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# Contents

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# Type 1 Diabetes Care: The West Bengal Model

Masuma Yasmin[1], Sujoy Ghosh[2*]

Type 1 diabetes (T1D) management is complex and requires a multifaceted approach. This includes daily multiple insulin injections, home monitoring of blood glucose, screening for potential complications, and patient education and support. Many T1D patients face untimely death due to lack of structured and timely care.[1] India has the highest number of children and adolescents (aged 0–19 years) living with T1D,[2] but there is no national health program or policy targeting this population.[3] The average life expectancy for a person diagnosed with T1D in India is only 29 years.[2]

In West Bengal, India, a structured model of care (West Bengal Model) for T1D was initiated with support from the Government of West Bengal to provide comprehensive health care to all patients living with T1D.[4,5] The model was developed along the lines of "intermediate care," which is recommended as the standard of care for T1D in low-resource settings.[6,7] This provides structured care that includes essential components such as multiple daily insulin injections (basal-bolus regimen of insulin treatment), regular home blood glucose monitoring, quarterly testing of glycated hemoglobin (HbA1c), annual screening for diabetes-related complications, and structured age-appropriate patient education and support including self-management of disease, dose adjustment, nutrition, meal planning, exercise, and sick day rules.[6,7]

The model was launched by piggybacking on the existing adult National Program for Prevention and Control of Non-Communicable Diseases (NP-NCD). There was no need for additional infrastructure or staff recruitment because the model made use of both physical infrastructure and human resources available in existing noncommunicable disease (NCD) clinics. Initially, it was implemented as a pilot project in five health districts in West Bengal, where model T1D clinics were established in each district hospital. After conducting needs assessment in the form of initial site visits, dedicated identified staff were rigorously trained to deliver care for T1D patients. Patients who were previously receiving unstructured care at tertiary hospitals in Kolkata were counseled and shifted to these new model clinics where the basal-bolus insulin regimen was the standard of care followed.[4,5]

An important aspect of this model is the provision of government-funded supplies to enrolled patients. With support from the state government and partial funding from the central government, patients receive insulin (regular insulin and glargine insulin), insulin syringes (both 100 IU and 40 IU), glucose measuring devices, blood glucose test strips, lancing devices, and lancets free of cost. Additionally, patient data are recorded and updated in electronic registry and physical formats, ensuring continuous monitoring and evaluation.[4,5]

The clinics are run by physicians, pediatricians, nurses, NCD counselors, and data entry operators, who underwent intensive training to deliver care. Despite the lack of specialized staff like diabetes educators or dietitians, nurses and NCD counselors were trained to provide basic nutritional advice and psychological support. This ensured that patients and their families are not only receiving medical treatment but also counseling on how to manage the disease in their daily lives. Patients are rigorously monitored on a monthly basis.[4,5]

One of the key operational strategies was to ensure that insulin and other supplies are dispensed directly from the T1D clinics, separate from the main hospital pharmacies. This streamlined the supply chain and made stock maintenance more efficient. Each patient is given an identity card, a logbook to track daily blood glucose readings, and educational materials in local languages to help them in self-management of the disease.[4,5]

The impact of the model on clinical parameters, psychological well-being, and financial burden on families was assessed and documented over 2 years. After 2 years, there was significant improvement in health outcomes, particularly in glycemic control, as indicated by lower glycated hemoglobin (HbA1c) values. The frequency of weekly blood glucose tests increased due to active counseling and availability of free blood glucose test strips. There were no reported cases of diabetic ketoacidosis, diabetes-related hospitalizations, or deaths during the study period. Episodes of hypoglycemia were also reduced, and there was a significant improvement in psychological well-being of both patients and their caregivers. There was also a reduction in both direct and indirect expenditures incurred by patients' families for managing T1D. These results were achieved despite the majority of the patients belonging to lower socioeconomic background and most of their parents not having completed primary education.

The success of this model has demonstrated that structured care for T1D can improve health outcomes, even in resource-limited settings. By using existing infrastructure and receiving government support, the model has proven to be both scalable and sustainable. Based on its success, the Government of West Bengal has given us permission to scale it up to cover the next 10 out of the remaining 22 health districts in West Bengal in phases. This has also been approved by the Central Government (National Health Mission) for Program Implementation Plan starting April 1, 2024.

We have provided inputs to the T1D section of the proposed national health policy on NCDs in children of the Government of India. Once launched, model T1D clinics will be established in every district hospital of India, where individuals with T1D will receive intermediate care, based on our model (West Bengal Model). Several state governments have shown interest in implementing this model in their states and have reached out to us. The United Nations International Children's Emergency Fund (UNICEF) and Breakthrough T1D along with their India partner William J Clinton Foundation (WJCF) have visited our model clinics and scoped whether they would be able to help and support other state governments to provide government-funded intermediate care by adopting/modifying our model. Based on our model

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in partnership with WJCF and their respective state NCD cells, Rajasthan, Madhya Pradesh, Uttarakhand, and Gujarat have started pilot programs in their respective states.

## Acknowledgement

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## Author Contributions

Sujoy Ghosh conceptualized the model and reviewed the draft manuscript. Masuma Yasmin was responsible for implementation of the model and wrote the first draft of the manuscript.

## Conflict of Interest

None.

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ORIGINAL ARTICLE

# Cavernous Sinus Involvement in Rhino-orbital Cerebral Mucormycosis and Impact of Concurrent COVID-19 on Patient Outcome: A Retrospective Observational Study

Harmeet Kaur[1*], Madhur Verma[2], Punit Tiwari[3], Paramdeep Singh[4], Vaibhav Saini[5], Anuradha Raj[6]

*Received:* 04 May 2024; *Accepted:* 21 May 2025


## Abstract

**Background:** Cavernous sinus thrombosis (CST) in rhino-orbital cerebral mucormycosis (ROCM) poses a challenge for clinicians in predicting outcomes and formulating management strategies, particularly with the concurrent coronavirus disease 2019 (COVID-19) infection.

**Purpose:** This study was done to evaluate cavernous sinus (CS) involvement in ROCM. Additionally, we explored the association between CS thrombosis and COVID-19, exploring its potential impact on patient mortality.

**Materials and methods:** A retrospective analysis was conducted on 106 ROCM patients, examining their COVID-19 status and reviewing imaging findings from contrast-enhanced computed tomography (CT) and magnetic resonance (MR). The imaging assessment focused on evaluating fungal sinusitis, identifying CS involvement qualitatively, and detecting extension to orbit or other intracranial areas. Findings were correlated with patient mortality.

**Results:** CS involvement in ROCM was 48.1%, with a higher distribution (clinically insignificant) in COVID-positive patients (51.8%) compared to the COVID-negative group (34.8%). Most participants showed unilateral (78%) and diffuse pattern (71%) of CS involvement. A statistically significant association was observed between CS imaging parameters (filling defect, diffuse involvement pattern, convex shape of the lateral wall, and orbital cellulitis) and patient mortality, according to bivariate analysis ($p < 0.05$). Among 106 ROCM patients, 9.4% succumbed to the disease, with significantly higher mortality in those with CS thrombosis. However, subgroup analysis for the additional effect of COVID-19 on mortality yielded nonsignificant results.

**Conclusion:** CS involvement in ROCM does not significantly impact mortality in both COVID-positive and negative patients. Imaging parameters such as filling defects, diffuse CS involvement, convex lateral wall, and orbital cellulitis may suggest the disease severity when observed.


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## Introduction

Rhino-orbital cerebral mucormycosis (ROCM) is the most common form of mucormycosis encountered concurrently or after coronavirus disease 2019 (COVID-19).[1] The prevalence of ROCM in India (0.14 cases per 1,000 population) exceeded that of developed nations, constituting 80% of COVID-19-associated ROCM cases during the second pandemic peak.[2] Intracranial dissemination of mucormycosis is associated with increased mortality.[3] The infection advances by infiltrating vascular and neural tissues, permeating the walls of blood vessels. It then extends from one sinus to neighboring sinuses, the orbit, the retro-orbital area, and eventually intracranial spread.[4]

Cavernous sinus thrombosis (CST), first described by Duncan in 1821, is a potentially fatal intracranial complication of mucormycosis.[5] CST is an uncommon condition, typically arising from septic, traumatic, or inflammatory causes.[6] Computed tomography (CT) and magnetic resonance (MR) imaging offer diagnosis through both direct signs, such as alterations in density/signal intensity on plain and contrast scans, changes in the size and contour of the CS, and indirect signs, including superior ophthalmic vein dilatation, exophthalmos, and increased dural enhancement along the lateral margin of the CS.[7] CS involvement in ROCM may arise from drainage *via* ethmoidal, facial, and ophthalmic veins, direct extension from the sphenoid sinus, or perineural spread along neural foramina.[8–10] CS can be directly involved due to contiguous spread, or there may be septic thrombophlebitis, a condition often regarded as life-threatening.

Numerous research studies have reported that COVID-19 infection can increase the likelihood of thrombotic events like pulmonary embolism, lower limb venous thrombosis, and strokes.[11] The underlying mechanisms driving these occurrences may involve a cytokine storm that triggers the onset of systemic inflammatory response syndrome and subsequent thrombotic processes.[11] Few cases have also been reported in the literature in which patients developed CST while getting infected with COVID-19, and these cases occurred without concurrent mucormycosis infection.[12] This highlights the significance of recognizing CST as a potential complication of COVID-19, even when mucormycosis is absent.

Chowdhary et al., in their study on 61 patients of mucormycosis during the COVID pandemic in 2021, concluded that 34.4% of patients developed CST and found no significant increase in the risk of death when patients had both COVID-19 and CST simultaneously.[13]

Given the complexities associated with managing ROCM patients, particularly amid the COVID-19 pandemic, our retrospective observational study aimed to determine the extent of CS involvement in these individuals. We sought to conduct a comprehensive qualitative assessment of CS on imaging, considering potential interactions with COVID-19, an aspect that has not been extensively documented. The correlation between CS involvement and COVID-19 and its impact on patient mortality were key objectives in this study.

## Materials and Methods

This retrospective observational study was conducted in a tertiary care institute

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between May 2021 and January 2022. The research protocol received approval from the Institutional Ethics Committee (Approval ID: IEC/AIIMS/BTI/168) to ensure ethical compliance throughout the study. Informed consent was taken from all the participants enrolled in the study. Patient data were retrieved from electronic hospital records. CECT and CEMRI scans were digitally archived for analysis as part of the study. Our study was conducted in adherence to the principles of human experimentation outlined in the Declaration of Helsinki.

## Study Population

The study included patients previously diagnosed with ROCM, either during hospitalization or in outpatient settings within the Department of Otolaryngology or Ophthalmology, and were subsequently referred to the Department of Radiodiagnosis for contrast-enhanced CT/MRI of the paranasal sinus region and brain. Upon retrospective analysis, the patients who were found to have presented with sinusitis and CST on imaging but tested negative for ROCM were excluded. Those who had undergone only a plain scan without administering contrast were also excluded.

## Sample Size and Sampling Strategy

The sample size was calculated using an online sample size collection software (https://www.openepi.com/SampleSize/SSPropor.htm). A sample size of 106 was calculated using the population proportion formula after considering the overall prevalence of CST in COVID-associated mucormycosis patients to be around 20%,[13] with an 80% confidence interval and a margin error of 5%.

## Scanning Protocol

The data of all such participants was analyzed where ROCM was confirmed through potassium hydroxide (KOH) testing, and contrast-enhanced CT (CECT) or contrast-enhanced MR (CEMR) was conducted based on the requests from the referring clinician. CECT and CEMR were performed on a 256-slice scanner (Siemens: Somatom Drive) and a 3 tesla MR scanner (Siemens: Skyra) with a defined scan protocol mentioned in Table 1. The scan acquisition encompassed plain and contrast-enhanced CT or MR imaging of the paranasal sinuses, face, orbits, suprahyoid neck, skull base, and the intracranial compartment in all anatomical planes. The imaging assessment focused on evaluating sinonasal fungal involvement, identifying the filling defect in CS, conducting a thorough qualitative evaluation based on a predefined set of parameters, and detecting any signs of orbital involvement or potential extension into other intracranial areas.

Mucor involvement of the sinonasal region was determined by the presence of mucosal thickening with hyperdense foci on NCCT and hypointense components on T2W MR and nonenhancement of involved mucosa on postcontrast CT or postcontrast MR, in conjunction with the presence of ancillary features (Figs 1 and 2). The presence of CST was defined by observing filling defects in either one or both sinuses on contrast imaging in conjunction with the criteria outlined below in the proposed criteria. COVID-positive status was taken as a positive COVID RT-PCR test conducted within the 3 months preceding the current presentation of ROCM.

## Proposed Qualitative Criteria

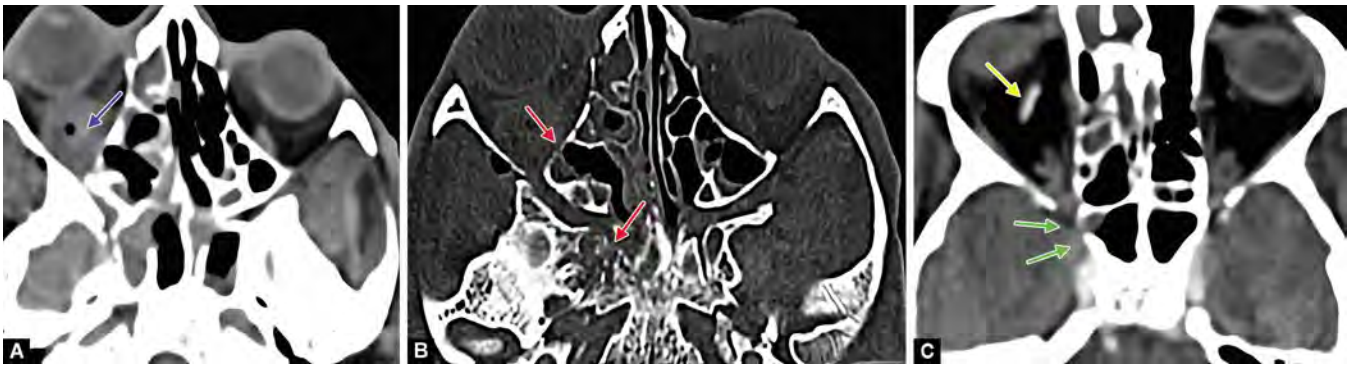
For the qualitative evaluation of CS involvement/thrombosis, the following variables were examined to assess the nature and characteristics of this entity in our study:

- Signal intensity on plain MR/heterogeneity on NCCT.
- Filling defects on contrast imaging.

**Table 1:** The scan protocol followed in the study

MR protocol followed in the study:
- T1-weighted TSE (turbo spin-echo) [repetition time TR ms/echo time TE ms (617/7)].
- T2-weighted TSE (turbo spin-echo) [repetition time TR ms/echo time TE ms (6780/90)].
- Short-tau inversion recovery sequence or STIR [repetition time TR ms/echo time TE ms (3200/47)].
- IV gadolinium-based macrocyclic contrast [0.1 mmol/kg at a 2–3 mL/second rate using a pressure jet injector].
- Postcontrast T1W in all three planes and one T1W 3D sequence obtained 7–10 minutes after contrast administration.

CT protocol followed in the study:
- Patient position: supine.
- Topogram: perpendicular to the hard palate.
- Tube voltage and tube current: 120 kV and 130–165 mAs.
- Scan extent: from the chin to above the end of the frontal sinuses.
- Scan direction: caudocranial.
- Scan geometry: field of view – 140 mm; slice thickness: 0.6–1.0 mm; pitch: 0.8; scan time: 6.0 seconds.
- Multiplanar reconstruction: coronal and sagittal planes.
- Contrast parameters: performed after injecting 60–80 mL of intravenous iodinated contrast material at a rate of 2–3 mL/second with a delay of at least 45 seconds after contrast material injection.




**Figs 1A to C:** Rhino-orbital cerebral mucormycosis with right orbital and CS invasion; (A) Axial NCCT image (soft tissue window) shows partial opacification of the right sinonasal region with heterogeneous mucosal thickening containing hyperdense foci extending to the right orbit (blue arrow) and resultant proptosis; (B) Axial NCCT image (bone window) shows erosion (red arrows) of bony septae, lamina papyracea, sinus walls, and sphenoid bone on the right side; (C) Axial CECT image reveals a partial filling defect in the anterior part of the right CS with a bulging convex lateral wall (green arrows). The right superior ophthalmic vein is also prominent (yellow arrow); CECT, contrast-enhanced computed tomography; NCCT, noncontrast computed tomography

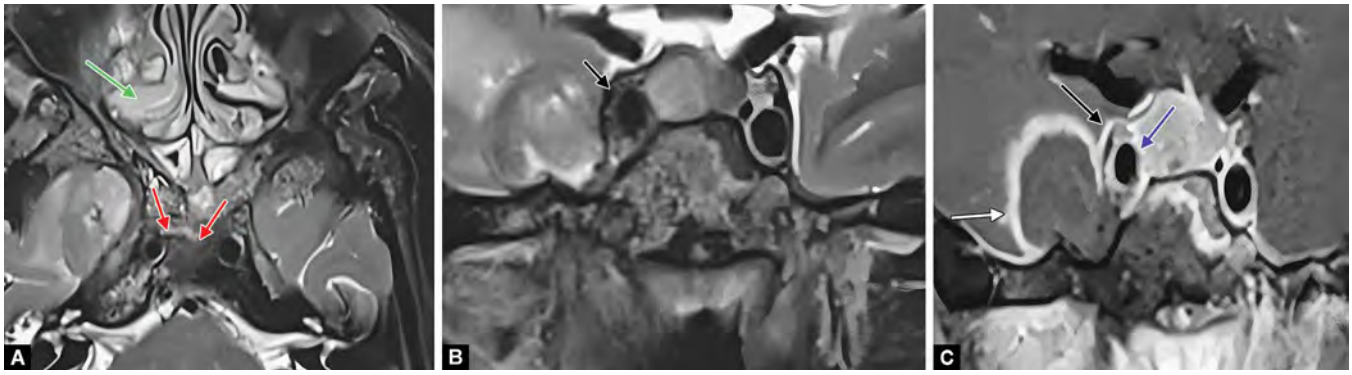
- The lateral wall's convexity or flatness.
- The presence of meningeal thickening and enhancement along the CS.
- The presence of proptosis (eye protrusion).
- Superior ophthalmic vein prominence.
- Orbital apex involvement.
- ICA involvement.

### Statistical Analysis

Statistical analysis utilized the Statistical Package for Social Sciences (SPSS for Windows; Version 28.0.1.0, Armonk, NY: IBM Corp). Descriptive statistics were employed to outline the sociodemographic and clinical characteristics of the study participants. Nominal data, including age, gender, sinus involvement, bony destruction, and orbital and intracranial involvement, were presented as frequencies and percentages, while continuous variables were represented using mean and interquartile range (IQR). Associations between dependent and independent variables were illustrated using Chi-square analysis. Statistical significance was considered for $p < 0.05$.

## Results

We included 106 ROCM patients in our analysis. The mean age of the patients was 52 (range: 9–76; IQR: 41–64) years. Table 2 depicts the distribution of the study participants based on the history of COVID-19 infection as per sociodemographic and clinical characteristics. Most participants with ROCM were COVID-




**Figs 2A to C:** Rhino-orbital cerebral mucormycosis with CS invasion and right temporal lobe abscess: (A) Axial T2W FS image shows heterogeneous mucosal thickening completely occluding bilateral sinonasal regions (green arrow); clival invasion is seen as altered marrow signal (red arrows); (B) Coronal T2W image shows a bulky right CS with a convex lateral wall and altered hypointense signal (black arrowhead), compared to the normal left CS; (C) Coronal postcontrast T1 MR image reveals a hypointense filling defect in the right CS and meningeal thickening along the sinus (black arrow). The flow void of the right ICA is also attenuated and displaced superiorly (blue arrowhead). A peripherally enhancing right temporal lobe abscess is also evident (white arrow); FS, fat-saturated; ICA, internal cerebral artery; MR, magnetic resonance

**Table 2:** Characteristics of ROCM patients based on the status of COVID-19 infection

| | *Present/past h/o COVID-19 infection* | | | |
|---|---|---|---|---|
| | *Negative* | *Positive* | *Total* | *p-value* |
| | *No. of participants (%)* | *No. of participants (%)* | *No. of participants (%)* | |
| Total | 23 (100) | 83 (100) | 106 (100) | |
| Age (completed years) | | | | 0.592 |
| <50 | 8 (34.8) | 34 (41) | 42 (39.6) | |
| >50 | 15 (65.2) | 49 (59) | 64 (60.4) | |
| Sex | | | | 0.877 |
| Female | 6 (26.1) | 23 (27.7) | 29 (27.4) | |
| Male | 17 (73.9) | 60 (72.3) | 77 (72.6) | |
| Comorbidities | | | | 0.086 |
| Nil | 0 (0) | 6 (7.2) | 6 (5.7) | |
| Single | 22 (95.7) | 62 (74.7) | 84 (79.2) | |
| Multiple | 1 (4.3) | 15 (18.1) | 16 (15.1) | |
| Paranasal sinus involvement | | | | |
| Frontal | 12 (52.2) | 50 (60.2) | 62 (58.5) | 0.487 |
| Maxillary | 22 (95.7) | 81 (97.6) | 103 (97.2) | 0.620 |
| Ethmoid | 15 (65.2) | 73 (88) | 88 (83) | 0.010 |
| Sphenoid | 19 (82.6) | 66 (79.5) | 85 (80.2) | 0.742 |
| Palate | 15 (65.2) | 43 (51.8) | 58 (54.7) | 0.253 |
| Nasal cavity | 17 (73.9) | 79 (95.2) | 96 (90.6) | 0.002 |
| CS involvement | | | | |
| Yes | 8 (34.8) | 43 (51.8) | 51 (48.1) | 0.148 |

**Table 3:** Proportion of CS involvement in ROCM as per demographics

| | *CS involvement* | | | |
|---|---|---|---|---|
| | *Present* | *Absent* | *Total* | *p-value* |
| | *No. of participants (%)* | *No. of participants (%)* | *No. of participants (%)* | |
| Total | 51 (48.1) | 55 (51.9) | 106 (100) | |
| Status of COVID-19 infection | | | | 0.148 |
| Negative | 8 (34.8) | 15 (65.2) | 23 (100) | |
| Positive | 43 (51.8) | 40 (48.2) | 83 (100) | |
| Age (completed years) | | | | |
| <50 | 17 (40.5) | 25 (59.5) | 42 (100) | 0.202 |
| >50 | 34 (53.1) | 30 (46.9) | 64 (100) | |
| Sex | | | | |
| Female | 16 (55.2) | 13 (44.8) | 29 (100) | 0.372 |
| Male | 35 (45.5) | 42 (54.5) | 77 (100) | |
| Laterality | | | | |
| Bilateral | 11 (100) | 0 (0) | 11 (100) | 0.000* |
| Unilateral | 40 (100) | 0 (0) | 40 (100) | |
| NA | 0 (0) | 55 (100) | 55 (100) | |
| Pattern of involvement | | | | |
| Diffuse | 36 (100) | 0 (0) | 36 (100) | 0.000* |
| Partial | 15 (100) | 0 (0) | 15 (100) | |
| NA | 0 (0) | 55 (100) | 55 (100) | |

*Indicates statistically significant value

positive, with a higher prevalence in those over 50 years of age and males. However, the distribution lacked statistical significance. More than three-fourths of the participants had at least a single comorbidity, and the proportion was higher in COVID-negative patients.

In overall ROCM patients, the majority showed involvement of the maxillary sinus at 97.2%, followed by the ethmoid sinus at 83% and the sphenoid sinus at 80%. In total, the proportion of CS involvement in ROCM was found to be 48.1%, with a higher distribution in COVID-positive patients at 51.8% compared to the COVID-negative group at 34.8% (Table 3). However, the involvement did not depict statistically significant distribution based on age, history of COVID-19, or gender. Among cases with CS involvement, the distribution of paranasal sinus involvement was as follows: 100% had maxillary sinusitis, 92.2% exhibited ethmoid sinusitis, 86.3% presented with sphenoid sinusitis, and 75.4% displayed frontal sinusitis. The majority of the study participants showed unilateral (78%) and diffuse patterns (71%) of CS involvement.

By considering mortality as the prognostic marker, we further gathered insights into the outcomes associated with detailed qualitative parameters of CS involvement in imaging (Table 4). We observed significant variations in the filling defect on contrast-enhanced scans, diffuse involvement pattern of the CS, convex shape of the lateral wall, and orbital cellulitis in patients and mortality among them as per the bivariate analysis ($p < 0.05$).

Table 5 depicts the outcome at discharge in ROCM patients based on CS involvement and COVID-19 infection status. The outcome of the 106 patients with ROCM enrolled in the study was predominantly favorable, with 96 patients discharged alive from the hospital. Overall, we observed significantly higher mortality in patients with CS involvement compared to those where the CS was not involved. However, a subgroup analysis to observe the additional effect of COVID-19 on mortality depicted nonsignificant results.

## Discussion

The presence of CST or direct infiltration of the CS by mucormycosis indicates a grim prognosis as per existing literature[13,14] and can significantly impact treatment strategies. This complexity may be further compounded when there is a history of or concurrent COVID-19 infection, as COVID-19 has the potential to contribute to CST through its known ability to alter the coagulation profile.[11,15] As a result, managing patients with concurrent mucormycosis and COVID-19 becomes particularly challenging due to the interplay of these factors, which may necessitate tailored and multidisciplinary care approaches.

Our study depicted certain interesting findings. Approximately 50% of patients with ROCM exhibited involvement of the CS. Among the numerous proposed imaging-based qualitative parameters, notable findings were observed in certain parameters, including the presence of filling defects on CEMR, the diffuse involvement pattern of the CS, convex lateral wall, and the presence of orbital cellulitis. Additionally, a higher mortality rate was observed in patients with CS involvement, although it did not reach statistical significance when calculating overall mortality in ROCM.

In our study, the incidence of CS involvement in ROCM was 48.1%. In cases of ROCM associated with COVID-19, the incidence was slightly higher at 51.8%, indicating an elevated rate compared to previous studies.[16,17] A notable involvement of the maxillary sinuses, followed by the ethmoid and sphenoid sinuses, in study participants with CS involvement corresponds to findings from prior research. These findings support the mechanism by which infection spreads from the ethmoid and sphenoid sinus to the CS, involving either contiguous spread or migration through the afferent veins, subsequently reaching the valveless CS and culminating in the development of classic fulminant CST.[18,19] Most participants exhibited unilateral CS involvement, likely due to the unilateral engagement of the corresponding paranasal sinuses on that side.

**Table 4:** Imaging-based qualitative evaluation of CST in ROCM patients

| | *Outcome at discharge* | | | |
|---|---|---|---|---|
| | *Expired* | *Good* | *Total* | *p-value* |
| | *No. of participants (%)* | *No. of participants (%)* | *No. of participants (%)* | |
| Total | 10 (9.4) | 96 (90.6) | 106 (100) | |
| Signal intensity on plain MR/appearance on NCCT | | | | 0.055 |
| Abnormal | 7 (15.9) | 37 (84.1) | 44 (100) | |
| Normal | 3 (4.8) | 59 (95.2) | 62 (100) | |
| Filling defect on CEMR/CECT | | | | 0.002* |
| Not present | 2 (3.6) | 53 (96.4) | 55 (100) | |
| Present | 8 (15.6) | 43 (86) | 51 (100) | |
| Laterality | | | | 0.100 |
| Bilateral | 2 (18.2) | 9 (81.8) | 11 (100) | |
| Unilateral | 6 (15) | 34 (85) | 40 (100) | |
| NA | 2 (3.6) | 53 (96.4) | 55 (100) | |
| Involvement | | | | 0.038* |
| Diffuse | 7 (19.4) | 29 (80.6) | 36 (100) | |
| Partial | 1 (6.7) | 14 (93.3) | 15 (100) | |
| NA | 2 (3.6) | 53 (96.4) | 55 (100) | |
| Lateral wall | | | | 0.014* |
| Convex | 8 (20) | 32 (80) | 40 (100) | |
| Flat | 0 (0) | 11 (100) | 11 (100) | |
| NA | 2 (3.6) | 53 (96.4) | 55 (100) | |
| Meningeal thickening along CS | | | | 0.326 |
| Absent | 4 (6.9) | 54 (93.1) | 58 (100) | |
| Present | 6 (12.5) | 42 (87.5) | 48 (100) | |
| Proptosis | | | | 0.182* |
| Absent | 2 (4.8) | 40 (95.2) | 42 (100) | |
| Present | 8 (12.5) | 56 (87.5) | 64 (100) | |
| Superior ophthalmic vein | | | | 0.080* |
| Involved | 6 (16.2) | 31 (83.8) | 37 (100) | |
| Not involved | 4 (5.8) | 65 (94.2) | 69 (100) | |
| Orbital cellulitis | | | | 0.021 |
| Absent | 2 (7.7) | 24 (92.3) | 26 (100) | |
| Present | 8 (10) | 72 (90) | 80 (100) | |
| Orbital apex involvement | | | | 0.935* |
| Involved | 7 (9.6) | 66 (90.4) | 73 (100) | |
| Not involved | 3 (9.1) | 30 (90.9) | 33 (100) | |
| ICA involvement | | | | |
| Absent | 9 (9.5) | 86 (90.5) | 95 (100) | 0.967 |
| Present | 1 (9.1) | 10 (90.9) | 11 (100) | |
| Intracranial extension | | | | |
| Meningitis | 5 (16.1) | 26 (83.9) | 31 (100) | 0.129 |
| Cerebritis | 3 (13.6) | 19 (86.4) | 22 (100) | 0.449 |
| Cerebral abscess | 2 (20) | 8 (80) | 10 (100) | 0.230 |
| Acute infarct | 2 (25) | 6 (75) | 8 (100) | 0.117 |

*Indicates statistically significant value

Although specific literature on the pattern of CS involvement is limited, various pathologies such as bacterial or fungal infections, tumors originating from the paranasal sinus region, skull base, lymphoma, and inflammatory conditions can affect the CS either partially or diffusely. In our study, a predominant diffuse pattern of involvement aligns with observations from other studies on ROCM.[16]

Previous literature on the pre-COVID era has reported the mortality rate for ROCM ranging from 30 to 90%.[20–25] In our study, the presence of CS involvement did not show a significant influence on patient mortality. Our findings are consistent with some recently published studies focusing on CS involvement during the first and second waves of the COVID-associated mucormycosis pandemic, reporting 25 and 13% mortality rates, respectively.[13,16] Based on our study data and analysis, we want to address a couple of

**Table 5:** Outcome at discharge in ROCM patients based on CS involvement and history of COVID-19 infection

| | | | | *Outcome at discharge* | | |
|---|---|---|---|---|---|---|
| | | | | *Expired* | *Good* | *p-value* |
| | | | | *No. of participants (%)* | *No. of participants (%)* | |
| CS involvement | | | Involved | 8 (15.7) | 43 (84.3) | <0.05 |
| | | | Not-involved | 2 (3.6) | 53 (96.4) | |
| CS involvement | Involved | Status of COVID-19 infection | Negative | 0 | 8 (100) | >0.05 |
| | | | Positive | 8 (18.6) | 35 (81.4) | |
| | Not-involved | Status of COVID-19 infection | Negative | 0 | 15 (100) | |
| | | | Positive | 2 (5) | 38 (95) | >0.05 |

points concerning patient outcomes. First, can the mortality among the ROCM patients be attributed to the CST alone? Second, why do our results differ from those observed in the pre-COVID era?

In this context, the authors align their perspective with existing research, suggesting that adverse outcomes observed in the majority of ROCM patients with CS involvement, leading to fatalities, are likely not solely attributable to CST. Instead, these outcomes may result from multifactorial causes, including the spread of the fungal infection to the brain parenchyma, the presence of concurrent comorbidities, multisystem involvement, and immune alterations associated with COVID-19, as reported in other studies.[16,26,27]

Before the onset of COVID-19, high mortality rates of ROCM patients were documented and primarily linked to the intracranial dissemination of the disease, often resulting from delay in seeking medical attention, diagnosis, and commencement of therapy. The lower mortality rate of ROCM patients, despite the involvement of CS observed in our study, may be attributed to the direct fungal infiltration of the ipsilateral CS, facilitated by the involvement of adjoining paranasal sinus instead of the vascular cause of CST. Fungal infiltration was effectively addressed with antifungal treatment, paranasal sinus debridement, and orbital exenteration.

Furthermore, increased patient awareness through mass media during the mucormycosis outbreak, coupled with a high index of suspicion, facilitated the early diagnosis of ROCM and CS involvement during the COVID-19 pandemic. Also, the lower number of patients presenting with significant CST on imaging may be attributed to the fact that they were already on anticoagulants due to their positive COVID status. Collectively, all these factors played a crucial role in decreasing patient mortality.

When characterizing a CST, we faced challenges in definitively attributing the thrombus to either a vascular cause, nonvascular cause, or direct fungal infiltration based solely on imaging findings. Both scenarios can manifest as a filling defect. However, the presence of mucosal thickening with hyperdensity on NCCT, T2 hypointensity on MR, and postcontrast heterogenous mucosal enhancement in the paranasal sinuses coupled with bony erosion in the sinus walls may indicate fungal sinusitis directly affecting the CS.[28]

More studies with larger sample sizes should be conducted to explore this association further, differentiate vascular vs nonvascular causes of CST on imaging, and accurately assess the likelihood of mortality in such patients. Collating data from multiple sources could enhance the statistical inferences drawn, contributing to a more robust understanding of predicting the prognosis in these patients.

