chromogranin, smooth muscle actin (SMA), desmin, NKX2.2, cluster of differentiation 99 (CD99), myogenin, myogenic differentiation 1 (MyoD1),

cluster of differentiation 34 (CD34), synovial sarcoma translocation, chromosome 18 (SS18), special AT-rich sequence-binding protein 2 (SATB2), and sal-like protein 4 (SALL4)

- Integrase interactor 1 (INI1) and Brahma-related gene (BRG1) expression were retained in the tumour cells, effectively excluding rhabdoid tumour. The Ki-67 proliferation index was approximately 15%.

The overall IHC profile was consistent with USRCS.

Treatment and clinical course

Neoadjuvant chemotherapy: The patient was commenced on vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE) chemotherapy on 21st June 2025. Following completion of four cycles, a response assessment CECT of the abdomen demonstrated a large, heterogeneously enhancing mass (approximately $61 \times 71 \times 75$ mm) persisting with multiple vascular channels, continued compression and displacement of the urinary bladder, compression of the rectosigmoid colon with large bowel dilatation, displacement of the iliac vessels, and displacement and compression of the lower third of the right ureter with leftward deviation. The limited radiological response prompted surgical intervention.

Surgery: Surgical excision of the pelvic mass with right pelvic lymph node dissection was performed. Postoperative IHC from the resected specimen was positive for macrophage inhibitory cytokine (MIC), cyclin D1, and cluster of differentiation 56 (CD56) (weak BCOR), while negative for desmin, MyoD1, WT1, and NKX2.2, further confirming the diagnosis of USRCS.

Adjuvant radiotherapy: External beam radiotherapy was administered to a total dose of 18 Gy, to address residual microscopic disease.

Post-radiotherapy adjuvant chemotherapy: The patient subsequently received adjuvant chemotherapy comprising two cycles of IVA (ifosfamide, vincristine, actinomycin D) and one cycle of ifosfamide/adriamycin.

Discussion

USRCS represent a heterogeneous group of high-grade malignancies characterised by primitive round cell morphology and the lack of clear lineage differentiation.^{1,3,4} These tumours are rare in infants,

and pelvic localisation further adds to their clinical complexity. The differential diagnosis for small round blue cell tumours in infancy is broad, encompassing neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, lymphoma, and desmoplastic small round cell tumour.^{1,3,4}

In the present case, an extensive IHC workup was crucial in excluding these entities. Strong vimentin positivity with focal cytokeratin, cyclin D1, and TLE1 expression, along with the absence of CD99, desmin, myogenin, WT1, and NKX2.2, together with retained INI1 and BRG1 expression (effectively excluding a rhabdoid tumour), supported the final diagnosis of USRCS. A Ki-67 index of approximately 15% reflected the high-grade but not maximally proliferative nature of the tumour.

The presence of congenital anomalies including polydactyly in this patient is noteworthy, although no direct syndromic association with USRCS has been clearly established to date. Additionally, the concurrent history of a tuberculous abscess and ongoing ATT introduced diagnostic complexity by potentially masking or confounding the clinical presentation and delaying suspicion of malignancy.

Radiologically, the tumour exhibited typical aggressive features, including large size, heterogeneous enhancement, prominent vascularity, and significant mass effect on adjacent pelvic structures including the urinary bladder, rectosigmoid colon, iliac vessels, and right ureter. PET-CT played an important role in staging and confirmed the absence of distant metastases at presentation.^{6–10}

Management of USRCS necessitates a multimodal approach. The patient was treated with neoadjuvant VDC/IE chemotherapy, the standard regimen for Ewing family tumours and related sarcomas. The limited radiological response prompted surgical excision, which remains the principal determinant of long-term prognosis. Adjuvant radiotherapy and chemotherapy were administered to address residual microscopic disease and reduce the risk of local and systemic recurrence.

Despite aggressive multimodal treatment, USRCS carries a guarded prognosis given its high-grade biology and propensity for recurrence and metastasis.^{3,4,9} Early diagnosis and prompt initiation of combined-modality therapy are essential to optimise outcomes.

Conclusion

We report an exceptionally rare case of USRCS arising in the retroperitoneal/pelvic space in a 4-month-old infant. This case highlights the diagnostic complexity posed by shared morphological features with other round blue cell tumours, the confounding influence of coexisting infections, and the imaging mimicry of benign lesions such as teratomas. A comprehensive multimodal diagnostic strategy incorporating imaging, histopathology, IHC, and molecular profiling is imperative for accurate diagnosis. Multimodal treatment incorporating chemotherapy, surgery, and radiotherapy remains the cornerstone of management. Our report contributes to the limited body of literature on retroperitoneal USRCS in infancy and raises awareness among clinicians, radiologists, and pathologists of this rare but aggressive entity.

Learning points

- USRCS is extremely rare in infancy and may present as an incidentally detected abdominal mass without specific clinical symptoms.
- Comprehensive IHC is essential for accurate diagnosis and systematic exclusion of other small round blue cell tumours in this age group.
- Multimodal treatment incorporating chemotherapy, surgery, and radiotherapy is critical for disease control and reduction of recurrence risk.
- Coexisting conditions such as tuberculosis may complicate and delay the diagnosis of malignancy and should not detract from timely oncological workup.

Krishna Kant Singh. Undifferentiated Small Round Cell Sarcoma of the Pelvic Space in an Infant: A Rare Case Report. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-13>

References

1. Choi JH, Ro JY. The 2020 WHO classification of tumors of soft tissue: selected changes and new entities. *Adv Anatomic Pathol*. 2021;28:44–58.
2. Wright A, Desai M, Bolan CW, *et al*. Extraskkeletal Ewing sarcoma from head to toe: multimodality imaging review. *Radiographics*. 2022;42:1145–60.
3. Antonescu CR, Owosho AA, Zhang L, *et al*. Sarcomas with CIC-rearrangements are a distinct pathologic entity with aggressive outcome: a clinicopathologic and molecular study of 115 cases. *Am J Surg Pathol*. 2017;41:941–9.
4. Kao YC, Owosho AA, Sung YS, *et al*. BCOR-CCNB3 fusion positive sarcomas: a clinicopathologic and molecular analysis of 36 cases with comparison to morphologic spectrum and clinical behavior of other round cell sarcomas. *Am J Surg Pathol*. 2018;42:604–15.
5. Liu L, Li L, Ding Y, *et al*. Report and literature review of four cases of EWSR1::NFATC2 round cell sarcoma. *Diagn Pathol*. 2024;19:19.
6. Qian X, Kai X, Shaodong L, *et al*. Radiological and clinicopathological features of pPNET. *Eur J Radiol*. 2013;82:e888–93.
7. Ulasan S, Koc Z, Canpolat ET, *et al*. Radiological findings of primary retroperitoneal Ewing sarcoma. *Acta Radiol*. 2007;48:814–8.
8. Somarouthu BS, Shinagare AB, Rosenthal MH, *et al*. Multimodality imaging features, metastatic pattern and clinical outcome in adult extraskkeletal Ewing sarcoma: experience in 26 patients. *Br J Radiol*. 2014;87:20140123.
9. Wei Y, Zhang Z, Long C, *et al*. Case report: colon malignant tumor caused by retroperitoneal small round cell undifferentiated sarcoma. *Front Oncol*. 2023;13:1212475.
10. Blight JEM, Puls JL. Collateral venous flow through uterus caused by retroperitoneal extraosseous Ewing sarcoma. *Urology*. 1981;17:386–9.

Bilateral Patellofemoral Arthroplasty for End-Stage Patellofemoral Osteoarthritis in a Young Adult with Ehlers-Danlos Syndrome and Lifelong Patellar Instability: A Case Report

Prateek Upadhyay^{1*}, Harshavardhan Hegde¹, Nitiraj Oberoi¹, Rakesh Mattoo¹,
Akshay Kumar Saxena¹, Ajay Dhanopeya¹

¹Department of Orthopaedics, Max Smart Super Speciality Hospital, Saket, New Delhi

Correspondence:

Prateek Upadhyay

E-mail: prateekrpp.upadhyay@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-14>

Abstract:

Isolated patellofemoral osteoarthritis in young adults is rare and typically secondary to recurrent patellar instability, dysplasia, or connective tissue disorders rather than primary degeneration, with Ehlers-Danlos syndrome (EDS) being a notable cause due to generalised ligamentous laxity that predisposes to lifelong instability and early compartment-specific cartilage failure. While patellofemoral arthroplasty (PFA) is an established joint-preserving option for end-stage isolated disease, its role in young patients with connective tissue disorders, especially bilaterally, remains poorly defined. We report the case of a 34-year-old woman with genetically confirmed EDS and lifelong bilateral patellar instability who presented with anterior knee pain and progressive disability despite multiple stabilising procedures, realignment osteotomy, and biologic injections. Magnetic resonance imaging (MRI) demonstrated isolated patellofemoral osteoarthritis with preserved tibiofemoral compartments and intact ligaments, and she underwent bilateral PFA using modern second-generation onlay components. At six weeks, she achieved full range of motion, no extensor lag, and complete pain relief, and by nine months reported high satisfaction and substantial functional improvement, including restoration of pain-free stair negotiation, with recovery maintained despite a two-month interruption of rehabilitation due to intercurrent illness. This case highlights that PFA can provide meaningful pain relief and functional restoration in carefully selected young patients with isolated patellofemoral arthritis secondary to EDS, emphasising the importance of meticulous patient selection, confirmation of preserved tibiofemoral compartments, use of modern onlay implants, and structured rehabilitation for successful outcomes.

Key words: Patellofemoral Arthroplasty, Ehlers-Danlos Syndrome, Patellar Instability, Patellofemoral Osteoarthritis, Joint Preservation, Young Adult.

Introduction

Isolated patellofemoral osteoarthritis (PFOA) is an uncommon diagnosis in young adults and rarely represents a primary degenerative disease. In this age group, it is most often a sequela of recurrent patellar instability, trochlear dysplasia, prior surgical realignment, or an underlying

connective tissue disorder.¹⁻³ Recurrent lateral patellar dislocation is a particularly important driver of early chondral failure. Magnetic resonance imaging (MRI) studies have demonstrated patellar cartilage lesions in more than 90% of patients after instability events, with full-thickness defects in almost half.^{1,4} Each dislocation generates abnormal lateral patellofemoral contact pressures that accelerate focal

cartilage loss, producing end-stage compartment-specific arthritis decades earlier than typical age-related diseases.^{2,5}

Ehlers-Danlos syndrome (EDS) comprises a heterogeneous group of heritable connective tissue disorders characterised by abnormal collagen architecture, generalised ligamentous laxity, and impaired soft tissue healing.^{6,7} Because patellofemoral stability depends heavily on capsuloligamentous restraints, such as the medial patellofemoral ligament,⁸ the joint is particularly vulnerable in EDS. Affected individuals demonstrate disproportionately high rates of patellar subluxation, patella alta, and lateral maltracking from childhood, compounded by impaired proprioception, which further degrades dynamic stability.^{9–11} The combination of mechanical instability and defective tissue repair predisposes patients to relentless chondral attrition despite otherwise appropriate treatment.

For end-stage isolated PFOA with preserved tibiofemoral compartments and acceptable limb alignment, patellofemoral arthroplasty (PFA) offers a bone- and ligament-preserving alternative to total knee arthroplasty (TKA).^{3,12} Early inlay designs were associated with high rates of maltracking and failure; however, contemporary second-generation onlay trochlear components, combined with stricter patient selection, have markedly improved tracking, function, and survivorship.^{12,13} Modern registry and cohort data report 10-year survivorship approaching 80% – 85%, with revision most frequently driven by the progression of tibiofemoral arthritis rather than implant-related failure.^{13–16}

Despite these advances, the role of PFA in young patients with connective tissue disorders remains poorly defined, and bilateral disease in this setting has rarely been reported.^{3,17} Outcomes in young, active patients are highly dependent on accurate selection and surgical execution.^{17,18} We present a 34-year-old woman with EDS and lifelong bilateral patellar instability who underwent single-stage bilateral PFA for end-stage isolated PFOA. We describe her clinical course, operative management, and nine-month outcome, together with the selection rationale relevant to this high-risk population. This case was reported in accordance with the CAsE REports (CARE) guidelines.

Case Report

History

A 34-year-old woman presented with long-standing bilateral anterior knee pain, recurrent patellar instability, and progressive functional limitation. Patellar instability was noted since early childhood, coinciding with the

onset of independent ambulation, with recurrent lateral displacement of both patellae observed during infancy, and conservative observation was advised at that time. Knee pain persisted throughout childhood and adolescence, particularly after physical activity. At 14 years of age, genetic evaluation confirmed EDS against a background of generalised connective tissue laxity. Conservative management in subsequent years, including collagen supplementation, chondroprotective agents, activity modification, and intermittent analgesia, failed to halt symptom progression.

At 22 years of age, the patient sustained her first documented traumatic lateral patellar dislocation of the right knee, associated with marked pain and functional impairment. At 24 years of age (2016), evaluation identified patella alta with lateral maltracking, and she underwent her first right knee stabilising procedure, which provided only temporary relief. In 2022, recurrent symptoms prompted a second right-knee procedure comprising peri-patellar cyst excision and arthroscopic chondral debridement, but subsequent platelet-rich plasma and hyaluronic acid injections did not provide sustained benefit. In 2023, persistent instability and worsening cartilage damage were addressed with open tibial tubercle distalisation and medialisation, fixed with titanium screws, combined with repeat chondral debridement. Increased loading of the contralateral limb thereafter precipitated progressive left knee pain and instability, for which left knee patellar stabilisation was performed in 2024, followed one month later by bilateral autologous adipose-derived stem cell injections, again without clinical improvement. The chronology of interventions is summarised in Table 1.

By December 2024, the patient reported significant bilateral pain, recurrent effusion after ambulation, and gait instability, requiring a single crutch for outdoor mobility. She could ambulate indoors unaided but had marked difficulty with stair climbing and prolonged walking. Clinical examination revealed generalised joint hypermobility and anterior knee pain with patellofemoral crepitus. The tibiofemoral compartments were clinically uninvolved, and there was no ligamentous deficiency.

Period	Intervention/event
Childhood	Bilateral patellar instability from the onset of ambulation; conservative observation
Age 14	EDS confirmed genetically
Age 22	First traumatic lateral patellar dislocation (right knee)
2016 (age 24)	First right-knee stabilisation for patella alta and lateral maltracking
2022	Right-knee peri-patellar cyst excision and arthroscopic chondral debridement; PRP and hyaluronic acid injections (no sustained benefit)
2023	Right-knee tibial tubercle distalisation and medialisation with screw fixation; repeat chondral debridement
2024	Left-knee patellar stabilisation; bilateral adipose-derived stem-cell injections (no improvement)
December 2024	End-stage isolated bilateral PFOA confirmed; decision for single-stage bilateral PFA
2025	Single-stage bilateral PFA (second-generation onlay components)
6 weeks postoperatively	Full range of motion, no extensor lag, complete pain relief
9 months postoperatively	High satisfaction and maintained functional gains; rehabilitation interrupted by intercurrent illness

Table 1: Chronological summary of the clinical course and interventions.

Abbreviations: EDS: Ehlers-Danlos Syndrome; PFA: Patellofemoral Arthroplasty; PFOA: Patellofemoral Osteoarthritis; PRP: Platelet-Rich Plasma.

Examination

The patient ambulated with a bilateral antalgic gait and was unable to stand independently. Her walking tolerance was limited to approximately 50 m before requiring rest, rendering her largely dependent on a wheelchair for daily ambulation. Both knees demonstrated marked patellofemoral crepitus throughout the range of motion, with positive patellar grind tests bilaterally. A 10° extensor lag was present in both knees; although a functional range of flexion was preserved, the terminal arc of movement was painful. Generalised ligamentous laxity, consistent with the established diagnosis of EDS, was evident on examination. The tibiofemoral joint lines were non-tender, and the collateral and cruciate ligaments were clinically stable, with no clinical evidence of tibiofemoral compartment involvement.

Imaging and diagnostic work-up

MRI demonstrated full-thickness patellar cartilage loss, trochlear degeneration, subchondral marrow oedema, lateral patellar tilt, mild lateral subluxation, and trochlear dysplasia (Figure 1). The medial and lateral tibiofemoral compartments and all major ligaments were intact, confirming that the disease was confined to the patellofemoral compartment. Weight-bearing and axial radiographs corroborated isolated patellofemoral involvement and showed retained tibial tubercle fixation on the right side from prior realignment (Figure 2). After a multidisciplinary review, the combination of end-stage isolated PFOA, preserved tibiofemoral cartilage, intact ligaments, and acceptable alignment was judged to fulfil the established prerequisites for PFA,^{3,12} and single-stage bilateral PFA was planned.

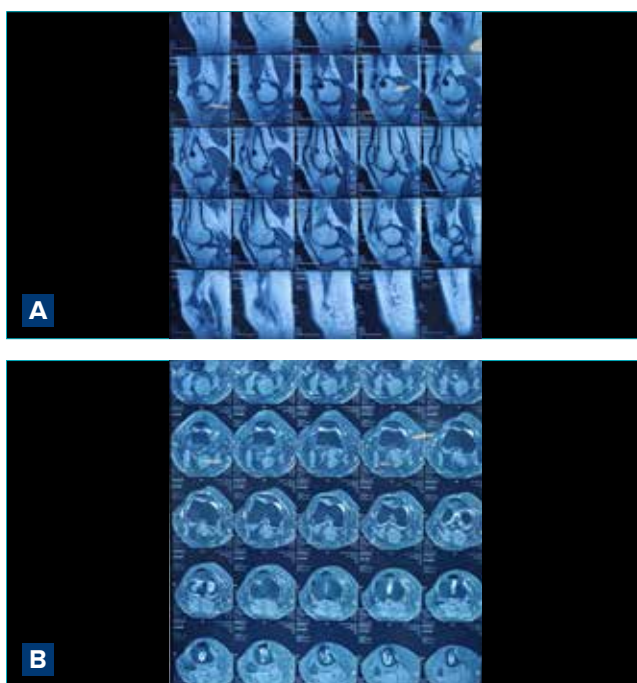


Figure 1A and B: Preoperative magnetic resonance imaging (MRI): **A.** Sagittal image demonstrating full-thickness patellar cartilage loss, trochlear degeneration, and subchondral marrow oedema; **B.** Axial image demonstrating lateral patellar tilt, mild subluxation, and trochlear dysplasia, with preserved tibiofemoral compartments.

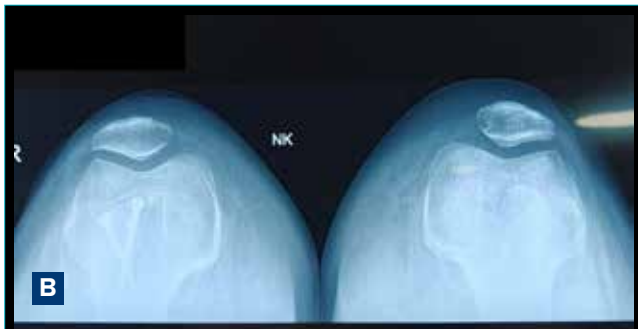


Figure 2A and B: Preoperative radiographs: **A.** Standing anteroposterior view of both knees showing isolated patellofemoral involvement and retained tibial tubercle screw fixation on the right; **B.** Axial (skyline) view of both patellae demonstrating patellofemoral degeneration.

Surgical procedure

Single-stage bilateral PFA was performed using modern second-generation onlay components in a single operative session. The procedure was performed under regional anaesthesia with the patient in the supine position and a thigh tourniquet applied to each limb. A standard anterior midline skin incision was followed by a medial parapatellar arthrotomy to expose the patellofemoral joint. Intraoperative inspection confirmed extensive full-thickness cartilage loss across the patella and trochlea, with macroscopically preserved tibiofemoral cartilage (Figure 3A), validating the preoperative imaging-based selection.

The trochlea was prepared with dedicated instrumentation to optimise the rotational alignment and resection depth, and a second-generation onlay trochlear component was implanted with cement fixation and seated flush with the adjacent articular cartilage to minimise catching during patellar excursion. The patella was resurfaced to restore the native thickness and centralise tracking (Figure 3B). Patellar tracking and stability were dynamically assessed through a full range of motion, confirming central engagement without tilt, subluxation, or the need for lateral release. The arthrotomy and soft tissue repair were performed in layers. No intraoperative complications occurred, and the contralateral knee was treated similarly during the same operative session.

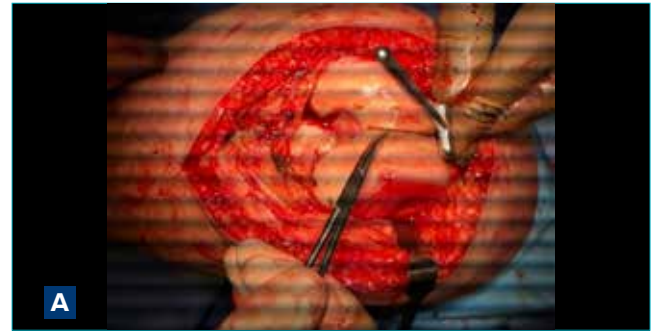


Figure 3A and B: Intraoperative photographs: **A.** Full-thickness patellofemoral cartilage loss with preserved tibiofemoral surfaces; **B.** Final patellofemoral prosthesis in situ after trochlear resurfacing and patellar resurfacing.

Postoperative course and follow-up

Rehabilitation followed an accelerated protocol with immediate weight-bearing as tolerated and early range-of-motion exercises. On the first postoperative day, the patient was mobilised with assistance using a walker (Figure 4). Postoperative radiographs confirmed well-aligned and well-fixed components in both knees, with restoration of patellofemoral congruence (Figure 5). By six weeks, she had regained a full range of motion with no extensor lag, a negative patellar grind test, and complete resolution of her preoperative pain.



Figure 4: Early postoperative mobilisation on the first postoperative day, ambulating with a walking frame.

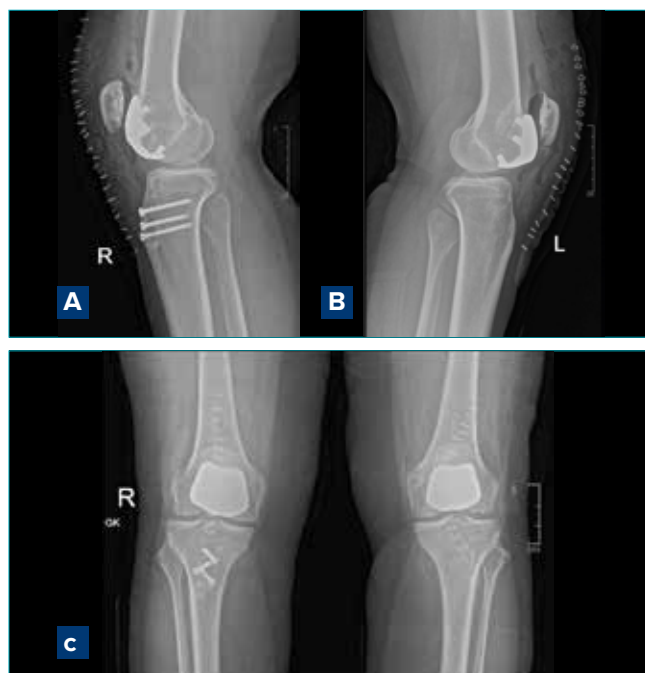


Figure 5A – C: Postoperative radiographs demonstrating well-aligned and well-fixed patellofemoral components: **A.** Right knee, with retained tibial tubercle screws from previous realignment; **B.** Left knee; **C.** Anteroposterior radiographs for both knees together.

At approximately nine months postoperatively, the patient was reviewed, including remote video assessment of gait and active range of motion. She reported high satisfaction and substantial, durable pain relief, with unaided indoor ambulation and use of a single crutch outdoors for activity-related anterior knee discomfort during prolonged walking. Recovery was asymmetric, with the left knee functioning better than the right, and mild effusion was noted after activity. Notably, the structured rehabilitation programme was interrupted for approximately two months due to an intercurrent gynaecological illness requiring medical therapy, limiting the prescribed physiotherapy during that interval. The patient was concurrently pursuing weight reduction to lower the patellofemoral load. Despite this interruption, the early gains were maintained: stair negotiation, previously a principal source of disabling pain, remained markedly improved, and video assessment demonstrated a guarded but functional, mildly antalgic gait with a near-full active arc of knee motion (Figure 6). No implant-related complications, instability, or extensor mechanism failure were observed during the latest review.

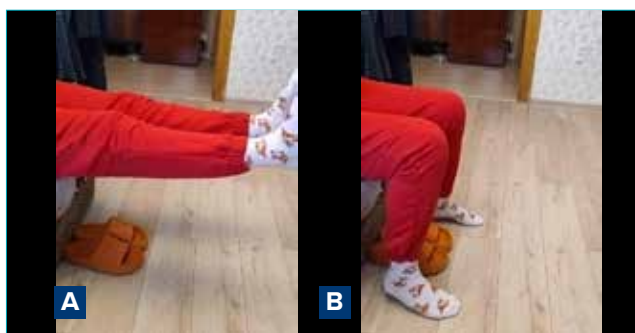


Figure 6A and B: Active range of motion at nine-month follow-up: **A.** Active terminal knee extension; **B.** Active knee flexion.

Discussion

This case illustrates the successful application of single-stage bilateral PFA in a 34-year-old woman with EDS and lifelong patellar instability, a rare and challenging indication. This demonstrates that when the disease is genuinely confined to the patellofemoral compartment, modern PFA can deliver substantial pain relief and functional restoration, even in a connective tissue disorder traditionally regarded as a relative contraindication to soft-tissue-dependent reconstruction.

Patellofemoral arthritis in young adults is biomechanically and aetiologically distinct from age-related tibiofemoral osteoarthritis, arising predominantly from instability, dysplasia, malalignment, or prior surgery.^{1–3} In EDS, defective collagen and generalised laxity create a self-perpetuating cycle of subluxation, abnormal lateral contact pressure, and accelerated chondral loss,^{7–11} compounded by impaired proprioceptive control of the extensor mechanism.¹⁰ This pathophysiology explains why our patient progressed to full-thickness patellofemoral cartilage loss and end-stage disease at an exceptionally young chronological age despite an extensive history of joint-preserving treatment.

Importantly, the sequential failure of stabilising procedures, tibial tubercle realignment, chondral debridement, and biologic injections in this patient reflects a recognised limitation of soft-tissue-dependent strategies in EDS: intrinsic collagen abnormality undermines the durability of ligamentous reconstruction and predisposes patients to recurrent instability and progressive degeneration despite technically adequate surgery.^{3,5,10} These interventions remain appropriate first-line options for instability-related patellofemoral pathology,^{3,5} but their diminished durability in connective tissue disease should temper expectations and inform earlier consideration of compartmental arthroplasty once cartilage failure becomes irreversible.

Contemporary evidence supports PFA as a durable, joint-preserving option for end-stage isolated diseases. Second-generation onlay designs have largely overcome the maltracking and failure rates of earlier inlay implants, and modern series report a 10-year survivorship of approximately 80% – 85%, with revision driven chiefly by tibiofemoral progression rather than implant failure.^{12–16} Compared with TKA, PFA preserves the bone stock, cruciate ligaments, and tibiofemoral kinematics, which is particularly valuable in young patients who are likely to require future revision.^{12,17} The favourable early outcome in our patient is consistent with these data and with the principle that meticulous selection and surgical execution are decisive determinants of success in young, active patients.^{17,18}

Patient selection was crucial in this case. The consensus criteria restrict PFA to truly isolated patellofemoral degeneration with preserved tibiofemoral compartments, acceptable limb alignment, and intact cruciate and collateral ligaments.^{3,12} Comprehensive MRI confirmed that these prerequisites were met despite the EDS diagnosis, supporting the decision to proceed with surgery. The bilateral and symmetrical nature of the disease in this patient reflects the systemic pathology of EDS rather than isolated mechanical failure, and bilateral PFA at 34 years of age remains rarely reported.

The clinical course also highlights the contribution of rehabilitation to PFA outcomes. Quadriceps conditioning and graded loading are essential to optimise tracking and offload the resurfaced compartment; the temporary interruption of physiotherapy by an intercurrent illness in this patient, together with persisting right-sided discomfort and activity-related effusion, is consistent with deconditioning rather than structural failure and is expected to improve with resumption of structured therapy and ongoing weight reduction. This underscores the value of integrating rehabilitation planning and comorbidity

management into the perioperative pathway for young arthroplasty patients.

This study has several limitations. As a single case with a nine-month follow-up, no inference can be drawn regarding long-term survivorship, which is the principal concern in young patients with EDS, given their predisposition to soft-tissue compromise and the recognised risk of tibiofemoral progression. Part of the latest assessment was conducted by video rather than an in-person examination, which limited the objective measurement of range of motion and effusion. Continued longitudinal surveillance with validated patient-reported outcome measures and serial radiographs is necessary to define durability and detect early tibiofemoral degeneration or component loosening.

Patient Perspective

The patient was highly satisfied with the outcome of the surgery. She described how, before the operation, she experienced severe knee pain even when climbing stairs, whereas afterwards, she was able to negotiate stairs without pain. She expressed gratitude for the improvement in her daily function and independence and remained motivated to continue rehabilitation and weight reduction to further improve her mobility.

Declarations

Informed consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Ethical approval: Institutional review board approval is not required for a single de-identified case report at the authors' institution; local requirements should be confirmed. This report adheres to the CARE guidelines.

Conflicts of interest: The authors declare that they have no competing interests.

Funding: This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conclusion

Single-stage bilateral PFA achieved substantial pain relief and functional restoration in a 34-year-old woman with EDS and end-stage isolated PFOA refractory to multiple joint-preserving procedures. With rigorous confirmation of preserved tibiofemoral compartments and intact ligaments, modern onlay PFA can be a rational, bone-preserving alternative to TKA in carefully selected young patients with connective tissue disease, deferring the morbidity of more extensive reconstruction. Long-term outcome-based follow-up remains essential to establish durability in this high-risk population.

Learning points

- In young adults, isolated PFOA is usually secondary to instability, dysplasia, or connective tissue diseases. EDS can cause end-stage compartmental cartilage failure at an exceptionally young age.
- Soft-tissue-dependent procedures (stabilisation, realignment, biologics) have diminished durability in EDS owing to intrinsic collagen abnormalities, and their sequential failure may herald irreversible cartilage loss.
- Modern second-generation onlay PFA can provide marked pain relief and functional gains in carefully selected patients, even bilaterally and in those with connective tissue disease, when the tibiofemoral compartments and ligaments are confirmed to be intact.
- Structured rehabilitation, quadriceps conditioning, comorbidity management, and long-term surveillance are integral to optimising and sustaining outcomes in young PFA patients.

Prateek Upadhyay, Harshavardhan Hegde, Nitiraj Oberoi, Rakesh Mattoo, Akshay Kumar Saxena, Ajay Dhanopeya. Bilateral Patellofemoral Arthroplasty for End-Stage Patellofemoral Osteoarthritis in a Young Adult with Ehlers-Danlos Syndrome and Lifelong Patellar Instability: A Case Report. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-14>

References

1. Nomura E, Inoue M. Cartilage lesions of the patella in recurrent patellar dislocation. *Am J Sports Med.* 2004;32(2):498–502.
2. Migliorini F, Colarossi G, Eschweiler J, et al. Patellofemoral chondromalacia after patellar instability: a systematic review. *J Orthop Surg Res.* 2022;17:63.
3. Hoogervorst P, van Sambeeck JDP, van den Bekerom MP, et al. Patient selection for patellofemoral arthroplasty: a systematic review. *J Exp Orthop.* 2022;9:91.
4. Smith TO, Donell ST, Song F, et al. The relationship between patellar instability and patellofemoral osteoarthritis: a systematic review. *Arthritis Care Res (Hoboken).* 2010;62(4):529–38.
5. Fulkerson JP. Diagnosis and treatment of patients with patellofemoral pain. *Am J Sports Med.* 2002;30(3):447–56.
6. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers–Danlos syndromes. *Am J Med Genet C Semin Med Genet.* 2017;175(1):8–26.
7. Castori M. Ehlers–Danlos syndrome(s) and joint hypermobility spectrum disorders: clinical and nosological aspects. *Am J Med Genet C Semin Med Genet.* 2017;175(1):26–37.
8. Nomura E, Inoue M, Osada N. Anatomical analysis of the medial patellofemoral ligament of the knee, especially the femoral attachment. *Knee Surg Sports Traumatol Arthrosc.* 2005;13(7):510–5.
9. Pacey V, Tofts L, Adams RD, et al. Joint hypermobility syndrome: a review for clinicians. *J Paediatr Child Health.* 2015;51(4):373–80.
10. Rombaut L, Malfait F, De Paepe A, et al. Joint position sense and vibratory perception sense in patients with Ehlers–Danlos syndrome. *Clin Rheumatol.* 2010;29(3):289–95.
11. Scheper MC, de Vries JE, Juul-Kristensen B, et al. Generalized joint hypermobility in professional dancers: a sign of talent or vulnerability? *Rheumatology (Oxford).* 2013;52(4):651–8.

12. van Jonbergen HP, Poolman RW, van Kampen A. Isolated patellofemoral arthroplasty: a systematic review. *J Arthroplasty*. 2010;25(6):1066–71.
13. Wang Y, Xu Y, Li Z, *et al*. Long-term outcomes of second-generation patellofemoral arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2023;31:2282–91.
14. Pagano A, Bosco F, Blonna D, *et al*. Survivorship and clinical results of modern patellofemoral arthroplasty: a registry-based analysis. *Knee Surg Sports Traumatol Arthrosc*. 2024;32:1402–11.
15. Vella-Baldacchino M, Chughtai D, Kow J, *et al*. Outcomes of patellofemoral joint arthroplasty: a systematic review of revision timelines and complication rates. *J Orthop Surg Res*. 2025;20(1):289.
16. Cimatti P, Rocchi M, Dallari B, *et al*. Systematic review and meta-analysis of implant-specific outcomes in inlay and onlay patellofemoral arthroplasty for isolated patellofemoral osteoarthritis. *J Exp Orthop*. 2025;12(4):e70541.
17. Noyes FR, Fleckenstein CM, Nolan J. Return to Sports in Patients Aged 50 Years or Younger After Robotic-Assisted Patellofemoral Arthroplasty: A 10-Year Experience Reporting High Clinical Benefits and High Patient Satisfaction With Return to an Active Lifestyle. *Am J Sports Med*. 2024;52(6):1514–26.
18. Vella-Baldacchino M, Davies AR, Bottle A, *et al*. Association between surgeon volume and patient outcomes after elective patellofemoral arthroplasty: a population-based cohort study using data from the National Joint Registry and Hospital Episode Statistics for England. *JBJS*. 2025;107(8):819–28.

Zolpidem Intoxication Leading to Coma and a Rapid Flumazenil Awakening Response: A Definitive Antidote

Bhanu Pratap Singh^{1*}, Mandeep Singh Gill², Vedvartya³, Harjit Singh⁴

¹Department of Internal Medicine, Max Super Speciality Hospital, Bathinda, Punjab

²Department of Anaesthesia, Max Super Speciality Hospital, Bathinda, Punjab

³Department of Emergency Medicine, Max Super Speciality Hospital, Bathinda, Punjab

⁴Medical Officer Emergency, Max Super Speciality Hospital, Bathinda, Punjab

Correspondence:

Bhanu Pratap Singh

E-mail: Bhanu.Singh1@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-15>

Abstract:

Zolpidem is a new imidazopyridine hypnotic that has a specific action on the central omega-1 receptor subtype and is a non-benzodiazepine hypnotic. A 39-year-old woman with a history of depression and living alone presented to our hospital in a coma with a Glasgow Coma Scale (GCS) score of 3 after consuming 25 – 30 zolpidem tablets. Previously, she had been on antidepressants and sedatives, the details of which were unknown. The patient remained on ventilatory support for 36 – 48 hours after conservative management. The decision to start flumazenil (a competitive antagonist at the benzodiazepine binding site on the gamma-aminobutyric acid type A [GABA_A] receptor) was made. The patient was started on a low-dose infusion and showed a positive response over the next day. Infusion titration was performed in incremental doses, and there was a complete response as the patient regained consciousness. The patient was extubated after 2 days of infusion and safely discharged from the hospital.

