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Patient as a living book-A master piece of knowledge

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Article

Neutrophil Lymphocyte ratio and red cell distribution width as prognostic marker for severity in acute pancreatitis–An Observational study

Editor-in-Chief: **Prof. Dr. Nandini Chatterjee**

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Second and third trimesters of pregnancy. Biliary obstructive disorders. Severe hepatic impairment. The concomitant use of Telmisartan with aliskiren containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m2). **Warnings And Precautions - Fetal Toxicity** Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible. **Hypotension** In patients with an activated renin-angiotensin system, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose. If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized. **Hyperkalemia** may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be considered particularly in patients at risk. **Impaired Hepatic Function** As the majority of Telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan should be initiated at low doses and titrated slowly in these patients. Impaired Renal Function as a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function should be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Dual Blockade of the Renin-Angiotensin-Aldosterone System**: Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, combined use of drugs from different classes of RAS inhibitors should be avoided. Blood pressure, renal function and electrolytes in patients on Telmisartan and other agents that affect the RAS should be closely monitored. Aliskiren must not be co-administered with Telmisartan in patients with diabetes. Concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR <60 mL/min/1.73 m²) must be avoided. **Nonclinical Toxicology:** Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when Telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m² basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Telmisartan. These same doses have been shown to provide average systemic exposures to Telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day). Genotoxicity assays did not reveal any Telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test. No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m² basis, the MRHD of Telmisartan. This dose in the rat resulted in an average systemic exposure (Telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day). **Use In Specific Populations: Nursing Mothers:** It is not known whether Telmisartan is excreted in human milk, but Telmisartan was shown to be present in the milk of lactating rats. **Pediatric Use:** Safety and effectiveness of Telmisartan in pediatrics has not been established. Thus, the drug is not recommended in pediatrics. **Geriatric Use:** No dose adjustment is needed in elderly patients

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Composition: Each film coated tablet contains:BisoprololFumarate IP2.5mg/5mgTelmisartan Ip40mg **Indications:** The fixed dose combination of Bisoprololfumarate and Telmisartan tablets is indicated for the treatment of stage 1 and stage 2 hypertension. **Dosage & Administration:** The recommended dose of the fixed dose combination of Bisoprolol and Telmisartan tablets is one tablet once a day or as directed by the Physician. **Mechanism of action:** Bisoprolol-Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and relevant membrane stabilising activity.Telmisartan is an orally active and specific angiotensin II receptor (type AT1) blocker. **Contraindication:** The fixed dose combination of Bisoprololfumarate and Telmisartan tablets is contraindicated in hypersensitivity to Bisoprolol and Telmisartan or to any of the excipients in the formulation. **Bisoprolol:** cardiogenic shock,AV block of second or third degree, symptomatic bradycardia and hypotension. **Telmisartan:** Second and third trimesters of pregnancy, Biliary obstructive disorders, severe hepatic impairment, The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2) **Warning & Precautions:** Bisoprolol-Especially in patients with ischaemic heart disease the cessation of therapy with Bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition. There is a risk of myocardial infarction and sudden death if the treatment is suddenly discontinued in patients with coronary heart disease.Bisoprolol must be used with caution in bronchospasm, diabetes mellitus, AV block of first degree, Prinzmetal's angina, Peripheral arterial occlusive disease. **Telmisartan** is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since Telmisartan is mostly eliminated with the bile.Volume- and/or sodium-depleted patients: Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. **Drug Interactions:** Bisoprolol-Combination not recommended-Verapamiil, Diltiazem, Methyldopa,Lidocaine. Combinations to be used with caution- Amlodipine,Amiodarone Digitalis, NSAIDs. **Telmisartan**-When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. Concomitant use requiring caution- NSAIDs, Diuretics, ACEi, ARBs, Aliskiren. **Special Populations: Pregnancy:** Bisoprolol is not recommended during pregnancy unless clearly necessary and breast-feeding.**Telmisartan**-Angiotensin II receptor blockers should not be initiated during pregnancy. Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blockers should be stopped immediately, and, if appropriate, alternative therapy should be started. Telmisartan is not recommended inbreast-feeding. **Hepatic or Renal impairment:Bisoprolol -** In patients with liver or kidney function disorders of mild to moderate severity, no dosage adjustment isnormally required. In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe liver function disorders it is recommended that a daily dose of 10 mg is not exceeded. **Telmisartan**-Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels isrecommended. **Adverse Reactions:Bisoprolol-** Most common adverse reactions includeheadache and dizziness. **Telmisartan**-sinus pain, stuffy nose, back pain. **Overdose:Bisoprolol:** With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, if overdose occurs, Bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided.Bradycardia: Administer intravenous atropine. Hypotension: Intravenous fluids and vasopressors should be administered. **Telmisartan:** The most prominent manifestations of Telmisartan overdose were hypotension and tachycardia; bradycardia dizziness, increase in serum creatinine, and acute renal failure have also been reported.The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdosage.

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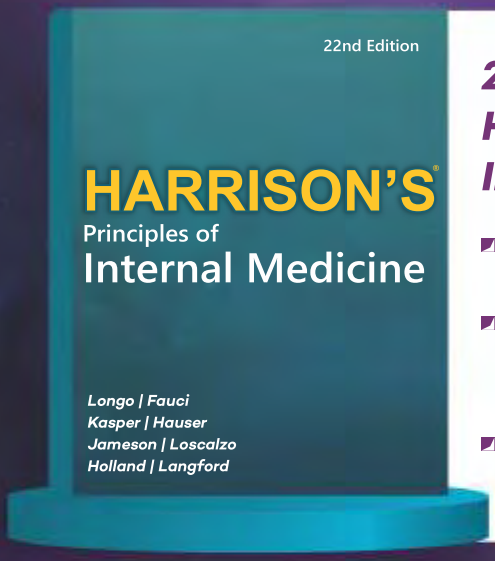

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Contents

Reference: 1. Ozempic® CDSCO approved package insert version dated 23 Oct 2025.

Abbreviated prescribing information (and not full package insert)
Generic Name: Semaglutide Injection 0.25 mg (r-DNA Origin), solution for injection in pre-filled pen, Semaglutide Injection 0.5 mg (r-DNA Origin), solution for injection in pre-filled pen, Semaglutide Injection 1 mg (r-DNA Origin), solution for injection in pre-filled pen **Brand Name:** Ozempic®. **Presentation:** Ozempic® is available in 0.25 mg, 0.5 mg and 1 mg. **Indication:** Semaglutide injection is indicated as; an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. To reduce the risk of sustained eGFR decline, end-stage kidney disease and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease. **Description:** Ozempic® is a clear and colorless or almost colorless solution for injection in a pre-filled pen. **Posology:** The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks, the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. **Method of administration:** Subcutaneous use. Ozempic® is administered once weekly at any time of the day, with or without meals. It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly. If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (>72 hours). Patients should be advised to read the instructions for use included in the package leaflet carefully before administering Ozempic®. **Special Population:** No dose adjustment is required based on age. No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited. No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. The safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients, with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration which could cause a deterioration of renal function. Increased risk of residual gastric content due to delayed gastric emptying should be considered prior to performing procedures with general anaesthesia or deep sedation. Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide. In patients with diabetic retinopathy treated with insulin and semaglutide, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin. **Use in special populations (Fertility, pregnancy and lactation):** Women of child-bearing potential are recommended to use contraception when treated with semaglutide. There are limited data regarding the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life. Semaglutide should not be used during breastfeeding. The effect of semaglutide on fertility in humans is unknown. **Drug Interaction:** Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. Paracetamol: Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardized meal test. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide. Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Atorvastatin: Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Digoxin: Semaglutide did not change the overall exposure or Cmax of digoxin following a single dose of digoxin (0.5 mg). Metformin: Semaglutide did not change the overall exposure or Cmax of metformin following dosing of 500 mg twice daily over 3.5 days. Warfarin: Semaglutide did not change the overall exposure or Cmax of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalized ratio (INR) were not affected in a clinically relevant manner. **Effects on ability to drive and use machines:** Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable effects:** In 8 phase 3a trials, 4792 patients were exposed to semaglutide up to 1 mg. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common). In general, these reactions were mild or moderate in severity and of short duration. **Overdose:** Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications. There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. **Shelf-life:** Before first use: 36 months. After first opening: 6 weeks. Store below 30 °C or in a refrigerator (2 °C–8 °C). **Storage:** Store in a refrigerator (2 °C–8 °C). Keep away from the cooling element. Do not freeze. Keep the pen cap on in order to protect from light.
Disclaimer: The abbreviated package insert is updated from the CDSCO approved package insert File No. BIO/IMP/25000051 dated 19 Sep 2025 and subsequent approval vide File No. I-DNA-1101113/2025-edffice dated 23 Oct 2025).

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Note: For detailed information on this product, please refer to full package insert*.

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EDITORIAL

Patient as a Living Book: A Masterpiece of Knowledge

Prasan Kumar Panda*

A patient comes to a doctor and presents live facts of medical science. As time passes, the doctor opens all the pages of the patient's life facts and reads them out to him/her, along with oneself. During this interaction, many queries come to the doctor's mind and are solved spontaneously based on prior knowledge from an external article or the internet (hereafter termed the 'book' for understanding purposes), or remain unanswered until a future patient solves them. In this conjecture, a real question comes: which is a masterpiece of knowledge, a patient, or a book?

A book is a medium for recording information in written or visual form. The first book ever written that we know of is "The Epic of Gilgamesh: A Mythical Retelling of an Important Political Figure" from history in the 20th century BC.[1] Since then, books have been the primary source, not only providing information from one person to many others but also passing knowledge from generation to generation. There is a saying in the old world that "A Book is a Gift you can open again and again." This signifies the value of the knowledge and information in the books that have been acknowledged by our ancestors. In the modern world, though, the emergence of the internet or even artificial intelligence (AI) may have partially replaced the requirement of books, but because of the authenticity and reliability of the information, including research, many publishers and authors back books as the primary source of knowledge.

In clinical medicine, we often rely on textbooks, evidence-based guidelines, and increasingly, AI tools such as ChatGPT and clinical decision support systems (CDSS).[2] Yet, every time a patient walks into the OPD/Clinic/Emergency, they carry within them a living story, one that reflects not just disease, but also the dynamic interplay of biology, emotion, experience, and context. If a textbook is a record of what was known, the patient is a revelation of what is real. In the spirit of the Bhagavad Gita, which teaches that knowledge must transcend into wisdom through the recognition of truth in the present, we offer this reflection: the patient is not a case to be solved but a masterpiece to be read, lived, and learned from.[3]

The Textbook is the Past; the Patient is the Present

Books are artifacts of frozen knowledge, records of yesterday's findings, summarized for today's learner. They offer guidelines, pathophysiology, treatment algorithms, etc: all essential, yet inherently retrospective. A patient, in contrast, is a live chapter, constantly being written in the present. No matter how up-to-date a book is, it cannot replicate the lived immediacy of a patient's evolving physiology and subjective experience. What a textbook outline in controlled, statistical terms, a patient manifests in complex, sometimes paradoxical ways. The book may tell us how a disease typically presents; the patient tells us how it actually unfolds, now, in this unique body, with this unique mind.

The Patient is a Questioning Teacher

A book answers what is already known. A patient asks what has yet to be understood. Unlike ChatGPT or CDSS models that respond based on past patterns and evidence hierarchies, a patient poses unanticipated, real-time questions that challenge those very patterns. Their queries are not limited to symptoms or signs but often extend into the moral, emotional, and existential domains: "Why me?" "Will I be the same again?" "What's the point of treatment?" These are questions that no AI or evidence table can fully address. They demand compassionate reasoning, a capacity for presence and perception that transforms the physician from a passive recipient of knowledge into an active participant in discovery.

Beyond Organs and Fragmentation: The Integral Precision

Medical knowledge has long been compartmentalized by systems: cardiovascular, respiratory, neurological, gastrointestinal, musculoskeletal, genitourinary, or others, but the patient defies this fragmentation. They are an integrated whole, often presenting with overlapping symptoms and multiple comorbidities. The core concept of "Patient: A Master Book" is an individualization of our approach to a disease process. The Human Genome Project has identified that the human genome is approximately 3.1 billion base pairs and that, by 2004, 22,300 protein-coding genes had been identified.[4] Every individual differs from others in the DNA they carry. This brings out the question: "Will a disease process be similar in each and every person?" The straightforward answer will be 'no'. A book will provide you with the most commonly found data about a particular disease. While each patient might belong to a different category of human beings, the differences are made by different genetic, environmental, and lifestyle factors. Hence, a patient as book will individualize every step of the disease process and give you a broad idea of the disease itself. This individualization of disease approach is going to help us in the future if we are targeting elimination and eradication of diseases, for example, in malaria and tuberculosis patients, most of the research which are done in the developed part of the world concentrates on the microorganism rather than on the patient, leading to difficulty in control of such disease processes. The latest example is SARS-CoV-2 infection, in which, despite knowing the virus's basic molecular nature, we had difficulty controlling its spread because of unknown individual components that help it transmit and cause disease.[5] In this sense, the patient becomes a teacher of integral precision medicine, showing that true understanding lies not in isolating organ dysfunction but in synthesizing biological, psychological, and social data into one coherent whole. This is true individualized medicine, taught not by genomics alone, but by the patient standing before us.

From Transient Knowledge to Eternal Truth

The Gita differentiates between knowledge that is temporal and wisdom that is eternal.[3] Books carry knowledge prone to biases: selection bias, publication bias, and cultural bias. They are shaped by consensus, not

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always by truth. The patient, however, represents unbiased, living evidence. What we see in a patient such as the texture of their skin, the rhythm of their breathing, the hesitation in their words, etc, is truth in its purest form. We are not interpreting data; we are witnessing reality. There is no scope for intellectual speculation; the patient demands discernment rooted in compassion. In that sacred presence, transient knowledge transforms into clinical wisdom, a knowing that is not just intellectual but deeply human.

The Physician's Sacred Book

In many traditions, the doctor is revered as a healer, even likened to a God, not for omniscience, but for the power to save lives. This reverence is not unidirectional. The patient, in turn, offers something sacred: their vulnerability, their truth, their trust. They reveal to us every chapter of their being, willingly or not, so that we may learn, heal, and evolve. Each patient becomes a sacred book, by handing over in hope, by opening with courage, and by ending with gratitude. This exchange is not transactional; it is sacred. The physician reads not only symptoms but suffering, not only pathology but poetry, making each encounter a profound act of mutual grace.

The Experiment for a Healthier Future

Every patient is also part of a collective scientific experiment, not in an exploitative sense, but as a willing participant in the betterment of future care. Clinical trials, public health strategies, vaccine studies, all depend on the lived truth of patients. It was not molecular biology alone but the observations of COVID-19 patients, their cytokine responses, their long-term effects, their social vulnerabilities, that shaped global health responses.[6] Patients teach us how diseases evolve, how they impact societies, and how our systems must adapt. They are the foundation of every future breakthrough: the live data, the voice of reality, the conscience of science.

Conclusion: The Unified Masterpiece

To truly learn medicine is not to memorize syndromes, but to recognize that every patient is a symphony of biology, story, and spirit. Each of the six reflections above: live presence, questioning mind, integrated body, eternal truth, sacred exchange, and future-oriented gift, represents a unique chapter in the grand book of humanity. When we learn from patients, we do not just become better doctors; we become better human beings. Let us honor the patient as the living masterpiece of knowledge, from whom the journey from transient knowing to eternal wisdom begins.

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Conflict of Interest

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Use, Misuse, and Rational Use of Proton Pump Inhibitors

Ramesh Satarkar*

Ever since their introduction in 1989, proton pump inhibitors (PPIs) have gained a significant place in prescriptions across all specialties. The market size of PPIs is estimated to be 3.45 billion USD and is expected to grow at a 5.50% compound annual growth rate (CAGR) to become 5.89 billion USD by 2034.[1] The rise in use is partly because of increased prevalence and awareness of diseases like gastroesophageal reflux disease (GERD), but also because of the overuse of these medicines for "slippery" indications. Of late, there has been a lot of awareness about overuse of PPIs, and many gastroenterological societies have issued guidelines toward their rational use.[2–5]

Indications for Use of Proton Pump Inhibitors

Short-term PPI use indications (up to 8 weeks):

- *Helicobacter pylori* eradication.
- First episode of dyspeptic symptoms in young patients, without warning symptoms like weight loss and gastrointestinal bleeding.
- Empiric therapy of uncomplicated GERD, diagnosed clinically in young patients.
- Low-grade esophagitis, LA grade A or B on endoscopy.

Long-term PPI use indications (>8 weeks):

- High-grade esophagitis, LA grade C or D.
- Barrett's esophagus.
- Zollinger–Ellison syndrome.
- Eosinophilic esophagitis.
- Patients on aspirin for cardiac prophylaxis, or using nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, who have a prior history of ulcer bleeding.
- Coadministration with pancreatic enzymes in chronic pancreatitis.
- Symptomatic GERD with failed attempts to reduce PPI dose.

Patterns of Misuse/Overuse

The most common being exceeding the duration of PPI use. Often, the prescription of a specialist doctor containing PPI is continued by family physicians or general practitioners. Availability of these medicines over-the-counter (OTC) makes it easy for patients to perpetuate their use.

Secondly, often they are used for incorrect indications. PPIs are used as a coprescription with antibiotics, NSAIDs, corticosteroids, and aspirin for cardioprophylaxis. They cannot be expected to reduce drug-induced nausea and vomiting, and using preemptively in all for ulcer prophylaxis has little justification, especially in young and low-risk patients.

Often, PPIs are used incorrectly for extraesophageal symptoms such as hoarseness of voice, globus sensation, asthma, etc., assumed to be due to reflux. Many of these patients do not have any esophageal symptoms and have normal pH-metry.

Reasons for Overuse

It is assumed that acid is responsible for all upper gastrointestinal symptoms. However, upper gastrointestinal symptoms can be due to excess acid, acid at the wrong place, disturbances of motility, and visceral hypersensitivity. Many patients having typical reflux symptoms have normal 24-hour pH-metry, the gold standard test for acid reflux.[6] They have "functional heartburn," due to visceral hypersensitivity, a disorder of the gut–brain axis. The term acidity is used so loosely that it can have umpteen meanings depending on patients' perspectives. Many patients who have migraine or even coronary artery disease describe their symptoms as "acidity." They take PPIs not only without any benefit, but also at risk of missing an important life-threatening disease.

Sometimes, PPIs are used when there is limited access or willingness to do investigations in cases of GERD or nonulcer dyspepsia (NUD). Patients often choose cheaper solutions over costly investigations. This is acceptable in a few situations, such as the first episode of symptoms, no warning symptoms, an obvious precipitating event, and a young patient. However, when the patient is not responding or has warning symptoms, investigations at the first go itself are the choice. Reluctance on the part of patients to modify behavior, for example, weight reduction or cessation of smoking to reduce reflux-like symptoms, is another hindrance. They prefer a simple pill of PPI over the difficult task of behavior modification. Physicians also need to consider alternative therapies such as H_2 receptor antagonists, sucralfate, or alginates for control of symptoms. In select patients, advising Nissen's fundoplication for those with a large hiatus hernia or bariatric surgery for morbid obesity and reflux is appropriate over long-term use of PPIs, especially when the patient is young. Patients, as well as physicians, have concerns about rebound symptoms after discontinuation of long-term PPI use. The rebound is due to hypergastrinemia, which occurs after long-term use of PPIs. Rebound symptoms are often transient and can be easily controlled.

Adverse Events of Long-term Proton Pump Inhibitor Use

The PPIs are safe when used appropriately. Long-term acid suppression adversely affects the physiological functions of gastric acid. Macrocytic or microcytic anemia, increased risk of bone fractures, small intestinal bacterial overgrowth, and increased risk of enteric infections are adverse events related to long-term acid suppression. Interstitial nephritis, drug interactions, especially reduced efficacy of clopidogrel, diarrhea, and vomiting are adverse events unrelated to acid suppression. Certain conditions, like dementia, increased risk of gastrinoma, and hypomagnesemia have very weak causal associations.[7]

Rational Use of Proton Pump Inhibitors

- The diagnosis for which PPI is being used should be clear, viz., reflux esophagitis, NUD, or duodenal ulcer. This can be a clinical judgment or based on investigations.
- There must be a definite plan about the duration of use and methods to stop PPI. Once decided, the plan must be conveyed to the patient clearly, and he must be informed about possible adverse events in long-term use.

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- If the patient is not responding at the end of the prescribed course, an alternative diagnosis needs to be considered, and appropriate investigations should be carried out.
- Short-term use of PPI can be stopped abruptly. Patients on long-term PPI can be taken off the medicine by various strategies, like alternate-day PPI or half-dose PPI for some period and then stopping it, or changing over to on-demand therapy, or replacement with H2RA blockers, alginates, or sucralfate for some period to control rebound symptoms.
- For patients on long-term PPI use for an appropriate indication, one must be watchful for adverse events.

Any medicine, when used appropriately, is a friend; otherwise, it can become a foe. We must increase awareness among medical practitioners as well as patients about the rational use of PPIs. This will help all to "choose wisely."

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ORIGINAL ARTICLE

Retrospective Observational Study for Assessment of Prevalence of Hypoglycemic Episode by Continuous Glucose Monitoring in Patients of Type 2 Diabetes Mellitus

Saurabh Vivek Padole[1*], Jitendra Ingole[2]

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and β-cell dysfunction, leading to chronic hyperglycemia and complications. Despite therapeutic advances, hypoglycemia remains a major challenge, especially in patients on insulin or secretagogues. Continuous glucose monitoring (CGM) provides comprehensive data on glucose variability, time-in-range (TIR), and time-below-range (TBR), offering superior insights compared to traditional monitoring. This study aimed to assess the prevalence and characteristics of hypoglycemia in T2DM using CGM.

Materials and methods: A retrospective observational study was conducted at a tertiary care center in India between April 2023 and October 2024. A minimum sample size of 46 was estimated, and 50 patients were included. Inclusion criteria: Adults >18 years with T2DM, HbA1c >8%, undergoing CGM, and consenting. Exclusion criteria: HbA1c <8%, nondiabetic steroid users, critically ill patients, or those unwilling to participate. CGM was used to detect hypoglycemia (<70 mg/dL). Episodes were classified as symptomatic or asymptomatic. Associations with different antidiabetic drugs and combinations were evaluated statistically.

Results: Demographics: mean age was 64.2 ± 7.9 years; 42% were aged 61–70 years. Mean body mass index (BMI) was 24.9 ± 3.0 kg/m^2, with 46% overweight. Hypoglycemia prevalence: 80% (40/50) experienced hypoglycemia; of these, 60% were asymptomatic and 40% symptomatic. Drug associations: metformin: not significantly associated ($p = 0.29$). Dipeptidyl peptidase-4 (DPP-4) inhibitors: significantly associated with hypoglycemia ($p = 0.003$). Sulphonylureas: trend toward increased risk, not statistically significant ($p = 0.76$). Sodium–glucose cotransporter-2 (SGLT-2) inhibitors: no significant association ($p = 0.18$). Insulin: high incidence of hypoglycemia, though not statistically significant ($p = 0.26$). Combination therapies: sulphonylureas + insulin: 62.5% of hypoglycemic patients were on this combination, compared to 50% in the nonhypoglycemic group ($p = 0.47$). Although not statistically significant, the high incidence suggests an additive risk. Sulphonylureas + DPP-4 inhibitors: 25% of hypoglycemic patients were on this regimen compared to 50% in the nonhypoglycemic group ($p = 0.12$). The incidence indicates that when combined, risk may vary depending on coexisting therapies.

Discussion: This study revealed a strikingly high prevalence of hypoglycemia (80%) in poorly controlled T2DM patients, with asymptomatic episodes being more frequent. CGM proved crucial in detecting silent hypoglycemia, which carries the risk of severe complications. Metformin showed no significant risk, confirming its safety. DPP-4 inhibitors, usually considered low risk, were significantly associated here, likely due to concomitant therapy. Sulphonylureas and insulin showed high incidence rates consistent with the literature, though statistical significance was not reached due to small sample size. Importantly, combination therapy with sulphonylureas and insulin was associated with a substantial proportion of hypoglycemic cases (62.5%), highlighting the need for careful use.

Limitations: Small sample size, single-center, limiting generalizability.

Conclusion: Hypoglycemia is highly prevalent in T2DM patients with poor control, especially asymptomatic forms, emphasizing the role of CGM. While metformin remains safe, insulin, sulphonylureas, and combination therapies (particularly sulphonylureas + insulin) markedly increase hypoglycemia risk.

Clinical implications: Routine CGM can detect hidden hypoglycemia and guide therapy. Drug regimens, particularly combinations, must be individualized. Elderly patients on insulin/secretagogues need close monitoring.

Future directions: Larger multicenter studies are needed to clarify long-term implications and refine therapeutic strategies.

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by insulin resistance and progressive pancreatic β-cell dysfunction. This results in hyperglycemia, significantly increasing the risk of microvascular and macrovascular complications. According to the International Diabetes Federation (IDF), approximately 537 million adults worldwide were affected by diabetes in 2021, with T2DM accounting for the vast majority of cases. This number is expected to rise to 783 million by 2045.[1] The pathogenesis of T2DM involves complex interactions between genetic and environmental factors, including obesity, physical inactivity, and dietary habits.[2] The condition often remains asymptomatic for years, leading to delays in diagnosis and early onset of complications. Optimal glycemic control is fundamental to preventing the acute and long-term complications of diabetes. Glycemic control is traditionally measured using glycated hemoglobin (HbA1c), which provides an average of blood glucose levels over the preceding 2–3 months. The target HbA1c for most patients is <7%, though individualized goals are recommended based on age, comorbidities, and the risk of hypoglycemia.[3] Emerging evidence emphasizes the significance of maintaining time-in-range (TIR), a metric provided by continuous glucose monitoring (CGM) systems, which tracks the percentage of time glucose levels remain within the target range of 70–180 mg/dL.[4] Maintaining a higher TIR is associated with reduced complications and improved quality of life.[5] Despite advances in diabetes care, hypoglycemia remains a significant challenge in managing T2DM. Traditional methods for monitoring glucose, such as fingerstick blood glucose testing,

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provide only snapshot readings, limiting their utility in capturing dynamic glucose fluctuations and identifying asymptomatic hypoglycemia. Continuous glucose monitoring (CGM) (Fig. 1) has emerged as a revolutionary tool, offering real-time insights into glycemic patterns.[6] CGM provides detailed metrics such as TIR, time below range (TBR), and glycemic variability (GV), enabling healthcare providers to optimize treatment strategies and reduce hypoglycemia risk.[7]

This study aims to evaluate the prevalence and characteristics of hypoglycemic episodes in T2DM using CGM data, bridging gaps in knowledge regarding real-world application and impact. By exploring CGM's potential, the study seeks to contribute to individualized diabetes management and improved patient outcomes.

Materials and Methods

Study Setting and Study Population

The study is conducted in a tertiary health care center and involves both urban and rural populations in India.

Sample size

$$N_0 = Z^2pq/e^2$$

N_0 is the sample size, Z^2 is the abscissa of the normal curve that cuts off area α at the tails; (1−α) equals the desired confidence level of 95%; *e* is the desired level of precision, *p* is the estimated proportion of an attribute that is present in the population, and *q* is (1−*p*). The value for *Z* is found in statistical tables, which contain the area under the normal curve, e.g., *Z* =1.96 for 95% level of confidence.

The sample size for the study = $(1.96)^2 \times 0.38 \times (1-0.38)/(0.14)^2$
= $3.84 \times 0.38 \times 0.62/0.0196$
= 0.905/0.0196
= 46.17

46 or more measurements/surveys are needed to have a confidence level of 95% that the real value of 38% is within ± 14% of the measured/surveyed value. *p* = 38% (proportion of diabetics with HbA1c ≥ 8%), *e* =14% margin of error, sample size =46. All indoor patients having diabetes mellitus meeting the inclusion criteria and attending medical services at this tertiary hospital during the study period.

Period of Study

This study included all patients who came to the hospital over 18 months, from 5th April 2023 to 5th October 2024, in whom CGM was indicated and performed as part of the treatment protocol.

Inclusion Criteria

All stable patients admitted with an age >18 years, both male and female.

- Diagnosed with diabetes mellitus (type 2) with unsatisfactory glycated Hb (HbA1c) >8%.
- Patients who were on CGM monitoring.
- Willing to participate.

Exclusion Criteria

- Patients with HbA1c below 8%.
- Nondiabetic patients who are on steroid therapy.
- Not willing to participate.
- Critically ill patients.
- Patients not able to provide consent.

Results

- *Demographics*: Mean age was 64.2 ± 7.9 years; 42% were aged 61–70 years (Table 1). Mean BMI was 24.9 ± 3.0 kg/m^2, with 46% overweight (Table 2).
- *Hypoglycemia prevalence*: 80% (40/50) experienced hypoglycemia; of these (Table 3 and Fig. 2), 60% were asymptomatic and 40% symptomatic (Table 4 and Fig. 3).
- *Drug associations*:
  - *Metformin*: Not significantly associated (*p* = 0.29) (Table 5 and Fig. 4)
  - *Dipeptidyl peptidase-4 (DPP-4) inhibitors*: Significantly associated with hypoglycemia (*p* = 0.003) (Table 6 and Fig. 5).
  - *Sulphonylureas*: Trend toward increased risk, not statistically significant (*p* = 0.76) (Table 7 and Fig. 6).
  - *SGLT-2 inhibitors*: No significant association (*p* = 0.18) (Table 8 and Fig. 7)
  - *Insulin*: High incidence of hypoglycemia, though not statistically significant (*p* = 0.26) (Table 9 and Fig. 8).

Fig. 1: Continuous glucose monitoring system

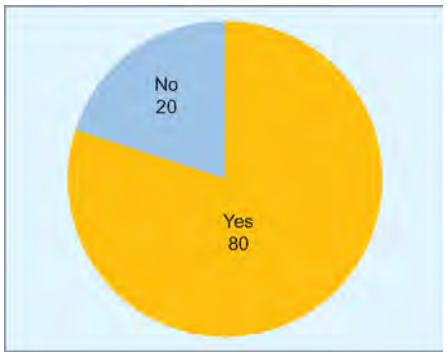

Fig. 2: Hypoglycemia distribution among study participants

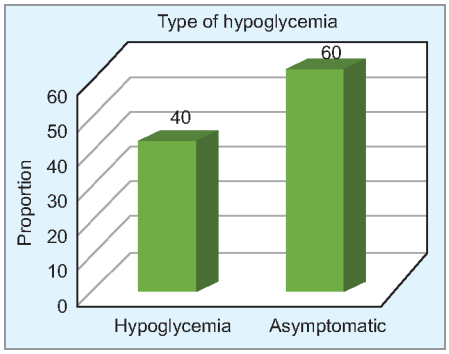

Fig. 3: Types of hypoglycemia among study participants

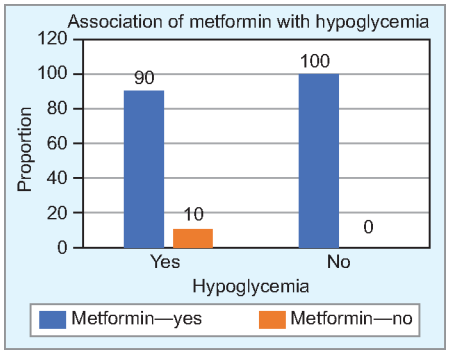

Fig. 4: Association of metformin with hypoglycemia among study participants

Table 1: Age distribution of the study participants (*N* = 50)

Age (years)	*Frequency (n)*	*Percentage (%)*
50–60	19	38.0
61–70	21	42.0
71–80	9	18.0
81–90	1	2.0
Total	50	100.0

The mean (SD) age of the study participants was 64.2 (7.9) years

Table 2: Body mass index distribution of the study participants (*N* = 50)

Body mass index (kg/m^2)[&]	*Frequency (n)*	*Percentage (%)*
Normal (18.5–24.9)	24	48.0
Overweight (25.0–29.9)	23	46.0
Obese (≥30)	2	4.0
Total	50	100.0

[&]WHO BMI classification; mean (SD) BMI of the study participants is 24.9 (3.0) kg/m^2

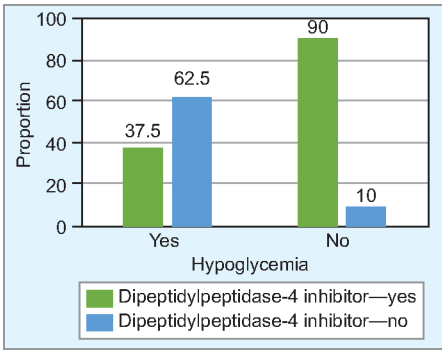

Fig. 5: Association of dipeptidyl peptidase-4 inhibitor with hypoglycemia among study participants

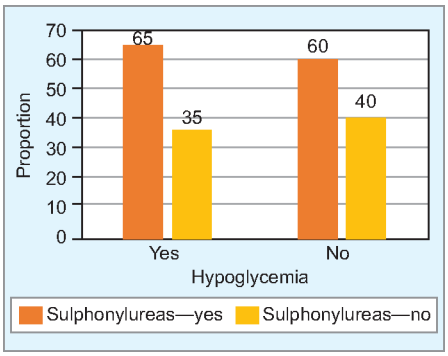

Fig. 6: Association of sulphonylureas with hypoglycemia among study participants ($N = 50$)

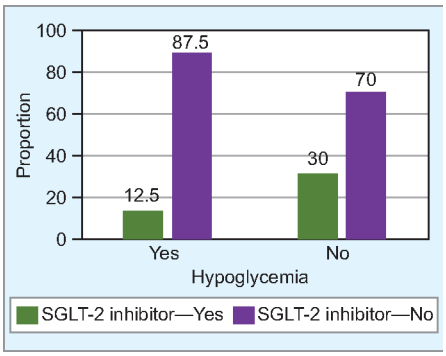

Fig. 7: Association of SGLT-2 inhibitor with hypoglycemia among study participants

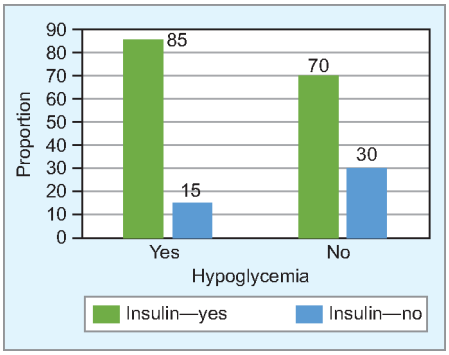

Fig. 8: Association of insulin with hypoglycemia among study participants

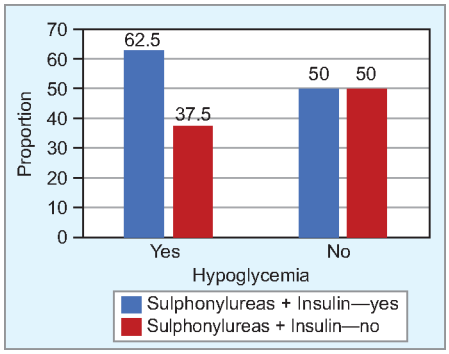

Fig. 9: Association of sulphonylureas plus insulin with hypoglycemia among study participants

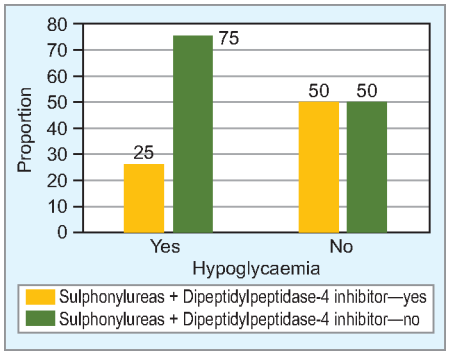

Fig. 10: Association of sulphonylureas plus dipeptidyl peptidase-4 inhibitor with hypoglycemia among study participants

Table 3: Hypoglycemia distribution of the study participants ($N = 50$)

Hypoglycemia	*Frequency (n)*	*Percentage (%)*
Yes	40	80.0
No	10	20.0
Total	50	100.0

Table 4: Type of hypoglycemia distribution of the study participants ($N = 40$)

Type of hypoglycemia	*Frequency (n)*	*Percentage (%)*
Symptomatic	16	40.0
Asymptomatic	24	60.0
Total	40	100.0

Table 5: Association of metformin with hypoglycemia distribution of the study participants ($N = 50$)

Metformin	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	36 (90.0)	10 (100.0)	0.29
No	4 (10.0)	0 (0.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

- *Combination therapies*:
  - *Sulphonylureas + Insulin*: 62.5% of hypoglycemic patients were on this combination, compared to 50% in the nonhypoglycemic group ($p = 0.47$). Although not statistically significant, the high incidence suggests an additive risk (Table 10 and Fig. 9).
  - *Sulphonylureas + DPP-4 inhibitors*: 25% of hypoglycemic patients were on this regimen compared to 50% in the nonhypoglycemic group ($p = 0.12$). The incidence indicates that when combined, risk may vary depending on coexisting therapies (Table 11 and Fig. 10).

Discussion

Hypoglycemia and Its Associations

Hypoglycemia was a significant finding in this study, with 80% of participants reporting episodes of low blood glucose. Among those experiencing hypoglycemia, 60% were asymptomatic, while 40% reported symptomatic episodes. The high prevalence of asymptomatic hypoglycemia raises concerns regarding the risk of severe hypoglycemic episodes, particularly in older adults who may not perceive the warning signs. Research conducted by Bremer et al. revealed that many older individuals with type 2 diabetes exhibit considerable unawareness of hypoglycemia. This lack of awareness does not appear to stem from changes in neuroendocrine counterregulation and may increase the likelihood of experiencing severe hypoglycemia, which is often reported in this group. Furthermore, the coexistence of unawareness of hypoglycemia and diminished cognitive abilities is an important consideration.[8]

The association between hypoglycemia and different classes of antidiabetic medications was examined. Metformin use was not significantly associated with hypoglycemia ($p = 0.29$), which is consistent with existing literature suggesting that metformin has a low risk of causing hypoglycemia due to its insulin-independent mechanism of action.[9] However, DPP-4 inhibitors showed a significant association with hypoglycemia ($p = 0.003$), suggesting that their use might increase the risk in certain populations, but this could also be due to concurrent use of other medications such as sulphonylureas and insulin for the treatment of uncontrolled diabetes. Florentin et al. found that DPP-4 inhibitors are considered safe and are unlikely to lead to low blood sugar or increased weight. They do not necessitate any dosage adjustments. These medications can also be given to individuals with chronic kidney disease, with appropriate dose modifications, and are suitable for older adults managing diabetes.[10]

Table 6: Association of dipeptidyl peptidase-4 inhibitor with hypoglycemia distribution of the study participants (*N* = 50)

Dipeptidyl peptidase-4 inhibitor	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	15 (37.5)	9 (90.0)	0.003
No	25 (62.5)	1 (10.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

Table 7: Association of sulphonylureas with hypoglycemia distribution of the study participants (*N* = 50)

Sulphonylureas	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	26 (65.0)	6 (60.0)	0.76
No	14 (35.0)	4 (40.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

Table 8: Association of SGLT-2 inhibitor with hypoglycemia distribution of the study participants (*N* = 50)

SGLT-2 inhibitor	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	5 (12.5)	3 (30.0)	0.18
No	35 (87.5)	7 (70.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

Table 9: Association of insulin with hypoglycemia distribution of the study participants (*N* = 50)

Insulin	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	34 (85.0)	7 (70.0)	0.26
No	6 (15.0)	3 (30.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

Table 10: Association of sulphonylureas + insulin with hypoglycemia distribution of the study participants (*N* = 50)

Sulphonylureas + Insulin	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	25 (62.5)	5 (50.0)	0.47
No	15 (37.5)	5 (50.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

Table 11: Association of sulphonylureas + dipeptidyl peptidase-4 inhibitor with hypoglycemia distribution of the study participants (*N* = 50)

Sulphonylureas + dipeptidyl peptidase-4 inhibitor	*Hypoglycemia n (%)*		*p-value**
	Yes	*No*	
Yes	10 (25.0)	5 (50.0)	0.12
No	30 (75.0)	5 (50.0)	
Total	40 (100.0)	10 (100.0)	

*Signify Chi-squared test

Sulphonylureas, which are known to increase the risk of hypoglycemia, did not show a statistically significant association in this study (p = 0.76), though the trend suggested a higher proportion of hypoglycemia cases in those using sulphonylureas. According to research by Dalem et al., individuals currently taking sulphonylureas face a significantly higher risk of hypoglycemia compared to those only on metformin, with an adjusted hazard ratio of 2.50 (95% confidence interval of 2.23 to 2.82). Furthermore, this risk is even higher among patients with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2, resulting in an adjusted hazard ratio of 4.96 (95% confidence interval: 3.76 to 6.55).[11] Similarly, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and insulin use were not significantly associated with hypoglycemia (p = 0.18 and p = 0.26, respectively), although insulin users showed a high prevalence of hypoglycemic episodes. Zaccardi et al. reviewed multiple trials involving SGLT-2 inhibitors and found that while these medications effectively lowered blood sugar levels and body weight, canagliflozin, in particular, posed a higher risk of hypoglycemia compared to others. Both canagliflozin and dapagliflozin were linked to an increased likelihood of experiencing low blood sugar. Additionally, dapagliflozin was associated with a higher incidence of urinary tract infections, and all inhibitors raised the risk of genital infections.[12]

In a study, Salvo et al. performed a systematic review that included 10 different studies, encompassing a total of 6,546 participants. Among these, 4,020 were treated with DPP-4 inhibitors alongside sulphonylureas, and 2,526 received a placebo combined with sulphonylureas. The analysis indicated a risk ratio of 1.52 for hypoglycemia, with a 95% confidence interval ranging from 1.29 to 1.80. The number needed to harm (NNH) was determined as follows: 17 (with a 95% confidence interval of 11 to 30) for treatment lasting 6 months or less, 15 (95% confidence interval 9 to 26) for treatment durations between 6.1 and 12 months, and 8 (95% confidence interval 5 to 15) for treatments extending beyond one year. Additionally, subgroup analyses revealed no significant differences between full and low doses of DPP-4 inhibitors. The risk ratio for those on full doses was 1.66 (95% confidence interval 1.34 to 2.06), while the risk ratio for low doses did not achieve statistical significance, reported as 1.33 (95% confidence interval 0.92 to 1.94).[13] We also did not find a significant relation between DPP-4 inhibitors alongside sulphonylureas.

Limitations of Study

- *Small sample size*: The study included only 50 participants, limiting the generalizability of the findings to larger diabetic populations.
- *Single-center study*: Data were collected from a specific population, and findings may not be representative of broader, more diverse diabetic cohorts.

Conclusion

Clinical Implications

- The high prevalence of asymptomatic hypoglycemia suggests a need for routine glucose monitoring, especially in older adults, to prevent severe episodes.
- Medication selection should be individualized, particularly when prescribing DPP-4 inhibitors, sulphonylureas, or insulin in patients at risk for hypoglycemia.
- Continuous glucose monitoring (CGM) or flash glucose monitoring may help better track glycemic variability and guide treatment adjustments.

Future Directions

Larger, longitudinal studies are needed to validate these findings and assess the long-term impact of hypoglycemia on diabetes-related complications.

This study highlights the significant burden of hypoglycemia among individuals with diabetes, with a high proportion of asymptomatic cases posing an increased risk of severe events. While metformin remains a safe option, the use of DPP-4 inhibitors, sulphonylureas, and insulin should be carefully evaluated to minimize hypoglycemic risk. The findings underscore the importance of individualized diabetes management, regular glucose monitoring, and optimizing glycemic control strategies to improve patient outcomes.

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ORIGINAL ARTICLE

To Study the Impact of Stewardship Program on Antibiotic Administration in a Community-acquired Pneumonia: A Before-and-after Interventional Study

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Abstract

Background: Community-acquired pneumonia (CAP) is a common lower respiratory tract infection that leads to millions of hospital admissions annually and contributes to substantial morbidity and mortality worldwide. Effective antimicrobial treatment is crucial for managing CAP. However, due to the high incidence, frequent misdiagnosis of its cause, and associated mortality risks, optimizing antibiotic use is essential. To promote best practices and minimize unnecessary antibiotic exposure in CAP patients, stewardship programs have been implemented. This study aims to evaluate the effect of these stewardship programs on antibiotic prescribing patterns in CAP.

Materials and methods: This prospective interventional study was conducted on patients in the emergency wards of Bowring and Lady Curzon Hospitals from October 23 to October 24. The total sample size is 120; the study population is divided into two phases: phase 1—preintervention—and phase 2—postintervention. The outcome of the study is analyzed.

Results: Of the 120 participants in the study, 60 were preintervention, and 60 were postintervention. Most of the participants in the study are under 60. The majority is male (46.7% and 60%), comprising 65% and 76.6%, respectively. Most patients had CURB-65 scores of 2 or 3. As for stages 1 and 2, the PSI is 2 and 3, respectively. The two most commonly isolated organisms are *Klebsiella pneumoniae* and *Streptococcus pneumoniae*. Following an antimicrobial stewardship (AMS) intervention, 75% of patients in this study adhered to the guidelines and followed de-escalation protocols, a difference that is statistically significant. Additionally, the mean length of hospital stay decreased from 6.1 to 4.9 days.

Conclusion: The implementation of an antibiotic stewardship program resulted in a notable improvement in adherence to clinical guidelines, optimized antibiotic selection, increased de-escalation rates, and a considerable reduction in the overall duration of empirical antibiotic treatment.

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Introduction

Community-acquired pneumonia (CAP) is a common lower respiratory tract infection that leads to millions of hospital admissions each year, contributing significantly to global morbidity and mortality.[1] While most cases are caused by well-established respiratory pathogens, the accuracy of microbiological confirmation is often limited due to the low sensitivity and specificity of respiratory secretions and challenges in obtaining adequate samples.[2]

Antimicrobial therapy plays a crucial role in the effective management of CAP.[3] However, the high prevalence of cases, frequent misdiagnosis of its etiology, and associated mortality risks contribute to increased antibiotic usage.

Antimicrobial resistance (AMR) among key respiratory pathogens is on the rise worldwide.[4] According to a recent report from the World Health Organization, antibiotic resistance is responsible for approximately 2,500 deaths annually within the European Union.[5]

To encourage adherence to best practices and minimize unnecessary antibiotic exposure in CAP patients, antimicrobial stewardship programs have been introduced. This study aims to evaluate the impact of such programs on antibiotic prescribing patterns for CAP prior to their implementation.

Aims and Objectives

To evaluate the influence of the antibiotic stewardship program on antibiotic utilization in CAP.

To assess its effectiveness by analyzing hospital length of stay (LOS), mortality rates, duration of intravenous antibiotic therapy, and overall antibiotic consumption.

Materials and Methods

Study Design

Prospective before-and-after interventional study.

Study Setting

Data for the study will be collected from patients in the ward and emergency ward at Bowring and Lady Curzon Hospitals from October 23 to October 24.

Sample Size

Based on a previous study by Fally et al., the impact of a stewardship program on antibiotic administration in CAP. Considering mortality in the whole cohort of 8.7%, the sample size is as follows:[6]

$$N = 4pq/d^2$$

where p = prevalence, $q = 100-p$, and d = absolute precision.

$$= 4 \times 8.7 \times 91.3/(7.5)^2$$
$$= 56$$

So, after rounding, the sample size would be 60 in each group.

Method of Collection of Data

Inclusion Criteria

- Patients who provide written informed consent.
- Patients diagnosed with CAP (defined by the presence of a new infiltrate on chest X-ray and at least one of the following symptoms: cough, sputum production, dyspnea, core body temperature >38.0 °C, and auscultatory findings of rales).
- Age >18 years.