Lastly, with the hypothesis of prognosticating the disease based on qualitative parameters of CST, we emphasized that the presence of filling defects on contrast-enhanced scans, the diffuse pattern of CS involvement, convex lateral wall, and the presence of orbital cellulitis could indicate the severity of the disease when observed. These observations were consistent with the findings reported in the study by Bhatia et al.[29]

Surgical intrusion into the CS is challenging and generally not recommended. In cases where sphenoid or ethmoid fungal sinusitis is confirmed through CT/MRI, it is advisable to perform surgical drainage of these infected sinus pockets promptly. Combining antifungals and endonasal sinus surgery is often considered the optimal treatment strategy for CST caused by mucormycosis.

Our study has certain strengths that should be acknowledged. The major strength of our study lies in its design, with a specific focus on CS and its relation to COVID-19. While the first three peaks of COVID-19 may have concluded, the persisting risks associated with it and the emergence of new variants of COVID-19 at the end of 2023[30] underscore the necessity for radiologists and clinicians to be aware of disease course and imaging findings and remain prepared for any potential escalation, akin to the challenges posed by COVID-19 and ROCM.

Our study has some limitations. Being a single-center study, the study lacks generalizability, and findings must be tested in similar settings. Regarding CST evaluation on imaging, including quantitative evaluation could have provided additional information, but it could not be done in the concurrent COVID-19 and mucormycosis pandemic era. The mortality of patients was recorded without incorporating long-term follow-ups into consideration, which we acknowledge and recognize as a factor potentially influencing the results. Lastly, a smaller sample size limited us from calculating the hazard ratio depicting the effect of COVID-19 infection and sinus involvement on mortality.

## Conclusion

The present study attempts to provide valuable insights into the true incidence, relation with COVID-19 infection, and detailed radiological assessment of CS involvement in patients with ROCM. We conclude that CS involvement in ROCM may not significantly impact patient mortality in both COVID-19-positive and negative patients. However, qualitative radiological parameters may serve as indicators of poor prognosis. Further, more research studies are required to elucidate the pathogenesis and imaging features of CST in mucormycosis, both among COVID-19 and non-COVID-19 patients.

### Clinical Significance

The presence of CS involvement in patients with ROCM does not significantly impact mortality, regardless of their COVID-19 status,

suggesting that other factors may play a more significant role in patient outcomes.

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ORIGINAL ARTICLE

# Preventing Premature Coronary Artery Disease: The Synergistic Role of Biomarker Screening and Physical Activity

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## Abstract

**Objective:** With the increasing prevalence of premature coronary artery disease (CAD), early detection and risk stratification are crucial. While physical inactivity is linked to CAD risk, its impact in the early stages remains underexplored. This study aims to identify biomarkers for early CAD diagnosis and their association with physical activity (PA), ultimately reducing morbidity and mortality rates.

**Methods:** This case–control study enrolled 300 subjects aged 18–45 years. They were subdivided into three categories. Additionally, the 200 subjects in groups I and II were classified into active, moderate, and sedentary categories based on World Health Organization (WHO) criteria. Serum levels of high-sensitivity C-reactive protein (hs-CRP), lipoprotein (a) [Lp(a)], apolipoprotein A1 (Apo-A1), apolipoprotein B100 (Apo-B100), and oxidized low-density lipoprotein (oxidized LDL) were analyzed, whereas non–high-density lipoprotein cholesterol (non-HDL-C) was calculated. The comparison of these biochemical parameters was done in terms of mean ± standard error of the mean (SEM) and area under the receiver operating characteristic curve (AUROC), and their significance with PA was determined using one-way analysis of variance (ANOVA) and Bonferroni test.

**Results:** Significant differences in hs-CRP, Apo-B100, Lp(a), non-HDL-C, and oxidized LDL were observed across groups. AUROC analysis confirmed their strong association with CAD risk. Additionally, the findings highlight that an active lifestyle is linked to a more favorable biochemical profile, which may help mitigate the risk of premature CAD.

**Conclusion:** The study suggests including hs-CRP, Apo-B, Lp(a), non-HDL-C, and oxidized LDL in routine screening for early CAD detection. Despite their proven effectiveness, these biomarkers are not widely used. Therefore, integrating early biomarker screening with lifestyle modifications can enhance risk assessment and improve treatment outcomes.


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## Introduction

Coronary artery disease (CAD) remains a leading cause in global rates of illness and death. The early onset of CAD, referred to as premature CAD, presents significant challenges due to its aggressive nature and the need for early intervention.[1] Emerging evidence suggests that the incidence of CAD in Indians is 50–400% more than in other ethnic groups.[2–4] This vulnerability to premature CAD is primarily driven by rapid socioeconomic and cultural transitions. Over the past three decades, economic liberalization has led to significant lifestyle and dietary changes with decreased physical activity (PA) and increased mental stress.[5] Regular PA has been shown to substantially lower the risk of cardiovascular mortality rates, while decreased PA is linked with a higher risk of morbidity. Additionally, a recent science advisory from the American Heart Association highlights the detrimental relationship between sedentary behavior and cardiovascular mortality.[6]

The standard approach of assessing CAD risk primarily relies on the standard lipid profile panel, which includes total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG). While this panel provides valuable insights, recent studies indicate that it may not be sufficient for accurate prediction, especially in young Indians at risk of premature CAD. Given the growing burden of premature CAD in this population, it is crucial to move beyond conventional lipid parameters in cardiovascular risk assessment. A more comprehensive cardiac screening panel, integrating novel biomarkers, could facilitate earlier detection of CAD and offer a deeper understanding of other contributing risk factors, such as sedentary behavior. This shift in approach would enhance prevention and intervention efforts, addressing the urgent need for more effective and personalized strategies to combat CAD. Therefore, this study seeks to identify biomarkers for the early diagnosis of CAD and explore their association with PA. The goal is to enhance screening and prevention strategies, mitigate the morbidity and mortality associated with CAD, and foster greater awareness of the role of lifestyle choices in cardiovascular health.

## Methods

This case–control study took place at a tertiary healthcare facility in Northern India, enrolling 300 subjects aged 18–45 years. Premature CAD was described as the occurrence of CAD before the age of 55 in women and 45 in men.[7] Patients with diabetes mellitus, hypertension, noncardiac inflammatory conditions (such as rheumatoid arthritis or osteoarthritis), and those on statin therapy were excluded from the study.

The subjects were subdivided into three categories:

- Group I: Angiographically proven cases of CAD ($n$ = 100); subjects having ≥50% diameter stenosis in at least one epicardial coronary artery were included in the study.
- Group II: Subjects who had one or two risk factors associated with CAD were recruited in group II category ($n$ = 100). The risk factors included positive family history and smoking.
- Group III: Noncardiac controls ($n$ = 100); subjects without any history or risk factors associated with CAD were recruited in group III category. The selection of the noncardiac controls was based on randomization.

Additionally, the 200 subjects in groups I and II were further categorized based on their PA levels—active, moderate, and sedentary—according to the criteria established by the World Health Organization (WHO).[8]

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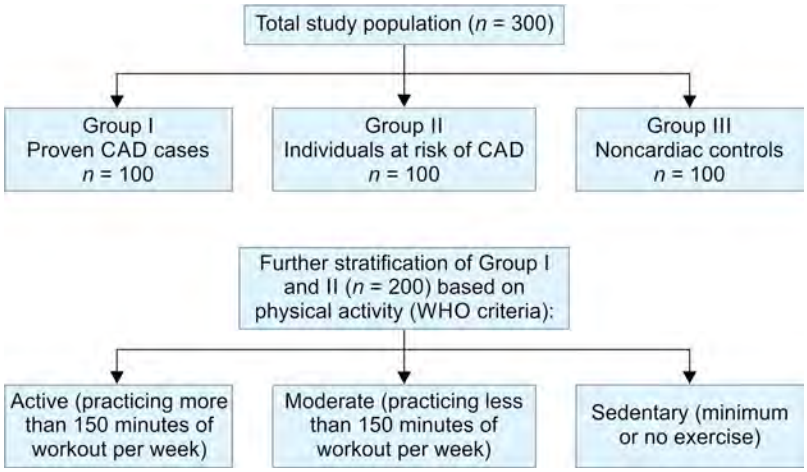


The Institutional Ethics Committee approved the study, and all participants provided informed consent. Blood samples (5 mL) were collected in plain vials, and serum was separated following standard protocols. Sample collection and preservation adhered to the STROBE-ME guidelines. The biochemical parameters analyzed in the study included high-sensitivity C-reactive protein (hs-CRP), Apo-B, lipoprotein (a) [Lp(a)], non–high-density lipoprotein cholesterol (non-HDL-C), Apo-A1, and oxidized LDL, in addition to the conventional lipid profile parameters.

After collecting blood samples, serum TG, HDL-C, and TC were assessed using the Siemens Dimensions RxL analyzer. LDL and very-low-density lipoprotein (VLDL) levels were determined using the Friedewald equation, whereas non-HDL-C was derived from TC to HDL-C. For the analysis of inflammatory and lipoprotein markers, hs-CRP was estimated using a latex-enhanced turbidimetric immunoassay, while Apo-B, Apo-A1, and Lp(a) were analyzed by the immunoturbidimetry method, and oxidized LDL was estimated using a sandwich enzyme-linked immunosorbent assay (ELISA).

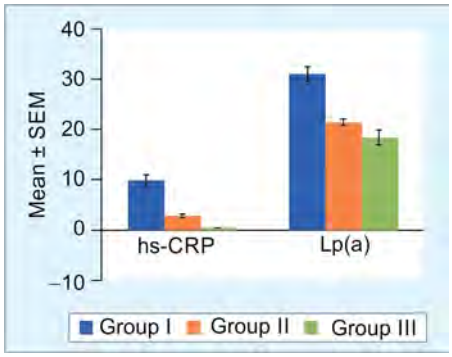


**Fig. 1:** Mean ± SEM level of hs-CRP and Lp(a)

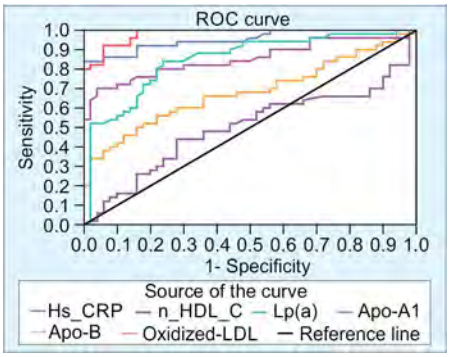


**Fig. 3:** ROC curve for all the parameters

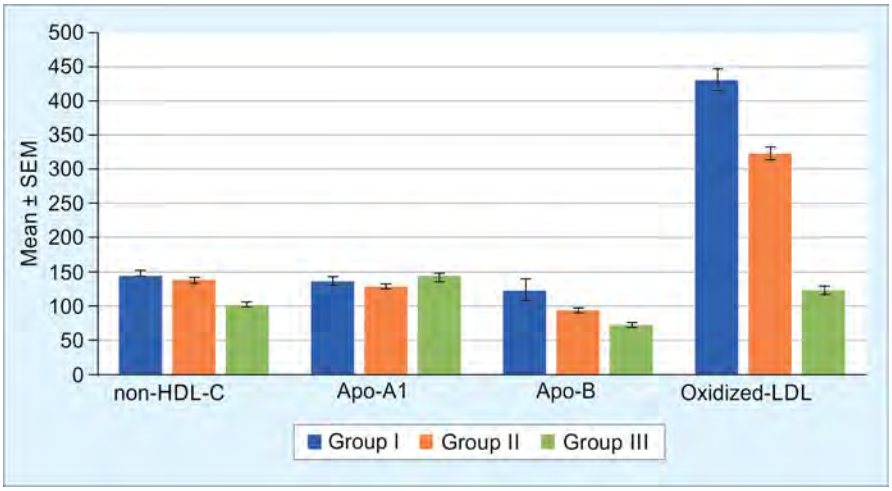


**Fig. 2:** Mean ± SEM level of non-HDL-C, Apo-A1, Apo-B, and oxidized LDL

## Statistical Analysis

Biochemical parameters were compared in terms of mean ± standard error of the mean (SEM) level and area under the receiver operating characteristic curve (AUROC) analysis. The association between biochemical parameters and PA was evaluated using one-way analysis of variance (ANOVA) followed by a *post hoc* analysis (Bonferroni) to identify the mean differences between the groups (active, moderate, and sedentary) for each biochemical parameter. All analyses were done by SPSS version 24. A *p*-value below 0.05 was interpreted as statistically significant.

# Results

Serum hs-CRP, Lp(a), apolipoprotein A1 (Apo-A1), Apo-B, and oxidized LDL were measured, while non-HDL-C was calculated for all the subjects. The findings revealed that hs-CRP was markedly elevated in group I but decreased substantially in group III. Similarly, Lp(a), non-HDL-C, Apo-B, and oxidized LDL exhibited the highest values in group I and progressively decreased across groups II and III, whereas the results were nonsignificant for Apo-A1. Figures 1 and 2 show the mean ± SEM levels of hs-CRP and Lp(a), and non-HDL-C, Apo-A1, Apo-B, and oxidized LDL, respectively.

The predictive values of hs-CRP, non-HDL-C, Lp(a), Apo-A1, Apo-B, and oxidized LDL were compared using ROC curve analysis. The AUROC for oxidized LDL was found to be 0.982 (95% confidence interval: 0.963, 1.000), followed by hs-CRP, 0.952 (95% confidence interval: 0.912, 0.992), followed by non-HDL-C, 0.852 (95% confidence interval: 0.773, 0.931), followed by Lp(a), 0.847 (95% confidence interval: 0.769, 0.924), followed by Apo-B, 0.680 (95% confidence interval: 0.574, 0.787), whereas Apo-A1 had the least AUROC of 0.498 (95% confidence interval: 0.381, 0.614) (Fig. 3).

The 200 subjects from groups I and II were further categorized based on their PA levels, with results showing that more than half of the participants exhibited sedentary behavior, 38% were moderately active, and only 9% were physically active (Fig. 4).

The one-way ANOVA analysis of biochemical parameters in relation to PA demonstrated a significant association with hs-CRP, Lp(a), non-HDL-C, Apo-B, and oxidized LDL levels, while results were nonsignificant for Apo-A1 (Table 1).

Additionally, the Bonferroni test was conducted, revealing a significant mean

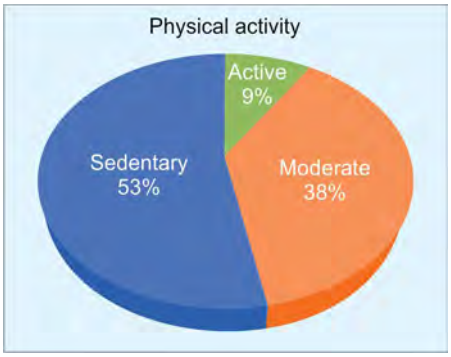


**Fig. 4:** Distribution of 200 subjects based on PA

difference among the active, moderate, and sedentary groups only with non-HDL-C and oxidized LDL-C. For hs-CRP, Lp(a), and Apo-B, the mean difference was significant between the active and both the moderate and sedentary groups, whereas no notable difference was detected between the moderate and sedentary groups. Regarding Apo-A1, no statistically significant differences were detected across the groups (Table 2).

Figure 5 highlights the relationship between physical activity levels and biochemical parameters.

## Discussion

The rising prevalence of premature CAD among young Indians has become a growing concern as affluence and urbanization have led to significant lifestyle and dietary changes, along with a decline in PA, which has exacerbated this public health challenge, underscoring the urgent need for preventive measures and awareness.[9,10] Numerous biomarkers have been identified to assess cardiovascular risk, yet conventional risk prediction algorithms still fall short of providing reliable and accurate

**Table 1:** ANOVA analysis of biochemical parameters in relation to PA

| | | *Sum of squares* | *Df* | *Mean square* | *F* | *Significance* |
|---|---|---|---|---|---|---|
| hs-CRP | Between groups | 1661.18 | 2 | 830.591 | 15.05 | <0.001*** |
| | Within groups | 16390.541 | 297 | 55.187 | | |
| | Total | 18051.722 | 299 | | | |
| Non-HDL-C | Between groups | 88044.28 | 2 | 44022.14 | 42.07 | <0.001*** |
| | Within groups | 310750.29 | 297 | 1046.29 | | |
| | Total | 398794.58 | 299 | | | |
| Lp(a) | Between groups | 2035.49 | 2 | 1017.74 | 5.5 | <0.01** |
| | Within groups | 54955.07 | 297 | 185.03 | | |
| | Total | 56990.56 | 299 | | | |
| Apo-A1 | Between groups | 2036.05 | 2 | 1018.02 | 0.491 | 0.612 |
| | Within groups | 615662.57 | 297 | 2072.93 | | |
| | Total | 617698.62 | 299 | | | |
| Apo-B | Between groups | 76187.59 | 2 | 38093.79 | 4.161 | <0.05* |
| | Within groups | 2718791.42 | 297 | 9154.18 | | |
| | Total | 2794979.01 | 299 | | | |
| Oxidized LDL | Between groups | 2529770.63 | 2 | 1264885.31 | 63.346 | <0.001*** |
| | Within groups | 5930501.17 | 297 | 19968.017 | | |
| | Total | 8460271.80 | 299 | | | |

Levels of statistical significance are denoted as follows: *$p < 0.05$ (significant), **$p < 0.01$ (highly significant), ***$p < 0.001$ (very highly significant)

**Table 2:** Bonferroni test of biochemical test in relation to PA

| *Dependent variable* | *(I) Is* | *(J) Is* | *Mean difference (I–J)* | *Std. error* | *p-value* | *95% confidence interval* | |
|---|---|---|---|---|---|---|---|
| | | | | | | *Lower bound* | *Upper bound* |
| hs-CRP | 1 | 2 | −4.494 | 1.096 | <0.001 | −7.132 | −1.856 |
| | | 3 | −5.892 | 1.100 | <0.001 | −8.539 | −3.244 |
| | 2 | 3 | −1.398 | 0.997 | 0.486 (NS) | −3.799 | 1.003 |
| Non-HDL-C | 1 | 2 | −27.846 | 4.770 | <0.001 | −39.331 | −16.360 |
| | | 3 | −43.838 | 4.788 | <0.001 | −55.366 | −32.310 |
| | 2 | 3 | −15.992 | 4.342 | <0.001 | −26.447 | −5.538 |
| Lp(a) | 1 | 2 | −5.752 | 2.006 | <0.05 | −10.581 | −0.922 |
| | | 3 | −6.108 | 2.014 | <0.05 | −10.956 | −1.260 |
| | 2 | 3 | −0.357 | 1.826 | 1 | −4.753 | 4.040 |
| Apo-A1 | 1 | 2 | −0.564 | 6.715 | 1 | −16.730 | 15.602 |
| | | 3 | −5.719 | 6.740 | 1 | −21.945 | 10.507 |
| | 2 | 3 | −5.155 | 6.112 | 1 | −19.870 | 9.560 |
| Apo-B | 1 | 2 | −33.984 | 14.110 | 0.05 | −67.956 | −0.013 |
| | | 3 | −38.236 | 14.163 | <0.05 | −72.335 | −4.138 |
| | 2 | 3 | −4.252 | 12.843 | 1 | −35.174 | 26.670 |
| Oxidized LDL | 1 | 2 | −115.978 | 20.840 | <0.001 | −166.152 | −65.805 |
| | | 3 | −234.002 | 20.917 | <0.001 | −284.362 | −183.641 |
| | 2 | 3 | −118.023 | 18.969 | <0.001 | −163.693 | −72.354 |

Note: 1 = active, 2 = moderate, and 3 = sedentary; The mean difference was considered significant at the 0.05 level

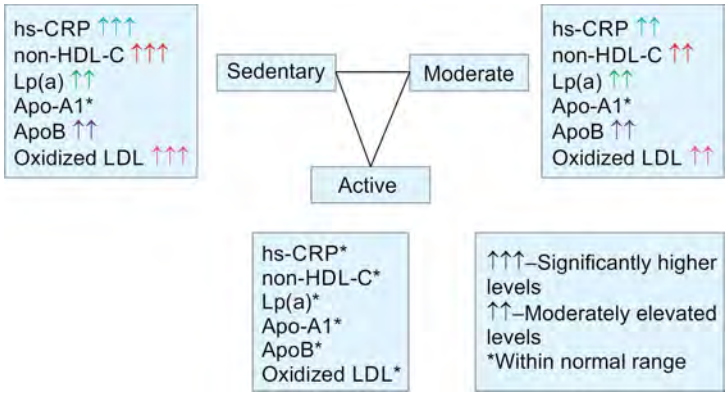


**Fig. 5:** The relationship between PA levels and biochemical parameters

markers for CAD.[11] Therefore, this study was designed to evaluate biomarkers for early risk prediction of premature CAD and their potential correlation with PA.

The mean ± SEM level of hs-CRP, a key inflammatory marker, was significantly elevated in group I, moderately elevated in group II, and within the normal range in group III (Fig. 1). The identified cutoff value for hs-CRP was 0.795 mg/L. The results are consistent with findings from studies by Gupta et al.[12] and Lee et al.,[13] where a significant difference in hs-CRP levels was observed between cardiac and noncardiac individuals. Similarly, Mokhtar et al.,[14] in their study of 45 subjects, reported findings comparable to those of the present study. Extensive research, including observational studies and clinical trials, has also highlighted the role of elevated hs-CRP levels in the development of atherosclerotic vascular disease.[15–18]

Similarly, the mean ± SEM level of non-HDL-C was significantly higher in group I, moderately elevated in group II, and within the normal range in group III (Fig. 2). These findings align with those reported by Li et al.,[19] Kathariya et al.,[20] and Cui et al.[21] The cutoff value for non-HDL-C in this study was found to be 113.65 mg/dL. A large-scale study spanning 44 cohorts across multiple countries, involving 5,24,444 individuals, utilized multivariate analysis to establish a significant relation between levels of non-HDL-C and long-term risk of CVDs.[22] Furthermore, the Lipid Association of India recognizes non-HDL-C as a coprimary target for assessing CAD risk.[23]

Likewise, the mean ± SEM level of oxidized LDL was found to be elevated in group I as compared to groups II and III, and its cutoff value was found to be 224 ng/mL in this study (Fig. 2). Oxidized LDL plays a crucial role in the atherosclerotic process, with its proinflammatory and proatherogenic properties contributing substantially to the development of cardiovascular disease.[24] Atherogenicity of oxidized LDL is due to alteration in its biological properties due to oxidative modification of LDL, resulting in increased chemotaxis, more retention in subendothelial cells, macrophages, cytokine production from smooth muscle cells, and alteration of growth factors and endothelial cells.[25] Numerous studies have identified oxidized LDL as a valuable lipid marker and risk factor for atherosclerotic cardiovascular disease.[26–28] The study carried out by Augsburg revealed notably elevated levels of oxidized LDL in CAD patients compared to the controls. Zhao et al.[29] observed elevated oxidized LDL levels in individuals with CAD compared to controls, which aligns with our study's results. Similarly, our findings are consistent with studies by Koenig et al.[30] and Bansal et al.[31] who also compared the oxidized LDL in terms of mean ± SD levels and found increased oxidized LDL levels in CAD patients as compared to the noncardiac controls.

Regarding Lp(a) and Apo-B, the mean ± SEM level was significantly higher in group I, moderately elevated in group II, and within the normal range in group III, as depicted in Figures 1 and 2, respectively. These findings are consistent with the studies conducted by Leistner et al.,[32] Tsimikas,[33] Nathir et al.,[34] and Walldius and Jungner.[35]

Recent meta-analyses link sedentary PA to higher CAD mortality.[36] To assess its impact, this study evaluated PA using a standard questionnaire.[37] Results showed that 53% subjects had sedentary PA, while 38% had moderate PA, suggesting its role in premature CAD.[38] The *post hoc* analysis revealed that individuals with an active PA had significantly lower hs-CRP levels than those with moderate or sedentary activity, suggesting that increased PA is associated with reduced inflammation, which is in accordance with the study conducted by Koeder et al.[39] Similarly, active individuals exhibited significantly lower non-HDL-C levels than those in the moderate and sedentary groups, further highlighting the cardiovascular benefits of increased PA. Likewise, oxidized LDL was significantly lower in active individuals compared to both moderate and sedentary groups. Additionally, moderate activity was associated with significantly lower oxidized LDL levels than a sedentary activity, emphasizing the role of PA in reducing oxidative stress and cardiovascular damage.

In the context of Lp(a), individuals with an active PA exhibited significantly lower Lp(a) levels compared to those with moderate or sedentary activity. This observation indicates that increased PA is linked to lower Lp(a) levels. Interestingly, no significant difference was observed between individuals with moderate PA and those leading a sedentary PA, indicating that merely moderate activity does not confer the same benefit in terms of Lp(a) reduction. Therefore, maintaining active PA is essential for achieving lower Lp(a) levels, rather than simply engaging in moderate PA. Likewise, Apo-B levels were notably reduced in physically active individuals relative to those in moderate and sedentary groups, while no notable difference was observed between the moderate and sedentary groups, indicating a protective effect of PA against elevated Apo-B levels. Therefore, addressing lifestyle factors is crucial for CAD prevention,[40] emphasizing the need to replace sedentary PA with an active PA.

### Limitation of the Study

The study was limited to a relatively small sample size from a single center. Therefore, extensive studies with larger and more diverse populations are necessary to enhance understanding and validate these findings.

## Conclusion

A comprehensive cardiac screening panel, including hs-CRP, Apo-B, Lp(a), non-HDL-C, and oxidized LDL, could enable earlier detection of CAD and significantly benefit public health. Moving beyond the traditional lipid profile, which still leaves residual risk despite achieving desired LDL levels, is crucial to address the growing global burden of premature CAD. Timely detection and accurate diagnosis through the inclusion of additional biomarkers would allow for disease prevention at an early stage, even before clinical symptoms appear. Incorporating this expanded panel into leading institutes and laboratories could notably reduce the CAD burden.

The study also highlights the positive relationship between an active lifestyle and improved biochemical markers, offering enhanced cardiovascular protection and lowering the risk of premature CAD. These

findings emphasize the need to combine early biomarker screening with lifestyle modifications to improve risk assessment and clinical outcomes.

## Acknowledgment

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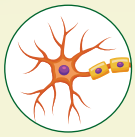

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ORIGINAL ARTICLE

# Postural Instability in Idiopathic Parkinson's Disease: Determination of VEP, BAER, and SSEP Cutoff Values for an Early Screening of Fall

Joydeep Mukherjee[1], Manoj K Roy[2], Jasodhara Chaudhuri[3], Amar K Misra[4], Kartik C Ghosh[5], Mrinal K Roy[6*]

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## Abstract

**Backgrounds and aims:** Idiopathic Parkinson's disease (IPD) patients had progressively increased slowness, rest tremors, rigidity, and postural instability (PI). Postural stability depends on sensory inputs from visual, auditory, and somatosensory modalities. We tried to find important cutoff values of visual evoked potential (VEP), brainstem auditory evoked response (BAER), and short-latency somatosensory evoked potentials (SSEP) for determining postural stability in IPD patients.

**Methodology:** About 50 IPD patients were recruited in a cross-sectional observational study. A pull test was used to determine postural stability. Patients were subgrouped into tremor dominant (TD variant) ($n$ = 37) and PI and gait disorder (PIGD) ($n$ = 13). We generated receiver operating characteristic (ROC) curves to classify patients into posturally stable and unstable and measured VEP, BAER, and SSEP cutoff values. The area under the curve (AUC) >0.8 was taken as significant.

**Results:** Significant VEP N75, P100, and N145 cutoff values were noted bilaterally in IPD and its subgroups (TD and PIGD). Except for wave I, the latency of all other BAER waves showed significant cutoff values bilaterally in IPD and subgroups (TD and PIGD). Most BAER cutoff values in the IPD and TD subgroups reached 100% specificity. No significant SSEP values were noted.

**Discussion:** Many significant VEP and BAER parameters with good sensitivity and specificity would guide clinicians in predicting PI and falls in IPD. The TD had lower BAER latency cutoff values than the PIGD. The postural stability of the TD subgroup was more dependent on the vestibular sensory input than that of the PIGD subgroup. Less vestibular compensatory support in PIGD led to a more severe phenotype than in TD.

**Conclusion:** We found many evoked potential significant cutoff values determining postural stability in IPD and its subgroups (TD and PIGD). Lesser vestibular compensatory support in PIGD led to a more severe phenotype than in TD.

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## Introduction

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disease of the brain. Patients have progressively increased slowness, rest tremors, rigidity, and postural instability (PI), apart from many other manifestations.[1] As the disease progresses, patients become more prone to recurrent falls, which lead to recurrent hospital admission, increased morbidity, and mortality. PI is a serious feature of IPD. Many factors are involved in PI, including loss of postural reflexes, medication side effects, freezing, festination, orthostatic hypotension, fear of falls, age-related reduced peripheral sensation, and leg muscle weakness.[2] If we can diagnose and treat PI at the earliest, we can give them a healthy, long life.

At present, the diagnosis of PI is subjective. Various scales are validated for the diagnosis of PI and the progression of Parkinson's disease.[3,4] A "pull test" is a simple test where the patient is quickly pulled forward or backward by the shoulder. If the patient takes more than two steps to recover balance or no postural response occurs, it is considered "positive" for PI.[1] Hoehn and Yahr's scale was published in 1967 by Hoehn and Yahr.[5] It had stages I to V as PI worsened and Parkinson's disease progressed. The Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was a modification of the original UPDRS score, which showed the motor and nonmotor symptom severity of IPD.[6]

Postural stability also depends on many factors, including the motor and sensory systems. Many articles discussed the role of visual evoked potential (VEP),[7] brainstem auditory evoked response (BAER),[7,8] and short-latency somatosensory evoked potentials (SSEP)[7,9–12] on postural stability. The studies showed that patients with Parkinson's disease had significant abnormalities in the evoked potentials compared to healthy subjects. Studies also pointed out a correlation between evoked potential changes and the severity of the disease.[12] As the role of various sensory inputs was revealed to be important in the postural stability of Parkinson's disease, we tried to find out important cutoff values of VEP, BAER, and SSEP determining the postural stability in Parkinson's disease patients.

## Methodology

### Study Subjects

This is a cross-sectional, observational study conducted in the inpatient and outpatient clinics of the Department of Neurology, Teaching Hospital, from September 2017 to August 2020. We enrolled 50 IPD patients of both genders and various age-groups. IPD patients were subgrouped into postural instability and gait disorder (PIGD) variant and tremor dominant (TD) variant according to their clinical phenotype. Detailed neurological examinations were performed. Informed consent was obtained before recruiting them. The Institutional Ethics Committee approved the study (NMC/958).

The inclusion criteria of this study are as follows:

- All IPD cases were diagnosed in adherence with the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.[13]

The exclusion criteria of this study are as follows:

- Cases of secondary Parkinsonism.

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- Patients with previously known ophthalmological disorders (uncorrected refractive errors, glaucoma, retinopathies, etc.) and hearing difficulties after thorough evaluation by specialist doctors were excluded.
- Patients having abnormalities in pain, touch, and joint position sense.
- Patients having motor weakness in the lower limbs.
- Patients with orthostatic hypotension and vertigo.

### Study Design

This is a cross-sectional, observational study. The pull test was used to detect PI. IPD patients and the subgroups (PIGD and TD) were divided into patients with PI and those without. Then, we analyzed the evoked potential values of the two groups.

### Parameters for Evaluation

Evoked potentials were recorded using Nihon Kohden NeuroPack II Plus.

#### *Visual Evoked Potentials*

The recording was made for the checkerboard-patterned reversal VEP (CBPR VEP). VEP was recorded from each eye separately with surface electrodes, with the reference electrode placed on Fz, the active electrode on Oz, and other electrodes on O1 and O2 as per the International 10–20 system. The analysis time was 500 ms, and 256 sweeps were averaged. N75 latency, P100 latency, and P100 amplitude were recorded. P100 latency is the interval between the stimulus and the peak of the major positive component.

#### *Brainstem Auditory Evoked Potential*

Auditory evoked responses were obtained by brief acoustic click stimuli delivering monophasic square pulses of 100 ms duration to headphones with a monoaural stimulus intensity of 60–65 dB HL. As many patients were experiencing subclinical hearing loss in this sample, we resorted to gradually increasing the decibel if a BAER waveform was not obtained. The contralateral ear was masked with continuous white noise at 30–40 dB below the BAER stimulus. Recording electrodes were placed at the vertex (location Cz of the International 10–20 system) and the mastoids (Mi and Mc). The amplitude and latency of waves I to V were recorded.

#### *Somatosensory Evoked Potential*

The anode was placed just proximal to the palmar crease, the cathode was placed between the tendons of the palmaris longus muscle, 3 cm proximal to the anode, and the median nerve was stimulated. The details of the SSEP measurements were already discussed in our other article on the evoked potentials.[12]

### Statistical Analysis

We performed standard statistical methods using IBM SPSS software version 26. The Kolmogorov–Smirnov test was done for the normality of data distribution. All VEP, BAER, and SSEP parameters were classified according to postural stability. Receiver operating characteristic (ROC) curves showed significant cutoff values to determine the PI in IPD and subgroups. The area under the curve (AUC) >0.8 was taken as a good result to classify them into patients with or without PI.