Key words: Zolpidem Overdose, Flumazenil, Drug-Induced Coma, Continuous Flumazenil Infusion, Hypnotic Toxicity.

Introduction

Zolpidem, commonly prescribed as Zolfresh in India, is widely used for the short-term management of insomnia because of its rapid onset of action and relatively short elimination half-life.^{1,2} It acts as a positive allosteric modulator of the gamma-aminobutyric acid type A (GABA_A) receptor, binding selectively to the alpha 1 subunit, to induce sleep.^{1,2}

Zolpidem toxicity can result from accidental overdose or self-harm,^{3,4} which can lead to central nervous system depression ranging from drowsiness, slurred speech, confusion, and ataxia to severe toxicity, coma, and respiratory depression requiring ventilatory support,

particularly if co-ingested with other drugs or alcohol. The management of this condition is generally supportive.

Zolpidem is absorbed quickly from the gastrointestinal tract^{2,5} and is widely distributed throughout the body. It readily crosses the blood-brain barrier, with a high plasma protein binding rate of approximately 92% – 95%. It is extensively metabolised in the liver via the cytochrome P450 (CYP) system, specifically CYP3A4 (61%) and CYP2C9 (22%). Less than 1% of the drug is excreted unchanged in urine. Metabolism is slower in older adults and in women.

Flumazenil is a potent benzodiazepine antagonist^{4,6} and an antidote used to reverse the sedative, hypnotic, or

toxic effects of benzodiazepines. It competitively binds to the GABA_A receptor complex in the brain, blocking benzodiazepines from binding and stimulating these receptors. However, it is cautiously used or generally avoided in patients with a history of seizures, severe head injury, or suspected tricyclic antidepressant overdose.

Case Report

A 39-year-old female with a history of family problems lived alone. She had depression and had previously visited multiple physicians and psychiatrists who prescribed various medications, the details of which were unknown, which induced sleepiness, according to her husband. On the morning of presentation, reportedly at 8:00 AM, the patient consumed some medications, according to the history provided by her husband. Around 25 – 30 tablets of zolpidem were consumed, as confirmed. The patient was taken to a local hospital, where no significant treatment was administered apart from intravenous fluids and proton pump inhibitors. The patient was admitted to our hospital at 4:30 PM, where the first gastric lavage was performed. On physical examination, the patient was unconscious with a Glasgow Coma Scale (GCS) score of 3, and there was no verbal response to verbal or painful stimuli. The pupils were relatively small but reactive to light. The patient was afebrile, and her breathing was shallow. Her vital signs were: heart rate (HR), 70 beats/min; blood pressure (BP), 130/80 mmHg; and peripheral oxygen saturation (SpO₂), 94% on room air. Systemic examination showed basal crepitations on chest auscultation, and some secretions had collected in the upper airways. The plantar reflexes were downgoing.

The patient was immediately intubated and placed on a ventilator with the following ventilatory settings: Mode, synchronised intermittent mandatory ventilation (SIMV) (volume control), fraction of inspired oxygen (FiO₂), 50%; respiratory rate, 16/min; tidal volume, 480 mL; and positive end-expiratory pressure (PEEP), 5 cmH₂O. Baseline investigations were done, including plain computed tomography (CT) of the brain, which was normal. Her investigations revealed a complete blood count with haemoglobin of 13.1 g/dL, total leucocyte count (TLC) of $11.1 \times 10^9/L$ (reference range, $4 - 10 \times 10^9/L$), normal kidney function, and normal liver function tests. Her serum sodium was 136 mmol/L (136 – 146), serum potassium 4.71 mmol/L (3.5 – 5.5), chloride 102 mmol/L (101 – 109), bicarbonate 25.4 mmol/L (21 – 31), serum calcium 8.8 mg/dL, and urine

examination, along with a urine drug assay, was normal and negative for most drugs, including benzodiazepines. Her viral markers were negative. The initial arterial blood gas analysis showed a pH of 7.41, a partial pressure of carbon dioxide (PaCO₂) of 47.3 mmHg (35 – 45 mmHg), which was elevated, a partial pressure of oxygen (PaO₂) of 81.4 mmHg (85 – 105 mmHg), and an HCO₃⁻ level of 28.8 mmol/L.

Her management started with measures to prevent aspiration pneumonia, intravenous fluids, metronidazole, proton pump inhibitors, multivitamins, and a 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist after gastric lavage. The patient was kept nil by mouth overnight and advised Ryle's tube aspiration if needed, along with suctioning. After 24 hours, the patient remained comatose, maintaining vital signs and parameters on the same ventilatory settings. The patient was started on oral feeds the next day through a Ryle's tube (150 mL every 3 hours) along with deep vein thrombosis (DVT) prevention by applying DVT pumps. The next day, the patient remained comatose, and flumazenil was continuously infused at an initial dose of 0.25 mg/h. The following day, the patient was conscious and responded to verbal commands. The dose of flumazenil was increased to 0.5 mg/h, and on the following day, the patient was fully conscious and extubated. Her Ryle's tube was removed, and she was started on a liquid diet and shifted to the ward. The urinary catheter was removed, and the patient was discharged the next day after resuming a normal diet.

Discussion

Isolated zolpidem overdose is generally considered to have a favourable prognosis.^{3,4} Most patients present with drowsiness, ataxia, dysarthria, confusion, or mild respiratory depression, and recovery usually occurs within 6 – 12 hours with supportive care alone. Severe neurological depression, prolonged coma, respiratory failure, or cardiovascular compromise are uncommon and are more frequently associated with mixed overdoses involving alcohol, benzodiazepines, opioids, antidepressants, or other sedative hypnotics.

Our patient developed profound coma (GCS score of 3) following ingestion of 300 mg of zolpidem and remained unconscious for nearly 48 hours despite appropriate management. Such prolonged neurological depression is unusual, considering the elimination half-life of zolpidem

of approximately 2 – 3 hours.^{2,5} Several mechanisms may explain the prolonged coma after massive zolpidem ingestion. First, saturation of hepatic metabolism may delay drug clearance. Zolpidem undergoes extensive hepatic metabolism,^{2,5} predominantly through CYP3A4, with additional contributions from CYP1A2, CYP2D6, and CYP2C19. Genetic polymorphisms, hepatic dysfunction, advanced age, and drugs affecting these enzymes may prolong elimination. Second, delayed gastric emptying and continued gastrointestinal absorption after large overdoses may maintain elevated plasma concentrations. Third, prolonged occupancy of GABA_A receptors at supratherapeutic concentrations may result in sustained central nervous system depression despite declining serum drug levels. These mechanisms explain the prolonged unconsciousness observed in our patient.

An important feature of this case was the marked neurological improvement after the initiation of continuous intravenous flumazenil infusion. Flumazenil is a competitive antagonist⁶ at the benzodiazepine binding site of the GABA_A receptor. Because zolpidem acts through this receptor despite its non-benzodiazepine structure, flumazenil can effectively reverse zolpidem-induced sedation. Numerous case reports have demonstrated rapid restoration of consciousness^{6,7} after flumazenil administration in cases of isolated zolpidem

poisoning, supporting receptor-mediated antagonism as the underlying mechanism. Most previously published reports have described reversal following a single intravenous bolus^{6,7} dose of flumazenil. However, recurrent sedation frequently occurs because the plasma half-life of flumazenil (40 – 80 minutes) is considerably shorter than that of zolpidem, particularly following massive ingestion. Continuous intravenous infusion provides sustained receptor antagonism⁸ and may prevent the recurrence of coma while the offending drug is gradually eliminated. In our patient, awakening occurred within 12 hours of starting flumazenil infusion without recurrence of neurological deterioration during treatment. This favourable response supports the use of continuous infusion in selected patients with persistent zolpidem-induced coma. The decision to administer flumazenil in cases of overdose requires careful patient selection. Although generally safe in isolated zolpidem poisoning,^{3,4} flumazenil may precipitate seizures in patients with chronic benzodiazepine dependence, epilepsy, or mixed overdoses involving antidepressants, opioids, and proconvulsant medications. The principal limitation of this report is the absence of serum concentrations of zolpidem. Furthermore, as this represents a single case, spontaneous neurological recovery cannot be completely excluded.

Conclusion

In summary, this case demonstrates that a massive, isolated zolpidem overdose may produce a prolonged coma extending well beyond the expected pharmacokinetic duration of the drug. Continuous flumazenil infusion was associated with rapid and sustained neurological recovery without adverse effects. In carefully selected patients with persistent coma, after exclusion of contraindications, continuous flumazenil infusion should be considered as a therapeutic option in addition to standard supportive care.

Bhanu Pratap Singh, Mandeep Singh Gill, Vedvartya, Harjit Singh. Zolpidem Intoxication Leading to Coma and a Rapid Flumazenil Awakening Response: A Definitive Antidote. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-15>

References

1. Sanger DJ, Depoortere H. The pharmacology and mechanism of action of zolpidem. *CNS Drug Rev.* 1998;4(4):323–40.
2. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs.* 2000;59(4):865–89.
3. Gunja N. The clinical and forensic toxicology of Z-drugs. *J Med Toxicol.* 2013;9(2):155–62.
4. Olson KR, editor. Poisoning and Drug Overdose. 8th Edition. New York: McGraw-Hill Education; 2022.
5. Greenblatt DJ, Harmatz JS, Roth T. Zolpidem and its use in insomnia. *J Clin Psychiatry.* 1998;59(Suppl 16):23–9.
6. Patat A, Naef MM, van Gessel E, *et al.* Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther.* 1994;56(4):430–6.
7. Lheureux P, Debailleul G, De Witte O, *et al.* Zolpidem intoxication mimicking narcotic overdose: response to flumazenil. *Hum Exp Toxicol.* 1990;9(2):105–7.
8. Quaglio G, Lugoboni F, Fornasiero A, *et al.* Dependence on zolpidem: two case reports of detoxification with flumazenil infusion. *Int Clin Psychopharmacol.* 2005;20(5):285–7.

Diagnostic Masquerade in Advanced Lymphoma: Angioimmunoblastic T-Cell Lymphoma Initially Mimicking Diffuse Large B-Cell Lymphoma

Kshirabdhi Tanaya Panda^{1*}, Sanjeev Kumar Sharma¹, Anamika Bakliwal¹, Anil Handoo², Pratyush Mishra², Rajan Duggal³, Nivedita Patnaik³

¹Department of Haemato-Oncology and Bone Marrow Transplant, BLK-Max Super Speciality Hospital, New Delhi

²Department of Lab Services, BLK-Max Super Speciality Hospital, New Delhi

³Department of Histopathology and Cytopathology, BLK-Max Super Speciality Hospital, New Delhi

Correspondence:

Kshirabdhi Tanaya Panda

E-mail: kshirabdhitanayapanda3@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-16>

Abstract:

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive peripheral T-cell lymphoma derived from T-follicular helper (TFH) cells and is known for significant diagnostic complexity. We report a 54-year-old male with Child-Pugh B chronic liver disease presenting with prolonged fever, generalised lymphadenopathy, weight loss, hepatosplenomegaly, ascites, and suspected marrow involvement. Initial lymph node histopathology demonstrated Epstein-Barr virus (EBV)-positive atypical large lymphoid cells with apparent B-cell predominance, strongly favouring diffuse large B-cell lymphoma (DLBCL). Additional differentials included classical Hodgkin lymphoma, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and EBV-associated reactive lymphoproliferative disorder. Further evaluation with bone marrow flow cytometry revealed an aberrant T-cell population expressing sCD3(dim), CD2, CD4, CD5, and CD10 with loss of CD7, establishing a TFH phenotype consistent with AITL. The final diagnosis was stage IV AITL with nodal, splenic, and marrow involvement. Treatment was challenging because of significant hepatic dysfunction and portal hypertension. The patient received carefully dose-modified cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone (CHOEP) chemotherapy with intensive supportive care and multidisciplinary monitoring. This case highlights the “diagnostic masquerade” of AITL, the decisive role of flow cytometry in resolving ambiguous lymphomas, and the therapeutic challenges of treating aggressive lymphoma in the setting of chronic liver disease.

Key words: Angioimmunoblastic T-cell Lymphoma (AITL), Diffuse Large B-Cell Lymphoma, Flow Cytometry, T-Follicular Helper Lymphoma, Chronic Liver Disease.

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive mature T-cell lymphoma derived from T-follicular helper (TFH) cells and accounts for approximately 15% – 20% of peripheral T-cell lymphomas. It commonly presents with generalised lymphadenopathy, constitutional symptoms, hepatosplenomegaly, immune dysregulation,

and extranodal involvement, including bone marrow infiltration.^{1,2} The recent 5th Edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours (WHO-HAEM5) (2022) categorises AITL within the spectrum of “nodal TFH-cell lymphomas” and emphasises the diagnostic importance of TFH-associated markers such as CD10, PD-1, ICOS, CXCL13, and BCL6.³ One of the hallmark pathological features of AITL is proliferation of

Epstein-Barr virus (EBV)-positive B immunoblasts, which may overshadow the neoplastic T-cell population and mimic diffuse large B-cell lymphoma (DLBCL), classical Hodgkin lymphoma, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), or reactive EBV-associated lymphoproliferative disorders. Consequently, diagnosis based solely on morphology and immunohistochemistry (IHC) may be misleading.^{1,4}

In the present case, initial lymph node histopathology strongly favoured DLBCL because of EBV positivity and apparent B-cell predominance. However, subsequent bone marrow flow cytometric immunophenotyping demonstrated an aberrant mature T-cell population expressing sCD3(dim), CD2, CD4, CD5, and CD10 with loss of CD7, establishing a TFH phenotype consistent with AITL. This case highlights the diagnostic complexity of AITL and underscores the importance of integrating morphology, flow cytometry, immunophenotyping, and clinicopathological correlation in diagnostically ambiguous lymphomas. It further emphasises the therapeutic challenge of administering anthracycline-based chemotherapy in a patient with underlying Child-Pugh B chronic liver disease.

Case Report

A 54-year-old male with chronic liver disease presented with four months of intermittent high-grade fever, painful swallowing, progressive cervical swelling, anorexia, generalised weakness, and significant weight loss. He later developed abdominal distension and exertional breathlessness. On presentation, examination revealed generalised lymphadenopathy, hepatosplenomegaly, ascites, and pedal oedema. Baseline laboratory investigations showed cytopenias, hypoalbuminaemia, and deranged liver function tests. Positron emission tomography-computed tomography (PET-CT) demonstrated extensive fluorodeoxyglucose (FDG)-avid lymphadenopathy involving cervical, mediastinal, axillary, abdominal, and pelvic nodal stations with hepatosplenomegaly, nasopharyngeal involvement, and suspected marrow infiltration, suggestive of disseminated stage IV lymphoma based on the Lugano classification.

At this stage, the foremost clinical concern was an aggressive lymphoma, particularly DLBCL, because of the rapid systemic progression, bulky disease, constitutional symptoms, and extensive extranodal involvement. Excisional axillary lymph node biopsy further reinforced

this concern. Histopathology demonstrated architectural effacement by atypical intermediate-to-large lymphoid cells within a polymorphous inflammatory background (Figure 1). Importantly, IHC analysis revealed EBV positivity with apparent B-cell marker expression and CD30 positivity, thereby strongly favouring an EBV-associated aggressive B-cell lymphoma (Figure 2A – E). However, the extensive inflammatory milieu and immune dysregulation raised suspicion for an underlying T-cell lymphoma. Differential diagnoses included DLBCL, classical Hodgkin lymphoma, PTCL-NOS, EBV-associated reactive lymphoproliferative disorder, and AITL.

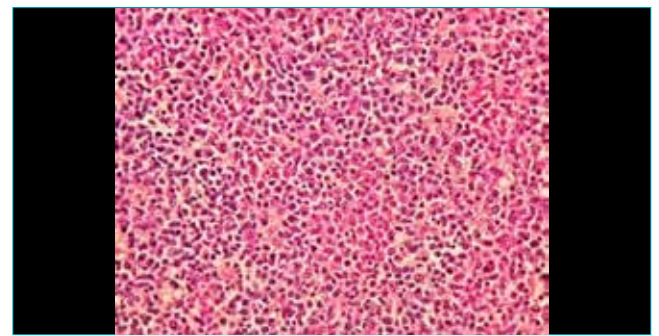


Figure 1: Histopathological examination of the lymph node biopsy showing diffuse effacement of nodal architecture by atypical intermediate-to-large lymphoid cells in a polymorphous inflammatory background (haematoxylin and eosin [H&E] stain, ×400).

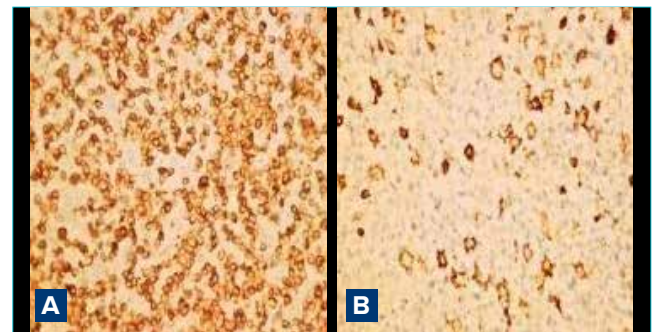


Figure 2: A. CD20 immunostaining showing diffuse positivity in large atypical lymphoid cells; **B.** CD3 highlighting the background T-cell population within the polymorphous infiltrate.

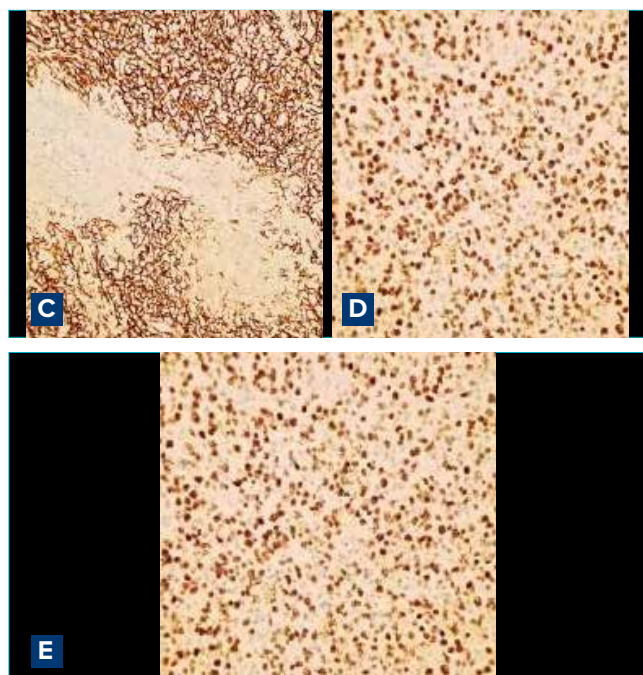


Figure 2: C. Epstein-Barr virus (EBV) immunohistochemical stain demonstrating positivity in scattered atypical lymphoid cells; D. CD21 immunostaining demonstrating expanded follicular dendritic cell meshwork supporting the T follicular helper (TFH)-cell lymphoma phenotype; E. Ki-67 immunostaining demonstrating high proliferative index in atypical lymphoid cells.

To resolve the diagnostic ambiguity, bone marrow examination and flow cytometric immunophenotyping were pursued. Bone marrow biopsy was inconclusive; however, flow cytometric immunophenotyping identified an aberrant T-cell population expressing sCD3(dim), CD2⁺, CD4⁺, CD5⁺, and CD10⁺ with loss of CD7, strongly supporting TFH-cell lymphoma/AITL (Figure 3A – C). The final diagnosis was established as stage IV AITL with nodal, splenic, and marrow involvement.

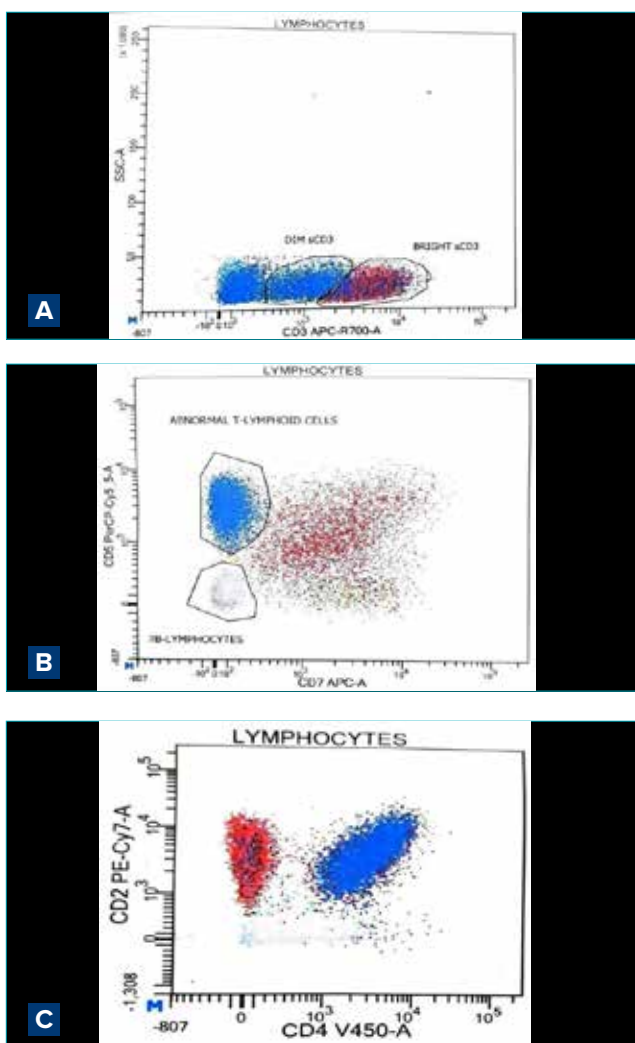


Figure 3: A. Flow cytometry demonstrating abnormal T-lymphoid cells with dim surface CD3 expression; B. Aberrant T-cell population showing loss/dim expression of CD7 with preserved CD5 expression; C. Abnormal T-lymphoid cells demonstrating CD4 positivity with retained CD2 expression, consistent with T follicular helper (TFH)-cell phenotype.

The patient's course was complicated by Child-Pugh B chronic liver disease with portal hypertension, ascites, pleural effusion, respiratory compromise, and hyponatraemia. These factors significantly limited safe administration of standard-dose chemotherapy. Following multidisciplinary discussion, the patient was initiated on dose-modified cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone (CHOEP) chemotherapy with hepatic dose adjustments and intensive supportive care including intravenous albumin, broad-spectrum antibiotics, tumour lysis monitoring, electrolyte correction, and therapeutic ascitic tapping. Despite advanced disease and fragile hepatic reserve, the patient tolerated the first cycle reasonably well with improvement in systemic symptoms.

Discussion

AITL is often described as a “great masquerader” because of its heterogeneous morphology and reactive tumour microenvironment. AITL originates from TFH cells and is characterised by profound immune dysregulation, cytokine excess, EBV-positive B-cell proliferation, and polymorphous inflammatory infiltrates.¹ EBV-positive B immunoblast proliferation may dominate tissue histology and obscure the underlying TFH-cell neoplasm, leading to misdiagnosis as DLBCL or other EBV-associated lymphoid disorders. This diagnostic pitfall has been repeatedly described in the literature, particularly in cases where EBV-positive immunoblasts become numerically prominent and histologically overshadow the underlying TFH-derived neoplasm.^{1,2}

The WHO-HAEM5 (2022) classification recognises AITL within nodal TFH-cell lymphomas and emphasises the diagnostic significance of TFH markers.³ In our patient, the final diagnosis became possible only after integrating morphology, clinical findings, and flow cytometric identification of a TFH phenotype.

An additional layer of complexity in our patient was the overlap with other lymphoma subtypes. The polymorphous infiltrate and CD30 positivity raised concern for classical Hodgkin lymphoma, whereas the aggressive systemic presentation and atypical T-cell infiltrates also prompted consideration of PTCL-NOS. Furthermore, EBV-associated reactive lymphoproliferative disorder remained a competing possibility because of the striking inflammatory milieu. Such broad differentials are not uncommon in AITL and reflect the biological complexity of the disease. In fact, AITL has historically been termed a “clinicopathological chameleon” because no single histological feature is pathognomonic in isolation.⁴

The pivotal diagnostic breakthrough in our patient came not from morphology, but from flow cytometric immunophenotyping of the bone marrow aspirate. A major learning point from this case is the decisive role of flow cytometry in diagnostically ambiguous lymphomas. The flow cytometry identified an aberrant T-cell population

expressing CD10 with loss of CD7, strongly supporting a diagnosis of TFH-cell lymphoma/AITL. Expression of CD10 on mature T-cells, particularly with aberrant pan-T-cell antigen loss, is highly suggestive of AITL and may provide the critical diagnostic clue when morphology remains misleading.⁵

Another important aspect highlighted by this case is the biological significance of EBV-positive B-cell expansion in AITL. EBV-positive immunoblasts are frequently encountered in AITL because of immune dysregulation induced by TFH-cell neoplasia. These reactive B cells may occasionally become clonal and can even evolve into secondary EBV-positive B-cell lymphomas.⁶ Consequently, the distinction between primary DLBCL and AITL-associated EBV-positive B-cell proliferation becomes critically important because therapeutic approaches differ fundamentally. Misclassification as DLBCL could potentially expose patients to rituximab-based regimens without adequately addressing the underlying T-cell malignancy.

Another important challenge was treatment in the setting of Child-Pugh B chronic liver disease with portal hypertension and ascites. Standard anthracycline-based regimens such as CHOEP carry increased risk of hepatic decompensation and severe toxicity in such patients.⁷ A carefully balanced multidisciplinary approach with dose-modified CHOEP, aggressive supportive care, and close monitoring allowed successful treatment delivery without hepatic deterioration.

This case emphasises that AITL should always be considered in patients with generalised lymphadenopathy, immune dysregulation, hepatosplenomegaly, and EBV-rich polymorphous histology, even when the biopsy initially suggests DLBCL. Early integration of flow cytometry and TFH-marker evaluation may prevent diagnostic misclassification and therapeutic misdirection.

Declarations

Conflict of Interest: The authors declare no conflict of interest.

Funding: No financial support or funding was received for this study.

Conclusion

This case highlights the remarkable diagnostic complexity of AITL and its ability to mimic aggressive B-cell lymphoma because of EBV-positive reactive B-cell proliferation. Initial histopathology strongly favoured DLBCL and other EBV-associated lymphoproliferative disorders; however, flow cytometric identification of an aberrant TFH-cell phenotype ultimately established the diagnosis of AITL.

The case underscores the importance of integrating morphology, immunophenotyping, and clinicopathological correlation in diagnostically ambiguous lymphomas. It further demonstrates the therapeutic challenges of treating aggressive lymphoma in the setting of significant hepatic dysfunction, where individualised chemotherapy modification and multidisciplinary care become essential.

Kshirabdhii Tanaya Panda, Sanjeev Kumar Sharma, Anamika Bakliwal, Anil Handoo, Pratyush Mishra, Rajan Duggal, Nivedita Patnaik. Diagnostic Masquerade in Advanced Lymphoma: Angioimmunoblastic T-Cell Lymphoma Initially Mimicking Diffuse Large B-Cell Lymphoma. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-16>

References

1. Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. *Blood*. 2017;129(9):1095–102.
2. de Leval L, Gisselbrecht C, Gaulard P. Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. *Br J Haematol*. 2010;148(5):673–89.
3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720–48.
4. Federico M, Rudiger T, Bellei M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. *J Clin Oncol*. 2013;31(2):240–6.
5. Baseggio L, Berger F, Morel D, et al. Identification of circulating CD10-positive T cells in angioimmunoblastic T-cell lymphoma by flow cytometry. *Haematologica*. 2006;91(4):566–8.
6. Yang QX, Pei XJ, Tian XY, et al. Secondary cutaneous Epstein-Barr virus-associated diffuse large B-cell lymphoma in a patient with angioimmunoblastic T-cell lymphoma: a case report and review of literature. *Diagn Pathol*. 2012;7:7.
7. Horwitz SM, Ansell SM, Ai WZ, et al. T-Cell Lymphomas, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20(3):285–308.

When the Node Fails and the Heart Follows: Anti-NF140 and Anti-GAD65 Autoimmune Nodopathy Presenting as Acute Quadriparesis with Takotsubo Cardiomyopathy and Type 2 Respiratory Failure

Prateek Bhanu¹, Rommel Tickoo¹, Shiveta Mattoo¹, Shubham Mishra¹, Sharanya Kohli¹, Anjali Mutreja¹, Manisha Agrawal¹

¹Department of Internal Medicine, Max Super Speciality Hospital, Saket, New Delhi

Correspondence:

Prateek Bhanu

E-mail: prateekbhanu2000@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-17>

Abstract:

Autoimmune nodopathy (AN) is a rare, mechanistically distinct immune-mediated neuropathy caused by IgG4 antibodies targeting nodal proteins at the node of Ranvier. Anti-NF140-positive AN is among the rarest subtypes, with fewer than 30 cases reported in the literature, and its multisystem complications remain poorly characterised. We report the case of a 51-year-old woman with a history of Guillain-Barré syndrome (GBS) (2019), type 2 diabetes mellitus, hypertension, and fibromyalgia who presented with subacute ascending quadriparesis and bilateral facial pain. Her clinical course was complicated by bulbar palsy requiring nasogastric feeding, Takotsubo (stress) cardiomyopathy confirmed by coronary angiography demonstrating non-obstructive coronary artery disease together with echocardiographic apical ballooning and a left ventricular ejection fraction nadir of 30% – 35%, and type 2 respiratory failure requiring mechanical ventilation. Nerve conduction studies demonstrated a mixed axonal-demyelinating polyneuropathy, while cerebrospinal fluid analysis showed cytoalbuminous dissociation (protein 113.3 mg/dL; total leucocyte count 2 cells/ μ L). Autoimmune neuropathy testing confirmed anti-NF140 and anti-GAD65 antibody positivity. Treatment with intravenous immunoglobulin (IVIg) (210 g over five doses) followed by rituximab (375 mg/m²) resulted in successful extubation on Day 10, complete resolution of bulbar dysfunction, and recovery of left ventricular ejection fraction to 45% – 50%. To our knowledge, this is the first reported case of anti-NF140 autoimmune nodopathy complicated by Takotsubo cardiomyopathy with concurrent anti-GAD65 seropositivity. This case highlights the diagnostic overlap between AN and GBS and underscores the importance of early autoimmune antibody testing, serial echocardiographic surveillance, and timely escalation to B-cell-depleting therapy.

Key words: Autoimmune Nodopathy, Anti-NF140, Anti-GAD65, Takotsubo Cardiomyopathy, Axonal-Demyelinating Neuropathy, Guillain-Barré Syndrome, Rituximab, Respiratory Failure, Dysautonomia.

Introduction

Autoimmune nodopathy (AN) encompasses a group of immune-mediated peripheral neuropathies caused by IgG antibodies, predominantly of the IgG4 subclass,

directed against structural proteins at the node of Ranvier. The 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines formally delineated four subtypes based on the target antigen:

anti-NF155 (paranodal), anti-CNTN1 (paranodal), anti-CASPR1 (paranodal), and anti-NF140/186 (nodal).¹ Anti-NF140 and anti-NF186 antibodies are axonal isoforms of neurofascin that organise the nodal sodium channel complex. IgG4-mediated disruption produces paranodal dissection and nodal gap widening, generating conduction failure without classical macrophage-mediated demyelination.² This pathophysiological distinction separates AN from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and has direct therapeutic implications: intravenous immunoglobulin (IVIG), effective in both Guillain-Barré syndrome (GBS) and CIDP, provides only partial and transient benefits in IgG4-dominant AN, whereas B-cell-depleting therapy with rituximab is increasingly recognised as the definitive treatment.^{1,3}

Anti-NF140/186 AN is the rarest of the four subtypes, with fewer than 30 documented cases in the published literature. The condition presents as an acutely progressive, GBS-mimicking syndrome with ascending paralysis, cranial nerve involvement, bulbar failure, and autonomic dysregulation, creating a diagnostic window that frequently results in the condition being managed as GBS until antibody results become available.^{3,4} Cardiovascular complications secondary to autonomic nerve fibre involvement, most notably Takotsubo (stress) cardiomyopathy, have been described in GBS but have not been reported in serologically confirmed AN. We present the first such case, further distinguished by concurrent anti-GAD65 seropositivity, and describe the diagnostic pathway and multisystem management that led to a favourable outcome.

Case Report

Clinical background

A 51-year-old woman with a documented history of GBS in 2019 (treated with plasmapheresis and IVIG), type 2 diabetes mellitus, hypertension, fibromyalgia (since 2015), and peripheral neuropathy presented to our centre on 5th May 2026. Her only notable new medication was tirzepatide (Mounjaro), which was initiated three to four months prior to presentation for weight management.

Presenting complaints

She reported a two- to three-day history of bilateral facial hypersensitivity and burning pain involving the temporal regions, earlobes, and cervical area, with intensification of chronic bilateral plantar burning. On the morning of

admission, she developed rapidly progressive bilateral limb weakness, inability to lift a towel or open a bottle cap, and gait instability. Pertinently, the neurology consultation of 9th May additionally documented perianal numbness and inability to defecate, tremulousness in the lower limbs, and difficulty swallowing — a constellation pointing to motor, sensory, and autonomic nerve fibre involvement from the outset.

Examination at admission

The findings on initial examination are summarised in Table 1.

System	Findings
General	Conscious, alert, oriented; afebrile
Haemodynamics	HR 112/min; BP 110/70 mmHg; RR 20/min; SpO ₂ 97% on room air
Cardiovascular	S1 S2 normal; no murmurs
Respiratory	Bilaterally clear, no added breath sounds
Neurological	Conscious and oriented; bilateral distal limb weakness; perianal numbness; no overt cranial nerve deficits at presentation



Table 1: Initial examination at presentation.

Abbreviations: BP: Blood Pressure; HR: Heart Rate; RR: Respiratory Rate; SpO₂: Peripheral Oxygen Saturation.

Hospital course

Phase 1 (Days 1 – 3, 5th – 7th May): Diagnostic workup and IVIG initiation

Computed tomography (CT) of the brain was normal. Brain and spine magnetic resonance imaging (MRI) with gadolinium revealed multilevel degenerative disc disease without cord signal change or gadolinium-enhancing nerve roots. Lumbar puncture (7th May) revealed cerebrospinal fluid (CSF) protein 113.3 mg/dL with a total cell count of 2 cells/μL, showing cytoalbuminous dissociation consistent with inflammatory polyradiculoneuropathy. Dysphagia evaluation on the same day confirmed bulbar involvement: pharyngeal phase, hyolaryngeal excursion, and swallowing reflex were all inadequate, with pharyngeal residue on the clinical swallowing trial. A nasopharyngeal airway was inserted, and biphasic positive airway pressure (BiPAP) was placed on standby. IVIG (Dose 1, 40 g) was commenced

on 7th May, and the autoimmune neuropathy panel was dispatched to an external reference laboratory.