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Exclusion Criteria

- Age <18 years.
- Hospital admission within the past 28 days.
- Active tuberculosis.
- Immunosuppression [corticosteroids (20 mg prednisolone-equivalent/day >14 days), were HIV positive, had received chemotherapy during the last 28 days, had neutropenia].

Procedure

After receiving approval from the institutional ethics committee and obtaining written informed consent, patients admitted to the hospital affiliated with Shri Atal Bihari Vajpayee Medical College and Research Institute will be included in the study.

All patients admitted to the ward and emergency ward with CAP are surveyed, and demographic, clinical, treatment, and laboratory data are collected.

Phase 1 (Preintervention Phase) 6 Months, 60 Patients

It is to observe the current practice of CAP treatment and antibiotic stewardship in our hospital. Data related to CAP is collected. At the end of 6 months, CAP guideline utilization and antibiotic use, along with length of hospitalization and mortality, are calculated.

Phase 2 (Intervention Phase) 6 Months, 60 Patients

- *Target groups*: Residents, nursing staff, treating faculties.
- *Intervention*: Engaging mass lectures will be conducted on key aspects of CAP management, including severity assessment, timely initiation of antimicrobial therapy, guideline-based selection of empirical regimens, de-escalation strategies, transition to oral therapy, and appropriate duration of treatment. Additionally, targeted bedside training, one-on-one discussions, educational posters, and monthly feedback sessions will be implemented.
- Compliance with the antibiotic stewardship approach for CAP, along with hospital LOS, mortality rates, and the duration of IV antibiotic therapy, will be assessed and compared before and after the intervention.

Outcome

- Primary outcome: An appropriate, correct antibiotic choice, duration, and de-escalation
- Secondary outcome: Days of Hospitalization.

Mortality

Statistical tool for analysis: The data were compiled in Microsoft Excel and analyzed using SPSS Statistics version 22. Categorical variables were assessed using the χ^2 test. The Mann–Whitney *U* test was applied to non-normally distributed nominal data, such as hospital LOS and duration of antibiotic therapy. For non-normally distributed ordinal or nominal data on a scale, such as time to antibiotic administration based on the CURB-65 score, the Kruskal–Wallis test was used.

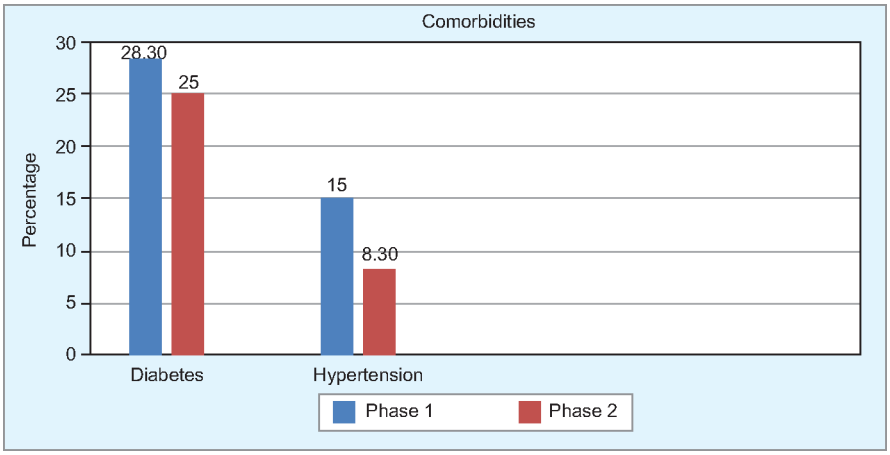

Fig. 1: Comorbidities distribution (In our study population, 28.3% and 25% are diabetics in both the phases)

Table 1: Demographic distribution among the study population

	Variables	*Preintervention (n = 60) (%)*	*Postintervention (n = 60) (%)*
Gender	Males	28 (46.7)	36 (60)
	Females	32 (53.3)	24 (40)
Age	<60 years	39 (65)	46 (76.6)
	>60 years	21 (35)	14 (23.4)

Among the study population, the majority are less than 60 years (65% and 76.6%), and the majority are male (46.7% and 60%), respectively

Table 2: Severity scoring

	Variables	*Preintervention (N = 60) (%)*	*Postintervention (N = 60) (%)*
CURB-65	Score 0	6 (10)	0 (0)
	Score 1	16 (26.7)	23 (38.4)
	Score 2	25 (41.7)	31 (51.6)
	Score 3	13 (21.6)	6 (10)
PSI	1	12 (20)	0 (0)
	2	33 (55)	34 (56.6)
	3	14 (23.3)	19 (31.7)
	4	1 (1.7)	7 (11.7)

In our study in phases 1 and 2, the majority of the CURB-65 scores are 2 and 3, and the PSI scores are 2 and 3

Discussion

Antimicrobial resistance is spreading rapidly worldwide, posing an urgent threat to global public health. Antimicrobial stewardship programs (ASP) and institution-specific guidelines for empirical antibiotic therapy play a vital role in preventing the development of antibiotic resistance and improving patient outcomes. CAP is one of the most common acute infections requiring antibiotic treatment, and improper prescribing practices contribute significantly to the overuse and misuse of these critical medications.[7]

In our study population, males constituted the majority, accounting for 46.7% in one group and 60% in the other, and a sizable majority were under 60 (65% and 76.6%) (Table 1). Additionally, 28.3% and 25% of patients were diabetics in both phases of the study (Fig. 1). The data indicate that the majority of patients had a CURB-65 score of 2 or 3 and a Pneumonia Severity Index (PSI) of 2 or 3, suggesting a higher severity of illness (Table 2). The most common organisms are *Streptococcus pneumoniae* and *Klebsiella pneumoniae* (Fig. 2).

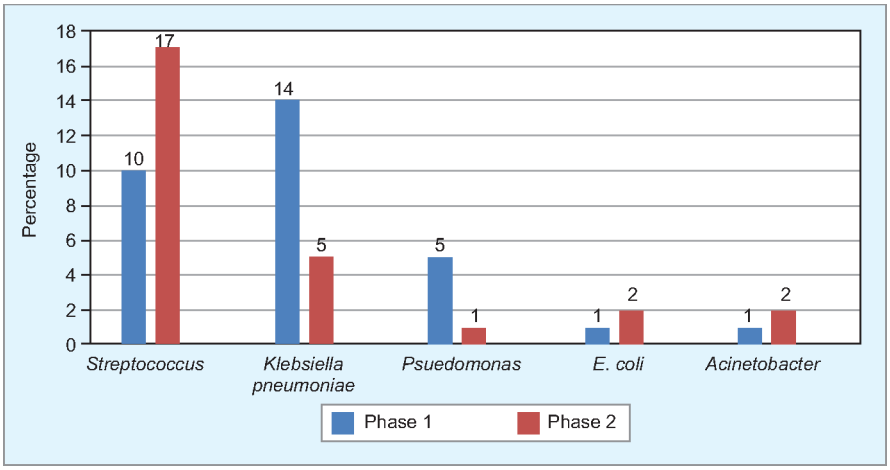

Fig. 2: Antibiogram (The most common organisms are *Streptococcus pneumoniae* and *Klebsiella pneumoniae*)

Table 3: Sputum analysis

Variables		*N (%)*	*N (%)*
Sputum sent for sputum culture		56 (93.3)	60 (100%)
Mean day of sputum culture sent		Second day	First day
Percentage of normal commensals		37 (61.6)	33 (55%)
Predominant pattern	Bronchopneumonia	20 (33.3%)	18 (30%)
	Lobar Pneumonia	36 (60%)	42 (70%)

In this study, in phase (1), 93.3% of sputum samples and in phase (2), 100% of sputum samples were sent for sputum culture. After intervention in phase 2, sputum was sent before starting antibiotics (on the first day). *In vivo*, the culture yield increased by 45%. Most CAP cases were lobar pneumonia (60% and 70%, respectively)

Table 4: Antibiotic utilization

Antibiotic	*Phase 1*	*Phase 2*	*p-value*
Amoxiclav	10 (17%)	21 (35%)	<0.009
Ceftriaxone	25 (42%)	30 (50%)	
Piperacillin tazobactam	23 (39%)	8 (13%)	
Meropenem	1 (2%)	1 (2%)	

In our post-ASP, there is a decrease in utilization of higher antibiotics with a statistically significant *p*-value <0.001

Table 5: Antibiotic stewardship (Guidelines, de-escalation, and duration of antibiotics)

Variables	*Category*	*Phase 1 N (%)*	*Phase 2 N (%)*	*p-value*
Guidelines followed	Yes	33 (55%)	45 (75%)	0.01
	No	27 (45%)	15 (25%)	0.01
De-escalation	Done	20 (33.3%)	45 (75%)	0.05
	Not done	40 (66.7%)	15 (25%)	0.05
Average duration of antibiotics	–	6.35 days	4.4 days	0.06
Mean duration of stay	–	6.11	4.93	<0.01

In this study, following the intervention about antibiotic stewardship, there is 75% to guidelines, and de-escalation is followed in 75% of patients, which is statistically significant ($p < 0.05$). The average duration of antibiotics after phase 2 is around 5 days. Mean duration of hospitalization is also reduced from 6.1 to 4.9 days, which is statistically significant with $p < 0.01$

Our intervention involved sending sputum cultures on the second day of admission preintervention, while postintervention cultures were collected on the first day before antibiotic administration. This strategic change led to a remarkable 45% increase in culture yields. Furthermore, the predominant form of CAP observed in the study was lobar pneumonia, affecting 60% and 70% of patients, respectively (Table 3).[8] In our post-ASP, there is a decrease in utilization of higher antibiotics with a significant statistical *p*-value < 0.001 (Table 4).

This study unambiguously demonstrates that during the preintervention period, nonadherence to antibiotic guidelines was alarmingly high, with a rate of 55% for CAP. However, the implementation of the ASP, which incorporated a written local guideline and restricted antibiotic usage, led to a substantial improvement in adherence for agent selection, increasing from 55% to 75%. Fesus et al. corroborated this trend, revealing that 41.7% of antibiotic use in the pulmonology department was nonadherent to guidelines.[9] Notably, the frequent and unnecessary combination of beta-lactams with metronidazole, comprising 8.7% of prescriptions, contributed to prolonged LOS. In stark contrast, during the ASP phase, adherence to agent selection guidelines surged from 58.3% to an impressive 93.3%.

Our findings conclusively show that implementing the ASP led to a significant reduction in the total duration of antibiotic therapy, from a median of 7 days to 5 days, which directly correlated with a marked decrease in empirical antibiotic use. Fesus et al. reported a comparable success, highlighting a 16.0% reduction in the total duration of antibiotic therapy, with the median decreasing from 8 days to 6 days, along with a decline in direct empirical antibiotic use. Similarly, a study by Avdic et al. supported these findings, showing a reduction in antibiotic usage from a median of 10 days to 7 days ($p < 0.001$) after the implementation of the ASP intervention.[10]

Moreover, in our analysis, the increase in antibiotic de-escalation from preintervention to postintervention was substantial, rising from 33.3% to 75%, with a statistically significant *p*-value < 0.05. Waagsbo et al. also recognized the pressing need for improved antibiotic de-escalation strategies in their research conducted at a teaching university hospital in Norway, revealing a notable increase in de-escalation from 28.3% to 64.8%.[11]

Finally, the length of hospitalization decreased significantly from 6.1 days to 4.9 days after the ASP was implemented ($p < 0.05$). Fesus et al. reported comparable results, revealing a striking 13.5% decrease in mean LOS (from 8.85 ± 6.10, with a median of 8 days, to 7.09 ± 5.84, with a median of 6 days) (Table 5). These findings unequivocally support the effectiveness of ASP in improving antibiotic prescribing practices and patient outcomes.[9]

Study Limitations

- Conducted at a single center.
- Limited sample size.

Conclusion

The implementation of the antibiotic stewardship program resulted in notable improvements in adherence to clinical guidelines, appropriate antibiotic use, and increased de-escalation. Additionally, it led to a significant reduction in the overall duration of empirical antibiotic therapy. The ASP was also associated with a considerable decrease in hospital LOS. Our findings suggest that the ASP may be instrumental in optimizing antibiotic treatment for CAP.

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ORIGINAL ARTICLE

Burden and Determinants of Renal Dysfunction among HIV Patients on ART in India: A Tertiary Care Experience

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Abstract

Background: HIV infection, primarily caused by human immunodeficiency virus type-1 (HIV-1), has become a chronic condition with the advent of multidrug antiretroviral therapy (ART). ART can lead to adverse effects, including renal dysfunction, especially in patients receiving tenofovir-based regimens.

Objectives: To find out the associations between renal function and serum parameters, and analyze the relationship between renal function and CD4 count in patients on tenofovir-based ART.

Materials and methods: A cross-sectional observational study was conducted at the ART clinic of SMS Medical College, Jaipur, from March 2023 to January 2024. The study included 300 HIV patients on tenofovir-based ART for at least 6 months. Demographic, clinical, and biochemical data, including renal function, serum parameters, and CD4 counts, were collected using a prevalidated and pretested structured questionnaire through convenience sampling. Data analysis by SPSS v. 25.

Results: Among 300 HIV patients on tenofovir-based ART for ≥6 months, 45% had mildly decreased renal function, while 0.3% experienced kidney failure. Mean age was 37.97 years (SD 11.15), with age showing a significant association with renal function ($p < 0.001$); younger participants predominantly had normal renal function, whereas older age groups had higher impairment rates. Serum potassium (mean 4.5 mmol/L) and albumin (mean 3.8 gm/dL) levels were also significantly associated with renal dysfunction ($p < 0.001$). Additionally, 87% of patients had undetectable viral loads, primarily among those with normal or mildly decreased renal function.

Conclusion: Age, body weight, serum potassium, and albumin levels are significant predictors of renal function in HIV patients on Tenofovir-based ART. These findings highlight the need for targeted monitoring to preserve renal health in this population.

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Introduction

Human immunodeficiency virus (HIV) infection remains a major global health challenge, with over 39 million people living with HIV (PLHIV) worldwide.[1] The advent of antiretroviral therapy (ART) has significantly improved survival and quality of life among PLHIV, transforming HIV from a fatal disease into a manageable chronic condition.[2] Among the various ART regimens, tenofovir disoproxil fumarate (TDF)-based therapy is widely used due to its potent antiviral efficacy, high genetic barrier to resistance, and favorable safety profile.[3] However, concerns regarding its long-term renal toxicity have been raised, as TDF is known to cause proximal tubular dysfunction, leading to renal impairment and altered serum biochemical parameters.[4]

Renal dysfunction in PLHIV is multifactorial, influenced by HIV-associated nephropathy (HIVAN), opportunistic infections, comorbidities such as diabetes and hypertension, and the nephrotoxic effects of ART.[5] CD4+ T-cell count serves as a critical marker of immune function in HIV-infected individuals, and its relationship with renal function remains a subject of ongoing investigation. Some studies suggest that lower CD4 counts may be associated with an increased risk of renal impairment, possibly due to heightened systemic inflammation and immune activation.[6] However, the specific impact of CD4 count on renal function in patients receiving TDF-based ART has not been fully elucidated, warranting further research.

This study aims to examine the associations between renal function and key serum biochemical parameters in HIV-positive patients on TDF-based ART. Additionally, we seek to analyze the relationship between renal function and CD4 count to better understand the interplay between immune status and renal health in this population. The findings of this study could have important implications for optimizing ART regimens and monitoring strategies to mitigate renal complications in PLHIV.

Materials and Methods

Before commencing the study, ethical approvals were obtained from the Institutional Clinical Trial Screening Committee (CTSC), Institutional Ethical Committee (IEC), Rajasthan University of Health Sciences (RUHS), and relevant authorities at SMS Medical College, Jaipur. Participant identities were anonymized, and participation was voluntary.

This observational cross-sectional study was conducted from March 2023 to January 2024 at the ART center, focusing on HIV patients on tenofovir-based ART. A sample of 300 patients was determined, accounting for a 5% attrition rate, based on the prevalence of proteinuria in HIV patients on ART for 6 months or more. Inclusion criteria were HIV patients on tenofovir-based therapy for at least 6 months, aged 18–65 years, with normal renal function before treatment. Patients with preexisting kidney disease or chronic illnesses were excluded. Eligible patients were sampled until the target was reached.

Renal function was defined using the estimated glomerular filtration rate (eGFR), calculated through common formulas, with six stages of kidney function identified based on eGFR values. Key serum parameters monitored included serum sodium, chloride, potassium, albumin, urea, creatinine, random blood sugar, CD4 count, and HIV viral load, forming a comprehensive methodology to assess renal function and related parameters in HIV patients receiving tenofovir-based ART.

Statistical Analysis

The collected data were analyzed using appropriate statistical software. Descriptive

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statistics were calculated for demographic and clinical characteristics, including means, medians, and standard deviations for continuous variables, and frequencies and percentages for categorical variables. The Chi-square test was used to examine associations between categorical variables, and independent *t*-tests or Mann–Whitney *U* tests were used to compare continuous variables as appropriate. A *p*-value of less than 0.05 was considered statistically significant, and confidence intervals were calculated to provide a measure of precision for the estimated prevalence rates.

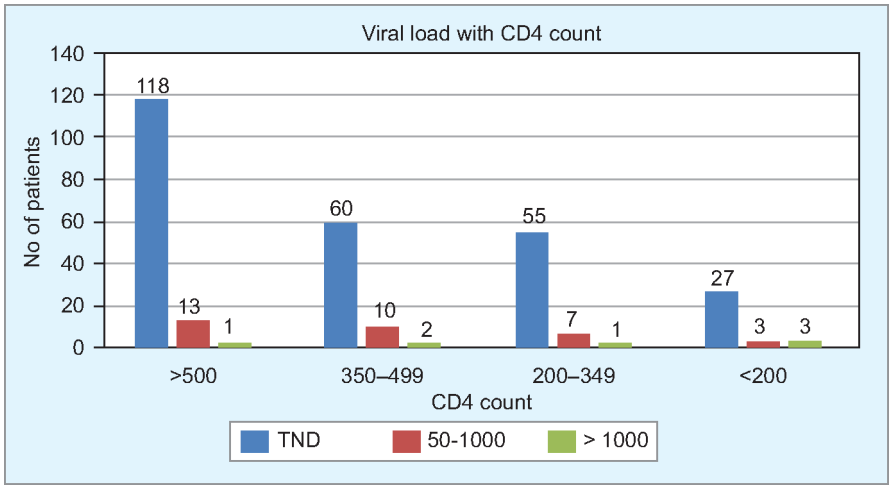

Fig. 1: Distribution of viral load with CD4 count among the study population

Table 1: Distribution of variables among the study population

Variables		*Number (n = 300)*	*Percentage (%)*
Age groups	18–37	153	51
	38–57	127	42
	58–77	20	7
Gender	Male	213	71
	Female	87	29
Body weight	45.13–55.13	126	42
	55.13–65.13	105	35
	65.13–75.13	65	22
	75.13–85.13	4	

Table 2: Distribution of renal functions among study population

Renal functions	*eGFR (mL/min/1.73 m²)*	*n = 300*	*Percentage (%)*
Normal renal function	≥90	131	43.7
Mildly decreased renal function	60–89	135	45.0
Mildly to moderately decreased renal function	45–59	21	7.0
Moderately to severely decreased renal function	30–44	12	4.0
Severely decreased renal function	15–29	0	0
Kidney failure	<15	1	0.3
Total		300	100.0

Results

The study population consists mainly of younger individuals, with 51% in the 18–37 age group and 42% in the 38–57 age group, while only 7% are aged 58–77 years. Males make up a significant majority (71%), whereas females account for 29%. Regarding body weight, most participants fall within the 45.13–65.13 kg range, with 42%. A smaller proportion (22%) falls within the 65.13–75.13 kg range (Table 1).

The association between viral load (copies/mL) and CD4 count among the study population. There is an observed increase in the number of individuals with viral loads >1000 copies/mL as CD4 counts decrease, suggesting a correlation between lower CD4 counts and higher viral loads (Fig. 1).

Table 2 shows that nearly half of the participants (45%) have mildly decreased renal function, while only 0.3% have kidney failure.

Distribution of renal function by viral load level among the study population. The data suggest that the majority of individuals with undetectable or low viral loads maintain normal or mildly decreased renal function, whereas severe renal impairment and kidney failure are rare across all viral load categories (Table 3).

Renal function in relation to the duration of tenofovir-based ART. The data do not show a clear trend over time, indicating varied renal function statuses across different ART durations. The mean study duration, based on the given data, is approximately 21.02 months (Fig. 2).

Serum potassium and albumin levels showed a significant association with renal function ($p < 0.001$), where lower serum albumin and higher serum potassium levels correlated with poorer renal function. However, serum sodium and chloride levels did not show significant associations. Regarding CD4 counts, patients with preserved renal function had higher counts, whereas those with impaired renal function had lower counts (Tables 4 and 5).

Table 3: Distribution of renal functions with viral load among study population

Viral load	*Total n (%)*	*Normal renal function*	*Mildly decreased renal function*	*Mildly to moderately decreased renal function*	*Moderately to severely decreased renal function*	*Kidney failure*
TND	260 (87%)	113	121	16	9	1
50–1000	35 (11%)	14	13	5	3	0
> 1000	5 (2%)	4	1	0	0	0

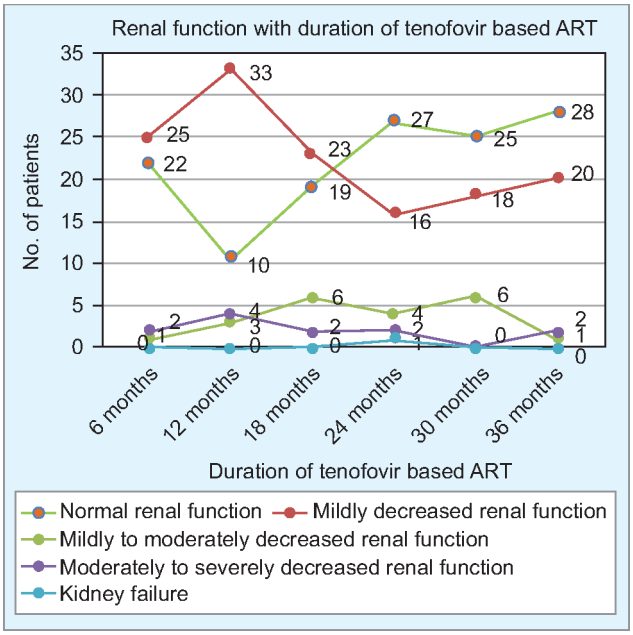

Fig. 2: Distribution of renal dysfunctions with duration of tenofovir-based ART among the study population

Table 4: Distribution of renal functions with S. potassium among study population

Renal function	*Grand total (n)*	*K^+ (mean ± SD)*	*p-value*
Normal renal function	131	4.04 ± 0.28	ANOVA test F =70.17; $p < 0.001$*
Mildly decreased renal function	135	4.03 ± 0.27	
Mildly to moderately decreased renal function	21	4.05 ± 0.27	
Moderately to severely decreased renal function	12	4.42 ± 0.43	
Kidney failure	1	5.3 ± 0	
Grand total	300	4.06 ± 0.30	

*signifies the *p*-value is statistically significant

Table 5: Association of renal functions with serum albumin among study population

Renal functions	*Grand total (n = 300)*	*S. albumin*	*One-way analysis of variance (ANOVA)*
Normal renal function	131	4.48 ± 0.05	F = 61.56; $p < 0.001$*
Mildly decreased renal function	135	4.14 ± 0.27	
Mildly to moderately decreased renal function	21	4.03 ± 0.49	
Moderately to severely decreased renal function	12	3.78 ± 0.64	
Kidney failure	1	3 ± 0	

*Statistically significant values, *p*-value < 0.05

Table 6: Association of Renal Functions with Post-ART CD4 count among study population

Renal functions	*Grand total (n = 300)*	*Post-ART CD4 count*	*One-way analysis of variance (ANOVA)*
Kidney failure	1	24 ± 0	F = 10.46; p-value = 0.225
Mildly decreased renal function	135	518 ± 48	
Mildly to moderately decreased renal function	21	541.95 ± 380.55	
Moderately to severely decreased renal function	12	383.83 ± 193.53	
Normal renal function	131	626.02 ± 766.26	

The post-ART CD4 counts across different renal function stages. The mean post-ART CD4 counts vary across the groups, with the highest mean count in the normal renal function category. The one-way ANOVA test shows that these differences are not statistically significant (F = 1.46, p = 0.225) (Table 6).

Multiple logistic regression analysis reveals that S. K^+ and S. albumin have a significant impact on the odds of the outcome occurring. However, S. Na^+ and S. Cl^- do not have a significant effect on the outcome (Table 7).

Discussion

Renal Function and Serum Parameters

Our study found that 45% of participants had mildly decreased renal function, with only 0.3% experiencing kidney failure. This aligns with Mwemezi et al.,[7] who reported a significant association between age and renal function. Serum albumin levels were significantly correlated with renal function, highlighting the role of nutrition.[8] Unlike Brennan et al.,[9] who reported higher renal dysfunction rates, our findings suggest a lower prevalence of severe impairment.[10,11]

Body Weight and Renal Function

Higher body weight correlated with better renal function. This contrasts with Nyende et al.,[12] who found no such association, but aligns with studies linking malnutrition to impaired renal function.

Duration of Tenofovir-based ART and Renal Function

No significant trend was found between renal function and prolonged tenofovir-based ART use, consistent with Msango et al.[13] This contradicts studies suggesting a progressive renal decline with extended ART use.

CD4 Count and Renal Function

No significant correlation was observed between renal function and CD4 count. This differs from Kumarasamy et al.,[14] who linked renal dysfunction to age and baseline eGFR. Other factors, such as body weight and serum albumin levels, may have a greater influence.

Comparison with Other Studies

Compared with Debeb et al.,[15] our study found a higher prevalence of renal dysfunction, possibly due to population differences. Our body weight findings ($p < 0.001$) contrast with Nyende et al.[16] The link between renal function and serum albumin aligns with Gayatri et al.,[17] emphasizing the importance of nutritional assessment.

Table 7: Multiple logistic regression among serum electrolytes and albumin

Multiple logistic regression	*S. E*	*OR*	*p-value*	*95% CI*	
				Lower	*Upper*
S. K^+	0.625	3.402	0.050	0.999	11.583
S. albumin	2.302	0.001	0.001	0.001	0.001

Conclusion

The study concludes that older age is associated with poorer kidney function, while higher body weight may protect against it. Serum potassium and albumin levels are key indicators of kidney health. No major gender differences were found, and better kidney function was associated with improved HIV treatment outcomes.

Declarations

Conflict of Interest

None.

Ethics Approval and Consent to Participate

The study was performed in accordance with the ethical standards of the Institutional Ethics Committee of Sawai Man Singh Medical College, Jaipur. Ethical clearance has been obtained from the Institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants where applicable. IEC Approval Number: 1023 MC/EC/2023. Date of Approval: August 18, 2023.

Authentication Statement

The manuscript is free from plagiarism. All data, images, and figures used in the manuscript are original or properly cited. This article has not been submitted to any other journal for simultaneous consideration.

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None.

Author's Contributions

MM, AA and DM conceptualized the study; MM and NE designed the methodology and applied the statistical analyses; MM and JR conducted the data collection, DM and JR data analysis and wrote the main manuscript; DM and NE (guide/other authors name) provided supervision. All the authors reviewed the final manuscript.

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ORIGINAL ARTICLE

Clinical Spectrum and Treatment Outcomes in Cluster Headache: A Retrospective Study of 55 Patients from a Tertiary Care Center in South India

Arul Selvan VL[1], Revathy Vijayaraghavan[2], Dhanya Sureddy[3*], Madhuri Kankanala[4]

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Abstract

Background: Cluster headache (CH) is an extremely painful trigeminal autonomic cephalalgia causing significant disability. However, it is frequently misdiagnosed and mismanaged.

Objective: To study the demographic and clinical characteristics of patients with CH and their response to prophylactic treatment.

Materials and methods: A retrospective study of 55 patients diagnosed with CH as per ICHD-3 criteria, seen in the Neurology OPD of a tertiary care hospital in South India (2011–2020), was conducted. The figure shows the case selection and treatment pathway.

Results: Of the 55 patients, 76.3% were men (M: F ratio 3.3:1). Mean age of onset was 33 years (range 12–69). Episodic CH was present in 56.3%. Headache was right-sided in 63.6% and orbitofrontal in 60%. Autonomic symptoms were present in 92%, most commonly lacrimation (70%) and conjunctival injection (59%). Nocturnal symptoms were reported by 72%, periodicity by 65%. Aura occurred in 5%. Four patients had associated migraine, and one had cluster-tic syndrome. Patients were treated with steroids, verapamil, lithium, and topiramate in resistant cases.

Conclusion: CH causes severe pain attacks. Prompt recognition and initiation of appropriate treatment, particularly verapamil and steroids, provide significant relief.

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Introduction

Cluster headache (CH) is one of the most painful primary headache disorders, with a prevalence of 0.1–0.4% of the population.[1] This trigeminal autonomic cephalalgia is characterized by unilateral headache attacks lasting for 15–180 minutes and occurring up to eight times per day, associated with cranial autonomic symptoms with or without restlessness.[2] The hallmark of CH is its daily and seasonal rhythmicity.[3] The headache, often described as "suicidal headache" due to its severity, can cause significant personal, social, and economic distress.[4]

Though the presentation is stereotypical and easy to diagnose, it is often missed by many practitioners. The hypothalamus is postulated to play a fundamental role in triggering headache episodes, and effective treatment options are available.[5] Various newer drugs and neuromodulatory therapies are also being investigated.

There are very few studies on this rare primary headache disorder from India. We report a retrospective study of 55 patients with CH and their clinical characteristics.

Materials and Methods

Case Selection

The study was conducted between May 2021 and June 2021. A retrospective list of cases diagnosed with CH seen in the OPD from 2011 was retrieved from the medical records department. The diagnosis was verified according to the International Classification of Headache Disorders, 3rd edition (ICHD-3). After excluding incomplete records, 55 cases with full details were included.

Diagnostic Criteria

International Classification of Headache Disorders, 3rd edition (ICHD-3) defines CH as at least five attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 15–180 minutes, associated with either cranial autonomic features (conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead/facial sweating, miosis, ptosis) or restlessness/agitation, occurring between once every other day and eight per day, not better accounted for by another diagnosis.[2]

Follow-up

Case records were reviewed for demographics, clinical features, and comorbidities. All patients underwent imaging to rule out other intracranial lesions. Patients received oral steroids for 3 days and were reviewed at day 3. Thereafter, steroids were continued for 10 days along with verapamil after ensuring a normal ECG. Patients were reviewed after 2 months. Those not responding to verapamil were started on lithium. Topiramate was used in resistant cases. Due to the retrospective nature, limited information on lifestyle and long-term follow-up was available.

Results

The cohort comprised 55 patients (42 men, 13 women; M:F ratio 3.2:1). Mean age of onset was 33 years (range 12–69) (Fig. 1 and Tables 1 to 3).

- *Subtype*: Episodic CH in 56.3% (31/55), chronic CH in 27.2% (15/55), first attack in 9 (16.3%).

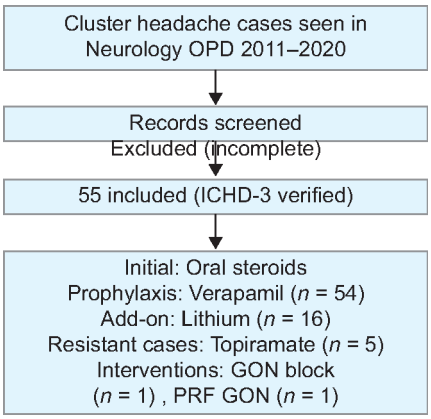

Fig. 1: Case selection and treatment pathway

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Table 1: Clinical profile of patients with cluster headache ($n = 55$)

Characteristics	*Patients (%)*
Gender	
Men	42 (76.3)
Women	13 (23.6)
Type	
Episodic cluster headache	31 (56.3)
Chronic cluster headache	15 (27.2)
First attack	9 (16.3)
Pain site	
Orbitofrontal	33 (60)
Hemicranial	13 (23.6)
Orbitofrontotemporal	9 (16.3)
Side	
Right	35 (63.6)
Left	19 (34.5)
Alternating	1 (1.8)
Autonomic features	
Lacrimation	38 (69)
Redness	33 (60)
Horner's	7 (13)
Swelling of the eye	12 (22)
Rhinorrhea	12 (22)
Nasal block	11 (20)
Restlessness	23 (42)
Nausea/vomiting	12 (22)
Photo/phonophobia	24 (44)
Others	
Aura	3 (5)
Nocturnal periodicity	39 (71)
Associated migraine	4 (7)
Family history of migraine	1 (2)
Family history of CH	Nil

- *Side/site*: Right-sided in 63.6%; most common site orbitofrontal (60%).
- *Attack profile*: Cluster interval varied (6 months–4 years). Mean cluster duration 6 weeks. Mean attacks 2.7/day, maximum 8/day. Mean episode duration 80 min.
- *Autonomic features*: Present in 92%; most common lacrimation (70%), conjunctival injection (59%).

Other features: Nocturnal symptoms in 72.7%; periodicity in 65%. Aura in three patients (5%). Excess yawning in three. Migraine association in four; cluster-tic in one; overlap with paroxysmal hemicrania in one. Family history of migraine in one; none with a family history of CH.

- *Imaging*: Normal in most; incidental lesions: two meningiomas, one pituitary macroadenoma, one trigeminal neurovascular conflict.
- *Treatment and outcomes*: All patients received oral methylprednisolone. Verapamil was used in 54 (49 with steroids). 16 required lithium, 5 required topiramate. One underwent a greater occipital nerve block (GON), and the other underwent pulsed radiofrequency thermocoagulation of the GON.
- *Follow-up*: Available for 28 patients; 26 improved, 2 had persistent symptoms. 11 recurred after stopping therapy.
- *Adverse effects*: Constipation, pedal edema, verapamil-induced Parkinsonism (improved after stopping), and lithium-induced tremor.

Table 2: Treatment modalities and outcomes in patients with cluster headache ($n = 55$)

Treatment modality	*No. of patients*	*Response/outcome*	*Side effects*
Oral methylprednisolone (48 mg/day × ≥1 week)	55	Initial symptomatic relief	Not reported
Verapamil (120 mg BD, after ECG)	54	The majority improved; 11 recurred after stopping	Constipation ($n = 1$), pedal edema ($n = 1$), Parkinsonism ($n = 1$)
Verapamil + steroids	49	Most improved	As above
Lithium (400 mg/day, add-on)	16	Clinical improvement	Tremors ($n = 1$)
Topiramate (50 mg/day, resistant cases)	5	Some improvement	Not reported
GON block	1	Significant improvement	Nil
PRF of GON	1	Long-term improvement	Nil
Follow-up (available)	28	26 improved, 2 persistent symptoms	–

Table 3: Comparison of clinical features with published literature

Feature	*Present study ($n = 55$)*	*Bahra et al., ($n = 230$)*	*Schürks et al., ($n = 246$)*	*Chakravarty, (India, $n = 44$)*
Male proportion	76.3%	72% (M: F 2.5:1)	77.6%	100%
Episodic CH	56.3%	79%	74.8%	86.4% (38/44)
Chronic CH	27.2%	21%	16.7%	13.6% (6/44)
Age of onset/diagnosis	33 yrs (mean)	28.4 yrs (ECH), 37 y (CCH)	Diagnosis 36.9 yrs; enrollment 44.8 yrs	Late 20–30s
Predominant site	Orbitofrontal 60%	Retro-orbital 92%, temporal 70%	NR	Orbitofrontal boring pain
Laterality	Right 63.6%	Right 60%, left 38%	Unilateral 97.2% (strictly 78.5%; side-changing 18.7%)	Right > left
Autonomic features	92%	≥90%	98.8%	"Classical" features are common
Restlessness	NR	93%	67.9%	NR
Aura	5%	14%	23%	NR
Nausea/vomiting	22%	50% nausea; 23% vomiting	27.8%	NR
Photo/phonophobia	44%	56%/43%	61.2%	NR
Attack duration	80 min (mean)	72–159 min	45–180 min in 67.9%	15–180 min
Attacks/day	2.7/day (mean)	4.6/day (max)	NR	~5/day
Bout duration	6 weeks	8.6 weeks	NR	~6 weeks
Nocturnal predictability	72.7%	73%	NR	More common

Discussion

Our study of 55 patients with cluster headache showed male predominance (76.3%), a mean onset age of 33 years, and predominance of episodic CH. These findings align with prior reports. Schürks et al.[6] reported 77.6%, Bahra et al. reported 72% men,[7] and Chakravarty's Indian series included only men.[8]

The proportion of episodic CH was lower in our study (56.3%) compared with Bahra (79%)[7] and Schürks (74.8%),[6] but closer to Chakravarty (86%).[8] Chronic CH was relatively higher (27.2%).

Autonomic features were common (92%), in line with Bahra[7] and Schürks.[6] Aura was reported in 5%, lower than Bahra (14%)[7] and Schürks (23%).[6] Nocturnal periodicity was present in 72.7%, almost identical to Bahra's 73%.[7]

Chronobiological differences between men and women have been demonstrated, though the overall clinical phenotype remains consistent.[9] Gender differences in CH have also been emphasized, with women showing distinct clinical characteristics,[10] and survey data from the US, revealing broader gender-specific variations.[11] Sleep and hypothalamic mechanisms are thought to play a central role in pathophysiology.[12] Regional data from Kuwait support the generalizability of the CH phenotype across Middle Eastern populations.[13] Comparative data are summarized in Table 3.

Management with verapamil and steroids was effective in most cases. Lithium and topiramate were used for refractory cases. Interventional procedures (GON block, PRF) were helpful in resistant patients. These findings are similar to those of Schürks et al., in which verapamil (70.3%) and glucocorticoids (57.7%) were the most frequently used preventive medications.[6] For acute therapy, subcutaneous sumatriptan remains an established option.[14]

Limitations

This was a retrospective study with limited follow-up and incomplete documentation of social and lifestyle factors. Treatment outcomes were not assessed with standardized scales.

Conclusion

Any patient with a side-locked headache should be evaluated for cluster headache. Attacks are easy to diagnose due to their characteristic features and must be differentiated from migraine. Education of physicians regarding timely diagnosis and appropriate treatment is essential to avoid misdiagnosis and undertreatment.

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ORIGINAL ARTICLE

Neutrophil-to-lymphocyte Ratio and Red Cell Distribution Width as Prognostic Marker for Severity in Acute Pancreatitis: An Observational Study

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Abstract

Introduction: Traditional scoring systems such as Ranson's, Glasgow, and APACHE II remain the cornerstone for assessing the severity of acute pancreatitis (AP), yet their early applicability is limited because they depend on multiple biochemical and clinical variables that may not be immediately available. In recent years, hematological parameters obtained from routine complete blood counts, particularly the neutrophil-to-lymphocyte ratio (NLR) and red cell distribution width (RDW), have emerged as promising inflammatory indicators. As these markers are inexpensive, readily measurable, and quickly obtainable, they may serve as useful adjuncts for early prediction of AP severity and patient outcomes.

Aim and objectives: This study evaluated the ability of NLR and RDW to predict disease severity in patients with AP. The primary objective was to determine the association between these inflammatory markers and clinical severity, while the secondary objective was to track their progression at 0, 24, and 48 hours following hospital admission.

Materials and methods: A prospective, hospital-based cross-sectional observational study was conducted at Fortis Escorts Hospital, Jaipur, Rajasthan, after institutional ethics approval. A total of 54 patients diagnosed with AP were enrolled and evaluated using standard clinical and laboratory parameters.

Results: The study population had a mean age of 41.96 ± 8.94 years; 18.5% were female, and 81.5% were male. Most participants presented with abdominal pain, nausea, and vomiting. A total of 40 patients (74.1%) had mild pancreatitis, whereas 14 (25.9%) had severe disease. The mean baseline NLR (7.57 ± 2.42) declined significantly over 48 hours. RDW values showed minimal temporal variation but were consistently higher among severe cases. All mild cases survived; four deaths occurred exclusively in the severe group.

Conclusion: NLR and RDW demonstrated significant prognostic value in assessing the severity of AP. Their early evaluation and serial monitoring can provide rapid risk stratification and guide timely clinical management.

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Introduction

Acute pancreatitis (AP) involves pancreatic inflammation ranging from mild, self-limiting episodes to severe systemic inflammation with potential organ failure and death.[1,2] While most cases are mild, characterized by interstitial edema and rapid recovery, approximately 15–20% progress to severe forms associated with significant morbidity and mortality.[3] The most frequent causes of AP include gallstones and alcohol use, with a smaller contribution from hypertriglyceridemia and other metabolic factors.[2,3]

AP severity is categorized as mild (no organ failure or complications), moderately severe (transient organ failure <48 hours, with or without complications), and severe (persistent organ failure >48 hours).[4] Approximately, one-fourth of AP cases progress to severe disease, characterized by a pronounced inflammatory response that may evolve into multi-organ dysfunction and elevated mortality rates.[5,6] In later stages, infected pancreatic necrosis and peripancreatic fluid collections further increase mortality risk.[7,8] Clinical warning signs include fever, hypovolemia, Grey-Turner's and Cullen's signs, hypercalcemic tetany, and fulminant pancreatitis; fever may indicate either infection or ongoing inflammation.[4,9] Diagnosis is based on the presence of characteristic abdominal pain, elevated serum amylase or lipase levels (≥3 times the upper normal limit), and imaging findings.[10]

Traditional scoring models provide useful guidance but are often less accurate when applied during the initial phase of patient assessment.[11,12] Therefore, simple and readily available biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR), derived from routine blood counts, are being explored as potential early indicators of disease severity, as they reflect systemic inflammation and immune response.[13–15]

The present study aims to assess the prognostic value of NLR and red cell distribution width (RDW) in predicting the severity of AP, with the goal of improving early risk stratification and clinical outcomes.

Aims and Objectives

The aim of this study was to evaluate the prognostic value of NLR and RDW in patients presenting with AP. The primary objective was to assess the severity of AP by analyzing these inflammatory markers. Additionally, the study sought to track the progression of NLR and RDW at three time points, at admission (0 hours), 24 hours, and 48 hours after hospital presentation, to better understand their role in disease progression.

Materials and Methods

The study was conducted on patients presenting with AP in the medicine and gastroenterology departments at Fortis Escorts Hospital, Jaipur. The study population included patients admitted with AP through the outpatient and emergency departments of medicine and gastroenterology who met the inclusion and exclusion criteria. This observational, prospective study was carried out at Fortis Escorts Hospital, Jaipur, over a duration of 1 year following approval from the Scientific Research Committee (SRC) and the Institutional Ethics Committee (IEC).

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Study Design and Type

This was a hospital-based, prospective, observational study.

Study Duration

From December 2022 to December 2023.

Sample Size

A total of 54 participants were studied.

Inclusion Criteria

The inclusion criteria for the study encompass patients over 18 years of age who meet the specified criteria for AP.

Exclusion Criteria

The exclusion criteria rule out patients with hematologic diseases, chronic infections, liver disease, or heart failure; those with hematological malignancies undergoing chemotherapy; pregnant patients; individuals who have had a COVID-19 infection within the past month; and those who do not provide consent.

Table 1: Distribution of study participants according to age-group and gender

Age-group	*Frequency*	*Percent*
≤30 years	6	11.1
31–40 years	17	31.5
41–50 year	27	50.0
>50 years	4	7.4
Total	54	100.0

Gender: females—10, males—44

Methodology

After obtaining written informed consent, patients underwent a detailed history and physical examination. Routine tests including complete blood count (CBC), serum amylase, lipase, creatinine, blood urea nitrogen (BUN), calcium, C-reactive protein (CRP), triglycerides, random blood sugar, liver function, arterial blood gas, electrolytes, and electrocardiogram (ECG) were performed. Radiological investigations such as ultrasound, computed tomography (CT) scan, and chest X-ray were done as needed. RDW and NLR were measured on days 0, 1, and 2 and correlated with clinical severity. The bedside index for severity in acute pancreatitis (BISAP) score was calculated using five parameters: blood urea nitrogen >25 mg/dL, impaired mental status, systemic inflammatory response syndrome, age >60, and pleural effusion. Diagnosis of AP required two of the following: continuous epigastric pain, elevated serum amylase/lipase ≥3 times normal, or characteristic imaging findings. After 48 hours, patients were classified as mild (no organ failure or complications) or severe (persistent organ failure or complications). RDW and NLR values were then correlated with severity.

Table 4: Distribution of study participants according to severity

Severity	*Frequency*	*Percent*
Mild	40	74.1
Severe	14	25.9
Total	54	100.0

Table 2: Comparison of NLR at different time intervals

	NLR	*NLR at 24 hours*	*NLR at 48 hours*
Mean	7.567	6.476	4.543
Median	7.200	5.900	4.300
Std. deviation	2.4156	1.9004	0.9338
Minimum	4.3	3.9	3.2
Maximum	13.5	11.3	7.1
p-value (ANOVA test)	0.0001		
p-value (compare to baseline)		0.0001	0.0001

Table 3: Comparison of RDW at different time intervals

	RDW baseline	*RDW at 24*	*RDW at 48*
Mean	13.967	14.111	13.769
Median	13.800	13.700	13.650
Std. deviation	1.1712	1.3155	1.8945
Minimum	12.2	12.4	7.1
Maximum	17.2	17.3	17.7
p-value (ANOVA test)	0.342		
p-value (compare to baseline)		0.156	0.477

Ethical Clearance

The study received approval from the Institutional Ethics Committee, reference number FEHJ/IEC/22/029, dated 20/12/2022.

Statistical Analysis

Predesigned proformas were checked for completeness and cleaned for errors and missing values. Cleaned data was entered into Excel using a master chart. After every 10 entries, one form was randomly rechecked for accuracy. Analysis was conducted with SPSS version 24.0. Univariate analysis results are shown in tables, text, bar graphs, and pie charts. Frequencies described categorical variables; central tendency and dispersion summarized continuous variables. Independent *t*-tests compared continuous variables, and Chi-squared tests analyzed categorical variables. Significance was set at $p < 0.05$.

Observation and Results

The study included 54 participants (81.5% male), aged 25–66 years (mean 41.96 ± 8.95), mostly aged 41–50 (50%). Mean weight was76.8 kg, height 1.71 m, BMI 26.44 kg/m^2 (Table 1). Common complaints were abdominal pain, nausea, and vomiting (87%), with fever in 59.3%. Comorbidities included hypertension (24.1%), diabetes (25.9%), CKD (13%), and CVD (11.1%). Smoking and alcohol use were reported by 22.2 and 25.9%, respectively.

The NLR decreased significantly over 48 hours (baseline 7.57 to 4.54, $p < 0.0001$), while RDW showed no significant change (Tables 2 and 3). Complications included pseudocyst (11.1%), pancreatic necrosis (5.6%), ARF, and MODS (each 3.7%). Severity was mild in 74.1% and severe in 25.9%; 13% required intensive care unit (ICU) stay (Table 4). Mean hospital and ICU stays were 7.93 and 2.86 days; mortality was 7.4%.

No significant differences in age, gender, symptoms, comorbidities, or habits were found between mild and severe cases (Tables 5 and 6). NLR and RDW values were significantly higher in severe pancreatitis at all time points ($p < 0.0001$), including at 48 hours (NLR $p = 0.015$, RDW $p = 0.012$) (Figs 1 and 2). Severe cases had higher mortality ($p < 0.0001$) and longer hospital stays ($p = 0.001$) (Table 7).