## Results

### Demography and Descriptive Parameters

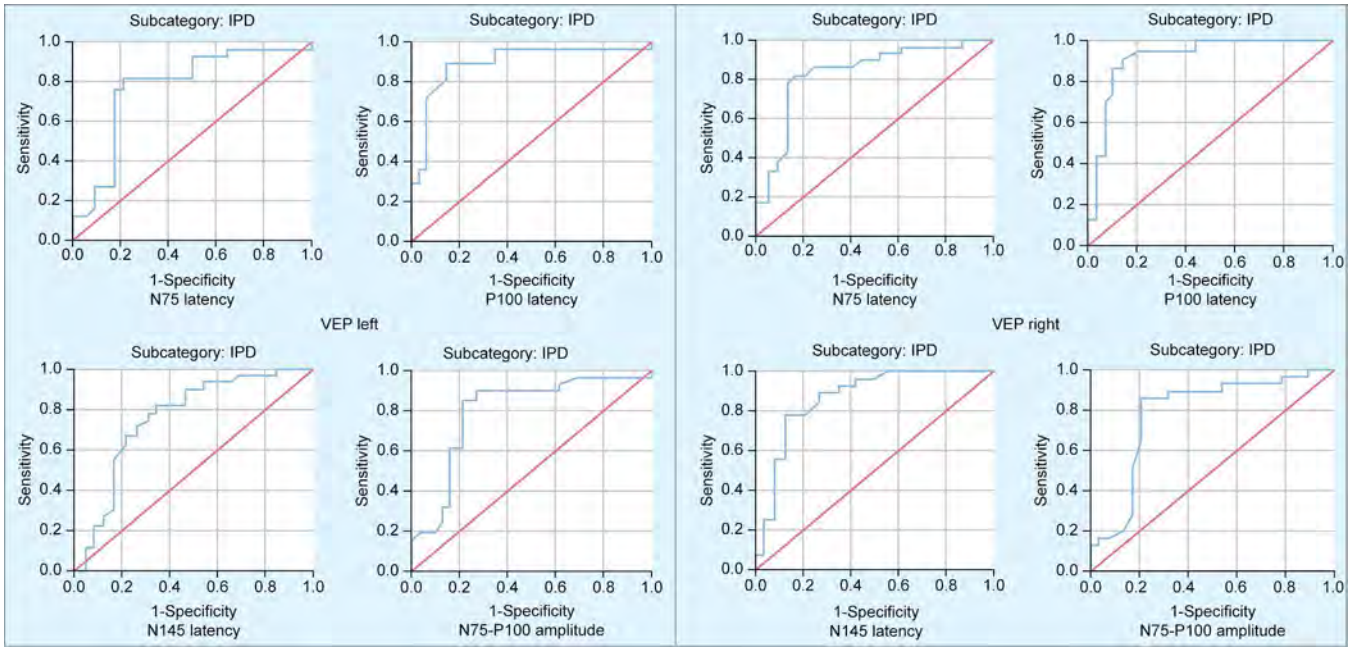
Idiopathic Parkinson's disease patients had an age at onset of 44–78 years (mean 57.4 years), a duration of illness of 1–6.5 years (mean 3 years), and an age at presentation of 47–80 years (60.4 years), which was mostly similar in its TD variety. Compared to the TD group, the PIGD subtype had a later age at onset (56.9 vs 58.9 years) and age at presentation (59.8 vs 61.9 years). IPD patients had a male preponderance (male = 58%). The PIGD subgroup had a female preponderance (male = 46.2%) in contrast to the TD group (male = 62.2%).

### VEP, BAER, and SSEP Parameters (Figs 1,2 and 3)

The minimum, maximum, mean, and standard deviation values of the VEP, BAER, and SSEP parameters of the IPD patients and their subgroups are mentioned in Table 1.

#### *VEP*

Significant N75, P100, and N145 cutoff values on the right side were 69.95 ms (AUC = 0.833), 111.65 ms (AUC = 0.91), and 152.1 ms (AUC = 0.858); those on the left side, P100, were 111.6 ms (AUC = 0.88) in IPD patients. Above those values, the patients became posturally unstable. In the TD patients, significant N75, P100, and N145 cutoff values on the right side

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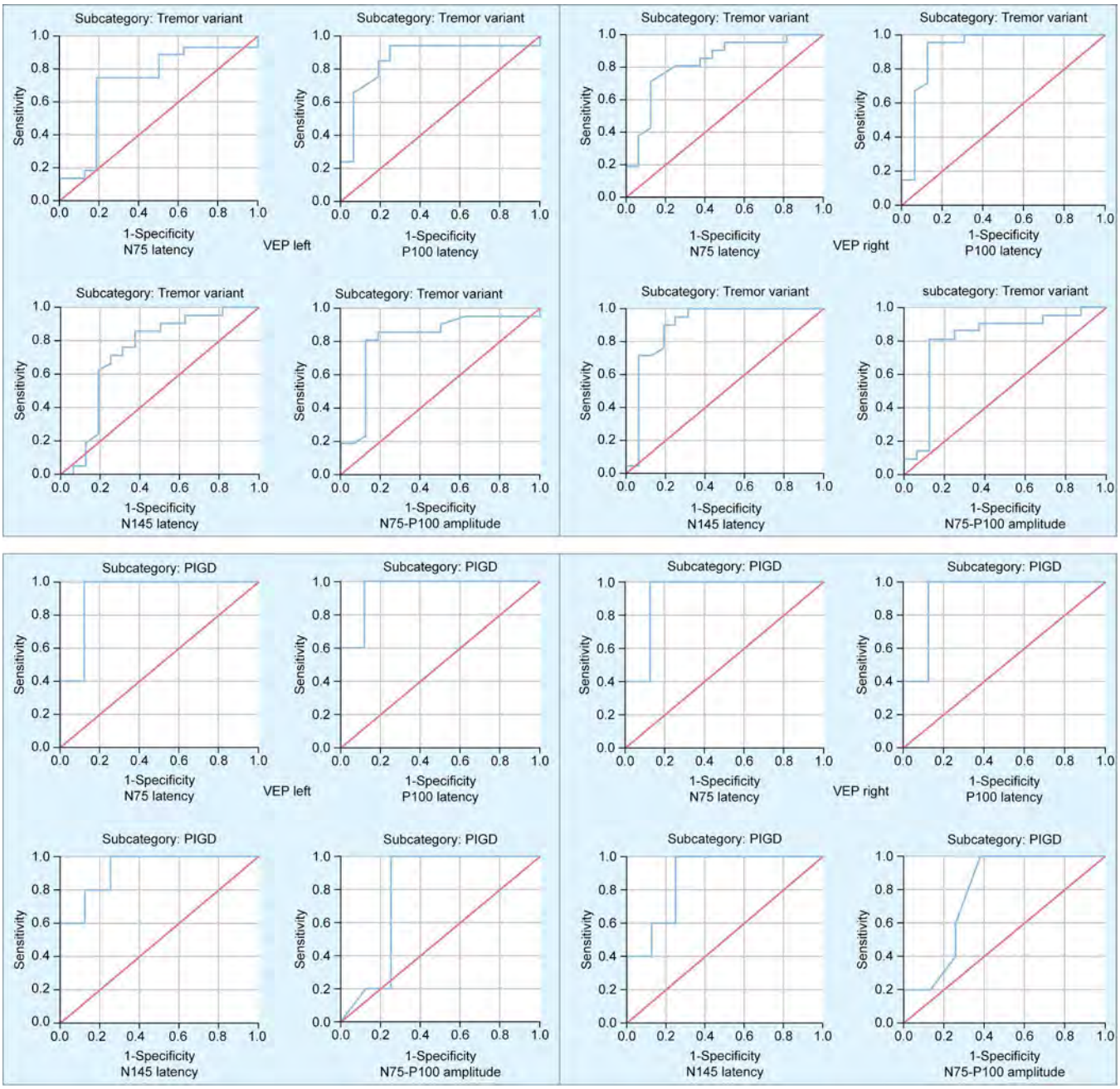



**Fig. 1:** ROC curves showing VEP in IPD and its subgroups—TD and PIGD variant

were 69.95 ms (AUC = 0.829), 113.7 ms (AUC = 0.918), and 153.25 ms (AUC = 0.897); those on the left side, P100, were 111.85 ms (AUC = 0.872). Additionally, the VEP amplitude cutoff was 4.04 µV (AUC = 0.81) on the right side and 4.12 µV (AUC = 0.817) on the left side, below which the TD patients became posturally unstable. PIGD patients' right side significant N75, P100, and N145 cutoff values were 69.55 ms (AUC = 0.925), 108 ms (AUC = 0.925), and 140.4 ms (AUC = 0.875); those on the left side were 73.05 ms (AUC = 0.925), 107 ms (AUC = 0.95), and 141.45 ms (AUC = 0.925). Patients' postural stability was hampered above the cutoff values (Table 2).

### *BAER*

Except for BAER wave I, the latency of all other waves showed significant cutoff values associated with the postural stability of the IPD patients, and both TD and PIGD subgroups were impaired. In IPD patients, the significant cutoff latencies of wave II, III, IV, V, I–III interval, III–V interval, and I–V interval on the right side were 2.685 ms (AUC = 0.952), 3.815 ms (AUC = 0.914), 4.825 ms (AUC = 0.884), 5.825 ms (AUC = 0.916), 2.31 ms (AUC = 0.938), 2.015 ms (AUC = 0.868), and 4.35 ms (AUC = 0.941). On the left side, the significant cutoff latencies of wave II, III, IV, V, I–III interval, and I–V interval were 2.735 ms (AUC = 0.955), 3.825 ms (AUC = 0.921), 4.83 ms (AUC = 0.863), 5.84

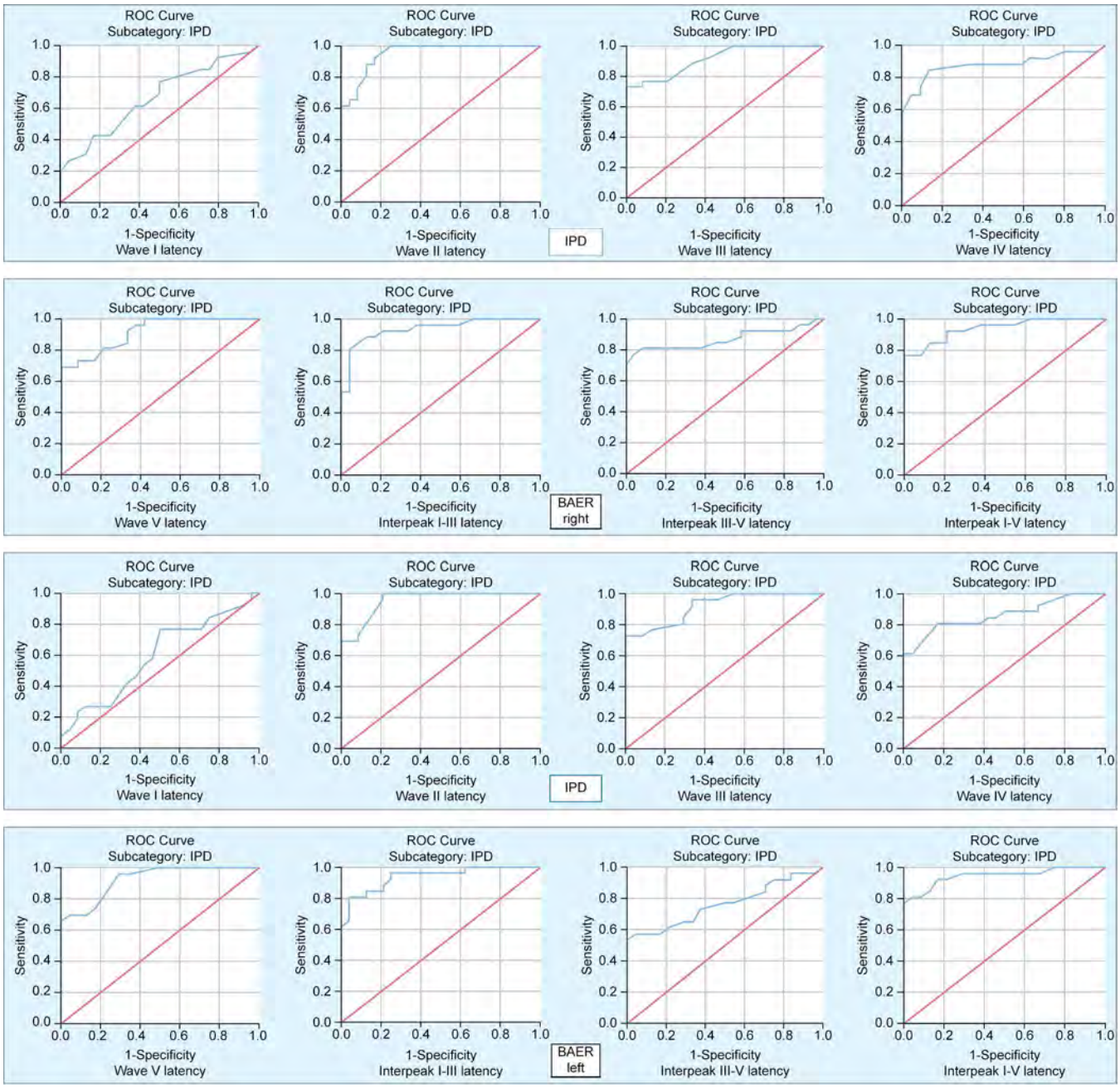



**Fig. 2:** ROC curves showing BAER in IPD

ms (AUC = 0.925), 2.275 ms (AUC = 0.938), and 4.36 ms (AUC = 0.947), respectively. Patients' postural stability was hampered above the cutoff values (Table 2).

The TD and PIGD subgroups followed a similar pattern, but their significant cutoff values were different. The TD variant had a lower BAER latency cutoff than the PIGD variant for PI. On the right side, the significant cutoff latencies for TD and PIGD were wave II (2.685 vs 2.83 ms), III (3.825 vs 3.945 ms), IV (4.825 vs 4.895 ms), V (5.825 vs 5.975 ms), I–III interval (2.31 vs 2.37 ms), III–V interval (2.02 vs 2.055 ms), and I–V interval (4.315 vs 4.35 ms). On the left side, the significant cutoff latencies for TD and PIGD were wave II (2.735 vs 2.81 ms), III (3.83 vs 3.935 ms), IV (4.83 vs 4.86 ms), V (5.84 vs 5.985 ms), I–III interval (2.275 vs 2.365 ms), and I–V interval (4.345 vs 4.405 ms). The latency of wave I did not show any significant cutoff values determining the postural stability in any patient group. The amplitude ratio of wave V/I had a significant cutoff value of 1.645 (AUC = 0.813) on the left side in PIGD patients. Most of the BAER cutoff values in the IPD and TD subgroups reached 100% specificity (Table 2).

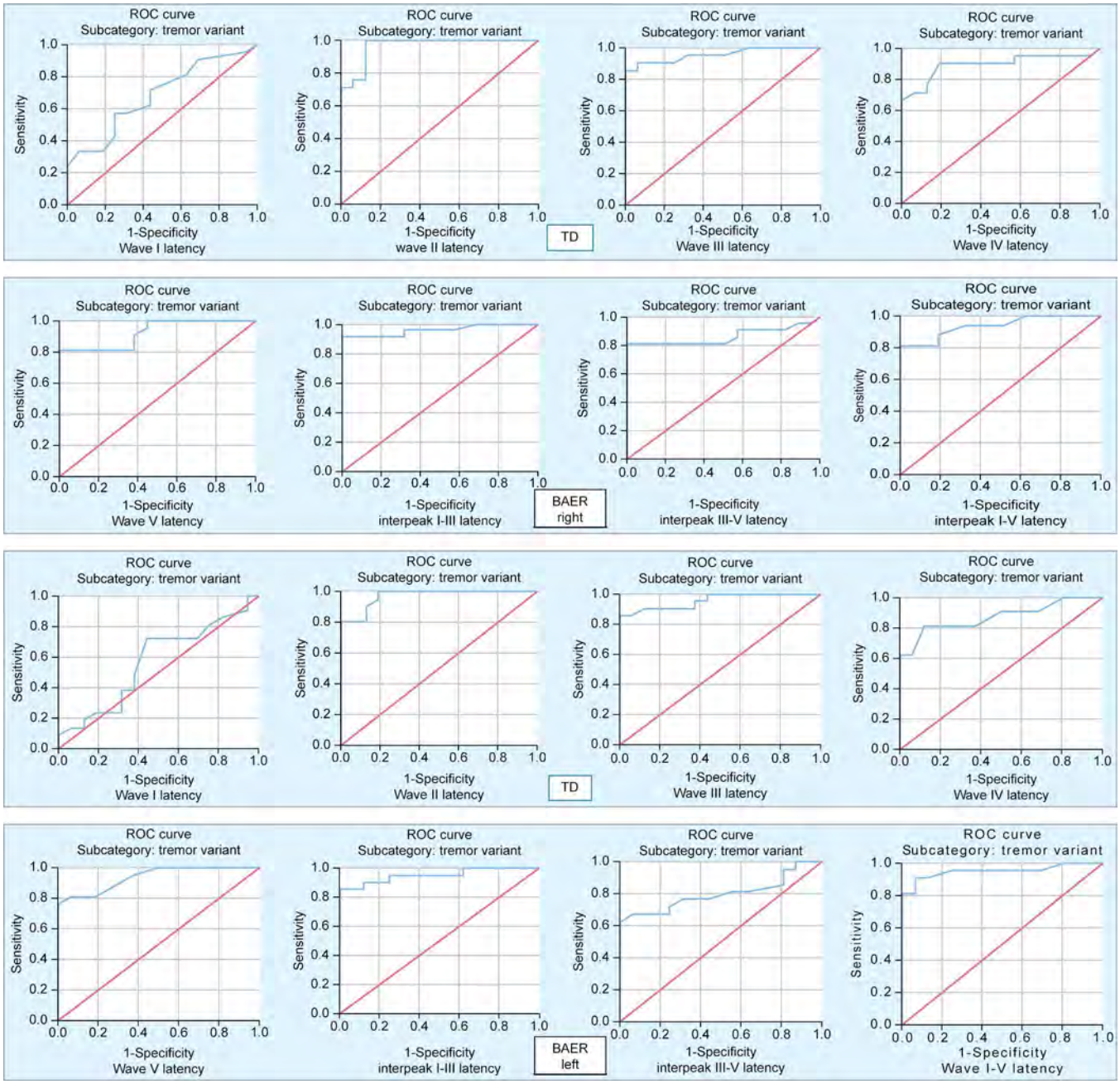
### *SSEP*

Since the upper limb SSEP values had not achieved AUC >0.8 in ROC curves, no significant cutoff value was found determining the postural stability in any patient (Table 2).

## Discussion

Dopaminergic and nondopaminergic neural circuits were involved in gross human postural control and associated with various sensory inputs (visual, vestibular, and somatosensory). These inputs were integrated into the premotor cortex, supplementary motor cortex, cerebellum, and basal ganglia.[14,15] The motor signal is refined in the cerebellum and basal ganglia and then transmitted to the primary motor cortex, the pedunculopontine nucleus in the brainstem, and downward to the corticospinal tract.[14,15] The basal ganglia also serve for somatosensory integration, automatic postural responses, and muscle tone maintenance.[16] Dysfunction in the basal ganglia and its connections leads to PI in IPD. We measured the cutoff values of VEP, BAER, and SSEP to find the threshold level of these parameters (visual, vestibular, and somatosensory inputs) in PI in IPD and its subgroups.

Petrova et al. found that abnormal VEP and BAER results in IPD, which denoted the specific dysfunctions of the brainstem and brain hemispheres, were associated with motor and nonmotor symptoms of IPD.[8] Bohnen et al. highlighted that imbalance in IPD depended on the inability to utilize vestibular information efficiently to maintain an upright stance.[17] This was independent of their visual and somatosensory processing and dopaminergic losses in the nigrostriatal area.[17] Another study showed that neurovestibular dysfunction measured with multimodality evoked potentials predicted falls in IPD over a 1-year follow-up.[18] We classified IPD patients according to their postural stability. We found many significant VEP and BAER parameters showing good sensitivity and specificity in classifying the IPD and its subgroups (TD and PIGD) according to their postural stability status. The values would guide clinicians to determine and predict PI and falls in those patients.

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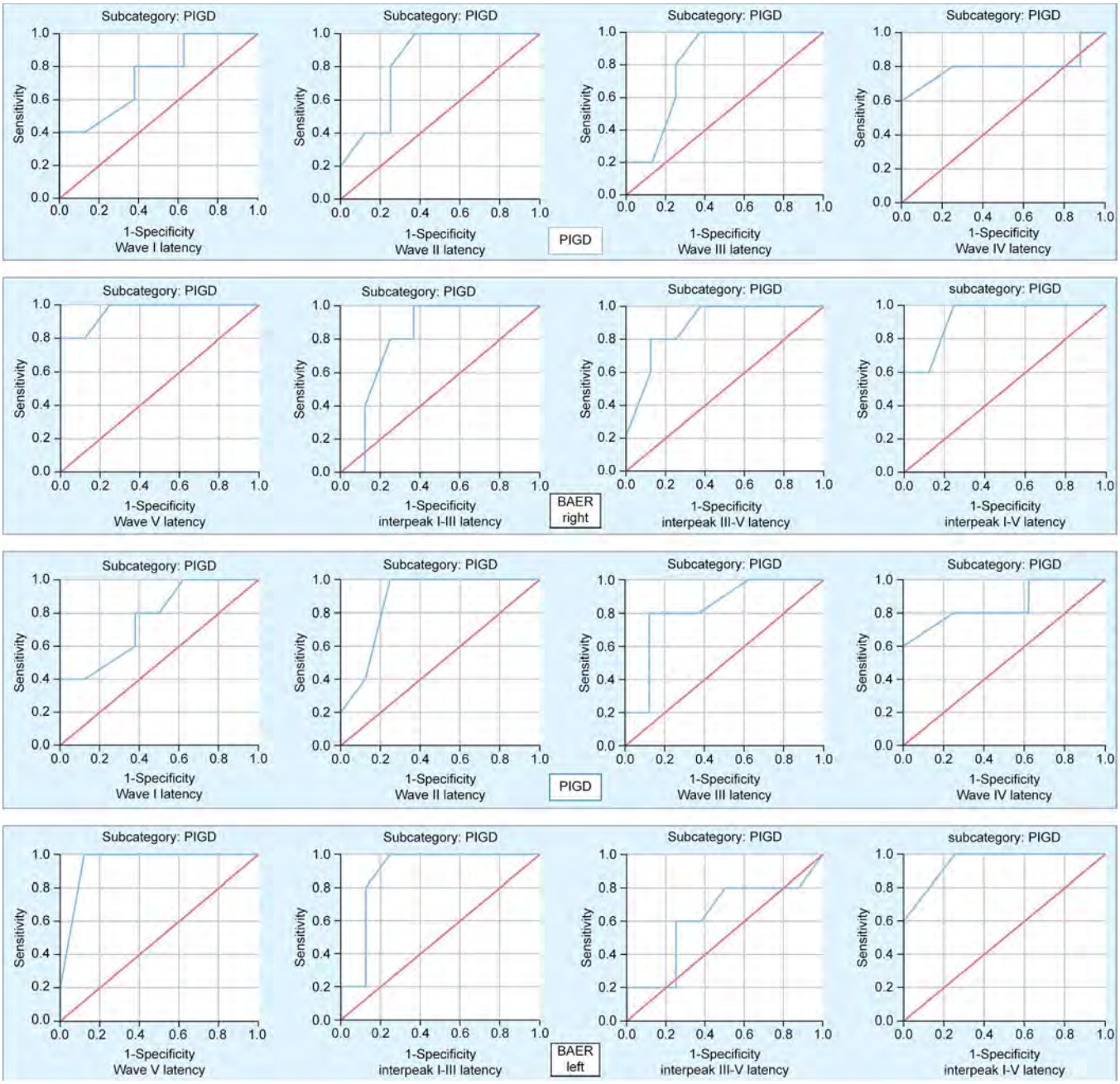


**Fig. 3:** ROC curves showing BAER in IPD subgroups—TD and PIGD variant

We noted that the TD variant had lower BAER latency cutoff values than the PIGD variant. We could hypothesize that the postural stability of the TD subgroup was more dependent on the vestibular sensory input than the PIGD subgroup. TD patients usually remain posturally stable for a longer time than PIGD patients. Previous studies.[19–21] showed that PIGD had aggravated motor and nonmotor symptoms compared to the TD. Lesser vestibular compensatory support might cause this severity in PIGD.

Tachibana et al. found no significant differences in N13, N20, and central conduction time (CCT) among IPD and healthy subjects. We found no significant AUC in SSEP values in IPD and its subgroups. However, before noting the SSEP parameters as insignificant, we need to study them with a larger sample size.

Though many studies have been done with VEP, BAER, and SSEP in IPD, our study first tried to find the cutoff values that determine the postural stability of the patients. In this respect, it is a novel idea. The PI cutoff values of VEP, BAER, and SSEP will help physicians across the globe identify patients prone to fall and injury. It will also help in understanding the progression of the disease.

## Conclusion

Visual, vestibular, and somatosensory inputs were necessary to maintain good postural stability. We found many significant evoked

**Table 1:** Descriptive details of demographical parameters, VEP, BAER, and SSEP in IPD and its subgroups (TD and PIGD variant)

| *Subcategory* | *IPD = 50* | | | | *TD = 37* | | | | *PIGD = 13* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Parameters* | *Min* | *Max* | *Mean* | *Std. deviation* | *Min* | *Max* | *Mean* | *Std. deviation* | *Min* | *Max* | *Mean* | *Std. deviation* |
| Age at onset (year) | 44 | 78 | 57.418 | 6.8107 | 44 | 78 | 56.903 | 7.2428 | 51 | 66 | 58.885 | 5.3741 |
| Duration of illness (year) | 1 | 6.5 | 2.962 | 1.3993 | 1 | 6.5 | 2.935 | 1.5555 | 2 | 5 | 3.038 | 0.853 |
| Age at presentation (year) | 47 | 80 | 60.38 | 6.884 | 47 | 80 | 59.84 | 7.167 | 53 | 70 | 61.92 | 5.993 |
| N75 (ms) R_VEP | 45.6 | 106.9 | 72.394 | 14.4143 | 45.6 | 106.9 | 72.638 | 15.2467 | 55.6 | 90.0 | 71.700 | 12.2598 |
| P100 (ms) R_VEP | 76.3 | 141.3 | 106.268 | 15.8845 | 76.3 | 141.3 | 106.286 | 16.6640 | 87.4 | 125.2 | 106.215 | 14.0439 |
| N145 (ms) R_VEP | 102.1 | 173.1 | 142.396 | 17.0263 | 113.1 | 173.1 | 144.268 | 17.3760 | 102.1 | 156.4 | 137.069 | 15.3760 |
| N75-P100 amp (μv) R_VEP | 1.20 | 6.78 | 4.1912 | 1.48062 | 1.20 | 6.78 | 4.0470 | 1.56032 | 2.74 | 6.70 | 4.6015 | 1.18379 |
| N75 (ms) L_VEP | 46.8 | 123.8 | 73.220 | 15.5129 | 46.8 | 123.8 | 72.930 | 16.1678 | 56.8 | 99.4 | 74.046 | 14.0520 |
| P100 (ms) L_VEP | 80.0 | 136.3 | 106.268 | 14.5480 | 80.0 | 136.3 | 106.638 | 15.1047 | 84.6 | 122.8 | 105.215 | 13.3468 |
| N145 (ms) L_VEP | 15.4 | 176.1 | 141.046 | 23.7688 | 15.4 | 176.1 | 142.192 | 25.7120 | 98.7 | 156.7 | 137.785 | 17.5499 |
| N75-P100 amp (μv) L_VEP | 1.47 | 7.20 | 4.2512 | 1.55713 | 1.47 | 7.20 | 4.1451 | 1.62457 | 1.96 | 6.20 | 4.5531 | 1.35997 |
| I (ms) R_BAER | 1.48 | 1.69 | 1.5564 | 0.05240 | 1.48 | 1.69 | 1.5489 | 0.05343 | 1.51 | 1.63 | 1.5777 | 0.04456 |
| II R_BAER | 2.38 | 3.01 | 2.7676 | 0.15026 | 2.38 | 3.01 | 2.7443 | 0.16220 | 2.65 | 2.98 | 2.8338 | 0.08272 |
| III R_BAER | 3.44 | 4.07 | 3.8454 | 0.15251 | 3.44 | 4.07 | 3.8146 | 0.16191 | 3.76 | 4.04 | 3.9331 | 0.07123 |
| IV R_BAER | 4.46 | 5.10 | 4.8452 | 0.14949 | 4.46 | 5.10 | 4.8292 | 0.15997 | 4.58 | 4.99 | 4.8908 | 0.10696 |
| V R_BAER | 5.38 | 6.12 | 5.8532 | 0.25086 | 5.38 | 6.12 | 5.8068 | 0.26607 | 5.56 | 6.12 | 5.9854 | 0.13782 |
| I–III R_BAER | 1.90 | 2.57 | 2.2892 | 0.16332 | 1.90 | 2.57 | 2.2659 | 0.17713 | 2.21 | 2.52 | 2.3554 | 0.09153 |
| III–V R_BAER | 1.60 | 2.25 | 2.0078 | 0.14248 | 1.60 | 2.19 | 1.9922 | 0.15325 | 1.80 | 2.25 | 2.0523 | 0.09765 |
| I–V R_BAER | 3.79 | 4.63 | 4.2968 | 0.26405 | 3.79 | 4.63 | 4.2578 | 0.28579 | 4.02 | 4.60 | 4.4077 | 0.14715 |
| V/I (amp μv) R_BAER | 1.57 | 1.76 | 1.6260 | 0.04703 | 1.57 | 1.76 | 1.6295 | 0.05071 | 1.57 | 1.68 | 1.6162 | 0.03429 |
| I (ms) L_BAER | 1.45 | 1.69 | 1.5666 | 0.06150 | 1.45 | 1.69 | 1.5635 | 0.06533 | 1.48 | 1.65 | 1.5754 | 0.05027 |
| II L_BAER | 2.44 | 3.10 | 2.7614 | 0.15020 | 2.44 | 3.10 | 2.7386 | 0.16264 | 2.65 | 2.96 | 2.8262 | 0.08140 |
| III L_BAER | 3.50 | 4.13 | 3.8410 | 0.15015 | 3.50 | 4.13 | 3.8151 | 0.15613 | 3.59 | 3.99 | 3.9146 | 0.10485 |
| IV L_BAER | 4.47 | 5.06 | 4.8476 | 0.13617 | 4.47 | 5.06 | 4.8354 | 0.14709 | 4.68 | 4.99 | 4.8823 | 0.09506 |
| V L_BAER | 5.37 | 6.14 | 5.8602 | 0.23982 | 5.37 | 6.14 | 5.8141 | 0.25132 | 5.56 | 6.14 | 5.9915 | 0.14177 |
| I–III L_BAER | 1.93 | 2.64 | 2.2818 | 0.16903 | 1.93 | 2.64 | 2.2616 | 0.17885 | 2.01 | 2.48 | 2.3392 | 0.12599 |
| III–V L_BAER | 1.67 | 2.38 | 2.0336 | 0.14924 | 1.67 | 2.23 | 1.9989 | 0.14102 | 1.97 | 2.38 | 2.1323 | 0.13046 |
| I–V L_BAER | 3.81 | 4.66 | 4.3010 | 0.25734 | 3.81 | 4.65 | 4.2605 | 0.27374 | 3.98 | 4.66 | 4.4162 | 0.16184 |
| V/I (amp μv) 0020 L_BAER | 1.57 | 1.72 | 1.6412 | 0.03761 | 1.57 | 1.72 | 1.6454 | 0.03739 | 1.57 | 1.70 | 1.6292 | 0.03707 |
| N9 R_SSEP | 8.59 | 9.27 | 8.9460 | 0.17826 | 8.59 | 9.27 | 8.9330 | 0.19719 | 8.79 | 9.13 | 8.9831 | 0.10531 |
| N13 R_SSEP | 11.95 | 14.24 | 13.1460 | 0.60388 | 11.95 | 14.24 | 13.1143 | 0.56434 | 11.96 | 14.19 | 13.2362 | 0.72233 |
| N20 R_SSEP | 17.63 | 20.28 | 19.0510 | 0.66140 | 17.63 | 20.28 | 19.0157 | 0.63577 | 17.75 | 20.19 | 19.1515 | 0.74756 |
| N13-N20 R_SSEP | 5.67 | 6.13 | 5.9050 | 0.12888 | 5.67 | 6.13 | 5.9014 | 0.14162 | 5.79 | 6.00 | 5.9154 | 0.08657 |
| N9 L_SSEP | 8.60 | 9.23 | 8.9484 | 0.16365 | 8.60 | 9.23 | 8.9376 | 0.18250 | 8.85 | 9.11 | 8.9792 | 0.08967 |
| N13 L_SSEP | 11.93 | 14.20 | 13.1432 | 0.60227 | 11.93 | 14.20 | 13.1141 | 0.55847 | 11.93 | 14.17 | 13.2262 | 0.73171 |
| N20 L_SSEP | 17.63 | 20.30 | 19.0352 | 0.66368 | 17.63 | 20.30 | 18.9986 | 0.63048 | 17.70 | 20.27 | 19.1392 | 0.76827 |
| N13–N20 L_SSEP | 5.65 | 6.10 | 5.8920 | 0.12558 | 5.65 | 6.10 | 5.8846 | 0.13266 | 5.75 | 6.10 | 5.9131 | 0.10467 |