Phase 2 (Days 4 – 6, 8th – 10th May): Cardiac event, respiratory failure, and Medical Intensive Care Unit (MICU) admission

Worsening dyspnoea and oxygen desaturation prompted transfer to the MICU on 8th May. Of diagnostic significance, a two-dimensional (2D) echocardiogram performed on the day of MICU admission demonstrated entirely normal left ventricular function with no regional wall motion abnormality, establishing an unequivocal cardiac baseline. IVIG second dose (50 g) was then administered. On 9th May, the 12-lead electrocardiogram (ECG) demonstrated de novo ST elevation in leads I and aVL with reciprocal ST depression in leads III and aVF, a new lateral pattern absent 24 hours prior. Troponin-I was 3.611 ng/mL (greater than 90 times the upper limit of normal), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 30,000 pg/mL. Coronary angiography (10th May) confirmed non-obstructive coronary artery disease in all three vessels, excluding primary acute coronary syndrome (ACS). Echocardiography revealed left ventricular (LV) apical ballooning with a depressed ejection fraction of 30% – 35%, confirming Takotsubo (stress) cardiomyopathy.

Concurrently, progressive bulbar paralysis and diaphragmatic weakness produced type 2 respiratory failure; the patient was intubated on 9th May and placed on pressure-regulated volume control (PRVC) ventilation with a fraction of inspired oxygen (FiO₂) of 30% and positive end-expiratory pressure (PEEP) of 6 cmH₂O, maintaining SpO₂ at 92%. Noradrenaline was required for haemodynamic support. Nephrology was consulted for reduced urine output, and Kidney Disease: Improving Global Outcomes (KDIGO) grade 2 acute kidney injury (AKI) was documented. IVIG was temporarily withheld for 24 hours due to haemodynamic instability and resumed on 10th May following a multidisciplinary review.

Phase 3 (Days 7 – 10, 11th – 14th May): Completion of IVIG and extubation

IVIG doses 3, 4, and 5 (40 g each) were administered on 10th, 11th, and 12th May, respectively, completing a cumulative dose of 210 g. Ventilatory requirements improved progressively: by 12th May, the mode had transitioned to continuous positive airway pressure (CPAP) with FiO₂ 25%; by 13th May, the patient was off sedation and tolerating

CPAP trials at room-air equivalent FiO₂. The patient was successfully extubated on 14th May and initially maintained on a high-flow nasal cannula (FiO₂ 21%, 60 L/min) and subsequently weaned to room air. Endotracheal secretion cultures (10th May) revealed *Haemophilus influenzae*, confirming hospital-acquired pneumonia, and antimicrobial therapy was rationalised accordingly. AKI resolved by 13th May.

Phase 4 (Days 15 – 18, 19th – 22nd May): Rituximab, serological confirmation, and bulbar recovery

Rituximab 375 mg/m² (Dose 1) was administered on 19th May on empirical neurology advice, prior to antibody confirmation, based on the clinical severity and pattern of an insufficient response to IVIG. Repeat dysphagia evaluation (20th May) demonstrated complete resolution of pharyngeal dysfunction: oral and pharyngeal phases were adequate, reflex was intact, and there was no aspiration, representing a clinically meaningful reversal of bulbar involvement. Echocardiography reassessment showed ejection fraction (EF) recovery to 45% – 50% with resolved apical ballooning. NT-proBNP had fallen from 30,000 to 3,630 pg/mL (88% reduction) by 16th May. On 22nd May, the autoimmune neuropathy panel confirmed anti-NF140 and anti-GAD65 antibody positivity, formally establishing the diagnosis of autoimmune neuropathy. The patient was discharged on 29th May, ambulatory and neurologically improved, with a PICC line in situ, and was scheduled to receive the second dose of Rituximab on 2nd June 2026.

Key Investigations

CSF analysis (7th May 2026)

The CSF findings are summarised in Table 2.

Parameter	Result	Reference	Remark
Cerebrospinal fluid (CSF) protein	113.3 mg/dL	15 – 45	Markedly elevated – cytoalbuminous dissociation
CSF glucose	164 mg/dL	50 – 80	Proportionate to serum hyperglycaemia; CSF: serum ratio normal
Total cell count	2 cells/ μ L	0 – 5	Classic dissociation – near-acellular
Malignant cells	Negative	Negative	Leptomeningeal malignancy excluded

Table 2: Laboratory markers and investigations of cerebrospinal fluid (CSF) sample done on 7th May 2026.

Cardiac investigations

Echocardiography – Serial

Serial echocardiographic findings during the hospital stay are presented in Table 3.

Date	EF	Findings	Clinical significance
8 th May (MICU admission)	Normal	Normal LV function; no RWMA	Establishes baseline – Takotsubo cardiomyopathy had not yet developed
9 th – 10 th May (Post ECG changes)	30% – 35%	Apical ballooning, Takotsubo pattern	EF nadir; developed within 24 hours of normal echocardiogram
15 th May (Post-extubation)	45% – 50%	Improving wall motion; residual hypokinesia	Partial EF recovery; full normalisation expected at 3 months

Table 3: Serial echocardiographic changes observed in the patient.

Abbreviations: EF: Ejection Fraction; ECG: Electrocardiogram; LV: Left Ventricle; MICU: Medical Intensive Care Unit; RWMA: Regional Wall Motion Abnormality.

Cardiac biomarkers

The serial changes in cardiac biomarkers are shown in Table 4.

Parameter	Result	Reference	Remark
Troponin-I (5 th May)	3.611 ng/mL	< 0.04	> 90 $\times$ ULN; acute myocardial injury
NT-proBNP (5 th May)	30,000 pg/mL	< 125	Severe LV dysfunction at nadir
Troponin-I (16 th May)	0.065 ng/mL	< 0.04	98% reduction from peak
NT-proBNP (16 th May)	3,630 pg/mL	< 125	88% fall – correlates with echo EF recovery
CK-MB (16 th May)	2.03 U/L	< 25	Fully normalised

Table 4: Serial cardiac biomarkers measured during the hospital stay.

Abbreviations: CK-MB: Creatine Kinase-Myocardial Band; EF: Ejection Fraction; LV: Left Ventricle; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; ULN: Upper Limit of Normal.

ECG and coronary angiography

The sequential ECG findings and subsequent coronary angiography are summarised in Table 5.

Investigation	Finding
ECG – 8 th May	Sinus rhythm; no ST-T changes (normal baseline)
ECG – 9 th May	De novo ST elevation in leads I and aVL; reciprocal depression in leads III and aVF 
CAG – 10 th May	Non-obstructive coronary artery disease – all three vessels; STEMI excluded; Takotsubo cardiomyopathy confirmed

Table 5: Serial ECG changes which mandated CAG that revealed Takotsubo cardiomyopathy.

Abbreviations: CAG: Coronary Angiography; ECG: Electrocardiogram; STEMI: ST-Elevation Myocardial Infarction.

Nerve conduction study (NCS)

NCS demonstrated mixed axonal-demyelinating sensorimotor polyneuropathy, symmetric and length-dependent, with greater involvement in the lower limbs. The co-existence of demyelinating features, such as prolonged distal latencies, motor conduction velocities reduced to 28 – 41 m/s, absent or prolonged F-waves, and focal conduction block across the ulnar nerve at the elbow, alongside axonal features, such as reduced compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes, absent distal peroneal and sural sensory responses, and fibrillation potentials with positive sharp waves on needle electromyography (EMG) in distal lower limb muscles, is characteristic of anti-NF140/186 nodopathy and distinguishes it electrophysiologically from classical acute inflammatory demyelinating polyradiculoneuropathy (AIDP)-GBS, which typically presents with a predominantly demyelinating pattern without significant axonal loss in the early phase.⁴⁻⁶ The principal electrophysiological findings are summarised in Table 6.

NCS feature	Finding
Overall pattern	Mixed axonal-demyelinating sensorimotor polyneuropathy
Demyelinating features	Prolonged distal latencies; MCV 28 – 41 m/s; absent/prolonged F-waves; conduction block (ulnar nerve)
Axonal features	Reduced CMAP (< 5 mV); absent distal SNAPs (peroneal, sural); fibrillation potentials on needle EMG
Significance	Consistent with anti-NF140 nodopathy: primary nodal conduction failure + secondary Wallerian axonal degeneration ^{4,5}

Table 6: Nerve conduction studies revealed mixed axonal-demyelinating sensorimotor polyneuropathy.

Abbreviations: CMAP: Compound Muscle Action Potential; EMG: Electromyography; IVIG: Intravenous Immunoglobulin; MCV: Motor Conduction Velocity; NF140: Neurofascin 140; SNAPs: Sensory Nerve Action Potentials.

Autoimmune neuropathy panel (22nd May 2026)

The results of the autoimmune neuropathy panel and associated investigations are summarised in Table 7.

Parameter	Result	Reference	Remark
Anti-NF140	Positive	Negative	Confirms autoimmune nodopathy (nodal isoform); dispatched 7 th May, received 22 nd May — 15-day turnaround
Anti-GAD65	Positive	Negative	Concurrent GABAergic autoimmunity (see Discussion)
ANA	Positive	Negative	Systemic autoimmune activation; ANA vasculitis panel (LIA) negative
AChR antibody	0.59 nmol/L	< 0.5	Borderline — NMJ involvement clinically minor
Antiphospholipid panel (Beta-2-GP1)	IgA 2.1/ IgM 2.9/ IgG 2.8	< 20	APS excluded

Table 7: Autoimmune neuropathy panel testing results.

Abbreviations: AChR: Acetylcholine Receptor; ANA: Antinuclear Antibody; APS: Antiphospholipid Syndrome; GABAergic: Gamma-Aminobutyric Acid-Ergic; GAD65: Glutamic Acid Decarboxylase 65; GP1: Glycoprotein 1; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LIA: Line Immunoassay; NF140: Neurofascin 140; NMJ: Neuromuscular Junction.

Dysphagia evaluation – Serial (Speech and language therapy)

Serial dysphagia assessments before and after immunotherapy are compared in Table 8.

Parameter	7 th May (Pre-IVIG)	20 th May (Post-IVIG + RTX Dose 1)
Pharyngeal phase	Inadequate	Adequate
Swallowing reflex	Inadequate	Adequate
Hyolaryngeal excursion	Inadequate	Adequate
Aspiration	Pharyngeal residue; effortful swallow	No aspiration
Overall	Bulbar involvement confirmed	Complete resolution

Table 8: Comparison table showing pre-IVIG and post-IVIG and Ritiuximab 1st dose.

Discussion

The diagnostic dilemma: Autoimmune nodopathy versus GBS

The initial clinical presentation of this patient — acute ascending quadriparesis, bilateral facial pain, and cytoalbuminous dissociation on CSF analysis — is clinically indistinguishable from AIDP-GBS, the diagnosis under which she was managed for the first 15 days of her admission. This diagnostic mimicry is a defining feature of anti-NF140/186 AN and represents its central clinical danger. In a case series by Kim *et al.* (2024), five of eight patients with anti-nodal antibodies were initially diagnosed with GBS before serological confirmation. The neurology team in our case, appropriately, documented the impression as 'recurrent GBS' or CIDP throughout the admission period, with formal reclassification occurring only after antibody confirmation on 22nd May.

Two electrophysiological features help distinguish AN from AIDP-GBS and prompt targeted antibody testing. First, the mixed axonal-demyelinating NCS pattern, rather than the predominantly demyelinating pattern of AIDP, reflects two simultaneous pathological processes: primary nodal conduction failure (producing prolonged latencies and slowed velocities) and secondary Wallerian-type axonal degeneration downstream of non-functional nodes (producing reduced amplitudes and electromyography [EMG] denervation). This mixed pattern has been specifically

described in anti-NF186 cohorts and is mechanistically explained by the inability of IgG4 antibodies to activate complement efficiently, producing structural nodal disruption without the acute inflammatory axonal injury seen in acute motor axonal neuropathy (AMAN)-GBS.^{4–7} Second, focal conduction block at a non-compressive site (ulnar nerve at the elbow in this patient) reflects discrete nodal failure rather than the proximal, rapidly reversible block of AIDP. These NCS features, in the context of acute ascending neuropathy, should lower the threshold for dispatching an autoimmune nodopathy panel test.

Takotsubo cardiomyopathy: A neurogenic complication

The Takotsubo cardiomyopathy in this case was established by the Modified Mayo Clinic Criteria: apical LV ballooning on echocardiography, troponin-I elevation greater than 90 times the upper limit of normal, ST elevation in a non-coronary distribution, and non-obstructive coronary arteries on angiography. Its neurogenic aetiology is supported by the echocardiographic timeline: a completely normal study on 8th May was followed by an EF nadir of 30% – 35% within 24 hours, at the precise point of maximal neurological deterioration and intubation. This rapid kinetics is characteristic of catecholamine-mediated myocardial stunning rather than ischaemia or inflammation, both of which evolve over longer timeframes.^{8–10}

The mechanism is autonomic: injury to sympathetic efferent fibres, whose NF140-containing nodal complexes are targeted by the same pathogenic antibody that produces motor neuropathy, generates a dysregulated catecholamine surge. The apical myocardium, with its higher density of beta-adrenergic receptors relative to the base, is disproportionately stunned, producing a characteristic ballooning pattern. The ECG demonstrating new lateral ST changes the day after a normal ECG in a patient with confirmed non-obstructive coronary disease on angiography exemplifies the diagnostic importance of serial cardiac monitoring in AN. Echocardiography performed at MICU transfer, which was normal, did not predict the event 24 hours later; this argues for repeat echocardiography every 24 – 48 hours during the acute phase of immune neuropathy rather than relying on a single baseline study.

Takotsubo cardiomyopathy in GBS has been reported in fewer than 14 cases globally; this is the first case in serologically confirmed AN. Kouhanjani *et al.* (2024), in a systematic review of 155 Takotsubo cardiomyopathy

cases with autoimmune diseases, found GBS to be one of the most common autoimmune triggers but did not identify any AN cases.¹¹ The cardiac biomarker trajectory in our patient, with troponin-I declining from 3.611 to 0.065 ng/mL and NT-proBNP from 30,000 to 3,630 pg/mL over 11 days, mirrors the EF recovery from 30% – 35% to 45% – 50% and is consistent with the published median Takotsubo recovery time of 18.5 days (interquartile range [IQR] 10 – 42 days).^{11,12}

Type 2 respiratory failure and the bulbar-respiratory interface

Respiratory failure in AN is a direct consequence of progressive motor neuropathy involving the phrenic nerve and intercostal muscles, compounded in this patient by bulbar paralysis, which increased the risk of aspiration and precluded airway protection. Dysphagia evaluation on 7th May — which documented an inadequate pharyngeal phase and impaired reflex with pharyngeal residue — identified bulbar failure two days before intubation, providing a clear prognostic signal. Family counselling regarding a possible tracheostomy was provided in accordance with the anticipated trajectory. The successful extubation on Day 10, followed by complete bulbar recovery confirmed on 20th May, is attributable to the IVIG course combined with the initiation of rituximab and reflects the partial but clinically meaningful efficacy of immunotherapy in halting neuropathic progression.

Anti-GAD65 co-seropositivity

The concurrent positivity for anti-GAD65 (glutamic acid decarboxylase 65 kDa isoform) antibodies introduces a second autoimmune axis. Anti-GAD65 antibodies at high titres are associated with stiff-person spectrum disorder, autoimmune cerebellar ataxia, limbic encephalitis, and — most relevant here — a painful sensory neuropathy.^{13,14} This patient's decade-long fibromyalgia diagnosis (2015), bilateral plantar burning, and bilateral facial pain may represent a GAD65-mediated pain syndrome operating in parallel with her background of diabetic neuropathy

and acute anti-NF140 nodopathic illness. The dual anti-NF140 and anti-GAD65 seropositivity in a single patient has not been previously reported and raises questions about shared polyclonal autoimmune activation. Clinically, GAD65-associated neurological syndromes respond to immunotherapy in approximately 50% of patients;¹³ long-term maintenance immunosuppression should be considered alongside the rituximab programmes.

Treatment rationale: IVIG, rituximab, and the sequencing question

IVIG was the appropriate first-line treatment given the diagnostic uncertainty at presentation. In anti-NF140/186 AN, however, IVIG provides only partial and transient benefits in the IgG4-dominant disease that characterises this subtype; the mechanism of benefit (Fc receptor competition, complement modulation) is less effective against monovalent IgG4 antibodies that are incapable of complement cross-linking.^{1,15} The partial clinical response observed here, with successful extubation on Day 10 and bulbar recovery by Day 13, is consistent with this pharmacodynamic profile. Rituximab, administered on 19th May (three days before antibody confirmation), targets the CD20-positive B-cell population producing pathogenic anti-NF140 IgG4. Published anti-NF155 AN series consistently document superior outcomes with rituximab versus IVIG-only regimens;^{3,5,16} the EAN/PNS 2021 guidelines support early escalation to B-cell depleting therapy in patients with acutely deteriorating suspected AN without awaiting serological confirmation.¹ The 15-day diagnostic turnaround in this case highlights a critical systems gap: in-house or rapid-access nodopathy antibody testing should be prioritised at referral centres managing inflammatory neuropathies.

Patient Consent

Written informed consent was obtained from the patient and family for the publication of this case report. The case has been de-identified in accordance with the institutional and journal guidelines.

Conclusion

We report the first confirmed case of anti-NF140 autoimmune nodopathy complicated by Takotsubo cardiomyopathy and concurrent anti-GAD65 seropositivity, a multisystem presentation in which the pathological consequences of IgG4-mediated nodal dysfunction extended from the peripheral nervous system to the myocardium and airway. The triad of acute ascending quadriparesis, bulbar failure, and stress cardiomyopathy, each mechanistically traceable to the same primary immunological event, underscores the systemic reach of anti-NF140 AN. The rarity of this condition (fewer than 30 cases of anti-NF140 AN in the world literature), its consistent mimicry of GBS, and the life-threatening cardiovascular complications associated with it make early antibody testing, serial echocardiographic monitoring, and proactive escalation to rituximab the defining priorities for management. The mixed axonal-demyelinating NCS pattern and concurrent anti-GAD65 positivity add additional diagnostic dimensions that, taken together, make this case a unique contribution to the evolving literature on autoimmune nodopathy.

Prateek Bhanu, Rommel Tickoo, Shiveta Mattoo, Shubham Mishra, Sharanya Kohli, Anjali Mutreja, Manisha Agrawal. When the Node Fails and the Heart Follows: Anti-NF140 and Anti-GAD65 Autoimmune Nodopathy Presenting as Acute Quadriparesis with Takotsubo Cardiomyopathy and Type 2 Respiratory Failure. MMJ.

2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-17>

References

- van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force - Second revision. *J Peripher Nerv Syst.* 2021;26(3):242–68.
- Appeltshauser L, Doppler K. Pan-neurofascin autoimmune nodopathy - a life-threatening but reversible neuropathy. *Curr Opin Neurol.* 2023;36(5):394–401.
- Krim E, Masri A, Delmont E, et al. Pan-neurofascin autoimmune nodoparanodopathy: a case report and literature review. *Medicine (Baltimore).* 2025;104(4):e41304.
- Kim MJ, Lyoo HJ, Chung YH, et al. Clinical features of autoimmune nodopathy with anti-neurofascin-155 antibodies in South Koreans. *J Clin Neurol.* 2024;20(2):186–93.
- Imamura M, Mizutani H, Nakahara K, et al. Clinical and radiological heterogeneity in anti-neurofascin-155 autoimmune nodopathy: a case series analysis. *J Peripher Nerv Syst.* 2025;30(4):e70077.
- Fels E, Bhatt P, Rudiger A, et al. Anti-NF186 nodopathy: electrophysiological features and treatment response. *Eur J Neurol.* 2021;28(4):1254–61.
- Lin L, Li C, Tian W, et al. Clinical profile of autoimmune nodopathy with anti-neurofascin 186 antibody. *Ann Clin Transl Neurol.* 2023;10(6):988–1001.
- Nguyen T, Lazaridis C, Bhatt A, et al. Takotsubo cardiomyopathy as a manifestation of dysautonomia in Guillain-Barre syndrome: a case series and review of the literature. *Cureus.* 2021;13(7):e16478.
- Barbey C, Douste-Blazy MY, Guittaut M, et al. Takotsubo cardiomyopathy associated with Guillain-Barre syndrome. *J Neurol Sci.* 2010;291(1-2):99–101.
- Chen Y, Cuthbert J, Khan L, et al. Takotsubo cardiomyopathy with immune-mediated comorbidities: a case report. *Eur Heart J Case Rep.* 2025;9(5):ytaf193.
- Kouhanjani MF, Rezaei Z, Hoseini S, et al. Takotsubo cardiomyopathy and autoimmune disorders: a systematic scoping review of published cases. *Int J Clin Pract.* 2024;2024:7259200.
- Miszalski-Jamka K, Kuniewicz M, Wierzbicki M, et al. Possible predictive factors for recovery of left ventricular systolic function in Takotsubo cardiomyopathy. *BMC Cardiovasc Disord.* 2017;17(1):87.

13. Honnorat J, Saiz A, Giometto B, *et al.* Glutamic acid decarboxylase antibodies in neurological disorders: a comprehensive review. *Nat Rev Neurol.* 2023;19:42–57.
14. Zuliani L, Saiz A, Tavalato B, *et al.* GAD-antibody neurological syndrome: 15 years of observation in 104 patients. *J Neurol Neurosurg Psychiatry.* 2012;83(6):572–8.
15. Qin K, Meng Q, Liu X, *et al.* Autoimmune nodopathy with concurrent serum and CSF IgG4 anti-neurofascin 155 antibodies. *Front Neurol.* 2022;13:1003617.
16. Choi Y, Park SK, Kim D, *et al.* Ofatumumab for the treatment of anti-neurofascin-155 autoimmune nodopathy: a case series. *Brain Behav.* 2025;15:e70717.

Multisystem Sarcoidosis Masquerading as Tuberculosis Despite Normal Serum Angiotensin-Converting Enzyme Levels: A Case Report

Nitin Rathod¹, Andrea Janice Fonseca¹, Snehal Sadanandan¹, Akshita Jain¹

¹Department of Internal Medicine, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

Correspondence:

Nitin Rathod

E-mail: drnmrathod@hotmail.com

DOI: <https://doi.org/10.62830/mmj3-03-21>

Abstract:

Sarcoidosis is a multisystem granulomatous disorder characterised by non-caseating granuloma formation that can involve multiple organs and often poses a significant diagnostic challenge in tuberculosis-endemic regions because of its overlapping clinical, radiological, and histopathological features with tuberculosis. We report the case of a 49-year-old Indian male with a history of treated pulmonary tuberculosis who presented with progressive dyspnoea, cough, and symptoms of congestive heart failure. Imaging demonstrated bilateral pulmonary nodules, mediastinal lymphadenopathy, and features suggestive of chronic liver disease. Echocardiography revealed dilated cardiomyopathy with reduced left ventricular ejection fraction, raising suspicion of cardiac sarcoidosis, while liver evaluation showed cirrhosis with portal hypertension and a cholestatic liver enzyme pattern. Bronchoscopic biopsy demonstrated multiple well-formed non-caseating epithelioid granulomas with Langhans-type giant cells; staining and molecular testing for tuberculosis and fungal infections were negative. Despite extensive multisystem involvement, the serum angiotensin-converting enzyme (ACE) level was normal, likely due to concurrent ACE inhibitor therapy. The patient was managed with corticosteroids along with supportive treatment for cardiac and hepatic manifestations, resulting in significant clinical improvement. This case underscores the diagnostic complexity of multisystem sarcoidosis in patients with a prior history of tuberculosis, emphasising that normal serum ACE levels should not exclude the diagnosis. Accurate diagnosis requires integration of clinical findings, imaging, histopathology, and exclusion of infectious aetiologies, while early recognition of multisystem organ involvement is critical to initiate timely therapy and prevent irreversible complications.

Key words: Non-Caseating Granuloma, Corticosteroids, Granulomatous Inflammation, Organ Infiltration.

Introduction

Sarcoidosis is a chronic multisystem granulomatous disorder of unknown aetiology, characterised by the formation of non-caseating granulomas in affected organs. Although virtually any organ can be involved, the lungs and intrathoracic lymph nodes are affected in more than 90% of patients, making thoracic disease

the most common clinical presentation.¹ Extrapulmonary manifestations are frequently encountered and contribute significantly to disease-related morbidities. Cardiac involvement is reported in approximately 20% – 25% of patients with systemic sarcoidosis and is associated with potentially life-threatening complications, including arrhythmias, conduction abnormalities, and

heart failure.² Hepatic involvement is the third most frequently affected organ system after the lungs and lymph nodes, with presentations ranging from asymptomatic biochemical abnormalities to portal hypertension and, rarely, advanced liver disease.³

The diagnosis of sarcoidosis remains challenging because no single clinical, laboratory, or radiological finding is pathognomonic of the disease. Histopathological demonstration of non-caseating granulomas, together with compatible clinical and radiological features and exclusion of other granulomatous disorders, remains the cornerstone of diagnosis.³ In tuberculosis (TB)-endemic regions, differentiating sarcoidosis from TB is particularly difficult because both conditions may present with constitutional symptoms, pulmonary infiltrates, mediastinal lymphadenopathy, and granulomatous inflammation. Although caseating granulomas are classically associated with TB and non-caseating granulomas with sarcoidosis, histological overlap may occasionally occur, necessitating careful clinicopathological correlation.^{3,4}

Serum angiotensin-converting enzyme (ACE) is frequently used as a supportive biomarker in sarcoidosis but has limited sensitivity and specificity. Normal ACE levels do not exclude the diagnosis, and reliance on this investigation alone may delay the recognition of the disease. Therefore, a comprehensive evaluation integrating clinical findings, imaging, histopathology, and microbiological studies is essential, particularly in patients with atypical or multisystem presentations.

We report a case of biopsy-confirmed multisystem sarcoidosis involving the lungs, heart, and liver in a patient with a history of TB and normal serum ACE levels. This case highlights the diagnostic challenges encountered in TB-endemic settings and underscores the importance of considering sarcoidosis in the differential diagnosis of granulomatous disease, despite the lack of supportive biochemical markers.

Case Report

A 49-year-old Indian male with a history of obesity, long-standing diabetes mellitus, and hypertension presented with progressive breathlessness and cough. He reported dyspnoea for two years, initially corresponding to New York Heart Association (NYHA) class I, which progressively worsened to class III over the

preceding two months. He also described orthopnoea and paroxysmal nocturnal dyspnoea, suggestive of congestive cardiac failure. His cough was productive of white mucoid sputum for three months without haemoptysis. The patient also reported occasional epigastric discomfort. One month before presentation, he had an episode of haematuria associated with burning micturition, which was treated as a urinary tract infection and resolved. There was no history of fever, rash, joint pain, or neurological symptoms.

The patient had a significant history of pulmonary TB seven years earlier, for which he had completed standard anti-tubercular therapy. His regular medications included metformin and antihypertensive therapy, including the ACE inhibitor perindopril.

On examination, the patient was alert and afebrile. His pulse rate was 110/min with sinus tachycardia, and blood pressure was 130/80 mmHg. The respiratory rate was 24/min, with an oxygen saturation of 94% on room air. Jugular venous pressure was mildly elevated, and bilateral pitting pedal oedema was present. Respiratory examination revealed bilateral basal crepitations and wheezing. Abdominal examination revealed mild tenderness with hepatomegaly approximately 3 cm below the right costal margin with a nodular surface. There was no clinical evidence of ascites in the patient. No peripheral lymphadenopathy or skin lesion was observed.

Initial laboratory investigations (Table 1) revealed a normal leucocyte count, mild anaemia (haemoglobin level of approximately 11 g/dL), and elevated inflammatory markers (Erythrocyte sedimentation rate [ESR] 50 mm/h and C-reactive protein [CRP] 20 mg/L). Liver function tests demonstrated a predominantly cholestatic pattern with elevated alkaline phosphatase and gamma-glutamyl transferase (GGT) levels, with relatively preserved transaminases. Cardiac biomarkers showed mildly elevated troponin T levels of 14.3 ng/mL and raised N-terminal pro-brain natriuretic peptide (NT-proBNP) levels of 385 pg/mL, suggestive of myocardial stress and heart failure. An autoimmune evaluation performed due to multisystem involvement revealed a positive antinuclear antibody (ANA) titre of 1:320 with a speckled pattern. Rheumatoid factor was negative. The serum ACE level was within the normal range of 27 U/L.

Test name	Test value	Normal range
Immuno-globulin G	1782 mg/dL	700 – 600 mg/dL
Troponin T	14.3 ng/L	< 14 ng/L
NT-proBNP	385 pg/mL	< 125 pg/mL
ALP	140 U/L	44 – 147 U/L
GGT	242 U/L	9 – 48 U/L
Hb	12.9 g/dL	12 – 16 g/dL
WBC	5830 cells/ μ L	4000 – 11000 cells/ μ L
Platelet count	330000 cells/ μ L	150000 – 450000 cells/ μ L
Creatinine	0.98 mg/dL	0.6 – 1.2 mg/dL
Sodium	139 mEq/L	135 – 145 mEq/L
Potassium	3.92 mEq/L	3.5 – 5.0 mEq/L
Chloride	100.3 mEq/L	98 – 107 mEq/L
PT	10.8 s	10 – 13 s
INR	0.98	0.8 – 1.2
Total protein	7.5 g/dL	6.0 – 8.3 g/dL
Total bilirubin	0.327 mg/dL	0.2 – 1.2 mg/dL
AFP	1.48 ng/dL	< 10 ng/dL
Lipase	31.8 U/L	13 – 60 U/L
Amylase	26.8 U/L	25 – 125 U/L
ACE levels	6.9 U/L	8 – 52 U/L
ANA BNH	Positive (speckled) 1:320	Negative
HIV 1 & 2 Rapid	Negative	–
HBsAg	Negative	–
HCV	Negative	–

Table 1: Investigations done during patient's hospital stay.
Abbreviations: ACE: Angiotensin-Converting Enzyme; AFP: Alpha Fetoprotein; ALP: Alkaline Phosphatase; ANA: Antinuclear Antibody; GGT: Gamma-Glutamyl Transpeptidase; INR: International Normalised Ratio; Hb: Haemoglobin; HBsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; NT-proBNP: N-Terminal Pro-B-Type Natriuretic Peptide; PT: Prothrombin Time; WBC: White Blood Count.

Chest radiography revealed bilateral reticulonodular opacities with bilateral hilar prominence, without evidence of cavitary lesions (Figure 1). High-resolution computed tomography (HRCT) of the chest revealed multiple bilateral pulmonary nodules with a predominantly perilymphatic distribution, centrilobular ground-glass opacities, mild bronchovascular bundle thickening, and enlarged mediastinal lymph nodes, including inferior pretracheal lymphadenopathy (Figure 2). These findings suggested granulomatous interstitial lung disease. Contrast-enhanced computed tomography (CT) also

revealed coronary artery calcifications and features suggestive of chronic liver disease, including an irregular liver surface and collateral vessels.



Figure 1: Chest X-ray: Bilateral reticulonodular opacities with bilateral hilar prominence, without evidence of cavitary lesions.



Figure 2: High-resolution computed tomography (HRCT) chest: Multiple bilateral pulmonary nodules with a predominantly perilymphatic distribution, centrilobular ground-glass opacities, mild bronchovascular bundle thickening, and enlarged mediastinal lymph nodes, including inferior pretracheal lymphadenopathy.

To establish a definitive diagnosis, fiberoptic bronchoscopy with an endobronchial biopsy was performed. Histopathological examination revealed multiple well-formed non-caseating epithelioid granulomas with Langhans-type multinucleated giant cells (Figures 3 and 4). No central necrosis was observed. Ziehl-Neelsen staining for acid-fast bacilli was negative, and tissue GeneXpert MTB/RIF did not detect *Mycobacterium tuberculosis*. Fungal stains and cultures were also negative. These findings, along with the clinical and radiological features, supported a diagnosis of sarcoidosis.

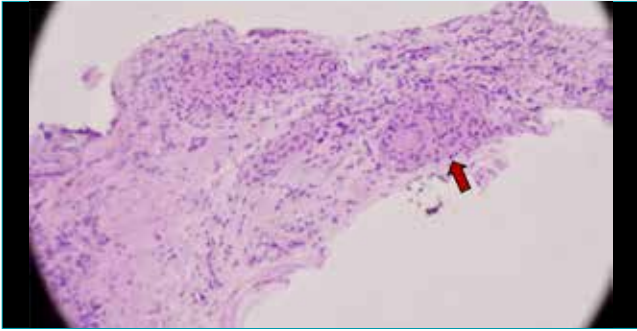


Figure 3: Granulomatous inflammation with multiple well-formed non-caseating epithelioid cell granulomas.

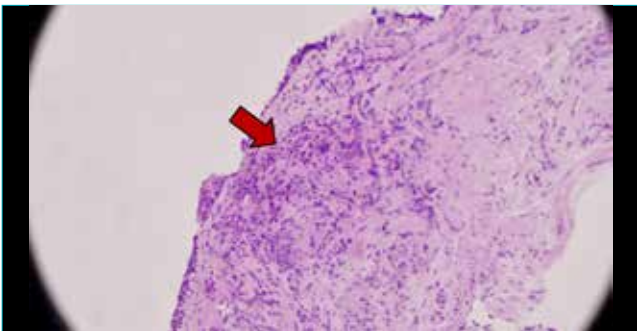


Figure 4: Langhans-type multinucleated giant cells.

Cardiac evaluation revealed sinus tachycardia with non-specific ST-T wave changes on electrocardiography (ECG). Echocardiography revealed dilated cardiomyopathy with global hypokinesia and a reduced left ventricular ejection fraction of approximately 35%, without regional wall motion abnormalities. Mild biatrial enlargement, functional tricuspid regurgitation, and mild pulmonary hypertension (estimated pulmonary artery systolic pressure of approximately 40 mmHg) were noted. These findings raised suspicion of cardiac involvement.

Abdominal ultrasonography revealed a coarse hepatic echotexture with irregular nodular margins suggestive of cirrhosis. Portal vein dilatation, splenomegaly, and the presence of collateral vessels indicate portal hypertension. No focal hepatic lesions were observed.

Intravenous dexamethasone was initiated during the acute phase and subsequently transitioned to oral prednisolone (1 mg/kg/day) with a planned gradual taper. Heart failure management included the continuation of perindopril and treatment with furosemide and spironolactone for volume control. Anticoagulation was initiated with low-molecular-weight heparin, followed by warfarin due to dilated cardiomyopathy and biatrial

enlargement. The patient was monitored for arrhythmia during hospitalisation.

Supportive respiratory therapy included nebulised bronchodilators for symptomatic relief. Hepatic management included ursodeoxycholic acid, lactulose, and rifaximin, along with nutritional support and dietary modification. Empirical antibiotic therapy with intravenous ceftriaxone and oral levofloxacin was administered due to the initial concern of enteric infection.

The patient demonstrated gradual clinical improvement during hospitalisation, with a significant reduction in dyspnoea, cough, orthopnoea, and peripheral oedema. The patient remained haemodynamically stable, with improvements in laboratory parameters. At discharge, he was continued on oral prednisolone, heart failure therapy, ursodeoxycholic acid, rifaximin, lactulose, and his regular diabetic and antihypertensive medications. Follow-up was planned at one and three months with repeat laboratory investigations, echocardiography, chest imaging, and abdominal ultrasonography to assess clinical response and disease progression.

Discussion

This case highlights the diagnostic challenge of differentiating sarcoidosis from TB, particularly in TB-endemic regions of the world. The patient's history of treated TB, along with chronic cough, weight loss, and pulmonary abnormalities, initially raised concerns regarding the reactivation of TB. However, the absence of microbiological evidence of active infection and the presence of non-caseating granulomas without necrosis or acid-fast bacilli on biopsy supported the diagnosis of sarcoidosis.⁵ Although granulomatous inflammation can be observed in both conditions, the diagnosis relies on the correlation between clinical findings, imaging, histopathology, and exclusion of infectious causes.