Discussion

Acute pancreatitis is an acute, potentially life-threatening inflammatory condition of the pancreas characterized by abdominal pain and systemic inflammation. Its severity ranges from mild, self-limiting forms to severe disease with necrosis and multiorgan failure. Accurate

Table 5: Comparison of severity of AP and complaints

Complaints	*Mild*		*Severe*		*p-value*
	Count	*%*	*Count*	*%*	
Pain abdomen	36	76.6%	11	23.4%	0.273
Nausea	35	74.5%	12	25.5%	0.864
Vomiting	36	76.6%	11	23.4%	0.273
Fever	25	78.1%	7	21.9%	0.413

Table 6: Comparison of severity of AP and comorbidities and history

Variable	*Mild*		*Severe*		*p-value*
	Count	*%*	*Count*	*%*	
Hypertension	8	61.5%	5	38.5%	0.237
CKD	5	71.4%	2	28.6%	0.864
CVD	5	83.3%	1	16.7%	0.583
DM	11	78.6%	3	21.4%	0.655
Smoking	9	75.0%	3	25.0%	0.934
Alcohol	10	71.4%	4	28.6%	0.069

Table 7: Comparison of severity of AP and final outcome, hospital and ICU stay

Outcome	*Mild*		*Severe*		*p-value*
	Count	*%*	*Count*	*%*	
Alive	40	80.0%	10	20.0%	0.0001
Dead	0	0.0%	4	100.0%	
Total	40	74.1%	14	25.9%	
Hospital stay (days)	4.512 ± 1.76		8.924 ± 3.6		0.001
ICU stay (days)	1.5 ± 0.271		2.6447 ± 1.6733		0.001

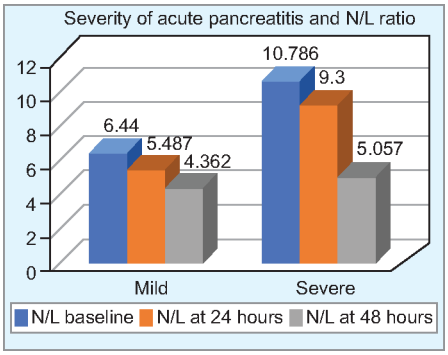

Fig. 1: Comparison between NLR and severity

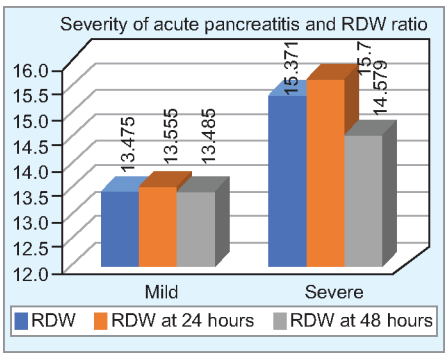

Fig. 2: Comparison between RDW and severity

early evaluation of disease severity is essential to guide prompt and appropriate therapeutic decisions. The NLR and RDW have emerged as useful, easily available prognostic markers for predicting disease severity and outcomes in AP.

In our cohort, NLR decreased over 48 hours but remained markedly higher among patients with severe disease, a trend comparable to previous studies reporting a correlation between elevated NLR and adverse outcomes.[16–20] RDW, on the other hand, was significantly higher in severe cases but did not vary substantially over time. These findings are partly in agreement with Raghavan and Ponraj,[18] who identified RDW cutoff values predictive of severity, and Goyal et al.,[21] who demonstrated its prognostic value, albeit with study limitations.

Comparable studies have also reported similar associations, further supporting the prognostic significance of these markers. O'Connell et al.[22] reported that elevated RDW and NLR at admission independently predicted ICU or high-dependency unit admission and increased mortality risk, highlighting their potential for early, cost-effective risk stratification compared with traditional scoring systems. Similarly, Jayalal et al.[23] found that both NLR and the platelet-to-lymphocyte ratio were independent negative prognostic indicators of AP severity. Jain et al.[24] further confirmed that inflammatory markers such as NLR and RDW performed comparably to established scoring systems in predicting disease severity.

In summary, this study reinforces NLR as a dynamic marker for monitoring AP severity, while RDW effectively distinguishes between mild and severe cases but lacks time-dependent predictive utility. Incorporating serial NLR assessments and RDW measurements into routine clinical evaluation can enhance prognostic accuracy and guide therapeutic decision-making, ultimately reducing morbidity and mortality. Taken together, our findings and prior evidence indicate that NLR and RDW are practical and economical indicators for assessing disease severity at an early stage.

Conclusion

This study highlights the prognostic importance of NLR and RDW in evaluating severity and predicting outcomes in AP. Although NLR values declined with time, they remained markedly higher among patients with severe disease, confirming their prognostic value. RDW was also notably elevated in the severe group versus the mild group, suggesting a potential role in forecasting severity, although evidence on RDW's predictive value is still inconclusive. Additionally, the study demonstrated a strong, statistically significant link between AP severity and mortality, with all fatalities occurring exclusively in the severe category.

Strength and Limitations of the Study

The study comprehensively assesses NLR and RDW as prognostic markers in AP, analyzing their changes over 0, 24, and 48 hours. It explores the relationship between disease severity, inflammatory markers, and clinical outcomes, including mortality, while evaluating how severity influences management decisions such as ICU admission and hospital stay duration. However, the single-center observational design limits generalizability, the relatively small sample size may reduce statistical power, and the lack of long-term follow-up restricts understanding of the extended prognostic value of NLR and RDW.

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ORIGINAL ARTICLE

Comparison of National Early Warning Score 2, Sepsis-related Organ Failure Assessment, and Quick Sequential Organ Failure Assessment Scores in Detecting Sepsis-induced Organ Dysfunction and Predicting the Outcome in Sepsis: A Prospective Observational Study

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Abstract

Background: We intended to compare the National Early Warning Score 2 (NEWS2), sepsis-related organ failure assessment (SOFA), and quick sequential organ failure assessment (qSOFA) scores for their ability to detect sepsis-induced organ dysfunction and to predict in-hospital mortality and length of hospital stay (LOHS) of survivors in sepsis patients, as such studies have been lacking in the literature.

Materials and methods: This is a prospective observational study of patients ≥ 18 years of age with suspected or documented infection and fulfilling SIRS criteria of ≥ 2. NEWS2, SOFA, and qSOFA scores were compared using the receiver operating characteristic (ROC) curve.

Results: We had 140 patients in the study. The SOFA score had the highest area under the curve (AUC) in identifying sepsis-induced organ dysfunction, followed by NEWS2 and qSOFA. NEWS2 on day 2, followed by qSOFA on day 2, had the highest AUC in predicting in-hospital mortality, but without a statistically significant difference between them ($p = 0.2720$). NEWS2 on day 2, followed by qSOFA on day 2, had the highest AUC in predicting LOHS among survivors, but without a statistically significant difference between them ($p = 0.1015$).

Conclusion: Among the on-admission scores, NEWS2 predicted in-hospital sepsis mortality the best. Overall, the day 2 NEWS2 and qSOFA were better than the on-admission scores in predicting both mortality and LOHS of survivors. However, the AUC difference between the scores was not statistically significant. So, we conclude that compared to NEWS2 and SOFA, qSOFA is still a simpler and quicker way to prognosticate sepsis patients. SOFA was better at identifying sepsis-induced organ dysfunction.

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Introduction

Sepsis, a critical condition characterized by organ dysfunction arising from an abnormal and dysregulated host immune response to infection, is often the terminal complication leading to death from various infections globally. Delayed recognition can result in progression to septic shock, development of multiorgan failure, and eventual mortality.[1,2] Early detection and prognostication of sepsis are of clinical importance, as they guide clinicians in choosing the appropriate level of care and management. Several scoring systems have been established to facilitate the early identification and prognostication of sepsis, including the systemic inflammatory response syndrome (SIRS), sepsis-related organ failure assessment (SOFA), quick sequential organ failure assessment (qSOFA), and National Early Warning Score 2 (NEWS2).[2–5] Although studies comparing various scores in sepsis mortality are available in the literature, studies comparing NEWS2, SOFA, and qSOFA are limited. In this study, we aimed to compare the NEWS2, SOFA, and qSOFA scores for their ability to detect sepsis-induced organ dysfunction and to predict in-hospital mortality and the length of hospital stay (LOHS) among survivors with sepsis.

Materials and Methods

A prospective observational study design was adopted, and the study was conducted in the Department of Internal Medicine at a tertiary care hospital (Kauvery Hospital, Tennur, Trichy, India) during the period from September 2022 to November 2023.

Inclusion Criteria

Any patient aged ≥18 years with both of the following: (i) suspected or documented infection, and (ii) a SIRS score ≥2. The "Sepsis-1" definition formed the basis of our inclusion criteria.[2,6]

Exclusion Criteria

- Trauma patients.
- Patients with a hospital stay of <2 days.
- Patients who succumbed on the day of admission.
- Patients discharged against medical advice.

The study received ethical approval from the Institutional Ethics Committee, and written informed consent was obtained from all enrolled participants.

Various clinical (vital) parameters and laboratory values were noted, and NEWS, SOFA, and qSOFA scores were calculated on admission. On day 2 of hospitalization, NEWS2 and qSOFA scores were calculated. The SOFA score in our study refers only to the on-admission score, as we did not calculate the SOFA score on day 2.

Patients with organ dysfunction were identified. NEWS2, SOFA, and qSOFA scores on admission were compared using the receiver operating characteristic (ROC) curve for the prediction of organ dysfunction. NEWS2, SOFA, and qSOFA scores on admission, as well as NEWS2 and qSOFA scores on day 2, were compared using the ROC curve for outcome prediction. In-hospital mortality was considered the outcome. The LOHS of survivors was divided into two groups: >5 days and ≤5 days. Prolonged length of stay

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was defined as an LOHS >5 days. The NEWS2, SOFA, and qSOFA scores on admission, along with NEWS2 and qSOFA scores on day 2, were compared using the ROC curve for predicting an LOHS of >5 days among survivors.

Statistical Analysis

The MDCalc application was used to calculate the NEWS2, SOFA, and qSOFA scores. Statistical analyses were performed using MedCalc version 22.026 and SPSS version 26. Tables were created using Microsoft Word 2021. Continuous variables were presented as mean ± standard deviation (SD) or median, while discrete variables were expressed as numbers (percentages). The Chi-square test was used to assess associations between categorical variables. Mortality prediction was performed using the ROC curve, and the ROC curve cut-off criterion was determined using the Youden Index. A *p*-value of <0.05 was considered statistically significant.

Definitions

Sepsis as per "Sepsis-1" Criteria

The systemic response to infection is manifested by two or more of the SIRS components: (i) temperature >38°C or <36°C, (ii) heart rate >90/min, (iii) respiratory rate >20/min or $PaCO_2$ <32 mm Hg, and (iv) total white blood cell (WBC) count >12,000/mm^3 or <4,000/mm^3 or >10% immature bands, as a result of infection.[2,6] This definition formed the basis for our inclusion criteria.

Sepsis-induced Organ Dysfunction

The criteria to define "sepsis-induced organ dysfunction" were based on the "severe sepsis" definition provided by the Surviving Sepsis Campaign 2012 guidelines.[7] The presence of any of the following, considered attributable to infection, was taken as indicative of sepsis-induced organ dysfunction:[7] (i) hypotension related to sepsis, (ii) serum lactate levels exceeding the laboratory's upper reference limit, (iii) urine output <0.5 mL/kg/hour for over 2 hours despite adequate fluid resuscitation, (iv) acute lung injury with a PaO_2/FiO_2 ratio <250 when pneumonia was not the presumed infection source, or a PaO_2/FiO_2 ratio <200 when pneumonia was the presumed infection source, (v) serum creatinine >2.0 mg/dL, (vi) total serum bilirubin >2 mg/dL, (vii) platelet count <1 lakh/µL, and (viii) coagulopathy, defined as an international normalized ratio (INR) >1.5.

Results

A total of 140 patients were included in the study. The recruitment process and study methodology are outlined in Figure 1. The baseline clinical characteristics are summarized in Table 1. The genitourinary tract (60%), especially urinary tract infection, was the most common infection source in our sepsis patients (Fig. 2), followed by gastrointestinal infections (12.1%), skin and soft tissue infections (11.4%), and respiratory infections (9.3%). The source of infection could not be determined in 7.1% of patients. The in-hospital mortality rate was 28.6% (*n* = 40). Out of 140 patients, 66 were males (47.14%), and 74 (52.86%) were females. The mean and median days of illness (DOI) on presentation were 6.34 ± 4.49 and 5 days, respectively. The mean and median LOHS among survivors were 7.76 ± 5.17 and 7 days, respectively. Out of 140 patients, 64 (45.7%) had hypotension, i.e., systolic blood pressure ≤ 90 mm Hg. The mortality rates among hypotensive patients, patients who required vasopressors, and patients who required ventilatory support (in the first 2 days) were 48.4%, 48.1%, and 59%, respectively, and the associations were statistically significant (Chi-square test, $p < 0.0001$). The median NEWS2, SOFA, and

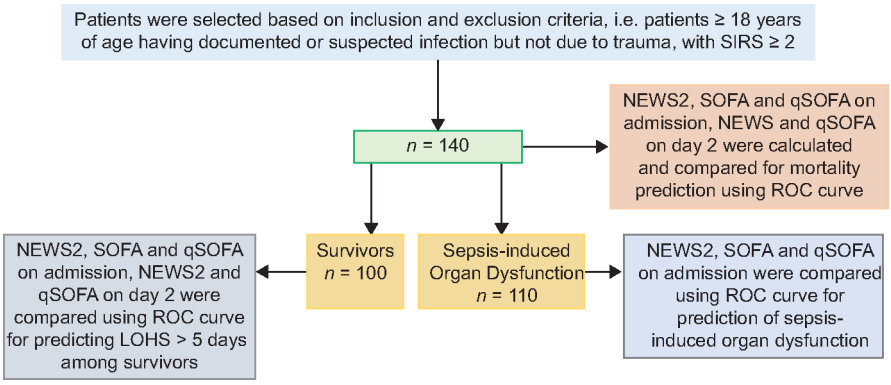

Fig. 1: Flowchart depicting the recruitment of patients and the methodology of our study

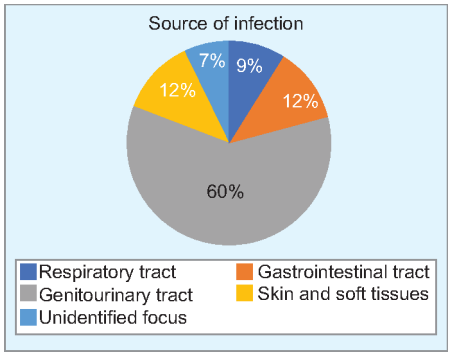

Fig. 2: Pie Chart illustrating the distribution of the source of infection in our patients

Table 1: Clinical characteristics of the patients in our study

Parameters		*Mean ± SD*	*Median*	*Minimum, maximum values*	*Total (n = 140) n (%)*	*Mortality n (%)*	*p-value (Chi-square test)*
Age		60.27 ± 15.73	63.5	18, 86	–	–	
Sex	Males		–		66 (47.14%)	–	
	Females				74 (52.86%)		
Day of illness on presentation		6.34 ± 4.49	5	1, 21	–	–	
Length of hospital stay among survivors (*n* = 100)		7.76 ± 5.17	7	2, 32	–	–	
Hypotension		–	–	–	64 (45.7%)	31 (48.4%)	<0.0001
Treatment with a vasopressor		–	–	–	54 (38.6%)	26 (48.1%)	<0.0001
Needed ventilatory support (in the first 2 days)		–	–	–	39 (27.9%)	23 (59%)	<0.0001

Table 2: ROC curve characteristics for various scores calculated on admission in predicting sepsis-induced organ dysfunction

Score (on admission)	*Area under ROC curve*	*95% CI for AUC*	*p-value for AUC*	*Criterion*	*Sensitivity (%)*	*Specificity (%)*
SIRS	0.604	0.518–0.685	0.0678	>2	67.27	56.67
qSOFA	0.727	0.646–0.799	<0.0001	>1	64.55	80.00
SOFA	0.938	0.885–0.972	<0.0001	>2	84.55	86.67
NEWS2	0.778	0.700–0.844	<0.0001	>9	46.36	100.00

Table 3: ROC curves comparison for various scores calculated on admission in predicting sepsis-induced organ dysfunction

Score comparisons	*AUC comparisons*			*p-value*
	Difference between AUC	*Standard error*	*95% CI for difference*	
NEWS2 vs SOFA	0.160	0.0361	0.0892–0.231	$p < 0.0001$
NEWS2 vs qSOFA	0.0509	0.0366	–0.0208–0.123	$p = 0.1638$
SOFA vs qSOFA	0.211	0.0426	0.127–0.294	$p < 0.0001$

Table 4: ROC curve characteristics for various scores in sepsis mortality prediction

Score	*Area under ROC curve*	*95% CI for AUC*	*p-value for AUC*	*Criterion*	*Sensitivity (%)*	*Specificity (%)*
SIRS	0.583	0.497–0.666	0.078	>2	72.50	42.00
qSOFA on admission	0.767	0.689–0.835	<0.0001	>1	85.00	57.00
qSOFA on day 2	0.916	0.858–0.956	<0.0001	>1	92.50	78.00
SOFA	0.777	0.699–0.843	<0.0001	>7	65.00	79.00
NEWS2 on admission	0.814	0.740–0.875	<0.0001	>10	67.50	83.00
NEWS2 on day 2	0.935	0.880–0.969	<0.0001	>9	82.50	92.00

Table 5: ROC curves comparison for various scores in sepsis mortality prediction

Score comparisons	*AUC comparisons*			*p-value*
	Difference between AUC	*Standard error*	*95% CI for difference*	
NEWS2 on admission vs NEWS2 on day 2	0.120	0.0321	0.0575–0.183	$p = 0.0002$
NEWS2 on admission vs SOFA	0.0375	0.0316	–0.0244–0.0994	$p = 0.2352$
NEWS2 on admission vs qSOFA on admission	0.0469	0.0275	–0.00694–0.101	$p = 0.0878$
NEWS2 on admission vs qSOFA on day 2	0.102	0.0365	0.0306–0.174	$p = 0.0051$
NEWS2 on day 2 vs SOFA	0.158	0.0376	0.0843–0.231	$p < 0.0001$
NEWS2 on day 2 vs qSOFA on admission	0.167	0.0371	0.0944–0.240	$p < 0.0001$
NEWS2 on day 2 vs qSOFA on day 2	0.0183	0.0166	–0.0143–0.0508	$p = 0.2720$
SOFA vs qSOFA on admission	0.00938	0.0385	–0.0660–0.0848	$p = 0.8074$
SOFA vs qSOFA on day 2	0.140	0.0382	0.0648–0.214	$p = 0.0003$
qSOFA on admission vs qSOFA on day 2	0.149	0.0343	0.0818–0.216	$p < 0.0001$

qSOFA scores on admission were 7.5, 5, and 2, respectively, while the median NEWS2 and qSOFA scores on day 2 were 5.5 and 1, respectively. NEWS2 ≥11 had a mortality rate of 61.4%, SOFA ≥15 had a mortality rate of 75%, and qSOFA of 3 had a mortality rate of 59.4%.

Out of 140 patients, 110 (78.6%) had sepsis-induced organ dysfunction. The SOFA score had the highest AUC (Table 2 and Fig. 3) for identifying sepsis-induced organ dysfunction compared to NEWS2 and qSOFA, and the difference was statistically significant ($p < 0.0001$) (Table 3). Apart from the SOFA score, NEWS2 had a higher AUC than qSOFA, but the difference between the two was not statistically significant.

The NEWS2 score on day 2, followed by the qSOFA score on day 2, had the highest AUC (Table 4 and Fig. 4) for predicting in-hospital sepsis mortality. However, the difference between their AUCs did not reach statistical significance ($p = 0.2720$) as shown in Table 5. Among the admission scores, NEWS2 was better than SOFA and qSOFA; however, the differences in AUCs between the scores were not statistically significant.

Out of 100 survivors, 58% ($n = 58$) had an LOHS of >5 days. The NEWS2 score on day 2, followed by the qSOFA score on day 2, had the highest AUC (Table 6 and Fig. 5) for predicting an LOHS of >5 days among survivors. However, the difference between their AUCs did not reach statistical significance ($p = 0.1015$) as shown in Table 7. Among the admission scores, SOFA demonstrated the highest AUC, and the difference between SOFA and qSOFA was statistically significant.

The number of comorbidities showed a significantly higher AUC for predicting mortality compared to age and DOI at admission ($p = 0.0002$) (Table 8 and Fig. 6).

Table 6: ROC curve characteristics for various scores in prediction of LOHS > 5 days among survivors

Score	*Area under ROC curve*	*95% CI for AUC*	*p-value for AUC*	*Criterion*	*Sensitivity (%)*	*Specificity (%)*
NEWS2 on admission	0.635	0.533–0.729	0.0149	>9	32.76	90.48
NEWS2 on day 2	0.757	0.661–0.838	<0.0001	>2	86.21	54.76
SOFA	0.675	0.574–0.765	0.0014	>2	72.41	57.14
qSOFA on admission	0.563	0.461–0.662	0.2455	>1	50.00	66.67
qSOFA on day 2	0.705	0.605–0.792	<0.0001	>0	84.48	47.62
SIRS	0.556	0.453–0.656	0.2798	>2	62.07	47.62

Table 7: ROC curves comparison for various scores in the prediction of LOHS > 5 days among survivors

Score comparisons	*AUC comparisons*			*p-value*
	Difference between AUC	*Standard error*	*95% CI for difference*	
NEWS2 on admission vs NEWS2 on day 2	0.123	0.0569	0.0110–0.234	$p = 0.0313$
NEWS2 on admission vs SOFA	0.0398	0.0517	−0.0615–0.141	$p = 0.4411$
NEWS2 on admission vs qSOFA on admission	0.0714	0.0390	−0.00498–0.148	$p = 0.0669$
NEWS2 on admission vs qSOFA on day 2	0.0700	0.0610	−0.0495–0.189	$p = 0.2509$
NEWS2 on day 2 vs SOFA	0.0827	0.0649	−0.0445–0.210	$p = 0.2024$
NEWS2 on day 2 vs qSOFA on admission	0.194	0.0634	0.0698–0.318	$p = 0.0022$
NEWS2 on day 2 vs qSOFA on day 2	0.0525	0.0321	−0.0103–0.115	$p = 0.1015$
SOFA vs qSOFA on admission	0.111	0.0530	0.00733–0.215	$p = 0.0359$
SOFA vs qSOFA on day 2	0.0302	0.0635	−0.0943–0.155	$p = 0.6346$
qSOFA on admission vs qSOFA on day 2	0.141	0.0623	0.0193–0.264	$p = 0.0232$

Table 8: ROC curve characteristics of various parameters in sepsis mortality prediction

Parameter	*Area under ROC curve*	*95% CI for AUC*	*p-value for AUC*	*Criterion*	*Sensitivity (%)*	*Specificity (%)*
Age	0.560	0.473–0.643	0.2480	>39	100	14
No. of comorbidities	0.687	0.604–0.763	0.0002	>2	55	76
DOI on admission	0.592	0.506–0.674	0.0745	>4	65	54

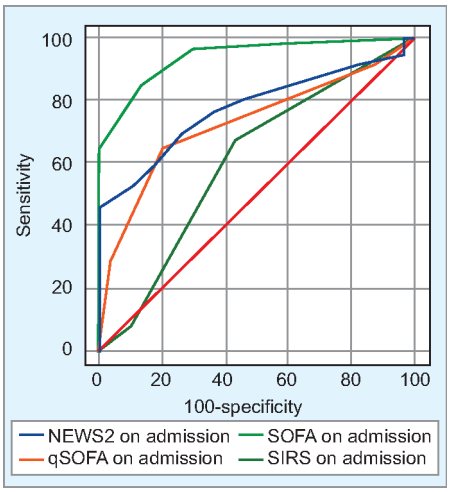

Fig. 3: Comparison of ROC curves with AUCs for NEWS2, SOFA, qSOFA, and SIRS scores calculated on admission in detecting sepsis-induced organ dysfunction

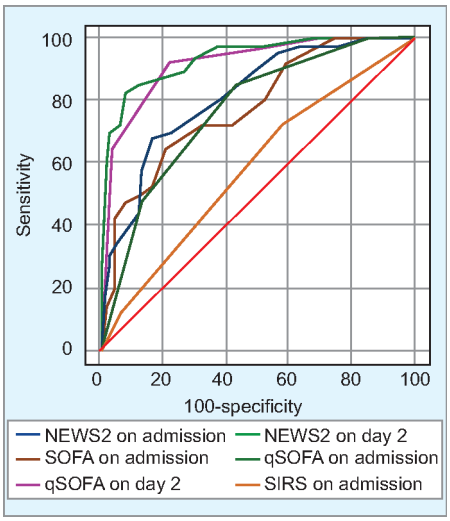

Fig. 4: Comparison of ROC curves with AUCs for NEWS2, SOFA, qSOFA, and SIRS scores calculated on admission, and NEWS2 and qSOFA scores calculated on day 2 in predicting the mortality of our patients

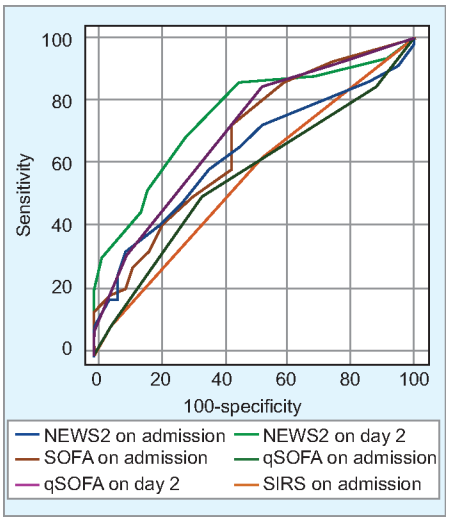

Fig. 5: Comparison of ROC curves with AUCs for NEWS2, SOFA, qSOFA, and SIRS scores calculated on admission, and NEWS2 and qSOFA scores calculated on day 2 in the prediction of LOHS > 5 days among survivors

Discussion

We enrolled 140 patients based on our inclusion and exclusion criteria. Our study population had a mean age of 60.27 ± 15.73 years and a median age of 63.5 years. This was similar to other sepsis studies,[8–12] in which the mean age has been reported to range

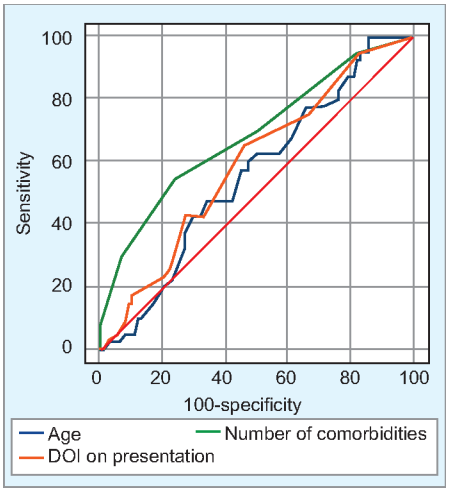

Fig. 6: Comparison of ROC curves with AUCs for age, number of comorbidities, and DOI on presentation in predicting mortality

between 60 and 65 years. The in-hospital mortality rate was 28.6% (n = 40). Mortality rates in other sepsis studies have ranged from 24 to 67%.[13–17]

A total of 110 patients (78.6%) had sepsis-induced organ dysfunction. The SOFA score (0.938) had the highest AUC in identifying sepsis-induced organ dysfunction, followed by NEWS2 and qSOFA scores. NEWS2 on admission >9 had the highest specificity, and SOFA >2 had the highest sensitivity in significantly predicting sepsis-induced organ dysfunction. The differences between the AUCs of SOFA and NEWS2, and SOFA and qSOFA, were statistically significant. However, the AUC difference between NEWS2 and qSOFA was not statistically significant. Mellhammar et al.,[18] in their 2019 study, reported that NEWS2 was significantly better than qSOFA in detecting sepsis-induced organ dysfunction. The superior performance of the SOFA score in detecting sepsis-induced organ dysfunction compared to NEWS2 and qSOFA could be due to the similarity between the SOFA score criteria and the definition of sepsis-induced organ dysfunction.

Several studies[18–25] are available comparing various scores in predicting in-hospital sepsis mortality. However, we could not find a study that compared NEWS2, SOFA, and qSOFA for sepsis mortality prediction. A study conducted by Asmarawati et al.[26] included NEWS2, SOFA, qSOFA, and the acute physiology and chronic health evaluation II (APACHE II) scores for predicting mortality; however, it was performed in COVID-19 patients. The study found that the initial NEWS2 had a higher AUC in predicting mortality compared to the other scores. A study conducted by Bhattacharya et al.,[13] which included 122 sepsis patients to determine the efficacies of SIRS, SOFA, and qSOFA scores for predicting sepsis mortality, concluded that both SOFA and qSOFA were superior to SIRS. However, their analysis did not include NEWS2, which was incorporated in our study.

In our study, NEWS2 on day 2 had the highest AUC (0.935) in predicting in-hospital mortality, followed by qSOFA on day 2 (0.916), NEWS2 on admission, SOFA, and qSOFA on admission. A NEWS2 score on day 2 >9 had the highest specificity, while a qSOFA score on day 2 >1 had the highest sensitivity for significantly predicting mortality. The AUCs of all these scores were statistically significant. Although NEWS2 on day 2 had a higher AUC compared to qSOFA on day 2, the difference between their AUCs was not statistically significant; thus, qSOFA on day 2 is not statistically inferior to NEWS2 on day 2. Additionally, the day 2 scores of NEWS2 and qSOFA were significantly better than the admission scores of NEWS2, SOFA, and qSOFA. Among the admission scores, NEWS2 was better than SOFA and qSOFA; however, the differences in AUC between the scores were not statistically significant. Myrstad et al.[20] in 2020 showed that the NEWS2 score on admission was superior to qSOFA and other risk scores for predicting in-hospital sepsis mortality.

We also compared the scores to predict an LOHS >5 days in survivors. Among the 100 survivors, 58 had a hospital stay exceeding 5 days, while 42 were hospitalized for 5 days or less. On comparing the scores, NEWS2 on day 2 had the highest AUC (0.757), followed by qSOFA on day 2 (0.705), SOFA, NEWS2 on admission, and qSOFA on admission. The AUCs of NEWS2 on admission, NEWS2 on day 2, SOFA, and qSOFA on day 2 were statistically significant. A NEWS2 score on admission >9 had the highest specificity, while a NEWS2 score on day 2 >2 had the highest sensitivity in significantly predicting an LOHS >5 days among survivors. Although NEWS2 on day 2 had a higher AUC compared to qSOFA on day 2, the difference between their AUCs was not statistically significant. NEWS2 assessed on day 2 performed significantly better than its admission scores as well as the admission qSOFA score. Similarly, the day 2 qSOFA score was significantly superior to the qSOFA score at admission. Among the admission scores, SOFA was better than NEWS2 and qSOFA, with SOFA being significantly better than qSOFA.

Prior studies have reported that 55.5–65% of patients with sepsis had preexisting comorbid conditions.[27–29] In our study population, 14.3% had no comorbidities, 30% had one comorbidity, 22.9% had two comorbidities, 19.3% had three comorbidities, 11.4% had four comorbidities, 1.4% had five comorbidities, and 0.7% had six comorbidities. Although not our primary objective, apart from sepsis scores, we also compared the number of comorbidities, DOI on admission, and age in predicting in-hospital sepsis mortality. We found that the number of comorbidities had the highest AUC (0.687) for predicting in-hospital sepsis mortality, and it was statistically significant.

Limitations

The limitations of our study are: (i) the SOFA score on day 2 was not included, as we do not routinely repeat blood tests on day 2 for all sepsis patients, and performing them for study purposes would increase the treatment cost for the patients; (ii) the superior performance of the SOFA score in identifying sepsis-induced organ dysfunction compared to NEWS2 and qSOFA scores could be due to the similarity between the SOFA score criteria and the definition of sepsis-induced organ dysfunction; (iii) our study has a limited sample size, and large-scale studies are needed to establish more definitive and reliable conclusions; and (iv) our study population did not represent the entire spectrum of sepsis foci.

Conclusions

To conclude, among the admission scores, NEWS2 was better than SOFA and qSOFA in predicting in-hospital sepsis mortality, although the differences in AUC between the scores were not statistically significant, while SOFA was better than qSOFA in predicting the LOHS of sepsis survivors. Overall, the day 2 scores of NEWS2 and qSOFA were better than the admission scores in predicting both in-hospital sepsis mortality and LOHS of sepsis survivors, with no statistically significant difference observed between the two. Compared to NEWS2 and SOFA, qSOFA remains a simpler and quicker tool to prognosticate sepsis patients on admission and day 2. The SOFA score was superior in identifying sepsis-induced organ dysfunction patients.

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ORIGINAL ARTICLE

A Randomized Multicenter Double-blind Placebo-controlled Prospective Study to Evaluate the Efficacy and Safety of Magnesium + Vitamin D Supplement as an Add-on Therapy to Oral Hypoglycemic Agents in Type 2 Diabetic Patients

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Abstract

Background: Diabetes mellitus (DM) is a growing global concern, with India projected to have 124.9 million cases by 2045. Magnesium (Mg) and vitamin D (VitD) deficiencies are linked to poor glycemic control. Both nutrients play essential roles in glucose metabolism and insulin function, but their combined supplementation in diabetes management remains underexplored. This study evaluates the efficacy and safety of Mg + VitD supplementation as an adjunct to oral hypoglycemic agents (OHAs) in patients with type 2 diabetes mellitus (T2DM).

Materials and methods: A randomized, multicenter, double-blind, placebo-controlled trial was conducted for 90 days across two hospitals in India. 100 T2DM patients were randomized (1:1) to receive Mg (250 mg) + VitD (600 IU) supplementation or placebo alongside standard OHA therapy. The primary outcome assessed changes in OHA dosage, fasting blood sugar (FBS), and postprandial blood sugar (PPBS). Secondary outcomes included HbA1c, serum insulin, HOMA-IR, Mg, and VitD levels, diabetes symptoms checklist (DSC) score, and quality of life score (SF-36).

Results: By day 90, the test group showed a significant reduction in FBS ($p = 0.01$) and HbA1c ($p < 0.0001$) compared to placebo. Serum Mg levels increased significantly ($p < 0.0001$), while serum insulin also improved ($p = 0.01$). HOMA-IR changes were not significant. SF-36 scores indicated significant improvements in physical function ($p = 0.049$), emotional well-being, and pain ($p < 0.05$). DSC scores showed symptom relief in hyperglycemia ($p < 0.0001$), cardiovascular symptoms ($p = 0.003$), neuropathy ($p = 0.028$), and ophthalmological symptoms ($p = 0.006$). No adverse effects were reported.

Conclusion: Mg + VitD supplementation as an adjunct to OHA therapy significantly improved glycemic control better than OHA therapy alone, HbA1c levels, insulin sensitivity, and quality of life in T2DM patients. The intervention was well-tolerated and may serve as a valuable addition to diabetes management, improving treatment outcomes significantly.

Trial registration: The current study has been duly registered with the CTRI (CTRI/2023/03/050877) (20/03/2023).

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Introduction

India, the diabetes capital, is expected to have 124.9 million (10.9%) patients by 2045, according to IDF.[1] Studies link micronutrient deficiencies, such as magnesium (Mg) and vitamin D (VitD), due to diet restrictions and medications, to rising diabetes prevalence and poor control, indicated by higher glycated hemoglobin.[2] Mg acts as a crucial cofactor supporting key enzymes in glucose transport, oxidation, insulin release, and action, activating ATPase and adenylate cyclase enzymes, in pancreatic islets and other tissues.[3]

Magnesium and VitD independently regulate pancreatic β-cell function, insulin release and sensitivity, and glucose metabolism and control. Deficiencies in these nutrients may compromise these functions and increase the risk of developing type 2 diabetes mellitus (T2DM), its persistence, and complications.[4] Research indicates that in T2DM, higher circulating Mg levels are associated with lower blood glucose, HbA1c, and markers of insulin resistance.[5]

Recent systematic reviews and meta-analyses found that oral VitD supplementation significantly reduced fasting blood glucose, HOMA-IR, HbA1c, and improved serum 25(OH) D levels.[6] Diabetic individuals showed low serum Mg levels, negatively associated with diabetes duration, poor glycemic control, and complications.[7] A pooled analysis of 24 RCTs demonstrated that Mg as an adjuvant therapy significantly improved serum Mg, fasting blood glucose, HOMA-IR, and HbA1c in T2DM patients.[8] Additionally, Mg plays a crucial role in VitD absorption, transportation, conversion, activation, and pharmacological action.[9] An Indian study found that in new-onset T2DM, VitD deficiency was more prevalent, with about 20% individuals being subclinically Mg deficient, with a strong negative correlation between these deficiencies and HOMA-IR, HbA1c, and specifically HOMA-B. Although this study did not investigate the effect of combined VitD and Mg on glycemic control parameters, the authors recommended routine estimation of VitD and Mg in all newly diagnosed type 2 diabetic patients.[10] Therefore, this study aims to evaluate the efficacy and safety of Mg + VitD combination as an adjunct to standard oral hypoglycemic therapy in T2DM. This has been suggested by many studies showing that nutraceuticals addressing common nutritional deficiencies in type 2 diabetes mellitus may offer promising adjunctive therapeutic options.

Materials and Methods

Trial Design

This was a multicentric, randomized, double-blinded, placebo-controlled trial conducted for 90 days at the outpatient departments of Pranav Diabetes Center, Bengaluru, and Care Multispecialty Hospital, Pune. The study was approved by the Institutional Ethics Committees of both centers. 100 participants were recruited into two parallel groups in a 1:1 randomization allocation.

Study Objective

Primary objective: Mean changes in oral hypoglycemic agents (OHAs) dose, fasting,

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and postprandial plasma glucose from baseline to day 90 between groups.

Secondary objectives included mean changes in HbA1c, serum insulin, HOMA-IR, Mg, and VitD levels; symptom improvement [diabetes symptoms checklist (DSC) score]; quality of life (SF-36 score); and safety and tolerability.

Inclusion and Exclusion Criteria

Adults of either sex aged 18–70 years with BMI 23–40 kg/m^2, diagnosed with T2DM (HbA1c > 6.5%), and receiving OHAs were eligible. Individuals on insulin therapy, glucose-control supplements, with diabetic complications, major systemic illnesses, pregnancy/lactation, corticosteroid therapy, or recent clinical trial participation were excluded.

Methodology

Adults aged 18–70 years with T2DM on standard therapy were enrolled after informed consent and baseline demographic, clinical, and laboratory assessments. Participants were randomized to receive Mg + VitD or placebo once daily, along with standardized diet and exercise advice. Follow-ups on days 45 and 90 included assessment of vitals, fasting blood sugar (FBS), and postprandial blood sugar (PPBS), adverse events, supplements, and compliance with interim telephonic assessments. SF-36, DSC scores, and laboratory parameters were evaluated at baseline and day 90. Data were analyzed using SPSS Version 24, with compliance ≥80% considered acceptable (Fig. 1).

Results and Observation

Demographic Characteristics

Of 108 subjects screened, 5 experienced screen failures and 3 withdrew consent; 100 subjects were enrolled, and all completed the study. Groups were comparable in age, sex, and waist circumference, but BMI differed significantly (placebo: 27.40 ± 4.80 vs test: 25.41 ± 3.29 kg/m^2, $p = 0.015$).

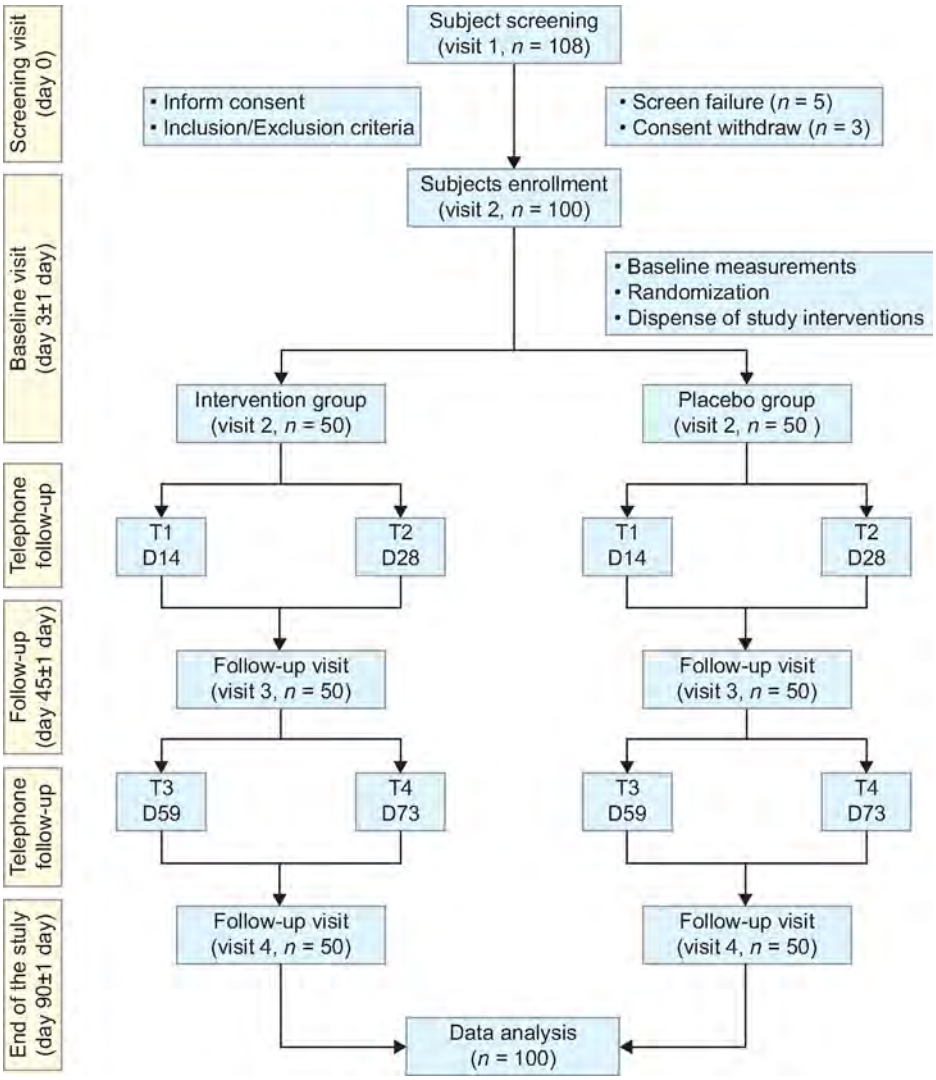


Fig. 1: CONSORT flow diagram

Assessment of Oral Hypoglycemic Agents Dose

No reduction in OHA dose was recommended for any participant, as FBS and PPBS levels, while trending downward, remained above normal ranges throughout the study.

Assessment of FBS and PPBS

By day 90, the test group demonstrated a significant between-group reduction in FBS ($p = 0.01$). Within-group analysis confirmed a significant reduction in FBS in the test group over time ($p = 0.03$), indicating the potential efficacy of the Mg + VitD supplement in lowering fasting glucose levels on continued supplementation. While the placebo group showed no significant change ($p = 0.98$). PPBS reductions in the test group showed a trend but did not reach statistical significance ($p = 0.50$) (Tables 1 and 2, and Fig. 2).

Assessment of Serum Biochemical Parameters

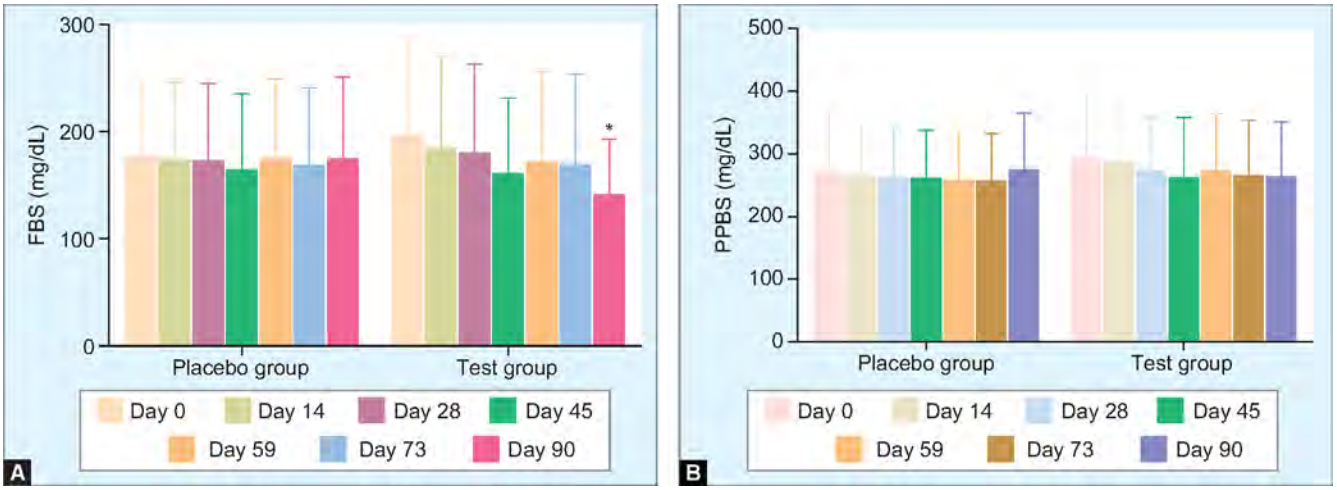
HbA1c declined significantly within the test group ($p < 0.0001$), with a significant between-group difference at day 90 ($p = 0.04$). Serum Mg increased significantly within the test group ($p < 0.0001$), and serum insulin also improved ($p = 0.01$). HOMA-IR and VitD 25-OH did not show significant changes in either group (Tables 3 and 4, and Figs 3 and 4). Results suggest that Mg + VitD supplementation as an add-on therapy to OHA may improve certain biochemical markers, particularly HbA1c and serum Mg, in type 2 diabetic patients.

Evaluation of the SF-36 Score

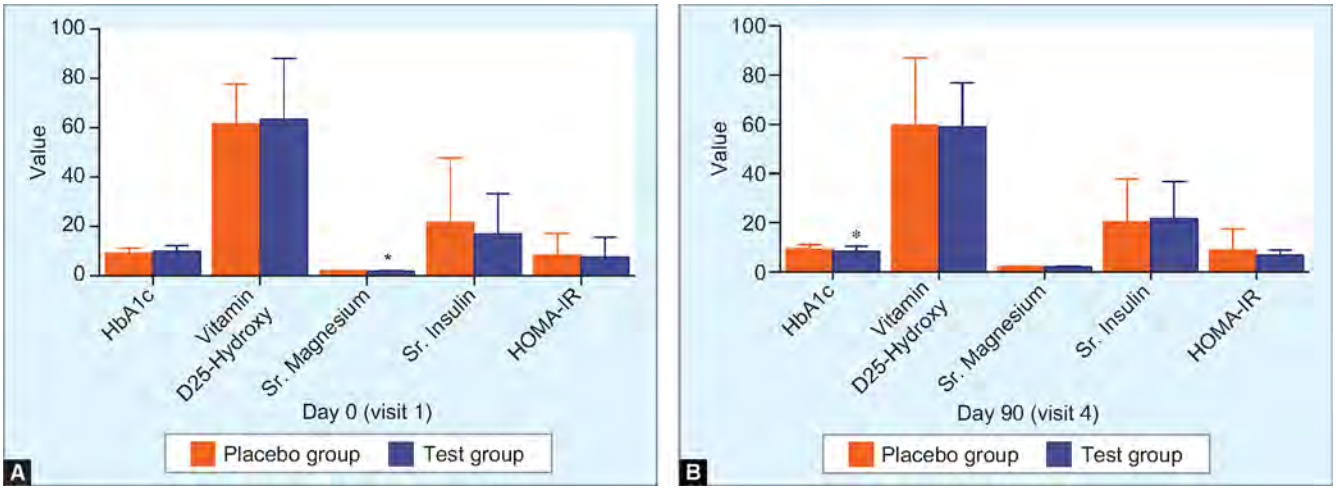
By day 90, the test group showed significant improvements across multiple SF-36 domains versus placebo: physical functioning ($p = 0.049$), role limitations due to physical health ($p = 0.0001$), role limitations due to emotional problems ($p = 0.0008$), vitality ($p < 0.0001$), pain ($p = 0.05$), and general health ($p < 0.0001$). Emotional well-being and social functioning did not differ significantly between groups. Overall, Mg + VitD supplementation significantly improved the quality of life in patients with type 2 diabetes.