L, left; PIGD, postural instability gait disorder variant of IPD; R, right; TD, tremor dominant variant of IPD

**Table 2:** Cutoff values with sensitivity, specificity, and AUC of VEP, BAER, and SSEP values in IPD and its subgroups (TD and PIGD variant)

| *Subcategory* | *IPD = 50* | | | | | *TD = 37* | | | | | *PIGD = 13* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Parameters* | *AUC* | *p-value* | *cutoff value* | *SN* | *SP* | *AUC* | *p-value* | *cutoff value* | *SN* | *SP* | *AUC* | *p-value* | *cutoff value* | *SN* | *SP* |
| N75 (ms) R_VEP | 0.833 | <0.001 | 69.95 | 76.9 | 87.5 | 0.829 | 0.001 | 69.95 | 71.4 | 87.5 | 0.925 | 0.013 | 69.55 | 100 | 87.5 |
| P100 (ms) R_VEP | 0.91 | <0.001 | 111.65 | 88.5 | 83.3 | 0.918 | <0.001 | 113.7 | 95.2 | 87.5 | 0.925 | 0.013 | 108 | 100 | 87.5 |
| N145 (ms) R_VEP | 0.858 | <0.001 | 152.1 | 92.3 | 62.5 | 0.897 | <0.001 | 153.25 | 90.5 | 81.2 | 0.875 | 0.028 | 140.4 | 100 | 75 |
| N75-P100 amp (μv) R_VEP | 0.776 | 0.001 | 4.04 | 84.6 | 79.2 | 0.81 | 0.001 | 4.04 | 81 | 88.5 | 0.788 | 0.092 | 5.25 | 60 | 75 |
| N75 (ms) L_VEP | 0.773 | 0.001 | 70 | 76.9 | 79.2 | 0.738 | 0.014 | 70 | 76.2 | 81.2 | 0.925 | 0.013 | 73.05 | 100 | 87.5 |
| P100 (ms) L_VEP | 0.88 | <0.001 | 111.6 | 88.5 | 83.3 | 0.872 | <0.001 | 111.85 | 85.7 | 81.2 | 0.95 | 0.008 | 107 | 100 | 87.5 |
| N145 (ms) L_VEP | 0.755 | 0.002 | 148.75 | 80.8 | 66.7 | 0.735 | 0.015 | 149.05 | 76.2 | 68.7 | 0.925 | 0.013 | 141.45 | 100 | 75 |
| N75-P100 amp (μv) L_VEP | 0.787 | 0.001 | 4.19 | 84.6 | 79.2 | 0.817 | 0.001 | 4.12 | 81 | 87.5 | 0.788 | 0.092 | 5.21 | 80 | 75 |
| I (ms) R_BAER | 0.668 | 0.041 | 1.555 | 61.5 | 62.5 | 0.683 | 0.059 | 1.525 | 71.4 | 56.2 | 0.75 | 0.143 | 1.575 | 80 | 62.5 |
| II R_BAER | 0.952 | <0.001 | 2.685 | 61.5 | 100 | 0.967 | <0.001 | 2.685 | 71.4 | 100 | 0.825 | 0.057 | 2.83 | 80 | 75 |
| III R_BAER | 0.914 | <0.001 | 3.815 | 73.1 | 100 | 0.957 | <0.001 | 3.825 | 85.7 | 100 | 0.813 | 0.067 | 3.945 | 80 | 75 |
| IV R_BAER | 0.884 | <0.001 | 4.825 | 57.7 | 100 | 0.897 | <0.001 | 4.825 | 66.7 | 100 | 0.8 | 0.079 | 4.895 | 80 | 75 |
| V R_BAER | 0.916 | <0.001 | 5.825 | 69.2 | 100 | 0.924 | <0.001 | 5.825 | 81 | 100 | 0.963 | 0.007 | 5.975 | 80 | 100 |
| I–III R_BAER | 0.938 | <0.001 | 2.31 | 80.8 | 95.8 | 0.955 | <0.001 | 2.31 | 90.5 | 100 | 0.8 | 0.079 | 2.37 | 100 | 62.5 |
| III–V R_BAER | 0.868 | <0.001 | 2.015 | 69.2 | 100 | 0.862 | <0.001 | 2.02 | 81 | 100 | 0.888 | 0.023 | 2.055 | 80 | 75 |
| I–V R_BAER | 0.941 | <0.001 | 4.35 | 76.9 | 100 | 0.943 | <0.001 | 4.315 | 81 | 100 | 0.925 | 0.013 | 4.35 | 60 | 100 |
| V/I (amp μv) R_BAER | 0.568 | 0.409 | 1.635 | 42.3 | 62.5 | 0.571 | 0.462 | 1.625 | 47.6 | 56.2 | 0.625 | 0.464 | 1.635 | 60 | 75 |
| I (ms) L_BAER | 0.596 | 0.244 | 1.575 | 46.2 | 62.5 | 0.571 | 0.462 | 1.56 | 47.6 | 62.5 | 0.763 | 0.124 | 1.575 | 80 | 62.5 |
| II L_BAER | 0.955 | <0.001 | 2.735 | 69.2 | 100 | 0.972 | <0.001 | 2.735 | 81 | 100 | 0.875 | 0.028 | 2.81 | 100 | 75 |
| III L_BAER | 0.921 | <0.001 | 3.825 | 73.1 | 100 | 0.957 | <0.001 | 3.83 | 85.7 | 100 | 0.825 | 0.057 | 3.935 | 80 | 87.5 |
| IV L_BAER | 0.863 | <0.001 | 4.83 | 61.5 | 100 | 0.869 | <0.001 | 4.83 | 61.9 | 100 | 0.85 | 0.04 | 4.86 | 80 | 75 |
| V L_BAER | 0.925 | <0.001 | 5.84 | 65.4 | 100 | 0.938 | <0.001 | 5.84 | 76.2 | 100 | 0.95 | 0.008 | 5.985 | 100 | 87.5 |
| I–III L_BAER | 0.938 | <0.001 | 2.275 | 80.8 | 95.8 | 0.952 | <0.001 | 2.275 | 85.7 | 100 | 0.888 | 0.023 | 2.365 | 80 | 87.5 |
| III–V L_BAER | 0.765 | 0.001 | 1.995 | 0.538 | 100 | 0.796 | 0.002 | 1.995 | 61.9 | 100 | 0.625 | 0.464 | 2.08 | 60 | 62.5 |
| I–V L_BAER | 0.947 | <0.001 | 4.36 | 76.9 | 100 | 0.949 | <0.001 | 4.345 | 81 | 100 | 0.95 | 0.008 | 4.405 | 80 | 87.5 |
| V/I (amp μv) L_BAER | 0.699 | 0.016 | 1.645 | 69.2 | 79.2 | 0.656 | 0.108 | 1.645 | 66.7 | 68.7 | 0.813 | 0.067 | 1.645 | 80 | 100 |
| N9 R_SSEP | 0.571 | 0.388 | 8.995 | 65.4 | 41.7 | 0.598 | 0.312 | 8.995 | 66.7 | 43.7 | 0.463 | 0.826 | 8.995 | 60 | 50 |
| N13 R_SSEP | 0.63 | 0.116 | 13.005 | 65.4 | 66.7 | 0.676 | 0.07 | 13.05 | 71.4 | 68.7 | 0.45 | 0.77 | 13.005 | 40 | 62.5 |
| N20 R_SSEP | 0.642 | 0.086 | 18.985 | 65.4 | 66.7 | 0.704 | 0.036 | 18.935 | 71.4 | 68.7 | 0.4 | 0.558 | 18.335 | 20 | 87.5 |
| N13–N20 R_SSEP | 0.569 | 0.404 | 5.825 | 38.5 | 75 | 0.622 | 0.209 | 5.825 | 42.9 | 81.2 | 0.288 | 0.213 | 5.83 | 20 | 62.5 |
| N9 L_SSEP | 0.553 | 0.522 | 8.875 | 34.6 | 79.2 | 0.598 | 0.312 | 8.885 | 42.9 | 75 | 0.35 | 0.38 | 8.925 | 20 | 62.5 |
| N13 L_SSEP | 0.624 | 0.132 | 13.045 | 65.4 | 62.5 | 0.671 | 0.078 | 13.045 | 71.4 | 68.7 | 0.425 | 0.661 | 13.08 | 40 | 50 |
| N20 L_SSEP | 0.647 | 0.076 | 18.705 | 50 | 87.5 | 0.711 | 0.03 | 18.705 | 57.1 | 81.2 | 0.375 | 0.464 | 18.325 | 20 | 87.5 |
| N13–N20 L_SSEP | 0.583 | 0.317 | 5.805 | 42.3 | 83.3 | 0.64 | 0.15 | 5.805 | 47.6 | 87.5 | 0.275 | 0.188 | 5.805 | 20 | 75 |

L, left; PIGD, postural instability gait disorder variant of IPD; R, right; SN, sensitivity; SP, specificity; TD, tremor dominant variant of IPD

potential cutoff values determining postural stability in IPD and its subgroups (TD and PIGD). Lesser vestibular compensatory support in PIGD led to a more severe phenotype than TD.

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ORIGINAL ARTICLE

# To Compare between CTP, MELD, MELD-Na, MELD + HDLc, RDW, and RDW to Platelet Ratio as a Predictor of Short-term Mortality in Cirrhosis of Liver

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## Abstract

**Background:** Liver cirrhosis indicates inflammation, necrosis, as well as fibrosis, resulting in progressively decreasing liver function. As the disease advances from a compensated to a decompensated stage, patients experience severe clinical complications, that result in elevated mortality, as well as morbidity, rates. Accurate predicting short-term mortality is essential for making clinical decisions, particularly when it comes to liver transplantation (LT). Several scores, encompassing model for end-stage liver disease (MELD), Child–Turcotte–Pugh (CTP), as well as their variants, along with specific biomarkers such as red cell distribution width (RDW) alongside RDW to platelet ratio (RPR), have been proposed for assessing these patients' prognosis. However, comparative effectiveness of these scoring systems in predicting outcomes remains underexplored.

**Methods:** This study involved a cohort of participants diagnosed with cirrhosis, who were evaluated to identify the most reliable predictors of 30-day mortality. The study compared the efficacy of multiple scoring systems, including CTP, MELD, model for end-stage liver disease-sodium (MELD-Na), model for end-stage liver disease-high-density lipoprotein cholesterol (MELD-HDLc), RDW, and RPR, by analyzing their correlation with patient outcomes. Data were collected on demographic profiles, clinical findings, and laboratory markers to calculate these scores and assess their predictive accuracy.

**Results:** The study found that among the various scores, the MELD as well as MELD-Na scores demonstrated the highest accuracy predicting 30-day mortality in liver cirrhosis patients. Alcohol emerged as the predominant etiology of cirrhosis, and there was a significant male predominance in the cohort. The results were consistent with existing literature, confirming the reliability of MELD alongside MELD-Na as stronger prognostic tools compared to the CTP score and other markers.

**Conclusion:** MELD along with MELD-Na scores constitute reliable indicators of mortality over the short term in individuals with cirrhosis and should be preferred in practice for assessing the need for LT and other critical interventions. These findings underscore the importance of using evidence-based scoring systems to improve patient management and outcomes in liver cirrhosis, a condition with a high global mortality burden.

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## Introduction

Cirrhosis encompasses inflammation, necrosis, as well as fibrosis resulting from multiple conditions. Liver cirrhosis is initiated by hepatocyte necrosis and subsequent regeneration, leading to hepatic sinusoid capillarization along with fibrosis. Reduced hepatic parenchyma, blood flow alterations, alongside development of portosystemic shunts contribute to various complications of cirrhosis, including hepatocellular carcinoma. The progression of cirrhosis unfolds in two distinct phases: asymptomatic compensated phase, succeeded by decompensated phase characterized by various clinical manifestations, including ascites, coagulation abnormalities, encephalopathy, bleeding, and jaundice.[1] Decompensation marks a significant turning point, leading to a faster progression toward mortality or necessity for liver transplantation (LT). Furthermore, additional complications encompassing acute kidney injury (AKI), rebleeding, hepatorenal syndrome (HRS), portopulmonary hypertension (PoPH), hepatopulmonary syndrome (HPS), cirrhotic cardiomyopathy (CCM), and bacterial infections can expedite disease progression, particularly in the decompensated stage. Cirrhosis's shift from compensated to decompensated manifests at an annual rate of approximately 5–7%. After decompensation sets in, cirrhosis evolves into a systemic condition and life expectancy drastically diminishes. Consequently, average lifespan diminishes from nearly 12 year in cirrhosis with compensation to approximately 2 year in decompensated cirrhosis. Clinical picture of decompensated cirrhosis is attributed to the hemodynamic disturbances resulting from peripheral arterial vasodilation, particularly in the splanchnic circulatory region.[2] Liver disease results in 2 million fatalities each year, around 4% of worldwide deaths, with most liver-related deaths occurring in men. Cirrhosis, as well as hepatocellular cancer, were main causes, primarily due to alcohol, viral hepatitis, as well as nonalcoholic fatty liver disease (NAFLD). Affecting 25% of adults in Europe as well as America, NAFLD is the second most common contributor to end-stage liver disease as well as LT. Deaths from hepatic viruses have declined due to hepatitis B virus (HBV) vaccination and effective hepatitis C virus (HCV) treatments. In high-income countries, conditions like primary sclerosing cholangitis (linked to higher cancer risk), primary biliary cholangitis, and autoimmune hepatitis are more common.[3] Early intervention is essential to halt the progression of cirrhosis and delay the onset of liver function decompensation.[4] A straightforward, alongside trustworthy, approach must be taken to evaluate these patients' mortality risk. Traditionally, cirrhosis prognosis has been evaluated using Child–Turcotte–Pugh (CTP) or model for end-stage liver disease (MELD) scoring systems.[5] Since 2002, MELD score—which relies on creatinine, bilirubin, as well as international normalized ratio (INR)—has been shown to be a valid indicator of early death.[6] An expansion of classic MELD, model for end-stage liver disease-sodium (MELD-Na) score adds serum sodium (S Na) levels to the equation.

Recent research has demonstrated that MELD-Na enhances precision of short-term

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death prediction in patients with cirrhosis.[7] Other prognostic markers gaining attention as minimally invasive techniques for evaluating liver disease include model for end-stage liver disease-high-density lipoprotein cholesterol (MELD-HDLc) scores, albumin-bilirubin (ALBI) score, red cell distribution width (RDW), RDW to platelet ratio (RPR), as well as fibrosis-4 (FIB-4) score.[8]

Given the evolving landscape of prognostic indicators in cirrhosis, comparing the predictive accuracy of these various scoring systems and biomarkers for short-term (30-day) mortality is critical. This comparative study aims to identify the most reliable predictors, facilitating improved patient management and potentially guiding clinical decision-making regarding the urgency of LT or other life-saving treatments.

## Materials and Methods

This hospital-based prospective observational investigation has been carried out in Northern India at the Department of Medicine in cooperation with the Department of Medical Gastroenterology. Following approval and clearance from the Institutional Ethics Committee and the acquisition of written consent, patients who satisfied the inclusion criteria were subsequently enlisted. The study spanned a duration of 1 year. Inclusion criteria—adults of 14–65 years old discovered with liver cirrhosis, as well as providing written informed consent. Exclusion criteria—individuals who declined to give informed consent voluntarily. The patient's medical history has been employed to determine the cirrhosis diagnosis, clinical features (e.g., ascites, jaundice, gastrointestinal bleeding, hepatomegaly, hepatic encephalopathy, and splenomegaly), elevated AST/ALT levels, hyperbilirubinemia, and supportive ultrasound findings. Patients suffering from tuberculosis (TB)-related ascites, malignancy, or nonhepatocellular carcinoma were excluded. Scores such as CTP, MELD, MELD-Na, MELD + HDLc, RDW, and RPR have been determined utilizing laboratory results obtained 24 hours after being admitted to the hospital. Outcomes were assessed at 30 days and classified as either "survived" or "deceased." CTP score comprised three categorical indicators (encephalopathy, ascites, as well as INR) alongside two continuous ones (bilirubin as well as albumin). Class A (5–6 points), class B (7–9 points), and class C (10–15 points) are three categories into which it falls. The following formulas can be used for related calculations:

MELD score = 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln (INR) + 9.57 × ln [serum creatinine (mg/dL)] + 6.43

MELD-Na score = MELD score + 1.59 × (135 – Na), with Na values capped at a maximum of 135 mmol/L and a minimum of 120 mmol/L. For MELD + HDLc, HDL was added to the MELD scores. The AUC for CTP, MELD, MELD + HDLc, MELD-Na, RDW, and RPR was calculated. Predictive values of MELD, CTP, RDW, MELD + HDLc, MELD-Na, and RPR regarding 30-day mortality were assessed and compared.

Outcome measures, including prevalence of cirrhosis in terms of age, sex, urban or rural dwellers, number of patients in each CTP class, mean scores in terms of MELD, MELD-Na, MELD + HDLc, RDW, RPR, mean laboratory values at time of admission, and incidence in relation to outcomes at the end of 30 days (survival or death), were calculated.

### Statistical Analysis

Data collected during the study were organized and entered into Microsoft Excel 2021 (Office 2021 package). Statistical analysis was carried out employing IBM SPSS software, version 24.0 (Chicago, Illinois, IBM Corp). Descriptive statistics were employed to summarize data. Categorical variables were represented as percentages alongside proportions, whereas mean and standard deviation (SD) were utilized for expressing continuous variables. Associations between variables were analyzed employing the Chi-squared test. In order to compare means of two distinct groups, an unpaired *t*-test was applied. ANOVA, on the contrary, was employed for assessing means of continuous variables among several groups. Receiver operating characteristics (ROC) analysis of prognostic scores was done, and their area under the ROC curve (AUROC), sensitivity, specificity, odds ratio, and *p*-value were calculated and compared.

## Results

A total of 150 patients with cirrhosis were incorporated into the investigation according to the criteria for inclusion and exclusion, and they were followed up for 30 days from their date of admission to compare various prognostic models as a mortality predictive score. Participants in the investigation were between 18 and 65 years old. The mean age was 46.41 ± 11.48. The median age was 47.00. Out of 150 patients enrolled, 31 (20.7%) were female participants, and 119 (79.3%) were male participants. The male-to-female participant ratio was 3.8:1. Out of 150 patients enrolled, 43 (31.6%) were urban residents, and 93 (68.4%) were rural residents. About 68 (45.6%) participants had a history of significant alcohol intake, 22 participants (14.8%) were hepatitis B reactive, 20 participants (13.4%) were hepatitis C reactive, 17 participants (11.4%) had NASH/NAFLD, 11 participants (8.1%) had an etiology under evaluation, 8 participants (5.4%) had autoimmune hepatitis, 2 participants (1.3%) had Wilson's disease, and 1 participant had cryptogenic cirrhosis.

Of the 68 patients who were alcoholic, 19 patients (28.8%) had a period of alcohol consumption of <20 years, and 49 patients (71.2%) had a history of alcohol consumption exceeding 20 years. Twenty-three patients (34.2%) had an amount of liquor (gm/day) <80, and 45 patients (66.2%) had an amount of liquor (gm/day) >80.

Out of 150 patients enrolled, 7 patients (4.7%) had no ascites, 39 patients (26.0%) had slight ascites, and 104 patients (69.3%) had moderate/severe ascites. Out of 150 patients enrolled, 11 patients (7.3%) had no encephalopathy, 24 patients (16.0%) had grade I encephalopathy, 59 patients (39.3%) had grade II encephalopathy, 43 patients (28.7%) had grade III encephalopathy, and 13 patients (8.7%) had grade IV encephalopathy.

An entire group of 150 participants has been selected for this research. The mean Hb level was 8.08 ± 2.30 gm/dL, with a range of 3.6–15.2 gm/dL. The mean total leukocyte count (TLC) was 10,042.71 ± 7,377.58/mm$^3$, ranging from 1180 to 46400/mm$^3$. The mean platelet count was 1.05 ± 0.75 lakhs, with values ranging from 0.12 to 6.7 lakhs. The mean total bilirubin level was 4.98 ± 6.01 mg/dL, with a range of 0.14–37 mg/dL. The mean serum glutamic-oxaloacetic transaminase (SGOT) level was 100.56 U/L (range: 1.05–888 U/L), and the mean serum glutamic-pyruvic transaminase (SGPT) level was 66.76 U/L (range: 11–696 U/L). Serum albumin levels averaged 2.71 gm/dL, with a range of 1.5–3.8 gm/dL, while serum creatinine levels had a mean of 2.04 mg/dL, ranging from 0.48 to 11.6 mg/dL. The mean INR was 2.10 ± 0.90, with a range from 0.89 to 4.9. Sodium levels had a mean of 130.16 ± 5.78 mEq/L, with a range from 111 to 145 mEq/L. The mean HDL level was 22.89 ± 10.74 mg/dL, ranging from 5 to 47 mg/dL.

All participants were followed for 30 days from admission to assess outcomes, categorized as "alive" or "expired." Of the 150 patients, 121 (80.7%) survived, while 29 (19.3%) died within 30 days. Among those who died, the mean time to mortality was 6.28 ± 3.76 days, ranging from 1 to 16 days.

Regarding disease severity, 0.7% of patients were designated as CTP class A, 23.3% as class B, and 76% as class C. The mean MELD + HDLc score was 45.86 ± 9.22, with a median of 46.50 (range: 18–67). The mean MELD

score was 23.11 ± 10.16, with a median of 21.00 (range: 6–40). The mean MELD-Na score was 24.69 ± 9.66, with a median of 24.00 (range: 6–40). RDW had a mean of 16.98 ± 2.35% and a median of 16.50% (range: 12–27.32%). The mean RPR was 23.69 ± 18.87, with a median of 17.80 (range: 2.5–136).

The Chi-squared test indicated a substantial correlation between gender and the etiology of cirrhosis ($\chi^2 = 62.560, p < 0.001$). Males predominantly had alcohol-related cirrhosis (68 cases), hepatitis B (20 cases), and Wilson's disease (2 cases), while females more frequently had cirrhosis due to hepatitis C (9 cases), NASH/NAFLD (5 cases), autoimmune conditions (7 cases), and cryptogenic causes (1 case).

Mean sodium levels were markedly elevated in the survivor cohort (131.32 mEq/L) compared to those who expired (125.31 mEq/L, $p < 0.001$). Likewise, HDL levels were markedly elevated in survivors (mean: 25.48 mg/dL) compared to deceased patients (mean: 12.07 mg/dL, $p < 0.001$). RDW rose substantially in the expired group (mean: 18.33%) compared to survivors (mean: 16.65%, $p < 0.001$).

Variables substantially correlated with 30-day mortality ($p < 0.05$) included encephalopathy, hemoglobin, TLC, platelet count, total bilirubin, direct bilirubin, SGOT, SGPT, serum creatinine, blood urea, prothrombin time (PT), INR, sodium, HDL, CTP class, MELD + HDLc, MELD, MELD-Na, RDW, and RPR (Table 1).

## Receiver Operating Characteristics Analysis of Prognostic Models

For the CTP score, although the sensitivity was found to be 100%, the specificity was low at only 0.8%. The diagnostic accuracy was 20%, and the *p*-value was 0.623, making it a poor prognostic marker for mortality within 30 days for cirrhosis patients.

## Receiver Operating Characteristics Analysis of MELD

Area under the ROC curve of MELD predicting outcomes: expired vs alive came out to be 0.978 (95% CI: 0.96–0.996), hence exhibiting superior diagnostic efficacy. Results were statistically significant ($p < 0.001$). At the MELD cutoff of ≥30, mortality predicted with sensitivity of 100% alongside specificity of 88% (Table 2).

## Receiver Operating Characteristics Analysis of MELD-Na

Area under the ROC curve of MELD-Na predicting outcomes of expired vs alive came out to be 0.977 (95% CI: 0.958–0.996), indicating exceptional diagnostic efficacy. Results were statistically significant ($p < 0.001$).

**Table 1:** Showing parameters significantly associated with outcome

| *Parameters* | *Outcome* | | *p-value* |
|---|---|---|---|
| | *Alive (n = 121)* | *Expired (n = 29)* | |
| Age (years) | 46.48 ± 11.34 | 46.10 ± 12.25 | 0.881 |
| Gender | | | 0.126 |
| Residence | | | 0.830 |
| Alcohol intake (yes) | 43 (43.4%) | 13 (59.1%) | 0.183 |
| CLD etiology | | | 0.384 |
| Type of liquor | | | 1.000 |
| Duration of alcohol intake (years) | | | 0.753 |
| Amount of liquor (gm/day) | | | 0.782 |
| Ascites | | | 0.275 |
| Encephalopathy | | | <0.001 |
| None | 11 (9.1%) | 0 (0.0%) | |
| Grade I | 24 (19.8%) | 0 (0.0%) | |
| Grade II | 55 (45.5%) | 4 (13.8%) | |
| Grade III | 28 (23.1%) | 15 (51.7%) | |
| Grade IV | 3 (2.5%) | 10 (34.5%) | |
| Hemoglobin (gm/dL) | 8.34 ± 2.36 | 7.00 ± 1.68 | 0.001 |
| TLC (/mm$^3$) | 9046.44 ± 6873.13 | 14199.55 ± 8062.00 | 0.001 |
| Platelet count (lakhs) | 1.17 ± 0.78 | 0.54 ± 0.22 | <0.001 |
| Total bilirubin (mg/dL) | 3.59 ± 5.02 | 10.79 ± 6.37 | <0.001 |
| Direct bilirubin (mg/dL) | 2.25 ± 3.19 | 7.73 ± 4.32 | <0.001 |
| SGOT (U/L) | 95.02 ± 109.98 | 123.68 ± 34.50 | <0.001 |
| SGPT (U/L) | 61.11 ± 97.88 | 90.32 ± 36.10 | <0.001 |
| Serum albumin (gm/dL) | 2.74 ± 0.45 | 2.56 ± 0.34 | 0.050 |
| Serum protein (gm/dL) | 6.42 ± 1.03 | 6.35 ± 0.86 | 0.743 |
| Serum creatinine (mg/dL) | 1.76 ± 1.64 | 3.21 ± 1.33 | <0.001 |
| B. urea (mg/dL) | 61.65 ± 44.02 | 145.97 ± 62.24 | <0.001 |
| PT (s) | 23.57 ± 8.62 | 36.91 ± 11.24 | <0.001 |
| INR | 1.81 ± 0.65 | 3.30 ± 0.78 | <0.001 |
| Sodium (mEq/L) | 131.32 ± 5.28 | 125.31 ± 5.29 | <0.001 |
| HDL (mg/dL) | 25.48 ± 10.15 | 12.07 ± 4.72 | <0.001 |

At the MELD-Na cutoff of ≥32, mortality was predicted with sensitivity of 97% as well as specificity of 89% (Table 3).

## Receiver Operating Characteristics Analysis of MELD-HDLc

Area under the ROC curve of MELD + HDLc predicting outcomes of expired vs alive came out to be 0.627 (95% CI: 0.53–0.724), indicating moderate diagnostic efficacy. Results were statistically significant ($p$ = 0.034). At the MELD + HDLc cutoff of ≥41, mortality was predicted with sensitivity of 97%, as well as specificity of 32% (Table 4).

**Table 2:** ROC curve analysis showing diagnostic performance of MELD in predicting" mortality ($n$ = 150)

| *Parameter* | *Value (95% CI)* |
|---|---|
| Cutoff ($p$-value) | ≥30 (<0.001) |
| AUROC | 0.978 (0.96–0.996) |
| Sensitivity | 100.0% (88–100) |
| Specificity | 88.4% (81–94) |
| Positive predictive value | 67.4% (51–81) |
| Negative predictive value | 100.0% (97–100) |
| Diagnostic accuracy | 90.7% (85–95) |
| Positive likelihood ratio | 8.64 (5.28–14.14) |
| Negative likelihood ratio | 0 (0–NaN) |
| Diagnostic odds ratio | Inf (NaN–Inf) |

**Table 3:** ROC curve analysis showing diagnostic performance of MELD-Na in predicting mortality" ($n$ = 150)

| *Parameter* | *Value (95% CI)* |
|---|---|
| Cutoff ($p$-value) | ≥32 (<0.001) |
| AUROC | 0.977 (0.958–0.996) |
| Sensitivity | 96.6% (82–100) |
| Specificity | 89.3% (82–94) |
| Positive predictive value | 68.3% (52–82) |
| Negative predictive value | 99.1% (95–100) |
| Diagnostic accuracy | 90.7% (85–95) |
| Positive likelihood ratio | 8.99 (5.35–15.09) |
| Negative likelihood ratio | 0.04 (0.01–0.27) |
| Diagnostic odds ratio | 232.62 (29.18–1854.5) |

## Receiver Operating Characteristics Analysis of RDW

Area under the ROC curve of RDW (%) predicting outcomes of expired vs alive came out to be 0.804 (95% CI: 0.733–0.874), indicating exceptional diagnostic efficacy. Results were statistically significant ($p$ < 0.001). At the RDW (%) cutoff of ≥17.5, mortality was predicted with sensitivity of 90%, as well as specificity of 72% (Table 5).

## Receiver Operating Characteristics Analysis of RPR

Area under the ROC curve of RPR predicting outcomes of expired vs alive came out to be 0.824–0.935 (95% CI), indicating exceptional diagnostic efficacy. Results were statistically significant ($p$ < 0.001). At the RPR cutoff of ≥23.7, mortality was predicted with sensitivity of 90%, alongside specificity of 78% (Table 6).

**Table 4:** ROC curve analysis showing diagnostic performance" of MELD + HDLc in predicting mortality ($n$ = 150)

| *Parameter* | *Value (95% CI)* |
|---|---|
| Cutoff ($p$-value) | ≥41 (0.034) |
| AUROC | 0.627 (0.53–0.724) |
| Sensitivity | 96.6% (82–100) |
| Specificity | 31.7% (23–41) |
| Positive predictive value | 25.5% (18–35) |
| Negative predictive value | 97.4% (87–100) |
| Diagnostic accuracy | 44.3% (36–53) |
| Positive likelihood ratio | 1.41 (1.23–1.63) |
| Negative likelihood ratio | 0.11 (0.02–0.76) |
| Diagnostic odds ratio | 12.98 (1.7–98.94) |

**Table 5:** ROC curve analysis showing diagnostic performance of RDW (%) in predicting mortality ($n$ = 150)

| *Parameter* | *Value (95% CI)* |
|---|---|
| Cutoff ($p$-value) | ≥17.5 (<0.001) |
| AUROC | 0.804 (0.733–0.874) |
| Sensitivity | 89.7% (73–98) |
| Specificity | 71.9% (63–80) |
| Positive predictive value | 43.3% (31–57) |
| Negative predictive value | 96.7% (91–99) |
| Diagnostic accuracy | 75.3% (68–82) |
| Positive likelihood ratio | 3.19 (2.34–4.35) |
| Negative likelihood ratio | 0.14 (0.05–0.42) |
| Diagnostic odds ratio | 22.18 (6.3–78.11) |

**Table 6:** ROC curve analysis showing diagnostic performance of RPR in predicting mortality ($n$ = 150)

| *Parameter* | *Value (95% CI)* |
|---|---|
| Cutoff ($p$-value) | ≥23.7 (<0.001) |
| AUROC | 0.88 (0.824–0.935) |
| Sensitivity | 89.7% (73–98) |
| Specificity | 78.5% (70–85) |
| Positive predictive value | 50.0% (36–64) |
| Negative predictive value | 96.9% (91–99) |
| Diagnostic accuracy | 80.7% (73–87) |
| Positive likelihood ratio | 4.17 (2.9–5.99) |
| Negative likelihood ratio | 0.13 (0.04–0.39) |
| Diagnostic odds ratio | 31.67 (8.88–112.92) |

## MELD, MELD-Na, RPR, RDW (%), and MELD + HDLc Significantly Predicted Mortality in the Enrolled Patients

In the study, MELD, MELD-Na, RPR, RDW (%), and MELD + HDLc have been acknowledged as substantial mortality predictors. No significant difference was observed between the diagnostic performance of MELD and MELD-Na. However, MELD demonstrated significantly better diagnostic accuracy than RPR (DeLong's Test, $p$ < 0.001), RDW (%) (AUC = 0.804, $p$ < 0.001), and MELD + HDLc (AUC = 0.627, $p$ < 0.001), with an AUC of 0.978. Similarly, MELD-Na (AUC = 0.977) outperformed RPR (AUC = 0.880, $p$ < 0.001), RDW (%) (AUC = 0.804, $p$ < 0.001), and MELD + HDLc (AUC = 0.627, $p$ < 0.001) in terms of diagnostic performance. When comparing RPR and RDW (%), RPR (AUC = 0.880) showed significantly better diagnostic accuracy (DeLong's Test, $p$ = 0.034). Additionally, RPR also had superior diagnostic performance compared to MELD + HDLc ($p$ < 0.001). RDW (%) (AUC = 0.804) was found to be significantly better than MELD + HDLc (AUC = 0.627, $p$ = 0.004) (Table 7 and Fig. 1).