Multisystem involvement in this patient further supports sarcoidosis as the unifying diagnosis. In addition to pulmonary disease, the patient had cardiac and hepatic involvement, which are recognised but less common manifestations of systemic sarcoidosis.^{1,3} Cardiac involvement was suspected based on a reduced left ventricular ejection fraction, elevated NT-proBNP levels, and features of non-ischaemic systolic heart failure, suggesting possible sarcoid-related cardiomyopathy.¹ The presence of bilateral hilar lymphadenopathy, a

characteristic thoracic finding, further strengthened the diagnosis.⁵

Hepatic involvement is another important feature of this case. Although hepatic granulomas are frequently observed in sarcoidosis, clinically significant liver disease occurs in a smaller proportion of patients.^{3,6} The cholestatic pattern of liver enzyme elevation, fibrosis, portal hypertension, and exclusion of other causes of chronic liver disease supported the diagnosis of hepatic sarcoidosis. Granulomatous involvement of the portal tracts can lead to periportal fibrosis and, rarely, cirrhosis and portal hypertension.^{3,6,7}

An important finding in this case was the normal serum ACE level, despite extensive organ involvement. Although ACE levels may be elevated in sarcoidosis, their sensitivity is limited, and normal values do not exclude the diagnosis.^{3,8} In this patient, long-term use of the ACE inhibitor perindopril may have contributed to the normal ACE level, as ACE inhibitors can suppress circulating ACE activity and potentially result in falsely low values.⁹ This highlights the importance of interpreting ACE levels within a clinical context rather than using them as an exclusionary test.

Positive ANA results initially raised suspicion of an underlying connective tissue disease; however, further

evaluation did not reveal evidence of an autoimmune disorder. ANA positivity can occur in sarcoidosis and is generally considered a nonspecific finding.¹⁰ Similarly, elevated IgG levels may reflect polyclonal immune activation associated with chronic granulomatous inflammation.^{11,12}

Accurate differentiation between sarcoidosis and TB is essential because their treatments differ significantly. In this case, the absence of microbiological evidence of TB, characteristic histopathological findings, multisystem involvement, and clinical response to corticosteroids supported a diagnosis of sarcoidosis rather than active TB.² Other granulomatous disorders, including fungal infections, chronic beryllium disease, and granulomatosis with polyangiitis, were considered but were unlikely based on the clinical, laboratory, and microbiological findings.

This case emphasises that sarcoidosis should remain a diagnostic consideration in patients with multisystem granulomatous disease, even in regions where TB is prevalent and despite normal ACE levels in the blood. A comprehensive evaluation combining clinical assessment, imaging, histopathology, and exclusion of alternative diagnoses is essential for establishing a diagnosis and guiding appropriate management.

Conclusion

This case highlights the importance of considering sarcoidosis in patients presenting with granulomatous disease, even in TB-endemic regions and in those with a history of TB infection. The overlap in clinical and radiological features between sarcoidosis and TB can make diagnosis challenging; however, careful assessment of multisystem involvement, histopathological findings, and microbiological investigations can help establish the correct diagnosis.

The presence of non-caseating granulomas, bilateral hilar lymphadenopathy, cardiac dysfunction, and hepatic involvement in this patient favoured a diagnosis of sarcoidosis over TB. Normal serum ACE levels should not exclude the diagnosis, particularly in patients receiving ACE inhibitors or those with active disease despite normal biomarker levels. Similarly, positive ANA findings should be interpreted cautiously, as they may indicate nonspecific immune abnormalities in sarcoidosis.

Accurate differentiation between sarcoidosis and TB is essential because their treatment approaches differ significantly. In this patient, an appropriate diagnosis allowed for the timely initiation of corticosteroid therapy, resulting in clinical improvement. This case emphasises the importance of a comprehensive diagnostic approach that integrates clinical features, imaging, histopathology, and laboratory investigations when evaluating multisystem granulomatous disorders.

Nitin Rathod, Andrea Janice Fonseca, Snehal Sadanandan, Akshita Jain. Multisystem Sarcoidosis Masquerading as Tuberculosis Despite Normal Serum Angiotensin-Converting Enzyme Levels: A Case

Report. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-21>

References

1. Hussain K, Shetty M. Cardiac Sarcoidosis. [Updated 2024 Mar 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-.
2. Strambu IR, Beer A. Case Report: Sarcoidosis or tuberculosis? A continuous challenge. *Front Med*. 2025;12:1602370.
3. Shah N, Mitra A. Gastrointestinal and Hepatic Sarcoidosis: A Review Article. *Clin Liver Dis (Hoboken)*. 2021;17(4):301–7.
4. Cremers J, Drent M, Driessen A, et al. Liver-test abnormalities in sarcoidosis. *Eur J Gastroenterol Hepatol*. 2012;24(1):17–24.
5. Jain R, Yadav D, Puranik N, et al. Sarcoidosis: Causes, Diagnosis, Clinical Features, and Treatments. *J Clin Med*. 2020;9(4):1081.
6. Graf C, Arncken J, Lange CM, et al. Hepatic sarcoidosis: Clinical characteristics and outcome. *JHEP Rep*. 2021;3(6):100360.
7. Dasani DB, Fiel MI, Simoes CC, et al. The varying histology of hepatic sarcoidosis and the relation of bile duct damage and loss to the presence of portal hypertension and cirrhosis. *Gastro Hep Advances*. 2025;4(2):100561.
8. Druyan A, Shuv N, Lidar M. Put down the ACE: low clinical utility for angiotensin-converting enzyme levels in sarcoidosis: a single-center retrospective cohort Study. *J Clin Med*. 2024;13(24):7657.
9. Lieberman J. Effect of converting enzyme inhibitors on serum ACE test. *Chest*. 1990;98(6):1538.
10. Kobak S, Yilmaz H, Sever F, et al. The prevalence of antinuclear antibodies in patients with sarcoidosis. *Autoimmune Dis*. 2014;2014(1):351852.
11. Hunninghake GW, Crystal RG. Mechanisms of hypergammaglobulinemia in pulmonary sarcoidosis: site of increased antibody production and role of T lymphocytes. *J Clin Invest*. 1981;67(1):86–92.
12. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA*. 2011;305(4):391–9.

Primary Vaginal Adenocarcinoma with Intestinal Differentiation: Diagnostic Complexity and Individualised Radiation Planning

Apoorva Singh¹, Garima Singh¹, Khushboo Rastogi¹, Nidhi Sharma¹, Varshu Goel¹,
Annu Dalal¹, Anusheel Munshi¹

¹Department of Radiation Oncology, BLK-Max Super Speciality Hospital, New Delhi

Correspondence:

Apoorva Singh

E-mail: apoorvasingh739@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-22>

Abstract:

Primary vaginal cancer is a rare entity, accounting for 1% – 2% of gynaecological malignancies, with squamous cell carcinoma and adenocarcinoma comprising 80% – 85% and < 10% of cases, respectively. Adenocarcinoma is generally a clear cell histology, with intestinal differentiation being an exceptionally rare neoplasm, representing one of the least common histological variants of vaginal cancer. Owing to its morphological and immunophenotypic resemblance to metastatic colorectal adenocarcinoma, establishing a diagnosis requires meticulous clinicopathological correlation and exclusion of a gastrointestinal primary. Given its rarity, evidence regarding the optimal management of vaginal adenocarcinoma remains inconclusive. We present a case highlighting the diagnostic complexity using immunohistochemistry, clinicopathological features, and multidisciplinary management, including chemotherapy and radiation, which required individualised planning in the setting of treatment-limiting toxicity.

Key words: Primary Vaginal Cancer, Adenocarcinoma, Intestinal Differentiation, Radiotherapy, External Beam Radiotherapy (EBRT) Boost, Brachytherapy Alternative.

Introduction

Primary vaginal carcinoma is a rare gynaecologic malignancy, accounting for approximately 1% – 2% of all female genital tract cancers, with nearly 80% of vaginal malignancies representing secondary involvement of adjacent organs or distant metastases.¹ Squamous cell carcinoma is the predominant histological subtype, contributing 80% – 90%, whereas adenocarcinomas constitute less than 10% of primary vaginal cancers.^{1,2} Among these, primary vaginal adenocarcinoma with intestinal differentiation is exceptionally rare, with fewer than 40 reported cases in the literature.^{1–3}

The diagnosis of intestinal-type adenocarcinoma is particularly challenging because of its striking morphological and immunohistochemical resemblance to metastatic colorectal adenocarcinoma.^{3,4} Consequently, thorough clinical evaluation, gastrointestinal (GI) endoscopy, cross-sectional imaging, and immunohistochemical analysis are essential to exclude an extragenital primary tumour before establishing the diagnosis.^{2,4} Although markers such as cytokeratin 20 (CK20), caudal-type homeobox 2 (CDX2), carcinoembryonic antigen (CEA), and special AT-rich sequence-binding protein 2 (SATB2) support intestinal differentiation, they cannot reliably distinguish primary vaginal tumours from metastatic GI malignancies.^{4,5}

Owing to the rarity of this tumour, evidence guiding its management is limited to isolated case reports and small case series, and no disease-specific treatment guidelines exist.^{5,6} Therefore, management requires a multidisciplinary approach with individualised treatment planning based on disease extent, patient characteristics, and available therapeutic modalities.⁶ We report a rare case of primary vaginal adenocarcinoma with intestinal differentiation managed with multimodal therapy, highlighting the diagnostic challenges and the role of individualised radiation treatment in achieving disease control.

Case Report

A 58-year-old postmenopausal woman, para 4, live 4 (P4L4), presented to the outpatient department of our hospital with complaints of postmenopausal per-vaginal bleeding and swelling in the left groin region for 6 months. General physical examination, including vital signs and neck and breast examinations, was unremarkable. There was no abdominal tenderness, and no masses were palpable. However, the bilateral inguinal region showed a large conglomerated nodal mass (8 × 9 cm in the largest dimension in the left inguinal region) and another similar nodal mass in the right inguinal region of size 4 × 4 cm. A gynaecological examination was also performed. External inspection revealed normal genitalia and anal region. On per-speculum examination, the cervix appeared grossly healthy, and a large ulceroproliferative growth measuring 4 × 5 cm was observed on the right lateral vaginal wall, extending from the upper one-third to the introitus. A per-vaginal examination was performed, which confirmed the per-speculum findings. Additionally, the paravaginal tissue was involved. This was followed by a per-rectal examination, which revealed smooth and intact rectal mucosa. Multiple punch biopsies were performed on the cervix and vaginal growth.

Cervical biopsy showed acute on chronic cervicitis, while the vaginal growth biopsy was suggestive of adenocarcinoma. The additional immunostains were positive for cytokeratin 7 (CK7), CEA and CDX2, while negative for CK20, SATB2, thyroid transcription factor 1 (TTF1), paired box gene 8 (PAX8), P40, Wilms tumour 1 (WT1), oestrogen receptor (ER), progesterone receptor (PR), Napsin A and prostate-specific antigen (PSA)

(Figure 1). The combined programmed death-ligand 1 (PD-L1) combined positive score (CPS) was 5. These results were consistent with those of adenocarcinoma with intestinal differentiation. Fine-needle aspiration cytology (FNAC) from the left inguinal nodes was suggestive of metastatic poorly differentiated carcinoma.

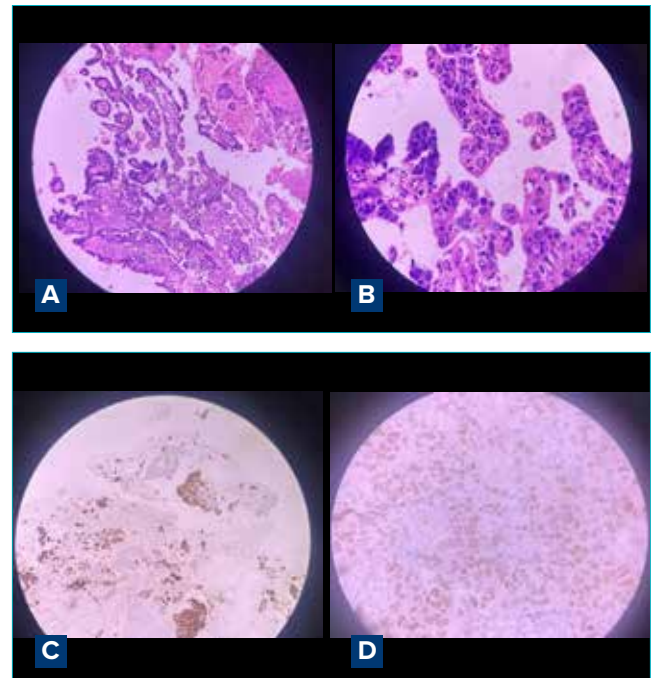


Figure 1A – D: Histopathological images of haematoxylin and eosin (H&E) stained sections showing tumour cells composed of infiltrating atypical glandular and papillary structures lined by pseudostratified columnar epithelial cells exhibiting intestinal differentiation in: **A.** 10× power; **B.** 100× power. Immunohistochemical stain showing tumour cell positivity for: **C.** Cytokeratin 7 (CK7); **D.** Caudal-type homeobox 2 (CDX2).

Whole-body positron emission tomography-computed tomography (WBPET-CT) imaging showed metabolically active thickening involving the vaginal vault with multiple metabolically active bilateral external iliac lymph nodes (right, 1.2 × 1.4 cm and left, 1.7 × 2.4 cm) and bilateral inguinal lymph nodes (largest, 2.8 × 4.7 cm) (Figure 2). Contrast-enhanced magnetic resonance imaging (MRI) of the pelvis revealed a soft tissue lesion in the lower half of the vagina with major bulk along the right anterolateral wall, extending into the right paravaginal space, abutting the levator ani muscles with focal loss of fat planes with the urethra/base of the bladder. Multiple enlarged bilateral iliac and inguinal lymph nodes were observed.

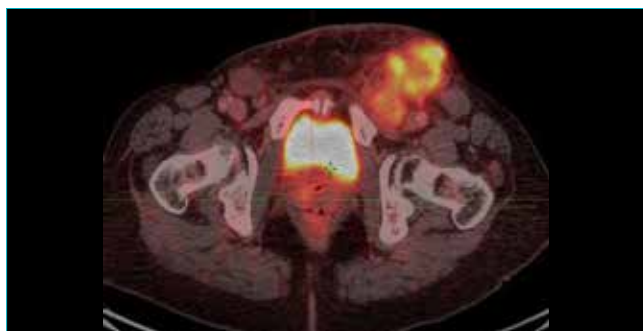


Figure 2: Baseline – whole-body positron emission tomography-computed tomography (PET-CT) axial sections showing metabolically active thickening of the vaginal vault with multiple metabolically active bilateral external iliac and bilateral inguinal lymph nodes.

Management

The case was discussed in a multidisciplinary tumour board, and neoadjuvant chemotherapy followed by concurrent chemoradiation and subsequent brachytherapy was planned. She received three cycles of paclitaxel and carboplatin-based chemotherapy. Follow-up WBPET-CT showed a clear reduction in the size and metabolic activity of the pelvic and inguinal lymph nodes, along with complete resolution of abnormal fluorodeoxyglucose (FDG) uptake in the vagina (Figure 3). The overall impression was of a partial response. The patient underwent computed tomography (CT) simulation, followed by contouring of the target volumes and organs at risk, in accordance with the latest contouring guidelines (National Comprehensive Cancer Network [NCCN] and European Society for Radiotherapy and Oncology/European Society of Gynaecological Oncology/European Society for Paediatric Oncology [ESTRO/ESGO/SIOPE]). An intensity-modulated radiotherapy (IMRT) plan was generated, and treatment was delivered using daily image-guided radiotherapy (IGRT) to ensure accurate target localisation and reproducible patient setup. External beam radiotherapy (EBRT) was administered at a dose of 50 Gy in 25 fractions to the pelvis and 58 Gy in 25 fractions to the bilateral inguinal region and gross pelvic nodes, followed by a boost of 6 Gy in 3 fractions to the bilateral inguinal gross nodes (Figure 4). She received weekly chemotherapy with cisplatin along with radiation. Despite adherence to the Radiation Therapy Oncology Group (RTOG) 0418-recommended bone marrow dose constraints ($V_{10} < 90\%$ and $V_{40} < 40\%$), the patient developed grade 3 haematological toxicity during the course of treatment (Figure 5).

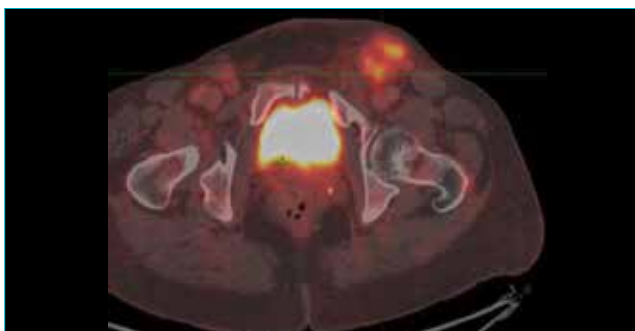


Figure 3: Post-neoadjuvant chemotherapy – whole-body positron emission tomography-computed tomography (PET-CT) axial sections showing reduction in size and metabolic activity of pelvic and inguinal lymph nodes with complete resolution of abnormal fluorodeoxyglucose (FDG) uptake in the vagina.



Figure 4: Axial section of the planning computed tomography (CT) scan showing isodose colour wash for planning target volumes (PTV): Yellow – 95% coverage for 50 Gy, Green – 95% coverage for 58 Gy, Pink – 100% coverage for nodal boost till 66 Gy (Equivalent dose in 2 Gy fractions [EQD2]).

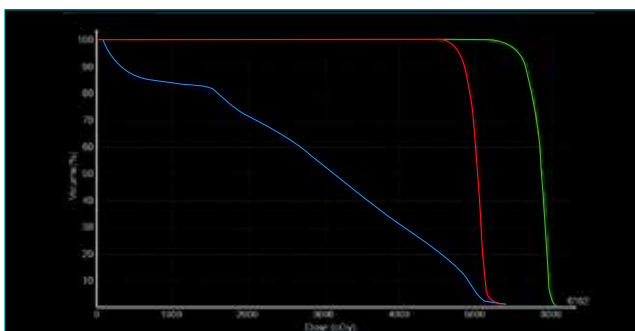


Figure 5: Detailed dose-volume histogram for planning target volume (PTV) (Red), PTV boost (Green) and bone marrow (Blue).

Post-phase 1 radiation WBPET-CT was performed, which showed no avid lesion in the vagina, with mildly avid residual nodes that decreased in size and avidity (Figure 6). It showed an encouraging response to the EBRT. Although brachytherapy was planned as part of the definitive treatment, it could not be delivered because of financial constraints and the risk of haematological toxicities. Therefore, the treatment plan was individualised

with an EBRT boost to a dose of 20 Gy in 5 fractions to the vagina with margins and 25 Gy in 5 fractions to the gross tumour volume present before neoadjuvant chemotherapy, allowing successful completion of definitive radiotherapy while maintaining disease control (Figure 7).

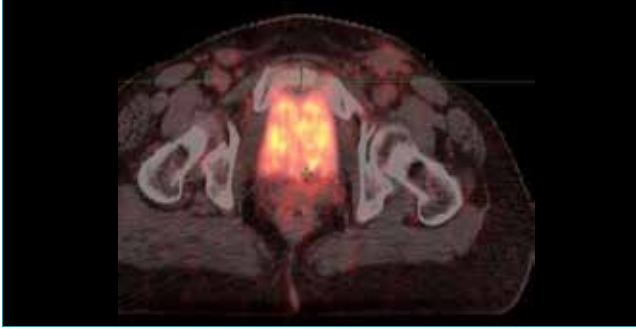


Figure 6: Post-phase 1 external beam radiotherapy (EBRT) whole-body positron emission tomography-computed tomography (PET-CT) axial sections showing no avid lesion in the vagina, with mildly avid residual nodes decreased in size and avidity.

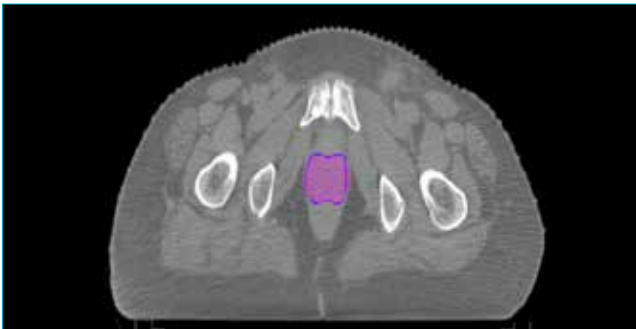


Figure 7: Axial section of planning computed tomography (CT) scan showing 100% isodose colour wash for phase II target volume (Pink).

The patient was on regular follow-up. Her WBPET-CT performed 6 months after treatment showed no vaginal lesions with metabolically inactive small inguinal nodes (Figure 8). FNAC was performed on the inactive inguinal node, which was negative for carcinoma.

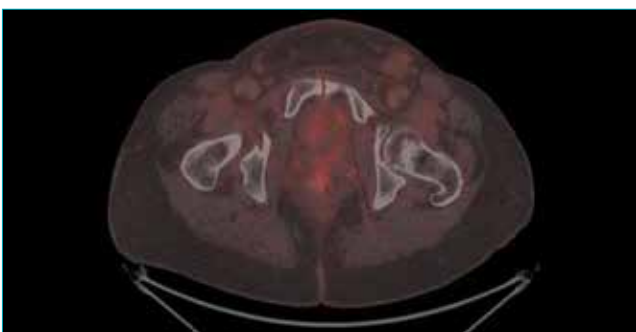


Figure 8: Post-6-month radiation – whole-body positron emission tomography-computed tomography (PET-CT) axial sections showed no vaginal lesion, with metabolically inactive small inguinal nodes.

Discussion

Primary vaginal adenocarcinoma with intestinal differentiation (also known as intestinal- or enteric-type adenocarcinoma of the vagina) is an exceedingly rare tumour. Since the first well-documented cases appeared in the late 1980s and the early 1990s, fewer than 30 well-characterised cases have been reported in the English literature.¹

Histologically, these tumours are difficult to distinguish from conventional colorectal adenocarcinomas. They exhibit gland-forming architecture, columnar cells, mucin production, goblet cells, and variable nuclear atypia. Immunohistochemistry helps but does not settle the question on its own; most cases express CK20, CDX2, CEA, and SATB2, with variable CK7, while PAX8, ER, and PR are usually negative. Because this immunoprofile overlaps significantly with metastatic colorectal adenocarcinoma, histopathology alone is insufficient for diagnosis. Colonoscopy, upper GI endoscopy where indicated, cross-sectional imaging, and careful clinical correlation are all needed to rule out a GI primary before a vaginal origin can be accepted.²

Given the rarity of this entity, no dedicated treatment guidelines exist. Management is largely borrowed from protocols for primary vaginal carcinoma and is individualised based on tumour size, stage, and institutional expertise. Reported approaches range from local excision in small, localised disease to radical surgery, definitive radiotherapy with or without brachytherapy, concurrent chemoradiotherapy, or multimodality treatment. More advanced diseases are generally treated with definitive chemoradiotherapy.³

Outcome data are still limited, largely because most reports involve single patients followed up for a short period. Evidence suggests that definitive chemoradiotherapy can achieve durable local control and a good metabolic response in selected patients. The literature also repeatedly states that when standard therapy cannot be completed as planned, individualised adaptation and multidisciplinary discussion become critical to preserving outcomes. Our case is a fairly direct illustration of this: when grade 3 haematological toxicity ruled out interstitial brachytherapy, an adapted EBRT boost allowed us to complete definitive treatment and still achieve a complete metabolic response.⁴

It is also worth noting that most of what we know about this entity comes from scattered single case reports, which limits the extent to which the findings can be generalised. Recent systematic reviews have called for more standardised reporting going forward — detailed

pathology, immunohistochemical and molecular profiling, treatment details, and long-term follow-up — so that the evidence base can move beyond anecdote toward something closer to actual practice guidance.⁵

Conclusion

Primary vaginal adenocarcinoma with intestinal differentiation is an exceptionally rare malignancy that closely mimics metastatic colorectal adenocarcinoma. Comprehensive clinical, radiological, endoscopic, and pathological evaluations are required for an accurate diagnosis. Owing to its rarity, treatment should be individualised using a multidisciplinary approach. This case demonstrates that definitive chemoradiotherapy can achieve a favourable response and highlights the importance of adaptive radiotherapy planning. When interstitial brachytherapy was precluded by grade 3 haematological toxicity with persistent thrombocytopenia, an EBRT boost enabled successful treatment completion. Reporting such rare cases expands the evidence base and may help guide future diagnostic and therapeutic strategies for this condition.

Apoorva Singh, Garima Singh, Khushboo Rastogi, Nidhi Sharma, Varshu Goel, Annu Dalal, Anusheel Munshi.
Primary Vaginal Adenocarcinoma with Intestinal Differentiation: Diagnostic Complexity and Individualised Radiation Planning. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-22>

References

1. Franchi M, Garzon S, Calì A, et al. Intestinal-type primary vaginal adenocarcinoma: Review of the literature with report of a case: from diagnosis to management. *J Obstet Gynaecol*. 2021;33(2):79–89.
2. Sabri A, Li C, Monika F, et al. Primary Vaginal Adenocarcinoma of Intestinal-Type: A Case Report of a Rare Tumor With Review of Histology, Differential Diagnosis, and Literature. *Cureus*. 2022;14:e25298.
3. Mudhar HS, Smith JH, Tidy J. Primary vaginal adenocarcinoma of intestinal type arising from an adenoma: case report and review of the literature. *Int J Gynecol Pathol*. 2001;20:204–9.
4. Ditto A, Martinelli F, Carcangiu ML, et al. Incidental diagnosis of primary vaginal adenocarcinoma of intestinal type: a case report and review of the literature. *Int J Gynecol Pathol*. 2007;26:490–3.
5. Ait Laalim S, Tourghai I, Ibnmejdoub K, et al. Primary vaginal adenocarcinoma of intestinal type: case report and review of literature. *Pan Afr Med J*. 2013;15:30.
6. Fox H, Wells M, Harris M, et al. Enteric tumors of the lower female genital tract: a report of three cases. *Histopathology*. 1988;12:167–76.

Endobronchial Watanabe Spigot Placement for a Tuberculosis-Associated Bronchopleural Fistula: A Stepwise Balloon Occlusion Technique

Sameer Arbat^{1*}, Manoj Pethe¹, Nitin Wadaskar²

¹Department of Pulmonology, Max Super Speciality Hospital, Nagpur, Maharashtra

²Department of Internal Medicine, Max Super Speciality Hospital, Nagpur, Maharashtra

Correspondence:

Sameer Arbat

E-mail: Sameer.Arbat@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-23>

Abstract:

Bronchopleural fistula (BPF) is an uncommon but potentially life-threatening complication of pulmonary tuberculosis (TB), resulting from cavitory necrosis and bronchial wall destruction, with persistent air leaks traditionally requiring surgical closure. We describe a 36-year-old man with extensive pulmonary TB who presented with left-sided tension pneumothorax, extensive subcutaneous emphysema, pneumomediastinum, and respiratory failure, and was subsequently diagnosed with a persistent air leak secondary to BPF. Sequential Fogarty balloon occlusion during check bronchoscopy, with the intercostal drain connected to continuous negative-pressure suction at -20 cm H₂O, enabled precise localisation of the fistula. Definitive closure was performed two days later under general anaesthesia using a 5-mm endobronchial Watanabe spigot (EWS) deployed through a flexible bronchoscope passed via a 12-mm rigid bronchoscope, with reinforcement using cyanoacrylate glue. Sequential balloon occlusion mapping combined with EWS placement and adjunctive cyanoacrylate glue provided a safe, effective, and minimally invasive approach for localisation and closure of TB-associated BPF, enabling this critically ill, high-risk patient to avoid thoracic surgery during the acute phase of infection.

Key words: Bronchopleural Fistula, Endobronchial Watanabe Spigot, Pulmonary Tuberculosis, Balloon Occlusion, Interventional Pulmonology, Rigid Bronchoscopy.

Introduction

A bronchopleural fistula (BPF) is an abnormal communication between the bronchial tree and the pleural space that permits continuous escape of air into the pleural cavity, resulting in persistent pneumothorax, prolonged chest-tube dependence, and a heightened risk of pleural infection and empyema. Pulmonary tuberculosis (TB) remains an important cause of BPF in high-burden regions, where cavitory disease, caseous necrosis, and destruction of the bronchial wall predispose to fistula formation.

Conventional management of persistent air leak has relied on surgical closure of the fistula. However, surgery carries significant morbidity in patients with active TB, inflamed and friable lung tissue, poor nutritional status, and reduced pulmonary reserve, and is often not feasible in the acute, critically ill setting. Advances in interventional pulmonology have introduced bronchoscopic alternatives, including endobronchial valves, coils, sealants, vascular plugs, and silicone spigots, that allow selected patients to avoid thoracotomy. We report a case in which sequential

balloon occlusion was used to precisely localise a TB associated BPF in a critically ill patient, followed by definitive closure with an endobronchial Watanabe spigot (EWS) reinforced with cyanoacrylate glue.

Case Report

A 36-year-old man presented with fever, cough, and progressively worsening breathlessness for six to seven days, together with weight loss and loss of appetite over the preceding two months. At the outside hospital where he first sought care, he was found to have pulmonary TB complicated by a left-sided tension pneumothorax, for which a pigtail catheter was inserted in the left fifth intercostal space in the mid-axillary line. He went on to develop extensive subcutaneous emphysema, for which a 24 Fr intercostal drain (ICD) was placed, and he was then transferred to a tertiary-care centre for further management.

On arrival, he was tachypnoeic and tachycardic, with a respiratory rate of 26 breaths per minute, an oxygen saturation of 96% on room air, and bilateral crepitations on chest auscultation; a swelling was also noted over the neck, in keeping with tracking of the subcutaneous emphysema and pneumomediastinum. He was admitted to the Intensive Care Unit (ICU) in isolation and started on intravenous fluids, broad-spectrum antibiotics, proton pump inhibitors, antiemetics, and other supportive measures.

Initial investigations revealed anaemia (haemoglobin 10.5 g/dL), a markedly elevated C-reactive protein (135 mg/L), hyponatraemia, and newly recognised hyperglycaemia (glycosylated haemoglobin 72.67 mmol/mol, International Federation of Clinical Chemistry [IFCC] units), later characterised as new-onset type 2 diabetes mellitus. Contrast-enhanced computed tomography (CT) of the thorax showed a large left hydropneumothorax with the ICD in situ, surrounding consolidation and fibrosis communicating with the tracheobronchial tree, and a suspected communication between the left upper lobe anterior segmental bronchus and the pleural space, in keeping with a BPF. Additional findings included bilateral apical fibrocavitary disease with volume loss, scattered centrilobular nodules, endobronchial infiltrates (right greater than left), extensive subcutaneous emphysema with pneumomediastinum, and mediastinal lymphadenopathy (Figure 1).

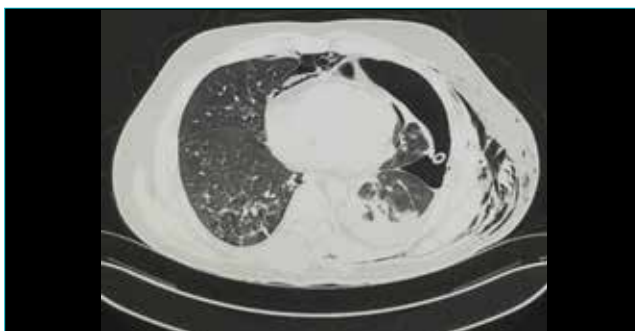


Figure 1: High-resolution computed tomography (HRCT) of the thorax showing a left-sided pneumothorax with an intercostal drain (ICD) in situ.

Pulmonology and general surgery were consulted in view of persistent breathlessness and the CT findings of a ruptured cavity communicating with the pleural space, and bronchoscopic evaluation was advised. GeneXpert MTB/RIF Ultra performed on respiratory secretions detected *Mycobacterium tuberculosis* complex with a low bacillary load, with rifampicin resistance not detected, and four-drug anti-TB therapy (rifampicin, isoniazid, ethambutol, and pyrazinamide) was initiated alongside management of the pneumothorax and BPF.

Procedure and Technique

Step 1: Balloon occlusion for fistula localisation

A check bronchoscopy was performed under local anaesthesia/conscious sedation. To maximise sensitivity, the ICD was connected to continuous negative suction of -20 cm H₂O, allowing real-time observation of the air leak throughout the procedure. A 4 Fr Fogarty balloon catheter was passed through the working channel of a flexible bronchoscope and used to sequentially occlude individual segmental and subsegmental bronchi, with the chest drain observed for cessation of bubbling after each occlusion (Figure 2). Complete disappearance of bubbling occurred on occlusion of the left upper lobe anterior subsegment, confirming this as the bronchus responsible for the fistula (Figure 3). The patient's condition was stabilised over the following day, and definitive bronchoscopic closure was planned once he was fit for a further general anaesthetic.



Figure 2: Bubbling noted in the intercostal drain (ICD) bag, suggestive of a bronchopleural fistula (BPF).



Figure 4: Endobronchial Watanabe spigot (EWS) held with bronchoscopy forceps.



Figure 3: Site of the bronchopleural fistula (BPF) identified following balloon occlusion.



Figure 5: Deployment of the 5-mm endobronchial Watanabe spigot (EWS) into the diseased segment with forceps.

Step 2: Endobronchial Spigot Placement

Two days after localisation, the patient underwent therapeutic bronchoscopy under general anaesthesia. A 12-mm rigid bronchoscope was introduced to secure the airway and provide optimal access, and an adult flexible bronchoscope was passed through it to visualise the previously identified segment. The site of the BPF was reconfirmed by re-occlusion with the 4 Fr Fogarty balloon. A 5-mm EWS was then grasped with forceps (Figure 4) and deployed into the diseased bronchial segment (Figure 5). Cyanoacrylate glue was instilled around the spigot to secure its position, minimise the risk of migration, and reinforce closure of the fistulous communication (Figure 6). The patient tolerated the procedure well, with no immediate complications.



Figure 6: Endobronchial Watanabe spigot (EWS) seen in the diseased segment.

Outcome and Follow-up

Following spigot placement, the patient remained haemodynamically stable and was continued on anti-TB therapy (Figure 7). At the time of discharge, the ICD was removed, with advice to continue anti-TB therapy (Figure 8).



Figure 7: Final endobronchial appearance after spigot placement and glue reinforcement.



Figure 8: Chest X-ray (CXR), posteroanterior (PA) view, showing the endobronchial Watanabe spigot (EWS) with resolution of pneumothorax.

Discussion

BPF in TB

Patients with BPF commonly present with persistent bubbling through the chest drainage system, failure of complete lung expansion, recurrent pneumothorax, prolonged chest-tube dependence, and an increased risk of pleural infection.¹ In active pulmonary TB, inflamed and friable lung tissue makes surgical repair technically demanding, active infection increases postoperative complications, and patients frequently have poor nutritional status and reduced respiratory reserve.^{1,2} Minimally invasive bronchoscopic techniques have therefore emerged as valuable alternatives in carefully selected patients.³

Role of sequential balloon occlusion

Precise localisation is the cornerstone of successful bronchoscopic BPF closure. Connecting the ICD to continuous negative suction while sequentially occluding individual bronchi with a Fogarty balloon allows real-time confirmation of the leaking airway. Accurate mapping

in this manner ensures precise deployment of the occlusive device and maximises the likelihood of fistula closure while preserving ventilation to unaffected lung segments, a strategy consistent with bronchoscopic localisation approaches described in prior reports of TB-associated BPF.^{3,4}

The EWS

The EWS is a silicone bronchial occlusion device originally developed in Japan for bronchoscopic management of persistent air leaks. It mechanically occludes the leaking bronchus, preventing further air escape into the pleural cavity, promoting spontaneous fistula healing, facilitating lung re-expansion, and shortening chest-tube duration.^{4,5} The device is soft, biocompatible, available in multiple sizes, and can be retrieved if clinically indicated. Compared with surgical repair, bronchoscopic EWS placement avoids thoracotomy or lung resection, carries lower procedural morbidity, permits faster recovery, and is repeatable and reversible, advantages that are particularly relevant in high-risk surgical candidates such as patients with active TB.^{2,3}

Reported experience with EWS in TB-related BPF and empyema,⁴ as well as in postoperative and infection-related fistulas more broadly,⁵ supports its efficacy and safety. Adjunctive cyanoacrylate glue has been described as a means of reducing the risk of spigot migration and reinforcing the seal,⁵ an approach that was also adopted in the present case.