Diabetes Symptoms Checklist Score

Diabetes symptoms checklist scores demonstrated significant improvements in the test group vs placebo for hyperglycemic symptoms ($p < 0.0001$), cardiovascular symptoms ($p = 0.003$), neuropathy symptoms ($p = 0.028$), and ophthalmological symptoms ($p = 0.006$). Improvements in hypoglycemic and psychological symptoms were noted but did not reach statistical significance. Overall, Mg + VitD supplementation as an add-on to OHA may help improve multiple diabetes-related symptoms.



Figs 2A and B: Within-group comparison of mean changes in (A) FBS and (B) PPBS at different assessment points. Statistical analysis was performed using an unpaired *t*-test. Day 0 vs days 14, 28, 45, 59, 73, and 90 (*$p < 0.05$)



Figs 3A and B: Between-group comparison of mean changes in different serum biochemical parameters at (A) day 0 (visit 1) and (B) day 90 (visit 4). Statistical analysis was performed using an unpaired *t*-test (Placebo group vs test group; *$p < 0.05$)

Table 1: Between-group comparison of mean change in FBS and PPBS at different assessment points

Visits	*Placebo group (mean ± SD)*	*Test group (mean ± SD)*	*Mean difference*	*95% CI*	*p-value*
FBS (mg/dL)					
Day 0	176.80 ± 72.7	195.80 ± 93.2	18.96 ± 16.73	−52.20 to 14.28	0.26
Day 45	164.40 ± 70.70	160.40 ± 70.85	4.02 ± 14.16	−24.11 to 32.15	0.78
Day 90	174.30 ± 76.31	140.70 ± 52.20	33.62 ± 13.08	7.634 to 59.61	0.01*
PPBS (mg/dL)					
Day 0	273.8 ± 91.75	294.90 ± 108.0	21.06 ± 20.04	−60.89 to 18.77	0.30
Day 45	261.20 ± 76.33	262.0 ± 96.0	0.84 ± 17.35	−35.31 to 33.63	0.96
Day 90	274.30 ± 90.89	263.50 ± 87.52	10.84 ± 17.84	−24.62 to 46.30	0.54

Statistical analysis was performed by an unpaired *t*-test. Placebo group vs test group; *$p < 0.05$

Table 2: Within-group comparison of mean changes in FBS and PPBS from screening to different assessment points

FBS (mg/dL)	*Day 0*	*Day 45*	*Day 90*	*p-value*
Placebo group (mean ± SD)	176.80 ± 72.72	164.40 ± 70.70	174.30 ± 76.31	0.98
Test group (mean ± SD)	195.80 ± 93.27	160.40 ± 70.85	140.70 ± 52.20	0.03*
PPBS (mg/dL)				
Placebo group (mean ± SD)	273.8 ± 91.75	261.20 ± 76.33	274.30 ± 90.89	0.90
Test group (mean ± SD)	294.90 ± 108.0	262.0 ± 96.0	263.50 ± 87.52	0.50

Statistical analysis was performed using ANOVA; *$p < 0.05$

Table 3: Between-group comparison of mean change in different serum biochemical parameters at different assessment points

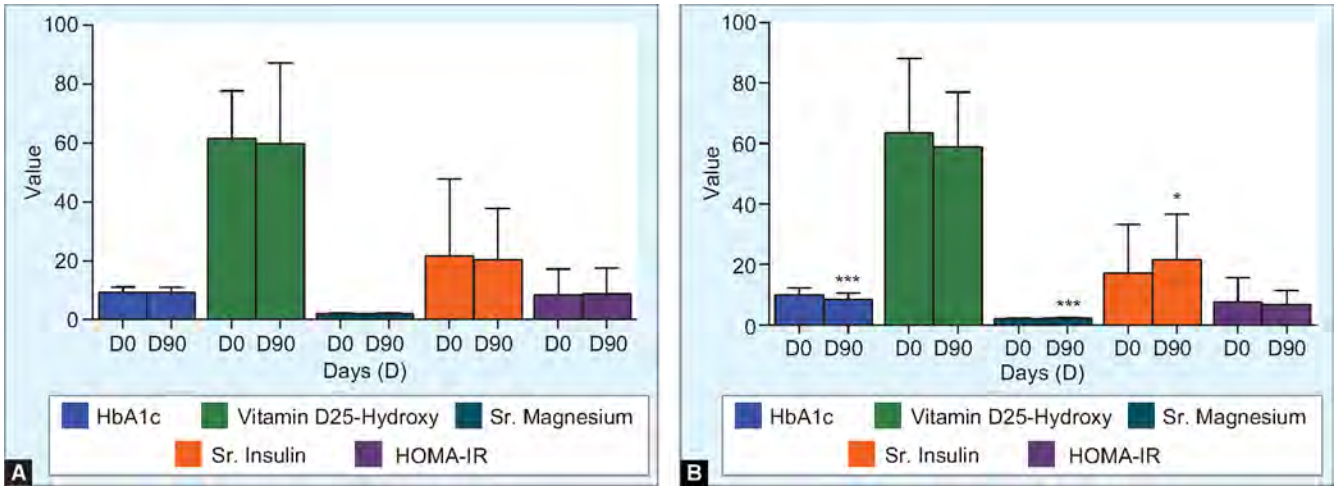
Visits	*Placebo group (mean ± SD)*	*Test group (mean ± SD)*	*Mean difference*	*95% CI*	*p-value*
HbA1c					
Day 0	9.24 ± 1.88	9.88 ± 2.37	0.648 ± 0.43	−1.496 to 0.201	0.13
Day 90	9.19 ± 1.87	8.36 ± 2.14	0.830 ± 0.40	0.034 to 1.630	0.04*
Vitamin D25-hydroxy (nmol/L)					
Day 0	61.55 ± 16.11	63.41 ± 24.59	−1.856 ± 4.16	−10.12 to 6.407	0.50
Day 90	59.69 ± 27.41	58.85 ± 18.12	0.84 ± 4.65	−8.392 to 10.07	0.86
Serum magnesium (mg/dL)					
Day 0	2.07 ± 0.22	1.98 ± 0.21	0.09 ± 0.04	0.005 to 0.176	0.04*
Day 90	2.07 ± 0.21	2.14 ± 0.25	0.07 ± 0.05	−0.168 to 0.017	0.14
Serum insulin (µU/mL)					
Day 0	21.78 ± 25.98	17.06 ± 16.17	4.72 ± 4.33	−3.878 to 13.32	0.28
Day 90	20.35 ± 17.45	21.51 ± 15.11	1.16 ± 3.26	−7.650 to 5.325	0.72
HOMA-IR					
Day 0	8.41 ± 8.79	7.60 ± 7.94	0.81 ± 1.68	−2.518 to 4.139	0.63
Day 90	8.75 ± 8.72	6.76 ± 4.51	1.99 ± 1.39	−0.7661 to 4.753	0.15

Statistical analysis was performed by an unpaired *t*-test. Placebo group vs test group; *$p < 0.05$

Table 4: Within-group comparison of mean changes in different serum biochemical parameters from screening to different assessment points

Group	*Day 0*	*Day 90*	*Mean difference*	*95% CI*	*p-value*
HbA1c					
Placebo group (mean ± SD)	9.24 ± 1.88	9.19 ± 1.87	0.042	−0.455 to 0.539	0.87
Test group (mean ± SD)	9.88 ± 2.37	8.36 ± 2.14	1.522	0.937 to 2.107	<0.0001***
Vitamin D25-hydroxy (nmol/L)					
Placebo group (mean ± SD)	61.55 ± 16.11	59.69 ± 27.41	1.86	−5.622 to 9.341	0.62
Test group (mean ± SD)	63.41 ± 24.59	58.85 ± 18.12	4.57	−2.424 to 11.54	0.20
Serum magnesium (mg/dL)					
Placebo group (mean ± SD)	2.07 ± 0.22	2.07 ± 0.21	0.007	−0.092 to 0.078	0.87
Test group (mean ± SD)	1.98 ± 0.21	2.14 ± 0.25	0.165	−0.237 to −0.093	<0.0001***
Serum insulin (µU/mL)					
Placebo group (mean ± SD)	21.78 ± 25.98	20.35 ± 17.45	1.44	−6.013 to 8.890	0.70
Test group (mean ± SD)	17.06 ± 16.17	21.51 ± 15.11	4.45	−7.948 to −0.946	0.01*
HOMA-IR					
Placebo group (mean ± SD)	8.41 ± 8.79	8.75 ± 8.72	0.336	−3.394 to 2.722	0.83
Test group (mean ± SD)	7.60 ± 7.94	6.76 ± 4.51	0.847	−1.038 to 2.733	0.37

Statistical analysis was performed by a paired *t*-test. Day 0 vs day 90; *$p < 0.05$; ***$p < 0.001$



Figs 4A and B: Within-group comparison of mean changes in different serum biochemical parameters in (A) the placebo group and (B) the test group from screening to the end of the study. Statistical analysis was performed using a paired *t*-test (day 0 vs day 90; ***$p < 0.001$ and *$p < 0.05$)

Assessment of Body Weight, BMI, and Waist Circumference

The assessment of body weight, BMI, and waist circumference in the study revealed no significant changes between or within groups over the study period.

Safety Analysis

The safety analysis, including physical examinations, vital signs, hematological parameters, serum biochemical parameters, and urinalysis parameters, revealed no significant adverse effects attributable to the intervention.

Discussion

This study demonstrated that Mg + VitD co-supplementation as an adjunct to standard OHA therapy significantly improved glycemic control in T2DM patients. Despite established recommended dietary allowances (370 mg/day in Indian females, 440 mg/day in males), Mg intake is often insufficient, resulting in intracellular Mg deficiency,[11,12] which can also be a significant contributor to insulin resistance. Low Mg status plays a key role in the pathogenesis of diabetes: there is a graded inverse link between serum Mg and T2DM risk.[13] However, Mg status does not always correlate with serum Mg because patients with normal Mg levels may even have subclinical intracellular Mg deficiency, because intracellular Mg levels are more representative end points of total body Mg.[14]

Diabetes itself induces low Mg status in 10–62.7% of diabetic patients, significantly higher than the 6–17.4% seen in healthy individuals.[15] Contributing factors include enhanced renal Mg loss, glycosuria-induced osmotic diuresis, and metformin, which downregulates the gene expression of Mg transporter TRPM-6, reducing absorption and reabsorption.[16] Inadequate VitD further impairs insulin secretion and increases insulin resistance. Since Mg is a vital cofactor for VitD metabolism, coexisting deficiencies of Mg and VitD worsen glycemic control and reduce OHA efficacy.[17] Thus, to achieve the desired glycemic control, cellular Mg status and VitD deficiency need to be corrected, and they may be supplemented in such patients as an adjunct to the standard therapeutic regimen.

Long-term metformin therapy may downregulate the Mg transporter TRPM6, thereby reducing intestinal and renal Mg absorption. This can lead to subclinical Mg deficiency, may impair VitD action, worsen insulin resistance, and reduce the efficacy of OHA.[18] Therefore, Mg and VitD supplementation may help improve outcomes in patients with uncontrolled diabetes on metformin-based therapy.

The efficacy analysis demonstrated significant improvement in glycemic control (FBS) in the test group compared to the placebo group. These findings may be attributed to the complementary roles of Mg and VitD in glucose metabolism, insulin secretion, and insulin sensitivity.[19] Mg acts as a cofactor in carbohydrate metabolism, while VitD influences insulin action; deficiencies in either nutrient impair insulin secretion due to impairment of Na^+–K^+-ATPase channels, whereby the pancreatic beta-cell functions are compromised.[20,21]

Postprandial blood sugar levels showed a nonstatistically significant decreasing trend in the test group. The finding differs from some earlier studies reporting significant PPBS improvement with Mg and VitD supplementation,[22,23] which may be due to variations in baseline VitD status or dietary intake among participants.

Serum biochemical analysis showed a significant reduction in HbA1c by day 90 in the test group, while the placebo group showed no significant change. Similar findings have been reported in earlier studies demonstrating that Mg and VitD supplementation can significantly reduce HbA1c,[24,25] supporting improved long-term glycemic control despite nonsignificant changes in PPBS. Additionally, serum Mg ($p < 0.0001$) and insulin levels ($p = 0.01$) increased significantly in the test group, whereas no such changes were observed in the placebo group.

Quality-of-life assessment using the SF-36 questionnaire showed significant improvements in the test group compared with placebo across multiple domains. These findings indicate that supplementation significantly improved overall health-related quality of life.

Evaluation using the DSC showed significant improvements in the test group compared to the placebo by day 90. These findings suggest that Mg + VitD supplementation provides comprehensive relief from diabetes-related symptoms.[26,27] Consistent with earlier reports, our study also demonstrated that supplementation restored serum Mg and improved insulin sensitivity and metabolic control in type 2 diabetes.[28,29]

Safety analysis, including physical examination, vital signs, hematological/biochemical parameters, and urinalysis, showed no significant adverse effects, indicating good tolerability of the supplementation. Treatment compliance was high (>97%), supporting regimen feasibility. However, the study was limited by a small sample size and short duration (90 days).

Conclusion

Mg + VitD supplementation as an adjunct to OHA therapy significantly improved FBS, HbA1c, serum Mg and insulin levels, and overall quality of life in T2DM patients over 90 days, with excellent tolerability and high compliance. These findings support the potential of Mg + VitD as a valuable, safe addition to standard diabetes management. Larger, longer-term trials are needed to validate these preliminary results and to explore dose reduction in OHAs.

Declarations

Ethics Approval and Consent to Participate

The study protocol complied with the Declaration of Helsinki and other relevant ethical guidelines. Ethical approval was obtained from the Institutional Ethics Committees of Pranav Diabetes Center, Bengaluru, and Care Multispecialty Hospital, Pune, and written informed consent was obtained from all participants.

Data Availability

The data supporting the findings of this study are available from the first author, Dr Sanjay Tandon, upon reasonable request.

Source of Support

This research was funded by Pharmed Limited, Bengaluru, Karnataka, India.

Conflict of Interest

None.

Acknowledgments

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Author's Contributions

All authors contributed to the study conception, design, execution, data acquisition, analysis, and interpretation. They also drafted or critically revised the manuscript, approved the final version for publication, and took responsibility for the work.

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ORIGINAL ARTICLE

Cost Variation with Respect to Drug Price Control Order in Different Brands of Cardiovascular Drugs: An Exploratory Analysis of Brands in India

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Abstract

Introduction: The Drug Price Control Order (DPCO) under the National Pharmaceutical Pricing Authority (NPPA) provides the ceiling prices (CPs) for the National List of Essential Medicines (NLEM) in India. As cardiovascular (CV) drugs are among the major drug categories, we aimed to identify the price differences between the NPPA-CP and marketed brands of CV drugs in the Indian market.

Materials and methods: We performed an exploratory analysis of the pricing of orally administered CV drugs from all categories except antithrombotic drugs from the NLEM and DPCO. The pricing of 13 drug brands was analyzed. The maximum retail price (MRP) of brands was obtained from the online pharmacy portal Tata 1mg (https://www.1mg.com/). The price per tablet or capsule was calculated by dividing the MRP by the number of tablets/capsules in a pack size.

Results: In total, we assessed the pricing of 274 different brands of 13 CV drugs from NLEM. Out of 13 drugs, only 3 (23.1%) had an average price below the NPPA-CP (acetylsalicylic acid, isosorbide dinitrate, digoxin). One drug (metoprolol), across all brands, had a price above the NPPA-CP. Overall, 125 (45.6%) and 149 (54.4%) brands had prices equal/lower and higher than NPPA-CP, respectively. Using metoprolol 25 mg (eight brands) as an example, we determined that the average price was ₹4.09 per tablet more than NPPA-CP. This translated to an additional expenditure of ₹1,488.76 over 1 year and ₹37,219 over 25 years.

Conclusion: Among the available brands of CV drugs, there is wide variation in prices as per NPPA-CP, with more brands having prices above the CP. Pricing differences among brands should be considered by treating physicians when prescribing these drugs.

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Introduction

The cost of pharmaceutical medicines is an important consideration in developing countries like India, where accessibility and affordability are major issues for a large population.[1,2] With a focus on providing access to medicines, especially for common infections and chronic infections that are a threat to public health, the World Health Organization (WHO) developed the Essential Medicines List. In India, the first National List of Essential Medicine (NLEM) was developed in 1996, and the latest revision was done in 2022.[2–4] Such efforts have been repeatedly taken in India owing to a constitutional imperative of the "Right to Life."[5] The right to health is an integral part of this right to life; hence, the government aims at affordability of medicines for the public. In NLEM, a total of 384 drugs are included, with 34 being dropped and 26 new drugs added from the previous list.[6] Furthermore, the National Pharmaceutical Pricing Authority (NPPA) exercised the Drug Price Control Order (DPCO) in 2013 to fix and implement the prices of drugs, and it was last updated in February 2025.[7] The price control policy from NPPA resulted in substantial price reduction in reference drugs.[8] When a drug is patented, it is necessary that the drug must have utility and industrial applicability. With expiry of patent after 20 years, drug falls into the public domain.[9] The rationale of all such mandates is to ensure the affordability of drugs. As India has substantial burden of cardiovascular (CV) diseases, ensuring access and affordability of CV medicines becomes a top priority. In India, there exists a wide difference in prices of different brands.[10,11] Despite the stringent policy directives, it may not be implemented by the stakeholders to the fullest, resulting in brand price differences.[12–15] With this background, our study explored the price differences among different drug brands with respect to NPPA ceiling price (NPPA-CP) of the drugs used for CV ailments.

Materials and Methods

Design and Ethics

This was an observational, exploratory analysis of the cost of different brands listed in NPPA that are used in CV ailments. As the study did not involve human or animal participation, there was no need for ethical permission to conduct this exploratory analysis.

Brand Price Control: Affordability and Availability

Every citizen has a fundamental right to available and affordable medicines. The basic medicines for CV ailments included in the study form part of essentiality for fulfillment of right to health. The cost of such medicines shall be affordable to all as well as sustainable for all for prolonged treatment. The affordability has to be ensured with accessibility for all without discrimination. These objectives are sought to be achieved by DPCO by specifying CP for the medicines.

NPPA Compendium

The compendium of CPs from the NPPA under the Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers, Government of India, was referred to for this study. The revised ceiling pricing was made effective from February 7, 2025. We selected only orally administered drugs for this exploratory analysis. Drugs that were listed as injectables only in the compendium such as adenosine, esmolol, lignocaine, sodium nitroprusside, dobutamine, dopamine, noradrenaline, alteplase, heparin, and streptokinase were excluded. We excluded the injectables as most of these injectables are emergency drugs and may not be administered chronically. The impact of price differences among

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injectables with respect to NPPA-CP may not be disturbing to the patients in comparison to orally administered drugs that are used on long-term basis. Considering these criteria, finally CPs of 13 drug brands were noted from the NPPA compendium.

Brands Pricing

We selected 13 drugs, which included acetylsalicylic acid (ASA), clopidogrel, diltiazem, isosorbide dinitrate, metoprolol, amiodarone, amlodipine, enalapril, ramipril, hydrochlorothiazide (HCTZ), telmisartan, digoxin, and atorvastatin. Pricing for these drug brands with different dose strengths was captured from the online pharmacy Tata 1mg (https://www.1mg.com/). In addition to Tata 1mg, we compared the maximum retail prices (MRPs) across two more online pharmacy stores namely Apollo Pharmacy and PharmEasy. Also, we cross-checked the prices of some commonly used brands for telmisartan, metoprolol, and atorvastatin at a local pharmacy to ascertain the accuracy of MRP of brands included in the analysis. The prices at local store and all three sites had similar pricing of checked brands. Hence, we decided to capture MRP for included drug brands from Tata 1mg pharmacy website. We avoided any discounts offered by the pharmacy and included MRP of each brand. We decided to include at least five brands of each drug to have a comparative analysis of appropriate pricing.

Calculation of Price Per Tablet/ Capsule

Tata 1mg pharmacy website provided MRP and per pack size of the brands. We calculated price per tablet or capsule (PPT/C) by dividing the MRP by pack size. For example, a brand of metoprolol had an MRP of ₹50 for 10 tablets, then PPT was ₹5. Such PPT/C was determined for all 13 drug brands including separate assessment of different dose strengths as available. The pricing was determined for all brands on a single day to avoid changes in MRP, if any. We included the pricing of all drugs as available from Tata 1mg pharmacy website on February 14, 2025. We determined the average PPT/C by combining the pricing of all brands divided by the number of brands. This calculated average price was then compared to NPPA-CP, and the number of brands was then categorized as equal/lower than NPPA-CP and higher than NPPA-CP.

Cost Saving and Expenditure Analysis

Before initiating the price analysis, we decided to perform an economic analysis of any one or two brands that are used as once-a-day treatment to determine the saving or expenditure on cost in a year for the given drug. From the average price derived from brands, we subtracted NPPA-CP. The difference, either lower or higher, was multiplied by 7 (for once-a-day dosing in 1 week) and multiplied by 52 to derive approximate yearly savings and expenditure. This was further assessed, assuming 25 years of drug consumption.

Statistical Analysis

The data were compiled in the Microsoft Excel spreadsheet version 2016 (Microsoft Corp., Redmond, Washington, United States), and the analysis was performed using the same. Descriptive statistics were used to determine the frequency and percentages. Average prices were calculated by dividing the cumulative price of all brands by the number of brands. Range denoted the minimum and maximum price range of the brands.

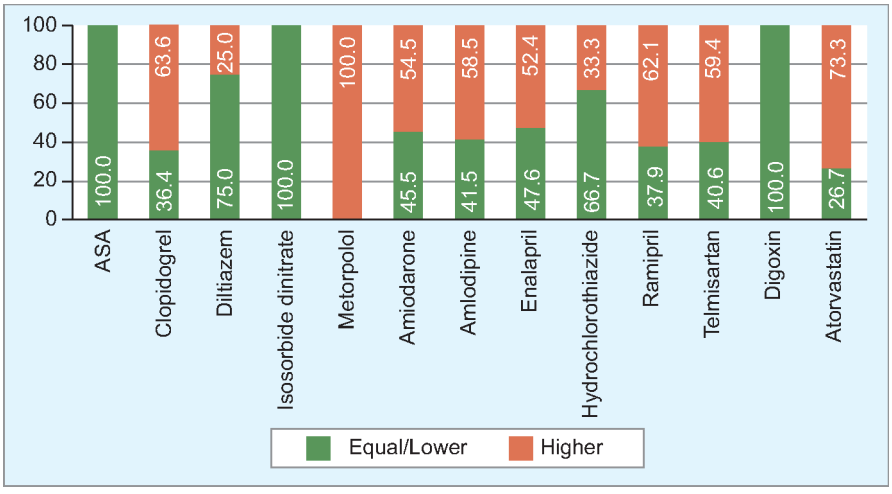

Fig. 1: Brands distribution by drug pricing with respect to CP (ASA, acetylsalicylic acid)

Results

In this study, we assessed the pricing of 274 different brands (with different dosages) of 13 orally administered CV drugs from the NLEM. Figure 1 demonstrates the total number of brands combined by drug strengths with prices with respect to NPPA-CP. Out of 13 drugs, only 3 (23.1%) (ASA, isosorbide dinitrate, and digoxin) had an average price below the recommended CP whereas all brands of one (7.7%) drug (metoprolol) had an average price above the CP. Among the other drugs, majority brands that had prices above NPPA-CP included clopidogrel (63.6%), amlodipine (54.5%), telmisartan (62.1%), and atorvastatin (73.3%). Majority of brands that had lower prices than NPPA-CP included diltiazem (75%) and HCTZ (66.7%). Figure 2 depicts the pricing of different drug brands and their respective NPPA-CP. It provides quick snapshots of the brand pricing. Majority of the drug brands had pricing higher than NPPA-CP. Figure 3 shows the segregated pricing of different brands by dosage strength. Among 274 brands, 125 (45.6%) were equal or lower than the NPPA-CP whereas 149 (54.4%) had price above the CP of NPPA. Maximum 15 brands were assessed for drugs like amlodipine (10 mg), enalapril (2.5 mg), ramipril (5 mg), telmisartan (40 mg), and atorvastatin (10, 20, and 40 mg). When critically looked at drugs like telmisartan, amlodipine, and atorvastatin, majority of brands had a higher pricing than NPPA-CP. For example, with telmisartan, 6, 8 and 5 brands from 20 mg (n = 10), 40 mg (n = 15), and 80 mg (n = 7) strengths were above the NPPA-CP. With amlodipine, 11 brands from 10 mg (n = 15) and 10 brands from 5 mg (n = 12), whereas only 3 brands from 2.5 mg strength (n = 14) had prices above NPPA-CP.

Table 1 shows the pricing comparison of different drug brands included in the study. For 75 mg enteric-coated ASA, average price of five brands (₹0.33) was lower than NPPA-CP (₹0.35). With clopidogrel, the majority (63.6%) of brands had an average price above (₹7.35) the NPPA-CP (₹6.66). For diltiazem 60 and 30 mg tablets, the average price of brands was lower than NPPA-CP. The average price of all six brands of isosorbide dinitrate (₹0.80) was lower than CP (₹0.81). Metoprolol 50 and 25 mg prolonged release brands were priced higher than CP with an average of ₹8.29 and ₹5.97 per tablet. From 12 to 10 brands of amiodarone 100 and 200 mg tablets, six (average: ₹5.88) and four (average: ₹9.87) were below the NPPA-CP (₹6.14 and ₹11.51), respectively. With amlodipine 10 mg and 5 mg, the average price of majority of brands (73.3% with average price ₹7.47 for 10 mg and

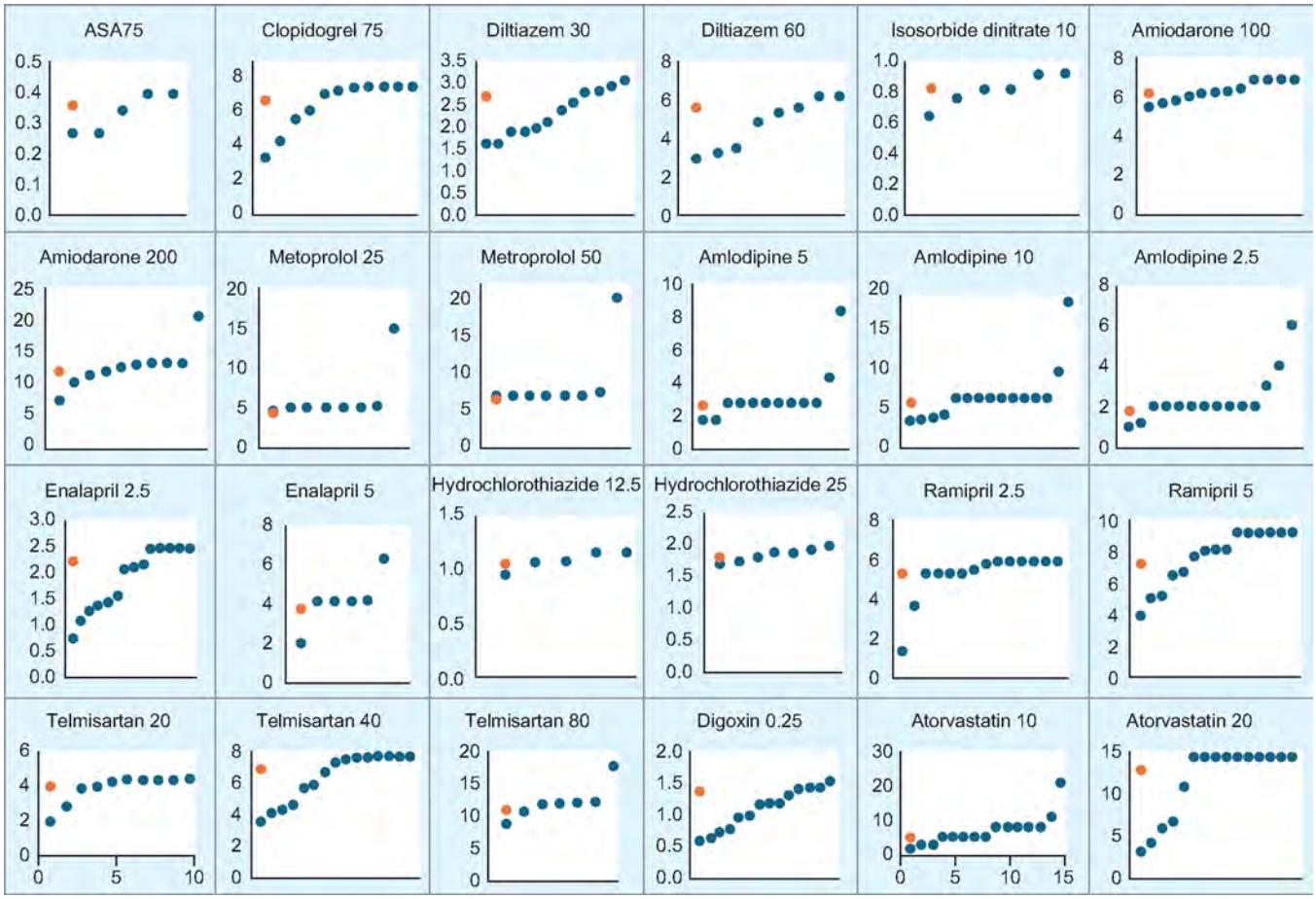

Fig. 2: Price of individual drug brands by dose strength with their CPs. Blue circles indicate price of each brand included in analysis; Single orange circle denotes the NPPA-CP of each brand; All brand strengths are included except for atorvastatin 80 mg brands, to maintain the symmetry of figure. Numbers in front of each drug name indicate the strength of the drug in milligrams (*x*-axis: Number of brands; *y*-axis: MRP in rupees)

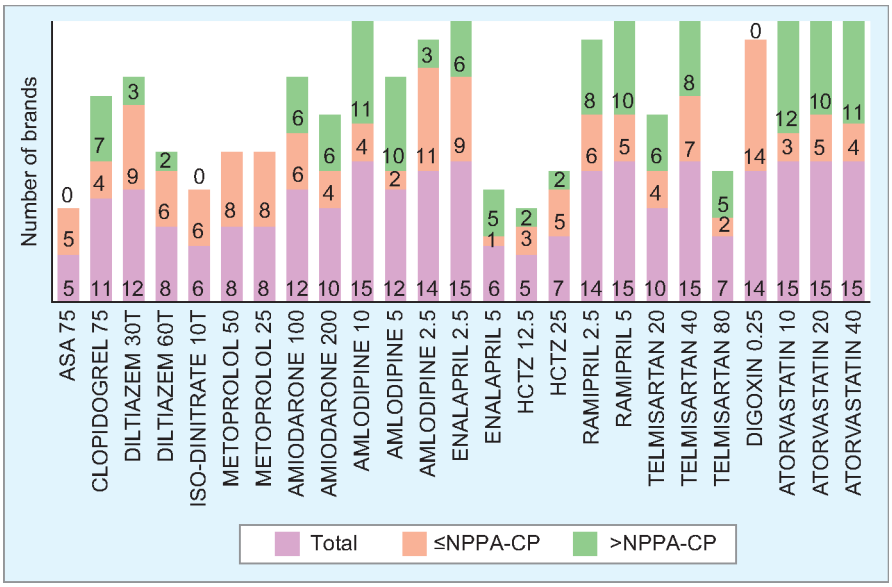

Fig. 3: Distribution of included brands according to the CP segregated by different dose strengths. Digits in front of drug name indicate dose strength; *T* denotes tablet; HCTZ, hydrochlorothiazide

83.3% with average price ₹3.35 for 5 mg) was higher than CP (₹5.45 and ₹2.50, respectively). Contrastingly, 11 out of 14 brands of 2.5 mg amlodipine had price lower than CP (₹2.89). The average price of 60% of enalapril 2.5 mg brands (₹1.49) was lower than NPPA-CP (₹2.19), whereas 83.3% of 5 mg brands were higher (₹4.55) than NPPA-CP (₹3.70). Similarly, variations were seen in the pricing of HCTZ 12.5 mg and 25 mg tablets. Ramipril 5 mg brands had either lower pricing (33.3% with average price ₹5.38) or higher pricing (66.7% with average price ₹8.67) than NPPA-CP (₹7.19). The average price of telmisartan 20 mg, 40 mg and 80 mg strengths was higher (₹4.23, ₹7.45 and ₹12.72, respectively) than NPPA-CP (₹3.88, ₹6.76 and ₹10.40, respectively) for 60%, 53.3% and 71.4% of included brands. All brands of digoxin 0.25 mg tablets had prices lower than NPPA-CP. With atorvastatin, the majority brands from 10 mg, 20 mg, and 40 mg tablet strengths had higher pricing, with averages of ₹8.39, ₹14.07, and ₹21.53, respectively, than the recommended NPPA-CP (₹4.94, ₹12.56, and ₹19.30, respectively).

Cost Saving and Expenditure

In this analysis, we included metoprolol 25 mg and atorvastatin 10 mg as examples to assess savings and expenditure in a year. For metoprolol 25 mg tablet, NPPA-CP is ₹4.20, which is subtracted from the average price of ₹8.29 of 8 brands. Thus, ₹4.09 per tablet is in excess of the NPPA-CP. Considering a once-a-day dose, 7-day excess expenditure with it is

Table 1: Price comparison of different CV drugs with CP from NPPA

Drug	*Dose (mg)*	*Dosage form*	*NPPA PPT/C (₹)*	*Brands assessed (n)*	*Lower/equal to DPCO price [n (%)]*	*Average lower PPT/C (range) (₹)*	*Higher than DPCO price [n (%)]*	*Average higher PPT/C (range) (₹)*
ASA	75	Tablet (EC)	0.35	5	5 (100.0)	0.33 (0.26–0.39)	–	–
Clopidogrel	75	Tablet	6.66	11	4 (36.4)	4.78 (3.29–6.07)	7 (63.6)	7.35 (7.04–7.46)
Diltiazem	30	Tablet	2.68	12	9 (75.0)	2.06 (1.06–2.75)	3 (25.0)	2.90 (2.80–3.01)
	60	Tablet	5.46	8	6 (75.0)	4.15 (2.84–5.48)	2 (25.0)	6.11 (6.10–6.11)
Isosorbide dinitrate	10	Tablet	0.81	6	6 (100.0)	0.80 (0.63–0.91)	–	–
Metoprolol	50	Tablet (PR)	5.84	8	–	–	8 (100.0)	8.29 (6.53–20.0)
	25	Tablet (PR)	4.20	8	–	–	8 (100.0)	5.97 (4.31–14.78)
Amiodarone	100	Tablet	6.14	12	6 (50.0)	5.88 (5.50–6.19)	6 (50.0)	6.69 (6.26–6.88)
	200	Tablet	11.51	10	4 (40.0)	9.87 (7.07–11.51)	6 (60.0)	13.95 (12.41–20.00)
Amlodipine	10	Tablet	5.45	15	4 (26.7)	3.52 (3.27–3.80)	11 (73.3)	7.47 (6.06–18.12)
	5	Tablet	2.50	12	2 (16.7)	1.66 (1.66–1.66)	10 (83.3)	3.35 (2.80–8.40)
	2.5	Tablet	1.79	14	11 (78.6)	1.84 (1.05–2.0)	3 (21.4)	4.34 (3.01–6.00)
Enalapril	2.5	Tablet	2.19	15	9 (60.0)	1.49 (0.7–2.10)	6 (40.0)	2.44 (2.41–2.45)
	5	Tablet	3.70	6	1 (16.7)	1.87	5 (83.3)	4.55 (4.13–6.22)
Hydrochlorothiazide	12.5	Tablet	1.04	5	3 (60.0)	1.03 (0.94–1.08)	2 (40.0)	1.66 (1.16–1.16)
	25	Tablet	1.75	7	5 (71.4)	1.77 (1.68–1.85)	2 (28.6)	1.92 (1.89–1.95)
Ramipril	2.5	Tablet	5.21	14	6 (42.8)	4.27 (1.22–5.22)	8 (57.2)	5.76 (5.39–5.84)
	5	Tablet	7.19	15	5 (33.3)	5.38 (3.79–6.66)	10 (66.7)	8.67 (7.64–9.16)
Telmisartan	20	Tablet	3.88	10	4 (40.0)	3.04 (1.90–3.87)	6 (60.0)	4.23 (4.13–4.33)
	40	Tablet	6.76	15	7 (46.7)	4.88 (3.50–6.61)	8 (53.3)	7.45 (7.20–7.57)
	80	Tablet	10.40	7	2 (28.6)	9.3 (8.4–10.2)	5 (71.4)	12.72 (11.40–17.40)
Digoxin	0.25	Tablet	1.33	14	14 (100.0)	1.06 (0.57–1.49)	–	–
Atorvastatin	10	Tablet	4.94	15	3 (20.0)	2.71 (1.95–3.10)	12 (80.0)	8.39 (5.53–20.4)
	20	Tablet	12.56	15	5 (33.3)	5.95 (2.98–10.57)	10 (66.7)	14.07 (14.07–14.07)
	40	Tablet	19.30	15	4 (26.7)	13.66 (8.71–17.61)	11 (73.3)	21.53 (21.16–21.62)

PR, prolonged release

₹28.63 which will be translated to ₹1,488.76 for 52-weeks (approximately 1 year). If a person consumes it for 25 years, the total expenditure will be nearly ₹37,219. With atorvastatin 10 mg, NPPA-CP is ₹4.94. Three brands had a lower price with an average of ₹2.71. The average per tablet saving is ₹2.23. With once-a-day dosing, 7-day saving will be ₹15.61 and that is translated to saving of approximately ₹811.72. Over a 25-year period, total savings could be ₹20,293.

Discussion

This exploratory analysis finds that there is variation in the pricing of different brands available in the Indian market with respect to prices recommended by DPCO. Multiple studies conducted in similar fashion have reflected varying prices among brands. A study from Bengaluru, India, by Aditya et al. observed variation in prices among the antihypertensives. They found that the majority of telmisartan brands listed in Current Index of Medical Specialties (CIMS) for 20 mg (78.12%), 40 mg (66.66%), and 80 mg (76.19%) were above the NPPA-CP. This trend was persistent when they compared the pricing at local pharmacy. Other drugs such as amlodipine 5 mg (40.81% brands) and HCTZ 25 mg (50% brands) were above the NPPA-CP.[16] Ray et al. from Bhopal, India observed wide variation in the prices of anticoagulants, fibrinolytics, and antiplatelet agents. Between the lowest and highest price of brands, highest variation of 1408.44% was reported for prasugrel followed by heparin (668.67%), clopidogrel (444.35%), and aspirin (333.33%).[14] However, in our analysis, all brands of ASA were below the NPPA-CP but for clopidogrel, majority were above the CP. Similar reports of high price variation among the brands for CV drugs and antibiotics,[17] antidiabetic drugs,[18] and antipsychotics[19] have been published from India. It is worth pointing out that the death rate due to cardiovascular disease (CVD) was 2.26 million in 1990, which has increased to 4.77 million in 2020.[20] A 2016 study by Prabhakaran et al. reported that nearly one out of four deaths from total deaths were due to CV diseases in India.[21] We observed that out of 13 drugs studied, only 3 drug brands were below the CP, and all the brands of one drug (metoprolol) were above the CP. On top of it, 54.4% of total brands studied were higher than CP. This discrepancy in the pricing of different brands can lead to an enormous burden on patients who may not be able to afford the common medications. With such high CV disease burden, higher costing of majority of the CV drugs arises the question of fulfillment of right to life and health of the common man. The issue of higher costs associated with NLEM drugs is not observed only in India. Studies from Malaysia and Belgium also reported similar findings.[22,23]

The repercussions of variations in prices can be huge. We further analyzed the expected expenditure with an example of metoprolol. There was an additional ₹1,500 loss per month as brands did not follow the CP limit. We must understand this was based on the average price of all the drug brands studied. Over the 25 years, this expenditure may be to the tune of nearly ₹37,000. Considering the CV ailments that generally require multiple drug therapy, there could be substantial expenditure on all the medications that go beyond the CPs. In a highly populated country like India with higher rate of CVD patients, substantial price discrepancy might lead to unaffordability. WHO finds that in the Southeast Asia region, despite improving the availability of essential medications in the region, there remains the challenge of accessibility because of high out-of-pocket (OOP) expenditure. This has

resulted in poverty stricken on 65 million people every year.[24] This finding highlights the urgent need to strongly implement the NPPA across the country. Interestingly, we have discussed this about the drugs under the DPCO. For the drugs that are not under the price control, the changes in prices are more significant that further impact the OOP expenditure and thereby the access to essential medicines.[25] Studies have identified variations in prices of various hypolipidemic drugs in the Indian market.[26] The findings have implications for policy implementation. Besides control of the price, accessibility to drugs is also important. In 2008 Government of India launched Pradhan Mantri Bhartiya Janaushadhi Pariyojana (PMBJP) to ensure availability of quality generic medicines that are available at affordable prices.[27] Recent study from Tamil Nadu highlighted that CV drugs are the commonly available drugs at Janaushadhi centers and overall, the cost was lower by nearly 65% compared to branded drugs.[28] Combined with DPCO, PMBJP offers to further improve the affordability of essential drugs to all. However, the experts believe that it is important to improve the implementation of policies, improve the supply chain, enhancing physicians' engagements and increasing public awareness of these schemes is still essential to enhance the adoptability across the country.[29]

Our study has certain limitations. We assessed only a limited number of drugs and their brands. Assessing a greater number of drugs and inclusion of higher number brands may provide the complete picture for the CV drugs. We did not compare the pricing of the drugs that are not under the DPCO to the counterpart drugs under DPCO. It is also important to understand that the DPCO list is updated frequently and thus the changes in brand pricing may not be reflected in real time. Analyzing prescription-based pricing can provide real-time insights related to expenditure on medications. Also, we did not assess the generic or Jan Aushadhi brands that could have potential differences in pricing compared to branded medications as the inclination of patients is more toward branded medicines. It is not clear whether there are any pricing differences at Tata 1mg pharmacy for rural or urban setting, and thus the findings of the study may have limitations.

Conclusion

This exploratory analysis of various CV drugs identifies variations in prices of different brands, majority being above the CP indicated by DPCO. This may result in excess expenditure on essential medicines. Changes to the NPPA policy are needed to expand the list of drugs under the DPCO to make medicines more affordable. Physicians should consider the pricing of the drug brands as long-term treatment may result in excessive economic burden on the individuals suffering from CV ailments.

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ORIGINAL ARTICLE

Prevalence of Capillary Leak Syndrome in Hemotoxic Envenoming: A Prospective Observational Study from Himachal Pradesh, India

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Abstract

Background: Himachal Pradesh, India, has a distinct *Viperidae* snake fauna and includes northern white-lipped pit viper (*Trimeresurus septentrionalis*), Himalayan pit viper (*Gloydius himalayanus*), Chamba pit viper (*Gloydius chambensis*), in addition to Russell's viper (*Daboia russelii*) and saw-scaled viper (*Echis carinatus*). The study was conducted to assess the prevalence of capillary leak syndrome (CLS) in patients with hemotoxic venomous snakebites.

Materials and methods: This open-cohort descriptive study was conducted among patients admitted with hemotoxic envenoming. The patients were enrolled through nonprobability sampling, and the study period was 1 year. Hemotoxic envenoming was defined as a positive bedside 20-min whole-blood clotting time (20-min WBCT) following a snakebite. CLS was defined by the clinical criteria of periorbital edema, conjunctival chemosis, parotid swelling, and systolic BP less than 90 mm Hg. Laboratory criteria for diagnosis included hemoglobin greater than 17 gm/dL in males and greater than 15 gm/dL in females, hematocrit greater than 50% in males and greater than 45% in females, and serum albumin less than 3.5 gm/dL. CLS was defined as the presence of one clinical feature and one laboratory criterion.

Results: 62 patients were enrolled in this study. The prevalence of CLS was 19.3% (12/62). Of the 12 patients with CLS, 6 (50%) improved, 5 (42.9%) received referral on request, and 1 (8.3%) patient expired.

Conclusion: CLS is not an uncommon entity following Viperidae envenoming in the Himachal Pradesh region of India.

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Introduction

Himachal Pradesh, India, falls in the lower burden snakebite envenomation region. The probability of death from snakebite is less than 0.25% before age 70 in the state.[1] The snakes of medical importance in the state are the "big four," i.e., Indian or spectacled cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and saw-scaled viper (*Echis carinatus*). In addition, the presence of "six more" species of medical importance has been identified and added to the list of the "big four." The three neurotoxic species are the king cobra (*Ophiophagus hannah*), central Asian cobra (*Naja oxiana*), and Macclelland's coral snake (*Sinomicrurus macclellandi*), and the three hemotoxic species are Northern white-lipped pit viper (*Trimeresurus septentrionalis*), Himalayan pit viper (*Gloydius himalayanus*), and Chamba pit viper (*Gloydius chambensis*). The geographical distribution of these species varies from the hills to the plains of the state. The state has an ideal environment for the human animal conflict, which coincides with increases in agricultural activity during the rainy season of monsoons and the postmonsoon period, the location of human dwellings in and around fields, sleeping on the floor, and abundant vegetation. The local distinct reptilian fauna makes it imperative to study the spectrum of envenomation from this geographic region. The classic toxidrome triggered by the venoms of the family *Viperidae* snakes includes local tissue damage and hemotoxic envenoming. Venom-induced consumption coagulopathy (VICC) is the most common hemotoxicity related to snake envenoming. Capillary leak syndrome (CLS) is recognized in a subgroup of patients with VICC and is characterized by facial and conjunctival edema, bilateral parotid enlargement, serous cavity effusion, hypotension, pulmonary edema, and laboratory evidence of hemoconcentration and hypoalbuminemia.[2] CLS has been reported in toxidrome with eastern (*D. russelii* in India) and western (*D. siamensis* in Myanmar) Russell's viper in Asia.[3] In India, the patients have been diagnosed in the medical institutions from the southern states of Kerala, Tamil Nadu, and Puducherry.[2] Clinical manifestations such as CLS have not been reported in the hospital-based studies from the hills of Himachal Pradesh, India. The objective of the study was to estimate the prevalence of capillary leak syndrome among patients with hemotoxic envenoming admitted to a tertiary care hospital located in the Kangra valley of Himachal Pradesh, India.

Materials and Methods

The design of this hospital-based study was an open-cohort prospective descriptive model. Participants were recruited between June 2023 and May 2024 using a nonprobability sampling method. The included patients were above the age of 18 years and admitted with hemotoxic envenomation after a snakebite. The exclusion criteria were patients with known preexisting kidney disease, chronic liver disease, hypothyroidism, and heart failure. Patients discharged within 48 hours of admission were not included in the study.