**Table 7:** Comparison of the diagnostic performance of various predictors in predicting mortality

| *Predictor* | *AUROC* | *95% CI* | *P* | *Sn* | *Sp* | *PPV* | *NPV* | *DA* |
|---|---|---|---|---|---|---|---|---|
| MELD + HDLc | 0.627 | 0.53–0.724 | 0.034 | 97% | 32% | 26% | 97% | 44% |
| MELD | 0.978 | 0.96–0.996 | <0.001 | 100% | 88% | 67% | 100% | 91% |
| MELD-Na | 0.977 | 0.958–0.996 | <0.001 | 97% | 89% | 68% | 99% | 91% |
| RDW (%) | 0.804 | 0.733–0.874 | <0.001 | 90% | 72% | 43% | 97% | 75% |
| RPR | 0.880 | 0.824–0.935 | <0.001 | 90% | 78% | 50% | 97% | 81% |

AUROC, area under ROC curve; CI, confidence interval; DA, diagnostic accuracy; NPV, negative predictive value; P, $p$-value; PPV, positive predictive value; Sn, sensitivity; Sp, specificity

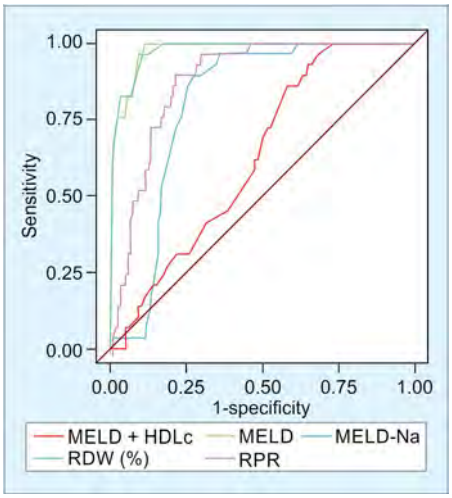


**Fig. 1:** Comparison of the diagnostic performance of various predictors in predicting mortality

## Discussion

In this study, patients included were 18–65 years old, with a mean age of 46.41 ± 11.48 years. This corresponds with observations from a systematic review by D'Amico, comprising 23,797 patients from 118 studies, which reported a mean age of 54 years.[9] Likewise, in an investigation conducted by Cholongitas et al., which enrolled 312 patients, the mean age was 49.3 ± 11 years.[10] Among 150 patients enrolled in our study, 79.3% (119) were male and 20.7% (31) were female, yielding a male-to-female ratio of 3.8:1. This male predominance aligns with an investigation conducted by Li et al., where 60.8% of participants were male.[11]

Regarding residency, 31.6% (43) of participants were urban dwellers, while 68.4% (93) were from rural areas. This lower proportion of urban participants contrasts with a multicenter study by Mukherjee et al., which examined chronic liver disease across eleven Indian hospitals and reported a higher proportion of urban participants.[12] The difference is likely due to varying demographic profiles.

Alcohol-related liver disease (45.6%) constituted the predominant etiology in this investigation, followed by hepatitis B (14.8%). These outcomes align with findings from research conducted by Mukherjee et al. and Swaroop et al.[12,13] Male predominance was observed across all etiologies, while in females, hepatitis C was the leading cause, followed by NASH-related cirrhosis. These findings are consistent with prior research.[12,13]

The mean Hb level in the study was 8.08 ± 2.30 gm/dL (range: 3.6–15.2 gm/dL), reflecting anemia caused by factors such as nutritional deficiencies and variceal bleeding.[14] The mean platelet count was 1.05 ± 0.75 lakhs, ranging from 0.12 to 6.7 lakhs. Thrombocytopenia in cirrhotic patients is commonly attributed to portal hypertension, which leads to platelet sequestration in an enlarged spleen and reduced hepatic thrombopoietin production.[15]

The mean total bilirubin level was 4.98 ± 6.01 mg/dL (range: 0.14–37 mg/dL). This discovery corresponds with an examination conducted by Ahmad et al., reporting a progressive increase in bilirubin with advancing liver disease and significant correlations with disease severity.[16] The mean SGOT and SGPT levels were 100 and 66.76 U/L, respectively. SGOT levels exceeding SGPT can be explained by reduced hepatic blood flow and a predominance of alcoholic liver disease, which is associated with decreased SGPT levels due to pyridoxal phosphate deficiency.[17]

Mean serum albumin level was 2.71 gm/dL, consistent with Carvalho and Machado, who reported reduced plasma albumin levels in advanced cirrhosis due to impaired hepatic synthesis, which can decline by up to 60–80% in severe cases.[18] Serum creatinine had a mean of 2.04 mg/dL, likely attributable to splanchnic vasodilation, reduced effective blood volume, renal hypoperfusion, and subsequent AKI, as described by Slack et al.[19] Mean sodium level was 130.16 ± 5.78 mEq/L, consistent with findings of Young et al., which showed a mean sodium level of 135.36 ± 1.41 mEq/L.[20] The mean HDL level was 22.89 ± 10.74 mg/dL, comparable to the findings of Trieb et al., who observed mean HDL levels of 22 mg/dL (range: 11–30 mg/dL) in patients with decompensated cirrhosis.[21]

Among the participants, 76% (114) were classified as CTP class C, which can be attributed to the enrollment of hospitalized patients with advanced disease. All patients were followed for 30 days, with 80.7% (121) surviving and 19.3% (29) expiring during this period. The mean time to mortality was 6.28 ± 3.76 days (range: 1–16 days).

Hyponatremia seemed markedly correlated with mortality. Mean sodium level within survivors was 131.32 mEq/L, compared to 125.31 mEq/L in those who expired. This discovery aligns with Biggins et al., who identified low S Na as a potential indicator of death in LT candidates.[22] Additionally, mean HDL level was much lower in the expired group (12.07 mg/dL) compared to survivors (25.48 mg/dL). This aligns with Habib et al., who found that low HDL levels indicate poor prognosis in noncholestatic cirrhosis.[23]

### Receiver Operating Characteristics Analysis

CTP score: While sensitivity was 100%, specificity was only 0.8%, and diagnostic accuracy was 20% ($p = 0.623$), indicating poor performance as a 30-day mortality predictor.

MELD score: The AUROC was 0.978, indicating excellent discriminatory ability, consistent with Kim et al., who found MELD to be an effective predictor of 1-, 2-, and 3-year mortality, especially 1-year mortality.[24]

MELD-Na: The AUROC of 0.977 also indicated excellent performance, aligning with findings from Peng et al., which highlighted the superior sensitivity and specificity of MELD-Na over CTP in critical care settings.[25]

MELD + HDLc: With an AUROC of 0.627 ($p = 0.034$), this model had limited predictive ability. While Wang et al. demonstrated improved predictive performance with MELD + HDLc,[26] our findings suggest a need for additional parameters to enhance its utility.

RDW (%): AUROC came to 0.804 ($p < 0.001$), with 72% specificity and 90% sensitivity, demonstrating moderate predictive accuracy. This aligns with Zhou et al., who associated RDW with advanced fibrosis in NAFLD.[27]

RPR: The AUROC was 0.88 ($p < 0.001$), with a sensitivity of 90% and specificity of 78% at a cutoff of ≥23.7. These findings are consistent with Chen et al., who described RPR as a reliable and cost-efficient predictor of significant fibrosis and cirrhosis.[28]

## Conclusion

Most cirrhotic patients in the study were middle-aged males from rural areas. Alcohol and hepatitis B were the leading etiologies. The cohort exhibited anemia, thrombocytopenia, elevated bilirubin, low albumin, and hyponatremia. At 30 days, 19.3% mortality was observed, primarily associated with low sodium and HDL levels. MELD and MELD-Na were the most reliable mortality predictors, followed by RDW and RPR, while MELD + HDLc showed poor performance.

### Limitations

The study's limitations include the sample size of 150, which, while reasonable, may not be large enough for broad generalization. The study's focus on ages 18–65 excludes older populations with cirrhosis. The majority of participants were from rural areas, limiting applicability to urban populations with different lifestyles and healthcare access. The 30-day follow-up may be too short to assess long-term outcomes. Acknowledging these limitations helps contextualize the findings and suggests areas for future research.

## Orcid

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ORIGINAL ARTICLE

# Assessment of Handgrip Strength and Its Clinical and Hematological Correlates of Inflammation among Adults with Pulmonary Tuberculosis: A Cross-sectional Study from a Tertiary Care Center of Western India

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## Abstract

**Background:** Pulmonary tuberculosis (TB) is a significant contributor to illness and chronic functional decline in developing countries. Although treated aggressively through powerful antibiotics, the after-effect of the disease and treatment often has a detrimental impact on overall health, especially muscle function of the person affected. This study aimed at assessing the handgrip strength and its association with common clinical and routine laboratory parameters tested.

**Materials and methods:** This was a cross-sectional study with a predetermined sample size of 72 participants. Sociodemographic data, symptoms, and complete blood chemistry (CBC) findings were noted. Handgrip strength was measured by a rather inexpensive and validated Camry handheld digital dynamometer, which determined handgrip strength in pounds after adjusting for the individual's age, sex, and weight.

**Results:** Among the total number of study subjects, 49% were females and 51% were males. Out of the total study population, 29 were newly diagnosed, while 43 were treated for the disease. Symptoms of the disease ($p < 0.001$) and poor clinical findings like tachycardia ($p < 0.001$), raised temperature ($p = 0.011$), low mid-arm circumference ($p < 0.05$), and abnormal chest auscultatory findings ($p = 0.002$) were reported more among newly diagnosed patients. There was no difference between handgrip strength or inflammatory indices among the two groups ($p > 0.05$). The respective calf circumference and monocyte count were significant factors determining handgrip strength.

**Discussion:** This study accounts for the introduction of a new concept of assessment of muscle function among patients and survivors of TB as an indicator of disease improvement and to prognosticate outcomes and quality of life.

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## Introduction

Pulmonary tuberculosis (TB) has been proven to be a significant contributor to illness in low- and middle-income countries. With a steadily rising prevalence, India alone accounts for one-fifth of the global burden of this disease. Once afflicted, it is known to result in an alarming 27% mortality among those individuals without access to appropriate and timely medical care.[1] With the advent of the National Tuberculosis Elimination Program (NTEP), active case finding has been emphasized upon greatly with door-to-door surveillance, especially after the COVID-19 pandemic.[2] The introduction of the new and improved directly observed treatment under supervision (DOTS and DOTS plus) has also been instrumental in rendering the affected population sputum negative, thereby controlling the rising tide of resistant cases.[3]

Symptoms in pulmonary TB can be classified as constitutional (fever, weight loss, anorexia) and locoregional (cough, breathlessness, and hemoptysis), which predilect the affected individual to a chronic debilitating state.[4] One of the many chronic complications is that of sarcopenia.[5] Sarcopenia has also been proven to act as a predisposing factor to acquiring primary TB, producing reactivation of a latent infection, and easing systemic dissemination of the involved organism.[6]

Sarcopenia, or declining muscle function *per se*, is not commonly reported. This is primarily attributed to the fact that the predominant symptoms of disease are discerning enough to make the patient feel better upon their resolution, and additionally to the accompanying nutritional deficits either as a result of disease-induced anorexia or a chronically developed catabolic state. The Asian Working Group for Sarcopenia (AWGS) 2019 contends that diagnosing sarcopenia requires measurements of both muscle quality and quantity.[7]

The Asian Working Group for Sarcopenia 2019 recommends using either dual-energy X-ray absorptiometry (DEXA) or multifrequency bioelectrical impedance analysis (BIA), both height-adjusted, for measuring muscle mass in diagnosing sarcopenia.[8] In day-to-day practice within resource-limited settings, the use of calibrated anthropometry devices has also been recommended for the same.[9] The gold standard for measuring handgrip strength is the JAMAR® hydraulic hand dynamometer (model J00105, Lafayette Instrument Company, United States of America). Although sensitive, financial constraints often restrict its utility to certain research facilities.[10] This study was conducted using the relatively inexpensive Camry digital handgrip dynamometer (model EH101, Zhongshan Camry Electronic Co., Ltd., China), which has been validated for its use in clinical settings.[11,12]

Circulating markers of sarcopenia have also been reviewed extensively. Sarcopenic patients, on average, have a high blood ratio of oxidized to reduced glutathione, accumulation of protein adducts, and an exaggerated innate immune response compared to their age-matched nonsarcopenic counterparts.[13]

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The detection of these markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), although accurate, is dependent on advanced instrumentation and molecular techniques, thereby limiting their utility in daily practice. In a country like India, with a majority of patients having economic hardships, these ancillary diagnostics deter the patient's will to receive any treatment at all. Complete blood chemistry (CBC)–derived inflammatory markers like neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammatory immune index (SIII), systemic inflammatory response index (SIRI), and monocyte-to-lymphocyte ratio (MLR) have proven association with poor outcomes in hospitalized patients.[14] Among individuals with solid organ malignancies, high levels of MLR and SIII are significant prognostic markers.[15] The calculation of these indices is simple, quick, and well suited for busy outpatient settings as is the case in most regions of India.

Literature pertaining to the clinical assessment of sarcopenia among individuals suffering from or treated for pulmonary TB in resource- and time-limited settings is deficient, especially in India,[3] a country where the prevalence of the disease is high (24,22,000 persons affected annually).

This study aims to assess handgrip strength as a marker of muscle function and a component of sarcopenia among TB patients. It also aims to utilize commonly prescribed tests such as CBC to derive inflammatory markers along with clinical parameters and study their relation to handgrip strength among both newly diagnosed as well as treated pulmonary TB patients.

## Materials and Methods

This was a cross-sectional study conducted at a single tertiary care center, Smt Kashibai Navale Medical College and General Hospital, Pune, Maharashtra, India, within the period of 1 year (December 2022–December 2023). Written informed consent was obtained from the patients in their vernacular language. Ethical approval was obtained from the Institutional Ethics Committee of Smt Kashibai Navale Medical College prior to commencement of the study (approval number: SKNMC/Ethics/App/2022/863).

### Sample Size Determination

The sample size required to run a linear regression analysis to predict handgrip strength (continuous) with the hematological parameters of inflammation (SIII, SIRI, NLR, PLR, MLR) (continuous) with four adjusting variables was 72 patients. The alpha error rate assumed is 5%, with a power of 90%. This sample size is calculated to detect a moderate coefficient of determination for the entire model ($R^2 = 0.2$, Cohen's $f^2 = 0.25$).[16,17]

### Patient Recruitment

The following patients were included:

- Patients 18–65 years of age, in the outpatient department or admitted to the inpatient department of the Department of Respiratory Medicine, Smt Kashibai Navale Medical College and General Hospital.
- Patients diagnosed with pulmonary or extrapulmonary primary TB by GeneXpert and confirmed by culture of samples.

The following patients were excluded:

- Secondary or reactivated TB.
- Skeletal and articular TB.
- Tuberculous meningitis or neural TB.
- Critically ill patients.
- Active or prior HIV infection.
- Active ischemic heart disease.
- Clinical evidence of heart failure.
- Clinical evidence of liver cirrhosis.
- Severe chronic obstructive pulmonary disease ($FEV_1$ <70%).
- Active malignancy with concurrent chemotherapy.
- Neuromuscular disorders.
- Thyroid disorders.
- Uncontrolled diabetes mellitus (HbA1c >7%).
- Psychiatric illnesses incapacitating the patient' ability to provide consent or perform the required tests.

### Data Collection

Data was collected as follows:

- Demography and preliminary details.
- Age in years, outpatient or inpatient ID, sex, education, and occupation were documented.

### History and Physical Examination

Symptoms and their duration, history of substance abuse, and comorbidities. Body mass index (BMI) was calculated as weight in kg/height in $m^2$, and additional components of the modified Bandim TB score.

- Axillary temperature, measured with a digital thermometer in a dry portion of the axilla.
- Anemic conjunctiva, assessed at the lower palpebral conjunctiva in daylight.
- Tachycardia (>90 beats per minute), assessed manually and digitally on a monitor with chest leads connected.
- Abnormal lung auscultatory findings, examined by a senior pulmonologist, lung fields auscultated anteriorly (supraclavicular, supramammary, mammary, axillary, and infraaxillary regions) and posteriorly (suprascapular, scapular, interscapular, and infrascapular regions).
- Mid-upper arm circumference (MUAC) in centimeters, measured using an elastic measuring tape at the midpoint of an imaginary line joining the acromion of the scapula to the olecranon process of the ulna. Calf circumference was documented in cm using an elastic measuring tape at the widest portion of the calf with the lower limb muscles relaxed.
- Details of treatment were noted with respect to the regimen being used for treatment (drug-sensitive or drug-resistant TB therapy).

### Nutritional Assessment

A standardized questionnaire, Mini Nutritional Assessment short-form (MNA-SF), was utilized to objectively assess nutritional status.[18]

### Grip Strength

Upper arm grip strength was measured with the patient sitting upright comfortably on a chair or the bed, the arm to be assessed held at 90° flexion at the elbow joint. A smooth but firm grip was used to squeeze the bar as much as possible and release. The reading was noted, and the process was repeated twice to obtain an average of three readings. Based upon the chart provided along with the dynamometer, the grip strength was classified as weak or normal for age, sex, and weight.

Hematological indices of inflammation were calculated as follows:

Systemic Inflammatory Immune Index = Neutrophil lymphocyte ratio × Platelet Count ($10^9$/L)/Lymphocyte Count ($10^9$/L)

Systemic Inflammatory Response Index = Neutrophil lymphocyte ratio × Monocyte Count ($10^9$/L)/Lymphocyte Count ($10^9$/L)

### Statistical Analysis

Continuous data were summarized as medians (interquartile ranges), while categorical data were summarized as frequencies (percentages). Continuous data were assessed for normality by visualizing histograms and Q–Q plots. Evaluation of the association between two categorical variables was performed using Pearson's Chi-squared test or Fisher's exact test as appropriate,

and between two continuous variables was performed using Spearman's rank correlation test. Evaluation of the difference between two continuous groups was performed using the Wilcoxon rank-sum test.

## Results

Among the total number of study subjects ($n$ = 72), 49% were females ($n$ = 35), and 51% were males ($n$ = 37). The study population was stratified into two groups based on treatment status (treated vs newly diagnosed), and both groups were age-matched. Sociodemographic features are mentioned in Table 1.

**Table 1:** Sociodemographic characteristics of the study participants

| *Characteristic* | *No. of patients* |
|---|---|
| Education | |
| Literate | 69 (95.8%) |
| Illiterate | 3 (4.2%) |
| Occupation | |
| Employed | 44 (61%) |
| Unemployed | 28 (39%) |
| Comorbidities | |
| Yes | 17 (23.6%) |
| No | 55 (76.4%) |
| Diabetes mellitus | 6 (8.3%) |
| Hypertension | 7 (9.7%) |
| Thyroid disorders | 4 (5.6%) |
| History of OR active substance use | |
| Yes | 28 (39%) |
| No | 44 (61%) |
| Type of substance used | |
| Alcohol | 8 (11.1%) |
| Tobacco chewing | 13 (18.2%) |
| Tobacco smoking | 7 (9.7%) |

Number of patient, $N$ = 72

Table 2 summarizes the findings on history which were assessed. Symptoms of the disease were reported more frequently among the newly diagnosed patients ($p$ < 0.001). Fever, cough, fatigue, night sweats, and fluctuation in body weight were documented more among newly diagnosed patients as opposed to treated patients ($p$ < 0.001), along with the alarming symptom of hemoptysis, which followed a similar trend ($p$ = 0.036). Figure 1 provides a pictorial representation of the symptoms among the two groups.

On physical examination, a lower value of MUAC (right arm, $p$ = 0.024; left arm, $p$ = 0.020), an increased body temperature ($p$ = 0.011), tachycardia ($p$ < 0.001), and abnormal lung auscultation findings ($p$ = 0.002) were reported among the group of participants who were newly diagnosed (Table 3). A similar observation was made with the nutritional assessment scores ($p$ < 0.0001), with lower mean scores obtained by newly diagnosed patients. The majority of the study participants were right-handed (91.6%). Among these, 96.6% of newly diagnosed patients ($n$ = 28) and 83.7% of treated patients ($n$ = 36) had a weak grip strength in their right hand ($p$ = 0.089), while 89.7% of newly diagnosed patients ($n$ = 26) and 72.1% of treated patients ($n$ = 31) had a weak grip strength in their left hand ($p$ = 0.072). The dominant handgrip strength, however, did not differ significantly between the two groups ($p$ > 0.9).

Table 4 describes the various laboratory hematological parameters among the two groups, wherein the red cell distribution width (RDW) was significantly higher among the treated group ($p$ = 0.044) as compared to that of the newly diagnosed patients. The value of the SIII, although higher in the newly diagnosed patient group, was not statistically significant ($p$ = 0.3). The NLR and the PLR showed similar statistical trends among the two groups.

Assessment of clinicohematological correlates of handgrip strength (Table 5) showed bilateral calf circumference values ($p$ = 0.000), MUAC of the right arm ($p$ = 0.009), and MUAC of the left arm ($p$ = 0.012) to have a positive association. The presence of anemia also correlated similarly with handgrip strength ($p$ = 0.021).

A robust linear regression model was utilized to ascertain the risk factors of poor handgrip strength. The association between the inflammatory parameter SIII and dominant handgrip strength (Fig. 2), after adjusting for age, sex, BMI, and treatment status, was not significant ($\beta$ = –0.22, 95% CI: –0.48 to 0.04, $R^2$ = 0.9769, $p$ = 0.11). Conversely, a stepwise regression analysis performed revealed the respective calf circumference and monocyte count to be significant predictive factors of changes in the grip strength of the concerned hand ($p$ = 0.000) (Table 6).

## Discussion

The management of pulmonary TB is arduous and multifactorial, with a considerable degree

**Table 2:** Clinical findings among newly diagnosed and treated participants

| *Characteristic* | *Total, (N = 72)*[1] | *Newly diagnosed, (N = 29)*[1] | *Treated, (N = 43)*[1] | *p-value*[2] |
|---|---|---|---|---|
| Height (cm) | 158.0 (155.0, 160.5) | 158.0 (156.0, 160.0) | 158.5 (154.9, 161.1) | 0.9 |
| Body weight (kg) | 60 (50, 68) | 59 (55, 61) | 61 (46, 70) | 0.4 |
| BMI (kg/m$^2$) | 23.7 (21.1, 26.3) | 23.7 (21.6, 25.0) | 24.8 (19.5, 27.7) | 0.3 |
| Fever | 42 (58%) | 26 (90%) | 16 (37%) | <0.001*** |
| Cough | 46 (64%) | 28 (97%) | 18 (42%) | <0.001*** |
| Fatigue | 49 (68%) | 13 (45%) | 36 (84%) | <0.001*** |
| Anorexia | 41 (57%) | 13 (45%) | 28 (65%) | 0.088 |
| Night sweats | 32 (44%) | 21 (72%) | 11 (26%) | <0.001*** |
| Chest pain | 16 (22%) | 7 (24%) | 9 (21%) | 0.7 |
| Dyspnea | 28 (39%) | 10 (34%) | 18 (42%) | 0.5 |
| Back pain | 1 (1.4%) | 0 (0%) | 1 (2.3%) | >0.9 |
| Hemoptysis | 6 (8.3%) | 5 (17%) | 1 (2.3%) | 0.036* |
| Total number of symptoms | 3.00 (3.00, 4.00) | 4.00 (4.00, 5.00) | 3.00 (2.00, 3.50) | <0.001*** |
| Duration of symptoms (weeks) | 12 (8, 20) | 16 (8, 20) | 12 (7, 16) | 0.5 |
| Change in body weight (kg) | 3.0 (–8.0, 6.0) | –9.0 (–10.0, –7.0) | 5.0 (4.0, 7.0) | <0.001*** |

[1]Median (IQR), $n$ (%); [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; *$p$ < 0.05; ***$p$ < 0.001

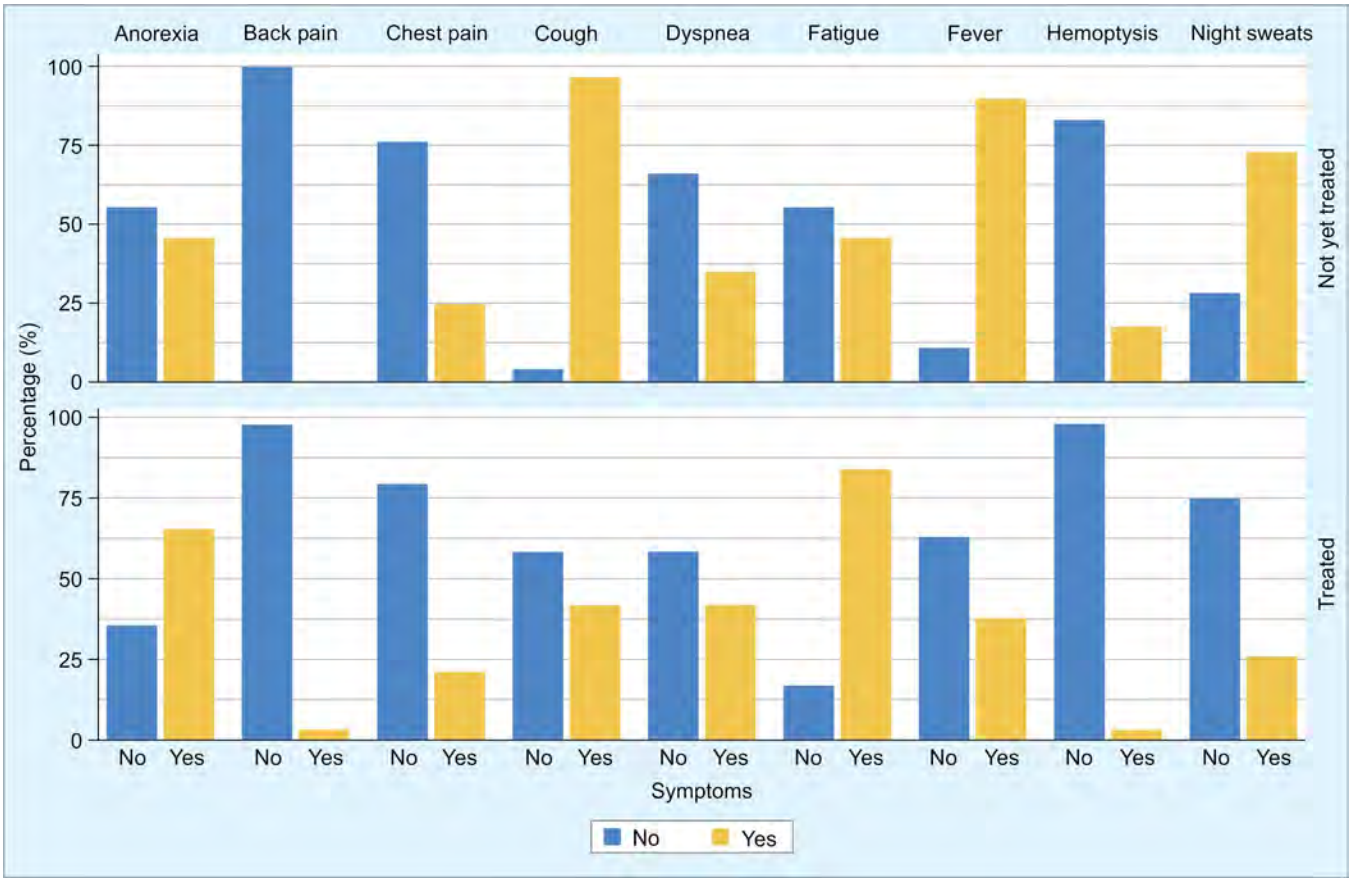


**Fig. 1:** Bar plot of symptoms among both newly diagnosed and treated individuals. The bar plot shows the prevalence of each symptom among the two groups, namely, the newly diagnosed and treated participants. A higher number of symptoms was noted among the newly diagnosed patients ($p < 0.001$)

**Table 3:** Physical examination findings among newly diagnosed and treated participants

| *Characteristic* | *Total, (N = 72)*[1] | *Newly diagnosed, (N = 29)*[1] | *Treated, (N = 43)*[1] | *p-value*[2] |
|---|---|---|---|---|
| Dominant hand | | | | |
| Left | 7 (9.7%) | 2 (6.9%) | 5 (12%) | |
| Right | 65 (90%) | 27 (93%) | 38 (88%) | |
| Grip strength in right hand | 67 (42, 75) | 70 (40, 75) | 53 (43, 75) | 0.563 |
| Grip strength in left hand | 65 (42, 77) | 71 (42, 76) | 51 (42, 77) | 0.589 |
| Grip strength in dominant hand | 65 (42, 75) | 71 (40, 75) | 52 (42, 75) | >0.9 |
| Calf circumference (right) | 29.00 (26.93, 30.00) | 28.40 (27.00, 30.00) | 30.00 (26.85, 30.80) | 0.3 |
| Calf circumference (left) | 29.05 (26.98, 30.05) | 28.00 (27.00, 30.00) | 29.60 (26.70, 30.85) | 0.3 |
| MUAC (right) | 20.00 (18.93, 21.00) | 19.30 (18.00, 20.00) | 20.00 (19.55, 21.30) | 0.024* |
| MUAC (left) | 20.00 (18.90, 21.00) | 19.00 (18.10, 20.30) | 20.10 (19.20, 21.50) | 0.020* |
| Tachycardia (>90 bpm) | 45 (63%) | 26 (90%) | 19 (44%) | <0.001**** |
| Lung auscultation | | | | 0.002** |
| Abnormal (crepts, wheeze, no sound) | 34 (47%) | 20 (69%) | 14 (33%) | |
| Normal | 38 (53%) | 9 (31%) | 29 (67%) | |
| Temperature (>37°C) | 39 (54%) | 21 (72%) | 18 (42%) | 0.011* |

[1]Median (IQR), *n* (%); [2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test; *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$

of dependence upon patient compliance with therapy and nutritional rehabilitation. Although antitubercular therapy functions well to provide bacteriological clearance, the resultant disease process, as well as adverse effects of medications involved, lead to a state of persistent inflammation. Hence, despite complete clinicopathological or clinicoradiological cure, the physical state of the affected individual continues to deteriorate.[19]

The overall prevalence of weak dominant handgrip strength was 85.7% in males and 91.8% in females ($p = 0.238$). This finding was similar to that in the national cohort study conducted by Yang et al.[20] It was concluded in this 8-year longitudinal follow-up study that women were at 20% (age-adjusted OR = 1.20, 95% CI: 0.98–1.47) higher risk of developing sarcopenia than men. However, TB by itself predisposes

**Table 4:** Laboratory studies among newly diagnosed and treated participants

| *Characteristic* | *Total, (N = 72)*[1] | *Newly diagnosed, (N = 29)*[1] | *Treated, (N = 43)*[1] | *p-value*[2] |
|---|---|---|---|---|
| Anemia (Hb) | 62 (86%) | 26 (90%) | 36 (84%) | 0.7 |
| Neutrophil count (cells/mm$^3$) | 5,456 (4,291, 6,515) | 5,997 (4,480, 6,644) | 5,132 (3,954, 6,352) | 0.3 |
| Lymphocyte count (cells/mm$^3$) | 1,343 (932, 1,731) | 1,160 (895, 1,653) | 1,420 (953, 1,823) | 0.5 |
| Platelet count (cells/mm$^3$) | 3,56,000 (2,99,650, 3,99,924) | 3,45,000 (2,86,000, 3,68,000) | 3,67,000 (3,03,000, 4,00,000) | 0.12 |
| Monocytes (cells/mm$^3$) | 488 (329, 618) | 489 (336, 624) | 487 (328, 615) | 0.7 |
| RDW | 17.00 (15.38, 18.53) | 17.00 (14.00, 18.00) | 17.80 (15.75, 19.00) | 0.044* |
| BTB score | 7.00 (6.25, 8.00) | 7.00 (6.00, 8.00) | 9.00 (9.00, 9.00) | 0.2 |
| Missing data | 42 | 0 | 42 | |
| SIII | 1,451 (1,111, 1,864) | 1,495 (1,316, 1,794) | 1,346 (1,019, 1,913) | 0.5 |
| NPLR | 0.026 (0.021, 0.036) | 0.025 (0.022, 0.036) | 0.026 (0.020, 0.035) | 0.9 |
| PLR | 322 (216, 16,274) | 299 (230, 471) | 359 (209, 21,028) | 0.4 |
| NLR | 4.06 (3.40, 5.35) | 4.28 (3.55, 6.16) | 3.84 (3.30, 4.79) | 0.14 |
| SIRI | 13 (9, 17) | 12 (9, 16) | 14 (9, 17) | 0.3 |

[1]Median (IQR), *n* (%); [2]Fisher's exact test; Wilcoxon rank sum exact test; Wilcoxon rank sum test; *$p < 0.05$

**Table 5:** Clinicohematological correlates of handgrip strength

| | | *Handgrip strength (right)* | *Handgrip strength (left)* |
|---|---|---|---|
| Calf circumference (right) | *r* | 0.417** | 0.434** |
| | *p* | 0.000**** | 0.000**** |
| Calf circumference (left) | *r* | 0.403** | 0.415** |
| | *p* | 0.000**** | 0.000**** |
| MUAC (right) | *r* | 0.306** | 0.309** |
| | *p* | 0.009** | 0.008** |
| MUAC (left) | *r* | 0.288* | 0.295* |
| | *p* | 0.014* | 0.012* |
| Neutrophil count in % | *r* | 0.075 | 0.068 |
| | *p* | 0.534 | 0.572 |
| Lymphocyte count in % | *r* | 0.065 | 0.067 |
| | *p* | 0.588 | 0.577 |
| Platelet count | *r* | –0.084 | –0.059 |
| | *p* | 0.484 | 0.620 |
| Monocyte count | *r* | 0.180 | 0.192 |
| | *p* | 0.130 | 0.106 |
| RDW | *r* | 0.042 | 0.033 |
| | *p* | 0.728 | 0.785 |
| SIII | *r* | –0.020 | –0.009 |
| | *p* | 0.868 | 0.937 |
| | *N* | 72 | 72 |
| SIRI | *r* | 0.119 | 0.127 |
| | *p* | 0.318 | 0.288 |
| PLR | *r* | -0.093 | -0.079 |
| | *p* | 0.436 | 0.510 |
| MLR | *r* | 0.171 | 0.170 |
| | *p* | 0.151 | 0.155 |
| NLR | *r* | 0.053 | 0.043 |
| | *p* | 0.661 | 0.722 |

*$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$

males to developing sarcopenia even after treatment (OR 3.44, 95% CI: 1.79–6.68), as shown by the derivations from the Korea National Health and Nutrition Examination Survey by Choi et al.[21]

Increased number of symptoms of both the disease and constitutional symptoms, with poor clinical examination findings, were also documented among the newly diagnosed patients in our study. Low BMI may be an innate host trait associated with TB infection and might also increase the risk of sarcopenia in the future.[22] In our study, we found BMI positively correlating with handgrip strength ($p = 0.007$) and low calf

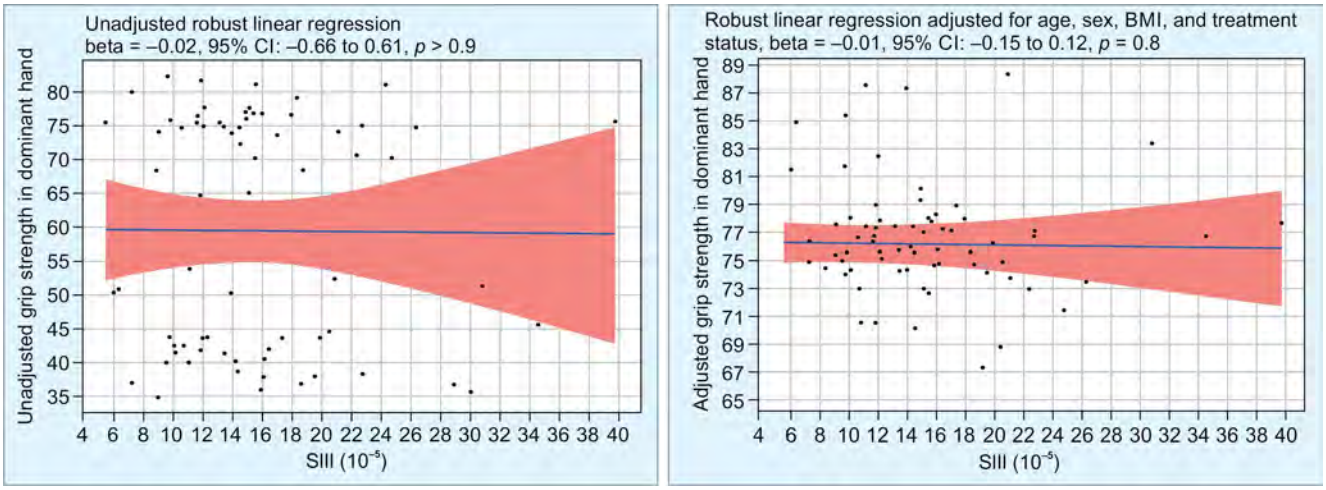


**Fig. 2:** Unadjusted and adjusted robust linear regression results for association of SIII with grip strength in dominant hand. The association between the inflammatory parameter SIII and dominant handgrip strength, after adjusting for age, sex, BMI, and treatment status, was not significant ($\beta = -0.22$, 95% CI: –0.48 to 0.04, $R^2 = 0.9769$, $p = 0.11$)

**Table 6:** Factors affecting handgrip strength

| *Model* | | *B*^ | *Std error*^ | *Beta*[I] | *t* | *Significance* | *R square* | *p-value* |
|---|---|---|---|---|---|---|---|---|
| Grip strength (in pounds) in left hand | | | | | | | | |
| 1 | Constant | –1.367 | 16.111 | | –0.085 | 0.933 | 17.20% | 0.000**** |
| | Calf circumference (left) | 2.126 | 0.557 | 0.415 | 3.818 | 0.000 | | |
| 2 | Constant | –26.035 | 17.468 | | –1.490 | 0.141 | 26.40% | 0.000**** |
| | Calf circumference (left) | 2.516 | 0.545 | 0.491 | 4.613 | 0.000 | | |
| | Monocyte count | 0.027 | 0.009 | 0.312 | 2.929 | 0.005 | | |
| Grip strength (in pounds) in right hand | | | | | | | | |
| 1 | Constant | –0.580 | 15.747 | | –0.037 | 0.971 | 17.40% | 0.000**** |
| | Calf circumference (right) | 2.091 | 0.545 | 0.417 | 3.837 | 0.000 | | |
| 2 | Constant | –23.298 | 17.101 | | –1.362 | 0.178 | 25.70% | 0.000**** |
| | Calf circumference (right) | 2.451 | 0.536 | 0.489 | 4.573 | 0.000 | | |
| | Monocyte count | 0.025 | 0.009 | 0.298 | 2.789 | 0.007 | | |

^Unstandardized coefficients; [I]Standardized coefficients; ****$p < 0.0001$

circumference as a strong risk factor for developing poor handgrip strength.