Alternative and emerging bronchoscopic options

Other bronchoscopic options for BPF closure described in the literature include endobronchial valves, biological glues, endobronchial coils, vascular plugs, and self-expanding metal stents for larger defects.^{3,5} These techniques have considerably expanded the therapeutic armamentarium available to the interventional pulmonologist and continue to improve outcomes in patients with persistent air leaks who are unfit for surgery. Surgical closure remains an option for larger or refractory fistulas but is reserved for patients who fail conservative and bronchoscopic measures, given its higher morbidity in the setting of active TB.²

Declarations

Informed consent: Written informed consent was obtained from the patient for publication of this case report and accompanying bronchoscopic images.

Conflicts of interest: None declared.

Funding: None.

Conclusion

This case demonstrates the bronchoscopic management of a TB-associated BPF in a critically ill patient, using a stepwise balloon occlusion technique for localisation followed by EWS placement reinforced with cyanoacrylate glue. This minimally invasive strategy allowed the acute air leak to be controlled without recourse to high-risk thoracic surgery during the acute phase of illness, though the patient was discharged against medical advice for financial reasons before long-term confirmation of fistula closure could be obtained. The case underscores both the expanding role of interventional pulmonology in the management of persistent air leaks in TB and the impact that socioeconomic factors can have on completion of care.

Learning points

- Sequential balloon occlusion with the ICD connected to -20 cm H₂O suction is a reliable bedside technique for accurately localising a BPF prior to definitive closure.
- Staged management, with diagnostic balloon occlusion followed by endobronchial spigot placement once the patient is stable for a further general anaesthetic, allows precise, minimally invasive closure of a TB-associated BPF.
- Combining the EWS with cyanoacrylate glue may reduce the risk of spigot migration and reinforce fistula closure.
- Bronchoscopic occlusion techniques allow high-risk, critically ill patients with active TB and compromised respiratory reserve to avoid the morbidity of thoracic surgery during the acute phase of illness.
- Socioeconomic and financial constraints can interrupt planned care even after a technically successful procedure, underscoring the importance of early counselling and coordination of follow-up when a patient is transferred or discharged against medical advice.

Sameer Arbat, Manoj Pethe, Nitin Wadaskar. Endobronchial Watanabe Spigot Placement for a Tuberculosis-Associated Bronchopleural Fistula: A Stepwise Balloon Occlusion Technique. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-23>

References

1. Bathobakae L, Shahid A, Wilkinson T, *et al.* Tuberculous bronchopleural fistula: a rare and life-threatening disease. *J Investig Med High Impact Case Rep.* 2023;11:23247096231220466.
2. Shen L, Jiang YH, Dai XY. Successful surgical treatment of bronchopleural fistula caused by severe pulmonary tuberculosis: a case report and review of literature. *World J Clin Cases.* 2023;11(10):2282–9.
3. Merali NM, Balasubramanian V, Munyu PW, *et al.* Bronchoscopic spigot occlusion of tuberculosis-associated bronchopleural fistula in a human immunodeficiency virus-positive high-risk patient. *J Pan Afr Thorac Soc.* 2025;6(1):24–7.
4. Dalar L, Kosar F, Eryuksel E, *et al.* Endobronchial Watanabe spigot embolisation in the treatment of bronchopleural fistula due to tuberculous empyema in intensive care unit. *Ann Thorac Cardiovasc Surg.* 2013;19(2):140–3.
5. Chai CS, Chan SK, Kho SS, *et al.* Successful treatment of pyopneumothorax with bronchopleural fistula using endobronchial Watanabe spigots. *Respirol Case Rep.* 2020;8(5):e00562.

Unmasking Steroid-Induced Psychosis in a Patient with Metastatic Spinal Tumour: A Clinical Challenge

Nitin Rathod¹, Andrea Janice Fonseca¹, Shweta Thadeshwar¹, Surbhi Padte¹

¹Department of Internal Medicine, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

Correspondence:

Nitin Rathod

E-mail: drnmrathod@hotmail.com

DOI: <https://doi.org/10.62830/mmj3-03-24>

Abstract:

Metastatic spinal cord compression (MSCC) is a serious oncological emergency that requires prompt recognition and multidisciplinary management to prevent irreversible neurological disability. Corticosteroids are a cornerstone of treatment due to their ability to reduce tumour-associated spinal cord oedema and preserve neurological function. However, they may cause significant adverse effects, including acute psychiatric disturbances. We report the case of a 73-year-old man with advanced metastatic hormone-sensitive prostate cancer who presented with progressive bilateral lower limb weakness, radicular pain, and urinary retention consistent with MSCC. Following urgent multidisciplinary assessment and initiation of high-dose corticosteroid therapy, he developed acute neuropsychiatric deterioration with features of steroid-induced psychosis, a recognised but challenging complication of corticosteroid treatment. His management required careful balancing of the neurological benefits of continued steroid therapy against the emergence of significant psychiatric adverse effects, while also considering his advanced malignancy, advanced age, and multiple comorbidities. This case highlights the complexity of managing oncological emergencies in elderly patients with advanced cancer and underscores the importance of maintaining a high index of suspicion for corticosteroid-induced neuropsychiatric complications. Early recognition, timely intervention, and a multidisciplinary, patient-centred approach are essential to optimise neurological outcomes while minimising treatment-related morbidity.

Key words: Neuropsychiatric, Prostate Cancer, Immunosuppression, Hallucinations.

Introduction

Metastatic spinal cord compression (MSCC) affects approximately 5% – 10% of patients with cancer, with prostate, lung, and breast malignancies accounting for the majority of cases.^{1,2} MSCC results from either direct metastatic epidural tumour infiltration or vertebral body collapse, leading to compression of the thecal sac and spinal cord.³ Its clinical manifestations, such as back pain, motor weakness, sensory changes, and autonomic dysfunction, represent a neurological emergency that requires prompt intervention to prevent irreversible deficits. Management strategies focus on preserving neurological

function, alleviating pain, and maintaining spinal stability, and typically involve corticosteroids, radiotherapy, and surgical decompression, depending on the tumour type, prognosis, and functional status.¹

Corticosteroids continue to play a central role in treating metastatic cancer, particularly in cases involving spinal metastases. They are commonly used to reduce peritumoural swelling, relieve pain, and prevent or manage spinal cord compression.^{4,5} While their clinical benefits are well recognised, these drugs are not without significant side effects, including hyperglycaemia, gastric complications, and infection.^{6,7} One important concern is

their potential to cause neuropsychiatric disorders. These effects can vary widely in severity, ranging from relatively mild symptoms, such as mood changes and irritability, to more serious conditions, including acute psychiatric syndromes, such as steroid-induced psychosis.^{4,5} Steroid-induced psychosis is categorised as a substance- or medication-induced psychotic disorder. Although relatively uncommon, it remains an important clinical concern. The risk tends to increase with higher doses. However, it can still occur with lower doses or after a short course of treatment.^{5,8} The onset is usually sudden, often appearing within a few days to weeks after treatment initiation or dose increase. Patients may present with symptoms such as insomnia, restlessness, paranoia, hallucinations, or clear-cut delusional thinking, which do not occur exclusively during delirium, affect functioning (social, occupational, or safety), and are reversible on reducing the dose or stopping steroids.^{4,8} In patients with metastatic spinal cancer, where high-dose corticosteroids are often necessary to preserve neurological function, this complication may easily go unrecognised due to the lack of awareness. This creates a difficult clinical paradox: a treatment intended to protect the nervous system can simultaneously and temporarily disrupt cognition, perception, and behaviour in ways that are both profound and distressing.

Case Report

A 73-year-old male with a history of metastatic hormone-sensitive prostate cancer (status post bilateral orchidectomy 1.5 years previously, completion of six cycles of docetaxel chemotherapy, and currently on enzalutamide therapy), prior periampullary carcinoma (status post Whipple procedure in 2008), type 2 diabetes mellitus, and hypertension

presented with a 15-day history of progressive lower back pain radiating to both legs (left > right), associated with difficulty walking, grade 3 lower limb weakness, and urinary retention.

Magnetic resonance imaging (MRI) of the lumbosacral spine demonstrated an L2 vertebral metastasis with an enhancing epidural soft-tissue component (8 mm) causing anterior thecal sac effacement and compression of the cauda equina nerve roots, consistent with impending cauda equina syndrome. Surgical decompression and vertebroplasty were performed. The patient was administered injectable steroids (methylprednisolone 1 g) to reduce inflammation three days before surgery. Initial investigations revealed acute kidney injury (creatinine 1.62 mg/dL), leucocytosis (total leucocyte count [TLC] 14,860/ μ L), and hyperglycaemia (random blood sugar [RBS] 257 mg/dL) (Table 1). He was treated with antibiotics, strict glucose monitoring, and supportive management.

He developed acute neuropsychiatric symptoms on the second postoperative day, including disorientation, pressured and irrelevant speech, and episodic visual hallucinations. The patient was evaluated for electrolyte imbalances, hypercalcaemia, abnormal glucose levels, and infections, with all investigations being unremarkable. Haloperidol was initiated and later transitioned to quetiapine. However, his condition remained unchanged. Given the recent administration of high-dose intravenous Solu-Medrol and after ruling out other possible causes of the above neuropsychiatric manifestations, a diagnosis of steroid-induced psychosis was made. Steroids were discontinued, following which the patient's sensorium began to improve. Five days after complete discontinuation

Test	Day 1	Day 3	Day 5	Day 7	Reference range
Haemoglobin (g/dL)	13.8	10.6	–	10.9	13 – 17
Total leucocyte count (/ μ L)	14,860	10,400	–	7,630	4,000 – 10,000
Serum creatinine (mg/dL)	1.62	1.27	1.11	0.66	0.7 – 1.2
eGFR (MDRD)	41.96	55.56	64.91	118.25	> 90
Fasting glucose (mg/dL)	–	176	–	–	60 – 100
C-reactive protein (mg/L)	–	–	–	18.5	< 5
Total calcium (mg/dL)	10.0	9.74	–	9.8	8.6 – 10.2
Urine protein	2+	–	–	–	Absent
Urine sugar	2+	–	–	–	Absent

Table 1: Key laboratory investigations during hospital stay.

Abbreviations: eGFR: Estimated Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease.

of steroids, he was vitally stable with normal consciousness and no disorientation or hallucinations; hence, he was discharged.

Discussion

This case presents the characteristic features of MSCC, including progressive lower limb weakness, radicular pain, and urinary retention, which reflect the established oncological emergency criteria.³ Prostate cancer remains one of the most common primary tumours causing MSCC.^{2,9} The patient's oncological history, including high prostate-specific antigen (PSA) levels and prostate-specific membrane antigen-positron emission tomography (PSMA-PET) demonstrating widespread metastases, strongly supported metastatic involvement as the underlying aetiology. Surgical decompression plays a central role in MSCC when there is mechanical instability, significant neurological deficit, or radioresistant tumours.^{1,2}

The most significant complication was steroid-induced psychosis, a well-recognised but unpredictable adverse effect of corticosteroid therapy. The onset typically occurs within days to weeks of high-dose steroid initiation, which is consistent with this patient's postoperative presentation. Data from the Boston Collaborative Drug Surveillance Program demonstrated a clear relationship between corticosteroid dose and the likelihood of psychiatric adverse effects. Psychiatric symptoms occurred in approximately 18.6% of patients receiving more than 80 mg/day of prednisone or methylprednisolone. The incidence decreased to 4.6% among those taking 41–80 mg/day and to 1.3% among those receiving doses below 40 mg/day, highlighting a dose-dependent increase in risk. Symptoms range from insomnia and agitation to hallucinations and frank psychosis, requiring prompt dose reduction or discontinuation of the drug. The patient's improvement after the cessation of Solu-Medrol and initiation of antipsychotic therapy aligns with established management protocols.^{6,7}

Metabolic complications further contribute to the complexity of the clinical course. Hyperglycaemia is multifactorial, steroid-induced, stress-related, and worsened by underlying diabetes mellitus.¹⁰ Reports from cancer patients, including those with lymphoma treated with high-dose corticosteroids, suggest that psychotic symptoms can develop quite quickly

after increasing the dose, sometimes within as little as 48 to 72 hours.¹¹ In several reported cases, patients developed persecutory delusions, agitation, or significant changes in behaviour that were clearly out of character, sometimes requiring urgent psychiatric care or hospitalisation.¹² Such presentations can be especially challenging to interpret in oncology patients, as similar symptoms are often attributed to delirium, progression of the underlying disease or emotional distress. Consequently, appropriate diagnosis and management may be delayed.¹²

The exact pathophysiology of steroid-induced psychosis is not yet fully understood, but several mechanisms have been suggested. These include disruption of the hypothalamic-pituitary-adrenal axis, changes in dopamine and serotonin signalling, and direct effects on limbic brain structures, such as the hippocampus.^{5,11} Physiological stress, which commonly increases in patients with advanced cancer, may further heighten susceptibility to neuropsychiatric effects.¹¹ Although higher corticosteroid doses are linked to a greater risk, the occurrence of psychosis, even at lower doses, suggests that individual susceptibility plays an important and unpredictable role.^{5,8} The cornerstone of management is to gradually lower the corticosteroid dose or stop the medication if it is clinically safe to do so. This approach often leads to the resolution of psychiatric symptoms. When symptoms are significant or do not improve promptly, treatment with antipsychotic medications may be necessary. Both typical antipsychotics, such as haloperidol, and atypical antipsychotics, including risperidone, olanzapine, and quetiapine, have been used to manage these symptoms.¹²

Steroid-induced psychosis underscores the double-edged nature of corticosteroid therapy in oncology. While these medications can be lifesaving, they may also temporarily disrupt a patient's thinking, behaviour, and sense of self. Recognising this possibility enables clinicians to intervene early, avoid unnecessary investigations, and reassure patients and their families that these symptoms are usually reversible with appropriate management.⁸

Conclusion

This case highlights the complex balance that clinicians must maintain when treating metastatic spinal tumours, where high-dose corticosteroids are often essential for reducing spinal cord compression and preserving neurological function. While steroids can be lifesaving, this report underscores their potential to precipitate serious neuropsychiatric complications, including steroid-induced psychosis. The patient's experience serves as a reminder that treatment is not only about managing the tumour but also about recognising and addressing the unintended effects of therapy on mental health. Early identification of behavioural changes, close monitoring, and a multidisciplinary approach are crucial for ensuring both physical and psychological well-being. Ultimately, this case reinforces the importance of individualised care, in which clinical vigilance and empathy are equally vital for achieving the best possible outcomes.

Nitin Rathod, Andrea Janice Fonseca, Shweta Thadeshwar, Surbhi Padte. Unmasking Steroid-Induced Psychosis in a Patient with Metastatic Spinal Tumour: A Clinical Challenge. MMJ. 2026, September. Vol 3 (3).
DOI: <https://doi.org/10.62830/mmj3-03-24>

References

1. Loblaw DA, Mitera G, Ford M, *et al.* A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys.* 2012;84(2):312–7.
2. Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol.* 2008;7(5):459–66.
3. Byrne TN. Spinal cord compression from epidural metastases. *N Engl J Med.* 1992;327(9):614–9.
4. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *J Affect Disord.* 1983;5(4):319–32.
5. Hall RC, Popkin MK, Stickney SK, *et al.* Presentation of the steroid psychoses. *J Nerv Ment Dis.* 1979;167(4):229–36.
6. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc.* 2006;81(10):1361–7.
7. Kenna HA, Poon AW, de los Angeles CP, *et al.* Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci.* 2011;65(6):549–60.
8. Fischer M, Kim PY. Corticosteroid-Induced Psychosis After a Single Transforaminal Epidural Steroid Injection. *WMJ.* 2019;118(2):91–4.
9. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer.* 2009;115(22):5349–61.
10. Kumar A, Shah K, Patel S. Steroid-induced diabetes: A clinical and molecular approach to diagnosis and management. *J Diabetes Metab Disord.* 2021;20(2):1–9.
11. Orgaz Álvarez B, Velasco Santos M, Ibáñez Mendoza P, *et al.* A case of steroid induced psychosis in a patient with mediastinal lymphoma. *Eur Psychiatry.* 2024; 67(Suppl 1):S317.
12. Bachu AK, Davis V, Abdulrahim M, *et al.* Corticosteroid-Induced Psychosis: A Report of Three Cases. *Cureus.* 2023;15(5):e39221.

Rapid Neurological and Multiorgan Recovery After Two-Session Automated Red Cell Exchange for Fulminant Sickle Cell Crisis: A Case Report

Vipul Sharma¹, Siddhi Karale¹, Nidhi Mehta^{1*}, Hemalata Arora²

¹Department of Transfusion Medicine, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

²Department of General Medicine, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

Correspondence:

Nidhi Mehta

E-mail: drnidhimehta@yahoo.co.in

DOI: <https://doi.org/10.62830/mmj3-03-11>

Abstract:

Sickle cell disease can deteriorate abruptly from an apparently nonspecific painful illness to life-threatening neurological and multiorgan dysfunction. We report the case of a 23-year-old male with known sickle cell anaemia who presented with drowsiness, vomiting, leg pain, and headache for one day and was unarousable on arrival. He had a Glasgow Coma Scale (GCS) score of 3, required mechanical ventilation, and had severe biochemical evidence of haemolysis and hepatic injury, thrombocytopenia, massive splenomegaly, and magnetic resonance imaging (MRI) evidence of multiple lacunar infarcts. In the setting of a suspected acute sickle cell crisis with cerebral, hepatic, and splenic involvement, therapeutic red cell exchange was initiated through double-lumen central venous access. Two exchange sessions were performed on consecutive days with additional component support, as clinically indicated. Haemoglobin S (HbS) decreased from 88% to 4% by Day 4 and 3.8% by Day 6. The patient regained consciousness, reached a GCS score of 15, was extubated on Day 8, transferred to the ward on Day 10, and discharged on Day 13. This case illustrates that early recognition of an organ-threatening sickle crisis and rapid multidisciplinary access to automated red cell exchange can achieve prompt HbS reduction while avoiding an excessive rise in blood viscosity.

Key words: Sickle Cell Disease (SCD), Vaso-Occlusive Crisis, Red Cell Exchange (RCE), Erythrocytapheresis, Acute Ischaemic Stroke, Splenic Sequestration, Hepatic Injury.

Introduction

Sickle cell disease (SCD) is an inherited haemoglobinopathy caused by a pathogenic β -globin variant that produces haemoglobin S (HbS). Deoxygenation promotes HbS polymerisation, erythrocyte deformation, haemolysis, endothelial activation, and microvascular obstruction. The clinical spectrum includes painful vaso-occlusive episodes, acute chest syndrome, splenic or hepatic sequestration, stroke, and multiorgan failure. Although the Arab-Indian haplotype is often associated with relatively high foetal

haemoglobin, contemporary Indian evidence shows that severe complications — including stroke — occur at a young age and should not be underestimated.^{1,2}

Red cell exchange (RCE) removes HbS-containing erythrocytes and replaces them with donor red cells. Compared with simple transfusion, it can rapidly lower HbS levels without a proportionate increase in haematocrit (HCT) or viscosity. International guidance favours prompt transfusion and suggests exchange transfusion for acute neurological deficits in SCD; Indian transfusion guidance

recognises stroke, acute chest syndrome, sequestration and multiorgan failure as organ-threatening transfusion indications.^{3–5}

We describe a case of severe cerebral and multiorgan presentation in which the decision to perform automated RCE was made based on clinical suspicion before irreversible deterioration.

Case Report

A 23-year-old male with a known case of sickle cell anaemia, not on treatment, presented to the accident and emergency department with a one-day history of drowsiness, vomiting, leg pain, and headache, followed by unresponsiveness. There was no history of alcohol or substance use. His medical history included pulmonary Koch's disease in 2018, for which eight months of treatment had been completed. Haemoglobin electrophoresis performed in 2018 had shown HbS at 88%, which led to suspicion of sickle cell anaemia.

On arrival, the patient was pale and unresponsive, with a Glasgow Coma Scale (GCS) score of 3. The patient required ventilatory support. He was afebrile, with a pulse of 100/min, blood pressure of 130/80 mmHg, respiratory rate of 20/min and oxygen saturation of 100% while receiving 70% oxygen. No icterus, cyanosis, or clubbing was recorded.

Laboratory investigations revealed anaemia with a haemoglobin level of 8.6 g/dL and an HCT of 26.9%, along with leucocytosis (total leucocyte count 12,930/ μ L) and thrombocytopenia (platelet count 96,000/ μ L). The prothrombin time was prolonged to 17.9 seconds, with an international normalised ratio (INR) of 1.68. The reticulocyte count was elevated at 3.59%, and the sickling test was positive in both early and late phases. There was a marked elevation in aspartate aminotransferase (AST) (2,191 U/L), alanine aminotransferase (ALT) (963 U/L), and lactate dehydrogenase (LDH) (3,220 U/L) levels. The fibrinogen level was 364 mg/dL, and the serum creatinine level was 0.85 mg/dL. C-reactive protein was significantly elevated at 120 mg/L.

Peripheral smear showed microcytosis, hypochromia, anisopoikilocytosis, polychromasia, target cells, and occasional sickle cells. The total and differential leucocyte findings were not otherwise abnormal; platelets were reduced on smear, and no haemoparasites were identified.

Brain magnetic resonance imaging (MRI) revealed multiple lacunar infarcts, possibly cardioembolic, with right vertebral artery hypoplasia. Abdominal ultrasonography revealed massive splenomegaly, leading to a provisional diagnosis of acute organ-threatening sickle cell crisis with acute cerebral infarction, hepatic involvement, and splenic sequestration.

Owing to profound neurological impairment and evidence of evolving multiorgan injury, automated therapeutic RCE was discussed in a multidisciplinary review and literature assessment. A double-lumen central venous catheter was inserted. RCE was performed on two consecutive days as outlined in Table 1. The patient's height was 170 cm, weight 60 kg, and pre-procedure HCT was 29%.

RCE procedure	Day 1	Day 2
Total blood volume processed	5,569 mL	6,630 mL
Procedure time	112 min	125 min
Acid citrate dextrose used	495 mL	600 mL
Calcium gluconate	40 mL in 120 mL normal saline	40 mL in 120 mL normal saline
RBC exchange replacement volume	2,023 mL (8 PRBC units)	2,185 mL (8 PRBC units)



Table 1: RCE process overview on Day 1 and Day 2.

Abbreviations: PRBC: Packed Red Blood Cells; RBC: Red Blood Cell; RCE: Red Cell Exchange.

The replacement red blood cell (RBC) volume was decided based on the fraction of (diseased) cells remaining (FCR) in the body and the target HCT of 60%, to be maintained for the patient post-procedure.

The FCR in sickle cell anaemia measures the percentage of the patient's original, sickled RBCs remaining in the body after an RCE procedure. It is calculated as:

$$\text{FCR}\% = (\text{post-exchange HbS}\% / \text{pre-exchange HbS}\%) \times 100$$

Vital signs were continuously monitored throughout both procedures. After the exchange, serial complete blood counts, electrolytes, liver function tests, LDH, calcium, glucose, and haemoglobin fractions were monitored. On Day 2, two packed red blood cell (PRBC) units and four random donor platelet (RDP) units were administered, and one additional PRBC unit was administered on Day 3.

Outcome and follow-up

Serial laboratory trends demonstrated recovery of haemoglobin, HCT and platelet count with a decline in LDH and liver enzymes. HbS fell from the pre-procedure value of 88% (last recorded 6 years ago) to 4% by Day 4 and 3.8% by Day 6, accompanied by neurological recovery and successful liberation from mechanical ventilation (Table 2).

Hospital day	Clinical course
Day 2	GCS remained 3; imaging had improved; 2 PRBC and 4 RDP units administered
Day 3	One PRBC unit administered
Day 4	HbS reduced to 4%
Day 6	HbS 3.8%
Day 7	Patient conscious and oriented
Day 8	GCS 15; extubated
Day 10	Transferred to the ward
Day 11	Abdominal pain reduced; discharge advised
Day 13	Discharged

Table 2: Patient's clinical course during hospitalisation.

Abbreviations: GCS: Glasgow Coma Scale; HbS: Haemoglobin S; PRBC: Packed Red Blood Cell; RDP: Random Donor Platelet.

Discussion

This case is notable for the convergence of several organ-threatening manifestations: deep coma, radiologically evident cerebral infarction, marked hepatocellular injury, thrombocytopenia, haemolytic activity, and massive splenomegaly. The presenting symptoms were initially nonspecific, but the known SCD diagnosis, positive sickling test, prior HbS fraction, and multiorgan pattern justified treating the presentation as a fulminant sickle crisis and therapeutic RCE.

The therapeutic objective of RCE is twofold: to improve oxygen-carrying capacity and replace sickled erythrocytes without producing a high post-transfusion HCT that can increase viscosity. The American Society of Hematology (ASH) recommends immediate transfusion for SCD with acute neurological deficits and suggests exchange rather than simple transfusion when feasible.³ The 2023 Government

of India Transfusion Medicine Technical Manual similarly identifies acute organ-threatening vaso-occlusive events — including stroke and multiorgan failure — and acute anaemic complications such as splenic or hepatic sequestration as transfusion indications.⁴

The favourable course is biologically coherent with rapid HbS reduction: the fraction fell to approximately 4% after the staged exchanges, while the neurological status improved over the following week. Causality cannot be assigned from a single case because ventilatory, critical care, and component support were provided concurrently. Nevertheless, the temporal association, magnitude of HbS reduction and recovery pattern are consistent with Indian and international reports describing successful emergency automated RCE in severe adult sickle crises.^{6–9}

This procedure also highlights practical considerations. Extended red cell antigen typing and Rhesus (Rh) and Kell (K)-matched, sickle-negative, leucocyte-reduced units should be used where available to reduce alloimmunisation and transfusion complications.^{4,5} Citrate-related hypocalcaemia requires surveillance and calcium replacement, as performed here. Automated RCE requires specialist staff, compatible blood inventory, vascular access and apheresis capability; where automation is unavailable, carefully performed manual exchange remains a potential alternative.¹⁰

This case is clinically distinctive as the crisis presented primarily as coma and multiorgan dysfunction rather than a typical isolated painful episode.

Acknowledgements

The authors thank the technical staff of the Department of Transfusion Medicine for quick support for the case management.

Blood grouping: Mr. Vinod Naik

Crossmatching: Mr. Ajit Pathare, Ms. Amita Narkar, Ms. Neha Ambede

HCT calculation and procedure: Mr. Milind Dalvi

Conclusion

In patients with known or suspected SCD, abrupt neurological depression accompanied by biochemical haemolysis, hepatic injury, thrombocytopenia, or sequestration should trigger immediate evaluation for an organ-threatening sickle crisis. This case demonstrates a successful multidisciplinary rescue strategy using a two-session automated RCE, with rapid HbS suppression and recovery from coma and multiorgan involvement. Early coordination between the departments of Medicine, Critical Care, Haematology, Neurology and Transfusion Medicine is central to delivering exchanges without avoidable delays.

Vipul Sharma, Siddhi Karale, Nidhi Mehta, Hemalata Arora. Rapid Neurological and Multiorgan Recovery After Two-Session Automated Red Cell Exchange for Fulminant Sickle Cell Crisis: A Case Report. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-11>

References

- Colah RB, Mukherjee MB, Martin S, et al. Sickle cell disease in tribal populations in India. *Indian J Med Res.* 2015;141(5):509–15.
- Gupta K, Krishnamurti L, Jain D. Sickle cell disease in India: the journey and hope for the future. *Hematology Am Soc Hematol Educ Program.* 2024;2024(1):1–9.
- DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv.* 2020;4(8):1554–88.
- Ministry of Health & Family Welfare, Government of India. Transfusion Medicine Technical Manual. 3rd Edition. New Delhi: Directorate General of Health Services NBTC and Blood Transfusion Services Division Ministry of Health & Family Welfare, Government of India; 2023.
- Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. *Blood Adv.* 2020;4(2):327–55.
- Gupta A, Chaudhary K, Kaushik R. Role of emergency automated red cell exchange in sickle cell crisis: a case report. *Clin Med Insights Case Rep.* 2020;13:1179547620970200.
- Mamdapur AB, Sagar MS, Madhusudan R, et al. Therapeutic red cell exchange transfusion as an adjuvant therapy for management of sickle cell crisis in adults. *Indian J Crit Care Med.* 2018;22(6):457–9.
- Mihalca D, Ahmad A, Mehta D, et al. Emergency red cell exchange for the management of acute complications in sickle cell disease: automated versus manual. *Transfus Med.* 2023;33(4):287–9.
- Saleh M, Asemota J. Severe acute chest syndrome in a sickle cell patient that required repeated exchange transfusion. *Cureus.* 2021;13(2).
- Mehra RA, Gupta SA, Borkar DB. Manual red cell exchange transfusion to avert sickle cell related complications. *Asian J Transfus Sci.* 2018;12(2):157.

Endoscopic Intersphincteric Dissection: A Novel Sphincter-Preserving Technique for Ultra-Low Rectal Tumours — A Case Report

Gaurav Patil¹, Ankit Dalal¹, Amol Vodgaonkar¹, Prathvi Alva¹

¹Department of Gastroenterology and Advanced Endoscopy, Nanavati Max Super Speciality Hospital, Mumbai.

Correspondence:

Gaurav Patil

E-mail: gauravkpatil@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-25>

Abstract:

Endoscopic intersphincteric dissection (EISD) is an emerging, minimally invasive, sphincter-preserving technique for the management of selected low rectal tumours. We report the case of an elderly patient with a low rectal tumour who underwent EISD following appropriate preoperative staging and a multidisciplinary assessment. The tumour was successfully excised using an endoscopic approach, achieving complete resection while preserving the anal sphincter and avoiding radical rectal surgery and permanent colostomy. The patient had a favourable postoperative course with preserved anorectal function. This case highlights the potential of EISD as a feasible alternative to conventional radical surgery in carefully selected patients with low rectal tumours. Accurate patient selection, thorough preoperative evaluation, and expertise in advanced endoscopic techniques are essential for optimal outcomes. Further studies with larger cohorts and long-term follow-up are warranted to establish the role of EISD in routine clinical practice.

Key words: Endoscopic Intersphincteric Dissection (EISD), Low Rectal Tumour, Sphincter Preservation, Permanent Colostomy, Anorectal Function, Endoscopic Resection.

Introduction

Low rectal tumours located close to the anal sphincter have traditionally required abdominoperineal resection (APR) with permanent stoma formation, which can substantially affect quality of life, particularly in elderly patients.¹ Advanced endoscopic resection techniques have progressively expanded organ-preserving options for selected rectal neoplasms, reducing the proportion of patients who require radical stoma-forming surgery for early or borderline lesions.

From endoscopic submucosal dissection (ESD) to endoscopic intermuscular dissection (EIMD) to endoscopic intersphincteric dissection (EISD): An evolving continuum

The foundation for this progression lies in ESD, first developed in Japan during the 1990s for the en-

bloc removal of early gastric cancer. ESD relies on submucosal fluid injection to expand and stabilise the submucosal space, followed by free-hand dissection along this plane using electrosurgical knives — a working space that came to be described as the “third space” of the gastrointestinal wall.² This concept was subsequently extended beyond the submucosa: Inoue *et al.* applied third-space principles to the intermuscular plane itself, performing the first human peroral endoscopic myotomy (POEM) for achalasia in 2008 and demonstrating that endoscopists could safely and reproducibly work within and beyond the muscularis propria, not merely superficial to it.^{3,4} This shift in working plane — from submucosa to intermuscular space — was the conceptual bridge that made deeper endoscopic dissection techniques possible.⁵

EIMD represents the direct clinical application of this bridge to rectal oncology.¹ By dissecting within the

plane between the circular and longitudinal layers of the muscularis propria, EIMD allows en bloc resection of rectal lesions with deep submucosal invasion that would otherwise be unresectable by conventional ESD, while still avoiding a full-thickness or transmural defect.² Since its first description, EIMD has been reported for early rectal cancer, rectal neuroendocrine tumours, and rectal gastrointestinal stromal tumours, and has since been extended to the stomach, reflecting rapid and ongoing evolution of the technique across the gastrointestinal tract.⁶

EISD is, to our knowledge, a novel conceptual extension of this same trajectory. Where EIMD stops at the intermuscular plane of the rectal wall, EISD carries dissection distally into the intersphincteric plane — the natural areolar plane between the internal and external anal sphincter that is more familiar as the surgical plane of intersphincteric resection (ISR).⁶ By accessing this plane endoscopically rather than surgically, EISD in principle allows an ultra-low rectal lesion abutting or approaching the sphincter complex to be excised en bloc, with a wider and more confident distal margin than submucosal plane dissection alone could offer, while the external anal sphincter, the principal determinant of continence, is left intact throughout. No prior indexed literature describing endoscopic dissection specifically within the intersphincteric plane was identified at the time of writing; the present case is therefore presented as an early, illustrative application of this concept rather than a confirmation of an established technique.⁷

Case Report

An elderly female patient presented with a low rectal tumour and was initially planned for definitive surgery involving a permanent stoma formation. Optical evaluation revealed features suggestive of deep submucosal invasion, including an avascular, amorphous pit pattern with loose microcapillary vessels, rendering the lesion unsuitable for conventional ESD. Pelvic magnetic resonance imaging (MRI) staged the lesion as cT1–2N0M0. Following a multidisciplinary evaluation, EISD was selected as the preferred approach to achieve complete oncological resection while preserving continence.

The procedure was performed under propofol sedation using a standard therapeutic gastroscope

(Olympus GIF-1TH190) fitted with a transparent tapered hood (Fujifilm DH-30CR) and a 1.5-mm BT dual knife (Olympus) in Endocut mode on an ERBE VIO 300D generator. The lesion perimeter was marked with soft coagulation, and submucosal lifting was performed using a saline-methylene blue solution. Submucosal incisions were made at the oral and anal margins of the lesion, and a tunnel entrance was created on the anal side (Figure 1).⁷ After approximately 1 cm, the circular muscle was incised between the muscle bundles to expose the longitudinal muscle layer, with the fibre orientation clearly identified. Gravity and a transparent hood provided countertraction to facilitate safe intersphincteric tunnelling. Following 2 – 3 cm of intermuscular tunnelling beneath the lesion, the submucosal plane was re-entered from the oral mucosal incision, and the lateral margins were incised to complete the en bloc resection (Figures 2 and 3). The total procedure time was 90 minutes, and the resection site was closed using the loop and clip technique.



Figure 1: Endoscopic view of the tumour resection site during intersphincteric tunnelling.



Figure 2: Large polypoidal, circumscribed, and laterally spreading area seen on retroflexion.

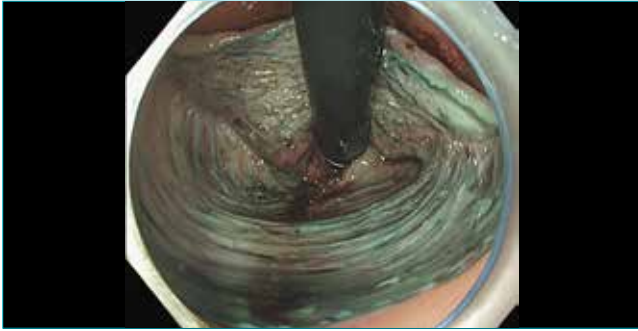


Figure 3: With the bridge technique, complete resection of the tumour is done, preserving the surrounding mucosa.