Definitions

Hemotoxic Envenomation

It was defined as a positive 20-min whole-blood clotting test (20 WBCT) subsequent to a snakebite.[4]

Capillary Leak Syndrome

It was defined by the clinical criteria of periorbital edema, conjunctival chemosis, parotid swelling, and systolic blood pressure of less than 90 mm Hg. Laboratory criteria for diagnosis included hemoglobin greater than 17 gm/dL in males and greater than 15 gm/dL in females, hematocrit greater than 50% in males and greater than 45% in females, and serum albumin less than 3.5 mg/dL. CLS was defined with the documentation of one clinical feature and one laboratory criterion.[5]

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Thrombotic Microangiopathy

Thrombotic microangiopathy was defined as the presence of thrombocytopenia, acute kidney injury (AKI), and microangiopathic hemolytic anemia (MAHA).[6]

Procedure

The information about the demographic profile, clinical features, treatment received, and investigations performed was recorded for each patient on a clinical research form. The laboratory investigations included complete blood counts, peripheral blood films, liver and renal profiles, and examination of urine. The time ranges for understanding the serial changes were defined as less than 48 hours, 48–96 hours, and at discharge. The maximum or the minimum value observed was used for analysis. Ultrasonographic evidence for the presence of pleural effusion and ascites was gathered. Species identification of the likely envenoming snake was done using the video and/or photographs provided by the patients or their attendants. To corroborate, the patient or his accompanied were shown images of various snake species prevalent in Himachal Pradesh, which were available on the public platform and provided by the authors AG and SR. Attempts were made to identify the snakes in the local dialect and to verify them against zoological names. Consultation with an expert was conducted to confirm the identity of the species. The data were entered in the Microsoft Excel spreadsheet and analyzed through Epi-Info 7. Quantitative data were stated as means with standard deviation, and qualitative data as frequencies and percentages. Median ± IQR was calculated for variable and wide distribution data. The Student's *t*-test and the Chi-square test were used to analyze continuous variables and proportions, respectively. Mann–Whitney *U* test was used for non-normal distribution. The study has been conducted after approval by the institutional ethics committee.

Results

In the present study, 62 patients were recruited over a period of 1 year. Information about the demography profile, presentation features, admission duration, and outcome is shown in Table 1. All the subjects were residents of rural localities. All the subjects were presented in the warm season from March to November. In the monsoon months of August and September, 54.8% patients were admitted. The biting snake could be identified in 48.4% (30/62) cases by the victim or their attendants. 12 cases identified the snake as Ghug (vernacular name for Russell's viper), 2 as Kodi wala saanp (vernacular name for Russell's viper), 6 as Sotad (vernacular name for both Himalayan pit viper and Russell's viper), 4 as "Saledu" (green colored *Trimeresurus septentrionalis*), and 1 each as Dhartranga (Russell's viper) and Surail (unidentified). Four were identified as Russell's viper, but patients and their attendants were unaware of their local names. Four were identified as green colored snakes. We could not come across any patient who could identify the Himalayan pit viper (*G. himalayanus*), Chamba pit viper (*G. chambensis*), or saw-scaled viper (*Echis carinatus*), or spell their local names. The frequency distribution of clinical manifestations is shown in Figure 1. The results of laboratory investigations are shown in Table 2. The prevalence of CLS was 19.3% (12/62) in this study. Of the12 patients with CLS, 6 (50%) improved, and 5 (42.9%) were referred on request and were therefore lost to follow-up. One (8.3%) patient expired. Eight patients with CLS required hemodialysis. Ultrasonography for evidence of pleural effusion and ascites was carried out in 58 patients. 12 patients had evidence of pleural effusion, and 4 patients had ascites. Pleural effusion was bilateral in eight, on the right side in one, and on the left side in three (Fig. 2A). Isolated ascites was observed in two, and bilateral pleural effusion with ascites was observed in two patients.

Among the 12 patients with CLS, 11 had ultrasonographic evidence of pleural effusion and ascites. In one patient with CLS, ultrasonography could not be done. One patient with bilateral pleural effusion, one patient with left-sided pleural effusion, and one patient with ascites did not fulfill the defined diagnostic criteria of CLS. All these three patients had periorbital puffiness (Fig. 2B). A comparison of demography, clinical features, and investigations of patients with and without CLS are illustrated in Table 3. Bilateral parotid enlargement was observed in one patient with CLS. The patient had a favorable outcome and recovered.

Proteinuria was observed in 67.7% (42/62) of patients. 20 (32.3%) patients had 2+, 16

Table 1: Demography, presentation profile, duration of admission, and outcome among study subjects

Parameter	*Frequency distribution (%) (n = 62)*
Sex	
Males	35 (56.5)
Females	27 (43.5)
Mean age (years ± SD)	43.2 ± 16.2
Median (IQR) time duration of snakebite to admission (hours)	4 (2–12)
Number of patients reporting within 1 hour	12 (19.3)
Site of distribution	
Lower limb	42 (67.7)
Upper limb	19 (30.6)
Head	1 (1.6)
First aid	
Allopathy centers	44 (70.9)
Alternative medicine	18 (29.0)
Tourniquet	45 (72.6)
Single	38 (61.3)
Multiple	7 (11.3)
Median (IQR) time duration of tourniquet application (minutes)	25 (0–60)
Median (IQR) duration of admission (days)	4 (3–5)
Median (IQR) duration for which 20-min WBCT remained positive (hours)	16 (12–24)
20-min WBCT normalized with ASV dose (mL)	
100	11 (17.7)
200	18 (29.0)
300	31 (50.0)
Outcome	
Expired	2 (3.2)
Recovered	53 (85.4)
Referred	7 (11.2)

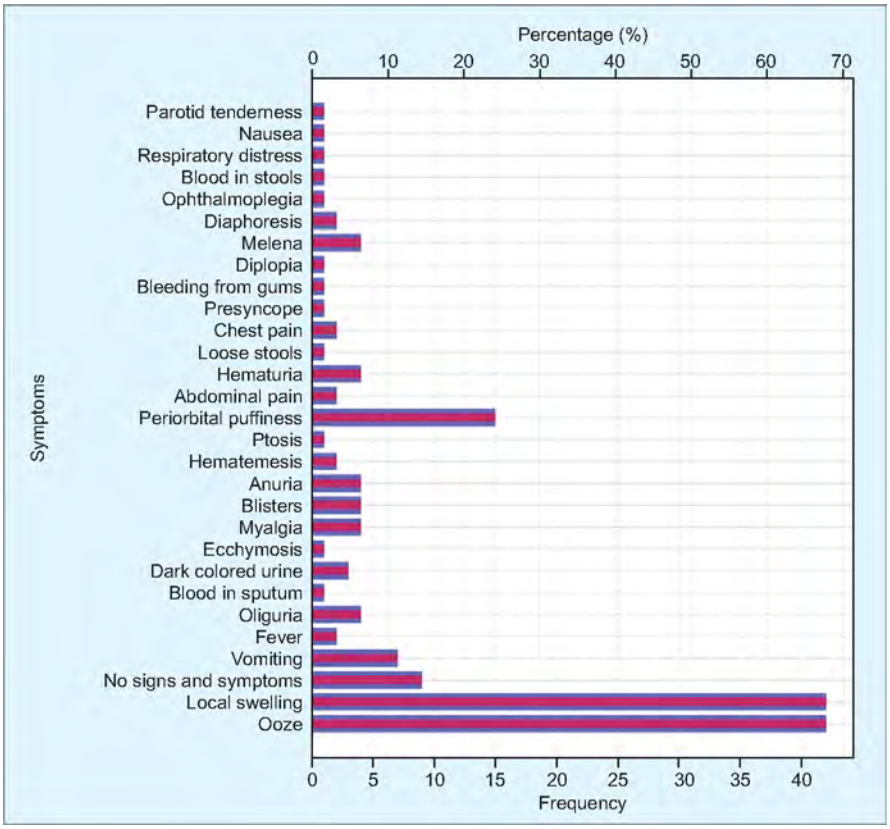


Fig. 1: Distribution of symptoms and signs among patients

(25.8%) patients had 1+, 5 (8.1%) patients had 3+ and 1 (1.6%) patient had 4+ proteinuria.

The prevalence of TMA was 6.4% (4/62). Among the four patients having TMA, concomitant CLS features were observed in three. All four patients with TMA were treated with hemodialysis. Two patients with TMA improved, and two were referred.

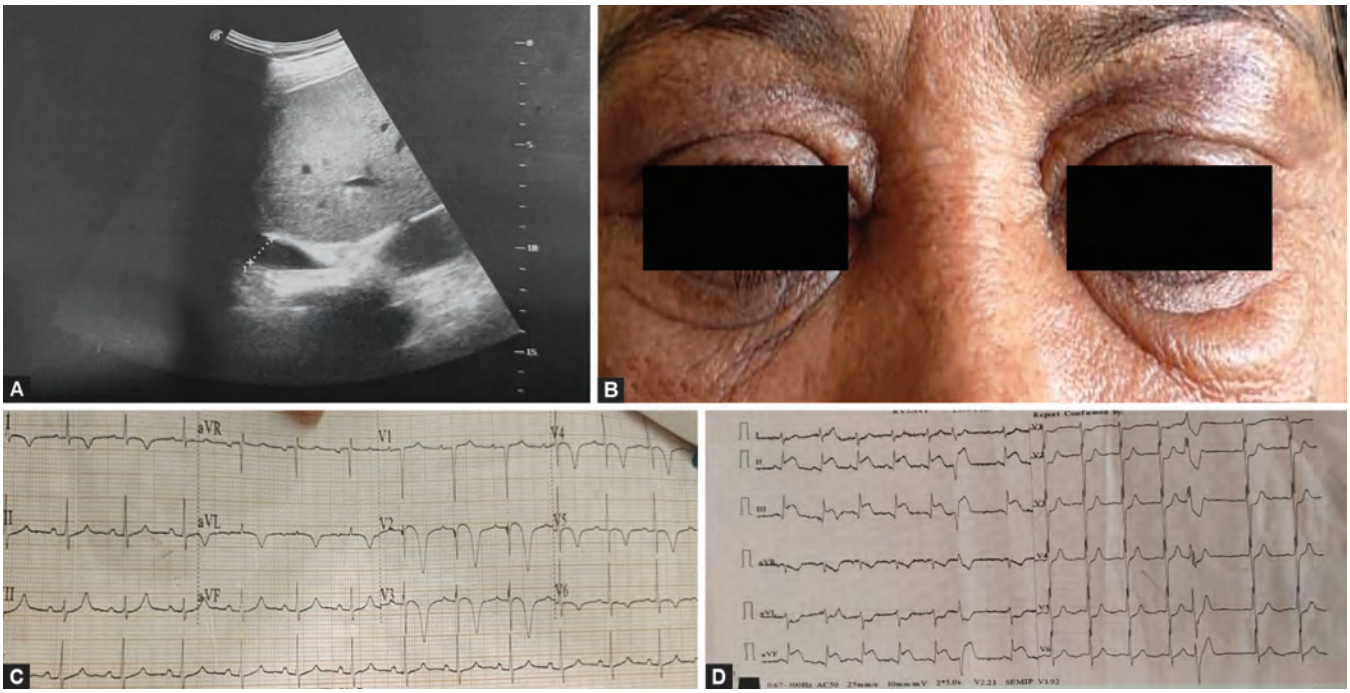
The 20 WBCT remained positive in two patients in spite of receiving the ASV dose of 300 mL. The 20-min WBCT became negative with 100 mL of ASV in 17.7% (11/62), with 200 mL of ASV in 29% (18/62), and with 300 mL of ASV in 50% (31/62). Adverse reactions in the form of anaphylaxis (1.6%), rash and urticaria (4.8%) were observed.

All patients received prophylactic antibiotics as oral amoxicillin–clavulanate. Secondary wound infection developed in two patients and was treated with oral linezolid. Three patients developed acute coronary syndrome, which included two patients with anterior wall non-ST-segment-elevated myocardial infarction (NSTEMI) and one patient with inferior wall ST-segment-elevated myocardial infarction (STEMI) (Figs 2C and D). One patient had features of myocarditis. One patient received FFP because of the hematemesis and mucosal bleeding.

Table 2: Distribution of laboratory, hematology parameters, prevalence of CLS, and TMA among study subjects

Parameter	*Total (%) (n = 62)*	*Male (%) (n = 35)*	*Female (%) (n = 27)*
Anemia	51 (82.2)	25 (40.3)	26 (41.9)
Leukocytosis	44 (70.9)	23 (37.0)	21 (33.8)
AKI	25 (40.3)	10 (16.1)	15 (24.1)
Transaminasemia (AST > ALT)	37 (59.6)	22 (35.4)	15 (24.1)
Thrombocytopenia	53 (85.4)	29 (46.7)	24 (38.7)
Schistocytes	6 (9.6)	3 (4.8)	3 (4.8)
Hypoalbuminemia	34 (54.8)	15 (24.1)	19 (30.6)
Raised LDH	57 (91.9)	25 (40.3)	32 (51.6)
Urine			
RBC	46 (74.1)	24 (38.7)	22 (35.4)
Proteinuria	42 (67.7)	23 (37.0)	19 (30.6)
Myoglobinuria	3 (4.8)	1 (1.6)	2 (3.2)
Raised CPK	45 (72.5)	25 (40.3)	20 (32.2)
Bilateral pleural effusion	7 (11.2)	4 (6.4)	3 (4.8)
Ascites	3 (4.8)	2 (3.2)	1 (1.6)
Bilateral effusion and ascites	2 (3.2)	1 (1.6)	1 (1.6)
Thrombocytopenia and AKI	25 (40.3)	10 (16.1)	15 (24.1)
RBC morphology			
Normocytic	46 (74.1)	29 (46.7)	17 (27.4)
Microcytic	2 (3.2)	–	2 (3.2)
Macrocytic	2 (3.2)	2 (3.2)	–
Dimorphic	10 (16.1)	3 (4.8)	7 (11.2)
TMA	4 (6.4)	1 (1.6)	3 (4.8)
Capillary leak syndrome	12 (19.3)	4 (6.4)	8 (12.8)

n, number; AKI, acute kidney injury; AST, aspartate transaminases; ALT, alanine transaminases; LDH, lactate dehydrogenase; RBC, red blood cells; CPK, creatine phosphokinase; TMA, thrombotic microangiopathy



Figs 2A to D: (A) Sagittal grayscale ultrasound of chest showing pleural effusion (dotted arrow) in subhepatic space; (B) Periorbital swelling; (C) ECG showing deep T-wave inversion in I, aVL, V2–V6; (D) ECG showing ST-segment elevation in II, III, aVF

Discussion

Capillary leak syndrome is a recognized complication of *Daboia russelii* envenoming, described from Southern India, Sri Lanka, and Myanmar. In southern India, CLS following snakebite has been reported from Kerala, Tamil Nadu, and Puducherry.[5,7–14]

Patients recruited in the present study had hemotoxic envenoming diagnosed on the basis of a positive 20 WBCT. The prevalence of capillary leak syndrome was 19.3% among patients in this study. The prevalence of CLS was 23% in a prospective hospital-based observational study on viper envenomation from Pondicherry, India.[14] In a study from the Malabar region, India, the prevalence of CLS among Russell's viper, hump-nosed pit viper (HNPV), and saw-scaled viper was 17%, 1.3%, and 0.09%, respectively. None of the patients with Malabar pit viper and bamboo pit viper envenomation developed CLS.[9] The striking feature of the study is that CLS is a manifestation of HNPV and saw-scaled viper, in addition to the already recognized complication of Russell's viper envenomation. These results are relevant from our study point of view due to the presence of Northern white-lipped pit viper (*Trimeresurus septentrionalis*), Himalayan pit viper (*G. himalayanus*) and Chamba pit viper (*G. chambensis*) in our region. Species identification was performed in the current study. Out of the 12 cases with CLS, nine patients had envenoming because of Russell's viper, and one due to Northern white-lipped pit viper. In the other two cases, with CLS species identification by the patients or their attendants was not possible. In a prospective study carried out in a cohort of children below 12 years and snakebite in a Kerala hospital, the prevalence of CLS was 6.9%.[11]

Capillary leak syndrome is due to additional permeability of proteins from capillaries and the spectrum of manifestations includes hypotension, pitting edema, noncardiogenic pulmonary edema, exudative serous cavity effusions, and hypovolemic shock with multiple-organ dysfunction. Diseases associated with CLS are sepsis, idiopathic systemic capillary leak syndrome or Clarkson's disease, cardiac surgery using cardiopulmonary bypass, anaphylaxis, major burns, engraftment syndrome, viral hemorrhagic fevers, hemophagocytic lymphohistiocytosis, snakebite envenomation, differentiation (retinoic acid) syndrome, the ovarian hyperstimulation syndrome, autoimmune diseases, and drugs.[15,16] Snake venom is a composite mixture of toxins, and the compound varies significantly from one species to another. The three dominant protein families in the venoms of Viperidae include snake venom metalloprotease (SVMP), phospholipase A_2 (PLA_2), and snake venom serine protease (SVSP). The secondary protein families include disintegrins (DIS), cysteine-rich secretory protein (CRiSP), C-type lectins (CTL), L-amino acid oxidase (LAAO), kunitz peptides (KUN), and natriuretic peptides (NP).[17] Two snake venom vascular apoptosis-inducing proteins (VAPs), VAP1 and VAP2, belonging to the SVMP family, have been postulated to be responsible for CLS.[2] Vascular endothelial growth factor, which injures endothelium, augments permeability, causes edema, and hypotension, has been indicated in the pathogenesis of CLS.[18]

Capillary leak syndrome can occur in spite of receiving adequate doses of ASV.[2] Antisnake venom and its neutralizing effect on CLS manifestations have been studied in a mouse model. It was observed that ASV has limited efficacy in neutralizing the CLS effect.[19] CLS has been identified as associated with increased mortality in adults and children with snakebite envenoming. The presence of CLS signs has been described as one of the seven admission clinical parameters that predict mortality in patients with viper envenoming in India.[20]

In India, CLS as a toxidrome due to snakebite envenoming has not been described from areas other than southern India. The likely reason could be that it is less recognized, overlooked, and underreported. The documentation of CLS among patients with hemotoxic snake envenoming in our study demonstrates that Russell's viper venom composition variability does not exist between the northern Himalayan state of Himachal Pradesh and the southern Indian state species. The current study further emphasizes that the venom components of the Russell's viper responsible for CLS are not unique to southern India. These

Table 3: Comparison of demographic, clinical features, and investigations in patients with and without CLS

Parameter	*CLS absent (n = 50)*	*CLS present (n = 12)*	*p-value*
Sex distribution			
Male	31	4	0.07
Female	19	8	
Age (years)	41.60 ± 16.1	50.08 ± 13.3	0.49
Median (IQR) time duration of snakebite to admission (hours)	4 (2–6)	13 (5–36)	0.01
Tourniquet applied			
Yes	35	10	0.35
No	15	2	
Median (IQR) time duration of tourniquet application (minutes)	25 (0–60)	42 (12–72)	0.31
Periorbital puffiness	3	12	0.02
Hypoalbuminemia	22	12	0.00
Pleural effusion	3	11	0.04
Median (IQR) duration for which 20-min WBCT remained positive (hours)	12 (6–24)	24 (15–27)	0.01
Total ASV dose received (mL)			
100	11	0	0.07
200	17	3	0.54
250	1	1	0.26
300	21	8	0.12
Median (IQR) duration of admission (days)	4 (3–4)	8 (4–12)	0.00
Hemoglobin (gm/dL)	11 ± 1	8.5 ± 3	0.00
TLC (per µL)	13682 ± 4110	15935 ± 8012	0.17
Platelet (per µL)	92960 ± 39301	61833 ± 27859	0.01
Urea (IQR), mg/dL	36 (26–48)	103 (83–141)	0.00
Creatinine (IQR), mg/dL	1 (0.7–1.4)	6.1 (3.4–7.2)	0.00
AST (IQR), U/L	52 (36–90)	111 (47–320)	0.05
ALT (IQR), U/L	30 (21.5–62.5)	51 (33.5–200)	0.01
ALP (IQR), U/L	103 (83.5–117)	101 (84–107)	0.83
S. albumin (gm/dL)	3.5 ± 0.5	3 ± 0.2	0.00
LDH (IQR), U/L	431 (329–639)	1995 (907–1995)	0.00
Total CPK (µg/L)	234 (129–547)	434 (312–576)	0.27
Uric acid (mg/dL)	5.8 ± 1.4	6.8 ± 2.8	0.09
TMA	1	3	0.01
Outcome			
Improved	47	6	0.00
Referred out	2	5	0.00
Expired	1	1	0.35

n, number; IQR, interquartile range; TLC, total leukocyte count; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase

observations may help formulate the state action plan envisaged under the National Action Plan for Prevention and Control of Snakebite Envenoming (NAPSE) in India, which aims to reduce disability and mortality due to snakebite by 50% before 2030.

Limitations

The number of cases included in this study was limited to a single center to derive a reliable conclusion on the epidemiology of Viperidae envenomation in this region. Further, given the low burden, either a single-center, longer study or a diverse-center study will be more informative. Follow-up of all the patients with CLS could not be established, as five patients were referred for treatment at other centers. Hemotoxic envenoming diagnosis was based on a positive 20-minute WBCT, and the prevalence of VICC or anticoagulant coagulopathy was not estimated in the present study. For snake species identification, immunodiagnostic methods were not used.

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Ethical Approval

The Institutional Ethics Committee approved the study vide no. HFW-H DRPGMC/Ethics/2023/016 dated: April 6, 2023.

Conflict of Interests

None.

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Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 1000 mg XR

1: Aiocdawacs Mat Jan 2026

Abridged Prescribing Information

Indication: It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. Dosage and Administration: The recommended dose is one tablet daily. Each tablet contains a fixed dose of dapagliflozin, Sitagliptin and Metformin Hydrochloride. Adverse Reactions: Most common adverse reactions reported are: Dapagliflozin- Female genital mycotic infections, nasopharyngitis, and urinary tract infections. Sitagliptin- Upper respiratory tract infection, nasopharyngitis and headache. Metformin- Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Warnings and Precautions: Dapagliflozin: Volume depletion; Ketoacidosis in Patients with Diabetes Mellitus; Urosepsis and Pyelonephritis; Hypoglycaemia; Genital Mycotic infections Sitagliptin: General- Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Acute pancreatitis: Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal product; Renal impairment; Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions- Stevens-Johnson syndrome; Bullous pemphigoid. Metformin Hydrochloride: Lactic acidosis; In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended.Contraindications: Hypersensitivity to the active substance of Dapagliflozin, Sitagliptin & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma; Severe renal failure (eGFR<30mL/min); Acute conditions with the potential to alter renal function such as: Dehydration, Severe Infection, Shock; Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure, Recent myocardial Infarction, Shock, Hepatic Impairment, Acute Alcohol intoxication, alcoholism Use in a special population: Pregnant Women: Due to lack of human data, drug should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Paediatric Patients: The safety and efficacy of drug has not yet been established. No data are available. Geriatric Patients: In Patients > 65 years, it should be used with caution as age increases. Additional information is available on request.
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Metformin Hydrochloride 1000 mg SR + Glimepiride 1 mg

Glycomet®-GP2 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 2 mg

Abridged Prescribing Information

Active Ingredients: Metformin hydrochloride (as sustained release) and glimepiride tablets Indication: For the management of patients with type 2 diabetes mellitus when diet, exercise and single agent (glimepiride or metformin alone) do not result in adequate glycaemic control. Dosage and Administration: The recommended dose is one tablet daily during breakfast or the first main meal. Each tablet contains a fixed dose of glimepiride and Metformin Hydrochloride. The highest recommended dose per day should be 8 mg of glimepiride and 2000mg of metformin. Due to prolonged release formulation, the tablet must be swallowed whole and not crushed or chewed. Adverse Reactions: For Glimepiride: hypoglycaemia may occur, which may sometimes be prolonged. Occasionally, gastrointestinal (GI) symptoms such as nausea, vomiting, sensations of pressure or fullness in the epigastrium, abdominal pain and diarrhea may occur. Hepatitis, elevation of liver enzymes, cholestasis and jaundice may occur; allergic reactions or pseudo allergic reactions may occur occasionally. For Metformin: GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, and loss of appetite are common during initiation of therapy and may resolve spontaneously in most cases. Metallic taste, mild erythema, decrease in Vit B12 absorption, very rarely lactic acidosis, Hemolytic anemia, Reduction of thyrotropin level in patients with hypothyroidism, Hypomagnesemia in the context of diarrhea, Encephalopathy, Photosensitivity, hepatobiliary disorders. Warnings and Precautions:: For Glimepiride: Patient should be advised to report promptly exceptional stress situations (e.g., trauma, surgery, febrile infections), blood glucose regulation may deteriorate, and a temporary change to insulin may be necessary to maintain good metabolic control. Metformin Hydrochloride may lead to Lactic acidosis; in such cases metformin should be temporarily discontinued and contact with a healthcare professional is recommended. Sulfonylureas have an increased risk of hypoglycaemia. Long-term treatment with metformin may lead to peripheral neuropathy because of decrease in vitamin B12 serum levels. Monitoring of the vitamin B12 level is recommended. Overweight patients should continue their energy-restricted diet, usual laboratory tests for diabetes monitoring should be performed regularly. Contraindications: Hypersensitivity to the active substance of glimepiride & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis, diabetic pre-coma). Severe renal failure (GFR<30ml/min). In pregnant women. In lactating women.Acute conditions with the potential to alter renal function (dehydration, severe infection, shock, intravascular administration of iodinated contrast agents); acute or chronic disease which may cause tissue hypoxia (cardiac or respiratory failure, recent myocardial infarction, shock); hepatic insufficiency; acute alcohol intoxication; alcoholism. Use in a special population: Pregnant Women: Due to a lack of human data, drugs should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Pediatric Patients: The safety and efficacy of drugs has not yet been established. Renal impairment: A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
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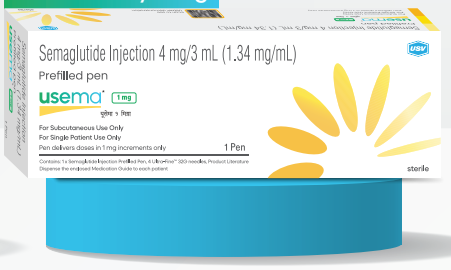

*Clinically proven efficacy and safety in people with T2DM with obesity.
(Sorli C, et al. Lancet Diab Endocrinol. 2017;5(4):251-260.)

REVIEW ARTICLE

Rapidly Progressive Dementia: A Quick Review

Sriramakrishnan Vayanakkan[1], Manoj Navamani[2*]

Received: 08 July 2025; *Accepted:* 17 December 2025

Abstract

Rapidly progressive dementias (RPDs) involve cognitive deterioration over weeks to months, sometimes extending up to 2 years. Although Creutzfeldt–Jakob disease (CJD) is the most well-known cause, around 44% of cases arise from non-CJD conditions, including infections, autoimmune disorders, Alzheimer's disease, vascular pathology, and toxic encephalopathies. Prompt and accurate diagnosis is vital, as certain forms are potentially reversible. Key diagnostic tools include CSF biomarkers (14–3–3 protein, tau, neurofilament light chain), advanced neuroimaging (MRI with DWI/FLAIR, PET), and EEG. Treating RPD as a neurological emergency and employing a multidisciplinary approach can improve outcomes, with ongoing research into novel biomarkers and precision medicine offering further promise for early detection and targeted therapy.

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Introduction

The term rapidly progressive dementia (RPD) encompasses a large group of disorders characterized by rapid cognitive decline in about 1–2 years.[1] Prompt identification and comprehensive assessment are vital for determining the underlying cause and initiating timely management. This article aims to outline the major differential diagnoses, clinical presentations, underlying mechanisms, neuroimaging characteristics, and the role of recent biomarkers. A thorough understanding of these elements enables clinicians to achieve accurate diagnoses, guide effective treatment, and improve overall patient outcomes.

Dementia Diagnosis

"Major cognitive impairment" is the current term for what was previously called "Dementia" (Fig. 1).

Causes of Rapidly Progressive Dementia

The importance of identifying reversible causes of dementia was analyzed at the University of California, San Francisco (UCSF), which revealed that a significant proportion of RPD cases were due to non-CJD etiologies (Fig. 2 and Table 1).[2]

The progression of dementia varies among different etiologies. Based on the time from the first symptom to full dementia syndrome, etiologies can be grouped as given in Figure 3.[3]

Autoimmune Causes

- Comorbid symptomatologies such as seizures, psychotic behavior, movement disorders, and ataxia, when present alongside cognitive decline, should prompt consideration of autoimmune encephalitis. The most common forms include NMDA receptor encephalitis, anti-VGKC, and GABA-B receptor encephalitis. Early recognition and treatment are crucial, as prompt immunotherapy can improve outcomes and prevent irreversible brain damage.
- NMDA receptor encephalitis is the most recognized form, presenting with rapid cognitive decline, psychiatric manifestations, seizures, and abnormal movements. LGI1 encephalitis typically involves the limbic system, leading to memory impairment, confusion, and characteristic faciobrachial dystonic seizures.
- CASPR2 encephalitis also affects the limbic regions and may present with cognitive and behavioral symptoms along with peripheral nerve hyperexcitability.
- GABA receptor encephalitis (involving either GABA-A or GABA-B antibodies) is marked by cognitive decline, seizures, and psychiatric features.

Table 1: Etiologies of RPD

V	Vascular
I	Infectious
T	Toxic/metabolic
A	Autoimmune
M	Metastasis
I	Iatrogenic
N	Neurodegenerative
S	Systemic

- DPPX encephalitis, although uncommon, can produce similar rapid deterioration, often accompanied by gastrointestinal symptoms (Table 2).

Diagnostic Criteria for Possible Autoimmune Encephalitis

Subacute onset, with rapid progression over less than 3 months, characterized by working memory deficits (such as short-term memory loss), changes in mental status, or psychiatric symptoms.

At least one of the following:

- New focal CNS findings.
- Seizures not explained by a previously known seizure disorder.
- CSF pleocytosis.
- MRI features suggestive of encephalitis.
- Reasonable exclusion of alternative causes (e.g., HSV encephalitis)
- Diagnosis can be made when all three of the criteria are met.

Vascular Dementia

Strokes can contribute to rapidly progressive dementias, often presenting as multi-infarct dementia (MiD), which involves a stepwise cognitive decline resulting from recurrent strokes.[4] Both large vessel and small vessel pathologies may manifest as rapidly progressive cognitive deterioration. According to a meta-analysis, 10% of individuals have dementia before the first stroke, 10% develop dementia after the initial stroke, and 33% experience dementia following recurrent strokes.[5]

Strategic infarcts—lesions in specific brain regions—can produce acute memory loss and mimic other dementias. Key locations include the bilateral posterior cerebral artery,[6] thalamus,[7] basal forebrain aneurysm rupture,[8] angular gyrus,[9] and caudate nucleus.[10]

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Table 2: Common autoimmune encephalitis

Antibodies	*Features*
Anti-NMDAR antibodies	The mean age of patients with NMDAR antibodies is approximately 20 years
Anti-LGI-1 antibodies	The mean age of patients with this is closer to 60 years
Anti-AMPAR, GABABR antibodies	These are associated with limbic encephalitis symptoms, which include confusion, behavioral changes, seizures, and memory disturbance in older patients
Anti-Hu antibodies	Paraneoplastic autoimmune encephalitis caused by small-cell lung cancer
Anti-Ma antibodies	Paraneoplastic autoimmune encephalitis caused by testicular germ cell tumors

Other antibodies associated with AE include anti-GQ1b, anti-DPPX, anti-CASPR2, anti-RI, anti-Yo, and anti-CV2

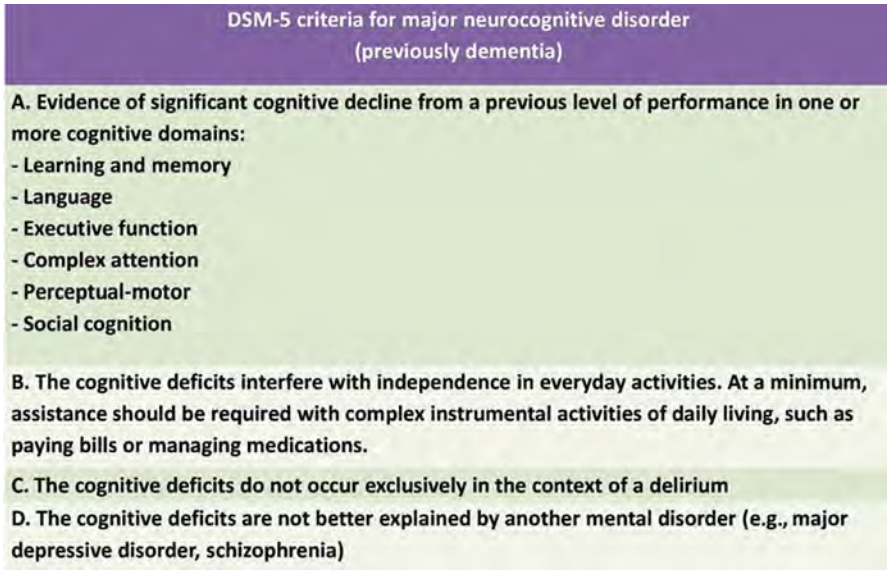

Fig. 1: Diagnosis of dementia–DSM-5

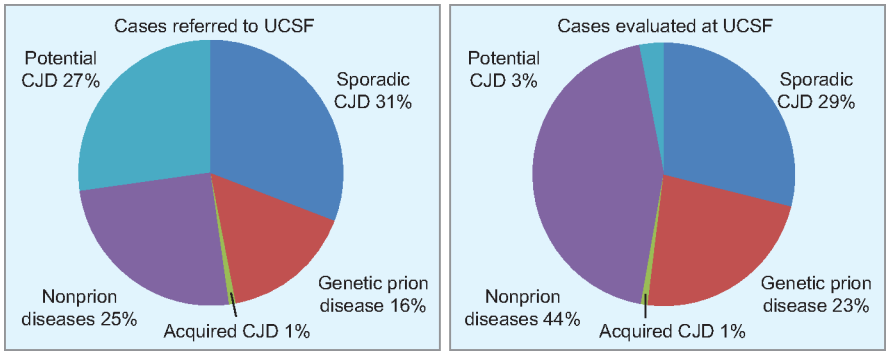

Fig. 2: Cases referred vs. cases evaluated at the tertiary care center, University of California, San Francisco (UCSF)

Leukoaraiosis (white matter hyperintensities) is increasingly recognized for its role in cognitive decline and is associated with hypertension, arteriosclerosis, amyloid angiopathy, Fabry's disease, vasculitis, and post-radiation status.[11] Clinically, it is linked with executive dysfunction and episodic memory impairment,[12] gait disturbances,[13] slowed cognitive processing,[14] depression,[15] and migraine.

COVID-19 and Rapidly Progressive Dementia

COVID-19 infection can mimic rapidly progressive dementia (RPD) through delirium, post- or parainfectious encephalitis, encephalomyelitis, cerebral hemorrhage, and infarction. Cognitive impairment is a common neurological manifestation. The pandemic-related lockdowns worsened cognitive deficits in patients with preexisting dementia. The long-term impact of COVID-19 on cognition is still under study, with potential mechanisms including:

- *Neuroinflammation*: Systemic inflammation may trigger brain inflammation.
- *Vascular effects*: COVID-19 can induce vascular changes contributing to cognitive decline.
- *Direct viral invasion*: SARS-CoV-2 may occasionally invade the central nervous system.

Infections and RPD

Several infections, including HSV encephalitis, coxsackie viral encephalitis, Lyme disease, syphilis, HIV, cryptococcosis, and prion diseases, can present as RPD, with Creutzfeldt–Jakob disease (CJD) being the classical prototype.

HSV encephalitis primarily affects the temporal lobes, leading to RPD via inflammatory neuronal damage. Neurological features may include aphasia, behavioral changes, seizures, and focal deficits.

Creutzfeldt–Jakob disease occurs in sporadic, iatrogenic, or familial forms, with sporadic CJD being most common. It progresses rapidly, with a median survival of 4.5–6 months and ~85% mortality within a year.[16] Onset typically occurs between 60 and 67 years.[17] Early signs include cognitive decline, behavioral and personality changes, motor and coordination difficulties, visual disturbances, and constitutional symptoms.[18] Cognitive deficits (confusion, memory impairment, poor concentration) appear first, while cortical involvement may cause aphasia, apraxia, or neglect. Motor signs include extrapyramidal and cerebellar symptoms and myoclonus; visual and sensory disturbances may also occur. Definitive diagnosis requires neuropathological confirmation via immunocytochemistry, Western blot for protease-resistant PrP, or identification of scrapie-associated fibrils (Table 3).

The diagnosis of CJD can be supported by a positive RT-QuIC assay in CSF or other tissues, which detects misfolded prion protein (PrPSc) through a fluorescent dye. RT-QuIC demonstrates high sensitivity (~92%) and specificity (~98%),[19] making it a reliable, less invasive alternative to brain biopsy, though repeat testing may be needed in cases of strong clinical suspicion due to rare false negatives. Brain MRI also aids diagnosis, with characteristic features including cortical ribbon sign, diffusion-weighted or FLAIR hyperintensities in the striatum, and thalamic changes such as the pulvinar and hockey stick signs.

Toxins and Dementia

Toxin-induced dementia arises from various exposures, with alcohol being a prominent cause, as seen in Marchiafava-Bignami disease, which damages the corpus callosum in chronic male alcoholics. Heavy metals—including mercury, arsenic, lead, toluene, and lithium—are significant contributors; mercury exposure can lead to Mad Hatter's syndrome (erethism),[20] marked by emotional, psychological, and motor disturbances. Chronic arsenic toxicity from contaminated groundwater can affect cognition and personality, especially in regions such as West Bengal and Bangladesh.[21] Certain medications, such as benzodiazepines, psychotropic drugs, and sodium valproate (via hyperammonemic encephalopathy),[22] may also cause cognitive and behavioral impairment. Additionally, radiation-induced encephalopathy from whole-brain irradiation in patients with metastatic tumors is a recognized cause of dementia.

Metabolic Causes

Cognitive impairment can result from various metabolic and endocrine disorders, many of which are reversible. Hypothyroidism, hyperthyroidism, and Hashimoto encephalopathy[23] may cause subacute cognitive decline, as can hypocalcemia, hypoparathyroidism, hypercortisolism, and repeated severe hypoglycemia in type 2 diabetes.[24] Other contributors include hepatic and uremic encephalopathy, while in chronic kidney disease, cognitive deficits are largely linked to hyperparathyroidism and anemia. Adult-onset inherited metabolic disorders—such as metachromatic leukodystrophy, adrenoleukodystrophy, adult polyglucosan body disease, cerebrotendinous xanthomatosis, Kufs disease, and rarer conditions such as advanced Wilson's disease, MELAS, and Leigh's disease—can also lead to dementia. Common, fully reversible causes include vitamin B1 and B12 deficiencies, frequently encountered in clinical practice.

Neurodegenerative Causes

Alzheimer's disease, frontotemporal lobar degeneration (FTLD), Dementia with Lewy bodies (DLBD), Corticobasal syndrome, and Progressive supranuclear palsy can cause RPD. Usually, Neurodegenerative diseases result in slowly progressive dementia exceeding 5 years.[25] Neurodegenerative dementias account for less than 5% of RPD.[26] Younger age of onset suggests FTLD, whereas DLBD occurs in older age. FTLD could also present with features of motor neuron disease. In conclusion, rapidly progressive neurodegenerative dementias with survival beyond 1 year typically represent non-CJD neurodegenerative dementias.[27] The terminal stage of late-life DLBD can sometimes resemble CJD.

Rare Possibilities

Primary CNS lymphomas, Metastases, Sarcoidosis, SLE, Sjögren, Celiac disease, Intravascular lymphomas, Atypical psychiatric disorders can present as rapidly progressive dementia. Whipple's disease, caused by *Tropheryma whippelii,* presents as a neuropsychiatric syndrome that progresses rapidly over months. Common clinical features include diarrhea, abdominal pain, weight loss, fever, and lymphadenopathy. CNS involvement occurs in 5–45% of cases.[28] Cognitive impairment occurs in 71% of cases, whereas psychiatric signs are seen in 44%.[29] Ataxia has been reported to occur in 45% of Whipple's cases.[30]

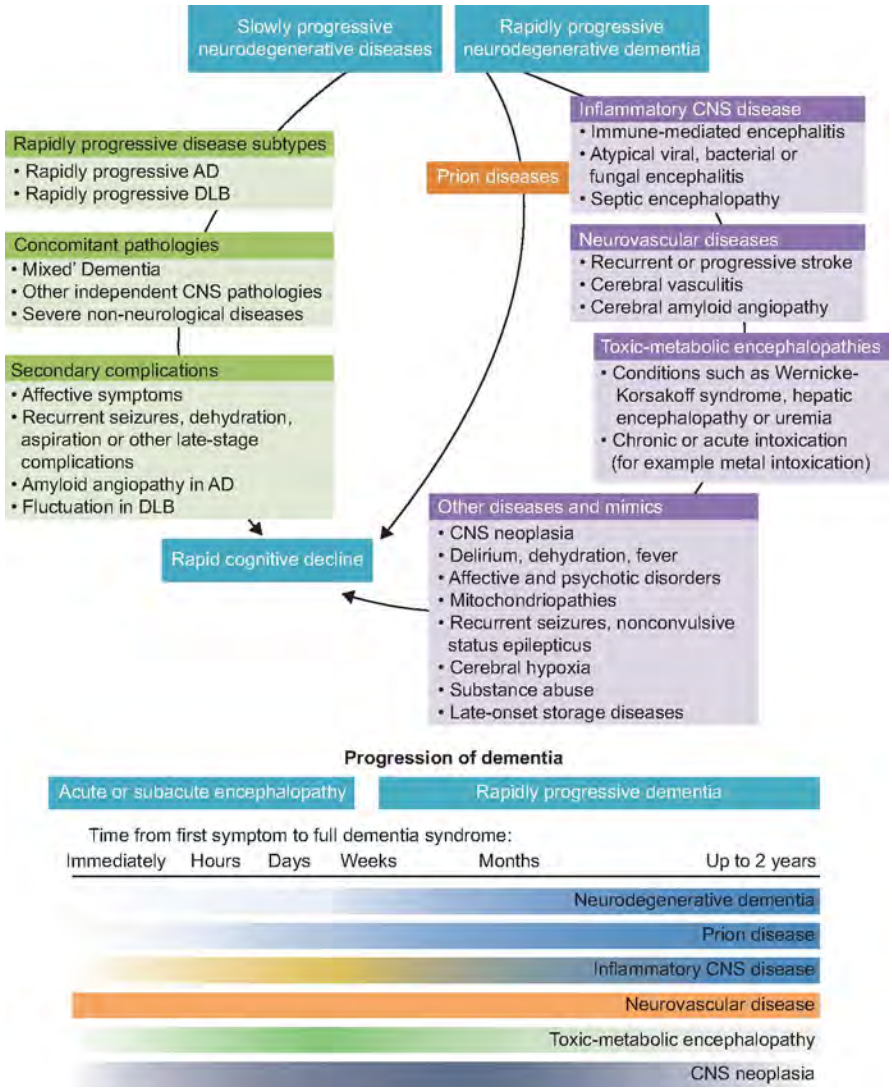

Fig. 3: Outlook of different etiologies of RPD and progression of dementia

Table 3: Diagnosis of probable CJD

Diagnostic criteria for sCJD	
1	RPD
2	At least two of the following: Myoclonus Visual or cerebellar signs Pyramidal/extrapyramidal signs Akinetic mutism
3	At least one of the following: Positive EEG findings Positive MRI findings Positive 14-3-3 protein test result
4	No indication of an alternate diagnosis

All four criteria must be satisfied to make a diagnosis of sCJD

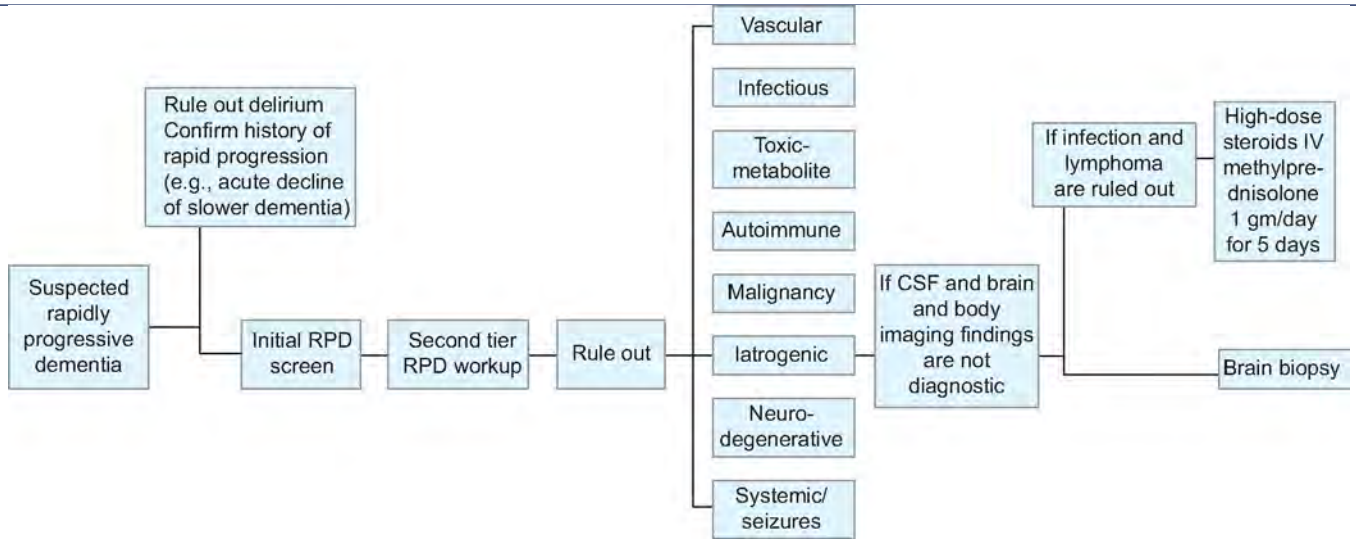

Fig. 4: Algorithm for evaluating RPD

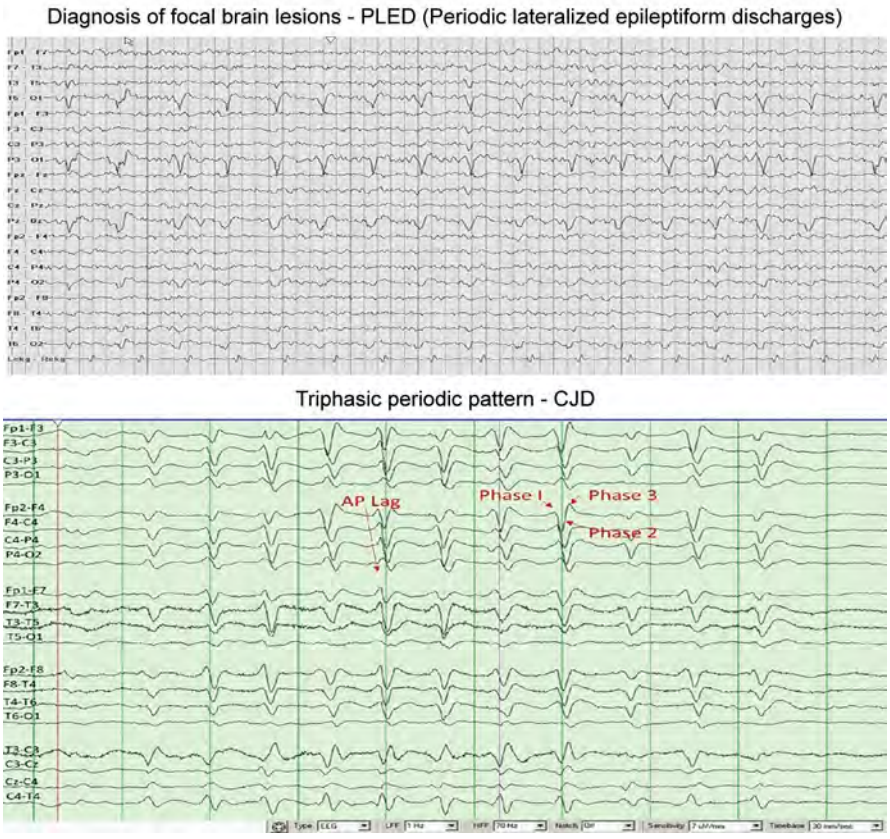

Fig. 5: Diagnosis of focal brain lesions–PLED (periodic lateralized epileptiform discharges) and triphasic periodic pattern–CJD

Diagnostic Algorithm for RPD

A structured diagnostic algorithm for rapidly progressive dementia is provided in Figure 4.