Anemia is an ignored parameter by virtue of erythrocytosis being adversely affected by disease processes. In this study, we found anemia (hemoglobin value <9 gm/dL) correlating positively with mean grip strength in both hands (right hand: $p = 0.021$; left hand: $p = 0.025$) but did not differ significantly among newly diagnosed and treated patients ($p = 0.7$). This was similar to the findings in a nationwide cohort and cross-sectional study China Health and Retirement Longitudinal Study (CHARLS) conducted by Liu et al.[23] It was in this aforementioned study that it was determined that, on average, a per 1 gm/dL higher hemoglobin level was associated with 5% lower odds of sarcopenia (OR = 0.95, 95% CI: 0.90–0.9).

A significantly higher RDW was documented among treated patients ($p = 0.044$). RDW is a surrogate marker of inflammation, and inflammation is a factor that increases the heterogeneity in red cell size, such as the red blood cell circulation half-life and membrane deformability, and thereby the RDW.[24] This proves the persistence of residual inflammation even after treatment of the underlying disease, which further predisposes a decline in muscle function and leads to sarcopenia.

In the present study, we found comparable values of dominant handgrip strength among the treated as well as newly diagnosed groups of participants ($p > 0.9$). In a nationwide analysis of TB survivors, this is postulated to be a result of the fact that TB is a wasting disease.[21] Although patients report gain in weight during treatment, dynamic changes in body composition after treatment suggest that TB can lead to permanent loss of lean tissue and fat mass.[25] This can predispose these individuals to developing sarcopenia and the complications that follow.[26]

Analysis of a national health survey conducted by Guo et al.[27] found raised counts of neutrophils, monocytes, and total white cells to have a strong association with sarcopenia. Additionally, a strong association of sarcopenia with SIRI OR: 1.397 (1.188–1.645), SIII OR: 1.311 (1.122–1.533) was reported by this study. A similar observation was obtained in our study, in which a higher absolute monocyte count was derived as a strong risk factor for poor handgrip strength; however, SIII and SIRI did not exhibit an association pattern with handgrip strength.

Through these findings, our study highlights the importance of periodic clinical assessment of muscle function among patients with pulmonary TB as one of the possible ways to improve quality of life for both patients and survivors alike. Our study impresses upon

the utility of deriving data from tests that are routinely conducted among all patients, which is well suited for a vast majority of those from low-income backgrounds. As part of DOTS-plus, the personnel in charge of therapeutic supervision can be educated further about means of quality-of-life assessment, which can improve not only outcomes but also survival among these individuals.

A greater sample size, however, would have permitted the extrapolation of the results of this study to a wider population. The present study was cross-sectional in nature; a prospective design would have allowed better comparison and outcome assessment, given that muscle function and its decline are dynamic entities. Furthermore, assessment of physical performance would have provided a changed perspective on this concept.

## Conclusion

Tuberculosis as a disease poses a great challenge to affected individuals, caregivers, and treating doctors alike. With widespread effects of the disease and intense treatment regimens, the definition of disease clearance often synonymizes with clinical improvement. India, a significant contributor to the global burden of the disease, finds itself deficient in documentation supporting outcome and quality assessment among afflicted persons and how it can improve the same. Poor muscle function, a component of sarcopenia, is known to worsen survival quality and outcomes if hospitalized among any individual, irrespective of the disease. Periodic examination of these factors with laboratory parameters already assessed can provide a time-efficient, cost-effective, and thorough insight into amenable variables and therefore alleviate patient care and life.

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*In T2DM Across Continuum,* Choose STRONG

# Glycomet®-GP

Glycomet®-GP 0.5
Metformin Hydrochloride 500 mg SR + Glimepiride 0.5 mg

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Metformin Hydrochloride 850 mg SR + Glimepiride 2 mg

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Glycomet®-GP 3 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 3 mg

Glycomet®-GP 4 FORTE
Metformin Hydrochloride 1000 mg SR + Glimepiride 4 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.
**Additional information is available on request.**
**Last updated:** March 13, 2023

*In uncontrolled T2DM with A1c >8.5%,*

# UDAPA-Trio

Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 500 mg XR


# UDAPA-Trio Forte

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

**In case of any adverse events, kindly contact pv@usv.in For use of registered medical practitioner, hospital or laboratory.*

**Abridged Prescribing Information**
UDAPA-TRIO Forte, UDAPA-TRIO, Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets
**Composition**: Dapagliflozin 10 mg, Sitagliptin 100 mg & Metformin Hydrochloride Extended Release 1000 mg tablets Dapagliflozin propanediol monohydrate eq. To Dapagliflozin 10 mg Sitagliptin Phosphate Monohydrate IP Eq. Sitagliptin 100 mg Metformin Hydrochloride IP (as Extended Release) 1000 mg Dapagliflozin10 mg, Sitagliptin 100 mg & Metformin Hydrochloride Extended Release 1000 mg tablets Dapagliflozin propanediol monohydrate eq. To Dapagliflozin 10 mg Sitagliptin Phosphate Monohydrate IP Eq. Sitagliptin 100 mg Metformin Hydrochloride IP (as Extended Release) 500 mg **Indication**: It is indicated as an adjunct to diet and exercise to improve Glycemic Control adults with type 2 diabetes mellitus **Recommended Dosage**: As directed by the physician. **Method of Administration**: Oral **Adverse Reactions**: Most common adverse reactions reported are: Dapagliflozin - Female genital mycotic infections, Nasopharyngitis, 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; Hypoglycemia; Genital mycotic infections Sitagliptin: General: Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of Diabetic Ketoacidosis. Acute pa ncreat iti s: Hypoglycemia is used in combinations when combined with other anti-hyperglycemic medicinal product; Renal impairment: Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions - Steven johnson syndrome; Bullous pemphigoid Metformin Hydrochloride: Lactic acidosis; In case of dehydration (severe diarrhea 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 < 30ml1min); 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, Renal Impairment, Acute intoxication, Alcoholism. Use In special population: Pregnant women: Due to 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. No data is available. Geriatric Patients: In patients >65 years, it should be used with caution as age increases. For Additional Information/full prescribing information, please write to us: USV Private Limited, Arvind Vithal Gandhi Chowk, B.S.D Marg, Govandi, Mumbai - 400088 Last updated on 02/04/2024.

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ORIGINAL ARTICLE

# Tackling the Growing Concern—Overweight and Obesity among Adolescents in India: An Analysis of National Institute of Nutrition Data

Raju Badiger[1], Dhruv Madaan[2*], Shivprasad S[3]

*Received:* 08 December 2024; *Accepted:* 17 July 2025


## Abstract

The escalating prevalence of overweight and obesity among Indian adolescents present a critical public health challenge requiring urgent attention and effective interventions. This study analyzes data from the National Institute of Nutrition's (NINs) Comprehensive National Nutrition Survey (CNNS) (2016–2018) to provide a comprehensive assessment of this issue. Recognizing the limitations of universal classifications, we utilize body mass index (BMI) cutoffs specifically adapted for the Indian/South East Asian population, offering a more accurate representation of weight status in this vulnerable group.

Employing a quantitative approach with secondary data analysis, our study examines a nationally representative sample of adolescents aged 10–19 years. Anthropometric measurements of weight, height, and BMI were collected and analyzed using the specific Indian/South East Asian criteria to categorize participants. Statistical analyses, including Chi-squared tests and multivariate logistic regression, were conducted using SPSS to explore prevalence, trends, and associated factors.

Findings reveal a statistically significant increase in overweight and obesity among Indian adolescents between 2006 and 2014 ($p < 0.001$), highlighting a concerning trend. Multivariate analysis identified male sex, urban residence, and increased screen time as significant predictors of overweight and obesity based on the adapted criteria. Conversely, higher parental education and engaging in moderate to increased physical activity were associated with decreased odds.

These results underscore the need for targeted interventions addressing socioeconomic disparities, urban–rural differences, and lifestyle factors. Promoting physical activity, reducing screen time, and increasing parental awareness, particularly among urban male adolescents, are crucial. A comprehensive approach involving schools, communities, and public health policies is essential to combat this growing public health concern and foster a healthier future for Indian adolescents.


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## Introduction

Adolescent obesity and overweight have become a significant global health concern. India is posing an alarming increase threat due to adolescent obesity and overweight, which requires immediate attention as well as intervention. This article aims to analyze the National Institute of Nutrition (NIN) data to understand the magnitude of this issue and explore potential contributing factors, specifically utilizing cutoffs appropriate for the Indian/South East Asian population. The findings will provide valuable insights for policymakers, health professionals, and researchers to develop effective interventional methods for preventing and managing adolescent obesity among the Indian population.

Obesity and overweight is defined as the accumulation of abnormal or excessive deposition of fat that impairs the health of the individual, as per the World Health Organization (WHO).[1] The body mass index (BMI) between 25 and 29.9 is termed as overweight, while BMI of 30 and over is termed as obese.[1] However, recognizing the need for population-specific criteria, this study will employ the NIN recommended cutoffs for assessing overweight and obesity among Indian adolescents. The adolescent obesity and overweight pose various risk factors for health impact, including long-term cardiovascular diseases, type II diabetes, psychosocial issues, and musculoskeletal disorders.[2]

There are numerous factors contributing to the alarming rise in obesity and overweight among the adolescent population. These include rapid urbanization, sedentary lifestyles, unhealthy diets, and inadequate physical activity.[3] The nutritional transition in India has led to a shift from traditional, balanced diets to high-calorie-rich diet, poor in nutrition diets, which are flooded with saturated fats, trans fats, high glucose, and salt content.[3] Moreover, increased exposure to technology-based gadgets such as mobile phones, television, and video games has led to decreased physical activity and outdoor games among adolescents.[3]

The NIN, a premier institute for nutritional research in India, has been conducting nationwide surveys to monitor nutrition-related indicators, including adolescent obesity and increased weight. The present study utilized the data from NIN to assess the prevalence of obesity and overweight among adolescents across different sociodemographic groups and geographical regions, applying the appropriate Indian cutoffs for classification.

The growing concern of increased weight among adolescents and obesity in India necessitates immediate attention and intervention. This article aims to provide a comprehensive analysis of the NIN data to understand the magnitude of the issue and identify potential contributing factors, based on classification using Indian-specific criteria. The findings will contribute to implementing and modifying the strategies to control and manage adolescent overweight and obesity, ultimately improving their health and well-being.

To combat the rising issue of adolescent obesity and overweight in India, a multisectoral approach is required. Some potential strategies include:

- School-based interventions: Implementing physical education programs, promoting healthy eating habits, and creating awareness about the consequences of overweight and obesity can contribute to a healthier school environment.[4]
- Community-based programs: Engaging local communities and stakeholders in

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awareness campaigns and promoting physical activity through community events can help create a supportive environment for adolescents.[5]

- Public health policies: Developing and enforcing policies that regulate food advertising targeting children, promote healthy food options in schools, and encourage physical activity, which contribute tremendously in decreasing the prevalence of adolescent obesity.[1]

The obesity and increased weight among Indian adolescents has emerged as a major public health concern. The national data from NIN have revealed an astonishing rise in adolescent obesity in India. This research aims to highlight the contributing factors based on NIN data, analyzing the prevalence using relevant Indian cutoffs. Furthermore, it will provide recommendations for addressing the problem.

## Methodology

The present research aims to analyze the growing concern of obesity and overweight among adolescents in India using data from the NIN. While global criteria for classifying weight status are widely used, it is crucial to acknowledge that these criteria may not be entirely appropriate for populations with different body compositions, such as those in South Asia. Therefore, this study will specifically utilize BMI cutoffs adapted for the Indian/South East Asian population to provide a more accurate assessment of the prevalence of overweight and obesity among Indian adolescents. The methodology employed in this research is primarily quantitative, with a focus on secondary data analysis. The data used for this analysis is extracted from the NIN database, specifically the Comprehensive National Nutrition Survey (CNNS), which was conducted between 2016 and 2018.[6–8]

To ensure the accuracy and reliability of the findings, a systematic sampling approach was adopted in the CNNS. The sample consisted of adolescents aged between 10 and 19 years, covering both genders and various socioeconomic backgrounds. The data was collected through anthropometric measurements, including weight, height, as well as BMI. This BMI was further used to categorize the adolescents into underweight, normal weight, overweight, and obese based on the specific Indian/South East Asian cutoffs.[1,6–10]

**Table 1:** Prevalence of overweight and obesity among adolescents in India (2006 and 2014)

| *Year* | *Overweight (%)* | *Obesity (%)* |
|---|---|---|
| 2006 | 10.1 | 1.9 |
| 2014 | 15.8 | 3.9 |

### Research Design

The present study was a quantitative study based on secondary data analysis. The source of the data was NIN's CNNS conducted during 2016 and 2018.[6,9]

### Data Source

The primary data source is the CNNS dataset, which includes information on anthropometric measurements (weight, height, and BMI) of adolescents aged 10–19 years. The dataset covers both genders and various socioeconomic backgrounds.[6]

### Classification of Participants

The specific BMI cutoffs used in this study for the Indian/South East Asian population are based on recommendations from the WHO Expert Consultation on "Appropriate Body-mass Index for Asian Populations and Its Implications for Policy and Intervention."[7,8] These recommendations acknowledge that the association between BMI, body fat percentage, and health risks differs in Asian populations compared to Caucasian populations.

The classifications used are as follows:
Underweight: BMI <18.5 kg/m$^2$.
Normal weight: BMI 18.5–22.9 kg/m$^2$.
Overweight: BMI 23.0–24.9 kg/m$^2$.
Obesity: BMI >25.0 kg/m$^2$.

### Data Analysis

We employed statistical software (SPSS) for data analysis. The following statistical tests were conducted. Calculated frequency distributions for BMI categories based on the Indian/South East Asian cutoffs. Examined mean BMI, standard deviation, and other summary measures. Investigated associations between sociodemographic factors like gender and socioeconomic status and BMI categories classified using the Indian/South East Asian cutoffs. Tested whether the distribution of BMI categories differed significantly across groups. Explored predictors (such as age, gender, and socioeconomic status) associated with being overweight or obese based on the Indian/South East Asian criteria.

Estimated odds ratios and confidence intervals.

This study, by employing BMI cutoffs appropriate for the Indian context, has contributed valuable insights into the increased prevalence of overweight and obesity among Indian adolescents and informs targeted interventions to address this public health challenge more effectively.

## Results

We performed a cross-sectional study utilizing the NIN data from the 2006 and 2014 surveys to examine the extent of the problem. Importantly, the BMI data from these surveys were reanalyzed using the Indian/South East Asian-specific cutoffs for classifying overweight and obesity. The Chi-squared test was used to assess the differences in the prevalence of overweight and obesity across these 2 years based on these adapted criteria. Additionally, we carried out a multivariate logistic regression analysis to determine the factors linked to overweight and obesity in adolescents as defined by the Indian/South East Asian cutoffs.[9]

As shown in Table 1, there was a statistically significant increase in the prevalence of overweight and obesity in adolescents in India between 2006 and 2014 when classified using the Indian/South East Asian BMI cutoffs ($p < 0.001$).

As shown in Table 2, the multivariate logistic analysis revealed that male sex, urban residence, and higher screen time were significantly associated with increased odds of adolescent overweight and obesity based on the Indian/South East Asian criteria. In contrast, having parents with higher education and engaging in moderate to increased physical activities was statistically associated with decreased odds of overweight and obesity according to these adapted classifications.

These findings emphasize the need for appropriate intervention to combat adolescent overweight and obesity in India. School-based interventions, community-based programs, and public health policies should focus on promoting physical activity, reducing screen time, and creating awareness about the consequences of overweight and obesity, particularly among male adolescents in urban areas. Additionally, involving parents and improving their education on the topic may contribute to a healthier environment for adolescents.

## Discussion

The adolescent obesity and overweight has become a significant concern in India, with its negative effect on both physical and mental health of children. This study aims to analyze the NIN data to understand the magnitude of the issue and discuss potential strategies for intervention.[1]

As per the data from the WHO, India has the second-highest number of overweight children globally. The NIN data reveals that there is an alarming rise in the obesity among children in India, which has increased from

**Table 2:** Factors associated with overweight and obesity among adolescents in India (2014)

| *Variable* | *Odds ratio (95% CI)* |
|---|---|
| Sex (male vs female) | 1.43 (1.12–1.83) |
| Urban residence | 1.95 (1.46–2.60) |
| Parental education (higher vs lower) | 0.66 (0.48–0.90) |
| Physical activity (moderate to high vs low) | 0.44 (0.32–0.60) |
| Screen time (>2 vs ≤2 hours) | 1.84 (1.38–2.44) |

10.1% in 2006 to 15.8% in 2014. This rise poses a threat to the future health of the nation, necessitating immediate attention.[1,9]

There are various contributing factors for the growing concern of childhood obesity and overweight in India. These include sedentary lifestyles, unhealthy dietary patterns, and sociocultural factors.[4] Urbanization and increased access to fast food have also played a significant role in this epidemic.[5]

Overweight and obesity during adolescence has a detrimental health impact like type 2 diabetes, cardiovascular disease, and psychosocial problems. Furthermore, these conditions can persist into adulthood, increasing the potential risk for noncommunicable diseases.[4,5]

Childhood obesity and overweight has emerged as a major public health concern in developing countries like India. The NIN data reveals a concerning trend in the increasing prevalence of childhood obesity and overweight in the country. This discussion aims to analyze the NIN data and explore the possible factors contributing to this issue. Furthermore, it will provide recommendations for addressing the problem.

Socioeconomic factors play a crucial role in the rising number of childhood obesity and overweight in India. A study by Singh et al. highlights that urbanization, higher income, and increased access to processed foods contribute to the issue.[11] These elements align with the research by Garg et al., which indicated that adolescents from affluent socioeconomic backgrounds have a higher propensity for being overweight or obese.[10–12]

## Dietary Habits

The trend toward poor dietary choices, marked by an increase in the intake of high-calorie foods and sugary drinks, significantly contributes to the growing rates of overweight and obesity among Indian adolescents. This issue is further compounded by sedentary lifestyles and decreased physical activity.[13–16]

## Sedentary Lifestyle

The rise in sedentary behavior, characterized by extended periods of screen use and lower levels of physical activity, is a critical risk factor for overweight and obesity in Indian adolescents. Rani et al. also emphasize the urgency for initiatives aimed at enhancing physical activity among this demographic.[17,18]

Psychosocial elements, such as stress, diminished self-esteem, and emotional eating, are associated with the increasing rates of overweight and obesity among adolescents in India. These factors can promote unhealthy dietary choices and diminish the motivation to engage in physical activity, exacerbating the problem.[13]

## Inadequate Public Health Policies and Programs

The absence of efficient public health initiatives targeting overweight and obesity in adolescents is a major concern.[12] This situation underscores the necessity for comprehensive and focused interventions to combat this issue.[13]

The escalating rates of overweight and obesity among adolescents in India represent a significant public health challenge. It is essential to adopt a holistic strategy that encompasses schools, community engagement, and relevant public health policies. By developing and applying effective intervention strategies, we can aspire to a healthier future for young people in India.

# Recommendations

- It is vital to establish detailed public health initiatives aimed at reducing the prevalence of overweight and obesity among adolescents in India. These programs should encourage nutritious eating, boost physical activity, and address psychosocial factors linked to these conditions.
- Schools should be encouraged to incorporate physical and health education into their programs to nurture healthy habits in students.
- Regulating the marketing and accessibility of high-calorie, low-nutrition foods and sugary drinks can help decrease their consumption among teens.
- Increasing awareness regarding the health risks linked to overweight and obesity through focused campaigns and community outreach can inspire families and individuals to adopt healthier lifestyles.
- Implementing regular assessments and monitoring of adolescent overweight and obesity trends can help gauge the success of current interventions and guide future policy actions.

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ORIGINAL ARTICLE

# Predictors of Mortality among Hospitalized Patients in a Tertiary Care Center across Three COVID-19 Waves

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## Abstract

**Background:** Several studies conducted across the globe have stated the most frequent risk factors linked to increased severity and death related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite the huge impact SARS-CoV-2 had on India, there is a lack of adequate research on the epidemiology and predictors of mortality due to coronavirus disease 2019 (COVID-19). The study aims to assess the predictors of mortality among COVID-19 patients admitted to a tertiary healthcare hospital in central India across the first, second, and third COVID-19 waves.

**Materials and methods:** This record-based cross-sectional study was conducted using secondary data of patients hospitalized with SARS-CoV-2 between September 2020 and October 2022 in a designated COVID-19 treatment center.

**Results:** Data on 861 adult patients were analyzed. The mean age of the patients was 52.87 ± 14.21 years, with the majority of them being females (573, 66.6%). Results showed no significant difference between men and women infected with COVID-19. During the complete course of the pandemic age patients, a history of hypertension, cough, dyspnea, myalgia, loss of taste, loss of smell, computed tomography (CT) score, and invasive ventilation was significantly associated with mortality of COVID-19 patients. Among the COVID-19 approved pharmacotherapy, steroids significantly ($p$-value < 0.000) lowered the risk of mortality [adjusted odds ratio (aOR): 0.134; 95% confidence interval (CI): 0.071–0.255] in COVID-19 hospitalized patients.

**Conclusion:** Various sociodemographic and clinical profile predictors were associated with COVID-19 infection among pharmacotherapies. Steroid use helped lower the risk of mortality associated with COVID-19. More studies will help us to understand the various characteristics of the SARS-CoV-2 virus more elaborately, so as to ensure the proper preparedness of the healthcare system for future COVID-19 impacts.

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## Introduction

There was a devastating impact brought by the coronavirus disease 2019 (COVID-19) pandemic, and nearly all parts of the world and societies were affected. It was caused by a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in China late in 2019.[1] COVID-19 has different prevalence and mortality rates depending on variables such as geographical location, transmission rate, vulnerability of the population, effectiveness of preventive measures, and the strength of the healthcare system.[1,2] According to the statistics released by the Ministry of Health and Family Welfare in India, the country logged over 44 million cases of COVID-19, with a mortality rate of 1.19%.[2]

The COVID-19 pandemic has brought immense challenges to mankind in that there is limited knowledge regarding disease pattern, genetic susceptibility, risk factors for mortality, long-term side effects, and the absence of an effective cure.[3] A wide range of studies carried out worldwide have reported several common risk factors for severe illness and death with SARS-CoV-2, including elderly age, male sex, hypertension, diabetes, smoking, and a history of heart disease. Elevated concentrations of certain biomarkers, such as C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH), D-dimer, and prothrombin time (PT), have also been associated with a higher severity and mortality of COVID-19.[4] Despite the significant milestones in the understanding of COVID-19, most studies provided a general outline of the pandemic. The nature of the disease and its effects on societies should be understood further by a more detailed elaboration of its characteristics for future management of the disease.

Other studies have been carried out within the country[3–5] and abroad[6–13] on COVID-19 mortality and its risk factors. However, the predisposing factors to mortality among populations with different demographic and clinical characteristics vary significantly, and, most importantly, the resilience of the health system plays an enormous role in determining outcomes.[5] Given that COVID-19 has a significant impact on India, there are not adequate studies on the epidemiology and predictors of mortality in the country.

Therefore, this research tries to assess predictors of mortality among patients admitted into a central Indian tertiary care hospital during the first, second, and third waves of the COVID-19 pandemic.

### Objectives

To assess the clinical profile and the predictors of mortality among patients admitted with COVID-19 in a tertiary care hospital.

## Materials and Methods

It is a record-based cross-sectional study which was carried out at a tertiary healthcare center in Central India, a superspeciality hospital at Gondia district in Maharashtra, which turned into a designated COVID-19 treatment center under the policies released by the government during the time of the COVID-19 pandemic. In the present study, inclusion was made of all patients above 18 years, who were admitted for >1 day in this hospital for the treatment of COVID-19. Hospital records were used for the analysis of all individuals hospitalized with SARS-

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CoV-2 [RTPCR positive or COVID-19 antigen (Ag) positive] between January 2020 and April 2022 (*N* = 861). The abovementioned inclusion criteria were used to enroll patients into the study, as it depicted the time period of the three COVID-19 pandemic waves within the country. Rapid antigen COVID-19 testing kits used for the cases in the study were J Mitra, Merril, SD Biosensor, and MyLab. All of which were approved by Indian Council of Medical Research (ICMR) for testing. Kits used for interleukin 6 (IL-6), ferritin, D-dimer, and C-CRP were Croma II and Snibe Co., Erba reg, Avecon, Delta, Coral, and DiaSys. The number of patients under treatment or undergoing testing depended upon the severity of the COVID-19 infection, and this has been denoted as "*N*" in the table. Computed tomography (CT) was used to assess grading in COVID-19 positive patients and was scored out of 45(*N* = 53) and 24 (*N* = 234). This change in scoring was because of an alteration in the grading of CORADS score as suggested by the COVID-19 Task Force. Steroids used for patient management were methylprednisolone and dexamethasone.

A universal sampling technique was utilized and included 861 participants: wave I-408, wave II-422, and wave III-31. The hospital record sheets were used to document patients' demographic characteristics, detailed histories, any underlying morbidities, clinical presentations, investigations done, treatments performed, and health outcomes.

### Statistical Analysis

Data were entered in Microsoft Excel sheets. For the purpose of analysis, SPSS version 27.0 and Strata statistical analysis software were used in this study. In this study, data were analyzed wave-wise, which comprises three waves: wave I (*n* = 408), wave II (*n* = 422), and wave III (*n* = 31). A combined analysis of the three waves was also done. For all the variables, descriptive statistics were obtained. The categorical variables were presented by percentages, while the continuous variables, such as mean, median, and standard deviation, were calculated. Cutoff levels for IL-6, Ferritin, D-dimer, and CRP kits were 0–7 ng/mL, 10–322 ng/mL, 0–500 ng/dL, and 6 mg/dL, respectively. Analysis concerning laboratory parameter values was done in two groups: laboratory parameters above the mean levels and other laboratory parameters below the mean levels. To check predictors of outcome (mortality), "0" was coded for no death, while "1" was given for death. The second objective-attempted to see the association of independent variables and outcome (death) using the Chi-squared tests for categorical variables and independent *t*-test for those continuous variables (IL-6, ferritin, D-dimer, CRP). Comparisons for CT score using medians were done since the CT score was rated using two different methods, and the Mann–Whitney test was employed for associating the median score. For assessing the third objective as far as the effectiveness of pharmacotherapy on mortality of COVID-19 is concerned, all variables (pharmacotherapy) with 0.2 on univariate analysis were considered for further analysis using logistic regression. A $p < 0.05$ was considered statistically significant.

In view of the confidentiality, all identifying details were made available for use by the investigators only in a single data sheet that is password accessed. All data have been deidentified prior to analysis. All methods complied with the Declaration of Helsinki regulations and guidelines.

## Results

### Sociodemographic and Clinical Profile

In total, the hospital records of 861 admitted patients were analyzed. The mean (SD) age of the patients was 52.87 ± 14.21 years. The majority of the patients hospitalized were females, *n* = 573 (66.6%). The clinical characteristics of the study participants across the three COVID-19 waves are summarized in Table 1. The maximum number of participants was in wave II (*n* = 422), followed by wave I (*n* = 408), then wave III (*n* = 31). The median age varied for all three waves; the youngest patients were noted in wave II (25 years), followed by wave I (39 years), and then wave III (57 years). More female patients were admitted than males across all three waves. Hypertension and diabetes were the commonest comorbidities present, followed by congestive heart disease, chronic kidney disease, and chronic obstructive pulmonary disease (COPD); similar presentation was noted in all three waves. Fever and cough were the commonest symptoms across all three waves. In the second wave, higher proportion of fever, dyspnea, and cough were seen, whereas symptoms of loss of taste and smell were commonly seen in the third wave.

Table 2 shows a comparison of laboratory parameters. A blood test was done only if recommended by the physician. The mean values of heart rate (HR), respiratory rate (RR), and mean arterial pressure (MAP) were almost similar in all three waves. CRP and ferritin were higher in the second wave, IL-6 in the first wave, and D-dimer in the third wave. Table 3 represents the treatment used across all three waves. High-flow nasal oxygen was used more in the second wave, remdesivir was used more in the first and second waves, and Favipiravir was used more in the second wave. In contrast, tocilizumab was equally used across all three waves. Only 40 patients in the second wave received bevacizumab. Steroid was the most common drug used in all three waves. Death outcome was higher in wave II (*n* = 59/422; 13.98%) than in wave I (*n* = 22/408; 5.39%) and wave III (*n* = 2/31; 6.45%), total *n* = 83/861 (9.63%).