The patient was discharged on postoperative Day 2 after a 5-day course of oral antibiotics. A per-anal digital examination before discharge confirmed retained continence. Histopathological examination confirmed complete resection with clear margins (Figure 4), and the patient demonstrated favourable early functional recovery with normal spontaneous bowel movements.



Figure 4: Extracted tumour from the site.

Discussion

Compared with EIMD, which dissects within the intermuscular plane of the rectal wall, EISD extends dissection into the intersphincteric plane and may offer a particular advantage for ultra-low rectal tumours requiring wider distal clearance while preserving sphincter integrity.⁷ This case illustrates that, in carefully selected elderly patients, lesions previously considered candidates only for radical, stoma-forming surgery may achieve complete oncological resection endoscopically,

with preserved anorectal function and favourable short-term recovery.³

The novelty of EISD lies not merely in a new set of steps, but in the deliberate transposition of a plane that has, until now, only been accessed surgically — the intersphincteric plane of ISR — into the endoscopic domain.⁶ This mirrors the earlier transposition that gave rise to the EIMD itself, which took a plane historically reserved for surgical full-thickness dissection (the intermuscular space) and made it accessible through a flexible endoscope.⁸ In that sense, EISD is best understood as the next incremental step along a single continuum — ESD (submucosa) → EIMD (intermuscular plane) → EISD (intersphincteric plane) — in which each advance has progressively pushed the endoscopic working plane deeper, while consistently preserving the principle that no full-thickness or transmural incision is required.⁹ This continuum-based framing is, we believe, important for readers: EISD is not a rebranding of EIMD, nor an incidental variation, but a distinct plane change with distinct anatomical stakes, since the intersphincteric plane sits immediately adjacent to the continence mechanism rather than within the bowel wall itself.⁴

Clinically, this distinction matters most for ultra-low rectal lesions within a few centimetres of the dentate line, where even a technically successful EIMD may not achieve an adequate deep margin if the lesion approaches or involves the upper sphincter complex.¹ EISD introduces a third option — extending the endoscopic dissection into the same plane a colorectal surgeon would use for a sphincter-preserving ISR, but without an abdominal or perineal incision, without general anaesthesia in many patients, and with a markedly shorter recovery, as reflected in this patient's two-day admission and preserved continence at discharge.² We recognise that a single case cannot establish the oncological adequacy, durability of function, or complication profile of this approach and that outcomes here should be interpreted as hypothesis-generating rather than confirmatory.

Conclusion

EISD represents a promising, minimally invasive, sphincter-preserving alternative to radical surgery in selected patients with low rectal tumours. In this elderly patient, the technique achieved successful tumour excision while preserving anorectal function and avoiding the physical and psychological burden of a permanent colostomy. Careful patient selection, accurate preoperative staging, multidisciplinary decision-making, and expertise in advanced endoscopic techniques are essential for achieving optimal outcomes. Larger comparative studies and long-term follow-up are needed to establish the role of EISD relative to conventional radical surgery.

Gaurav Patil, Ankit Dalal, Amol Vodgaonkar, Prathvi Alva. Endoscopic Intersphincteric Dissection: A Novel Sphincter-Preserving Technique for Ultra-Low Rectal Tumours — A Case Report. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-25>

References

1. Liao S, Li B, Huang L, *et al.* Endoscopic intermuscular dissection in the management of a rectal neuroendocrine tumor. *Endoscopy*. 2023;55(S 01):E977–9.
2. Schaefer M, Albouys J, Geyl S, *et al.* Endoscopic intermuscular dissection of a residual rectal neuroendocrine tumor with high-pressure injection and double-clip traction. *Endoscopy*. 2023;55(S 01):E1126–7.
3. Inoue H, Navarro MJH, Shimamura Y, *et al.* The Journey from Endoscopic Submucosal Dissection to Third Space Endoscopy. *Gastrointest Endosc Clin N Am*. 2023;33(1):1–6.
4. Ramos-Zabala F, Pérez-Rodríguez FJ, Alzina-Pérez A, *et al.* Saline-tunneling endoscopic intermuscular dissection for the removal of rectal cancer using the hydrodissection method. *Endoscopy*. 2023;55(S 01):E987–9.
5. Ichita C, Sasaki A, Kawachi J, *et al.* Endoscopic intermuscular dissection for a lower rectal gastrointestinal stromal tumor. *Endoscopy*. 2023;55(S 01):E258–9.
6. De Cristofaro E, Rivory J, Masgnaux LJ, *et al.* Repeat endoscopic intermuscular dissection of the visible scar after noncurative endoscopic intermuscular dissection of a rectal neuroendocrine tumor. *Endoscopy*. 2024;56(S 01):E205–6.
7. Despott EJ, Lucaciu LA, Murino A, *et al.* First report of gastric endoscopic intermuscular dissection. *Endoscopy*. 2024;56(S 01):E132–3.
8. Mirminachi B, Ha A, Jain V, *et al.* Endoscopic intermuscular dissection of a rectal gastrointestinal stromal tumor. *VideoGIE*. 2026.
9. Fukuzawa M, Gotoda T. History of endoscopic submucosal dissection and role for colorectal endoscopic submucosal dissection: A Japanese perspective. *Gastrointest Interv*. 2012;1(1):30–5.

Peripheral T-Cell Lymphoma Masquerading as Prolonged Pyrexia of Unknown Origin and Culminating in Carbapenem-Resistant *Acinetobacter baumannii* Septic Shock: A Case Report

Osheen Gera¹, Richa Nema¹, Adiba Rao¹, Akanksha Verma², Supriya Bali^{*}

¹Department of Internal Medicine, Max Super Speciality Hospital, Saket, Delhi

²Department of Internal Medicine, Max Hospital, Panchsheel, Delhi

Correspondence:

Supriya Bali

E-mail: sbali@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-28>

Abstract:

Pyrexia of unknown origin (PUO) may result from infection, malignancy, or inflammatory disease, with diagnostic difficulty increasing when these processes coexist. A 63-year-old man presented with a 45-day history of intermittent high-grade fever, constitutional symptoms, and polyarthralgia, with transient responses to multiple empirical antimicrobials. He subsequently developed septic shock and respiratory failure, requiring mechanical ventilation. Investigations revealed carbapenem-resistant *Acinetobacter baumannii* (CRAB) pneumonia, *Staphylococcus haemolyticus* bacteraemia, thrombocytopenia, acute kidney injury, pleural effusion, hepatosplenomegaly, and lymphadenopathy. During critical illness, an erythematous rash progressed to vesiculobullous lesions with acral bluish discoloration. Purpura fulminans secondary to sepsis-associated consumptive coagulopathy versus drug hypersensitivity was considered. Although septic shock and organ dysfunction improved, lymphadenopathy, hepatosplenomegaly, and cytopenia persisted despite a decrease in inflammatory markers. An excisional lymph node biopsy confirmed peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS). Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) was detected in the blood. Pre-phase cyclophosphamide, vincristine, and prednisolone were initiated. At subsequent follow-up, the patient developed generalised bluish discoloration despite preserved peripheral blood flow and the absence of gangrene. This case highlights how severe multidrug-resistant infections can obscure underlying lymphoproliferative disorders and why persistent abnormalities should prompt diagnostic reassessment.

Key words: Peripheral T-Cell Lymphoma, Pyrexia of Unknown Origin, Septic Shock, *Acinetobacter baumannii*, Epstein-Barr Virus, Purpura Fulminans.

Introduction

Pyrexia of unknown origin (PUO) remains a diagnostic challenge, with infection, malignancy, and inflammatory disorders representing the major categories. Lymphoma may mimic chronic infection through constitutional symptoms, cytopenia, and organomegaly.¹ Peripheral T-cell lymphomas (PTCLs) are uncommon, aggressive

non-Hodgkin lymphomas. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a heterogeneous mature T-cell lymphoma diagnosed after exclusion of other defined entities.² We describe a case of prolonged PUO followed by life-threatening carbapenem-resistant *Acinetobacter baumannii* (CRAB) septic shock, ultimately revealing PTCL-NOS.

Case Report

A 63-year-old man presented with a 45-day history of intermittent high-grade fever (101 – 102°F), chills, and fatigue. He received cefixime and cefuroxime, which resulted in transient improvement, followed by severe polyarthralgia and facial puffiness. Borderline-positive scrub typhus immunoglobulin M (IgM) levels led to doxycycline treatment, again without a sustained response. He subsequently developed hypotension and breathlessness requiring noradrenaline and was transferred to our centre.

On admission, he was in septic shock (80/40 mmHg) with a lactate level of 3.3 mmol/L. Examination revealed an erythematous rash, pedal oedema, reduced bilateral air entry, and abdominal distension (Figure 1). Investigations showed anaemia, thrombocytopenia, hypoalbuminaemia, mild renal/hepatic dysfunction, and a procalcitonin level of 6.56 ng/mL.



Figure 1: Vesicular rash over the antecubital fossa at presentation.

Endotracheal aspirate grew CRAB, paired blood cultures grew *Staphylococcus haemolyticus*, and *Klebsiella pneumoniae* was isolated from a lymph node culture. Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) was detectable at 270 copies/mL. Evaluation for dengue, malaria, enteric fever, scrub typhus, autoimmune disease, tuberculosis, and invasive fungal infection was unrevealing.

Computed tomography (CT) revealed bilateral pleural effusions, right lower lobe ground-glass opacities with consolidation, mediastinal and axillary lymphadenopathy, hepatosplenomegaly, ascites, and anasarca. The patient developed respiratory failure requiring mechanical ventilation and pleural drainage. Antimicrobial therapy was escalated to colistin, sulbactam, and minocycline.

During the Intensive Care Unit (ICU) stay, the platelet count decreased to 20,000/mm³. The rash progressed to vesiculobullous and peeling lesions with bluish discoloration and mottling of the fingers and toes (Figures 2 and 3). Purpura fulminans secondary to sepsis-associated consumptive coagulopathy versus drug hypersensitivity was considered by the Dermatology and Vascular Surgery departments. The lesions partially improved with clinical recovery; however, distal bluish discoloration persisted despite preserved peripheral blood flow and the absence of gangrene.



Figure 2: Dusky violaceous discoloration involving the fingers.



Figure 3: Dusky violaceous discoloration involving the toes.

The patient was extubated on Day 10, and renal function recovered. Despite C-reactive protein (CRP) levels decreasing from 161 to 19.3 mg/L, lymphadenopathy, hepatosplenomegaly, and cytopenia persisted. Excisional lymph node biopsy showed a T-cell population positive for CD3, CD5, and CD7, with variable loss of CD2, CD4, and CD8, scattered CD30-positive immunoblasts, and Ki-67 30% – 35%, supporting PTCL-NOS. Positron emission tomography-computed tomography (PET-CT) revealed bilateral axillary and inguinal lymphadenopathy. Beta-2 microglobulin was 6.02 mg/L.

Pre-phase cyclophosphamide, vincristine, and prednisolone were initiated. He was discharged in a

haemodynamically stable, afebrile state with recovered renal function for definitive lymphoma treatment.

Follow-up

On subsequent outpatient follow-up, the acral discolouration persisted and progressed to striking generalised bluish discolouration involving the body. Peripheral perfusion remained preserved, with no documented gangrene. The patient remained under haemato-oncology follow-up.

Discussion

This case highlights the diagnostic difficulty created by prolonged PUO, occult lymphoma, and severe multidrug-resistant infection. PTCL may present with fever, cytopenias, lymphadenopathy and hepatosplenomegaly, closely mimicking infection.^{1,3}

The distinctive feature was that the lymphoma was actively obscured by a superimposed, near-fatal episode of CRAB septic shock. CRAB infections have limited therapeutic options and substantial mortality; current guidance recommends sulbactam-durlobactam with imipenem or meropenem as preferred therapy for invasive CRAB infection.⁴

The key diagnostic clue was the discordance between improving sepsis and persistent systemic abnormalities. Shock resolved, renal function recovered, and CRP fell, yet lymphadenopathy, hepatosplenomegaly, and cytopenias persisted. This prompted tissue diagnosis and established PTCL-NOS. Similar diagnostic difficulty has been reported in PTCL presenting as PUO.³

EBV DNAemia was noteworthy and has been associated with advanced disease and poorer outcomes in PTCL.⁵ However, circulating EBV DNA does not establish tumour

EBV-encoded small ribonucleic acid (EBER) positivity; therefore, it should be regarded as an associated finding rather than evidence of EBV-associated PTCL.^{5,6}

The cutaneous findings added further complexity. Purpura fulminans secondary to sepsis-associated consumptive coagulopathy and drug hypersensitivity were considered during the acute illness. In view of the subsequent cutaneous manifestations, lymphadenopathy and mature T-cell phenotype, Sézary syndrome was also considered as a differential; however, the overall clinicopathological findings supported PTCL-NOS.⁷ The persistent and later generalised bluish discolouration despite preserved blood flow and absence of gangrene remains an unusual feature.

The case reinforces an important principle: resolution of one plausible diagnosis should not close the search for a coexisting one. When infection improves but lymphadenopathy, organomegaly, or cytopenias persist, the diagnostic hypothesis should be revisited and tissue diagnosis pursued.

Declarations

Consent for publication: Written informed consent for publication of the case and accompanying clinical images was obtained from the patient/legally authorised representative.

Conflict of interest: None declared.

Funding: None.

Author contributions: All authors contributed to patient management, manuscript preparation/review and approved the final manuscript.

Conclusion

This case illustrates a diagnostically layered presentation in which occult PTCL lay concealed behind prolonged pyrexia and was subsequently compounded by life-threatening CRAB septic shock. The lymphoma became apparent only when important abnormalities persisted despite objective control of infection.

One diagnosis should not be allowed to explain away the entire patient. In prolonged PUO, resolution of one plausible diagnosis should not close the search for a coexisting disorder, particularly when lymphadenopathy, organomegaly, or cytopenias persist. Early tissue diagnosis may transform a prolonged diagnostic dilemma into a treatable diagnosis.

Learning points

- Persistent lymphadenopathy, hepatosplenomegaly or cytopenias after adequate sepsis control should prompt consideration of an underlying lymphoproliferative disorder.
- PTCL-NOS may masquerade as prolonged infection and require tissue diagnosis.
- Severe multidrug-resistant infection can obscure an underlying malignancy.
- Vesiculobullous lesions with acral discolouration during sepsis warrant consideration of purpura fulminans and drug hypersensitivity.
- Persistent unusual cutaneous findings require continued evaluation even after haemodynamic recovery.

Osheen Gera, Richa Nema, Adiba Rao, Akanksha Verma, Supriya Bali. Peripheral T-Cell Lymphoma Masquerading as Prolonged Pyrexia of Unknown Origin and Culminating in Carbapenem-Resistant *Acinetobacter baumannii* Septic Shock: A Case Report. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-28>

References

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)*. 1961;40:1–30.
2. d'Amore F, Federico M, de Leval L, et al. Peripheral T- and natural killer-cell lymphomas: ESMO-EHA Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2025;36(6):626–44.
3. McKay C, Hong LT, Nizam Uddin AKM, et al. Peripheral T-cell lymphoma presenting as fever of unknown origin in a man with deranged liver function tests and pancytopenia. *BMJ Case Rep*. 2021;14(3):e237806.
4. Infectious Diseases Society of America. IDSA 2026 guidance on the treatment of antimicrobial resistant gram-negative infections. Arlington (VA): Infectious Diseases Society of America 2026. [Internet]. Available at: <https://www.idsociety.org/practice-guideline/amr-guidance/>. Accessed on: 20th July 2026.
5. Kim YR, Kim SJ, Cheong JW, et al. Pretreatment Epstein-Barr virus DNA in whole blood is a prognostic marker in peripheral T-cell lymphoma. *Oncotarget*. 2017;8(54):92312–23.
6. Chen YP, Jones D, Chen TY, et al. Epstein-Barr virus present in T cells or B cells shows differential effects on hemophagocytic symptoms associated with outcome in T-cell lymphomas. *Leuk Lymphoma*. 2014;55(9):2038–47.
7. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer. *Blood*. 2007;110(6):1713–22.

Giant Cervicothoracic Schwannoma Involving the Brachial Plexus and Thoracic Inlet

Prem Kumar Ganesan^{1*}, Narottam Khadaria¹, Dhruv Dinesh Jain¹, Anchal Singh¹

¹Department of Radiology, BLK-Max Super Speciality Hospital, New Delhi

Correspondence:

Prem Kumar Ganesan

E-mail: drpremkumarganesan@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-29>

Abstract:

Schwannomas are benign peripheral nerve sheath tumours that arise from the cranial, sympathetic, spinal, or peripheral nervous systems. Mediastinal schwannomas are rare and most commonly arise in the posterior mediastinum. Schwannomas involving the brachial plexus are rarely encountered and may present with neurological deficits when they involve the trunks or cords of the plexus. Owing to their proximity to the pleura, lung apex, superior vena cava (SVC), subclavian arteries, and brachial plexus, extension across the thoracic inlet into the supraclavicular and intrathoracic compartments poses considerable diagnostic and surgical challenges.

Key words: Schwannoma, Brachial Plexus, Cervicothoracic Tumour, Thoracic Inlet, Mediastinal Schwannoma, Contrast-Enhanced Computed Tomography (CECT), Video-Assisted Thoracoscopic Surgery (VATS), Neurogenic Tumour, Magnetic Resonance Imaging (MRI), Brachial Plexus, Subclavian Artery.

Introduction

Schwannomas, also known as neurilemmomas, are benign tumours that arise from Schwann cells of the peripheral nerve sheath. They can occur along the cranial, spinal, and peripheral nerves, and sympathetic chains. Although most schwannomas are solitary and slow-growing, their clinical presentation depends largely on their anatomical location and the structures involved. Brachial plexus schwannomas are rare and may manifest as a slowly growing supraclavicular mass accompanied by sensory or motor complaints in the affected limb.^{1,2}

Neurogenic tumours constitute an important group of posterior mediastinal masses, with schwannomas being among the most frequent benign solid lesions in this compartment.^{3,4} Mediastinal schwannomas are usually asymptomatic for prolonged periods and

may become clinically apparent only after achieving substantial size or producing compression of adjacent structures.⁵

Tumours originating from the brachial plexus and extending into the thoracic cavity are particularly rare. These lesions may occupy the thoracic inlet and are closely related to the subclavian artery and vein, lung apex, pleura, vertebral structures, and major components of the brachial plexus. This anatomical complexity can make surgical resection challenging and may increase the risk of neurological and vascular complications.^{6,7}

Magnetic resonance imaging (MRI) is the preferred imaging modality for the evaluation of brachial plexus tumours because of its superior soft tissue contrast and ability to highlight the relationship between a mass and specific nerve roots, trunks, cords, and neurovascular structures.¹ Surgical management is

usually preferred for symptomatic or progressively enlarging schwannomas, with the objective of complete tumour removal while preserving functional nerve bundles. Function-preserving intracapsular enucleation has also been reported for brachial plexus schwannomas to lower the risk of postoperative complications.⁸

We present a rare case of a right cervicothoracic schwannoma involving the brachial plexus, extending from the supraclavicular area into the mediastinum via the thoracic inlet, and producing significant neurovascular and neurological compression of the surrounding structures.

Case Report

A 20-year-old female presented with a long-standing, painless swelling in the right supraclavicular region. The swelling was associated with weakness of the right upper limb and wasting of the thenar and hypothenar muscles of the right hand. There was no history of significant trauma, previous surgery, systemic illness, or other relevant medical conditions.

Clinical findings

Clinical examination revealed a right supraclavicular swelling. Neurological examination revealed weakness of the right upper limb and wasting of the thenar and hypothenar muscles. The remaining systemic examinations were unremarkable. Additionally, there was no significant past medical or surgical history.

Radiological findings

The patient underwent a chest X-ray, which revealed a right-sided posterior mediastinal/apical mass (Figure 1). Contrast-enhanced computed tomography (CECT) of the chest demonstrated a well-defined, heterogeneously enhancing extrapleural lesion in the right apical region, with extension into the supraclavicular area and possible continuation with the right brachial plexus. Encasement and narrowing of the right subclavian artery were also noted (Figure 2). MRI of the brachial plexus was subsequently performed to confirm communication with the brachial plexus and further characterise the mass. It revealed a large, lobulated, heterogeneous T2 hyperintense lesion in the right supraclavicular region, inseparable from the middle and inferior trunks (Figure 3).

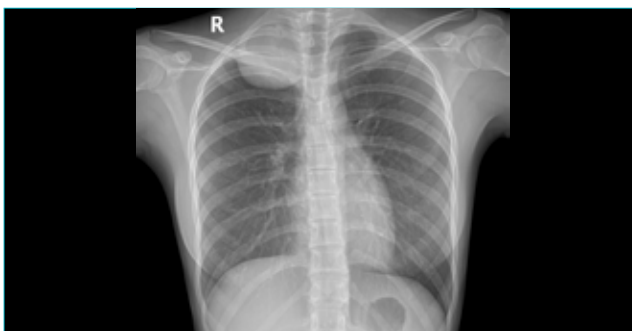


Figure 1: Chest X-ray showing well-defined right-sided posterior mediastinal/apical mass.

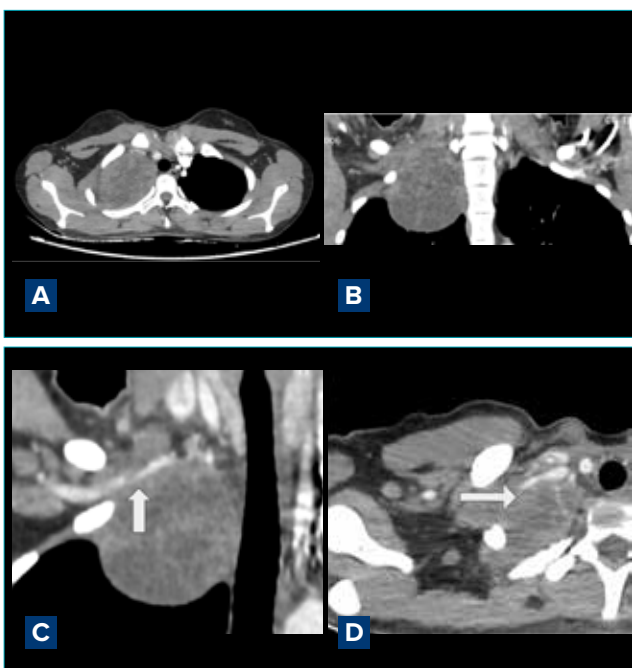


Figure 2A – D: Contrast-enhanced computed tomography (CECT) of the chest: **A.** Well-defined, heterogeneously enhancing extrapleural lesion in the right apical region; **B.** Extension into the supraclavicular area and possible continuation with the right brachial plexus; **C, D.** Encasement and narrowing of the right subclavian artery were also noted (arrow).

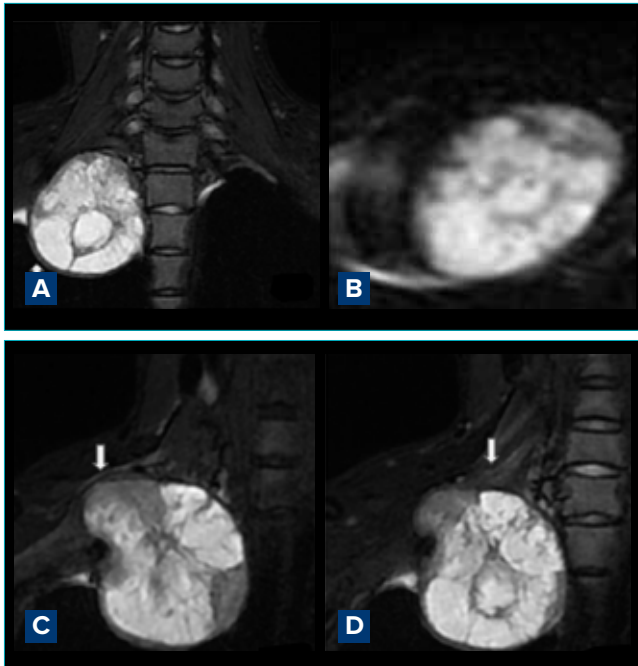


Figure 3A – D: Magnetic resonance imaging (MRI) of the brachial plexus: **A.** Large, lobulated, heterogeneous T2 hyperintense lesion in the right supraclavicular region, indenting the apex of the right lung (arrow); **B.** The lesion showed restricted diffusion; **C.** The superior trunk (arrow) of the right brachial plexus was draped along the cranial aspect of the lesion; **D.** The lesion was inseparable from the middle and inferior trunks (arrow).

The possibility of a large brachial plexus-related neurogenic tumour with cervicothoracic and mediastinal extension was considered based on the radiological findings and clinical neurological deficits.

Management

Owing to the extensive cervicothoracic involvement and close relationship between the tumour and the brachial plexus and subclavian vessels, a multidisciplinary surgical approach involving neurosurgery and thoracic surgery was planned. The patient underwent right supraclavicular tumour decompression, followed by video-assisted thoracoscopic surgery (VATS) excision of the mediastinal component.

During supraclavicular exploration, the neurosurgeon identified a soft, vascular tumour intimately entangled with the brachial plexus. The tumour extended internally into the infraclavicular region and was adherent to the subclavian artery and pleura. Careful dissection and decompression of the tumour from the involved neurovascular structures were performed.

Thoracoscopic surgery revealed that the tumour occupied the apex of the right thoracic cavity and

extensively involved the thoracic inlet. This resulted in compression of the superior vena cava (SVC), right subclavian artery and vein, and brachial plexus.

The combined surgical approach allowed for the exposure and management of both the supraclavicular/brachial plexus and intrathoracic components. The excised specimen was submitted for histopathological examination.

Histopathological Findings

Histopathological examination revealed a benign nerve sheath tumour consistent with schwannoma. Immunohistochemical examination showed positivity for S100 and SOX10, supporting schwannoma cell differentiation and confirming the diagnosis of schwannoma.

Discussion

Schwannomas are usually slow-growing benign tumours of the peripheral nerve sheath that arise from Schwann cells. Mediastinal schwannomas are rare and form a subgroup of neurogenic tumours of the posterior mediastinum, but schwannomas arising from the brachial plexus are distinctly rare and represent an unusual cause of supraclavicular masses and thoracic inlet lesions.^{3,4} Because of their slow growth, symptoms are often delayed until compression of adjacent nerves or vascular structures occurs.

This case is unusual because of the coexistence of several rare features, including the origin from the brachial plexus, extensive extension beyond the cervicothoracic junction into the superior mediastinum, and significant encasement and compression of the subclavian artery. Such extensive involvement of the cervicothoracic region by a benign schwannoma has rarely been reported previously.

The clinical symptoms of brachial plexus schwannomas vary depending on the affected nerve bundle and tumour size. Patients typically present with a slowly growing supraclavicular mass accompanied by pain, paraesthesia, motor deficits, or muscle atrophy. In the present patient, weakness of the right upper limb along with wasting of the thenar and hypothenar muscles indicated significant lower brachial plexus involvement.

Imaging plays a pivotal role in the diagnosis, characterisation, and surgical planning of these tumours. Computed tomography (CT) revealed a well-circumscribed extrapleural apical mass with heterogeneous enhancement extending from the supraclavicular region into the superior mediastinum. The lesion displaced and narrowed the subclavian artery without imaging evidence of vascular invasion, findings that favoured a benign neurogenic tumour, while highlighting the complexity of surgical resection. MRI further delineated the tumour's continuity with the brachial plexus and its relationship with adjacent neurovascular structures. Owing to its superior soft tissue contrast and multiplanar capability, MRI remains the imaging modality of choice for evaluating brachial plexus tumours and defining their anatomical extent.¹

The differential diagnosis of a well-defined thoracic inlet or posterior mediastinal mass in a young adult includes schwannoma, neurofibroma, malignant peripheral nerve sheath tumour (MPNST), ganglioneuroma, and other neurogenic tumours. Imaging features favouring schwannoma include a well-circumscribed, encapsulated lesion with smooth margins, heterogeneous enhancement related to Antoni A and Antoni B histologic components, and the absence of aggressive osseous destruction or infiltrative growth. Nevertheless, imaging findings may overlap, and definitive diagnosis requires histopathological evaluation.^{9,10}

Histopathological examination confirmed a benign schwannoma with diffuse immunoreactivity for S100 and SOX10, markers that are characteristic of Schwann cell differentiation and widely used to distinguish schwannoma from other peripheral nerve sheath tumours.^{11,12}

Preoperative imaging is critical for determining the optimal surgical approach for cervicothoracic schwannomas. The choice of surgical technique depends on the tumour size, cranial and caudal extent, relationship to the brachial plexus, subclavian vessels, neural foramina, and mediastinal structures. While VATS is considered an effective minimally invasive option for many posterior mediastinal schwannomas and is associated with shorter postoperative recovery compared with thoracotomy, tumours involving the thoracic inlet frequently require alternative or combined approaches because visualisation of the superior aspect is limited by the clavicle, first rib, subclavian vessels, and brachial plexus.¹³

In our case, the patient underwent a staged surgical approach, with right supraclavicular tumour decompression, followed by VATS for excision of the mediastinal component. This approach facilitated adequate management of both the supraclavicular and intrathoracic components of the tumour while allowing minimally invasive access to the mediastinum.

Conclusion

Cervicothoracic schwannomas with brachial plexus involvement and intrathoracic extension are rare tumours that can present with progressive neurological deficits. A high index of suspicion is essential in patients presenting with a supraclavicular mass accompanied by upper limb weakness or muscle wasting. Detailed CT and MRI evaluation is crucial for defining the extent of the tumour and its relationship with major vessels and thoracic structures. Complete surgical excision remains the treatment of choice for symptomatic lesions. A multidisciplinary approach is required to access both the cervical and intrathoracic components while facilitating safe tumour decompression and excision. The diagnosis is confirmed by histopathological examination. Early recognition and meticulous surgical planning can facilitate safe and effective management of these uncommon tumours.

Prem Kumar Ganesan, Narottam Khadaria, Dhruv Dinesh Jain, Anchal Singh. Giant Cervicothoracic Schwannoma Involving the Brachial Plexus and Thoracic Inlet. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-29>

References

1. Rettenbacher T, Sogner P, Springer P, *et al.* Schwannoma of the brachial plexus: cross-sectional imaging diagnosis using CT, sonography, and MR imaging. *Eur Radiol.* 2003;13:1872–5.
2. Xiao Y, Feng SQ, Luo T, *et al.* Plexiform schwannoma of brachial plexus in axilla: a rare case report. *J Musculoskelet Neuronal Interact.* 2023;23(3):371–6.
3. Kapoor A, Singhal MK, Narayan S, *et al.* Mediastinal schwannoma: a clinical, pathologic, and imaging review. *South Asian J Cancer.* 2015;4(2):104–5.
4. Husodo S, Wati FF. Mediastinal schwannoma: a case report. *Int J Surg Case Rep.* 2023;109:108564.
5. Wang L, Ge L, Ren Y. Case report: combined cervical incision with an intercostal uniportal video-assisted thoracoscopic surgery approach for mediastinal brachial plexus schwannoma. *Front Oncol.* 2023;13:1168963.
6. Kocaturk CI, Sezen CB, Aker C, *et al.* Surgical approach to posterior mediastinal lesions and long-term outcomes. *Asian Cardiovasc Thorac Ann.* 2017;25(4):287–91.
7. Kayawake H, Chen-Yoshikawa TF, Date H. Dual approach for large mediastinal tumors in the thoracic outlet: transmanubrial osteomuscular sparing approach and video-assisted thoracoscopic surgery. *J Cardiothorac Surg.* 2019;14:42.
8. Roh JL. Function-preserving intracapsular enucleation of brachial plexus schwannomas: is it safe and effective? *Oral Oncol.* 2022;134:106102.
9. Carter BW, Benveniste MF, Madan R, *et al.* ITMIG Classification of Mediastinal Compartments and Multidisciplinary Approach to Mediastinal Masses. *Radiographics.* 2017;37(2):413–36.
10. Nguyen ET, Villalobos J, O'Neill AC, *et al.* Imaging of Thoracic Neurogenic Tumors. *Radiographics.* 2016;36(5):1362–81.
11. Lubelski D, Pennington Z, Ochuba A, *et al.* Natural history of brachial plexus, peripheral nerve, and spinal schwannomas. *Neurosurgery.* 2022;91(6):883–91.
12. Testori A, Alloisio M, Cariboni U, *et al.* Voluminous schwannoma type 'ancient' of the cervicothoracic district removed through a cervicotomic approach. *J Surg Case Rep.* 2020;2020(9).
13. Gologorsky RC, Velotta JB. Video-assisted thoracoscopic resection of a thoracic inlet schwannoma with neuroforaminal involvement: a case report. *AME Case Rep.* 2022;6:12.



THE IMAGES

169

Inflammatory Pseudotumour of the Gallbladder Mimicking an Aggressive Malignant Process: Correlation of Magnetic Resonance Cholangiopancreatography, Triple-Phase Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, and Histopathology - **Shubham Aggarwal, Mitusha Verma, Deepak Patkar**

174

Cone-Beam Computed Tomography: The Evolution of Volumetric Imaging in Dentistry - **Shreya Naik, Anurag Luharia, Gaurav Mishra, Suhas Tivaskar, Albert Varghese, Vinay Tiwari**

Inflammatory Pseudotumour of the Gallbladder Mimicking an Aggressive Malignant Process: Correlation of Magnetic Resonance Cholangiopancreatography, Triple-Phase Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, and Histopathology

Shubham Aggarwal¹, Mitusha Verma¹, Deepak Patkar¹

¹Department of Radiodiagnosis, Nanavati Max Super Speciality Hospital, Mumbai, Maharashtra

Correspondence:

Shubham Aggarwal

E-mail: drshubhamaggarwal96@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-18>

Abstract:

Inflammatory pseudotumour (IPT) of the gallbladder is an exceptionally rare benign fibroinflammatory lesion that frequently mimics gallbladder carcinoma on cross-sectional imaging, making preoperative diagnosis extremely challenging because of overlapping morphological and metabolic imaging characteristics. We report the case of a 74-year-old female who presented with nausea, abdominal pain, and weight loss. Magnetic resonance cholangiopancreatography (MRCP) demonstrated multiple gallstones with diffuse asymmetric near-circumferential gallbladder wall thickening, pericholecystic inflammatory changes, and effacement of the common hepatic duct. Subsequent triple-phase fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) revealed a highly FDG-avid gallbladder mass with delayed tracer retention, apparent hepatic invasion, duodenal abutment, and encasement of the right hepatic artery and portal vein, findings highly suggestive of advanced gallbladder carcinoma. The patient underwent surgical resection owing to the strong radiological suspicion of malignancy; however, histopathological examination unexpectedly demonstrated IPT of the gallbladder without evidence of malignancy. This case highlights the diagnostic challenge posed by IPT and underscores the importance of correlating multimodality imaging findings with histopathology to avoid potential diagnostic pitfalls and unnecessary radical management.

Key words: Gallbladder Inflammatory Pseudotumour, Gallbladder Carcinoma Mimic, Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG PET-CT), Magnetic Resonance Cholangiopancreatography (MRCP), Gallbladder Mass, Cholecystitis.

Introduction

Inflammatory pseudotumour (IPT) is a rare benign lesion characterised by fibroblastic and myofibroblastic proliferation accompanied by chronic inflammatory infiltrates. Although most commonly reported in the lung, liver, orbit, and gastrointestinal tract, gallbladder involvement is exceedingly uncommon.^{1–4}

Preoperative diagnosis remains difficult because imaging findings often overlap with those of gallbladder carcinoma. Features such as asymmetric wall thickening, adjacent hepatic infiltration, vascular encasement, and intense fluorodeoxyglucose (FDG) uptake may strongly suggest malignancy.^{5–7} Histopathological examination therefore remains the gold standard for diagnosis.^{1,3,4}

We report a rare case of gallbladder IPT in a 74-year-old female that closely mimicked locally advanced gallbladder carcinoma on triple-phase FDG positron emission tomography/computed tomography (PET-CT).