Role of Electroencephalography

Electroencephalography (EEG) helps to differentiate between various underlying causes and identify specific patterns associated with certain conditions.

Diagnosis of NCSE–Salzburg criteria

- Epileptiform discharges (ED) >2.5 Hz, or
- ED ≤2.5 Hz or rhythmic delta/theta activity (>0.5 Hz) and one of the following:
  - EEG and clinical improvement after intravenous antiepileptic drug, or
  - Subtle clinical phenomena, or
  - Typical spatiotemporal evolution (defined as incrementing onset - increase in voltage and change in frequency >1 Hz or change in location, or decrementing termination).
- If EEG improvement occurs without clinical improvement and if fluctuation without definite evolution occurs, those cases are considered possible NCSE.

Key Roles of EEG in RPD

- Differentiating delirium from dementia: Delirium often shows more pronounced diffuse slowing on EEG compared to dementia.
- Supporting diagnosis of prion diseases: In CJD, EEG may reveal characteristic periodic sharp wave complexes (PSWCs).
- Detecting seizure activity: EEG can identify epileptiform discharges and subtle seizures, including non-convulsive status epilepticus (NCSE) based on Salzburg criteria.
- Evaluating encephalopathies: Diffuse slowing helps assess brain dysfunction due to infections, toxins, or autoimmune disorders.
- EEG results are interpreted in conjunction with other investigations such as MRI, cerebrospinal fluid analysis, and laboratory tests to achieve an accurate diagnosis and guide management (Fig. 5).

Serum and CSF Markers of RPD

Serum and CSF biomarkers play an important role in the diagnosis of rapidly progressive dementias and related disorders. Increased proinflammatory cytokines (IL-6, IL-13, TNF-α, G-CSF) and specific antibodies—anti-NMDAR, anti-LGI1, anti-AMPA-R, and anti-GABA-BR—are indicative of autoimmune encephalitis, while anti-Hu and anti-Ma suggest paraneoplastic

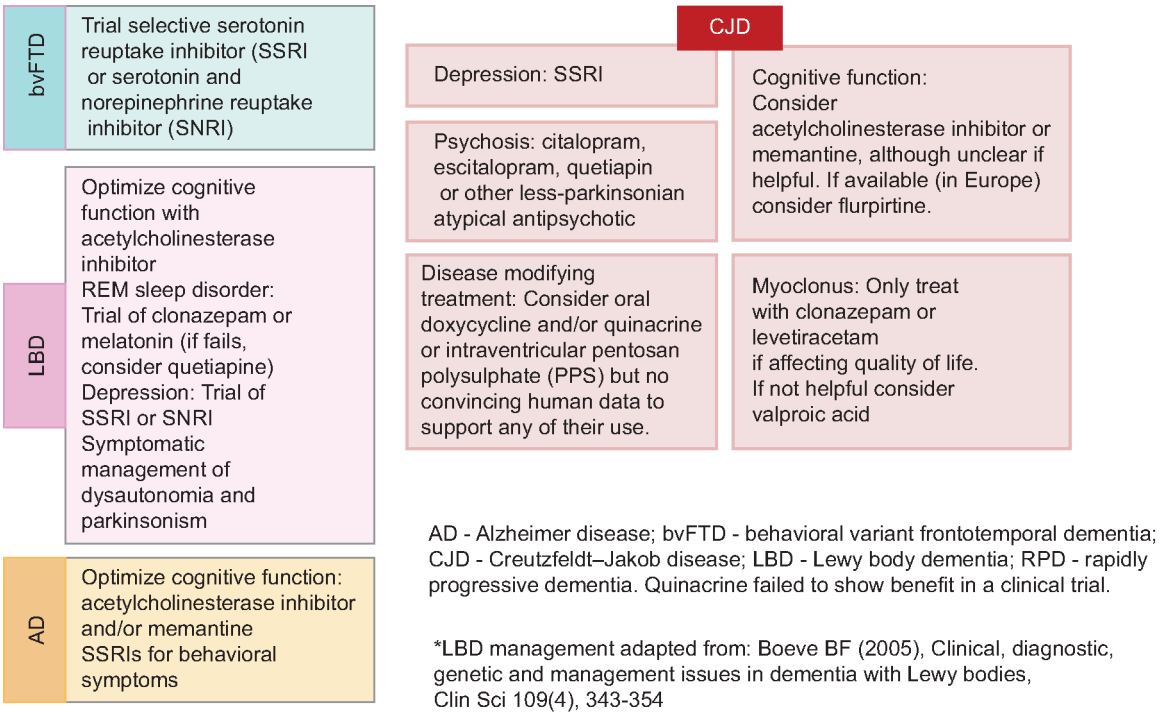

Fig. 6: Management algorithm for more common neurodegenerative causes of RPD

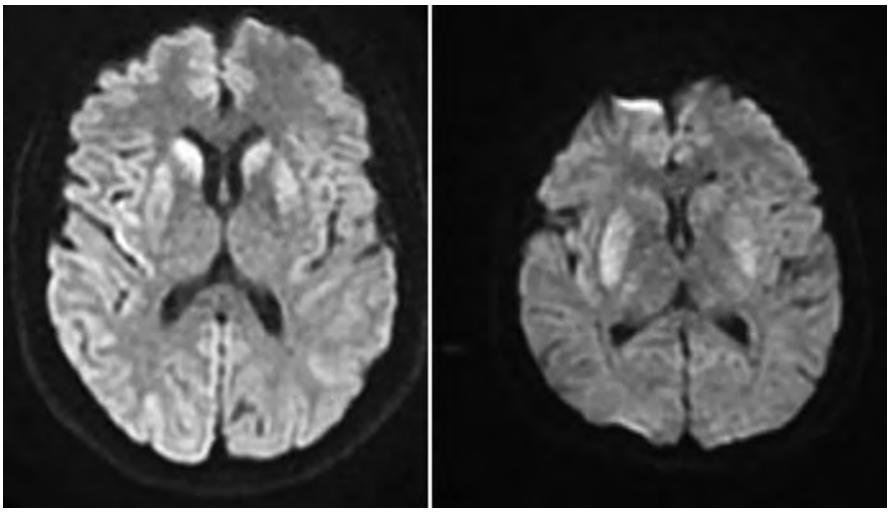

Fig. 7: MR Imaging showing striatal diffusion restriction in cases 1 and 2, respectively

variants. In Alzheimer's disease, t-tau, p-tau, and the t-tau/Aβ42 ratio serve as markers of neuronal and axonal injury. Neurofilament light chain (NfL) and YKL-40 reflect inflammatory processes, and MCP-1 is particularly elevated in vascular dementia. For CJD, CSF 14–3–3 protein demonstrates high sensitivity (92%) and specificity (80%). Although CSF NfL is nonspecific, it is frequently elevated in cases of RPD.

Newer Treatment Modalities

Quinacrine, an antimalarial drug, was tried for the management of RPD. The PRION-1 trial conducted at the National Prion Clinic in the UK found no benefit of Quinacrine on disease progression.[31] San Francisco trial also had the same results.

PRN 100, a monoclonal antibody, resulted in disease stabilization in three CJD patients. This research is ongoing. Brain autopsies also showed no neurotoxicity.[32]

The "Fastball" test, an at-home EEG-based device, has shown promise in detecting early signs of Alzheimer's disease within minutes, potentially aiding in earlier diagnosis (Fig. 6).[33]

Institutional Experience

Case 1: We had a 47/F, a homemaker, without any comorbidities, born to nonconsanguineous parents, without any family history, who presented with slowness of activities of daily life and stiffness of all four limbs for 6 months. History of decreased mood and anhedonia for 6 months. She has started misplacing things like her spectacles and room keys over the past 5 months. She had also started avoiding major discussions in the family. She was unable to utilize the mobile phone as she had previously. Over the last 1 month prior to presentation, she had a history of well-formed visual hallucinations as well. No history of fever. No history of prior TIAs. No history of loss of weight or appetite.

Overall, she had Parkinsonism, depression, psychosis, and rapidly progressive cognitive decline in the form of recent memory impairment and dysexecutive functions. On investigation, her total counts, serum B12, lipid profile, thyroid function tests, liver and renal function tests, and HbA1C were normal. ESR and CRP were elevated. MRI brain showed bilateral striatal diffusion restriction and T2/FLAIR hyperintensity.

The *second case* was a 55/F, known case of diabetes mellitus, who presented with Parkinsonism with postural instability and rapidly progressive cognitive decline over 8 months. There was no psychosis, cranial nerve involvement, weakness, myoclonus, dystonia, seizures, sensory involvement, or ataxia. Blood investigations, CSF, and EEG were noncontributory. The MRI brain was also similar to the previous presentation.

The probable differential diagnoses were autoimmune encephalitis, Hashimoto

encephalopathy, paraneoplastic syndrome, toxic encephalopathies such as carbon monoxide poisoning, and CJD (Fig. 7).

The breaking point in case 1 was CSF analysis, which showed elevated protein, normal glucose, and no cells. EEG was showing periodic sharp waves. CSF viral encephalitis panel was negative. CSF 14–3–3 is negative. CSF was positive for CASPR-2 antibodies. She was started on an IV pulse dose of steroids, which showed significant improvement in 1 week. She was continued on oral steroids and started on IV rituximab. Currently under follow-up. The second case had no such supporting investigations. On probing, she had a history of vomiting and loose stools prior to the onset of symptoms and was managed for hyponatremia. Hence, after excluding all possible causes, she was suspected of having developed extrapontine myelinolysis. She showed very minimal improvement with IV pulse steroids and was put on supportive therapy. Thus, RPDs need extensive workup to identify a possible treatable cause, as in case 1.

Conclusion

Rapidly progressive dementias (RPDs) present a diagnostic challenge due to their aggressive nature and the urgency for intervention. While the specter of prion diseases, such as CJD, often looms large in clinical considerations, it is crucial to recognize that RPDs encompass a diverse array of etiologies, many of which are treatable. These treatable conditions range from autoimmune encephalopathies and infectious diseases to metabolic disorders and toxic exposures. This article intends to provide a thorough overview of the wide range of differential diagnoses, highlighting the critical need for practicing neurologists to remain vigilant in identifying potentially reversible causes, by systematically evaluating each RPD case, and employing thorough diagnostic workups, we can strive to identify and address these treatable conditions, potentially preventing irreversible neurological decline and improving patient outcomes in the years to come.

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Informed Consent

Informed written consent was obtained from the patients for the publication of their data.

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REVIEW ARTICLE

Metabolic Syndrome and Tribal Population in India: A Review Article

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Abstract

Background: Metabolic syndrome (MetS), a cluster of risk factors including central obesity, hypertension, dyslipidemia, and insulin resistance, has emerged as a significant public health concern in India. While tribal populations have traditionally been perceived as protected from noncommunicable diseases, emerging evidence suggests a rising burden of MetS in these communities due to rapid lifestyle and nutritional transitions.

Objective: To synthesize current evidence on the prevalence, risk factors, diagnostic challenges, and health system gaps related to MetS among tribal populations in India, and to identify research and policy directions for inclusive healthcare planning.

Methods: A narrative review was conducted using peer-reviewed literature sourced from national and international databases, including Google Scholar, PubMed, and Scopus. A total of 42 studies were reviewed, including cross-sectional surveys, meta-analyses, and regional health assessments among various Scheduled Tribes and Particularly Vulnerable Tribal Groups (PVTGs) across India.

Results: The prevalence of MetS among tribal populations ranges from 3.8% in adolescents to over 39% in adults, with higher rates in females and increasing with age. Common risk factors include a shift from traditional to processed diets, physical inactivity, high alcohol and tobacco use, and socioeconomic deprivation. Genetic predispositions such as hemoglobinopathies also contribute to metabolic risk. Diagnostic inconsistency, small sample sizes, and underrepresentation in national surveys hinder effective disease surveillance. Health system barriers include poor access to diagnostics, low health literacy, and limited outreach of national NCD control programs.

Conclusion: Tribal populations in India are increasingly vulnerable to MetS, reflecting a double burden of undernutrition and metabolic risk. There is an urgent need for culturally adapted screening programs, tribe-specific diagnostic thresholds, community-based interventions, and longitudinal research to address this emerging public health challenge.

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Introduction

Metabolic syndrome (MetS)—a cluster of interrelated metabolic abnormalities including central obesity, insulin resistance, hypertension, dyslipidemia, and hyperglycemia—has emerged as a major global public health challenge. It substantially increases the risk for cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and overall mortality.[1] The worldwide prevalence of MetS has risen sharply over the past two decades, particularly in low- and middle-income countries undergoing rapid urbanization.

In India, recent pooled data indicate that approximately 30% of adults are affected by MetS, with higher rates among urban dwellers (32%) compared to rural (22%) and tribal (28%) populations.[2] These estimates, however, may obscure the complex epidemiology of MetS in indigenous populations who are often underrepresented in national surveys.

Several organizations, including the National Cholesterol Education Program (NCEP ATP III), International Diabetes Federation (IDF), and World Health Organization (WHO), have developed diagnostic criteria for MetS. These differ primarily in their cut-offs for waist circumference and the centrality of obesity in diagnosis. The IDF, for instance, mandates central obesity as a prerequisite, while NCEP ATP III permits diagnosis based on any three of five factors.[3–5] Such variation can lead to inconsistencies, particularly in tribal populations where body habitus may not align with standard thresholds.

Pathophysiologically, insulin resistance is considered the common denominator in MetS. Visceral adiposity, systemic inflammation, and dysregulated lipid metabolism form the foundation for metabolic dysfunction.[6] However, the concept of "lean MetS"—observed in undernourished populations with normal body mass but abnormal metabolic markers—challenges the conventional obesity-centric model.[7]

Among tribal communities in India, studies have identified both undernutrition and metabolic dysfunction, indicating a double burden of disease. For example, research in rural West Bengal and Chhattisgarh has reported significant rates of MetS and its components, even in individuals without obesity.[7,8] These findings highlight the limitations of current diagnostic frameworks and suggest the need for region- or tribe-specific anthropometric cut-offs.[9]

Tribal communities, which comprise 8.6% of India's population across 705 recognized groups, are disproportionately affected by structural health inequities, limited access to healthcare, and nutrition transition.[10] With increasing exposure to packaged foods, sedentary lifestyles, and substance use, these communities are becoming increasingly vulnerable to MetS and its sequelae.

This review aims to synthesize current evidence on the epidemiology, risk factors, diagnostic challenges, and health policy implications of MetS among India's tribal populations. By critically examining both national datasets and tribe-specific studies, we seek to illuminate a neglected dimension of India's noncommunicable disease burden.

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Overview of Tribal Populations in India

India is home to one of the world's largest and most diverse tribal populations, officially categorized as "Scheduled Tribes" (STs). According to the 2011 Census, approximately 104 million individuals, or 8.6% of the Indian population, belong to tribal communities, spread across 705 recognized tribes in 30 states and union territories.[11] These communities differ widely in language, culture, ecology, and socioeconomic conditions, from the Bhils and Gonds of Central India to the Santhals in the East and the Todas in the South.

Most tribal populations reside in remote, ecologically sensitive regions—forests, hills, and plateaus—where health and social services remain scarce. Historically dependent on hunting, shifting cultivation, and subsistence agriculture, many tribal groups are undergoing rapid socioeconomic and lifestyle transitions due to deforestation, displacement, urban migration, and market integration.[12]

A subcategory within STs—the Particularly Vulnerable Tribal Groups (PVTGs)—represents communities with the lowest literacy rates, poorest health outcomes, and least integration into state health infrastructure. Evidence from Odisha suggests extremely poor health indicators among PVTGs, including rising prevalence of hypertension, diabetes, and undernutrition, with minimal access to diagnosis or treatment.[13]

Multiple studies indicate that tribal communities are experiencing an epidemiological transition, marked by the coexistence of infectious and noncommunicable diseases. Drivers of this shift include nutritional transition (from millet- and tuber-based diets to polished rice and processed foods), increased alcohol and tobacco use, physical inactivity, and low health literacy.[8] Despite this, many tribes still rely heavily on traditional healers, spiritual beliefs, and ethnomedicine—often delaying modern medical intervention.[14]

There are also inter-tribal disparities in metabolic and cardiovascular health. For example, the Katkaris of Maharashtra show high rates of underweight and stunting, while the Bhils and Kokanas show higher prevalence of hypertension and overweight.[15] In Chhattisgarh, the Bhatra, Gond, Kondh, and Paraja tribes have high frequencies of genetic disorders such as sickle cell anemia and thalassemia, complicating both diagnosis and management of metabolic risk factors.[14]

Given this heterogeneity, tribe-specific epidemiological baselines are essential. Generalized health data and policies often fail to capture the nuanced needs of tribal subpopulations. Any assessment of MetS in these communities must therefore account for regional, cultural, and biological variability.

Prevalence of Metabolic Syndrome in Tribal Groups

Metabolic syndrome, once considered rare among indigenous populations, is now increasingly prevalent among Indian tribal groups. Epidemiological studies conducted over the last two decades reveal wide variation in MetS prevalence, ranging from 3.8% in adolescents to over 39% in adults, depending on region, age, tribe, and diagnostic criteria used.[7,15–18]

A study by Mahajan and Kshatriya among tribal adolescents in Gujarat estimated the prevalence at 3.8%, highlighting a disturbing early onset of metabolic risk factors.[16] In contrast, studies from Kerala, West Bengal, Chhattisgarh, and Maharashtra report much higher rates in adult populations—ranging from 21% to 39%.[16–18] For instance, in a tribal region of Kerala, the prevalence was 28.3% using NCEP-ATP III criteria, and notably higher in women (32.5%) than in men (21%).[17]

The burden also varies based on tribe-specific factors and ecological zones. In Maharashtra, the Bhils, Katkaris, and Thakars showed metabolic abnormalities despite being underweight, illustrating that MetS can coexist with chronic undernutrition.[16] Among Rang Bhotias, 39.2% had MetS, 43.4% had hypertension, and 33.7% had abdominal obesity, underscoring the transition from traditional to modern risk profiles.[18]

Gender disparities have been reported consistently, with most studies finding higher prevalence in women, potentially due to compounded effects of obesity, lower physical activity, and hormonal profiles.[7,17] Additionally, the age-wise trend shows a sharp increase in MetS prevalence beyond the age of 30, suggesting that early adulthood is a critical window for intervention.[7,16]

Importantly, when tribal populations are compared with their rural and urban nontribal counterparts, MetS prevalence is only marginally lower or similar, despite socioeconomic disadvantages. In fact, Krishnamoorthy et al. showed that tribal adults have a pooled prevalence of 28%, nearly closing the gap with urban adults (32%).[2]

These findings not only dismantle the assumption of tribal protection against metabolic disorders but also emphasize the need for targeted screening programs using culturally sensitive, tribe-specific diagnostic approaches (Table 1).

Comparison of MetS prevalence across different population groups in India. Urban adults show the highest prevalence (~32%), followed by tribal (~28%) and rural adults (~22%). Data synthesized from national and regional studies (Fig. 1).[2]

Risk Factors among Tribal Populations

The etiology of MetS among tribal populations in India reflects a complex interplay of lifestyle transitions, environmental changes, cultural practices, and genetic predispositions.

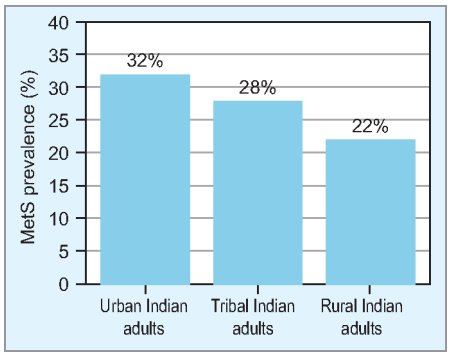

Fig. 1: Metabolic syndrome prevalence across the Indian population

Table 1: Summary of studies on MetS prevalence in Indian tribes

Study	*Year*	*Tribe/region*	*Sample size*	*Prevalence (%)*	*Criteria used*
Mahajan and Kshatriya[16]	2020	Kukana tribe, Gujarat	296 adolescents	3.8	ATP III (Cook's criteria)
Ismail et al.[17]	2016	Kannavam tribal, Kerala	120 adults	28.3	NCEP-ATP III
Mukhopadhyay et al.[7]	2018	Tribals in West Bengal	200 STs	21.4	IDF/ATP III
Kandpal et al.[18]	2016	Rang Bhotia, Uttarakhand	288 adults	39.2	NCEP-ATP III
Deo et al.[15]	2018	Bhils, Katkaris, Kokana, Thakars	1,864 adults	11.7–28.0	Field protocol
Krishnamoorthy et al.[2]	2020	National (meta-analysis)	133,926	28.0 (tribal subgroup)	Pooled

Unlike the traditionally active and minimally processed diets of the past, tribal populations are now experiencing a rapid nutrition transition, marked by reduced dietary diversity and increased consumption of high-calorie, low-nutrient foods.[17]

Staples such as millets, forest tubers, and wild greens are being replaced with polished rice, maize, and packaged foods, contributing to a higher glycemic load and micronutrient deficiencies.[7] This transition is also tied to declining physical activity, as mechanization of agriculture, deforestation, and migration to urban settlements reduce manual labor and daily energy expenditure.[19]

In parallel, alcohol and tobacco consumption are widespread and culturally ingrained in many tribal groups. Studies show that daily or binge alcohol use is common among both men and women, significantly contributing to hypertension, liver dysfunction, and lipid abnormalities.[12]

Sedentarism, particularly among tribal youth and women, is an emerging concern. Increased screen time, joblessness due to migration, and reduced agricultural engagement all contribute to a more sedentary lifestyle, a core risk factor for insulin resistance and central obesity.[19]

Socioeconomic deprivation is another powerful determinant. Limited access to healthcare, low health literacy, poor sanitation, and food insecurity increase vulnerability to both undernutrition and overnutrition.[13] Simultaneously, a number of studies highlight genetic susceptibility, especially in tribal groups with high prevalence of hemoglobinopathies such as sickle cell disease and thalassemia, which are associated with chronic inflammation and metabolic disruption.[15]

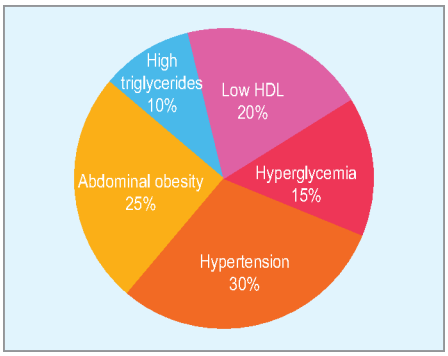

Fig. 2: Distribution of MetS components among tribal groups

This confluence of environmental and biological factors underscores the importance of context-specific, tribe-sensitive interventions in both research and policy (Table 2).

The estimated distribution of key components of MetS among tribal populations in India. Hypertension (30%) and abdominal obesity (25%) are the most prevalent features, followed by low HDL (20%), hyperglycemia (15%), and elevated triglycerides (10%) (Fig. 2).

Health System and Policy Gaps

Despite the rising burden of MetS and associated noncommunicable diseases (NCDs) among India's tribal populations, structural health system limitations continue to hinder early diagnosis, management, and prevention efforts. A core challenge is the lack of routine screening and surveillance in tribal belts, where even basic anthropometric measurements, blood pressure checks, and glucose monitoring are inconsistently conducted.[12]

Health infrastructure in many tribal areas remains inadequate, with primary health centers (PHCs) often understaffed, underequipped, and geographically inaccessible. In remote regions, diagnostic tools such as lipid profiling kits, autoanalyzers, and trained technicians are often unavailable, resulting in underdiagnosis and misclassification of metabolic risk factors.[13] Studies have also documented delays in transporting blood samples, improper sample handling, and cultural reluctance to provide blood specimens due to traditional beliefs.[15]

Compounding these gaps is the low health literacy among tribal populations. Many individuals are unaware of the asymptomatic nature of hypertension, dyslipidemia, and glucose intolerance, contributing to poor care-seeking behavior. Additionally, the dominance of magico-religious beliefs and reliance on traditional healers means that symptoms are often attributed to supernatural causes rather than biological ones.[16]

India's national NCD control programs—such as the NPCDCS (National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke)—have limited reach in tribal areas. Although screening has been scaled up under the Ayushman Bharat scheme, tribal districts remain underrepresented in data reporting, and culturally adapted outreach strategies are lacking.[19]

There is also an evident gap in tribal health research funding, with relatively few large-scale studies focused specifically on tribal populations. Methodological limitations such as small sample sizes, cross-sectional designs, and nonstandardized criteria further restrict generalizability and policy relevance.[20]

To bridge these gaps, health policies must adopt a tribe-centric approach. This includes mobile health units, community-based screening drives, training of local health workers in MetS diagnostics, and inclusion of tribal-specific health indicators in national surveys. Additionally, strengthening IEC (Information, Education, Communication) tailored to tribal languages and beliefs is vital to promote preventive care.

Research Gaps and Methodological Concerns

Despite growing awareness of the rising burden of MetS among India's tribal populations, research on this topic remains methodologically fragmented and underpowered. Key gaps limit the utility of current evidence for large-scale policy formulation.

A fundamental issue is the variation in diagnostic criteria across studies. Some investigations apply NCEP ATP III, others use IDF, and a few rely on modified thresholds adapted for adolescents or South Asians.[17] This inconsistency creates difficulties in comparing prevalence estimates or aggregating data for meta-analyses. Moreover, many studies do not justify their choice of criteria relative to the tribal population's anthropometric characteristics.[7]

Another challenge is the lack of longitudinal and large-sample studies. Most research is cross-sectional, with small, nonrepresentative

Table 2: Risk factors identified across reviewed studies

Study	*Tribe*	*Risk factors*	*Notes on lifestyle/occupation*
Mahajan and Kshatriya[16]	Kukana (Gujarat)	Low HDL, high BP	Adolescents; high-starchy diet
Ismail et al.[17]	Tribals of Kerala	High BMI, high WHR	Alcohol use, reduced physical work
Kandpal et al.[18]	Rang Bhotia	Abdominal obesity, smoking	Age + inactivity linked with high MetS
Shrivastava et al.[12]	Multiple tribes	Hypertension, high glucose	Shift from millet to rice; alcohol use
Balgir[14]	Gond, Bhatra, Paraja	SCD, thalassemia	Genetic load + undernutrition

Table 3: Methodological variability in reviewed studies

Study	*Sample size*	*Diagnostic criteria*	*Limitation*	*Suggestion*
Mahajan and Kshatriya[16]	296	Modified ATP III (adolescents)	Narrow age band, not generalizable	Include adult and adolescent strata
Ismail et al.[17]	120	NCEP ATP III	Small, convenience sample	Use probability sampling
Mukhopadhyay et al.[7]	200 STs	IDF + ATP III	Mixed criteria, no follow-up	Use a consistent diagnostic model
Kandpal et al.[18]	288	ATP III	No adjustment for behavior confounders	Apply multivariate regression
Tripathi et al.[20]	Meta-analysis	Mixed (21 studies)	High heterogeneity	Tribe-specific subgroup analyzes

samples limited to one or two villages, thus precluding causal inference or generalizability.[18] Very few studies employ multivariate modeling to account for confounding variables such as income, access to healthcare, or dietary diversity.[19]

Underreporting is also a systemic issue. Tribal populations are poorly represented in national health surveys such as the NFHS and DLHS. This leads to data invisibility, especially for Particularly Vulnerable Tribal Groups (PVTGs), who are excluded even from stratified reporting frameworks.[20]

Additionally, biomedical and cultural barriers to participation—such as mistrust of blood sampling, logistical delays, or poor translation of informed consent—further restrict data accuracy.[17]

For future research to be policy-informative, studies must emphasize:

- Standardized and context-sensitive diagnostic criteria.
- Larger sample sizes and geographic diversity.
- Inclusion of both biological and sociocultural risk dimensions (Table 3).

Conclusion and Recommendations

The burden of MetS among India's tribal populations has been historically underrecognized but is now increasingly evident across both adolescents and adults. The synthesis of current research shows that tribal communities are no longer insulated from the metabolic shifts associated with urbanization and globalization. Prevalence estimates ranging from 3.8% in adolescents to over 39% in adults challenge the outdated perception of tribal populations as purely undernourished or immune to noncommunicable diseases (NCDs).[17]

A confluence of dietary shifts, reduced physical activity, socioeconomic deprivation, substance use, and genetic vulnerability is accelerating the rise of MetS in these communities. Yet, tribal-specific screening, diagnostic benchmarks, and preventive interventions are nearly absent from India's national health strategy.[12]

The heterogeneity among tribes—in ecology, culture, health beliefs, and disease burden—demands context-sensitive approaches to screening and care delivery. Standard national policies must be tailored to reflect the lived realities of tribal people, particularly those in remote or forested regions with high barriers to care.[13]

Based on the evidence reviewed, we propose the following recommendations:

- *Diagnostic reform*: Adopt tribe- and region-specific criteria for obesity and waist circumference to improve detection of MetS in lean or undernourished individuals.
- *Community-based screening*: Integrate MetS screening into existing tribal health and nutrition outreach programs, such as PHCs, Mobile Medical Units, and Anganwadi centers.
- *Health literacy initiatives*: Develop culturally appropriate IEC materials in tribal languages, involving local leaders and traditional healers to improve acceptability.
- *Longitudinal studies*: Fund multicentric, longitudinal studies with standardized criteria to better understand trends and design evidence-based interventions.
- *Policy integration*: Ensure tribal districts are fully included in the implementation and reporting frameworks of the NPCDCS and Ayushman Bharat programs.
- Ultimately, achieving equitable health outcomes for India's tribal populations requires a decisive shift toward inclusion, customization, and continuity of care in both research and policy.

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REVIEW ARTICLE

Dementia and Alzheimer's Disease: A Panoramic Review of Recent Advances in Pathogenesis, Diagnosis, Therapy, and Public Health

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Abstract

Dementia, particularly Alzheimer's disease (AD), has emerged as one of the most pressing global health challenges. With populations aging rapidly, the demand for updated knowledge on disease mechanisms, diagnostics, and therapeutic strategies has never been greater. This review synthesizes recent findings from 2024 to 2025 on dementia and AD, covering the pathophysiology, modern diagnostic techniques, emerging treatments, preventive strategies, and policy frameworks. Special attention is given to breakthroughs in biomarker research, combination therapies, nonamyloid therapeutic targets, and the implementation of the expanded Global Plan on Dementia. By consolidating evidence from the World Health Organization (WHO), the Lancet Commission, and leading academic studies, this review aims to guide clinicians, researchers, and policymakers in shaping the future of dementia care.

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Introduction

Globally, dementia affects over 57 million people, with Alzheimer's disease (AD) representing the majority of cases.[1–3] Projections indicate that by 2050, the prevalence may double, placing an unprecedented burden on healthcare systems, caregivers, and economies, particularly in low- and middle-income countries. The economic toll of dementia is staggering; in the United States alone, costs are expected to reach $781 billion in 2025, with much of it stemming from long-term care and informal caregiving.[4]

In response, the WHO has expanded its Global Action Plan on Dementia through 2031, emphasizing the development of national strategies, improved diagnostics, caregiver support, and the integration of dementia-friendly policies into public health frameworks.[3,5] Alongside these global initiatives, research advances in molecular biology, imaging, and therapeutics have created opportunities to transform both the understanding and management of dementia.

Etiology and Pathogenesis

A Multifactorial Landscape

Alzheimer's disease does not arise from a single cause. Age remains the most potent risk factor, but genetic predisposition, sex differences, environmental exposures, lifestyle behaviors, and chronic diseases all play pivotal roles.[6,7] The APOE ε4 allele is widely recognized as a key genetic risk factor for late-onset AD. However, contemporary studies reveal that factors such as chronic inflammation, insulin resistance, and hormonal changes—particularly estrogen deficiency after menopause—also contribute substantially to disease development.[7,8]

Infection and Systemic Health

Emerging evidence indicates that infections promote neurodegenerative processes. *Porphyromonas gingivalis*, a bacterium linked to periodontal disease, can accelerate amyloid–β deposition and tau pathology, potentially by breaching the blood–brain barrier and triggering neuroinflammation.[6] Such findings underscore the importance of oral and systemic health as modifiable contributors to dementia risk, suggesting that preventive interventions could extend beyond conventional lifestyle modifications.

Metabolic, Vascular, and Lifestyle Factors

Metabolic disorders, ranging from insulin resistance and diabetes to hypertension and dyslipidemia, are closely associated with increased dementia risk.[7,9] Lifestyle behaviors, including sedentary habits, limited cognitive stimulation, poor diet, and exposure to environmental pollutants, compound these risks. Importantly, these factors are modifiable, providing a clear rationale for early lifestyle interventions to delay the onset or progression of cognitive decline.[10]

Epidemiology and Public Health

Recent WHO surveillance data and the global dementia observatory show a steady rise in global dementia cases, exceeding 57 million today.[1,2] The 2024 Lancet Commission report estimates that up to 45% of cases could be prevented or delayed through modification of 14 key risk factors, including sensory impairments, hypertension, obesity, diabetes, low education, smoking, and social isolation.[10–12]

Despite the evidence, many nations have yet to implement comprehensive national dementia strategies, and public awareness often remains limited. This highlights the urgent need for policies that promote early detection, caregiver support, and dementia-friendly societal infrastructures. Coordinated global efforts are essential to translate scientific advances into practical health solutions.

Advances in Diagnosis and Biomarkers

Biomarker Innovation and Early Detection

The integration of biomarkers with clinical assessment has revolutionized early diagnosis. Cerebrospinal fluid analysis measuring amyloid-β, total tau, and phosphorylated tau, coupled with advanced imaging techniques such as amyloid/tau PET and MRI, enables the detection of disease processes even before

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clinical symptoms manifest.[6,7] Artificial intelligence now enhances image analysis, increasing accuracy and reproducibility. Risk stratification algorithms, combining genetic, metabolic, and lifestyle data, facilitate personalized monitoring and intervention strategies.

Recognizing Disease Heterogeneity

Dementia is often heterogeneous, with mixed pathologies complicating diagnosis. AD may coexist with vascular changes, Lewy bodies, or frontotemporal degeneration, while early-onset cases frequently involve distinct genetic or infectious factors.[8,12] Accurate subtyping is essential to guide therapy and predict disease trajectory, emphasizing the importance of multidisciplinary evaluation.

Therapeutic Strategies and Clinical Breakthroughs

Symptomatic Treatments

Traditional treatments, such as cholinesterase inhibitors and memantine, continue to offer modest but meaningful improvements in cognition, function, and behavioral symptoms, particularly in mild-to-moderate AD.[6]

Disease-modifying Therapies

Monoclonal antibodies targeting amyloid–β, including lecanemab and donanemab, have been approved for early stage AD and have demonstrated moderate slowing of cognitive decline[9]. Administration is intravenous, and careful monitoring is required due to potential side effects such as amyloid–related imaging abnormalities. These therapies highlight the shift toward precision medicine in dementia care.

Beyond Amyloid: Emerging Targets

Research from MIT and Harvard has identified alternative pathways involved in neurodegeneration, including DNA repair, RNA modification, and neuroinflammatory mechanisms.[6–8] Combination therapies addressing multiple pathogenic mechanisms are being explored. Tau-targeted drugs, autophagy modulators, and kinase inhibitors are undergoing preclinical and early clinical trials, representing next-generation treatment approaches.

Drug Repurposing and Technology-enhanced Interventions

Repurposing existing drugs and integrating digital therapeutics, such as AI-guided cognitive training and tele-rehabilitation, are emerging as adjunctive strategies. Early evidence suggests these approaches may enhance cognitive resilience and extend functional independence in patients with early or mild dementia.[6,7]

Nonpharmacological and Multimodal Interventions

Nondrug interventions remain central to comprehensive dementia care. Cognitive stimulation, physical activity, diet optimization, sleep hygiene, social engagement, and sensory support (hearing and vision correction) improve quality of life and reduce caregiver burden.[10–12] Structured programs that integrate caregiver education, social support, and behavioral management enhance patient outcomes and help sustain long-term care at home or in community settings.

Prevention, Risk Factor Modification, and Multidomain Trials

Prevention strategies focus on managing cumulative risk factors. Evidence supports multifactorial interventions targeting education, vascular and metabolic health, head injury prevention, and sensory rehabilitation.[10,11] Randomized multidomain trials confirm that combining lifestyle, cognitive, and pharmacologic interventions can delay dementia onset and slow progression, particularly when applied early.

Socioeconomic and Global Policy Considerations

Dementia imposes a substantial economic burden, with costs exceeding $780 billion in the US alone, primarily due to informal caregiving, hospitalization, and productivity losses.[1,4] Globally, policymakers are advocating for dementia-friendly legislation, national registries, trained workforces, and integrated social and healthcare systems.[3,5,13] Investment in preventive strategies and public health infrastructure is both ethically and economically essential.

Future Directions and Research Gaps

While recent advances, from antiamyloid therapies to multiomic research, have been promising, critical gaps remain. These include equitable access to diagnostics and therapeutics, personalized multimodal interventions, strengthened interdisciplinary collaborations, and better support for caregivers.[6–8] Future research must also explore scalable interventions suitable for diverse healthcare contexts and low-resource settings.

Conclusion

The period 2024–2025 marks a transformative phase in dementia and AD research. Progress in molecular biology, diagnostics, therapeutic innovations, and public health frameworks is reshaping how dementia is understood and managed. By integrating evidence-based clinical strategies, holistic nonpharmacological care, and robust policy initiatives, the global community can begin to mitigate the burden of dementia. Sustained investment, interdisciplinary collaboration, and strategic implementation are essential to translate scientific discoveries into meaningful improvements in patient outcomes and societal well-being.

Source of Support

None.

Conflict of Interest

None.

Ethical Clearance

Not applicable.

Patient Consent

Not applicable.

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API Announcement

Elections of API, ICP and PRF

(Full details circular No. 1 & 2/2026)

Election for Governing Body of API, Board of PRF and Faculty Council of ICP are announced for the following posts:

Governing Body of API:
President-Elect: One; Vice President: Two (One VP for 3 years & One VP for 1 year); Hon. General Secretary: One; Elected Members: Six and Hilly Zone (Himachal Pradesh, Uttarakhand, Jammu & Kashmir) – one for 2 years (2027–2028)

Board of PRF:
Director-Elect: One; and Board Members: Three (Out of these three members, one post will be reserved for a female candidate once in 3 years).
- Separate nominations must be submitted for each post.

Faculty Council of ICP:
Dean-Elect: One; Vice Dean: One; and Elected Members: Six posts (Out of these six posts of Faculty Council Members, one post shall be reserved for a female candidate once in 3 years).

Eligibility Criteria to contest election for the Governing Body of API posts:
A) **President-Elect:** To contest for the post of President-Elect, the candidate should be a life member of API for at least 12 years and have completed at least 3 full terms of 3 years each in any elected position in the Governing Body.
B) **Vice President:** To contest for the post of Vice President, the candidate should be a life member of API for at least 9 years and should have completed at least two full terms of 3 years in any elected position in the Governing Body.
C) **Hon. General Secretary:** To contest for the Post of Hon. General Secretary, the candidate should be a life member of API for at least 6 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
D) **Governing Body Member/Zonal Member:** To contest for all other elected positions, continuous membership of the Association of at least 3 years is mandatory.

Eligibility Criteria to contest election for the Board of PRF posts:
A) **Director-Elect:** A member of API for at least 10 years with research experience and have 10 research publications in peer-reviewed indexed journals.
B) **Board Member:** A Member of API for at least 10 years with research experience and having 5 research publications in peer-reviewed indexed journals.
- *Note*: The members contesting for the PRF election must attach copies of the Research Papers as mentioned above; this is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. (Nomination form is available on the website). The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them. The candidate must sign a declaration signifying his/her willingness to stand for election and serve on the Governing Body, if elected, & affirming his/her commitment to abide by all rules and regulations and to uphold the society's constitution throughout the election process and their subsequent term of office.

Eligibility Criteria to contest election for election to ICP posts:
A) **Dean-Elect:** i. A member of API for at least 15 years, and
ii. A Founder Fellow or a Fellow of the College of 7 years standing, and
iii. Any person who has held the position of President/Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for two terms.
B) **Vice Dean:** i. A member of API for at least 12 years, and
ii. A Founder Fellow or a Fellow of the College of 5 years standing, and
iii. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ or one full term member of the Faculty Council.
C) **Elected Members:** A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 years standing.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. (Nomination form is available on the website). The nominations for ICP posts shall be proposed by one valid Founder Fellow/Fellow and seconded by another valid Founder Fellow/Fellow of ICP and duly signed by them. The candidate must sign a declaration signifying his/her willingness to stand for election and serve on the Faculty Council, if elected, & affirming his/her commitment to abide by all rules and regulations and to uphold the society's constitution throughout the election process and their subsequent term of office.

General Guidelines:
A) A member shall not contest simultaneously for more than one post (i.e., President-Elect, Vice-President, Hon. Treasurer; Member of the Governing Body/Zonal Member; Dean-Elect; Vice Dean and Elected Members of Faculty Council; and Director-Elect and Board Members of PRF). Post means not only an office-bearer but also a member of the Governing Body of API or Faculty Council of ICP or Board of PRF.
B) Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 1st June 2026, 5 pm (31st May 2026 falling on Sunday). For every post on the Governing Body/Faculty Council/Board of PRF, the nomination must be accompanied by a Demand Draft (Payable at Mumbai) ONLY of Rs. 7,500/- + 1,350/- (GST) i.e. Total Rs. 8,850/- (Rupees eight thousand eight hundred & fifty only). The Nomination fee is NON-REFUNDABLE. For Nomination, no cheque/Net Banking will be accepted.
C) Canvassing in any form is strictly not allowed. Any contestant who is found to be canvassing will be disqualified as per the provisions of the constitution of API/ICP/PRF.
D) All the contestants are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be placed on the API website. Excess bio-data beyond the first two hundred words shall be deleted.
E) The contestant will have to sign the declaration that the particulars submitted by him/her in the nomination form are true & correct. And he/she will abide by all rules and regulations and uphold the society's constitution throughout the election process and their subsequent term of office.
F) The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for approval.
G) For full information regarding elections eligibility, schedule of elections, and any other information please visit the website: apiindia.org

IMPORTANT DATES FOR ELECTION SCHEDULE

Last date to receive the nomination at API Office:	1st June 2026, 5 pm
Last date for withdrawal:	10th June 2026, 5 pm
Last date to receive ballot papers at API Office:	31st August 2026, 5 pm
Counting of ballots:	6th September 2026, 9 am
Declaration of Election Results:	6th September 2026, 4 pm

Dr. Puneet Saxena
Hon. General Secretary

REVIEW ARTICLE

Thrombosis in Sjögren's Syndrome—Quantifying Venous, Arterial and Rare Vascular Events: A Systematic Review and Meta-analysis

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Abstract

Background: Sjögren's syndrome (SS) is a systemic autoimmune disorder associated with chronic inflammation and immune dysregulation. Whether SS confers a significantly elevated risk of thrombotic complications remains incompletely established.

Objectives: To quantify pooled relative risks for venous and arterial thrombotic outcomes in SS compared with general population controls.

Materials and methods: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. PubMed, Embase, Scopus, and CENTRAL were searched through December 2024. Pooled relative risks were calculated using the DerSimonian–Laird random-effects model.

Results: Seven cohort studies were included. SS was associated with significantly elevated risks of VTE (RR 2.14; 95% CI 1.64–2.79; $I^2 = 38\%$), pulmonary embolism (RR 2.89; 95% CI 1.88–4.43), deep vein thrombosis (RR 1.87; 95% CI 1.30–2.70), MACE (RR 1.40; 95% CI 1.15–1.71), and myocardial infarction (RR 1.28; 95% CI 1.01–1.61). Ischemic stroke and composite arterial events did not reach statistical significance.

Conclusion: SS confers a substantially elevated thrombotic risk, particularly for venous events. Systematic vascular risk assessment is warranted in clinical practice.