### Association of Demographic and Clinical Profile Characteristics with Mortality across Three Waves of COVID-19

In wave I, patients with the following characteristics were associated with a higher risk of mortality–dyspnea, increased RR, increased HR, high D-dimer, and IL-6. In wave II, patients with the following characteristics were associated with a higher risk of mortality—diabetes, hypertension, dyspnea, cough, loss of smell, myalgia, raised white blood cell (WBC) count, and raised CT score. No variable was found to be significant in the third wave, but when combined, all three waves of patients with the following risk factors were found to have a risk of mortality; age, hypertension, dyspnea, cough, loss of taste and smell, myalgia, increased RR, high IL-6, and D-dimer score (univariate analysis to assess predictors of mortality across three waves of COVID-19 is shown in Table 4).

### Assessing the Effect of Pharmacotherapy on Mortality in COVID-19 Patients

In wave I, steroid use significantly lowered the risk of mortality [adjusted odds ratio (aOR): 0.055; 95% confidence interval (CI): 0.015–0.195] with a *p*-value < 0.000. Tocilizumab was not significant, with a *p*-value of 0.393and an odds ratio of 4.7 (95% CI: 0.132–173.2).

In wave II, steroid use significantly (*p*-value < 0.000) reduced mortality (aOR: 0.125; 95% CI: 0.055–0.281). Remdesivir and bevacizumab were also found to be significantly associated with *p*-value of 0.013 (aOR: 15.349; 95% CI: 1.795–131.2) and *p*-value < 0.000 (aOR: 5.036; 95% CI: 2.294–11.058), respectively. Tocilizumab and favipiravir were not significantly associated with a *p*-value of 0.419 and 1.0, respectively.

In wave III, invasive ventilation was significantly associated (*p*-value < 0.001) with reduced mortality (aOR: 0.144; 95% CI: 0.088–0.265).

Combining all waves, steroid use was found to significantly (*p*-value 0.000) reduce mortality (aOR: 0.134; 95% CI: 0.071–0.255). Remdesivir and bevacizumab

were also significant, with a *p*-value of 0.005 (aOR: 5.238; 95% CI: 1.633–16.804) and *p*-value < 0.000 (aOR: 6.856; 95% CI: 6.856–3.270), respectively. The higher odds ratio in remdesivir and bevacizumab in wave II and combined waves suggests that patients with severe symptoms received these medications. Whereas favipiravir and tocilizumab were not significantly

**Table 1:** Comparison of clinical presentation of patients admitted with COVID-19 across three consecutive waves

| *Variable* | *Wave I (N = 408)* | *Wave II (N = 422)* | *Wave III (N = 31)* | *Waves I + II + III (N = 861)* |
|---|---|---|---|---|
| Sociodemographic | | | | |
| Age (median) (years) | 39 (13–87) | 25 (4–88) | 57.4 (25–83) | 52.87 (4–88) |
| Gender | | | | |
| Male | 121 (29.65) | 154 (36.49) | 13 (41.93) | 288 (33.40) |
| Female | 287 (70.35) | 268 (63.51) | 18 (58.07) | 573 (66.60) |
| Comorbidities | | | | |
| Hypertension | 201 (49.26) | 170 (40.28) | 21 (67.74) | 392 (45.53) |
| Diabetes | 137 (33.74) | 119 (28.19) | 16 (51.61) | 272 (31.60) |
| CHD | 67 (16.42) | 42 (9.95) | 9 (29.03) | 118 (13.70) |
| CKD | 10 (2.4) | 3 (0.7) | 2 (6.45) | 15 (1.74) |
| COPD | 1 (0.2) | 4 (0.94) | 0 | 5 (0.58) |
| Symptoms | | | | |
| Fever | 329 (80.63) | 366 (86.72) | 17 (54.83) | 712 (82.70) |
| Dyspnea | 186 (45.58) | 227 (53.79) | 11 (35.48) | 424 (49.25) |
| Cough | 313 (76.71) | 374 (88.62) | 8 (25.80) | 695 (80.72) |
| Cold | 193 (47.3) | 216 (51.18) | 1 (3.22) | 410 (47.62) |
| Loss of taste | 72 (17.64) | 32 (7.58) | 6 (19.35) | 110 (12.78) |
| Loss of smell | 79 (19.36) | 23 (5.45) | 9 (29.03) | 111 (12.89) |
| Chest pain | 24 (5.88) | 19 (4.5) | 0 | 43 (4.99) |
| Myalgia | 55 (13.48) | 56 (13.27) | 12 (38.70) | 123 (14.29) |
| Headache | 49 (12.01) | 47 (11.13) | 2 (6.45) | 98 (11.38) |
| Dizziness | 56 (13.72) | 33 (7.8) | 1 (3.22) | 90 (10.45) |
| Others* | 64 (15.6) | 68 (16.11) | 3 (9.6) | 135 (15.6) |

*Others include nausea, vomiting, and diarrhea; The number in parentheses represents row-wise percentages

**Table 2:** Comparison of laboratory results of patients admitted with COVID-19 across three consecutive waves

| *Variable* | *Wave I (Mean ± SD)* | *Wave II (Mean ± SD)* | *Wave III (Mean ± SD)* | *Waves I + II + III (Mean ± SD)* |
|---|---|---|---|---|
| RR (breaths per minute) | 23 ± 3.9 (*n* = 408) | 24.5 ± 5.4 (*n* = 422) | 25 ± 6.5 (*n* = 31) | 23.8 ± 4.8 (*n* = 861) |
| HR (beats per minute) | 89.46 ± 16.3 (*n* = 408) | 93.6 ± 15.1 (*n* = 422) | 92 ± 14 (*n* = 31) | 91.6 ± 15.8 (*n* = 861) |
| MAP (mm Hg) | 94.1 ± 9.3 (*n* = 408) | 93.4 ± 10 (*n* = 422) | 91.2 ± 7.4 (*n* = 31) | 93.7 ± 9.6 (*n* = 767) |
| WBC ($\times 10^9$/L) | 8.3 ± 4.13 (*n* = 236) | 8.9 ± 4.7 (*n* = 381) | 9.3 ± 3.4 (*n* = 30) | 8.7 ± 4.4 (*n* = 647) |
| Platelets ($\times 10^9$/L) | 243 ± 100 (*n* = 237) | 223 ± 96.5 (*n* = 379) | 246 ± 80.7 (*n* = 30) | 232 ± 98 (*n* = 646) |
| CRP (mg/dL) | 31.9 ± 35.6 (*n* = 290) | 44.9 ± 45.8 (*n* = 218) | 18 ± 18.8 (*n* = 24) | 36.6 ± 40.2 (*n* = 532) |
| Ferritin (ng/mL) | 423 ± 763 (*n* = 370) | 452 ± 910 (*n* = 363) | 305.6 ± 340 (*n* = 7) | 436 ± 835.7 (*n* = 740) |
| IL-6 | 78.4 ± 219 (*n* = 287) | 71.4 ± 154 (*n* = 95) | 22 ± 42 (*n* = 14) | 74.7 ± 201.2 (*n* = 396) |
| D-dimer (ng/mL) | 812 ± 1721 (*n* = 370) | 760 ± 1406 (*n* = 223) | 2524 ± 3654 (*n* = 16) | 841 ± 1717 (*n* = 609) |
| CT score* | 18 (0–38) (*n* = 171) | 17 (0–25) (*n* = 164) | 17 (0–22) (*n* = 21) | 17 (0–38) (n = 356) |

*Median values

**Table 3:** Comparison of treatment of patients admitted with COVID-19 across three consecutive waves

| *Variable* | *Wave I N (%)* | *Wave II N (%)* | *Wave III N (%)* | *Waves I + II + III N (%)* |
|---|---|---|---|---|
| High-flow nasal cannula | 144 (35.29) | 108 (25.59) | 1 (3.22) | 253 (29.38) |
| Invasive ventilation | 70 (17.15) | 108 (25.59) | 4 (12.90) | 182 (21.14) |
| Mechanical ventilation | 1 (0.24) | 4 (0.94) | 0 | 5 (0.58) |
| Remdesivir | 327 (80.14) | 321 (76.06) | 12 (38.70) | 660 (76.66) |
| Bevacizumab | 0 | 40 (9.47) | 0 | 40 (4.65) |
| Favipiravir | 17 (4.16) | 43 (10.18) | 0 | 60 (6.97) |
| Tocilizumab | 2 (0.5) | 2 (0.47) | 2 (6.44) | 6 (0.70) |
| Steroids | 351 (86.02) | 386 (91.46) | 21 (67.74) | 758 (88.04) |

**Table 4:** Univariate analysis to assess predictors of mortality among patients admitted with COVID-19 across three consecutive waves

| *Variable* | *Wave I (p-value)* | *Wave II (p-value)* | *Wave III (p-value)* | *Waves I + II + III (p-value)* |
|---|---|---|---|---|
| Age (years) | 0.203 | 0.149 | 0.367 | 0.000 |
| Gender | 0.933 | 0.057 | 0.811 | 0.215 |
| Diabetes | 0.914 | 0.047 | 0.157 | 0.114 |
| Hypertension | 0.115 | 0.000 | 0.313 | 0.001 |
| CHD | 0.897 | 0.318 | 0.350 | 0.871 |
| CKD | 0.545 | 0.483 | 0.701 | 0.684 |
| COPD | 0.814 | 0.523 | NA | 0.427 |
| Fever | 0.000 | 0.113 | 0.185 | 0.888 |
| Dyspnea | 0.017 | 0.000 | 0.657 | 0.000 |
| Cough | 0.491 | 0.037 | 0.419 | 0.007 |
| Cold | 0.419 | 0.286 | 0.790 | 0.490 |
| Loss of taste | 0.085 | 0.065 | 0.474 | 0.003 |
| Loss of smell | 0.061 | 0.047 | 0.350 | 0.001 |
| Myalgia | 0.489 | 0.016 | 0.066 | 0.049 |
| Other symptoms | 0.570 | 0.036 | NA | 0.141 |
| Respiratory rate* | 0.010 | 0.162 | 0.278 | 0.00 |
| Heart rate* | 0.006 | 0.149 | 0.321 | 0.21 |
| Mean arterial pressure* | 0.423 | 0.386 | 0.939 | 0.151 |
| While blood cell count* | 0.632 | 0.005 | 0.695 | 0.20 |
| Platelets* | 0.813 | 0.738 | 0.854 | 0.461 |
| C-reactive protein* | 0.614 | 0.980 | 0.977 | 0.562 |
| IL-6* | 0.000 | 0.805 | 0.203 | 0.000 |
| D-dimer* | 0.000 | 0.601 | 0.206 | 0.000 |
| Ferritin* | 0.934 | 0.166 | 0.021 | 0.213 |
| CT score* | 0.011 | 0.006 | NA | 0.001 |
| High-flow nasal cannula | 0.319 | 0.000 | NA | 0.220 |
| Invasive ventilation | 0.000 | 0.000 | 0.000 | 0.000 |
| Mechanical ventilation | 0.807 | 0.037 | NA | 0.022 |
| Remdesivir | 0.506 | 0.004 | 0.735 | 0.021 |
| Bevacizumab | NA | 0.000 | NA | 0.000 |
| Favipiravir | 0.303 | 0.018 | NA | 0.029 |
| Tocilizumab | 0.006 | 0.141 | 0.701 | 0.051 |
| Steroids | 0.000 | 0.000 | 0.312 | 0.000 |

*Independent *t*-test was used for continuous variables; NA, not applicable if there was an absence of the respective variables

associated with a *p*-value of 1.00 and 0.719, respectively.

## Discussion

In our study, age of the patients was not a significant parameter affecting their outcome in individual waves; however, when all the waves were considered together, increasing age was found to be a significant parameter. Similar results were also found in studies conducted by Lalani et al.[3] and Gayam et al.[10] In a letter to the editor by Ruan et al.,[13] there was also a significant difference in age-groups between the death group and the discharge group. In a study by Nguyen et al.,[14] male gender was a predictor of higher mortality among hospitalized adults with COVID-19. Total deaths (9.6%) reported in our study during the COVID-19 pandemic were lower than the study by Baruah et al.[5] and higher than the study by Vig et al.[4] The difference in death rates is a known aspect of COVID-19 infection, and it has been attributed to several factors such as local COVID-19 containment strategies, mitigation policies and healthcare capacity and delivery, and patient factors such as population age structure, ethnicity, geography, and socioeconomic status.[11,12,15] The death rate in the third wave was very low across the country. In our study, two individuals in the third wave were reported dead, of which one was diagnosed with a mass lesion in a CT scan, suggesting neoplasm. Both these patients were around 80 years of age and admitted for <24 hours with multiple comorbidities.

Dorjee et al.[15] stated that among the COVID-19 deaths reported in their study, 27% were suffering from hypertension. History of diabetes mellitus, COPD, and malignancy were found to be the significant predictors of mortality among COVID-19 patients in a study by Corona et al.[16] A study by Beltramo et al.[17] found that COVID-19 patients with chronic respiratory diseases developed significantly more ventilator-associated pneumonia. However, in the present study, among the various comorbidities, a history of hypertension and malignancy was only found to significantly affect the outcome of the patients. In the meta-analysis performed, Corona et al.[16] discovered dyspnea, fatigue, and myalgia to be the significant predictors of mortality among COVID-19 patients. In the present study, dyspnea and myalgia were the predictors of outcome, along with cough and neurological manifestations—loss of taste and smell. Decreased lymphocyte counts, lower platelet counts, and elevated ferritin and D-dimer levels were found to be significant lab parameters affecting COVID-19 mortality in various studies.[8,10,16] Raised ferritin levels, D-dimer, and IL-6 levels were the laboratory parameters significantly related to mortality in the present study. CT scores of the patients were found to be significantly associated with treatment outcomes in the present study. The use of mechanical and invasive ventilation in treating patients significantly reduced mortality in our study. Studies by Khamis et al.[8] conducted in Oman also found that the majority of the patients admitted with COVID-19 were on mechanical ventilation during their hospital stay.

Studies conducted in various parts of the world have proved that treatment with steroids is an important predictor in reducing mortality among COVID-19 patients, whereas other studies have not established this association.[18–20] Various meta-analyses and systematic reviews conducted have shown a significant reduction in deaths of COVID-19 patients in the steroidal group as compared to the nonsteroidal group.[21–23] The current study also revealed a significant association of COVID-19 mortality among patients on remdesivir therapy as well as steroid treatment. This suggests that patients with severe signs and symptoms would likely receive these treatment measures. Meta-analyses and systematic reviews by Hariyanto et al.[24] and Elsawah et al.[25] have also stated similar findings. Other treatment modalities that were found to be significant predictors associated with the mortality rate among COVID-19 patients in the present study were bevacizumab and favipiravir.

### Strengths and Limitations

The strength of the study is that it is a single-center study where records were electronically maintained. It was one of the first COVID-19-designated hospitals in the district. It received a large number of patients in all waves across the COVID-19 pandemic. Limitations could be that the results may not be generalizable as it is a single-center study, and the current study design may not be ideal to infer causal association.

## Conclusion

In this record-based cross-sectional study of hospitalized patients with COVID-19 infection, each wave of COVID-19 represented a different sociodemographic and clinical profile of patients. On assessing the COVID-19 pandemic as a whole, characteristics such as age, presence of symptoms such as dyspnea, cough, myalgia, and a few neurological manifestations were found to be significantly affecting COVID-19 mortality along with laboratory and treatment factors such as CT score, invasive ventilation, and steroids use. Being a newer strain of the virus, these data are helpful to understand various characteristics of SARS-CoV-2 and to ensure better preparedness of the healthcare system for the future.

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REVIEW ARTICLE

# Splenic Abscess Complicating *Salmonella paratyphi* A Infection: A Case Report and Systematic Review of Literature (2001–2024)

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## Abstract

**Introduction:** Recently, there is an upsurge of splenic abscess due to typhoidal *Salmonella* in India.

**Methods:** We present a case of splenic abscess caused by *Salmonella paratyphi* A in an immunocompetent male and conducted a systematic review of splenic abscess cases attributed to typhoidal *Salmonella* described between January 2001 and May 2024.

**Results:** Of 33 cases reviewed, 26, 2, and 1 case each were reported from India, Sri Lanka, Turkey, Qatar, and Pakistan, respectively. *S. typhi* and *S. paratyphi* A were reported from 29 and 4 cases, respectively. Mean age was 21 years, with 13 children and 8 females. About 28 were immunocompetent and two had diabetes mellitus. Blood, pus, stool, and pleural fluid grew the isolate in 13, 20, 1, and 1 case, respectively. Ultrasonography (USG) abdomen was diagnostic in 28 cases and normal in two cases. Computed tomography (CT) abdomen was diagnostic in all the 27 cases tested. About 17, 12, and 1 patient showed multiple abscesses, solitary lesion, and multiloculated lesion, respectively. USG/CT-guided percutaneous drainage and splenectomy were performed in 25 and 7 cases, respectively. All 33 patients recovered from the infection.

**Conclusion:** We aspire to raise acquaintance among health professionals regarding this uncommon entity and foresee it in pertinent contexts.


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## Introduction

A spectrum of infectious agents could be ascribed for splenic abscesses, inclusive of bacterial, fungal, mycobacterial, and parasitic. Common bacterial agents include *Klebsiella pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*. Unusual organisms include *Burkholderia pseudomallei*, *Salmonella* species, *Mycobacterium*, and actinomycetes. In untreated typhoid fever, splenic abscess develops as one of the complications in the 3rd or 4th week of infection.

## Methods

We describe a patient with splenic abscess caused by *Salmonella paratyphi* A in an immunocompetent male and conducted a systematic review of splenic abscess cases caused by typhoidal *Salmonella* described between January 2001 and May 2024. Medical record was analyzed to evaluate demography, clinical characteristics, management, and outcome.

### Literature Search

We formally analyzed reported cases of splenic abscess owing to typhoidal *Salmonella*. We scrutinized the literature, including PubMed and every single reference for publications of original articles, single cases, or case series including the ensuing keywords: "splenic abscess," and "typhoidal *Salmonella*." Besides, the bibliography of each publication was explored to verify if all reported cases were collected for this review. It was ensured to exclude cases prone to cause duplication.

## Case Report

A 24-year-old male presented with fever for 10 days and loose stools (two episodes for 1 day). The fever was insidious in onset, associated with chills and rigor. He was initially treated for typhoid fever elsewhere, became symptomatically better for a few days, and then again developed symptoms. There was a history of abdominal pain and intake of food outside the home. He also had a history of tobacco use (chewable) for 10 years and an allergy to penicillin. On examination, he was afebrile, nontoxic, and his abdomen was soft without tenderness. Investigations showed hemoglobin of 10 gm/dL, total white blood cells (WBC) of 4600 cells/mm$^3$, total bilirubin of 4.28 mg/dL, direct bilirubin of 1.84 mg/dL, indirect bilirubin of 2.44 mg/dL, aspartate aminotransferase (AST) of 114 U/L, alanine aminotransferase (ALT) of 124 U/L, and alkaline phosphatase (ALP) of 203 U/L. Widal test results were suggestive of paratyphoid fever with O 1:160, H <1:20, AH 1:320, and BH <1:20 dilution. Peripheral smear showed microcytic hypochromic anemia with a left shift of WBCs. Blood culture was sterile, and the human immunodeficiency virus (HIV) test was negative. Ultrasonography (USG) abdomen showed multiple peripheral nonenhancing hypodense areas in the spleen, the largest measuring 9 × 6.5 cm. Empirical treatment was initiated with ceftriaxone. The patient remained febrile (102°F) and developed an episode of loose stools. The antibiotic was escalated to meropenem 1 gm 8th hourly. Computed tomography (CT) abdomen contrast was not taken due to financial constraints. With ultrasound guidance, 50 mL of hemorrhagic pus was aspirated from the largest splenic collection; the rest of the collections were not fully liquefied, hence not aspirated. Pus aspirate from the splenic abscess grew *S. paratyphi* A, sensitive to cotrimoxazole, ampicillin, chloramphenicol, ceftriaxone, meropenem, and resistant to fluoroquinolones. After 11 days of meropenem, he was discharged with an uneventful recovery.

### Literature Review

Database search yielded a total of 35 cases. After screening, we excluded one duplicate and one case report with inadequate details. Overall, 33 cases with full text were assessed for eligibility and included for review, with seven cases recently in 2023 (21%).[1–29] Table 1 illustrates the presentation, laboratory and

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**Table 1:** Clinical presentation, treatment, and outcome of splenic abscess cases due to typhoidal *Salmonella*

| *Authors/year/country* | *Age/sex* | *Presentation* | *Radiology* | *Total WBC (cells/mm$^3$)* | *Pus aspirate culture* | *Blood culture* | *Widal* | *Typhi-dot* | *Lung* | *Drainage* | *Splenectomy* | *Antibiotics* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chaudhry et al., 2003/India[1] | –/M | – | – | – | *S. typhi* | | – | – | – | – | – | – | Cured |
| Sathiyasekaran and Shivbalan, 2005/India[2] | 15/F | Fever for 3 weeks, pain in left shoulder for 1 week | Multiple splenic abscess | Normal | *S. typhi* | Sterile | 160 (O and H) | – | Lt pleural effusion | 30 mL pus drained | – | Ceftriaxone for 2 weeks | Cured |
| Yuksel et al., 2005/Turkey[3] | 12/M | Fever and abdomen pain for 2 weeks | Multiple splenic abscess | 5,600 | Not done | *S. typhi* | Positive | – | | – | Yes | Ceftriaxone for 10 days | Cured |
| Piplani et al., 2011/India[4] | 21/M | Fever with chills and rigors and productive cough of 10 days | Multiple splenic abscess | 6,900 | *S. typhi* | Sterile | Negative | | – | 400 mL pus drained | Emergency splenectomy | Ceftriaxone 4 weeks | Cured |
| | 19/M | Fever for 1 day | USG normal, CT-multiple splenic abscesses | 8,800 | Not done | *S. paratyphi* A | Positive 1:80 | | | Percutaneous drainage | | Ciprofloxacin for 1 week followed by ceftriaxone | Cured |
| Thapa et al., 2007/India[5] | 10/M | Fever and abdominal pain for 15 days | Multiple splenic abscesses | 4,800 | Not aspirated | *S. typhi* | Positive O 1:320 | | | | Yes | Ceftriaxone and ofloxacin | Cured |
| | 10/M | Fever for 1 monthand pain in abdomen for 7 days | Solitary splenic abscess | 19,200 | *S. typhi* | Sterile | Positive 1: 160 | | | 70 mL drained followed by deroofing of abscess cavity | | Ceftriaxone and ofloxacin | Cured |
| Hota, 2009/India[6] | 21/M | Fever for 10 days | Multiple splenic abscess | 6,900 | *S. typhi* | Sterile | O 1:80 | | | 400 mL pus drained | Yes | Ceftriaxone 2 gm BD for 1 week then cipro 500 mg BD for 7 days | Cured |
| | 19/M | Fever for 5 days | Solitary splenic abscess | | Not done | *S. paratyphi* A | O 1:80 | | | Aspiration done | | Cipro 200 mg IV for 5 days/ ceftriaxone 2 gm BD | Cured |
| Naranje et al., 2011/India[7] | 6/F | Fever for 3 weeks and diffuse abdominal pain for 2weeks, jaundice for 10 days | Multiple splenic abscess | 18,530 | Sterile | *S. typhi* | H 1:320 | | | CT-guided aspiration of the largest abscessyielded only 2 mL pus | | Ceftriaxone 4 weeks | Cured |
| Doddaiah et al., 2012/India[8] | 13/M | High-grade fever, diffuse intermittent abdomen pain for 8 days/nausea, loose stools for 3 days | Multiplesplenic abscesses | 13,200 | *S. typhi* | Sterile | Negative | | | USG-guided aspiration | Yes | Ceftriaxone for 3 weeks | Cured |
| Sudhaharan et al., 2014/India[9] | | | – | | *S. typhi* | – | | | | Percutaneous drainage | | Ceftriaxone | Cured |
| | | | – | | *S. paratyphi* A | – | | | | Percutaneous drainage | | Ciprofloxacin | Cured |

*Contd…*

*Contd…*

| *Authors/year/country* | *Age/sex* | *Presentation* | *Radiology* | *Total WBC (cells/mm$^3$)* | *Pus aspirate culture* | *Blood culture* | *Widal* | *Typhi-dot* | *Lung* | *Drainage* | *Splenectomy* | *Antibiotics* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bhongle et al., 2013/India[10] | 14/F | Fever with chills and pain in abdomen on the left side | Multiple splenic abscesses | 11,000 | *S. typhi* | Sterile | O and H 1:320 | | | USG-guided aspiration | | Amoxi-clav then ceftriaxone sulbactam | Cured |
| Sonavane et al., 2015/India[11] | 9/F | Fever, nausea, and abdominal pain for 2 days. Intermittent course of similar episodes for last 1 year | Multiple splenic abscess | 22,200 | *S. typhi* | Not done | | | | 450 mL fluid aspirated | | Ceftriaxone 7 days | Cured |
| Sahu and Talwalkar, 2015/India[12] | 34/F | Dry cough on and off for 1.5 months with mild fever with shivering and diaphoresis | Solitary splenic abscess | 7,400 | *S. paratyphi* A | Sterile | | | Lt pleural effusion/CT-lung atelectasis | CT-guided aspiration | | Amoxiclav for 7 days | Cured |
| Handa et al., 2015/Srilanka[13] | 20/M | Fever for 5 days | Multiple splenic abscess | 3,700 | Sterile | *S. typhi* | | | CT-pleural effusion | Aspirations were done on two occasions | | Ceftriaxone for 5 days/then piptaz | Cured |
| Sharavanan et al., 2016/India[14] | 20/M | Fever high-grade, intermittent for >2 months | Multiloculated hypodense lesion in the upper pole of the spleen | 5,200 | *S. typhi* from intra-operative pus | Not done | O 1:80, H 1:40 | | | – | Yes, since multiloculated | Cefoperazone but no response | Cured |
| Sahu et al., 2017/India[15] | 19/M | Fever with chillsand rigor, jaundice for 15 days and pain in abdomen, left shoulder pain, and jaundice for 7 days | Solitary splenic abscess | 28,500 | *S. typhi* | Sterile | O and H 1:320 | Positive | CT-pleural effusion | USG-guide-daspiration and pigtail catheter wasinserted | Yes due to rupture of splenic abscess into pleural cavity | Ceftriaxone | Cured |
| Shamanna et al., 2017/India[16] | 45/F | Low-grade fever with chills, rigors, and abdominal pain for 10 days | Splenic abscess with partial thrombosis of left portal vein and splenic vein, cholelithiasis with minimal left pleural effusion and hepatosplenomegaly | 15,000 | *S. typhi* | Not done | | | CT-Lt pleural effusion | USG-guide-daspiration and pigtail catheter wasinserted | | Amikacin, amoxicillin + clavulanic acidfor 7 days | Cured |
| Jha and Vidhale, 2018/India[17] | 36/M | Fever for 5 days, associated with chills and severe noncolicky-pain in left hypochondriac region of 3 days | Multiple splenic abscess | 14,000 | | *S. typhi* | | Positive | | USG-guide-daspiration and pigtail catheter wasinserted | No | Ceftriaxone and amikacin for 2 weeks/then meropenem and clindamycin | Cured |

*Contd…*

*Contd…*

| *Authors/year/country* | *Age/sex* | *Presentation* | *Radiology* | *Total WBC (cells/mm$^3$)* | *Pus aspirate culture* | *Blood culture* | *Widal* | *Typhi-dot* | *Lung* | *Drainage* | *Splenectomy* | *Antibiotics* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Khan, 2019/Qatar[18] | 25/M | Fever and left upper abdominal pain for 7 days | Multiple splenic abscess | | *S. typhi* | *S. typhi* | | | | | No | Piptaz for 4 weeks | Cured |
| Dutta and Chatterjee, 2020/India[19] | 19/F | High-grade intermittent fever for7 days, abdominal pain, nausea, and vomiting for2 days and loose stools for 3 days | Multiple splenic abscess and atelectatic changes in the left lung basesuggestive of infarcts and abscesses | Leukocytosis | | *S. typhi* | Negative | | CT-lung atelectasis | | No | Ceftriaxone 2 gm BD for 7 days/cefixime 200 mg twice daily/after readmission, ceftriaxone 2 gm BD and meropenem 1 gm TDS fora month | Cured |
| Kaur et al., 2021/India[20] | 20/M | Abdominal pain for 2 weeks/fever with chills | Solitary splenic abscess | 11,000 | *S. typhi* | Sterile | O 1:160, H 1:320 | Positive | | USG-guided percutaneous drain and 90 mL purulent fluid drained | No | Meftriaxone and azithro for 5 days | Cured |
| Zubair et al., 2021/Pakistan[21] | 18/M | Fever with rigors, anorexia, and pain in left side of abdomen for 1 month | Multiple splenic abscess | | Not done | *S. typhi* | O 1:160 H 1:40 | | | – | No | Meropenem and azithro for 2 weeks | Cured |
| Gupta et al., 2022/India[22] | 15/M | Fever with chills and left hypochondrium pain for 1 month | Multiple splenic abscess | 2,500 | *S. typhi* | Sterile | | | | USG-guided aspiration | No | Ceftriaxone 2 gm BD | Cured |
| Navik et al., 2023/India[23] | 5/M | Fever, decreased appetite, and abdomen distension | USG normal. CT abdomen showed multiple splenic abscess | 6,800 | | *S. typhi* | 1 in 256 | | | – | No | Meropenem 3 weeks | Cured |
| Shaji et al., 2023/India[24] | 25/M | Abdominal discomfort, over left side/high-grade fever with chills. Several episodes of vomiting associated with nausea and decreased appetite | Solitary splenic abscess | 12,210 | | Sterile | H 1:160 | | CT-pleural effusion | – | No | Piperacillin 3.75 gm TDS/after culture azithro 500 mg OD for 2 weeks | Cured |
| Gupta et al., 2023/India[25] | 16/M | High-grade fever for 7 days and left-sided-lower chest pain | Multiple splenic abscess with left-sided pleural effusion and consolidation | | | *S. typhi* | | | CT-Lt pleural effusion | USG-guidedsplenic aspiration200 mL of pus | No | IV antibiotics 4 weeks and 2 weeks of oral antibiotics | Cured |

*Contd…*

*Contd…*

| *Authors/year/country* | *Age/sex* | *Presentation* | *Radiology* | *Total WBC (cells/mm$^3$)* | *Pus aspirate culture* | *Blood culture* | *Widal* | *Typhi-dot* | *Lung* | *Drainage* | *Splenec-tomy* | *Antibiotics* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pius et al., 2023/India[26] | 33/M | High-grade fever with chills for 6 days and abdominal pain for 4 days | Multiple splenic abscess | 15,000 | Sterile | *S. typhi* | | Positive | | USG-guided percutane-ous drain using pigtail catheter 220 cc pus | No | Ceftriaxone and amikacin for 2 weeks/ then IV mero-penem and clindamycin for 2 weeks | Cured |
| Dubey et al., 2023/India[27] | 23/M | High-grade fever with chills and rigor for 4 weeks, pain in left upper abdomen for 3 weeks, headache for 1 week, and vomiting for 2 days | | | *S. typhi* | | | | | Diagnostic tapping | No | Meropenem 7 days/oral cefexime and doxy for 7 days | Cured |
| Sundaresan et al., 2023/ India[28] | 71/M | Fever,generalized weakness, left sided chest pain and left upperquadrant ab-dominal pain on and off for 17 days | Well definedcollection measuring 4 × 5.3 × 5 cm in ventraland superior aspect of the spleen, minimal left pleural effusion | 6,250 | *S. typhi* | Sterile | | | CT-minimal pleural effusion | CT-guided aspiration15 mL of pus was aspirated | No | Cefepime IV for 4 weeks/ oral cefixime 200 mg BD for 2 weeks | Cured |
| Gamage et al., 2023/ Srilanka[29] | 22/F | High-grade fever, chills, and rigors/mild diffuse abdominal pain for 2 weeks | Solitary splenic abscess | | *S. typhi* | Not done | | | | USG-guide-daspiration | | Meropenem 1 gm TDS and subsequently downgraded to ceftriaxone 1 gm BD for 14 days and switched to oral cipro-floxacin 500 mg BD for another 2 weeks | Cured |

Amoxyclav, amoxicillin clavulanate; Azithro, azithromycin; Cipro, ciprofloxacin; IV, intravenous; Piptaz, piperacillin tazobactam

radiological findings, treatment, and outcome of the cases.

### Clinical Characteristics

About 26, 22, and 1 case each were reported from India, Sri Lanka, Turkey, Qatar, and Pakistan, respectively. *S. typhi* and *S. paratyphi* A were reported in 29 and 4 cases, respectively. Complete clinical details could not be extracted for three cases. Among the remaining 30 cases, the mean age was 21 years (range 5–71 years), with 13 pediatric cases. Eight were females. Twenty-eight patients were immunocompetent, and two patients had diabetes mellitus. Two patients sustained blunt trauma to the left side of the abdomen prior to presentation, and another patient had a similar episode of splenic abscess 5 years ago, which was managed conservatively with pigtail drainage.

### Laboratory Diagnosis

Blood culture was positive in 13 cases, and pus aspirate from abscess grew the isolate in 20 cases. Additionally, *Salmonella* was isolated from stool to pleural fluid in one case each. USG of the abdomen was diagnostic of splenic abscess in 28 cases and normal in two cases. CT abdomen was diagnostic in all 27 cases tested. About 17, 12, and 1 patient showed multiple abscesses, a solitary lesion, and a multiloculated lesion, respectively. Widal test showed positive results in 15 of 18 tested, and Typhidot was positive for IgM and IgG in all four cases tested. Two cases were also positive for Leptospira IgM antibodies by ELISA.