Case Report

A 74-year-old female presented with nausea, upper abdominal pain, and progressive weight loss. Previous upper gastrointestinal endoscopy had demonstrated a duodenal diverticulum. A prior DOTA scan performed one year earlier was reported as normal.

Magnetic resonance cholangiopancreatography (MRCP) findings

Magnetic resonance imaging (MRI) with MRCP demonstrated mild hepatomegaly with the liver measuring approximately 16 cm in the long axis. Mild periportal cuffing was identified in the form of band-like T2 hyperintensity along the portal tracts. The gallbladder was distended, with a maximum transverse diameter of 4.3 cm. Multiple signal void calculi were identified within the lumen, the largest measuring approximately 2.4 × 2.1 cm. One calculus was impacted at the gallbladder neck (Figure 1). Diffuse near-circumferential asymmetric gallbladder wall thickening was present, measuring up to 8 mm in thickness. Mild-to-moderate pericholecystic inflammatory changes and fat stranding were observed (Figure 2).

Inflammatory soft tissue at the gallbladder neck caused effacement of the adjacent common hepatic duct.

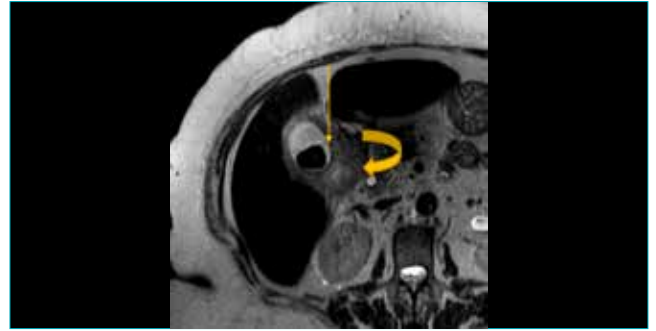


Figure 1: Axial and coronal T2-weighted single-shot fast spin echo sequence (SSFSE/HASTE) shows multiple signal-void, well-defined foci representing calculi within (yellow arrow). One of these is seen impacted at the gallbladder neck.

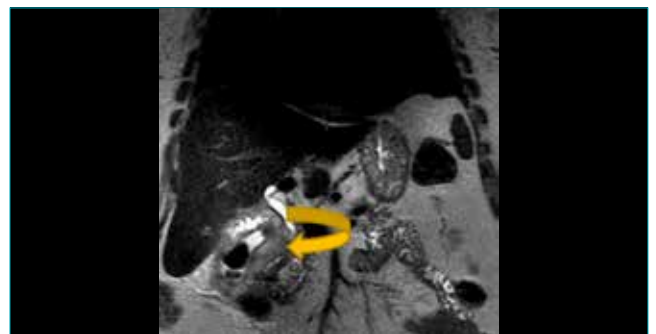


Figure 2: Near-circumferential asymmetric gallbladder wall thickening (curved yellow arrow) is seen, with a maximum wall thickness of 8 mm. Mild-to-moderate pericholecystic fat stranding is identified.

However, the common bile duct was normal in calibre, measuring approximately 6 mm, without evidence of choledocholithiasis or an intraductal mass.

No focal hepatic lesions, significant lymphadenopathy, or ascites were identified.

Based on these findings, the differential diagnosis included xanthogranulomatous cholecystitis, IPT, and gallbladder carcinoma.^{5,6,8,9}

PET-CT findings

A triple-phase whole-body FDG PET-CT performed the following day demonstrated a heterogeneously enhancing, metabolically active mass-like lesion involving the neck, body, and fundus of the gallbladder, measuring approximately 5.0 × 5.0 cm.

The lesion extended to the serosal surface and demonstrated an exophytic component closely abutting the first and second (D1 – D2) parts of the duodenum (Figure 3). The mass appeared inseparable from hepatic

segments IVB and V, raising suspicion for direct hepatic invasion.

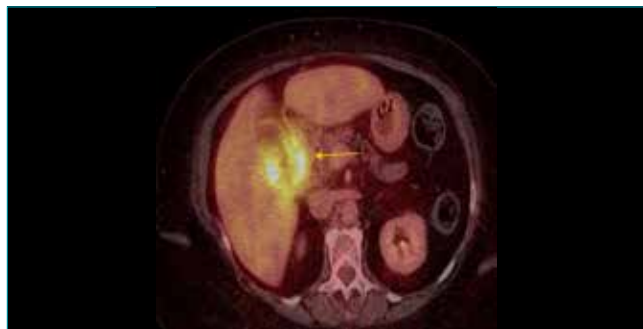


Figure 3: Axial fused fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) demonstrates a heterogeneously enhancing, metabolically active gallbladder mass involving the neck, body, and fundus with an exophytic component abutting the first and second parts of the duodenum.

An extraserosal soft tissue component extended into the porta hepatis and encased the right hepatic artery and adjacent portal vein without significant luminal compromise. The lesion demonstrated intense FDG uptake with a maximum standardised uptake value (SUV_{max}) of 11.4 and a metabolic tumour volume of approximately 111 cm^3 . Delayed imaging demonstrated marked tracer retention with SUV_{max} increasing to 23.9, representing a 109% increase in metabolic activity (Figure 4). No metabolically active regional lymphadenopathy, peritoneal deposits, distant metastases, or skeletal lesions were identified.

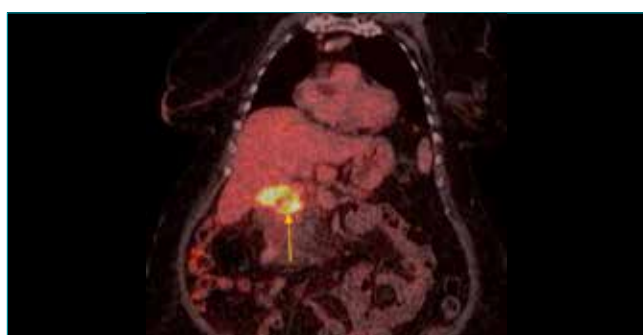


Figure 4: Coronal fused fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) demonstrates close apposition of the lesion to hepatic segments IVB and V with intense FDG uptake, with a maximum standardised uptake (SUV_{max}) value of 11.4. Delayed imaging demonstrates increased tracer retention (SUV_{max} 23.9; 109% increase).

Given the combination of aggressive local morphology and intense delayed FDG uptake, the lesion was interpreted as highly suspicious for gallbladder carcinoma.

Surgical and histopathological findings

In view of the strong radiological suspicion of malignancy, surgical resection was undertaken. Gross pathological examination demonstrated marked gallbladder wall thickening with a firm mass-like lesion. Microscopic evaluation revealed dense fibroinflammatory tissue composed of spindle-shaped myofibroblasts within a collagenised stroma associated with abundant lymphocytes, plasma cells, and chronic inflammatory infiltrates. No evidence of dysplasia, adenocarcinoma, or other malignant neoplasm was identified. The final diagnosis was IPT of the gallbladder. The patient recovered uneventfully following surgery.

Discussion

Gallbladder IPT is an extremely uncommon benign lesion and remains a significant diagnostic challenge because its clinical and imaging findings frequently overlap with those of gallbladder carcinoma.^{3,4,7,10} The present case is noteworthy because both MRCP and FDG PET-CT demonstrated imaging features that strongly suggested locally advanced gallbladder carcinoma.^{6,8,9} MRCP revealed diffuse asymmetric near-circumferential gallbladder wall thickening with gallbladder distension, an impacted gallstone at the gallbladder neck, associated pericholecystic inflammatory changes, and effacement of the adjacent common hepatic duct. Although these findings were indicative of severe inflammatory disease, they could not reliably exclude an underlying malignancy, and the differential diagnosis included IPT, xanthogranulomatous cholecystitis, and gallbladder carcinoma.^{5,6,8}

Triple-phase FDG PET-CT further complicated the diagnostic evaluation by demonstrating intense FDG avidity (SUV_{max} 11.4), marked delayed tracer accumulation (SUV_{max} 23.9), apparent hepatic extension, duodenal abutment, and encasement of the right hepatic artery and portal vein. These imaging features are generally regarded as highly suspicious for advanced gallbladder carcinoma, particularly the marked delayed FDG retention, which is often considered a characteristic favouring malignancy.^{11,12} Consequently, the benign histopathological diagnosis of IPT was unexpected.

A notable aspect of this case is that the original MRCP interpretation appropriately included IPT in the differential diagnosis despite the subsequently alarming

PET-CT appearance. Histopathological examination ultimately confirmed this possibility, highlighting the importance of correlating multimodality imaging findings with tissue diagnosis in cases with equivocal radiological features. The presumed pathogenesis in the present case is likely related to chronic inflammation induced by longstanding cholelithiasis, as multiple gallstones, including an impacted calculus at the gallbladder neck, were present. Persistent inflammatory stimulation may lead to exuberant fibroblastic and myofibroblastic proliferation, producing a mass-forming inflammatory lesion that closely simulates gallbladder carcinoma on both anatomical and metabolic imaging.^{3,4,12,13}

Acknowledgements

I, Dr. Shubham Aggarwal, would like to acknowledge Dr. Deepak Patkar (Head of Department [HOD], Department of Radiology) and Dr. Mitusha Verma (Consultant Radiologist) at Nanavati Max Super Speciality Hospital, Mumbai, for their valuable guidance and support in the preparation of this case report. We also thank the patient and their family for consenting to share the clinical details for academic and educational purposes.

Conclusion

IPT of the gallbladder is a rare benign fibroinflammatory lesion capable of closely mimicking advanced gallbladder carcinoma on FDG PET-CT. The present case demonstrated diffuse asymmetric gallbladder wall thickening, intense FDG avidity, delayed tracer retention, apparent hepatic invasion, duodenal involvement, and vascular encasement, all of which are features strongly suggestive of malignancy.

Histopathological examination ultimately established the benign diagnosis of IPT. This case highlights the importance of maintaining IPT within the differential diagnosis of gallbladder masses, particularly in the setting of cholelithiasis and chronic inflammatory changes, even when PET-CT findings appear highly suggestive of cancer.

Shubham Aggarwal, Mitusha Verma, Deepak Patkar. Inflammatory Pseudotumour of the Gallbladder Mimicking an Aggressive Malignant Process: Correlation of Magnetic Resonance Cholangiopancreatography, Triple-Phase Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, and Histopathology. *MMJ*. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-18>

References

1. Coffin CM, Watterson J, Priest JR, *et al.* Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor): a clinicopathologic and immunohistochemical study of 84 cases. *Am J Surg Pathol*. 1995;19(8):859–72.
2. Narla LD, Newman B, Spottswood SS, *et al.* Inflammatory pseudotumor. *Radiographics*. 2003;23(3):719–29.
3. Kwon AH, Matsui Y, Uemura Y. Inflammatory pseudotumor of the gallbladder: a case report and review of the literature. *J Hepatobiliary Pancreat Surg*. 2001;8(1):97–101.
4. Horiuchi A, Watanabe Y, Kawai K, *et al.* Inflammatory pseudotumor of the gallbladder: report of a case. *Surg Today*. 2000;30(8):740–3.
5. Levy AD, Murakata LA, Abbott RM, *et al.* From the archives of the AFIP: benign tumors and tumorlike lesions of the gallbladder and extrahepatic bile ducts: radiologic-pathologic correlation. *Radiographics*. 2002;22(2):387–413.
6. Patel NB, Oto A, Thomas S. Multimodality imaging of gallbladder carcinoma and its mimics. *Radiographics*. 2013;33(7):1879–900.
7. Nishimura A, Shirai Y, Wakai T, *et al.* Inflammatory pseudotumor of the gallbladder diagnosed after radical surgery for suspected gallbladder carcinoma. *J Gastroenterol*. 2004;39(5):495–9.

8. Kim SJ, Lee JM, Lee JY, *et al.* Analysis of enhancement pattern of flat gallbladder wall thickening on MDCT to differentiate gallbladder cancer from benign conditions. *AJR Am J Roentgenol.* 2008;191(3):765–71.
9. Yeh TS, Jan YY, Chiu CT, *et al.* Preoperative differentiation of gallbladder carcinoma and chronic cholecystitis: clinical and radiologic considerations. *World J Surg.* 2004;28(6):543–7.
10. Ishida H, Komatsuda T, Ohnishi H, *et al.* Inflammatory pseudotumor of the gallbladder: sonographic and CT findings. *Abdom Imaging.* 1998;23(1):74–6.
11. Higashi T, Saga T, Nakamoto Y, *et al.* Relationship between retention index in dual-time-point FDG PET and pathological characteristics of malignant tumors. *Eur J Nucl Med Mol Imaging.* 2002;29(7):913–20.
12. Rosenbaum SJ, Lind T, Antoch G, *et al.* False-positive FDG PET uptake—the role of PET/CT. *Eur Radiol.* 2006;16(5):1054–65.
13. Koo HJ, Lim S, Choe J, *et al.* Radiographic and FDG PET/CT features of inflammatory lesions mimicking malignancy. *Radiographics.* 2020;40(4):1014–34.

Cone-Beam Computed Tomography: The Evolution of Volumetric Imaging in Dentistry

Shreya Naik¹, Anurag Luharia², Gaurav Mishra², Suhas Tivaskar³, Albert Varghese⁴, Vinay Tiwari¹

¹Department of Radiology, Max Institute of Allied and Paramedical Education (MIAPE), Noida, Delhi

²Department of Radiology, J.N.M.C., Sawangi (Meghe), Wardha, Maharashtra

³Department of Radiology, Datta Meghe Institute of Higher Education and Research, Sawangi (Meghe), Wardha, Maharashtra

⁴Department of Radiology, Max Institute of Allied and Paramedical Education (MIAPE), Rohini, Delhi

Correspondence:

Shreya Naik

E-mail: shreya.naik@maxhealthcare.com

DOI: <https://doi.org/10.62830/mmj3-03-19>

Abstract:

A major advancement in maxillofacial imaging is cone-beam computed tomography (CBCT), which has led to the advancement of dental diagnostics from existing two-dimensional (2D) views to true three-dimensional (3D) volumetric imaging. Cone-beam imaging confers notable advantages in spatial resolution, lower radiation exposure, and increased clinical accessibility for evaluating dental and jaw pathologies, whereas conventional computed tomography (CT) remains the gold standard for complex craniofacial trauma. This review discusses the evolution, clinical utility, current limitations, and future trajectory of CBCT in contemporary dental practice.

Key words: Cone-Beam Computed Tomography, Dental Imaging, Maxillofacial Radiology, Three-Dimensional Imaging, Diagnostic Imaging.

Introduction

Computed tomography (CT) is the gold standard for maxillofacial injuries and complex facial fractures involving the frontal sinus, nasoethmoid region, and orbits. It is particularly useful in identifying and defining displaced fractures of the mandible and condyle, which are often unclear on panoramic radiographs, before surgical reduction and fixation are performed. Furthermore, it offers excellent visualisation of impacted teeth and their relationships with adjacent anatomical structures, thereby facilitating surgical treatment planning and extraction.

CT has advanced dental radiographic imaging since its introduction in the mid-1970s by combining X-ray and computer-assisted image reconstruction to capture thin, detailed slices of tissue. Continued technological advancements led to the emergence of cone-beam

computed tomography (CBCT) in the late 1990s, which is now widely used in contemporary dental practice.¹⁻³

Evolution of CBCT

Shift from analogue two-dimensional (2D) to volumetric three-dimensional (3D) imaging

Until a few years ago, routine dental imaging predominantly relied on 2D imaging techniques, including periapical, bitewing, panoramic, and cephalometric radiography. This was largely replaced by the introduction of CBCT, which allows for enhanced 3D visualisation of the maxillofacial region. Although it is referred to by several names, including dental volumetric tomography (DVT), cone-beam volumetric tomography (CBVT), dental computed tomography (DCT), and cone-beam imaging (CBI), CBCT is the most preferred term.^{4,5}

CBCT versus multidetector CT

CBCT was primarily designed to overcome the limitations of conventional CT. Compared to CT, it differs in terms of patient positioning, acquisition time, radiation exposure, and clinical uses, including scanning the entire head and chin region in a single exposure. Although the effective dose varies depending on the field of view, exposure parameters, and imaging system, CBCT can deliver equivalent doses ranging from 3 to 200 panoramic radiographs. Additionally, CBCT provides high spatial resolution, improved osseous structure visualisation, and cost-effectiveness.

Originally developed for angiographic applications, it was later used in maxillofacial imaging as well. One of the principal advantages of this method is its ability to produce 3D images of the area of interest without superimposing other structures. Multiplanar and 3D images with a lower radiation dose and higher spatial resolution than CT can be achieved with this technique, providing better visualisation of mineralised tissues.^{6–9}

Image Acquisition and Reconstruction

Working principle of CBCT

The working principle of CBCT is based on the fundamental concept of CT, which reconstructs a 3D anatomical volume from a series of 2D projection images. The CBCT system comprises a flat-panel detector and a dedicated scanner equipped with a collimated X-ray source that produces a cone- or pyramid-shaped beam and performs a single full or partial circular rotation around the patient's head. Multiple sequential planar projections are acquired and subsequently reconstructed into a 3D volumetric dataset using reconstruction algorithms after exposure (Figure 1).



Figure 1: Representative gantry and flat-panel detector configuration of a clinical cone-beam computed tomography (CBCT) system.
Source: Image courtesy of the United States Food and Drug Administration (US FDA) official website.

Patient positioning differs among various CBCT systems, with image acquisition performed when the patient is seated, standing, or supine. Modern systems are relatively easy to operate, enabling 3D image reconstruction and visualisation through software access.^{9–12}

Diagnostic and Clinical Applications

With its expanding clinical applications, CBCT has proven to be a valuable adjunctive imaging modality for diagnosis, treatment planning, and follow-up in several dental fields. It enables a more accurate evaluation of furcation involvement, buccal and lingual periodontal defects, and bony lesions than conventional radiographs in periodontology. It is routinely used to assess cysts, tumours, developmental anomalies, traumatic injuries, and complex maxillofacial fractures. One of the most distinguished applications of CBCT remains in implant dentistry, where multiplanar cross-sectional imaging permits the precise evaluation of the height, width, and density of the bone and its relationship with vital anatomical structures before implant placement.

CBCT has also facilitated the diagnosis of temporomandibular joint disorders by offering detailed visualisation of osseous changes, including fractures, ankylosis, osteophytes, erosions, flattening, subchondral sclerosis, and other degenerative alterations. Data regarding the precise localisation of the mandibular canal can help clinicians avoid damage to the neurovascular structures during surgery. CBCT has also been shown to be useful in evaluating soft-tissue calcifications and salivary gland pathologies, especially when used in conjunction with sialographic techniques, despite the lower soft-tissue contrast compared to that of conventional CT and magnetic resonance imaging (MRI). Moreover, it has provided significant improvements in periapical lesion detection, 3D assessment of orthodontic tooth movement, and forensic investigations when a detailed evaluation of craniofacial hard tissues is needed.^{12–18}

Limitations and Clinical Considerations

Technical disadvantages

Despite these advantages, photon starvation, scattering, and beam hardening caused by high-density neighbouring structures, such as enamel, metal posts, and restorations, affect the image quality, contrast, and overall diagnostic accuracy. Motion artifacts resulting from patient movement

and the presence of metallic orthodontic brackets can produce noise or metallic artifacts. Furthermore, CBCT systems generally require a larger capital cost and space than conventional dental X-ray equipment.^{6–9}

Image quality and radiation dosimetry

CBCT should not be used routinely as a substitute for conventional dental radiography. Its use should be predicated on a discernible clinical justification, particularly given that the radiation dose is generally higher than that of conventional intraoral or panoramic radiography. The image quality may be influenced by beam-hardening artifacts, scatter radiation, patient movement, and metallic restorations, which affect the results of CBCTs across different systems based on their detector technology, field of view (FOV), acquisition protocols, and reconstruction algorithms. Consequently, the acquisition of images must always be performed according to radiation optimisation principles so that the predicted benefit in diagnosis outweighs the inherent risks.^{5,7–13}

Future Prospects

Future developments are aimed at improving image quality while decreasing the radiation dose and acquisition time. Improved diagnostic accuracy with lower patient radiation exposure will be more achievable through advances in detector technology, reconstruction, dose reduction algorithms, and task-specific imaging protocols. Panoramic and cephalometric imaging combined with CBCT systems, enhanced soft-tissue visualisation, and the potential application of artificial intelligence (AI) for automated image interpretation and workflow optimisation may improve its clinical utility. However, further investigation and well-conducted validation studies are required to standardise imaging protocols and improve the evidence base for these novel applications.

Ultimately, proper research-backed utilisation and technological refinements are likely to further establish CBCT in the dental imaging armamentarium while parading with developments in digital dentistry.^{15–18}

Conclusion

One of the most significant breakthroughs in dental imaging is the introduction of CBCT, which can generate high-resolution 3D images of the maxillofacial region while significantly reducing the patient's radiation exposure and time. It has positively impacted all dentistry domains in terms of diagnosis, treatment planning, and clinical decision-making. While limitations persist due to image artifacts, poor soft-tissue contrast, and high capital costs of the equipment, CBCT remains an unparalleled diagnostic tool when used with an evidence-based clinical framework guided by established and appropriate protocols.

Shreya Naik, Anurag Luharia, Gaurav Mishra, Suhas Tivaskar, Albert Varghese, Vinay Tiwari. Cone-Beam Computed Tomography: The Evolution of Volumetric Imaging in Dentistry. *MMJ*. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-19>

References

1. Gala Z, Bai D, Halsey J, *et al*. Head Computed Tomography Versus Maxillofacial Computed Tomography: An Evaluation of the Efficacy of Facial Imaging in the Detection of Facial Fractures. *Eplasty*. 2022;22:e22.
2. Sandeep Reddy B, Naik D, Kenkere D. Role of Multidetector Computed Tomography in the Evaluation of Maxillofacial Trauma. *Cureus*. 2023;15(2):e35008.
3. Yadav D, Jha A, Mukhi S, *et al*. Role of computed tomography in the evaluation of patients with maxillofacial trauma. *Mod App Dent Oral Health*. 2019;4:310–5.
4. Ahmad M, Freymiller E. Cone beam computed tomography: evaluation of maxillofacial pathology. *J Calif Dent Assoc*. 2010;38(1):41–7.

5. Lorenzoni DC, Bolognese AM, Garib DG, *et al.* Cone-beam computed tomography and radiographs in dentistry: aspects related to radiation dose. *Int J Dent.* 2012;2012:813768.
6. Kailash S. CBCT – Cone beam computed tomography. *J Dent Educ.* 2014;1(1):9–15.
7. Bromberg N, Brizuela M. Dental Cone Beam Computed Tomography. Treasure Island (FL): StatPearls Publishing; 2023.
8. Schilling R, Geibel MA. Assessment of the effective doses from two dental cone beam CT devices. *Dentomaxillofac Radiol.* 2013;42(5):20120273.
9. Scarfe WC, Farman AG. Cone beam computed tomography: A paradigm shift for clinical dentistry. *Australasian Dental Practice.* 2007:104–8.
10. Jain A, Shil M, Sreepradha C, *et al.* A Review on Cone-Beam Computed Tomography and its Application in Dentistry. *J Pharm Bioallied Sci.* 2024;16(Suppl 1):S38–40.
11. White SC, Pharoah MJ. White and Pharoah's Oral Radiology: Principles and Interpretation. 8th Edition. Elsevier; 2014. p. 431–3.
12. Mah J. The genesis and development of CBCT for dentistry. *American Dental Association.* 2014.
13. Mah JK, Yi L, Huang RC, *et al.* Advanced applications of cone beam computed tomography in orthodontics. *Semin Orthod.* 2011;17(1):57–71.
14. Venkatesh E, Elluru SV. Cone beam computed tomography: basics and applications in dentistry. *J Istanbul Univ Fac Dent.* 2017;51(3 Suppl 1):S102–21.
15. Nasseh I, Al-Rawi W. Cone beam computed tomography. *Dent Clin North Am.* 2018;62(3):361–91.
16. Wong J, Zhang C, Lee AH. Clinical Benefits and Limitations of Cone-Beam Computed Tomography in Endodontic Practice: A Contemporary Evidence-Based Review. *Diagnostics (Basel).* 2025;15(24):3117.
17. Jain S, Choudhary K, Nagi R, *et al.* New evolution of cone-beam computed tomography in dentistry: Combining digital technologies. *Imaging Sci Dent.* 2019;49(3):179–90.
18. Feinberg L. The future of CBCT in modern dentistry. *BDJ In Practice.* 2025;38:149.



STUDENTS' CORNER

179 Clinical Signs – The Forgotten Art (Part 3): Ten
More Bedside Signs Every Clinician Should Master
- **Narinder Pal Singh, Vanraj N Padhiyar**

Clinical Signs – The Forgotten Art (Part 3): Ten More Bedside Signs Every Clinician Should Master

A review of classic bedside clinical signs, their described method, positive findings, clinical significance, and evidence-informed discussion, with original illustrations.

Narinder Pal Singh^{1,2*}, Vanraj N Padhiyar³

¹Department of Nephrology and Renal Transplant Medicine, Max Super Speciality Hospital, Saket, New Delhi

²Department of Research, Eternal University, Himachal Pradesh

³Department of Medicine, Dr. L. H. Hiranandani Hospital, Powai, Mumbai, Maharashtra

Correspondence:

Narinder Pal Singh

E-mail: nanusingh58@gmail.com

DOI: <https://doi.org/10.62830/mmj3-03-31>

Abstract:

Despite the dominance of imaging and laboratory diagnostics in modern medicine, bedside clinical signs retain enduring value for their immediacy, reproducibility, and zero cost. This third article in a review series examines ten classic eponymous signs across endocrinology, neurology, cardiology, dermatology, trauma, and vascular surgery, detailing for each the historical background, examination technique, positive finding, and clinical significance. Original schematic illustrations accompany each sign to clarify the bedside method, while an evidence-informed discussion appraises their diagnostic accuracy and limitations. These signs are presented not as replacements for investigation but as adjuncts that, when integrated with history and examination, can guide the urgency and direction of further workup.

Key words: Clinical Signs, Bedside Examination, Eponymous Signs, Physical Diagnosis.

Introduction

The bedside clinical examination — inspection, palpation, percussion, and the deliberate provocation of a physical sign — is often described as a 'forgotten art' in an era of rapid access to imaging and laboratory testing. Yet eponymous clinical signs continue to earn their place at the bedside: they are free, immediate, reproducible, and frequently guide the urgency and direction of further investigation before a scan or blood result is ever available.

This review, the third in a series, revisits ten classic clinical signs spanning endocrinology, neurology, cardiology, dermatology, trauma, and vascular surgery. For each sign, we summarise the system involved, its historical description, the bedside method, the positive finding, its clinical significance, and a short evidence-informed discussion of its diagnostic value and limitations, illustrated with an original schematic figure.

As with all clinical signs, these tests are best interpreted as part of a complete history and examination rather than in isolation, and modern imaging or laboratory confirmation remains the reference standard for most of the conditions discussed below.

At a Glance (Table 1)

Sr. No.	Sign	System	Key significance
1	Pemberton's sign	Endocrinology/ Surgery	Suggests retrosternal goitre or any superior mediastinal mass causing thoracic inlet obstruction
2	Beever's sign	Neurology	Weakness of the lower abdominal muscles relative to the upper segments
3	Quincke's capillary pulsation	Cardiology	Suggests severe aortic regurgitation
4	Nikolsky's sign	Dermatology	Indicates loss of epidermal cohesion (acantholysis or subepidermal cleavage)
5	Trousseau's sign	Endocrinology	Suggests latent hypocalcaemia
6	Froment's sign	Neurology/ Hand surgery	Indicates ulnar nerve palsy
7	Battle's sign	Trauma	Suggests a basilar (posterior fossa) skull fracture
8	Tinel's sign	Neurology/ Orthopaedics	Seen in nerve entrapment (e.g. carpal tunnel syndrome) and during nerve regeneration
9	Prayer sign	Endocrinology	Suggests diabetic cheiroarthropathy (limited joint mobility syndrome)
10	Milking (Strip) sign	Vascular surgery	Indicates valvular incompetence in varicose veins

Table 1: Classic eponymous clinical signs: Systems involved and clinical significance.

Ten Bedside Signs Every Clinician Should Master

1. Pemberton's sign (Figure 1)



Figure 1: Positive Pemberton's sign in retrosternal goitre.

System: Endocrinology/Surgery

First described by: Hugh Pemberton (1946)

Method: Ask the patient to raise both arms until they touch the sides of the head.

Positive sign: Within 30 – 60 seconds, the patient develops facial plethora, cyanosis, respiratory distress, and distended neck veins.

Significance: Suggests retrosternal goitre or any superior mediastinal mass causing thoracic inlet obstruction.

Why it matters: A simple bedside test that predicts airway compromise before computed tomography (CT) imaging.

Discussion

Elevating the arms lifts the clavicles and further narrows the already compromised thoracic inlet, producing venous congestion and, in severe cases, stridor. Reported sensitivity varies widely (approximately 40% – 75% across case series), but the sign is highly specific and inexpensive, making it a useful triage step before requesting cross-sectional imaging in patients with large or retrosternal goitres. It is not specific to thyroid disease; thymomas, lymphomas, and other mediastinal masses causing superior vena cava or thoracic-inlet compromise can also produce a positive sign.¹

2. Beevor's sign (Figure 2)

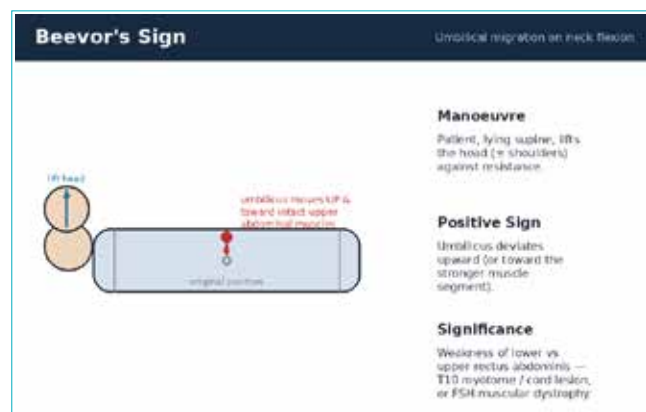


Figure 2: Positive Beevor's sign: The umbilicus migrates cephalad.

Abbreviation: FSH: Facioscapulohumeral.

System: Neurology

First described by: Charles Edward Beevor (1903)

Method: Ask the patient to lift the head (or perform a partial sit-up/cough) while lying supine.

Positive sign: The umbilicus moves upwards.

Significance: Weakness of the lower abdominal muscles relative to the upper segments.

Why it matters: Seen in facioscapulohumeral (FSH) muscular dystrophy and T10 spinal cord lesions.

Discussion

The rectus abdominis is segmentally innervated (roughly T7 – T12), so a positive sign requires an asymmetric pattern of weakness — intact upper segments pulling the umbilicus cranially while weak lower segments fail to counteract the movement. Classically taught for a T10 cord lesion, it is equally useful in FSH muscular dystrophy, where selective abdominal and paraspinal involvement is characteristic, and it can be elicited more comfortably by asking the patient to cough rather than perform a full sit-up.²

3. Quincke's capillary pulsation (Figure 3)



Figure 3: Quincke's capillary pulsations in the nail bed.

System: Cardiology

First described by: Heinrich Quincke (1868)

Method: Lightly compress the nail bed (or a glass slide against the lip mucosa).

Positive sign: Alternating blanching and flushing of the capillary bed, synchronous with the pulse.

Significance: Suggests severe aortic regurgitation.

Why it matters: A classic peripheral sign of a markedly widened pulse pressure.

Discussion

Quincke's pulsation reflects a wide pulse pressure rather than aortic regurgitation specifically, so it can also be elicited in thyrotoxicosis, fever, pregnancy, large arteriovenous fistulae, and patent ductus arteriosus. It takes its place among a family of eponymous 'wide pulse pressure' signs — de Musset's head bob, Corrigan's water-hammer pulse, Duroziez's murmur, and Traube's 'pistol-shot' femoral sounds — that were once relied upon to grade severity before echocardiography. They remain useful teaching signs and quick bedside clues, but modern quantification of aortic regurgitation severity rests on echocardiographic assessment.³

4. Nikolsky's sign (Figure 4)

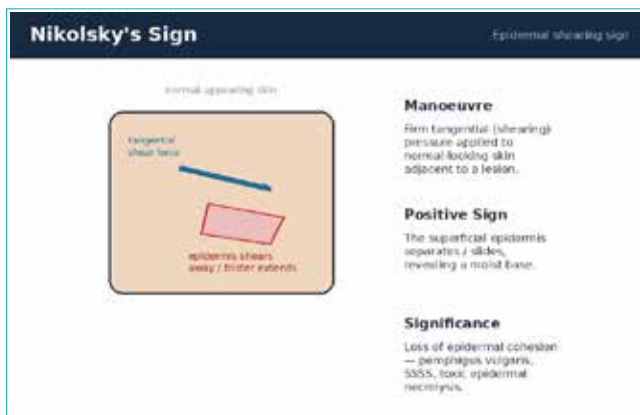


Figure 4: Positive Nikolsky's sign.

Abbreviation: SSSS: Staphylococcal Scalded Skin Syndrome.

System: Dermatology

First described by: Pyotr Nikolsky (1896)

Method: Apply firm tangential (shearing) pressure to normal-appearing skin adjacent to a lesion.

Positive sign: The epidermis shears away, revealing a moist base.

Significance: Indicates loss of epidermal cohesion (acantholysis or subepidermal cleavage).

Why it matters: Seen in pemphigus vulgaris and toxic epidermal necrolysis/Stevens-Johnson syndrome.

Discussion

A positive Nikolsky sign is sensitive for active pemphigus vulgaris but is not specific to it. It is also positive in staphylococcal scalded skin syndrome (SSSS) and toxic epidermal necrolysis, albeit through different mechanisms (intraepidermal acantholysis versus full-thickness epidermal detachment). A related 'pseudo-Nikolsky' sign, elicited by applying lateral pressure directly on an existing bulla to extend it into adjacent skin, is used similarly at the bedside. Because the test can enlarge blistering, it should be performed gently and only where clinically indicated.⁴

5. Trousseau's sign (Figure 5)

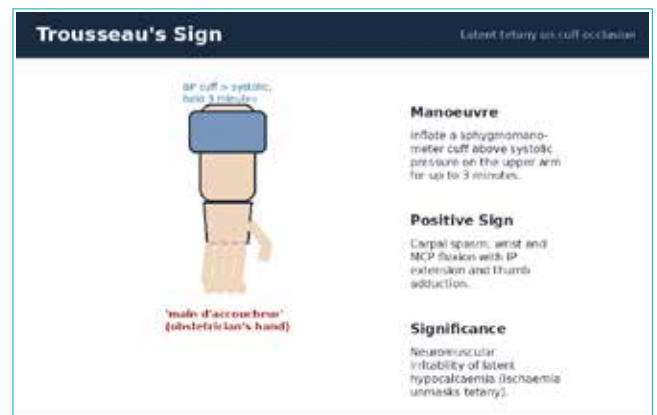


Figure 5: Trousseau's sign: Carpopedal spasm.

Abbreviations: BP: Blood Pressure; IP: Interphalangeal; MCP: Metacarpophalangeal.

System: Endocrinology

First described by: Armand Trousseau (1861)

Method: Inflate a blood pressure cuff above systolic pressure for up to 3 minutes.