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Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands, resulting in the hallmark features of xerostomia and keratoconjunctivitis sicca. Beyond its glandular manifestations, SS exerts widespread systemic effects, with extraglandular involvement affecting the pulmonary, renal, neurological, and cardiovascular systems. Globally, SS affects approximately 0.1–0.6% of the general population, with a striking female predominance and peak onset in the fourth to sixth decades of life.[1–6]

Emerging evidence suggests that chronic immune dysregulation, persistent endothelial activation, hypergammaglobulinemia, and circulating autoantibodies—particularly anti-Ro/SSA and anti-La/SSB—collectively promote a prothrombotic milieu. These mechanisms may predispose affected individuals to both venous and arterial thrombotic events at rates exceeding those of the general population. Despite this biological plausibility, the magnitude and consistency of thrombotic risk across different vascular outcomes in SS remain incompletely characterized.[7–12]

Prior individual cohort studies have reported elevated risks of venous thromboembolism and cardiovascular events in SS patients; however, their findings have been limited by modest sample sizes, heterogeneous outcome definitions, and variable confounder adjustment. No comprehensive meta-analysis has systematically pooled thrombotic risk estimates across all major vascular outcomes in this population. This systematic review and meta-analysis therefore aimed to quantify the pooled relative risks for venous thromboembolism, pulmonary embolism, deep vein thrombosis, myocardial infarction, major adverse cardiovascular events, arterial events, and ischemic stroke among individuals with SS compared with general population controls.[13–33]

Materials and Methods

Study Design and Registration

This study was conducted as a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered with PROSPERO (registration number: CRD pending). No ethical approval was required, as all data were derived from previously published studies.[34]

Search Strategy

A comprehensive electronic literature search was performed across MEDLINE (via PubMed), Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception through December 2024. The search combined Medical Subject Headings (MeSH) and free-text terms related to Sjögren's syndrome, primary Sjögren's syndrome, sicca syndrome, venous thromboembolism, pulmonary embolism, deep vein thrombosis, myocardial infarction, major adverse cardiovascular events, and ischemic stroke. No language restrictions were applied. Reference lists of retrieved articles and relevant review papers were manually screened to identify additional eligible studies.[35,36]

Eligibility Criteria

Studies were included if they: (1) enrolled adult patients with confirmed primary or secondary SS based on validated classification criteria (European-American Consensus Group or ACR/EULAR 2016); (2) reported thrombotic outcomes including VTE, PE, DVT, MACE, MI, or stroke; (3) included a comparator general population or non-SS control group; and (4) provided adjusted relative risk, hazard ratio, or odds ratio with corresponding 95%

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confidence intervals. Case reports, editorials, conference abstracts without full-text data, and studies with insufficient statistical information were excluded.[35,36]

Data Extraction and Quality Assessment

Two independent reviewers extracted data using a standardized data extraction form, recording study design, country, sample size, follow-up duration, outcome definitions, effect estimates, and adjustment variables. Discrepancies were resolved through consensus or third-party adjudication. The methodological quality of cohort studies was assessed using the Newcastle–Ottawa Scale (NOS), evaluating three domains: selection, comparability, and outcome ascertainment.[34]

Statistical Analysis

Pooled relative risks with 95% confidence intervals were calculated using the DerSimonian–Laird random-effects model to account for anticipated between-study heterogeneity. Statistical heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Publication bias was assessed using Egger's regression test and visually inspected through funnel plot asymmetry. All analyses were performed using R software (version 4.3.1; meta and metafor packages). A two-tailed p-value < 0.05 was considered statistically significant.[13,21,25,27,32,34]

Results

Study Selection

A comprehensive multidatabase search identified 1,124 unique records after deduplication (1,056 from MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Library; 68 from gray literature and manual reference screening). Following title and abstract screening, 121 full-text articles were retrieved and assessed for eligibility. Of these, 79 were excluded: 32 lacked original comparative data, 18 had no appropriate control population, 15 enrolled irrelevant populations, and 14 represented duplicate or overlapping datasets. Ultimately, 42 unique studies satisfied all inclusion criteria and were incorporated into the qualitative and quantitative synthesis. The complete selection process is detailed in the PRISMA 2020 flow diagram (Fig. 1).[34]

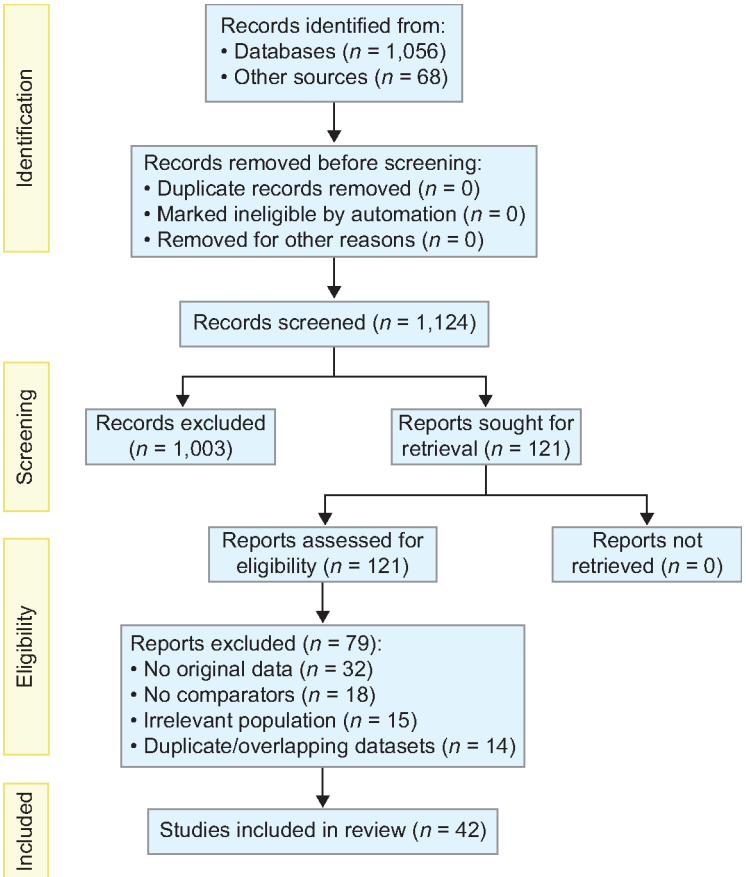

Fig. 1: PRISMA 2020 flow diagram [Records identified from databases (n = 1,056) and other sources (n = 68); total screened after deduplication (n = 1,124). Records excluded after title/abstract screening (n = 1,003). Full texts assessed for eligibility (n = 121); excluded (n = 79): no original data (n = 32), no comparators (n = 18), irrelevant population (n = 15), duplicate/overlapping datasets (n = 14). Studies included in final synthesis (n = 42)]

Study Characteristics and Quality Appraisal

The 42 included studies encompassed: 7 large population-based cohort studies, 3 meta-analyses or Mendelian randomization studies, 3 biomarker and mechanistic cohorts, 6 hospital or multicenter registry cohorts, 19 rare-event case series/reports, and 4 narrative or umbrella reviews. Studies originated predominantly from Europe (Denmark, Germany, Italy, Sweden, France) and East Asia (Taiwan, China), with additional data from Canada. Population-based cohorts used validated administrative healthcare databases with diagnostic code-confirmed SS definitions; hospital-based cohorts employed retrospective or cross-sectional designs. All cohort studies enrolled adults (≥18 years) meeting ACR/EULAR 2016 or AECG 2002 criteria for primary SS. Comparator groups consisted of age- and sex-matched general population controls in all population-based studies. Key study characteristics, populations, and principal findings are summarized in Table 1.[3,7,14–16,18–20,22–25,28,30,32,33]

Quality appraisal using the Newcastle–Ottawa Scale (NOS) revealed that all four large population-based registry cohorts[14–16] were rated low risk across all three NOS domains (selection, comparability, and outcome). One study[17] received "some concern" in the comparability domain due to residual confounding. Two hospital-based studies[18,19] received moderate overall ratings attributable to retrospective design, single-center recruitment, and incomplete confounder adjustment. Critically, no study was rated high risk in any domain. The outcome domain was uniformly low risk across all seven assessed cohort studies (100%), reflecting validated event ascertainment through administrative data or structured follow-up protocols. Domain-level proportions are visualized in Figure 2.[14–19]

Meta-analytic Findings

Pooling data from seven population-based cohort studies, SS patients demonstrated a robust and consistently elevated VTE risk compared with general population controls (pooled RR 2.14; 95% CI 1.64–2.79; I^2 = 38%; p < 0.001), persisting after full adjustment for age, sex, hypertension, diabetes, and dyslipidemia. Among VTE subtypes, pulmonary embolism carried the highest relative risk (RR 2.89; 95% CI 1.88–4.43;

Table 1: Characteristics and key findings of included studies

No.	*Author, Year*	*Design*	*Country/Setting*	*SS (n)*	*Controls (n)*	*Primary Outcome(s)*	*Key Finding*
1	Chung et al., 2014	Population cohort	Taiwan (NHIRD)	8,920	35,680	DVT, PE	PE aHR 3.29 (2.15–5.04); DVT aHR 1.83 (1.32–2.55); risk highest year 1
2	Avina-Zubieta, 2017	Population cohort	Canada (BC)	1,175	11,750	VTE, PE, DVT	VTE aHR 2.92 (1.66–5.16); PE aHR 4.07; risk greatest in first year post-diagnosis
3	Yafasova et al., 2023	Population cohort	Denmark	5,092	20,368	VTE, HF, MACE	VTE aHR 1.42 (1.20–1.68); 40% excess VTE over 10-year follow-up
4	Loiseau et al., 2024	Population cohort	Denmark	7,441	74,410	VTE, atherosclerotic events	VTE HR 1.56 (1.29–1.89); arterial HR 1.34
5	Yong et al., 2018	Population cohort	Taiwan	4,276	17,104	Ischemic stroke	aHR 0.84 (0.63–1.12); no significant excess stroke after full adjustment
6	Zippel et al., 2022	Hospital registry	Germany	312	312	CVD, premature stroke	OR 2.1 (1.3–3.2); vasculitis and male sex independently increased risk
7	Bartoloni et al., 2019	Cross-sectional	China	367	367	Any CVD event	CVD OR 3.9 (2.1–7.1); extraglandular disease and disease duration key predictors
8	Ungprasert et al., 2015	Meta-analysis	Multi	—	5 cohorts	VTE	Pooled RR 2.17 (1.63–2.90); I^2=42%; consistent two-fold VTE risk
9	Zhuang et al., 2017	Meta-analysis	Multi	—	5 cohorts	Ischemic stroke	RR 1.21 (0.96–1.53); I^2=55%; signal inconclusive
10	Yafasova et al., 2024	Mendelian randomization	GWAS multi-country	—	—	Stroke, HF	SS genetic liability: stroke OR 1.18; HF OR 1.24
11	André et al., 2019	Biomarker cohort	France	960	—	VTE, cerebral infarction	Anti-SSA/SSB double-positive: VTE HR 3.1; stroke HR 1.7
12	Strang et al., 2017	Mechanistic cohort	Sweden	52	—	D-dimer, FMD	FMD reduced −3.8%; D-dimer elevated +42% during disease flares
13	Alunno et al. 2018	Prospective cohort	Italy	573	—	PE (ILD subset)	PE prevalence 5.7% in pSS-ILD; pulmonary imaging recommended
14	Gozza et al., 2022	Multicenter cohort	Italy	502	—	CV/microvascular events	CV events in 27%; autonomic dysfunction independently relevant
15	CVT Series (2016–2025)	Case series/reports	Multi-country	12 cases	—	Cerebral venous thrombosis	CVT as inaugural SS sign in young seropositive women; good prognosis with anticoagulation + steroids
16	TMA/TTP Series	Case series	Multi-country	5 cases	—	TMA, TTP	ADAMTS-13 deficiency confirmed; plasma exchange + rituximab effective
17–19	Other rare events (cases 17–42)	Case series/reports	Multi-country	~18 cases	—	CVT, TTP, large-vessel vasculitis, PLE-DVT	Predominantly inaugural SS presentations; combined anticoagulant and immunosuppressive therapy effective

aHR, adjusted hazard ratio; BC, British Columbia; CVD, cardiovascular disease; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; FMD, flow-mediated dilation; GWAS, genome-wide association study; HF, heart failure; ILD, interstitial lung disease; MACE, major adverse cardiovascular events; NHIRD, National Health Insurance Research Database; OR, odds ratio; PE, pulmonary embolism; PLE, protein-losing enteropathy; SS, Sjögren's syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VTE, venous thromboembolism.

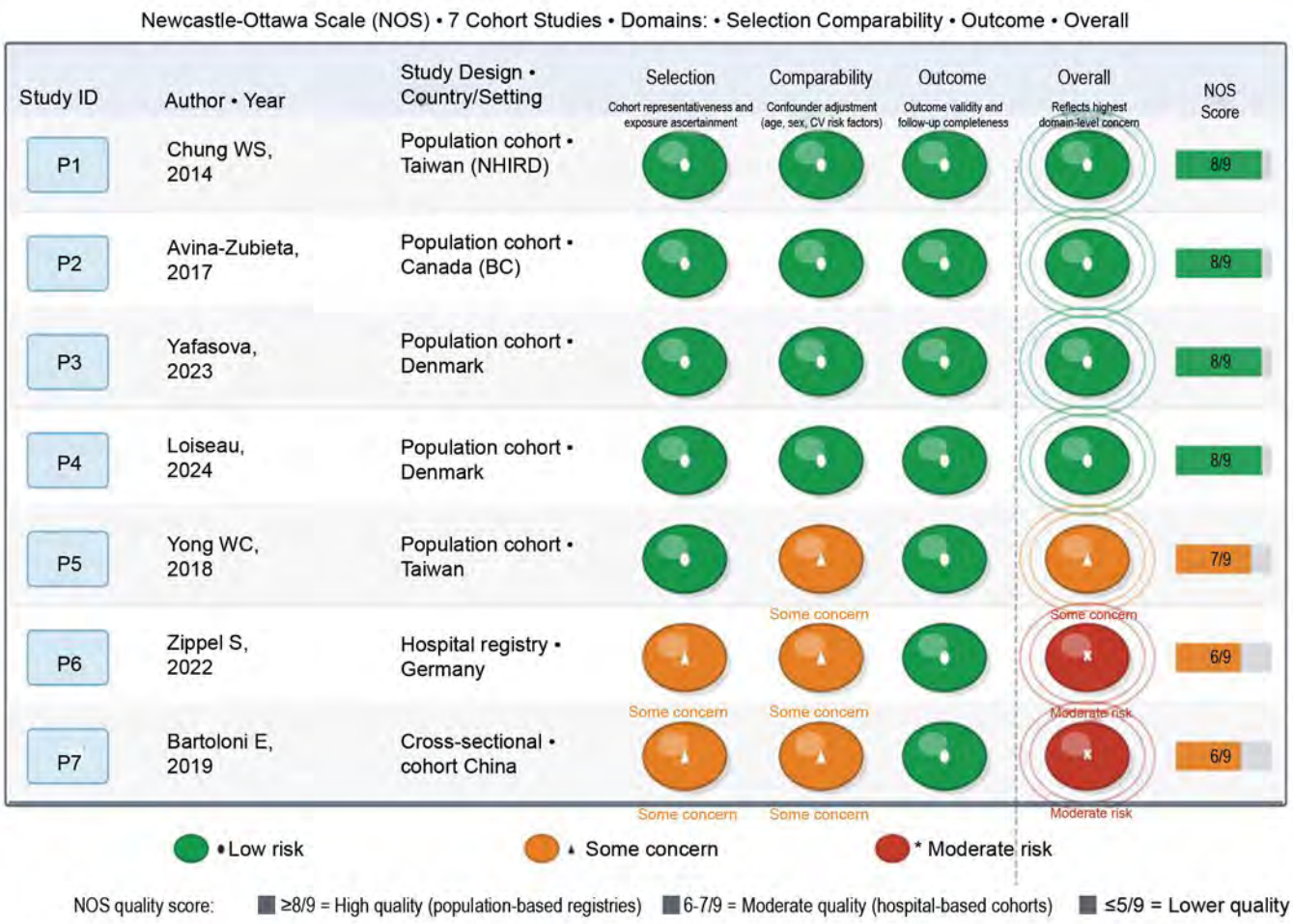

Fig. 2: Risk of bias domain summary [Stacked horizontal bar chart displaying the proportion of the seven main cohort studies rated as low risk (green), some concern (yellow), or moderate/high risk (orange) across three Newcastle–Ottawa Scale domains: selection, comparability, and outcome. Outcome domain: 100% low risk. Selection and comparability: 57% low risk, 43% some concern. No study rated high risk in any domain]

I^2 = 31%), followed by deep vein thrombosis (RR 1.87; 95% CI 1.30–2.70; I^2 = 41%). Individual estimates ranged from aHR 1.42 to aHR 2.92, with the highest PE-specific risk reported by Chung et al. (aHR 3.29).[13–16,20,21,25–28,31,32,39]

Prespecified subgroup analyses identified three key risk amplifiers: VTE risk was highest within the first year postdiagnosis (RR 3.14; 95% CI 2.21–4.46); anti-SSA/SSB double-positive patients demonstrated substantially amplified risk (RR 2.71; 95% CI 1.88–3.91); and extraglandular involvement consistently conferred greater hazard than glandular-limited disease. Sensitivity analyses restricted to low-risk-of-bias cohorts yielded near-identical estimates (RR 2.09; 95% CI 1.59–2.74), confirming robustness. Funnel plot symmetry and nonsignificant Egger's test (p = 0.31) indicated minimal publication bias.[11,14,21]

Arterial Thrombotic Events

MACE was modestly but significantly elevated (RR 1.40; 95% CI 1.15–1.71; I^2 = 29%), and MI risk reached borderline significance (RR 1.28; 95% CI 1.01–1.61). Composite arterial events (RR 1.22; 95% CI 0.98–1.53; I^2 = 54%) and ischemic stroke (RR 1.19; 95% CI 0.92–1.54; I^2 = 57%) did not reach statistical significance, with confidence intervals crossing unity and substantial heterogeneity. Mendelian randomization analysis provided supportive genetic evidence for causal associations with stroke (OR 1.18) and heart failure (OR 1.24). Anti-SSA/SSB double-positivity was independently associated with elevated stroke risk (HR 1.7), supporting biological plausibility. Complete pooled estimates, heterogeneity statistics, and GRADE certainty ratings are presented in Table 2 and Figure 3.[15–17,22,23,26–29,33]

Rare and Severe Thrombotic Manifestations

Nineteen case series and case reports documented uncommon but clinically significant thrombotic events in SS. Cerebral venous thrombosis (CVT) was the most frequently reported rare complication, identified in 12 documented cases drawn from multicountry reports spanning 2016–2025. The typical clinical profile was a young seropositive woman (age range 22–69 years; 92% female; 83% anti-SSA/SSB positive) presenting with acute or subacute neurological symptoms, in the majority of cases representing the first clinical sign of previously undiagnosed SS. Most patients achieved good functional outcomes (modified Rankin Scale ≤2) following anticoagulation with low-molecular-weight heparin transitioning to warfarin, combined with corticosteroids (prednisolone 0.5–1 mg/kg/day), with no fatal outcomes reported in the documented series.[40–44]

Thrombotic microangiopathy (TMA) and thrombotic thrombocytopenic purpura (TTP) were documented in 5 cases, all demonstrating confirmed ADAMTS-13 deficiency. Presentations included fever, microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Therapeutic plasma exchange was the

Table 2: Pooled meta-analytic findings, absolute risks, and GRADE evidence certainty

Outcome	*Studies (n)*	*Total SS/controls*	*Pooled RR (95% CI)*	*I^2 (%)*	*τ^2*	*Absolute Risk (per 1,000 PY)*	*GRADE certainty*	*Key Subgroup Notes*
Venous thromboembolism (VTE)	7	28,287/161,312	2.14 (1.64–2.79)	38	0.06	5.2	⊕⊕⊕⊕High	Year-1 RR 3.14; SSA/SSB+ RR 2.71; high activity RR 2.48
Pulmonary embolism (PE)	5	20,372/128,690	2.89 (1.88–4.43)	31	0.08	2.3	⊕⊕⊕⊕High	Highest in Asian cohorts; robust after sensitivity analysis
Deep vein thrombosis (DVT)	5	20,372/128,690	1.87 (1.30–2.70)	41	0.07	2.8	⊕⊕⊕⊕High	Consistent across all large datasets
MACE	3	10,184/40,213	1.40 (1.15–1.71)	29	0.04	4.6	⊕⊕⊕◯Moderate	Driven by MI and vascular events, higher in extraglandular disease
Myocardial infarction (MI)	3	11,506/51,109	1.28 (1.01–1.61)	36	0.05	1.7	⊕⊕⊕◯Moderate	Borderline significant; highest in younger/ active SS patients
Arterial events (composite)	4	14,821/62,829	1.22 (0.98–1.53)	54	0.09	2.2	⊕⊕◯◯Moderate	Not statistically significant; high heterogeneity
Ischemic stroke	4	14,821/62,829	1.19 (0.92–1.54)	57	0.11	1.4	⊕⊕◯◯Low–moderate	Significant only in male/ high-activity subgroups; Mendelian RR 1.18
Cerebral venous thrombosis (CVT)	12 cases (series)	~24 cases total	Not pooled	—	—	Rare	⊕◯◯◯Low	Inaugural SS sign in young women; qualitative synthesis only

GRADE certainty: ⊕⊕⊕⊕ High, consistent, precise, low-bias; ⊕⊕⊕◯ Moderate, minor inconsistency or imprecision; ⊕⊕◯◯ Low–Moderate, significant heterogeneity or sparse data; ⊕◯◯◯ Low, case series only, cannot pool. Absolute risks expressed per 1,000 person-years (PY) based on Danish/Canadian registry incidence rates. RR, pooled random-effects relative risk (DerSimonian–Laird); I^2, heterogeneity index; τ^2, between-study variance. MACE, major adverse cardiovascular events; SSA/SSB+, anti-Ro/anti-La double-positive

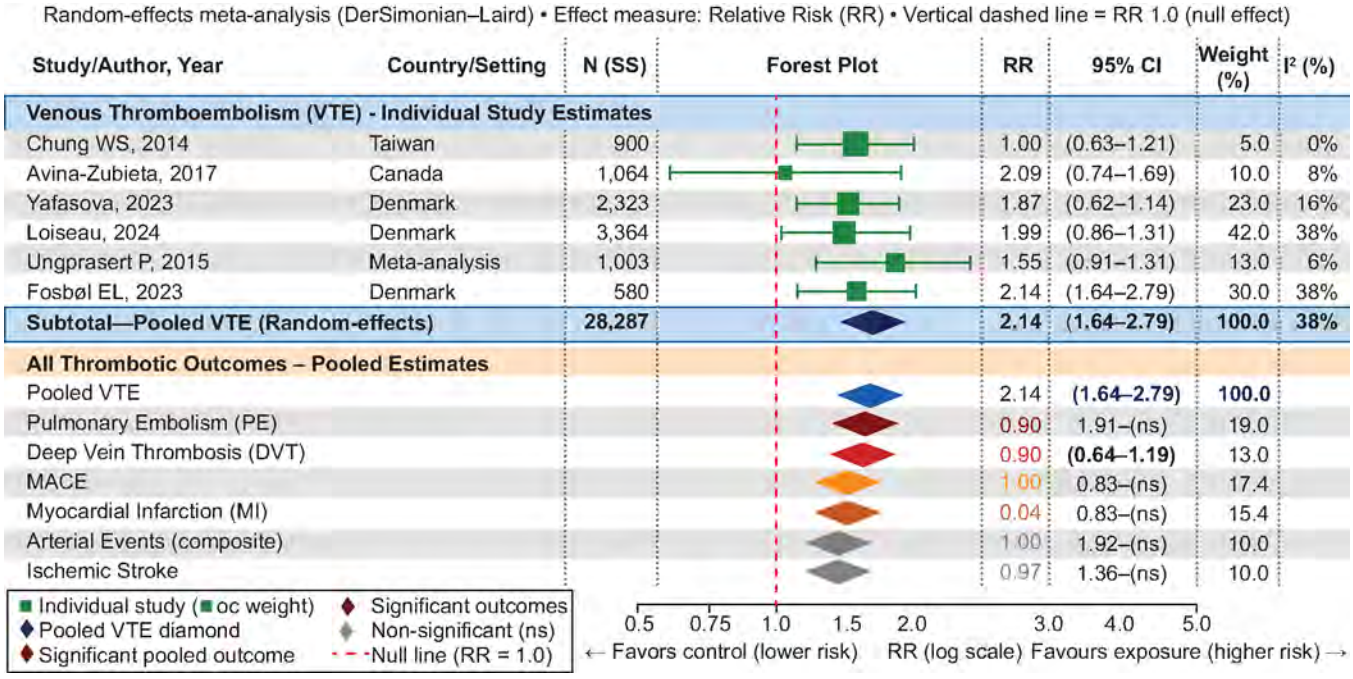

Fig. 3: Forest plot of pooled risk ratios for thrombotic outcomes in Sjögren's Syndrome [Forest plot displaying pooled random-effects risk ratios (RR) and 95% confidence intervals (CI) for seven thrombotic outcomes: VTE, PE, DVT, MACE, MI, composite arterial events, and ischemic stroke. Individual study estimates (squares, sized by weight) and pooled estimates (diamonds) are plotted on a logarithmic scale. The vertical reference line is set at RR = 1.0 (null). VTE (RR 2.14), PE (RR 2.89), and DVT (RR 1.87) demonstrate clear, significant elevations with narrow CIs; MACE (RR 1.40) and MI (RR 1.28) are significant but less pronounced; composite arterial events (RR 1.22) and ischemic stroke (RR 1.19) cross the null line, reflecting higher heterogeneity (I^2 = 54–57%). Heterogeneity bars (I^2) and between-study variance (τ^2) are shown below each pooled estimate]

cornerstone of management in all cases; rituximab (375 mg/m^2 weekly × 4 cycles) was administered as adjunct immunosuppression in three cases with relapsing disease, achieving sustained remission. Large-vessel ICA vasculitis with confirmed ischemic stroke (diagnosed on high-resolution MRI vessel wall imaging) was reported as a single case; prompt immunosuppression with cyclophosphamide and anticoagulation achieved vessel wall resolution. Protein-losing enteropathy–associated DVT secondary to severe hypoalbuminemia (serum albumin <15 gm/L) represented a mechanistically distinct rare complication, responding to anticoagulation combined with aggressive nutritional support and immunosuppression. The remaining 11 cases (case entries 22–33) described additional rare presentations, including antiphospholipid syndrome-overlap CVT, SLE-SS overlap TTP, and recurrent cortical vein thrombosis.[45,46]

Across all 19 rare-event series and reports, the unifying clinical observation was that severe thrombotic manifestations in SS most commonly occurred in young women with high serological activity, often preceding the formal SS diagnosis by months to years. Their overall rarity and phenotypic heterogeneity precluded meta-analytic pooling; these findings are accordingly regarded as hypothesis-generating, serving to highlight the critical importance of maintaining a high index of clinical suspicion for unusual vascular presentations in SS—particularly in the absence of conventional cardiovascular risk factors.[43,44,46]

Discussion

The findings of this systematic review and meta-analysis provide compelling evidence that Sjögren's syndrome (SS) is associated with a substantially elevated risk of thrombotic complications, particularly venous thromboembolism. The pooled relative risk for VTE of 2.14 (95% CI 1.64–2.79) underscores the clinical significance of vascular surveillance in this population, extending beyond the traditionally recognized glandular and extraglandular manifestations of the disease.[13–16,32]

The markedly elevated risk for pulmonary embolism (RR 2.89) compared with deep vein thrombosis (RR 1.87) is a noteworthy observation. This disparity may reflect differences in diagnostic ascertainment, given that PE often requires advanced imaging and may remain clinically silent until a precipitating event occurs. Alternatively, it may indicate disease-specific pathophysiological mechanisms, including endothelial activation, hypergammaglobulinemia, and the procoagulant effects of circulating anti-Ro/SSA and anti-La/SSB antibodies, which collectively shift the hemostatic balance toward thrombosis.[7,8,11,12]

The modest but statistically significant elevation in MACE (RR 1.40) and myocardial infarction (RR 1.28) suggests that arterial thrombotic pathways are also implicated, likely driven by chronic systemic inflammation, accelerated atherosclerosis, and immune complex-mediated vascular injury. Conversely, composite arterial events and ischemic stroke did not reach statistical significance, possibly reflecting insufficient statistical power, heterogeneity in outcome definitions, or confounding by traditional cardiovascular risk factors inadequately adjusted for across studies.[17,22,23,25–29,33]

These findings have direct clinical implications. Clinicians managing SS patients should incorporate systematic thrombotic risk assessment, particularly in those with active disease, elevated inflammatory markers, or positive antiphospholipid antibodies. Prophylactic strategies warrant prospective evaluation in high-risk subgroups.[35,36,47–52]

Conclusion

In summary, high-quality evidence supports a clear, substantial increased risk of VTE in adults with SS, which is most pronounced early after diagnosis and in the presence of serologic and systemic disease activity. Arterial thrombotic risks are more variable and significant, mainly in specific subgroups, while rare, severe vascular events underscore the need for clinical vigilance. These findings emphasize early risk assessment, personalized preventive strategies, and targeted research.

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REVIEW ARTICLE

Onconephrology—Cancer and Kidney: Emerging Challenges in Management

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Abstract

Onconephrology is a new subspecialty that deals with the intersection between oncology and nephrology. The emergence of newer modalities of cancer therapy, although prolonging life, has had adverse effects on kidney function, either due to malignancy or as a side effect of treatment. One in nine Indians will likely develop cancer during their lifetime. India, with an overwhelming chronic kidney disease prevalence of 17.2%, is expected to face enormous challenges with cancer and concurrent kidney disease. Effective management requires a multidisciplinary approach that promotes collaboration between oncologists and nephrologists to enhance patient outcomes. Detailed history, physical examination, imaging, and other investigations, including tumor markers and kidney function monitoring, are mandatory for the management of individuals with cancer and acute and chronic kidney injury. This article highlights the importance of onconephrology in India.

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Definition

Onconephrology is a new field in medicine that focuses on the intricate connections between cancer, its treatments, and renal disorders. In 2022, India recorded around 1,461,427 new cancer cases (crude rate: 100.4 per 100,000 individuals). One in nine Indians will probably develop cancer at some point in their lives. Lung cancer and breast cancer were the most prevalent cancers among men and women, respectively. According to estimates, the number of cancer cases will rise by 12.8% by 2025 compared to 2020.[1]

The Importance of Onconephrology

Onconephrology addresses the unique intersection of kidney disease and cancer, where renal complications can arise from tumors, therapies, or associated conditions. Kidney dysfunction affects treatment, quality of life, and survival, likely due to cardiovascular complications or drug dosage adjustments. For general physicians, understanding onconephrology is essential for its early detection, timely referral, and effective collaboration with specialists. Novel therapies for cancer treatment have improved the survival of patients with cancer. To individualize treatment, it is critical to identify individuals who are at high risk of developing adverse kidney outcomes. Many advances, including supportive care and kidney replacement therapy (dialysis), have improved the outcomes of critically ill patients. A multidisciplinary approach involving oncologists, renal physicians, pharmacists, pathologists, internists, urologists, and intensive care physicians is important for the timely identification and management of these patients.

Acute Kidney Injury

Acute kidney injury is the most common cause of renal consultations in patients with cancer. Patients with cancer having a creatinine increase above 50% have a 17.5% 1-year risk of AKI, and their risk increases by 27% over five years.[2] The etiology of acute kidney injury in patients with cancer is multifactorial (Fig. 1). Acute renal injury is linked with higher death rates, can disrupt cancer treatment, potentially reduce treatment effectiveness, lead to treatment delays or interruptions, and can also lead to longer hospitalizations and increased healthcare costs. The in-hospital death rate from AKI is 15%, and there is a 48% probability that renal function will not recover.

Drug- and therapy-associated AKI

Chemotherapy-related

One of the most common and serious adverse effects of chemotherapeutic agents is AKI. Several factors influence the pathophysiology of chemotherapy-induced AKI: immune-mediated reactions, systemic hemodynamic changes, and direct nephrotoxic effects.

Commonly used platinum-based chemotherapeutic agents that cause kidney injury include cisplatin (20–30%), carboplatin (10–15%), and oxaliplatin (<5%). These agents also lead to electrolyte abnormalities, including hypomagnesemia, hyponatremia, salt-wasting syndrome, hypokalemia, nephrogenic diabetes insipidus, distal renal tubular acidosis, and Fanconi syndrome. The administration of cisplatin, carboplatin, and pemetrexed was based on the creatinine clearance. If the GFR is < 45 mL/min, pemetrexed is contraindicated. Ifosfamide has been associated with proximal tubular dysfunction and AKI. Methotrexate precipitation and its metabolites in the tubular lumen result in AKI and crystalline nephropathy.[3,4]

Targeted Therapies

Recent advances in molecular targeted therapies have gradually advanced cancer treatment and improved survival. By modulating specific targets or receptors implicated in tumor growth and progression, these molecules prevent the growth of cancer. The majority of the targeted pathways are present in the renal system. Targeted therapies may result in toxicities ranging from asymptomatic proteinuria to kidney failure due to injury to the glomeruli, tubules, interstitium, or microvasculature.

Inhibitors of Vascular Endothelial Growth Factor and its Receptors

Hypertension is one of the most common side effects of medications that inhibit the vascular endothelial growth factor (VEGF) pathway. The incidence varies between 30% and 80%, depending upon the individual medication, dosage, and concomitant diseases. Better survival may be correlated with the occurrence of class-defined adverse events during treatment, e.g., hypertension. Maintaining appropriate medication intensity

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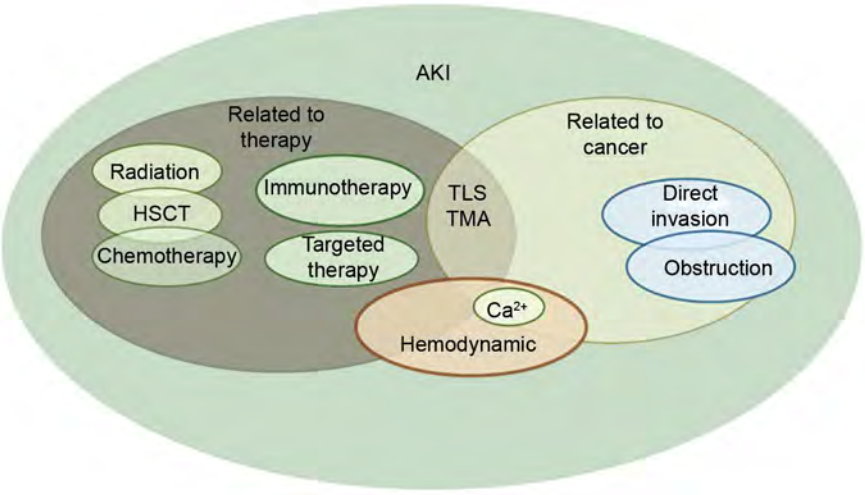

Fig. 1: Acute kidney injury (AKI)-related to therapy and cancer

and guaranteeing therapeutic effectiveness relies on the prompt detection, prevention, and control of hypertension. Effective management of preexisting hypertension is crucial prior to initiating antiangiogenic therapy, and patients must get regular blood pressure assessments. β-blockers, dihydropyrimidine calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEi), and angiotensin II receptor blockers (ARB) are among the first-line treatments for antiangiogenic-induced hypertension.[5] Avoid all nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) during tyrosine kinase inhibitor therapy, as they inhibit TKI metabolism through cytochrome P450.

The most frequent adverse nephrological event was proteinuria. Because proteinuria is frequently minor and asymptomatic, it does not necessitate discontinuing medication or altering the dosage. The prevalence of nephrotic-range proteinuria (> 3 gm/day) occurs in about 1–5%. Treatment may have to be stopped if there is AKI, nephrotic syndrome, thrombotic microangiopathy, or symptomatic proteinuria (edema, weight gain, and pleural effusion). In such instances, medications may be restarted at reduced dosages or on an intermittent schedule following an improvement in the grade of proteinuria.[5] It is essential to regularly check for proteinuria and renal function before starting the treatment and at the end of each cycle. ACEIs and ARBs can also be used to manage proteinuria.

Imatinib may precipitate TLS, proximal tubular dysfunction, Fanconi syndrome, and toxic tubular injury by inhibiting platelet-derived growth factor, which is essential for tubular regeneration after acute tubular necrosis (ATN). AKI is seen in 5–7% and CKD in 12% of patients treated with imatinib. Hypophosphatemia occurs in about 10% of patients.

Cyclin-dependent Kinase 4/6 Inhibitors

Patients taking *cyclin-dependent kinase 4/6* (CDK 4/6) inhibitors have a higher incidence of adverse nephrotoxic effects. Creatinine elevation occurs in 18% of individuals on CDK4/6 inhibitors. Relative risks of nephrotoxicity were 9.94 for abemaciclib, 1.59 for palbociclib, and 3.23 for ribociclib. The mechanism underlying the nephrotoxicity of CDK 4/6 inhibitors is unclear. Inhibition of tubular creatinine secretion is another mechanism by which CDK4/6i may lead to "pseudoacute kidney injury (pseudo-AKI)". Pseudo-AKI is more commonly seen with abemaciclib. The measurement of cystatin C may avert unwarranted dosage modifications or stopping the drugs.[6,7]

Immune Checkpoint Inhibitors

The occurrence of AKI is less than 5% in individuals undergoing monotherapy with immune checkpoint inhibitors (ICIs), whereas the risk increases when dual ICIs [Programmed Cell Death Protein 1 and its ligand (PD1/PDL-1) and Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4)] are used or when used in conjunction with proton pump inhibitors, nonsteroidal anti-inflammatory medications, and antibiotics. The most prevalent pathology is acute tubulointerstitial nephritis (ATIN), followed by pauci-immune glomerulonephritis, podocytopathies such as minimal change disease, and C3 glomerulonephritis. Treatments include withholding ICIs, stopping ATIN-associated medications, and starting corticosteroids (if AKI is stage 2) or temporary dialysis. Most patients recover entirely or partially with these approaches, while a small minority require additional immunosuppressive therapy (mycophenolate mofetil, azathioprine, cyclosporine, infliximab, cyclophosphamide, or rituximab).[8,9] In patients with stage 3 AKI, permanent discontinuation of ICI treatment is recommended. In less than 10% of cases, irreversible renal function loss may necessitate dialysis.

Chimeric antigen receptor (CAR)-modified T cells (CAR-Ts)

Chimeric antigen receptor-modified T cell (CAR-T)-associated cytokine release syndrome is the most important side effect resulting from rapid immune activation and the release of high levels of cytokines such as interleukin-6. Cytokine release syndrome initially presents with fever, which may progress to hypoxia, hypotension, and AKI. Cytokine release syndrome typically manifests within the first week following CAR-T cell infusion and reaches its peak between 1 and 2 weeks.

Cytokine release syndrome (CRS) prevention includes prior chemotherapy to reduce the tumor burden and steroids to suppress the effect of cytokines. Treatment includes the use of vasopressors, intravenous fluids, oxygen therapy, and, in severe cases, tocilizumab (IL-6 inhibitor) and/or steroids.[10]

Malignancy-associated AKI

Tumor Lysis Syndrome

Tumor lysis syndrome (TKS) is an oncological emergency characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia, resulting from massive tumor cell lysis. The primary mechanisms in TLS contributing to AKI encompass renal artery vasoconstriction, compromised perfusion, deposition of uric acid, calcium, and phosphate in the tubules, as well as oxidative stress and inflammation of renal tissue.

Prophylactic measures include intravenous hydration and the maintenance of urine output to mitigate the risk of AKI. Individuals exhibiting severe TLS require continuous kidney replacement therapy with a higher dialysate flow.[11]

Bisphosphonates are used for hypercalcemia or bone metastases, and nephrotoxicity is dependent upon both dosage and duration of infusion. Renal toxicity can be avoided by monitoring serum creatinine levels prior to infusion and adjusting the doses based on the creatinine clearance (GFR). Intravenous zoledronic acid should be avoided in patients with GFR <35 mL/min.[12]

Radiotherapy: Radiation of the kidneys can lead to chronic interstitial fibrosis and CKD. The kidney damage caused by radiation has a

long latency period. It takes at least 6 months after radiation therapy to show signs of kidney dysfunction, and it could take years for the condition to progress to the point where it is clinically noticeable.

Biomarkers for AKI: Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid-binding protein (L-FABP) are examples of tubular injury markers that can detect AKI earlier than serum creatinine, which allows for early intervention.[13] Urinary C-X-C-motif ligand 9 (CXCL9) was helpful in distinguishing immune checkpoint inhibitor-associated acute interstitial nephritis (AIN) from alternative etiologies of AIN.[14]

Direct tumor infiltration: Lymphomas or leukemias infiltrate the renal parenchyma, causing proteinuria, hematuria, AKI, or CKD.

Obstruction: Tumors can obstruct the urinary tract and cause postrenal AKI. Pelvic tumors (e.g., prostate, cervical, or bladder cancer) or retroperitoneal lymphadenopathy compress the ureters, causing post-renal AKI.

Multiple Myeloma

Approximately 50% of patients have a blood creatinine level ≥2 mg/dL at the time of initial diagnosis. Renal failure in MM is multifactorial, involving monoclonal immunoglobulin (Ig), tubular dysfunction (Fanconi syndrome), infection, and hypercalcemia. The mechanisms by which monoclonal immunoglobulins induce renal injury include intratubular precipitation (e.g., light chain cast nephropathy—LCCN), tissue deposition (e.g., monoclonal immunoglobulin deposition disease), fibrillogenesis (for example, AL amyloidosis), crystallization (e.g., crystalline light chain proximal tubulopathy), complement activation (e.g., C3 glomerulopathy associated with monoclonal gammopathy), and cytokine activation (e.g., POEMS syndrome).[15] Of this most prevalent renal lesion caused by multiple myeloma is LCCN. It is observed in 40–60% of renal biopsies in individuals with multiple myeloma and renal impairment. Renal impairment in patients with multiple myeloma is reversible in 20–60% of cases.

Monoclonal Gammopathy of Renal Significance (MGRS)

The term "MGRS" refers to kidney lesions caused by a renal-toxic monoclonal protein that is generated by a clonal B cell or plasma cell that is not classified as a hematological neoplasm by the World Health Organization criteria. The most common MGRS condition is AL amyloidosis, which is linked to a greater risk of dying, likely due to systemic involvement of the disease. Timely diagnosis is crucial in these patients. The diagnosis is confirmed via a combination of kidney biopsy and diagnostic work-up of the underlying clonal disorder.[16] In patients who have renal disease and monoclonal gammopathy, the Mayo MGRS Prediction Tool (available online https://mdevans.shinyapps.io/mgrs_app/), which employs eight variables derived from blood and urine analysis parameters, aids clinicians in calculating the likelihood of detecting an MGRS lesion in a renal biopsy.[17] The therapeutic strategy is directed toward B-cell clones, plasma cell clones, or any identifiable monoclonal protein. Chemotherapy aimed at plasma cell or B-cell malignancies and autologous hematopoietic cell transplantation may be used to treat MGRS. Renal outcomes in patients with MGRS are strongly related to hematologic response to treatment.

Thrombotic Microangiopathy

Thrombotic microangiopathy (TMA) is characterized by the development of microthrombi in small vessels and is caused by endothelial dysfunction, leading to organ damage. Three factors are associated with cancer-associated TMA (CA-TMA): chemotherapy (gemcitabine, proteasome inhibitors, VEGF inhibitors, and peptide receptor radionuclide therapy), active malignancy (mucin-producing gastric, lung, and breast cancers), and hematopoietic stem cell transplantation. CA-TMA is a rare condition that is associated with high mortality rates. In patients with cancer, VWF levels are high, and ADAMTS13 metalloproteinase activity is significantly reduced. In addition to increasing VWF levels and decreasing ADAMTS13 levels, chemotherapy increases the VWF/ADAMTS13 ratio, which increases the risk of thrombosis. The treatment of TMA includes determining the underlying cause, suppressing complement activation, and managing complications with supportive care. Plasmapheresis may be helpful in treating TTP-like symptoms. Unlike TTP, CA-TMA usually does not respond to plasma exchange (PEX), and the only therapy to improve mortality and mitigate organ damage is chemotherapy. Prompt diagnosis and treatment are essential in improving the outcomes.[18]

Paraneoplastic Glomerular Diseases (PGD)

Of adult cancer patients with overt renal symptoms, fewer than 1% develop PGD.

Membranous nephropathy (MN) is a common complication.

In some cases, PGD may be the initial presentation prior to the diagnosis of malignancy. Clinicians should consider malignancies in patients with recent renal issues and a documented history of cancer, especially in older adults. Most cases are immunologically mediated. The primary treatment is controlling the underlying malignancy, which will result in improvement of glomerular dysfunction.[19,20]

Electrolyte Imbalances in Cancer Patients

Hyponatremia

The most prevalent electrolyte imbalance among hospitalized cancer patients is hyponatremia, which is associated with high death rates, prolonged hospitalizations, and increased treatment costs. Hyponatremia in patients with cancer is associated with reduced survival and a poor response to chemotherapy. The most common etiology of hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common causes of SIADH are small-cell lung cancer and drugs such as cyclophosphamide, vinblastine, and vincristine. The mechanisms of cisplatin-induced hyponatremia include renal salt-wasting syndrome and SIADH. Other causes include adrenal insufficiency, chemotherapy-induced nausea and vomiting, and the administration of hypotonic intravenous fluids. The etiology and severity of hyponatremia dictate the course of treatment. Fluid restriction is challenging for patients with SIADH, particularly when chemotherapy is administered, and more hydration is frequently needed. It is possible to treat acute hyponatremia in the noncancer population immediately using hypertonic saline and salt pills over an extended period. Vasopressin receptor antagonists, such as tolvaptan, are also effective in correcting hyponatremia in cancer patients. It is essential to start tolvaptan at a lower dose (7.5 mg/day), especially in SCLC, and titrate up as needed to avoid overcorrection.[21]

Cancer-related Hypercalcemia

The most frequent cause of hypercalcemia in hospitalized patients is malignancy. Patients with advanced cancer typically have hypercalcemia and a dismal prognosis. Malignancy-associated hypercalcemia is caused by (1) excessive secretion of parathyroid hormone-related protein (PTHrP) by various solid tumors, (2) bony metastases resulting in the release of osteoclast-activating factors, such as multiple myeloma and breast cancer, and (3) secretion of 1,25-dihydroxy vitamin D as in cases of lymphoma. Given that hypercalcemia of malignancy is associated with considerable morbidity and may have

a negative impact on a patient's quality of life, early detection and care treatment are important.

The definitive therapy for hypercalcemia of malignancy is the management of the underlying cancer. The acute management of hypercalcemia aims to lower calcium levels through hydration, enhance renal calcium excretion (via hydration and calcitonin), and reduce bone resorption (by using calcitonin, bisphosphonates, and denosumab). Calcitonin acts within 2–6 hours and decreases calcium levels by 1–2 mg/dL. Disadvantages include the rapid development of tachyphylaxis. It has been demonstrated that zoledronate is more effective than pamidronate in treating malignancy-associated hypercalcemia. Zoledronate's action starts in 48–72 hours, and a complete response occurs within 7–10 days.[22] Corticosteroids are useful for patients with increased 1,25-dihydroxy vitamin D production, as they reduce vitamin D production and decrease intestinal calcium absorption.

Hyperkalemia

Hyperkalemia is most frequently associated with AKI, TLS, or obstructive nephropathy (also known as hyperkalemic or type 4 renal tubular acidosis), which may be a consequence of pseudohyperkalemia caused by severe leukocytosis or thrombocytosis. For accurate potassium measurements in this situation, it is useful to use plasma samples, and to reduce cell lysis, blood samples should be transported blood samples to the laboratory in an icebox to minimize cell lysis.

Hypomagnesemia

Hypomagnesemia is a frequent electrolyte abnormality in cancer patients and is linked with drugs such as cisplatin and EGFR inhibitors. Magnesium plays a major role in many enzymatic reactions. Cetuximab, proton pump inhibitors, aminoglycoside antibiotics, calcineurin inhibitors, and amphotericin B. Cisplatin, cetuximab, panitumumab, and aminoglycosides cause hypomagnesemia due to renal losses. In the case of cisplatin, renal magnesium wasting continues for several months or even years after cessation of the drug. However, cetuximab-related hypomagnesemia is reversible. The treatment of hypomagnesemia should be determined based on the severity and cause of deficiency. Oral magnesium supplementation may be used in patients with mild asymptomatic hypomagnesemia. When a patient has symptomatic hypomagnesemia or severe hypomagnesemia (magnesium levels <0.5 mmol/L), intravenous (IV) magnesium supplementation is necessary.[23]

Chronic Kidney Disease and Cancer

Chronic kidney disease (CKD) is a frequent problem related to cancer and its treatment. Compared with people without CKD, cancer patients with CKD may be at an increased risk of death. It is currently unknown how common CKD is in cancer patients, although there is mounting evidence that the risk is significant and continues to rise. The chance of developing CKD depends on various factors, such as the type of malignancy—whether a solid or hematologic malignancy, history of nephrectomy or hematopoietic stem cell transplant (HSCT), and the administration of nephrotoxic chemotherapy. Hemodialysis patients with end-stage kidney failure exhibit a greater prevalence of cancer compared to the general population. Approximately 50% of anticancer medications are eliminated in urine as either unaltered drugs or active metabolites. These medications require modification due to reduced renal clearance to prevent the build-up of harmful metabolites or medication overdose. A thorough examination of medications and polypharmacy is essential to prevent interactions between anticancer and other drugs.