Positive sign: Carpopedal spasm — flexion at the wrist and metacarpophalangeal (MCP) joints with extension of the interphalangeal (IP) joints and thumb adduction ('main d'accoucheur').

Significance: Suggests latent hypocalcaemia.

Why it matters: More sensitive than Chvostek's sign for detecting neuromuscular irritability.

Discussion

Ischaemia induced by cuff inflation unmasks neuromuscular hyperexcitability in hypocalcaemia; the sign is generally considered more sensitive (and more specific) than Chvostek's sign, though it is also positive in hypomagnesaemia and in respiratory alkalosis from hyperventilation. A small proportion of normocalcaemic individuals show a false-positive response, and some patients with confirmed hypocalcaemia never develop a positive sign, so a negative test does not exclude the diagnosis.⁵

6. Froment's sign (Figure 6)



Figure 6: Positive Froment's sign in ulnar nerve palsy.

Abbreviations: FPL: Flexor Pollicis Longus; IP: Interphalangeal.

System: Neurology/Hand Surgery

First described by: Jules Froment (1915)

Method: Ask the patient to hold a sheet of paper between the thumb and the radial side of the index finger while the examiner pulls it away.

Positive sign: The thumb IP joint flexes because the flexor pollicis longus (FPL) (median-innervated) compensates for a weak adductor pollicis.

Significance: Indicates ulnar nerve palsy.

Why it matters: A simple substitution test for weak thumb adduction.

Discussion

Froment's sign tests the ulnar-innervated adductor pollicis; when it is weak, the median-innervated FPL substitutes to maintain pinch, producing visible thumb IP flexion. It is often paired with Jeanne's sign (compensatory hyperextension at the thumb MCP joint). The pattern of associated findings — for example, sparing versus involvement of flexor digitorum profundus to the ring and little fingers, or sensory loss over the dorsal ulnar hand — helps localise the lesion to the elbow (cubital tunnel) versus the wrist (Guyon's canal).⁶

7. Battle's sign (Figure 7)

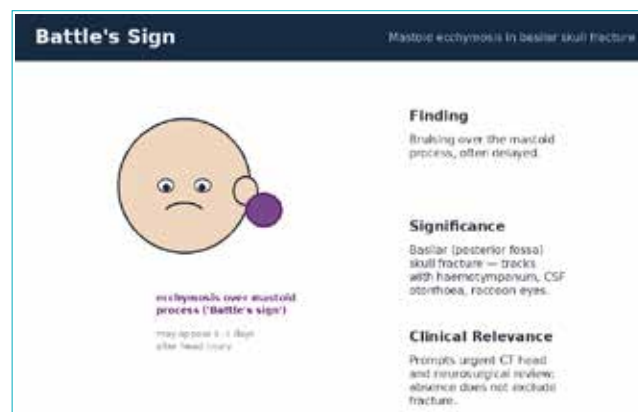


Figure 7: Battle's sign: Post-auricular ecchymosis.

Abbreviations: CSF: Cerebrospinal Fluid; CT: Computed Tomography.

System: Trauma

First described by: William Henry Battle (1890)

Method: Inspect the skin overlying the mastoid process after head trauma.

Positive sign: Ecchymosis (bruising) over the mastoid process.

Significance: Suggests a basilar (posterior fossa) skull fracture.

Why it matters: May appear hours to days after trauma and should prompt urgent neuroimaging.

Discussion

Battle's sign results from blood tracking along the mastoid emissary veins from a fracture of the petrous temporal bone; it is frequently delayed, appearing one to three days after injury, and reported sensitivity for basilar skull fracture is low (often cited around 30%). It is best interpreted alongside other basilar-fracture signs — periorbital ecchymosis ('raccoon eyes'), haemotympanum, and cerebrospinal fluid (CSF) otorrhoea or rhinorrhoea. Because of its low sensitivity, its absence does not exclude a fracture, and clinical suspicion based on mechanism should still prompt CT imaging.⁷

8. Tinel's sign (Figure 8)

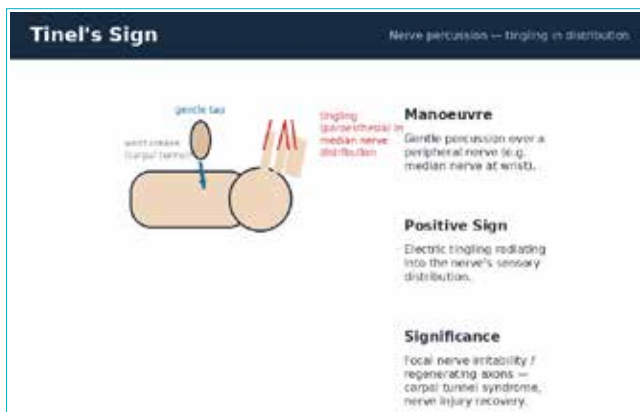


Figure 8: Tinel's sign at the wrist (carpal tunnel).

System: Neurology/Orthopaedics

First described by: Jules Tinel (1915)

Method: Tap gently over the course of a peripheral nerve.

Positive sign: Tingling (paraesthesia) is felt in the nerve's sensory distribution.

Significance: Seen in nerve entrapment (e.g. carpal tunnel syndrome) and during nerve regeneration.

Why it matters: Also used serially to track the advancing front of axonal regrowth after nerve repair.

Discussion

For carpal tunnel syndrome, Tinel's sign has moderate sensitivity (roughly 50% – 60% in most series) and lower specificity than the Phalen manoeuvre, so it is best used alongside history, Phalen's test, and, when needed, nerve conduction studies rather than in isolation. A distinct and clinically valuable use is monitoring nerve recovery after injury or repair: an 'advancing' Tinel sign, moving distally over serial examinations at roughly 1 mm per day, indicates successful axonal regeneration.⁸

9. Prayer sign (Figure 9)

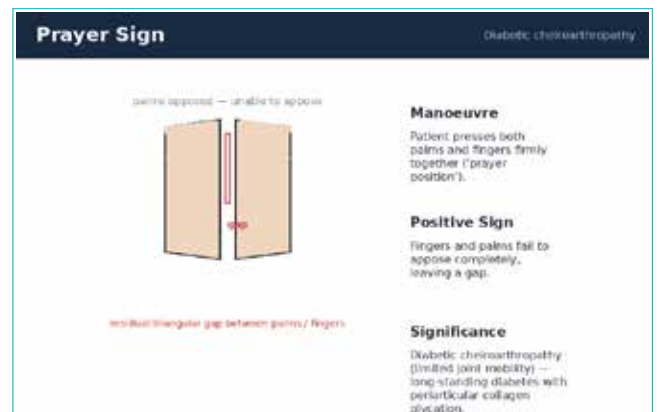


Figure 9: Positive Prayer sign.

System: Endocrinology

First described by: Widely used bedside sign in diabetes care (no single credited originator).

Method: Ask the patient to oppose both palms and fingers completely, as if praying.

Positive sign: Inability to fully approximate the palms and fingers, leaving a gap.

Significance: Suggests diabetic cheiroarthropathy (limited joint mobility syndrome).

Why it matters: Suggests long-standing diabetes and an increased likelihood of microvascular complications.

Discussion

Diabetic cheiroarthropathy results from non-enzymatic glycation and thickening of periarticular collagen and skin, restricting extension at the small joints of the hand. A positive prayer sign correlates with diabetes duration and has been associated with an increased prevalence of retinopathy, nephropathy, and other microvascular complications, making it a useful trigger to review glycaemic control and screen for other end-organ effects. It should be distinguished from Dupuytren's contracture (nodular palmar fascial thickening with digital flexion contracture) and scleroderma-related sclerodactyly.⁹

10. Milking (Strip) sign (Figure 10)

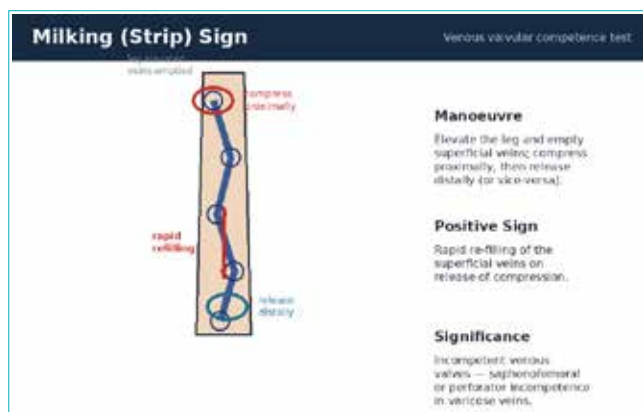


Figure 10: Milking (Strip) test for venous valve competence.

System: Vascular surgery

First described by: Bedside variant of the Brodie-Trendelenburg test tradition.

Method: Elevate the leg to empty superficial veins, then compress the vein proximally and release distally (or the reverse sequence).

Positive sign: Rapid venous filling on release of compression.

Significance: Indicates valvular incompetence in varicose veins.

Why it matters: A quick way to localise incompetent segments before duplex ultrasound.

Discussion

The milking or strip test is part of the same bedside tradition as the Brodie-Trendelenburg tourniquet test, both aiming to demonstrate retrograde flow through incompetent valves — whether at the saphenofemoral junction, saphenopopliteal junction, or individual perforators — by controlling where filling is permitted. These manoeuvres are quick, cost nothing, and remain useful for rapid bedside assessment, but duplex ultrasonography is now the diagnostic gold standard, offering precise mapping of reflux that guides modern endovenous treatment planning.¹⁰

Conclusion

Classic bedside clinical signs remain valuable components of clinical examination despite the increasing availability of advanced imaging and laboratory investigations. The ten signs reviewed in this article demonstrate how careful observation and simple examination manoeuvres can provide immediate diagnostic clues, help localise disease, and guide the urgency and direction of further investigation. Their value is greatest when interpreted in the context of a complete history and physical examination rather than as isolated diagnostic tests. At the same time, clinicians should recognise their limitations, including variable sensitivity and specificity, and avoid allowing a negative or positive bedside sign to substitute for appropriate confirmatory investigations. Modern imaging, laboratory testing, electrophysiological studies, echocardiography, and duplex ultrasonography remain essential where indicated. Preserving familiarity with these examination signs therefore represents not a return to outdated medicine, but a reinforcement of a fundamental clinical skill: using the bedside examination to formulate, refine, and appropriately test a diagnostic hypothesis.

Narinder Pal Singh, Vanraj N Padhiyar. Clinical Signs — The Forgotten Art (Part 3): Ten More Bedside Signs Every Clinician Should Master. MMJ. 2026, September. Vol 3 (3).

DOI: <https://doi.org/10.62830/mmj3-03-31>

References

1. Pemberton HS. Signs of retrosternal goitre. *Lancet*. 1946;248(6423):509.
2. Beevor CE. Remarks on paralysis of the movements of the trunk in hemiplegia, and the muscles which are affected. *Br Med J*. 1909;1(2519):881–5.
3. Norton SA. Keratoderma with pseudo-Quincke's pulse. *Cutis*. 1998;62(3):135–6.
4. Maity S, Banerjee I, Sinha R, et al. Nikolsky's sign: A pathognomic boon. *J Family Med Prim Care*. 2020;9(2):526–30.
5. Yale SH, Tekiner H, Yale ES. Revisiting the meaning of Trousseau sign and syndrome. *J Gynecol Oncol*. 2024;35(3):e90.
6. Konin JG, Wiksten DL, Isear JA, et al. Special Tests for Orthopedic Examination: 3rd Edition. Thorofare, NJ: SLACK Incorporated; 2006.
7. Battle WH. Three Lectures on Some Points Relating to Injuries to the Head. *Br Med J*. 1890;2(1542):141–7.
8. Mossman SS, Blau JN. Tinel's sign and the carpal tunnel syndrome. *Br Med J (Clin Res Ed)*. 1987;294(6573):680.
9. Persad-Paisley EM, Lee C, Bhatt RA. Understanding diabetic cheiroarthropathy: a focus on clinical presentation. *J Surg Case Rep*. 2024;2024(3):rjae123.
10. Talley NJ, O'Connor S. Clinical Examination: A Systematic Guide to Physical Diagnosis. 8th Edition. Chatswood: Elsevier; 2017.

Max Institute of Medical Education Announcements

September – 2026

Max Institute of Medical Education (MIME), the educational division of Max Healthcare Institute Ltd., was established to address and strengthen the training needs of medical and non-medical professionals across healthcare organisations. MIME is committed to empowering medical, nursing, and paramedical professionals with the confidence, competence, and practical expertise required to deliver healthcare at the highest standards while ensuring patient safety.

Core Elements of Our Training



Extensive Practical Training



Advanced Simulation Lab



World-Class Faculty



Learning Management System (LMS)



Customised Training Programmes



Online Library – Elsevier ClinicalKey

Delivering Unparalleled Quality in Medical Education

Diplomate of National Board (DNB)

National Board of Examinations (NBE) has recognised Max Healthcare Institute Ltd. for practical training in DNB broad and super speciality courses across more than 40 disciplines in India. Currently, over 607 DNB residents are training across the Max Healthcare hospital network.



Internal Medicine Training – IMT (MRCP-UK)

A 3-year full-time postgraduate programme in Internal Medicine integrating the full MRCP (UK) curriculum. This programme is a collaboration between Max Healthcare and the Joint Royal College of Physicians Training Board (JRCPTB-UK).

The programme delivers internationally benchmarked physician training equivalent to UK standards. Teaching and assessments are conducted by consultants trained through the Royal College of Physicians.

- **Current Enrolment:** 70 residents
- **Training Locations:** Max Super Speciality Hospitals – Delhi & Mumbai



RCOG – MHC Obstetrics & Gynaecology Programme

A joint initiative between Max Healthcare Institute Ltd. and the Royal College of Obstetricians and Gynaecologists (RCOG).

This programme is equivalent to:

- Basic training (ST1-2)
- Intermediate training (ST3-5) in the UK

The curriculum includes:

- RCOG curriculum framework
- Membership of the Royal College of Obstetricians and Gynaecologists (MRCOG) examinations
- RCOG e-Portfolio
- Annual Review of Competence Progression (ARCP) with UK external evaluation
- **Current Enrolment:** 15 residents
- **Training Locations:** Delhi & Lucknow



MEM-GWU International

A 3-year residency programme in Emergency Medicine, conducted by MIME in collaboration with The Ronald Reagan Institute of Emergency Medicine, USA, under George Washington University Medical Center.

The programme equips residents with the knowledge, clinical skills, and compassion required for effective emergency medical care.

- **Current Enrolment:** 90 residents
- **Training Locations:** Pan Max

Fellowship Courses (Non-NBE)

MIME offers advanced fellowship programmes across multiple specialities to enhance physician competency. Programme duration ranges from 6 months to 2 years.

Specialities Offered

- Abdominal & Transplant Imaging
- Aesthetic Medicine & Surgery
- Bariatric Anaesthesia
- Breast Imaging
- Critical Care Medicine
- Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)
- Emergency Medicine
- Dialysis
- Orthopaedic Oncology & Reconstruction
- Foot & Ankle

- Gastroenterology
- General Nephrology
- Gynaecological Onco-Surgery
- Gastrointestinal (GI) Endoscopy
- Head & Neck Surgery
- Hip & Knee
- Pulmonology
- Radiology
- Invitro Fertilisation (IVF)
- Robotic & Renal Transplant
- Neuro Imaging
- Non-invasive Cardiology
- Pain Management
- Rheumatology
- Robotics
- Spine Surgery
- Surgical Oncology
- Transplant Hepatology
- Ultrasound-Guided Regional Anaesthesia (UGRA)
- Uro-Oncology & Robotic Surgery
- Women's Imaging and more

Post-Graduate (PG) Diploma & Master of Science (MSc) Courses

MIME offers full-time postgraduate programmes designed to provide advanced knowledge, industry exposure, and strong career opportunities in healthcare.

Admissions Open: FY 2026 – 2028

Programmes Offered

- PG Diploma & Master of Public Health – Certified by the Academy of Scientific and Innovative Research (AcSIR)
- PG Diploma & Master of Healthcare Quality Management– Certified by AcSIR
- PG Diploma & MSc in Clinical Research – Certified by the Regional Centre for Biotechnology
- PG Diploma in Artificial Intelligence (AI) in Healthcare – In collaboration with Bennett University

Eligibility

Bachelor's degree/Graduation in science

Duration

- PG diploma: 1 Year
- MSc programme: 2 Years

PG Diploma in AI in Healthcare

A pioneering programme launched in collaboration with Bennett University to prepare healthcare professionals for the digital future of medicine.

Programme Highlights

- AI & machine learning
- Deep learning & predictive analytics
- Computer vision & natural language processing (NLP)
- AI-enabled diagnostics
- Clinical decision support systems
- Real-world healthcare applications

The programme combines technical expertise with clinical relevance, preparing professionals for technology-driven healthcare transformation.

PhD Programmes

MIME is affiliated with the AcSIR, an Institution of National Importance established by an Act of Parliament, Government of India.

Research Areas

- Medical research
- Public health
- Biological sciences

NCVET Programmes

In collaboration with the National Council for Vocational Education and Training (NCVET), MIME has launched AI-focused healthcare certificate programmes through the Skill India Digital Hub (SIDH) digital learning platform.

Programmes

- Foundation Course in AI for Digital Health
- Applied AI for Healthcare Systems

These programmes focus on:

- AI in healthcare operations
- Machine learning concepts
- Predictive analytics
- Clinical decision support systems
- Ethical AI & patient privacy
- Digital health workflows

Observerships

Customised observership programmes are available across various clinical departments for Indian and international medical graduates. These programmes focus on practical exposure and skill enhancement under departmental mentorship.

Internships

Hands-on internships are available for durations ranging from 1 to 6 months.

Allied Health

- Physiotherapy
- Dietetics
- Psychology

Support Services

- Biomedical engineering
- Service excellence
- Human resources
- Finance
- Medical records
- Information technology
- Fire & safety
- Healthcare supply chain management

Life Saver Training Programmes

Max Healthcare Institute is an International Training Centre certified by the American Heart Association.

Courses Offered

- Basic Life Support (BLS) – Provider & Instructor
- Advanced Cardiac Life Support (ACLS) – Provider & Instructor
- Paediatric Advanced Life Support (PALS) – Provider & Instructor

Max Hospital, Saket

- 1st Sep: BLS Provider (HeartCode)
- 1st – 2nd Sep: ACLS Provider Course with Video Prework
- 11th Sep: ASLS
- 16th Sep: Heartsaver First Aid CPR & AED Provider
- 20th Sep: BLS Provider (HeartCode)
- 20th – 21st Sep: ACLS Provider Course with Video Prework
- 28th Sep: BLS Provider (HeartCode)
- 28th – 29th Sep: ACLS Provider Course with Video Prework
- 30th Sep: BLS Instructor
- 1st Oct: ACLS Instructor

Max Hospital, Patparganj

- 24th Sep: BLS Provider (HeartCode)
- 24th – 25th Sep: ACLS Provider Course with Video Prework

Max Hospital, Shalimar Bagh

- 8th Sep: BLS Provider (HeartCode)
- 8th – 9th Sep: ACLS Provider Course with Video Prework

Max Hospital, Mohali

- 25th Sep: BLS Provider (HeartCode)
- 25th – 26th Sep: ACLS Provider Course with Video Prework

Bespoke/Short-Term Courses

MIME provides upskilling for physicians and other healthcare professionals through various short-term courses. All our workshops and courses are conducted by experienced and knowledgeable faculty. We have a well-equipped high-fidelity simulation lab with state-of-the-art training manikins to help conduct these courses.

- Mammography Reporting
 - Duration: 8 Weeks
 - Eligibility: Doctor of Medicine (MD)/DNB/Diploma in Radiodiagnosis (DMRD)
- Paediatric Cardiac CT
 - Duration: 8 Weeks
 - Eligibility: MD/DNB/DMRD

- Liver Transplant Donor Evaluation Imaging
 - Duration: 3 days
 - Eligibility: MD/DNB/DMRD
- Musculoskeletal Cross-Section Imaging Programme
 - Duration: 25 Weeks
 - Eligibility: MD/DNB/DMRD
- Infection Control Nurse
 - Duration: 3 Months
 - Eligibility: General Nursing and Midwifery (GNM), Bachelor of Science (BSc) Nursing or MSc Nursing professionals with clinical experience
- Certificate Course in Applied Cardiac Nursing
 - Duration: 3 Months
 - Eligibility: GNM, BSc Nursing or MSc Nursing professionals with clinical experience
- Aditya Birla Nursing Training
 - Duration: 3 Months
 - Eligibility: GNM, BSc Nursing or MSc Nursing professionals with clinical experience
- Masterclass on Musculoskeletal Imaging
 - Duration: 2 days
 - Eligibility: Open to all Radiologists, and Radiology residents interested in musculoskeletal imaging

FMG Clinical Skills Courses

Designed for Foreign Medical Graduates (FMGs), these programmes strengthen clinical competencies and prepare candidates for Foreign Medical Graduate Examination (FMGE)/National Exit Test (NExT) examinations through practical exposure and hands-on training.

Duration

- Basic Programme – 15 Days
- Advanced Programme – 20 Days

MIME Online Courses

Self-paced hybrid online courses designed for doctors, nurses, and paramedical professionals.

Online Fellowship Courses

- Diabetes Management
- Infectious Disease
- Emergency Medicine
- Critical Care
- Clinical Cardiology
- Obstetrics & Gynaecology
- Bariatric Anaesthesia
- Management of Liver Disorders

New Launches – June 2026

- Family Medicine
- Paediatrics
- Geriatric Medicine

Online Certificate Courses

- Aesthetic Medicine & Surgery
- Healthcare Quality Management
- Public Health
- Clinical Research
- Bariatric Nutrition
- Acute Liver Failure (ALF)
- Geriatric Care
- Difficult Airway Management

Key Highlights

MIME, in partnership with Learna (Diploma MSc) and validated by the University of Buckingham, offers globally aligned healthcare education.

Programme Highlights

- Comprehensive training in sepsis, trauma, respiratory support, and critical care ethics
- Case-based learning with observership opportunities at Max Healthcare
- Mentorship by Dr. Rajesh Pande and Dr. Nick Stallard
- Flexible hybrid learning model for working professionals

For more information, contact us:

Max Institute of Medical Education (MIME)

Max Healthcare Institute Ltd, Press Enclave Road, Saket, New Delhi-110 017

Call: +91 8826 600 461, 9999 853 797

E-mail: education@maxhealthcare.com / jay.prakashpandey@maxhealthcare.com

Website: www.maxhealthcare.in



Scan for more details

Office of Research

Research in Numbers

25

Grant Studies Underway

115

Ongoing Clinical Trials

23

National & International
Research Partnerships

123+

Scientific Publications in
High-Impact Journals

Drug and Device Trials

Max Healthcare continues to strengthen its position as a leading research-driven healthcare institution with over 115 ongoing clinical trials and 25 grant studies across multiple specialities. This quarter also marked the successful completion of the pioneering first-ever human trial in robotic surgery, with the Clinical Study Report submitted to the Central Drugs Standard Control Organisation (CDSCO).

Further expanding its research footprint, Max Hospital, Lucknow, initiated its first cardiology clinical trial, led by Dr. Nakul Sinha. At Max Hospital, Vaishali, India's first Hepatitis E vaccine trial, led by Dr. P. Kar, further underscored Max Healthcare's commitment to advancing innovative research and contributing to landmark clinical developments in India.

Publications

During Q1 FY27, Max Healthcare researchers contributed more than 123 scientific publications in high-index and high-impact-factor journals across specialities, including Nephrology (The Lancet Infectious Diseases: 5.55), Gastroenterology (Alimentary Pharmacology and Therapeutics: 3.01), and Endocrinology (Age and Ageing: 2.15).

Grants and Collaborations

Max Healthcare expanded its global research network through collaborations with Columbia University, USA, adding to the 23 partnerships with national and global academic and industry partners including Imperial College London, Monash University, National Centre for Biological Sciences (NCBS), Tata Institute for Genetics and Society (TIGS), Deakin University, Indian Institute of Technology (IIT) Bombay, IIT Delhi, Birla Institute of Technology and Science (BITS) Pilani, Ashoka University, Boston University, Rajiv Gandhi Centre for Biotechnology (RGCB), Indraprastha Institute of Information Technology (IIIT) Delhi, Pfizer Inc, and Mazumdar Shaw Medical Foundation (MSMF).

Dr. Bharat Aggarwal and Aniket Aman, along with Prof. Kshitij Jadhav (IIT Bombay), received the India AI & National Cancer Grid (NCG) Cancer AI & Technology Challenges (CATCH) grant for AI-driven healthcare innovation. Dr. Ambrish Mithal, in collaboration with Ashoka University, was awarded the Centre for Advanced Research (CAR) grant for the Centre for Precision Metabolic Health (CPMH) focused on digital twin-enabled precision diabetes care. Dr. Bharat Aggarwal also received support from the Wadhwani Foundation for translational healthcare innovation.

Recent Events

Max Research Conclave

The Office of Research, Max Healthcare, hosted the Annual Research Symposium 2026 on 6th August 2026 at Max Super Speciality Hospital, Saket, Delhi, bringing together clinical researchers, academic leaders and healthcare experts under the theme "Connecting Minds • Advancing Research • Transforming Lives." The symposium featured scientific sessions spanning cardiometabolic and kidney health, precision oncology, translational research in hepatology and gastroenterology, infectious diseases and antimicrobial resistance, AI and clinical innovation, and research translation, alongside an awards and recognition session celebrating excellence in research and innovation. The event provided a platform for knowledge exchange, interdisciplinary collaboration and discussion on advancing impactful research from discovery to clinical translation.



New Efforts in Research

This quarter marked important milestones in translational research, including two patent applications in radiomics filed with IIT Bombay and the completion of the first-ever human trial in robotic surgery.

Scope of the Journal

The Max Medical Journal is dedicated to publishing high-quality scientific, clinical, and translational research that contributes to the advancement of healthcare and patient outcomes. The journal provides a platform for clinicians, researchers, academicians, and healthcare professionals to share evidence-based knowledge, innovative practices, and emerging developments across all disciplines of medicine and allied health sciences.

The journal welcomes manuscripts covering clinical, diagnostic, therapeutic, preventive, ethical, and public health aspects of medicine. Submissions involving original investigations, multidisciplinary research, healthcare innovation, and quality improvement initiatives will be considered for publication.

The Max Medical Journal aims to promote the timely dissemination of clinically relevant information that directly enhances patient care, medical education, and healthcare delivery. The journal encourages contributions from both established and emerging researchers worldwide.

The journal publishes original and impactful work in the field of General Medicine and all major medical and surgical specialties.

Article types

- Original Articles
- Review Articles
- Case Studies
- The Images
- Students' Corner

Vision

To become a leading platform for the dissemination of evidence-based medical knowledge and advancement of excellence in patient-centred healthcare.

Mission

- To promote high-quality clinical and scientific research.
- To encourage interdisciplinary academic collaboration.
- To support ethical and evidence-based medical practice.
- To publish clinically relevant research that improves patient outcomes.
- To foster innovation, education, and continuous advancement in healthcare.

Author Guidelines

Articles submitted to The Max Medical Journal must adhere to the author guidelines mentioned below:

Writing and formatting

The manuscript should be written in clear English using UK spelling and arranged in the following order: Title, Abstract and Keywords, Introduction, Main Heading(s), Discussion, Conclusion, Declarations, and References.

Copyright statement

A copyright statement signed by all the authors must be submitted.

Title

The title should be concise, informative, and specific to the topic of the article. Abbreviations should be avoided in the title.

Author names and affiliations

Provide the first name or initials (if used), middle name or initials (if used), and surname for all authors. Affiliation details should include department, institution/university/organisation, city, state, and country. One author should be designated as the corresponding author with an asterisk (*) against his/her name. Only the corresponding author's email address should be provided.

Abstract and keywords

The abstract should be unstructured, written as a single paragraph, and should not exceed 300 words. Authors should provide 4–6 keywords below the abstract.

Abbreviations

All abbreviations used in the manuscript should be expanded upon first use (acronym in parentheses) in the abstract and text separately, unless they represent standard units of measurement.

Figures and tables

All figures and tables must be cited in the text. Authors should indicate where they should be inserted within the text. Figure legends and table titles should be concise and included in the manuscript file. Footnotes may be used to explain abbreviations. For figures with sub-parts, each part should be clearly labelled using uppercase letters followed by a period (e.g., A., B., C.), along with a brief description for each part.

Example

Figure 1: Renal biopsy: **A.** PAS stain (20×); **B.** Silver stain (20×); **C.** Silver stain (40×).

Word limit

Manuscripts should preferably remain within the following word limits:

- Case Studies – 1500 words
- The Images and Students' Corner submissions – 2000 words
- Original and Review Articles – 3000 words

The word count excludes abstract, references, tables, and figure legends.

References

References should be cited in the text using superscript Arabic numerals in the order of appearance. A complete reference list should be provided at the end of the manuscript and should follow the Vancouver style. Only published or accepted manuscripts should be included in the reference list. Meetings, abstracts, conference presentations, and manuscripts submitted but not yet accepted for publication should not be cited as references.

Example:

Rajput R, Yadav Y, Nanda S, *et al.* Prevalence of gestational diabetes mellitus & associated risk factors at a tertiary care hospital in Haryana. *Indian J Med Res.* 2013;137(4):728–33.

Declarations

Acknowledgements, conflict of interest, funding details, ethical approval, informed consent, and author contributions should be included under a separate "Declarations" section before references, wherever applicable.

Covering Letter

A covering letter signed by all authors must accompany the submission, confirming that the manuscript has not been published previously, is not under consideration elsewhere, and has been approved by all authors for submission.

All the articles to be sent to this email ID:
mmjeditorialboard@maxhealthcare.com

About Max Healthcare

Max Healthcare Institute Limited (Max Healthcare) is one of the largest integrated healthcare providers in the country. We own, operate and provide medical services to facilities in Delhi NCR, Mumbai, Punjab, Uttar Pradesh, Uttarakhand, and Odisha. Max Lab supplements our commitment towards patient care by providing accurate testing and diagnostics. We are also revolutionising the care-continuum through Max@Home, ensuring treatment options are available to our patients in the comfort of their homes. Our continued emphasis on patient-centric care accompanied by our patients' trust has strengthened our position to become one of India's top private healthcare providers.

FACILITIES - **21**

BED CAPACITY - **6,100+**

CLINICIANS - **6,200+**

EMPLOYEES - **42,000+**

4 JCI accredited hospitals

1 AACI accredited hospital

19 NABH accredited hospitals

15 NABL accredited labs

750 ongoing clinical research projects

3,400+ high index journal research publications till date

1.62 Lakh+ students enrolled in various courses every year

OUR FACILITIES

SOUTH DELHI

Max Super Speciality Hospital (East Block), Saket

(A Unit of Devki Devi Foundation)
2, Press Enclave Road, Saket,
New Delhi - 110 017
Phone: +91-11-2651 5050

Max Super Speciality Hospital (West Block), Saket

1, Press Enclave Road, Saket,
New Delhi - 110 017
Phone: +91-11-6611 5050

Max Smart Super Speciality Hospital, Saket

(A Unit of Gujarmal Modi Hospital and Research Centre for Medical Sciences)
Mandir Marg, Press Enclave Road, Saket,
New Delhi - 110 017
Phone: +91-11-7121 2121

Max Multi Speciality Centre, Panchsheel Park

N - 110, Panchsheel Park,
New Delhi - 110 017
Phone: +91-11-4609 7200

Max MedCentre, Lajpat Nagar

First Floor, Plot No. 7, Ring Road, Lajpat Nagar-4, New Delhi - 110 024
Phone: +91-11-4720 3030

CENTRAL DELHI

BLK-Max Super Speciality Hospital

Pusa Road, Rajendra Place,
New Delhi - 110 005
Phone: +91-11-3040 3040

EAST DELHI

Max Super Speciality Hospital, Patparganj

(A Unit of Balaji Medical and Diagnostic Research Centre)
108 A, Indraprastha Extension, Patparganj,
New Delhi - 110 092
Phone: +91-11-4303 3333

NORTH WEST DELHI

Max Super Speciality Hospital, Shalimar Bagh

FC - 50, C & D Block, Shalimar Bagh,
New Delhi - 110 088
Phone: +91-11-6642 2222, 7194 1000

SOUTH WEST DELHI

Max Super Speciality Hospital, Dwarka

(A Unit of Muthoot Hospitals Pvt. Ltd.)
Plot No. 1, Sector 10, Dwarka,
New Delhi - 110 075
Phone: +91-11-3511 3511

NCR

Max Super Speciality Hospital, Vaishali

(A Unit of Crosslay Remedies Ltd.)
W-3, Sector - 1, Vaishali,
Ghaziabad - 201 012, (U.P.)
Phone: +91-120-4173 000, 4188 000

Max Hospital, Gurugram

(A Unit of ALPS Hospital Ltd.)
Opposite HUDA City Centre Metro Station,
B - Block, Sushant Lok - I,
Gurgaon - 122 001
Phone: +91-124-6623 000

Max Super Speciality Hospital, Noida

(A Unit of Crosslay Remedies Ltd.)
Wish Town, Sector-128, Noida - 201 303
Phone: +91-120-4122 222

Max Multi Speciality Centre, Noida

(A Unit of Crosslay Remedies Ltd.)
A-364, Sector - 19, Noida - 201 301
Phone: +91-120-662 9999

MAHARASHTRA

Nanavati Max Super Speciality Hospital, Mumbai

S.V. Road, Vile Parle (West),
Mumbai - 400 056
Phone: +91-22-6836 0000

Max Super Speciality Hospital, Nagpur

(A Unit of Alexis Multispeciality Hospital Pvt. Ltd.)
Survey No. 232, House No. 1313,
Mankapur Square, Koradi Road,
Nagpur - 440030, Maharashtra
Phone: +91-712-7120 000

ODISHA

Max Super Speciality Hospital, Bhubaneswar

(A Unit of Kalinga Hospital Limited)
Chandrasekharapur, Bhubaneswar,
Khurda, Odisha - 751 023,
Phone: +91-674 6665 200

PUNJAB

Max Super Speciality Hospital, Mohali

(A Unit of Hometrail Buildtech Pvt. Ltd.)
Near Civil Hospital, Phase - 6, Mohali,
Punjab - 160 055
Phone: +91-172-521 2000

Max MedCentre, Mohali

Plot No - A-19, Industrial Area Phase VI,
S.A.S Nagar, Mohali - 160 055
Phone: +91-172 521 2000

Max Super Speciality Hospital, Bathinda

(A Unit of Hometrail Buildtech Pvt. Ltd.)
NH - 64, Near District Civil Hospital, Mansa Road, Bathinda,
Punjab - 151 001
Phone: +91-164-521 2000

UTTARAKHAND

Max Super Speciality Hospital, Dehradun

Near Indian Oil Petrol Pump, Malsi,
Mussoorie Diversion Road,
Dehradun - 248 001
Phone: +91-135-7193 000

UTTAR PRADESH

Max Super Speciality Hospital, Lucknow

(A Unit of Starlit Medical Centre Pvt. Ltd.)
Viraj Khand, Gomti Nagar,
Lucknow - 226 010, U.P.
Phone: +91-522-6780 001, 6780 002



MAX HEALTHCARE INSTITUTE LIMITED

CIN: L72200MH2001PLC322854

Registered Office:

401, 4th Floor, Man Excellenza,
S. V. Road, Vile Parle (West), Mumbai City, Maharashtra - 400 056

Corporate Office:

2nd Floor, Capital Cyberscape,
Sector-59, Gurugram - 122 011, Haryana

For more information, write to us: mmjeditorialboard@maxhealthcare.com

or visit www.maxhealthcare.in

Submit your articles for the December 2026 edition by 31st October 2026.
Email us at mmjeditorialboard@maxhealthcare.com