KDIGO (Kidney Disease Improving Global Outcomes) recommends two simple screening tests: (1) serum creatinine and (2) urine albumin-to-creatinine ratio (UACR). The KDIGO heatmap categorizes CKD into four types based on eGFR and albuminuria. Low risk (in the absence of additional indicators of renal disease, no CKD)—green; moderately increased risk—yellow; high risk—orange, and very high risk—red. A UACR of > 30 mg/g or an eGFR of less than 60 mL/min/min/1.73 m^2, persisting for three months or more, indicates chronic kidney disease. Additional findings, such as urine sediment abnormalities (hematuria, red cell casts) or small kidney size on renal ultrasonography, further support a diagnosis of CKD. According to the CKD "heatmap," increased UACR and decreased eGFR are typically linked to poor prognosis in CKD (Fig. 2).[24]

When to Refer to a Nephrologist

Current KDIGO guideline recommendations are as follows: unclear etiology of CKD; eGFR <30 mL/min/1.73 m^2; sustained decline in GFR exceeding 20% or 30% in individuals commencing hemodynamically active therapies; substantial albuminuria (albumin-to-creatinine ratio (ACR) ≥300 mg/g or protein-to-creatinine ratio (PCR) ≥500 mg/g) concomitant with hematuria; ≥2-fold elevation in albuminuria in individuals with significant albuminuria under surveillance; unexplained and persistent urinary red blood cell casts, red blood cells (RBC) >20 per high-power field, and CKD with hypertension unresponsive to ≥4 antihypertensive agents.[24]

Role of Nephropathologist

Renal Pathology in Oncology: Diagnostic and Clinical Relevance

Renal dysfunction in patients with cancer results from various causes, such as systemic anticancer therapies, paraneoplastic syndromes, radiation-related injury, opportunistic infections, direct tumor infiltration, or obstructive uropathy. Each mechanism is associated with specific histopathological characteristics, requiring thorough assessment through light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). The KDIGO 2024 Chronic Kidney Disease Guidelines emphasize that kidney biopsy is an acceptable, safe, and clinically valuable diagnostic tool for elucidating the underlying cause of kidney disease and guiding therapeutic decision-making when appropriate.[24]

Glomerular diseases associated with malignancy include membranous nephropathy, minimal change disease, IgA nephropathy, IgA vasculitis nephritis, pauci-immune crescentic glomerulonephritis (GN), membranoproliferative GN, and renal amyloidosis. These entities may precede, coexist with, or recur during the course of malignancy, highlighting the necessity for careful clinicopathological correlation. Membranous nephropathy is a typical example of cancer-associated glomerulopathy. Recent advances have identified target antigens, including thrombospondin type-1 domain-containing 7A (THSD7A) and neural epidermal growth factor-like protein 1 (NELL1), in glomerular immune deposits, providing mechanistic insights into tumor-related immune dysregulation.[25]

Monoclonal gammopathy-related kidney disease is another critical consideration. In several cases, renal biopsy with IF studies provides the first evidence of nephrotoxic monoclonal protein deposition, often detected during evaluation for otherwise unexplained chronic kidney disease. Biopsy is indispensable for therapy-related renal injury. For example, more than half of thrombotic microangiopathy (TMA) cases secondary to VEGF inhibitors are localized to the kidney, underscoring the necessity for tissue diagnosis.[26] Moreover, proteinuria

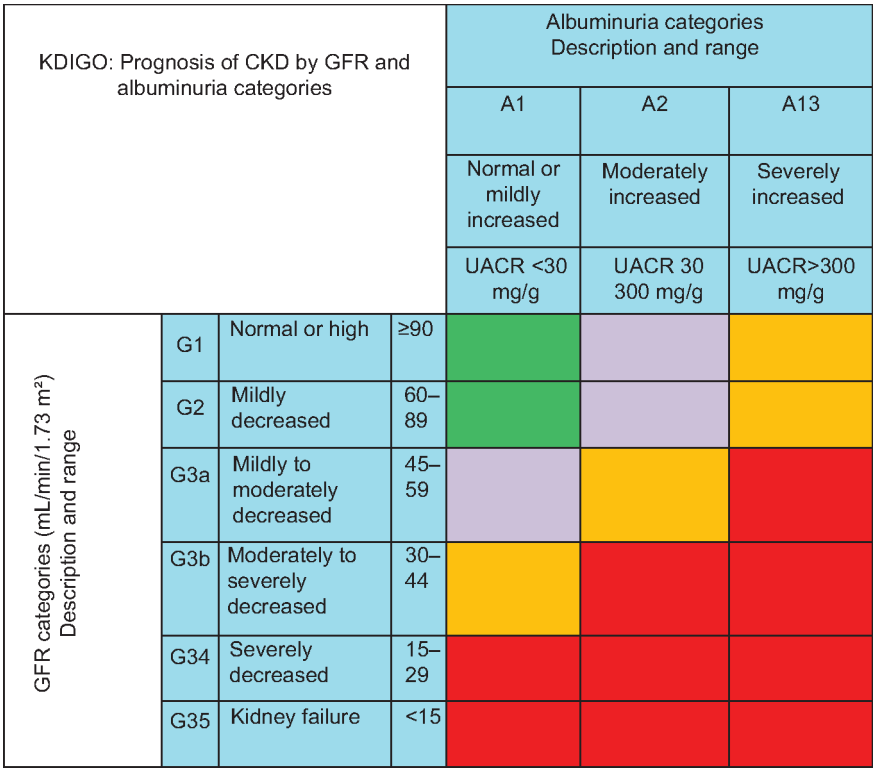

Fig. 2: KDIGO heatmap illustrating the prognosis of CKD based on categories of eGFR and albuminuria [Green—low risk (if no other markers of kidney disease, no CKD); Yellow—moderately increased risk; Orange—high risk; Red—very high risk]

linked to anti-VEGF therapy, even if mild and without evident renal dysfunction, may indicate clinically relevant histopathological damage. Proteinuria may indicate treatment toxicity and could also represent paraneoplastic membranous nephropathy, necessitating therapy intensification instead of discontinuation.[26]

Nephropathologists play a crucial role in the multidisciplinary management of cancer patients experiencing renal dysfunction. In addition to establishing a precise histopathological diagnosis, they provide prognostic information by evaluating activity and chronicity indices in the glomerular, tubulointerstitial, and vascular compartments, which is crucial for customizing oncologic and nephrological treatments, informing choices regarding renal replacement therapy, and predicting the likelihood of renal recovery. The integration of nephropathology into oncology practice is essential to optimize patient outcomes in the context of targeted therapies, ICIs, and precision medicine. Administration of cytotoxic chemotherapy in patients receiving dialysis

The Onconephrotoxin Library Collaboration (OLIC) was launched online in 2022 (https://www.olic-app.info/items-1-1). It was created by a group of nephrologists, pathologists, and pharmacists, in collaboration with the American Society of Onconephrology (ASON). The goal is to raise knowledge of possible side effects and interactions, as well as suggestions on how various chemotherapeutic medicines should be managed in dialysis patients.[27]

Cancer Treatment in Individuals with Impaired Renal Function

To obtain the best clinical results, anticancer drugs must be correctly administered. Therefore, estimating kidney function is an essential part of the dosage process. Underestimating kidney function will lead to dose reduction and decreased efficacy, treatment failure, adoption of second- or third-line medications that are less effective or more toxic, and, eventually, a lower survival rate.[28] However, overestimation of kidney function leads to higher toxicity. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula performed better than other creatinine-based GFR estimation formulas in both cancer and noncancer populations and should be used to determine kidney function for drug dosing.

The 2021 CKD-EPI creatinine and cystatin levels are best for GFR assessment in patients with hematologic and solid cancers.[29]

Transplant Onconephrology

Patients with chronic renal illness exhibit an increased risk of cancer and cancer-related mortality after transplantation. Kidney transplant recipients face a two-to threefold increased chance of developing cancer and dying from cancer relative to the general population. Most of the heightened risk is attributable to viral-mediated malignancies, including post-transplant lymphoproliferative disease, anogenital tumors, and Kaposi sarcoma. Nonmelanoma skin cancer is the most common malignancy among recipients of a kidney transplant. Both immunological and nonimmune factors predispose patients to cancer development after kidney transplantation, including age at transplantation, sex, ethnicity, duration of dialysis, history of malignancy, sun exposure, and virus exposure. Recipients of kidney transplants must adhere to age-appropriate cancer-screening protocols and implement preventive strategies against the most common solid organ malignancies.[30]

Physicians should monitor patients with cancer proactively (perform kidney function tests, electrolytes, and urine analysis in routine cancer patient follow-ups, especially during nephrotoxic treatments), recognize red flags such as rapid decline in eGFR, proteinuria, hematuria, or severe electrolyte imbalances, and refer to onconephrologists. Patients should be made aware of hydration and avoid the use of nephrotoxic drugs (for example, NSAIDs, aminoglycosides, and alternative drugs) and adhere to monitoring schedules.

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POINT OF VIEW

Glycemia Risk Index—A Novel Glycemic Parameter: A Composite Metric to Better Quantify Glycemic Risk Beyond Time-in-range

Abhijit Anil Trailokya[1*], Suhas Erande[2]

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Abstract

The glycemia risk index (GRI) was developed in 2022. This novel metric is designed to provide a single, comprehensive value that encapsulates the overall quality of a patient's glycemic control. Unlike conventional indicators such as HbA1c or time-in-range (TIR), the glycemia risk index places greater emphasis on severe glycemic fluctuations and more closely reflects clinicians' understanding of glycemic risk. It integrates hypoglycemia and hyperglycemia into a single numerical value, placing greater weight on hypoglycemia and extreme glycemic excursions. In this article, we highlight the clinical rationale behind GRI, its calculation, and its potential utility in diabetes management compared to traditional metrics such as TIR.

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Introduction

Continuous glucose monitoring (CGM) systems have emerged as vital technologies for evaluating glycemic control, offering round-the-clock measurement of glucose levels in the interstitial fluid beneath the skin.[1] According to the American Diabetes Association (ADA) guidelines, time-in-range (TIR) derived from continuous glucose monitoring (CGM) is a recognized parameter for evaluating glycemic control. While widely adopted by clinicians as a summary indicator of glycemic quality, TIR has limitations—particularly its insufficient sensitivity to hypoglycemic events—thereby making it suboptimal as a standalone metric.[2]

The Glycemia Risk Index

The glycemia risk index (GRI), introduced in 2022, is a novel composite metric designed to quantify the overall quality of glycemic control by integrating the frequency and severity of both hypo- and hyperglycemic excursions into a single, interpretable score.

Development of GRI

The GRI was developed by a team of over 330 international diabetes experts, including Dr David Klonoff, Dr Rich Bergenstal, Dr Anne Peters, Dr Roy Beck, Dr Jane Seley, Dr Boris Kovatchev, and many more.[3]

The glycemia risk index is an integrated scoring system designed to evaluate the overall quality of glycemic control by factoring in the potential risks associated with both hypoglycemia and hyperglycemia. Developed by a global panel of 330 diabetes experts using CGM data from 225 individuals receiving insulin therapy, the GRI addresses the need for a more holistic approach to glucose management. By consolidating various CGM-derived metrics, it aids clinicians in making informed treatment decisions. As a singular metric, the GRI places greater weight on clinically significant hypoglycemia and shows a strong alignment with TIR, making it a valuable tool for monitoring and adjusting glucose levels effectively.[4]

About Glycemia Risk Index

The glycemia risk index is a novel composite parameter that quantitatively captures the frequency and severity of both hypoglycemic and hyperglycemic events, enabling a comprehensive evaluation of glycemic control in individuals with type 1 or type 2 diabetes. It serves as a valuable tool for longitudinal patient monitoring, population-level diabetes management, and outcome prediction in interventional research.

The expert assessments were primarily influenced by two key components: the duration of hypoglycemia, referred to as the hypoglycemia component (CHypo), and the duration of hyperglycemia, referred to as the hyperglycemia component (CHyper). Greater weight was assigned to hypoglycemia relative to hyperglycemia, with additional emphasis placed on extreme deviations in glucose levels—both severely low and high. The GRI is computed as a weighted sum of these two components using predefined coefficients. This composite score showed a strong correlation (r = 0.95) with expert ratings of glycemic profiles in the original validation study. The GRI is expressed as a percentile (Pc) ranging from 0 to 100, where lower scores indicate better glycemic control, reflecting minimal time spent in hypo- and hyperglycemic ranges.[3]

Glycemia Risk Index Calculation

The glycemia risk index is derived from CGM data and provides a quantitative measure of the overall glycemic risk. It assigns greater weight to hypoglycemic episodes compared to hyperglycemic ones, with particular emphasis on extreme glucose values—specifically, levels below 54 mg/dL and above 250 mg/dL.

$$GRI = 3.0 \times [TBR < 54 + (0.8 \times TBR\ 54–70)] + 1.6 \times [TAR > 250 + (0.5 \times TAR\ 180–250)]$$

Glycemic Risk Estimation Tool

To calculate the GRI using CGM data, enter the percentage of time glucose readings are within the very low, low, high, and very high ranges into the respective input fields (Fig. 1).

The GRI can be calculated for individual patients or cohorts using the online GRI calculator, accessible at www.diabetestechnology.org/gri.

Quick interpretation of GRI

The glycemia risk index can be visualized using the GRI grid, a graphical tool that plots the hypoglycemia component on the X-axis and the hyperglycemia component on the Y-axis. The grid is segmented into five percentile-based zones, ranging from optimal glycemic control (Pc: 0–20) to poor control (Pc: 80–100). This visual representation facilitates rapid identification of predominant glycemic disturbances and aids healthcare professionals in targeting specific areas for therapeutic intervention. The GRI scale extends from 0, indicating minimal risk,

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% Very Low (<54 mg/dL; <3.0 mmol/L)
% Low (54–<70 mg/dL; 3.0–< 3.9 mmol/L)
% Very High (>250 mg/dL; > 13.9 mmol/L)
% High (>180–250 mg/dL;>10.0–13.9 mmol/L)
Hypoglycemia Component = Very Low + (0.8 x Low)
Hyperglycemia Component = Very High + (0.5 x High)

GRI = (3.0 x Hypo-Component) + (1.6 x Hyper-Component)
Equivalently,
GRI = (3.0 x Very Low) + (2.4 x Low) + (1.6 x Very High) + (0.8 x High)

GRI

Fig. 1: Glycemia risk index calculator

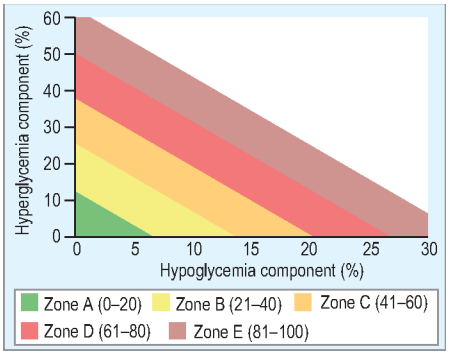

Fig. 2: Visual (graphical) depiction of the glycemia risk index (GRI) using a grid format

No	TIR	Vlow	Low	Vhigh	High	Results →	Hypo-component	Hyper-component	GRI	Zone
1	59%	2	10	5	24		10	17	57	C
2	85%	0	0	1	14		0	8	13	A
3	74%	0	0	1	24		0	13	21	B
4	91%	0	1	0	8		0.8	4	9	A
5	92%	0	8	0	0		6.4	0	19	A
6	80%	0	14	0	6		11.2	3	38	B

Fig. 3: Analysis using CGM and GRI (online tool) (https://www.diabetestechnology.org/gri/)

to values exceeding 100, reflecting severe glycemic risk, thereby enhancing clinical interpretation of glucose variability.

The GRI grid displays the hyperglycemia component along the vertical (Y) axis and the hypoglycemia component along the horizontal (X) axis. Glycemic control is categorized into five distinct zones (A–E) based on percentiles, ranging from optimal control (Pc: 0–20) to poor control (Pc: 80–100) (Fig. 2).

Need for GRI

With broader access to continuous glucose monitoring (CGM) data among nonspecialist healthcare providers, there is a growing need for simplified yet effective tools to interpret glycemic patterns. The glycemia risk index (GRI) represents a valuable advancement in this context, offering a practical means to assess the overall quality of glycemic control in individuals with diabetes. Its applicability in both clinical trials and real-world settings makes it a useful parameter for monitoring the impact of emerging therapeutic interventions. Unlike traditional metrics such as HbA1c or time-in-range, the GRI provides a more nuanced view of glycemic variability, serving as both an early warning signal and a guide for therapeutic optimization. It empowers healthcare professionals to make informed decisions regarding treatment adjustments by highlighting specific areas of glycemic risk.[3]

The glycemia risk index offers distinct advantages over conventional metrics such as HbA1c and TIR by emphasizing extreme glycemic fluctuations and better reflecting clinical assessments of glycemic risk. It shows strong concordance with other CGM-based measures and has demonstrated utility across diverse clinical contexts, including among individuals utilizing hybrid closed-loop insulin delivery systems. Notably, in patients with HbA1c ≤ 7%, the GRI can uncover residual glycemic risk not evident through HbA1c alone, underscoring its added value in comprehensive glycemic evaluation.[5]

Limitations of GRI

Despite its potential, the GRI has certain limitations. Its development was based on CGM data from healthy adults undergoing intensive insulin therapy, which may restrict its applicability to broader patient populations. Additionally, unlike established measures such as HbA1c and TIR, the GRI has not yet been validated against definitive clinical outcomes. Nonetheless, with ongoing advancements in CGM technology, the GRI remains a promising tool, contingent on further validation and integration into clinical practice through future research.[4]

Our Experience with CGM and GRI

We analyzed CGM data from six patients using the GRI calculator alongside traditional metrics such as TIR. The GRI tool provided immediate classification of glycemic control into zones A to E, using a color-coded system. This visual representation proved to be highly intuitive and time-efficient, particularly beneficial for clinicians and paramedical staff with limited time to review comprehensive CGM reports. Moreover, the GRI facilitated straightforward tracking of patient progress over time, offering a practical approach for monitoring and guiding diabetes management (Figs 3 and 4).

Use of GRI

The glycemia risk index has gained considerable attention within the diabetes care research community, with a growing body of evidence supporting its application across various patient populations, including pediatric and adult groups, individuals on continuous subcutaneous insulin infusion (CSII), and those with type 2 diabetes. Notably, the GRI offers superior sensitivity in detecting hypoglycemic episodes compared to TIR, enhancing its clinical utility. Its ability to capture extreme glucose excursions also makes it a valuable tool in managing insulin-treated pregnancies. As a single, easy-to-calculate, and actionable metric, the GRI streamlines the interpretation of CGM data—particularly benefiting clinicians with limited experience in data analysis. Furthermore, it supports efficient clinical decision-making by helping prioritize patients with poor glycemic control and informing targeted therapeutic strategies based on its CHypo and CHyper components. These features position the GRI as a highly promising tool in the context of precision medicine and big data analytics in diabetes care.[1]

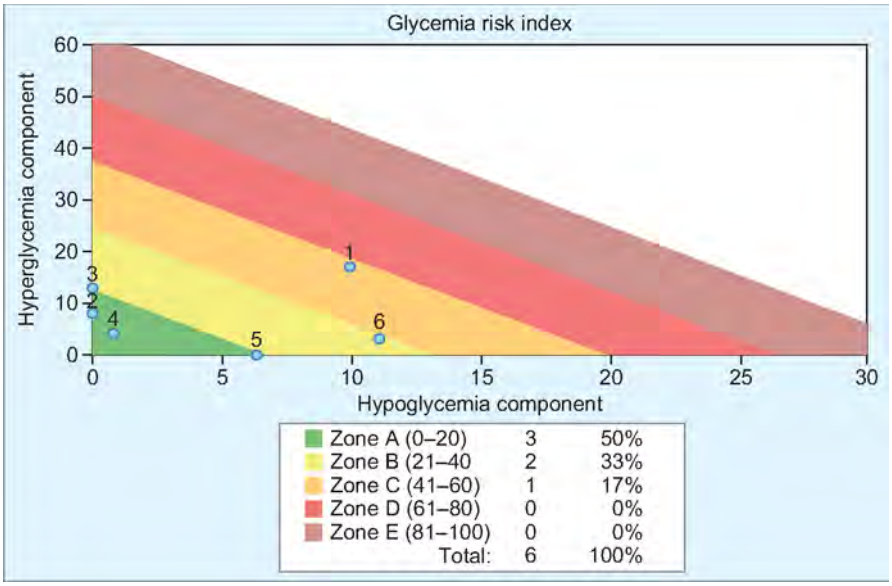

Fig. 4: GRI plot (online tool) (https://www.diabetestechnology.org/gri/)

Conclusions

The glycemia risk index is an emerging metric designed to provide a comprehensive assessment of an individual's glycemic control by integrating both hypoglycemic and hyperglycemic components into a single, quantifiable value. Its key advantage lies in its simplicity, ease of calculation, and clinical actionability, enabling healthcare professionals to efficiently identify patients at higher risk and tailor interventions accordingly. Compared to TIR, the GRI offers enhanced sensitivity in capturing hypoglycemia and extreme glycemic excursions, which makes it especially useful for certain groups, including children and individuals using CSII. Moreover, the GRI has shown associations with chronic diabetes-related complications and quality-of-life outcomes, underscoring its potential as a meaningful tool in routine diabetes management. As an adjunct to TIR and HbA1c, GRI may offer a more holistic and risk-sensitive glycemic assessment, particularly in individuals with frequent hypoglycemia or high glycemic variability.

Clinical Recommendation

Given its comprehensive nature and clinical relevance, GRI should be routinely used by all physicians, diabetologists, and endocrinologists involved in diabetes care. It enables better identification of patients at risk, supports personalized treatment adjustments, and complements existing metrics such as TIR and HbA1c.

Future Directives

The glycemia risk index represents a novel and meaningful advancement in CGM-based glycemic assessment. Further real-world studies are warranted to validate its predictive value and integrate it into routine diabetes care.

Acknowledgments

We acknowledge the foundational work of Klonoff DC, Wang J, Rodbard D, Kohn MA, Li C, Liepmann D, Kerr D, Ahn D, et.al. in the development of the GRI algorithm.

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POINT OF VIEW

Proposing a Universal Informed Written Consent for Publication of Case Reports or Case Series

Atanu Chandra[1*], Rupak Chatterjee[2], Sugata Dasgupta[3], Nandini Chatterjee[4], Jyotirmoy Pal[5]

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Abstract

Case reports and case series play a pivotal role in advancing medical knowledge by highlighting rare conditions, novel treatments, and unique clinical presentations. Despite their importance, ethical considerations surrounding patient autonomy, privacy, and confidentiality remain central to their publication. Informed written consent is a cornerstone of this process, yet the current system for obtaining consent is fragmented and inconsistent across journals. Authors are often required to secure new, journal-specific consent forms for each submission, creating unnecessary administrative burdens and risking patient dissatisfaction or noncompliance. This inefficiency may ultimately hinder the timely dissemination of valuable clinical insights. With the rise of open-access publishing and the broader reuse of published material under Creative Commons licenses, the limitations of traditional anonymization techniques further underscore the need for robust and standardized consent practices. This article proposes the development of a universal informed written consent form that could be accepted across all medical journals. Such a form, developed collaboratively by journals, ethical committees, and legal experts, would simplify the publication process, protect patient rights, and maintain ethical integrity. Adoption of a universal consent framework represents a critical step toward safeguarding patient dignity while facilitating the responsible advancement of medical science.

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Introduction

Case reports and case series are a valuable means of advancing medical knowledge. These reports provide insights into rare conditions, innovative treatments, and unusual presentations, contributing to the knowledge base for personalized health care and serving as an important educational resource. However, ethical considerations are paramount, particularly the need for informed written consent from patients.[1] Informed consent is crucial in maintaining patient privacy and autonomy.[2] Case reports must ensure patient confidentiality by excluding unnecessary details and identifiable features from images. Even with direct identifiers removed, obtaining consent for the publication of both the report and associated images is essential, as clinical details and images can still potentially reveal individuals' identities.[3] Despite its importance, the current process for obtaining informed written consent for case report publication is fragmented and inconsistent across journals. This article proposes the development of a universal informed consent form that can be accepted across all journals, simplifying the process for authors and ensuring ethical standards are maintained.

Why is Informed Written Consent Necessary for Publication?

The Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE) have provided guidelines for publishing case reports.[1,4,5] These guidelines generally require that patient consent be obtained before publication. Authors must inform patients that their case will be publicly accessible and that, despite efforts to anonymize, there is still a risk of identification. With the shift to online and open-access publishing, and the use of Creative Commons licenses that allow free reuse of material, including patient photographs, there is a concern about the potential for patients' images to be repurposed in different contexts without proper consent. Techniques such as blurring or covering the eyes have proven insufficient for ensuring anonymity.[6] Additionally, once published, consent cannot be withdrawn. Patients should be given the chance to review the manuscript and any accompanying images as part of the consent process. In the context of case reports and series, it ensures that patients understand the nature of the publication, how their information will be used, and the potential risks of making their case details public. The primary goal is to respect patient autonomy, confidentiality, and dignity.[4,7] For minors, deceased patients, or those unable to give consent, additional considerations are necessary. In such cases, consent must be obtained from legal guardians, next of kin or legally authorized representatives. For minors, the consent should include assent from the child, where appropriate, along with the consent from the guardian. For deceased patients, the consent must respect the patient's previously expressed wishes if known, and should be obtained from the family.

Challenges with the Current Consent Process Applicable to Different Journals

A major issue with the current consent process for publishing case reports is the inconsistency among journal requirements. Different journals often have varied formats, content specifications, and wording for consent forms, creating confusion and adding administrative burdens for authors.[8] When a manuscript is submitted to multiple journals, authors frequently need to secure new consent forms tailored to each journal's specific guidelines, even if consent was previously obtained in another format. This repetitive process is both time-consuming and impractical.

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For example, if a manuscript is first submitted to a high-impact journal and rejected, it might then be sent to a second and third journal before being accepted. Each journal might require a different consent form, forcing authors to repeatedly approach patients or their representatives for new consents. Additionally, the process of repeatedly seeking consent can strain relationships with patients or guardians, who may become reluctant or refuse to sign multiple forms, particularly if they are facing health issues. If patients become unreachable between submissions, obtaining updated consent becomes difficult, potentially halting the publication process. Conflicting guidelines among journals can also create confusion and raise ethical and legal risks if specific consent forms do not align with legal standards. The time and cost involved in managing multiple consent processes further complicate the situation. Implementing a universal, standardized consent form could address these issues, streamlining the publication process and ensuring consistent patient privacy protection.

Proposal for a Universal Informed Consent Form

To resolve the challenges associated with the current consent process, the development and adoption of a universal informed consent form is essential. This standardized form would be created in collaboration with major medical journals, ethical bodies, and legal experts to ensure it meets diverse requirements and adheres to best practices across the field.

The universal consent form would feature several essential components to ensure comprehensive and consistent consent across case reports.[1,5] It would include sections for recording patient details, such as demographics and relevant medical history, while maintaining privacy. The form would also provide a clear description of the scope of the report, detailing what patient information will be included, how it will be used, and the extent of its disclosure. Explicit language would outline the implications of consenting to publication, including the handling of information and images, potential future reuse, and associated risks. Special provisions would address unique cases, such as obtaining consent from minors, with sections for parental or guardian consent and minor assent and securing consent from relatives or legal representatives for deceased patients. Additionally, the form would include a revocation policy detailing the conditions under which consent can be withdrawn and its implications. Finally, it would ensure compliance with all relevant legal and ethical standards, including privacy laws and regulations such as the General Data Protection Regulation (GDPR).

Conclusion

The need for a universal informed written consent form for the publication of case reports and series is clear. The current fragmented approach is inefficient, frustrating for authors, and could potentially discourage the publication of valuable medical cases. By implementing a standardized consent form accepted across all journals, we can ensure ethical standards are maintained while making the publication process smoother and more practical for authors. Collaboration among medical journals, ethical committees, and other stakeholders is necessary to bring about this change, ultimately benefiting both medical research and patient care.

Author's Contributions

All the authors prepared the manuscript with adequate planning and execution. All had contributed to review of literature, critical revision of content, and final approval of the manuscript. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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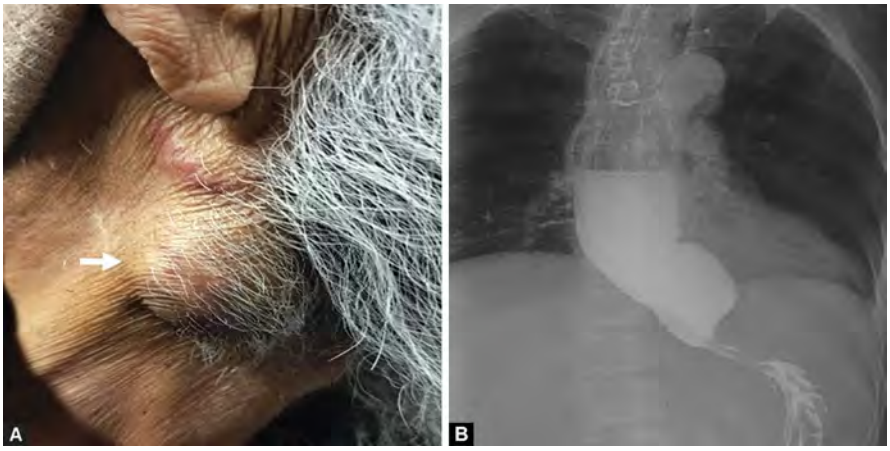
Paraneoplastic Pseudoachalasia in a Patient with Metastatic Salivary Gland Tumor

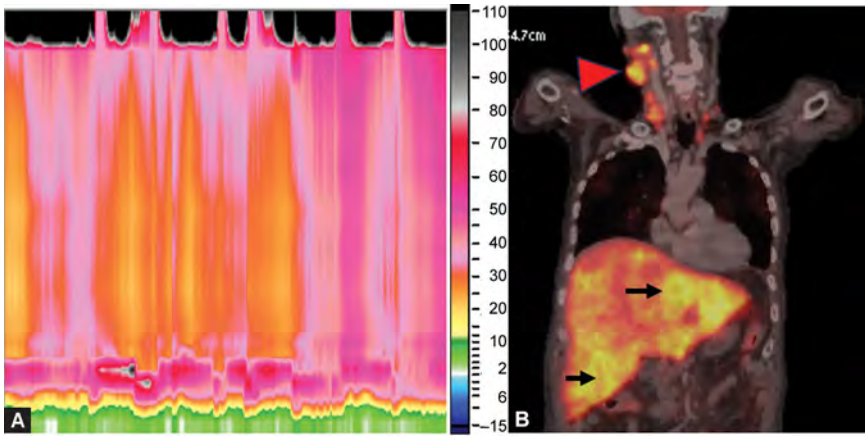
Venkatesh Vaithiyam[1*], Siddharth Srivastava[2], Surbhi Goyal[3], Sanjeev Sachdeva[4]

Received: 01 September 2025; *Accepted:* 06 December 2025

A 73-year-old man presented with a 6-month history of dysphagia and regurgitation of food particles. He also complained of a hard swelling in the right cheek, jaundice, and a 10 kg weight loss over the past month. Examination showed pallor, icterus, nontender, hard right salivary gland swelling (Fig. 1A), and severe cachexia (body mass index 15.2 kg/m^2). Abdominal ultrasonography revealed multiple hypoechoic space-occupying lesions (SOL) in the liver, suggesting hepatic metastasis. Upper GI endoscopy, barium swallow (Fig. 1B), and high-resolution manometry (Fig. 2A) showed features of achalasia cardia. 18-FDG positron emission computed tomography confirmed a right salivary gland tumor with lymph node, skeletal, and hepatic metastases (Fig. 2B). Cytopathology of the salivary gland mass and liver SOL confirmed metastatic salivary gland tumor (Figs 3A to D). With the presence of a metastatic tumor and clinical, radiological, endoscopic, and manometric patterns resembling achalasia, the possibility of paraneoplastic pseudoachalasia was kept. Due to poor performance status, endoscopic pneumatic dilation was performed; however, he developed hospital-acquired pneumonia and sepsis and died of progressive respiratory failure.



Figs 1A and B: (A) Clinical image showing a hard right parotid gland swelling (white arrow); (B) Barium swallow showing dilated esophagus with bird-beak appearance



Figs 2A and B: (A) High-resolution manometry showing pan-esophageal pressurization and elevated integrated relaxation pressure; (B) 18-FDG positron emission computed tomography showing a heterogeneously enhancing ill-defined mass lesion in the right parotid region infiltrating the parotid gland (red arrowhead; SUVmax 8.71), suggestive of right parotid gland malignant neoplasm, and FDG-avid extensive hypodense heterogeneously enhancing lesions completely occupying the liver parenchyma (SUVmax 8.12), suggestive of bilobar hepatic metastasis (black arrow)

Pseudoachalasia refers to disorders that clinically, manometrically, and radiographically resemble primary achalasia and are seen in various malignant and nonmalignant conditions.[1] Malignancy-associated pseudoachalasia

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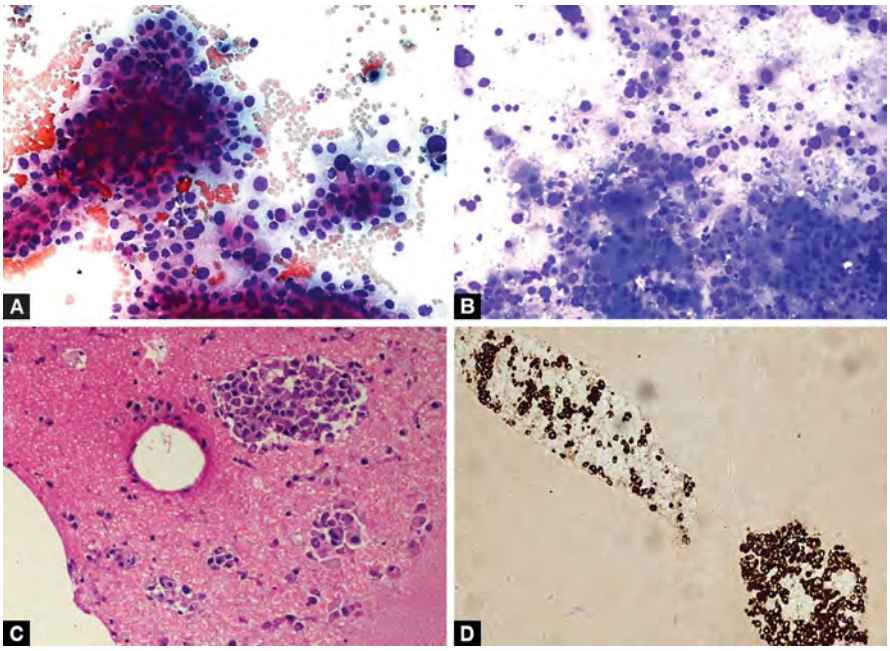

Figs 3A to D: FNA from salivary gland: (A) Cytosmears showing tumor cells that were cuboidal to plasmacytoid in appearance, with eccentrically placed enlarged nuclei, moderate eosinophilic cytoplasm, coarse chromatin, and 1–2 prominent nucleoli. Significant cytological atypia and nuclear overcrowding with a few bizarre pleomorphic tumor cells were noted (Papanicolaou ×200); (B) USG-guided FNA from liver SOL: Cytosmears showing a moderate degree of pleomorphism and cytological atypia in the form of a high N:C ratio, nuclear hyperchromasia with coarse chromatin, and 1–2 prominent nucleoli. Many bizarre tumor giant cells were also seen. A few benign reactive hepatocytes were noted in the background (MGG ×200); (C) Cell block showing tumor cells arranged in sheets as well as singly scattered. Individual cells show moderate pleomorphism with a high N:C ratio and nuclear enlargement. Cells are cuboidal with a moderate amount of cytoplasm and have enlarged hyperchromatic nuclei and 1–2 prominent nucleoli (H&E ×100); (D) On IHC, tumor cells were positive for CK7, suggestive of metastatic salivary gland tumor

can be a paraneoplastic syndrome with isolated esophageal involvement or part of a generalized gastrointestinal motility disorder.[2] The pathophysiology involves autoantibody-induced (type 1 antineuronal nuclear autoantibody) destruction of the esophageal myenteric plexus. Treatment includes management of the underlying malignancy and therapies to lower the lower esophageal sphincter pressure.

Informed Consent

Informed consent was obtained from the patient's son for the publication of his information and imaging.

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PICTORIAL CME

Wrist and Elbow Clonus in Amyotrophic Lateral Sclerosis: A Rare Feature

Siddharth Maheshwari[1*], Rajinder K Dhamija[2], Mridula Singh[3], Sourav Hazra[4]

Received: 18 June 2025; *Accepted:* 25 June 2025

A 62-year-old man presented with progressive, asymmetric limb weakness over 1.5 years, beginning in the right hand and later involving other limbs. Symptoms included difficulty gripping, clumsiness, and progressive thinning of the muscles in the right lower and left upper limbs. He reported muscle twitching, slurred speech, weight loss, and spasticity. Examination revealed significant wasting in distal muscles, fasciculations, brisk reflexes, bilateral Hoffmann signs, and sustained clonus at wrist and elbow—an unusual finding. Investigations ruled out amyotrophic lateral sclerosis (ALS) mimics, with EMG and nerve studies consistent with probable ALS as per revised El Escorial criteria (Supplementary Video 1).

Sustained clonus, including jaw clonus, a marker of upper motor neuron dysfunction, is rare in the upper limbs, with few cases reported in cervical myelopathy and cerebrovascular disease.[1–3] Many studies highlight the importance and pathophysiology of UMN signs in ALS, including clonus.[4,5] This case highlights an uncommon presentation of ALS with sustained wrist and elbow clonus, expanding its clinical spectrum. Elbow and wrist clonus are rarely reported in ALS.

Supplementary Material

Supplementary Video S1 is available online at the journal website.

Video S1: Demonstration of sustained wrist and elbow clonus in ALS Maheshwari S, 2026

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Letter to the Editor (Correspondence) on the Article Entitled "Gastric Emptying Patterns in Type 2 Diabetes Mellitus Patients with Symptoms of Gastroparesis and the Impact of Levosulpiride on These Patterns"

Nitin Chintaman Gawari[1], Sujata Prakash Shingare[2], AV Tilak[3], Krupa H Vasani[4]

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Dear Editor,

We read with interest the expert consensus by Kant et al. on levosulpiride for the management of symptoms of gastroparesis in type 2 diabetes mellitus (T2DM) patients. The article is timely and informative, particularly in view of the increasing complexity of treatment in Indian diabetes care. The debate around the novel mechanism of levosulpiride—addressing the relationship both gastric motility patterns and therapeutic outcomes—is well articulated and is in line with the increasing emphasis on both.[1]

The recommendation on the use of levosulpiride in patients with symptoms of gastroparesis in T2DM is practical and relevant. Levosulpiride, in particular, has been shown to effectively alleviate symptoms such as nausea, vomiting, and early satiety, likely due to its action on the chemoreceptor trigger zone.[2]

However, we would like to make a few comments:

- The authors have clearly established the global and Indian burden of diabetes, which is strong. However, the introduction could flow more smoothly from general (diabetes mellitus burden) to specific (gastroparesis) to research gap. The research gap ("limited research on the correlation between scintigraphic patterns and symptoms") is mentioned at the end but could be more explicit and earlier in the text. The rationale for using levosulpiride is stated but not linked directly to the research gap.[3]
- Data transparency: A flow diagram of participant recruitment and attrition was not provided. Adding a participant flow diagram showing numbers at each stage will be better (screened, eligible, included, followed up, analyzed). There is no accounting for missing data, and it is unclear whether all 27 participants completed follow-up. The number of participants who did not improve or who worsened was not mentioned.
- Confounding variables (glycemic control, concomitant medications, and diet) are not discussed. The article does not connect to the local (North India) study context, which is important for external validity. There is also a lack of discussion on generalizability to other populations.

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Gonadotropin-releasing Hormone Agonist-induced Autoimmune Thyroiditis in a 49-year-old Woman

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Dear Editor,

Goserelin is a synthetic gonadotropin-releasing hormone (GnRH) agonist that initially stimulates and then profoundly suppresses pituitary gonadotropin secretion through receptor desensitization. It is commonly prescribed in the management of hormone-dependent conditions such as prostate cancer, breast cancer, endometriosis, and adenomyosis.[1] Typical side effects of goserelin are attributable to the resulting hormonal deprivation, including vasomotor symptoms, bone mineral loss, mood disturbances, and injection site reactions. However, rare endocrine complications beyond expected hypoestrogenism, such as thyroid dysfunction, have also been described.[2,3] Here we discuss the case of a 49-year-old woman, a known case of prediabetes (glycosylated hemoglobin: 6.2%), hypertension, and dyslipidemia, who presented to the gynecology outpatient department with complaints of menorrhagia and infertility. Laboratory investigations revealed normal blood counts and normal kidney and liver functions, with a standard thyroid function test [free T4/thyroid-stimulating hormone (TSH): 11.1 pmol/L and 2.10 mU/L, respectively]. Hormonal workup, including luteinizing hormone, follicle-stimulating hormone, and serum anti-Mullerian hormone, was normal. CA-125 was normal. A Pap smear showed no evidence of malignancy, and mammography showed breast imaging-reporting and data system (BI-RADS) 1. Ultrasound of the pelvis revealed a markedly bulky uterus (172 mL) and no significant fibroids. Evaluation revealed abnormal uterine bleeding associated with adenomyosis (AUB-A). Considering this to be a mechanical barrier to successful embryo implantation, she was initiated on GnRH agonist therapy. She was administered a monthly dose of goserelin (Zoladex) 3.6 mg subcutaneously for a total of 6 months. Treatment successfully induced a hypoestrogenic menopausal-like state, leading to amenorrhea. A follow-up pelvic ultrasound after completion of therapy showed a significant reduction in uterine volume from 172 to 93.4 mL, confirming a good anatomical response to GnRH therapy. No thyroid-related symptoms were reported during the treatment course. Six weeks after her last dose of GnRH agonist, she presented to us with complaints of palpitations, episodic tremors, heat intolerance, anxiety, and insomnia. There was no history of neck pain or visual disturbances. On examination, she had fine tremors with tachycardia (pulse rate: 102/minute, regular). The rest of the hemodynamic and systemic examination was normal. Physical examination of the eyes and thyroid gland revealed no abnormalities. Initial investigations revealed a normal complete blood count and liver and kidney function tests. Thyroid function tests revealed overt thyrotoxicosis [Low TSH (0.004 µIU/mL), low fT3 (1.098 pg/dL) and high fT4 (3.6 ng/dL)]. Thyroid antibody testing revealed markedly elevated antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) levels, 764

and 142 IU/mL, respectively. TSH receptor antibody (TRAb) was mildly positive (3.51 IU/L). Fasting glucose and lipid profiles were normal. To differentiate thyroiditis from Graves' disease, a technetium-99m pertechnetate thyroid scan was performed, which showed normal thyroid morphology with a total uptake of 0.6% (normal range: 0.2–3%), without any evidence of nodules. This normal uptake despite suppressed TSH strongly favored a diagnosis of painless autoimmune thyroiditis. Other causes of thyrotoxicosis, such as toxic multinodular goiter, iodine-induced hyperthyroidism, or medication-induced thyroid dysfunction, were ruled out. Symptomatic treatment with propranolol for palpitations and tremors was initiated. Serial monitoring after 8 weeks showed gradual normalization of thyroid function (T3: 3.1 pg/mL, T4: 1.01 ng/dL, TSH: 2.21 µIU/mL), indicating a return to a euthyroid state. She continues to be on regular follow-up with no clinical features of hypothyroidism. Her menstrual symptoms and metabolic parameters are well-controlled.

Though uncommon, there is emerging evidence linking GnRH agonist therapy to disturbances in thyroid function, particularly autoimmune thyroiditis and transient thyrotoxicosis.[2–4] The precise pathophysiological mechanism remains unclear but is hypothesized to involve immune dysregulation secondary to abrupt withdrawal of estrogen, which typically exerts protective, immunosuppressive effects. This disruption may unmask subclinical autoimmune thyroid disease or trigger *de novo* thyroiditis in genetically susceptible individuals, paralleling the pathogenesis observed in postpartum thyroiditis.[5–7] Several features in our patient support a diagnosis of goserelin-induced painless autoimmune thyroiditis. The delayed onset of thyrotoxic symptoms 6 weeks after the final goserelin dose is consistent with the time course observed in immune-mediated thyroid dysfunction. Laboratory investigations revealed markedly elevated thyroid peroxidase (TPO) and thyroglobulin antibodies, suggesting an autoimmune basis. Furthermore, the technetium thyroid scan demonstrated normal uptake, differentiating the condition from Graves' disease, which typically exhibits increased tracer uptake. There was no thyroid tenderness, nodularity, or orbitopathy, making other differentials such as subacute thyroiditis unlikely. Nakashima et al. reported two women with endometriosis developing transient thyrotoxicosis following prolonged GnRH-agonist therapy, hypothesizing that hypoestrogenism-related immune shifts contributed to the thyroid dysfunction.[4] Similarly, Van Bon and Wiersinga described transient thyrotoxicosis in a hypothyroid woman undergoing goserelin therapy, highlighting a rare but plausible immune-mediated mechanism.[2] In contrast to some cases where radionuclide scans showed low uptake, our patient's imaging revealed normal thyroidal activity, possibly reflecting early or mild autoimmune involvement rather than destructive thyroiditis. Importantly, spontaneous normalization of thyroid function over several weeks without antithyroid therapy mirrored the self-limiting course observed in autoimmune thyroiditis.

The management of GnRH-induced thyroid dysfunction is typically conservative. Since the hyperthyroid phase results from the release of preformed thyroid hormones rather than active synthesis, beta-blockers suffice for symptomatic control, and antithyroid medications are unnecessary. Regular monitoring of thyroid function is advised to detect potential progression to hypothyroidism during recovery.

This case illustrates a rare occurrence of GnRH agonist-induced thyrotoxicosis, likely triggered by an autoimmune mechanism analogous to postpartum thyroiditis. It emphasizes high vigilance for thyroid dysfunction, even several weeks after completion of GnRH agonist therapy, particularly in individuals with a potential autoimmune predisposition. Early recognition and patient counseling regarding the benign, self-limited nature of this complication play a crucial role in the management of this disease.

Author's Contributions

Sruthi Yalamanchili: Data curation, formal analysis, investigation, methodology, resources, writing—original draft, visualization; Nikhil Gupta: Methodology, resources, writing—original draft; Tanvi Batra: Conceptualization, software, writing—review and editing; Atul Kakar: Project administration, funding acquisition, supervision.

Sources of Support

None.

Conflict of Interest

There is no conflict of interest.

Patient Consent Statement

Participant's consent has been obtained.

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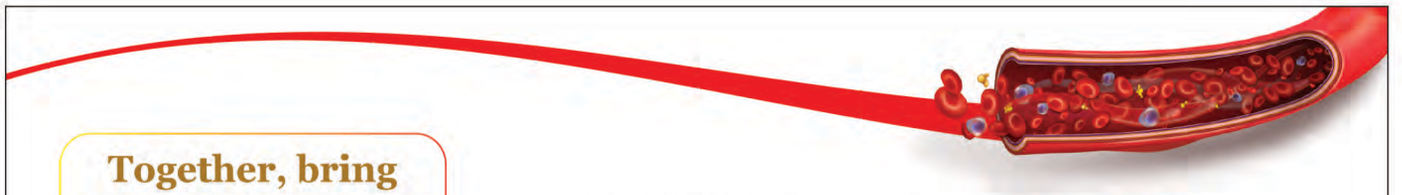

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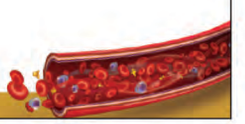

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