### Treatment

Antibiotics administered include ceftriaxone (70%), meropenem (20%), fluoroquinolone (20%), amoxicillin clavulanate (10%), piperacillin tazobactam (6%), azithromycin (6%), and cefixime (6%). USG/CT-guided percutaneous drainage was carried out in 25 cases, and splenectomy was performed in seven cases. In splenectomized patients, five had multiple splenic abscesses, one had a multiloculated collection, and in another case, splenectomy was considered due to rupture into the pleural cavity. In four of the seven splenectomized cases, percutaneous drainage was initially performed.

### Outcome

Respiratory complications were observed in nine cases, which were identified by abnormal chest X-ray in four cases and by CT imaging in the others. Findings included left pleural effusion in all nine cases, concurrent lung atelectasis in two cases, and consolidation in another case. All 33 patients recovered from the infection.

## Discussion

The incidence of splenic abscess in typhoid fever is 0.29–2%.[30] Recently, many cases of splenic abscess due to typhoidal *Salmonella* have been reported in India. Preceding splenic injury and bacteremia are requisites for an abscess to develop. In the reviewed literature, two patients sustained blunt trauma, and 13 cases had positive blood cultures. Given the nonspecific clinical presentation of splenic abscess, which mimics other conditions such as pneumonia and pyelonephritis, clinical diagnosis is challenging. However, USG and CT (the gold standard) play a major role in diagnosis and treatment. There are no current treatment guidelines for splenic abscess due to *Salmonella*. In most reports, ceftriaxone was used, with the duration ranging between 1 and 4 weeks. Though appropriate antibiotics are of paramount importance, to circumvent fulminant and grave infection, drainage of the abscess is very important. Depending on the abscess characteristics, management varies. Percutaneous aspiration is fruitful in the case of unilocular or bilocular abscesses with a complete thick wall without internal septations. For multilocular abscesses with ill-defined cavities, thick necrotic debris, and viscous collections, either laparoscopic or open surgery may be required. Splenic abscess, if left untreated, can lead to many complications such as left-sided pleural effusion, pneumothorax, atelectasis, pneumonia, and others like subdiaphragmatic abscess, gastric or intestinal perforation, and pancreatic fistula. The prognosis of splenic abscess has remarkably improved in recent times with the use of CT-guided percutaneous drainage. Splenectomy remains an extreme option, as most cases are managed with percutaneous drainage and antibiotics. Clinical diagnosis of splenic abscess due to *Salmonella* can be taxing, provided the unconventional descriptions in the published works. By virtue of this report, we aspire to augment awareness among health professionals regarding this uncommon entity and foresee it in pertinent contexts.

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REVIEW ARTICLE

# Treatable Neuropathies

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## Abstract

Peripheral neuropathy is one of the most common neurological problems encountered by physicians, and the broad diagnosis of neuropathy has a wide variety of underlying etiologies and varied clinical presentations. This review aims to cover the spectrum of treatable neuropathies, their etiologies, diagnostic criteria, and advances in treatment. Clinical pattern recognition and neuropathy characterization help narrow the list of differential diagnoses and thus direct the investigations. The list of treatable neuropathies is increasing and mainly includes metabolic, immune, infectious, toxic, and nutritional etiologies. Prompt recognition of treatable neuropathies with early treatment reduces morbidity and disability. In this review, we shall discuss the common treatable neuropathies in detail and tabulate the uncommon conditions.


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## Introduction

Peripheral neuropathy is a spectrum of diseases affecting a peripheral nerve from preganglionic roots, roots, dorsal root ganglion (DRG), postganglionic roots, plexus, and trunk to single or multiple nerves. Neuropathic disorders can affect the cell body (neuronopathy) or they can affect peripheral processes (peripheral neuropathy).[1] Neuronopathies mainly affect the DRG and anterior horn cells, named sensory ganglionopathy or ganglionopathy and motor neuron diseases. Peripheral neuropathies can be classified as per their etiologies, types of nerve fibers affected (sensory, motor, or autonomic), and the portion of the nerve fiber affected (axon or myelin). A proportion of neuropathies respond to treatment. Treatable neuropathies have the potential for treatment and hence reversibility or remission, as seen in chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants, drug/toxin-induced neuropathies, and infectious neuropathies. The groups of treatable neuropathies are many, and some of these conditions are more common than others in clinical practice. Table 1 gives a comprehensive list of the treatable neuropathies with their salient clinical and investigative features and treatments. The common treatable neuropathies are discussed in some detail in this review.

Commonly encountered treatable neuropathies are discussed below under the following headings:

- Metabolic-related neuropathy—diabetic and other uncommon neuropathies.
- Immune-mediated neuropathies—acute inflammatory demyelinating polyneuropathy (AIDP), CIDP, and others.
- Infections-related neuropathy—leprous neuropathy and human immunodeficiency virus (HIV)-related neuropathy.
- Drug/toxin induced neuropathy.
- Cranial neuropathies.
- Entrapment neuropathies.
- Autonomic neuropathy.

## Metabolic-related Neuropathy

### Diabetes-related Peripheral Neuropathy

Diabetic neuropathy (DN) is the most common cause of peripheral neuropathy worldwide. As per the Diabetes Control and Complications Trial (DCCT), the prevalence of DN is approaching almost 50% in both type 1 and type 2 diabetes mellitus (DM).[11] DN has a much higher incidence in type 2 DM (6,100 per 1,00,000 person-years) compared to type 1 DM (2,800 per 1,00,000 person-years).[12]

### Risk Factors

The duration of diabetes and glycosylated/glycated hemoglobin (HbA1c) levels are among the most important risk factors for DN and other microvascular complications.[13] Other metabolic factors that are most associated with diabetes, such as hypertension, hypertriglyceridemia, abdominal obesity, uric acid levels, and low high-density lipoprotein (HDL), are also major predictors of DN. Metabolic syndrome, along with its components, has been found to be an independent risk factor for peripheral neuropathy, especially sensory peripheral neuropathy.[14] Prediabetes is the earliest stage of glucose dysregulation, including the impaired glucose tolerance (IGT) test or impaired fasting glucose (IFG) (American Diabetes Association guidelines). The recent MONICA/KORA trial demonstrated that neuropathy was more common in IGT as compared to the control group, with preferential small fiber involvement in the prediabetes group.[15]

### Clinical Manifestations

Diabetic neuropathy involves varied neurological patterns of neuropathy. Distal symmetric polyneuropathy (DSPN) is the most common pattern encountered in DM, which can affect predominantly small fibers, large fibers, or both together. Following is the spectrum of DN, starting from roots on the left to the peripheral nerve on the right (Table 2 and Fig. 1).

### Management of Diabetic Neuropathy

#### *Prevention of Diabetic Neuropathy*

Periodic assessments for neuropathy with clinical sensory testing with 10 gm monofilament test,[16] correcting any coexistent B12 deficiency,[17] optimizing glycemic control,[10,16] a high suspicion for autonomic involvement, and foot care is important in the prevention, early detection, and reducing the complications of DN.

#### *Pharmacological and Nonpharmacological Treatment of Diabetic Neuropathy*

The stability of HbA1c levels is more important than the actual level of control in the treatment of DN. Long-term follow-up of the landmark DCCT demonstrated that more intensive glucose control ameliorated the onset of neuropathy as well as the progression of surrogate electrophysiologic markers of neuropathy.[11,21] The Food and Drug Administration (FDA)-approved

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**Table 1:** List of treatable neuropathies with salient features and treatment

| *Etiology* | *Clinical hallmarks* | *Treatment strategies* |
|---|---|---|
| *Metabolic* | | |
| DM | Distal symmetric axonopathy usually with a chronic course, fluctuations in relation to glycemic control<br>Small fiber predominant neuropathy early in the course<br>Less often, asymmetric, painful affection of roots/plexus/isolated nerves | Adequate glycemic control and correction of other metabolic factors like hyperlipidemia, obesity, etc.<br>Drugs for neuropathic pain<br>Trial of immunotherapy in proper clinical settings |
| Hypothyroidism | Carpel tunnel syndrome<br>Distal symmetric sensorimotor polyneuropathy[2] | Thyroid hormone supplements<br>CTS may require decompression additionally[3] |
| Renal failure | Distal axonopathy[4] | Correction of uremia, for example, hemodialysis, transplantation[5] |
| Critical illness polyneuropathy | Generalized sensorimotor polyneuropathy with or without myopathy[6] | Aggressive neurorehabilitation, avoidance of steroids, neuromuscular blockers, and control of hyperglycemia and infections |
| Celiac disease | Generalized sensorimotor polyneuropathy, small fiber neuropathy, and neuromyotonia | Gluten-free diet may prevent neuropathy and halt the progress of neuropathy[7] |
| *Immunological* | | |
| AIDP | Acute onset nonlength dependent polyradiculoneuropathy with additional facial, bulbar, respiratory, or autonomic involvement and a preceding history of infection (refer to text for the common and uncommon variants) | IVIG, PE, and complement inhibitors |
| CIDP | Subacute or chronic or relapsing-remitting course of nonlength dependent sensorimotor weakness and areflexia usually in a middle-aged male<br>Atypical presentations are known as pure sensory or motor involvement, distal predominant or multifocal involvement, pure sensory ataxia, etc. (refer to the text for details) | Steroids, IVIG, PE, Rtx<br>Maintenance immunosuppressant drugs—AZA and MMF |
| Vasculitis | Acute/subacute onset mononeuritis multiplex, painful, asymmetric, or multifocal involvement<br>Look for systemic signs of rheumatological disorders, vasculitic skin lesions[8] | Immunomodulatory drugs (Mtx, AZA, MMF, cyclophosphamide, IVIG, etc.) |
| *Infections* | | |
| Leprosy | Commonly, mononeuritis multiplex with predominant loss of pain and temperature sensations<br>Look for hypopigmented and hypoesthetic skin patches and thickened nerves | MDT as per WHO recommendations |
| HIV | Distal symmetric axonopathy is common in chronic infection or related to HAART AIDP and CIDP both presentations are known to occur | HAART, supportive management for neuropathic pain |
| Cytomegalovirus (CMV) | Lumbosacral polyradiculopathy<br>Mononeuritis multiplex[9] | Ganciclovir, foscarnet, and cidofovir as monotherapy |
| Lyme's disease | Bilateral facial neuropathy most common<br>Asymmetric polyradiculoneuropathy<br>Mononeuritis multiplex<br>Primary axonopathy<br>Associated systemic features like rash, fever | Cephalosporins and amoxycillin |
| *Toxic* | | |
| Drugs like antibiotics, chemotherapy<br>Heavy metals like lead, arsenic, thallium, mercury etc.<br>Alcohol related | Detailed account of all the drugs/alternative medicines and temporal relation to the neuropathic symptoms should be noted<br>Sensory involvement is more common, whereas motor predominance can be seen in lead toxicity, GBS-like syndrome with arsenic or thallium[10] | Removal of the toxin<br>Chelation therapy in metal exposure<br>Supportive measures |

*Contd…*

*Contd…*

| *Etiology* | *Clinical hallmarks* | *Treatment strategies* |
|---|---|---|
| *Nutritional* | | |
| Vit B12 deficiency | Sensorimotor axonopathy involving large fibers—loss of kinesthetic sense<br>Additional visual or cognitive changes<br>Myelopathy in the form of SACD<br>Systemic signs, for example, skin pigmentation, clinical settings for malabsorption etc. | Vitamin B12 and folate supplements |
| Other causes are B6 deficiency, thiamine deficiency, and Vit E deficiency | Large fiber sensory predominant axonopathy<br>Systemic signs: atrophic skin changes, cognitive impairment, background of malnutrition, or alcoholism (thiamine deficiency)<br>Disorders of fat absorption and lipoproteins, additional spinocerebellar involvement (Vit E deficiency) | Nutritional supplements |

**Table 2:** Spectrum of DN

| *Radiculoplexopathy* | *Type C nerve fibers/autonomic neuropathy* | *Mononeuropathy* | *DSPN* |
|---|---|---|---|
| • Three types—lumbar, cervical, and thoracic radiculoplexopathy<br>• Lumbar radiculoplexopathy is most common<br>• Subacute in onset, monophasic<br>• Asymmetric, severe pain in thigh initially followed by proximal muscle weakness with atrophy<br>• Secondary to ischemic injury from altered immunity and hence may respond to some extent with IVIG[16] | • Cardiovascular: reduced HRV, resting tachycardia, orthostatic hypotension, and sudden death (malignant arrhythmia)<br>• Gastrointestinal: diabetic gastroparesis, diabetic enteropathy (diarrhea), and colonic hypomotility (constipation)<br>• Urogenital: diabetic cystopathy (neurogenic bladder), erectile dysfunction, and female sexual dysfunction[17] | • Isolated cranial neuropathy (III nerve, IV nerve)<br>• Peripheral nerve—median nerve, ulnar nerve, femoral nerve, and peroneal nerve<br>• When mononeuropathy is sudden in onset, restricting to the area supplied by the nerve, it is less likely to be associated with entrapment and more likely to be secondary to uncontrolled diabetes[18] | • Small-fiber neuropathy—positive symptoms like burning sensation, tingling, allodynia, hyperalgesia, and negative symptoms like numbness, sensory loss (pinprick and temperature). Type C and A delta are affected. Autonomic dysfunction is noted. Nerve conduction studies will be usually negative. It is specifically seen in patients with prediabetes and metabolic syndrome[19,20]<br>• Large-fiber neuropathy—imbalance, sensory ataxia, loss of vibration sensation, loss of position sense, and areflexia. Nerve conduction studies usually show distal symmetric length-dependent sensorimotor loss with ± abnormal somatosensory evoked potentials (SSEP). Patients are at higher risk of falls, fractures, and the development of Charcot neuropathy[12,19,20] |

first-line therapy includes duloxetine, pregabalin, gabapentin, venlafaxine, and amitriptyline.[22–24] The time to peak response is different for different drugs, but in general, 2–3 months is typically required for titration and to gauge the initial response of medications. In patients with inadequate response to initial treatment, either switching to second-line therapy or the addition of second first-line therapy is recommended. Topical treatments with capsaicin 8% with or without lignocaine are effective local therapy for DN-related pain.[24,25] Nutraceutical agents like alpha-lipoic acid (ALA), benfotiamine, acetyl-L-carnitine, gamma-linolenic acid (GLA), vitamin B12, and vitamin D3 are a few of the important molecules that have shown modest decreases in pain related to DN. Table 3 depicts the medications that can be used in the management of pain.

## Immune-mediated Neuropathies

### Acute Inflammatory Demyelinating Polyneuropathy

Acute inflammatory demyelinating polyneuropathy or Guillain–Barré syndrome (GBS) is acute immune-mediated polyneuropathy presenting as a variable degree of symmetrical ascending weakness of all limbs with occasional respiratory failure and autonomic dysfunction that reaches maximal severity within 4 weeks. The main pathophysiology behind GBS is molecular mimicry between microbial and nerve antigens causing an aberrant autoimmune response. Preceding infection, mostly by *Campylobacter jejuni*, triggers an autoimmune response that mainly targets peripheral nerves and their spinal roots. The variants of GBS include:

| | |
|---|---|
| 1. Acute inflammatory demyelinating polyneuropathy | |
| • Acute motor axonal neuropathy<br>• Acute motor-sensory axonal neuropathy | IgG autoantibodies to GM1 and GD1a |
| • Acute motor conduction block neuropathy<br>• Pharyngeal-cervical-brachial weakness | IgG autoantibodies to GT1a, GQ1b, and GD1a |
| 2. Miller Fischer syndrome | |
| • Acute ophthalmoparesis without ataxia<br>• Acute ataxic neuropathy without ophthalmoplegia | IgG autoantibodies to GM1 and GD1a |
| 3. CNS variant—Bickerstaff's Brainstem encephalitis | |

Given the immune-mediated nature of the illness, standard treatment includes intravenous immunoglobulin (IVIG) and plasma exchange (PE). One or the other should be started as soon as possible after the diagnosis of GBS has been made. PE was reported to be first used in GBS between 1978 and 1981. PE is a therapeutic procedure that separates plasma from cells using a filter in a dialysis machine, where cells are reinfused back into circulation and plasma is removed and replaced with either fresh frozen plasma (FFP) or reconstituted human protein (albumin). Trials comparing the efficacy of IVIG with PE showed equal efficacy in decreasing hospital stay, hastening recovery, and preventing mechanical ventilation and respiratory depression.[26–28] Different dosages of IVIG (0.4 gm/kg/day) were administered over 3 vs 6 days, which showed the time required to regain the ability to walk with assistance was shorter in the latter group with lower infusion-related side effects.[29] For a proportion of patients with refractory GBS, the utility of a second course of IVIG was studied in a recent RCT (SID-GBS), but the outcomes were negative.[30]

Treatment-related fluctuations (TRF) are often seen in 10% of GBS within 2 weeks to 2 months after first treatment initiation.[31] Retrospective studies have shown that treating with more than one modality in cases of clinical deterioration, lack of improvement, or TRF has no significant benefits. Distinguishing such cases from acute-onset CIDP or subacute inflammatory demyelinating polyneuropathy (SIDP) becomes important since the therapeutic and prognostic implications vary. Recently, a new method has been experimented with in children, known as the "Zipper method," using immediate IVIG after each session of PE in nine patients, which has been shown to reduce mortality,[32,33] speed up weaning from mechanical ventilation, and shorten

**Table 3:** Medication to treat neuropathic pain

| *Drug class* | *Dose* | *Comorbidities favoring use* | *Comorbidities favoring avoidance* | *Side-effects* |
|---|---|---|---|---|
| Serotonin norepinephrine reuptake inhibitors | | | | |
| • Duloxetine<br>• Venlafaxine | Duloxetine—starting dose of 20–30 mg/day titrated up to a max of 60–120 mg/day | Depression and anxiety | Restless leg syndrome<br>Sexual dysfunction<br>Angle-closure glaucoma[22] | Nausea, somnolence, dizziness, decreased appetite, constipation, diaphoresis, and sexual dysfunction[22,24] |
| Tricyclic antidepressants (TCA) | | | | |
| Amitriptyline | Starting dose—10–25 mg/day titrated up to a maximum 200 mg/day | Depression, anxiety, and insomnia | Dry mouth, somnolence, and urinary retention | Cardiac dysfunction, prolonged Qtc, and orthostatic hypotension |
| Gabapentoid antiseizure medications | | | | |
| Gabapentin, pregabalin | Starting dose of 75–150 mg/day titrated up to a maximum dose of 600 mg/day | Restless leg syndrome, essential tremor, and insomnia | COPD and substance abuse | Peripheral edema, weight gain, somnolence, and dizziness[23] |

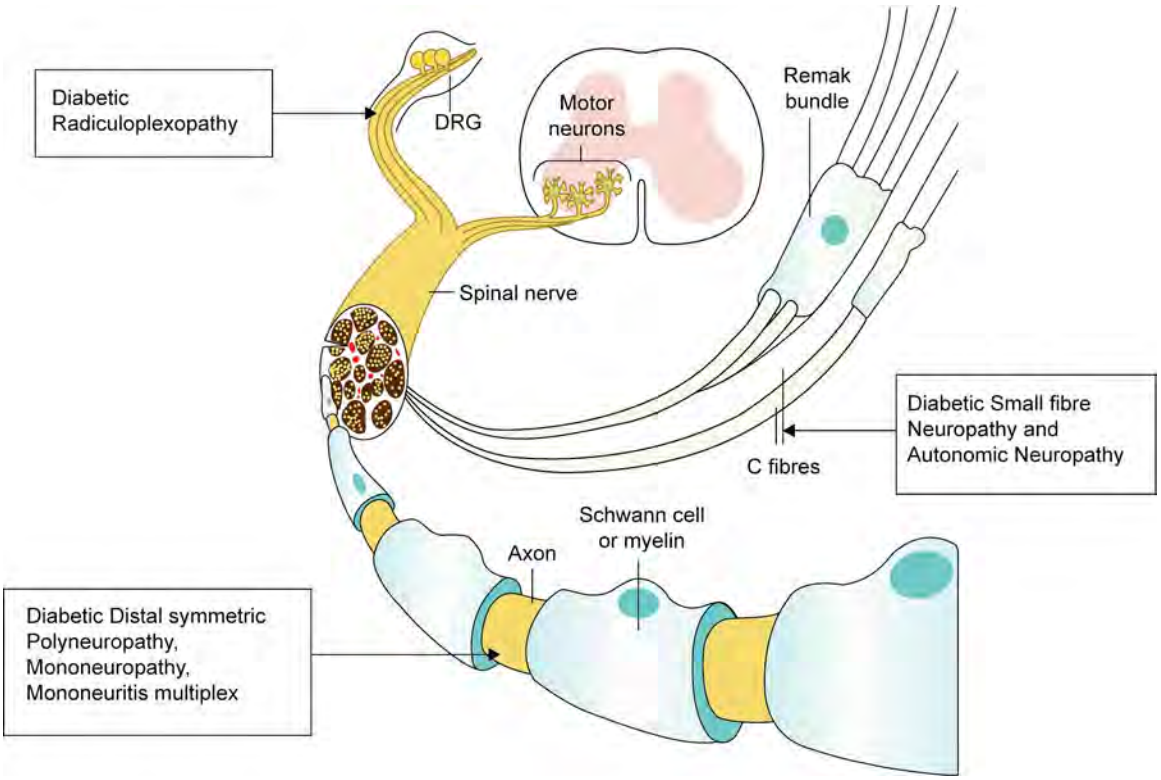



**Fig. 1:** Spectrum of DN affecting different levels of a peripheral nerve

hospital stay, although RCT is not available for this method and hence the efficiency of this method is currently questionable. Eculizumab, a humanized monoclonal antibody against the complement protein C5, was tested in two randomized, double-blind, placebo-controlled phase 2 trials. Neither showed benefit vs immunoglobulins alone on disability level at 4 weeks, although one study importantly suggested possible, clinically highly relevant late effects on normalizing function. A phase 3 trial is in progress.[34,35] One RCT with 19 participants compared interferon beta-1a (IFNβ-1a) and placebo. It is uncertain whether IFNβ-1a improves disability after 4 weeks (very low-certainty evidence).[36]

### Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy is an immune-mediated neuropathy that has a progressive or relapsing nature extending over 2 months. It can be divided into two types based on clinical presentation, typical and atypical. Typical CIDP presents with largely symmetrical weakness involving proximal and distal parts of extremities. Atypical CIDP takes many forms. For example, the distal acquired demyelinating symmetric (DADS) presents as symmetric length-dependent sensory or sensorimotor distal weakness with increased distal latencies; multifocal acquired demyelinating sensory and motor neuropathy [MADSAM or Lewis–Sumner syndrome (LSS)] has a multifocal distribution and the electrophysiological hallmark of conduction block, while chronic immune sensory polyradiculopathy (CISP) is restricted to sensory nerve roots only. Patients with POEMS syndrome have organomegaly, skin pigmentation, endocrinal changes, and M band in the serum. Pathophysiology of CIDP involves cellular as well as humoral immune mechanisms. Inflammatory T cells and macrophages infiltrate a nerve through the perivascular space and thus disrupt the blood–nerve barrier.[37] The humoral immune mechanism plays an equally important role; this can be inferred by the rapid response of a few CIDP patients with PE.[38] Antibodies to myelin proteins P0, P2, and PMP22, along with nodal and paranodal proteins like neurofascin NF186 and NF185, respectively, are a few of the detected target antigens in various studies.[38,39]

Owing to immune-mediated mechanisms, the mainstay of treatment in CIDP remains IVIG, PE, and corticosteroids. The first study to demonstrate the short- and long-term efficiency of IVIG in CIDP is the ICE study[26] (IVIG-C CIDP efficacy trial), which is a double-blind, placebo-controlled RCT of 24 weeks. The standard dose for maintenance IVIG used in this study was 1 gm/kg every 3 weeks. Subcutaneous immunoglobulin (SCIG) as a maintenance therapy has been shown to have similar efficacy as IVIG with better tolerance and convenience. This has been demonstrated in the PATH and PATH open-label extension study.[40] PE is an effective modality for CIDP as demonstrated by multiple studies,[41,42] but its effect lasts only for a few weeks, leading to mainly short-term benefits. IV pulse corticosteroids have been proven to show benefits in active CIDP patients. The PREDICT trial compared daily oral prednisolone with high-dose monthly dexamethasone and demonstrated moderate-quality evidence of shorter median time to improvement in the latter group.[43] Side effects like cushingoid facies, uncontrolled diabetes, and hypertension were more common in the daily oral steroid limb. IFNβ initially was considered as an adjunctive option for CIDP based on case reports, but RCT of IM IFNβ in CIDP did not show any superiority compared to the placebo.[44] Methotrexate (Mtx) as an immunomodulatory agent in CIDP was tested in an RCT recruiting 56 patients,[45] which demonstrated no benefit of Mtx as compared to a placebo. Mycophenolate mofetil (MMF) is used as an add-on steroid-sparing drug for maintenance therapy in CIDP; it is found to stabilize the clinical condition and help in reducing the steroid dose, but in a controlled trial, the agent did not show any significant improvement in modified Rankin score or muscle strength.[46] The most recent treatment modality for CIDP is rituximab (Rtx), a selective B-cell-depleting monoclonal antibody. As per a systematic review by Chaganti et al.,[47] RTX was effective in 63% of CIDP patients, 48% of anti-MAG neuropathy, and 96% of patients with autoimmune nodopathy. Neurophysiological improvement was evident in 58% of CIDP and 40% of anti-MAG neuropathy patients. Rtx has been used in resistant CIDP, but it may be used earlier in the coming years based on its efficacy. Multifocal motor neuropathy, MADSAM, is treated on the lines of typical CIDP. Gammopathies need to be treated as per the primary reason for the gammopathy, and DADS patients can prove resistant to available treatment options (Fig. 2).

### Vasculitis Neuropathy

Vasculitis of small and medium vessels frequently affects peripheral nerves secondary to inflammation and eventually causes ischemic injury to the vasa nervorum. Vasculitis-related neuropathy can be broadly divided into systemic and nonsystemic vasculitic neuropathy (NSVN) depending on the presence of multiorgan involvement and systemic features. Peripheral neuropathy is most frequently associated with polyarteritis nodosa (PAN) and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[48] Distal asymmetric, multifocal, or nonlength-dependent sensorimotor weakness, mononeuritis multiplex with lower limb predominance, is the most common pattern observed. Pain is the hallmark of vasculitic neuropathy. Nerves with moderate clinicoelectrophysiological involvement should be used for biopsy, which may show transmural inflammation with vascular damage.[49,50] The treatment recommendations in the Peripheral Nerve Society guidelines on NSVN are based on observational studies of NSVN and extrapolation from studies of systemic vasculitis, suggesting pulse glucocorticoids as monotherapy and the addition of other immunomodulatory agents like cyclophosphamide, Mtx, and azathioprine (AZA) for rapidly progressive NSVN.[50]

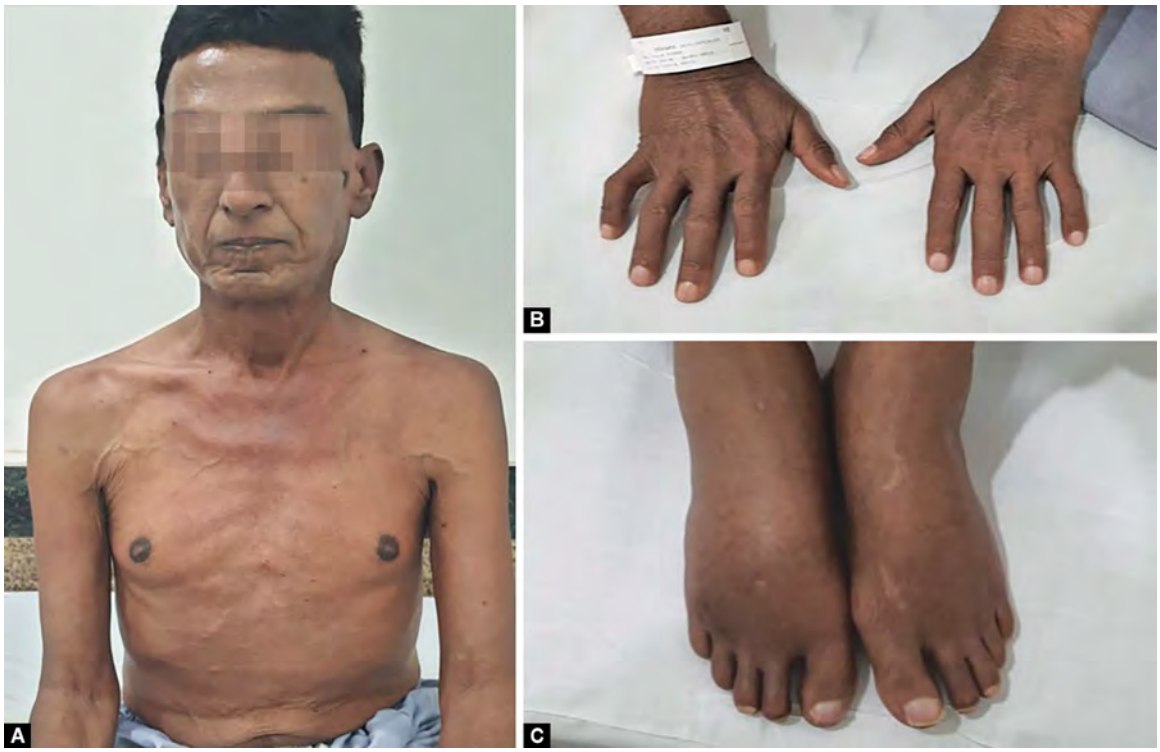
## Infection-related Neuropathy

### Neuropathy in Leprosy

Leprosy is one of the most common treatable infectious causes of peripheral neuropathy, especially in tropical countries like India, Brazil, and other Southeast Asian countries. Leprosy classically presents with cutaneous symptoms, with a spectrum ranging from tuberculoid leprosy (TT), in which there are well-defined lesions, to lepromatous leprosy (LL) with ill-defined multiple skin lesions. Cutaneous features include hypo-/anesthetic skin patches in the buttock, back, trunk, face, and earlobes (predominantly cooler areas of the body). Pure neuritic leprosy, presenting as predominant neurologic features without significant cutaneous symptoms, causes a delay in diagnosis and treatment, thus causing increased disability related to progressive neuropathy.[51] The clinical spectrum of leprous neuropathy is wide and has been presented in Table 4 (Fig. 3).

Diagnosis of leprosy is mostly clinical, but tests like nerve conduction, skin and nerve biopsy, nerve ultrasonography, and MR neurography help confirm the clinical findings. The WHO Expert Committee on Leprosy defines a case of leprosy as an individual who has one of the following cardinal signs of leprosy but who has not received a full course of multidrug therapy (MDT) appropriate for the type of leprosy.[60]

- Definite loss of sensation in a pale (hypopigmented) or reddish skin patch.




**Figs 2A to C:** A 55-year-old male, with atypical CIDP (distal > proximal sensorimotor weakness in all four limbs with paresthesia) along with systemic features like; (A) hepatosplenomegaly, facial hyperpigmentation, dilated veins on trunk, and fixed and raised Jugular venous pressure: (B) white nails, clubbing, and hyperpigmentation of skin; and (C) bilateral pedal edema. The patient had POEMS syndrome with monoclonal gammopathy of IgG subtype

**Table 4:** Neuropathies in leprosy

| *Type of neuropathy* | *Clinical features* |
|---|---|
| Mononeuritis and mononeuritis multiplex | • Most common presentation<br>• Upper limb nerves are affected more than lower limb[52]<br>• Can be associated with rheumatological manifestations like positive rheumatoid factor, arthralgia, and rash |
| Polyneuropathy | • Distal symmetric small fiber sensory polyneuropathy[53]<br>• Usually, no muscle weakness and deep tendon reflexes are preserved<br>• Preferentially involves temperature > touch > pain.[54] Proprioception is rarely involved in multibacillary leprosy[55]<br>• Higher association with ulceration and deformities |
| Autonomic neuropathy | • Seen in patients with multibacillary leprosy[52]<br>• Anhidrosis causing dry and scaly skin with ulcerations<br>• Widespread dysautonomia involving the cardiac and respiratory systems is well documented[56,57] |
| Cranial neuropathies | • Cranial nerves may be involved in up to 18% cases[52,58]<br>• Facial nerve is the most common cranial nerve affected in leprosy[57]<br>• Hallmark of cranial neuropathy in leprosy is its patchy involvement of the nerve[59] |
| Acute neuritis | • Seen during lepra reactions more commonly with type I lepra reaction<br>• Spontaneous nerve paresthesia and pain followed by objective sensory-motor loss |
| Ganglionitis | • DRG involvement causing severe proprioceptive impairment, pseudoathetosis with areflexia in ataxic limbs<br>• The extent and the severity of the process do not seem to link to the duration of the disease; but to an extent, correlate with the bacterial load[55] |

**Table 5:** Treatment schedules in leprosy[60]

| | *Paucibacillary* | *Multibacillary* |
|---|---|---|
| Drugs | Dapsone 100 mg daily and clofazimine 50 mg daily<br>Rifampicin 600 mg monthly and clofazimine 300 mg monthly | Dapsone 100 mg and clofazimine 50 mg daily<br>Rifampicin 600 mg and clofazimine 300 mg monthly |
| Duration | 6 months | 12 months |

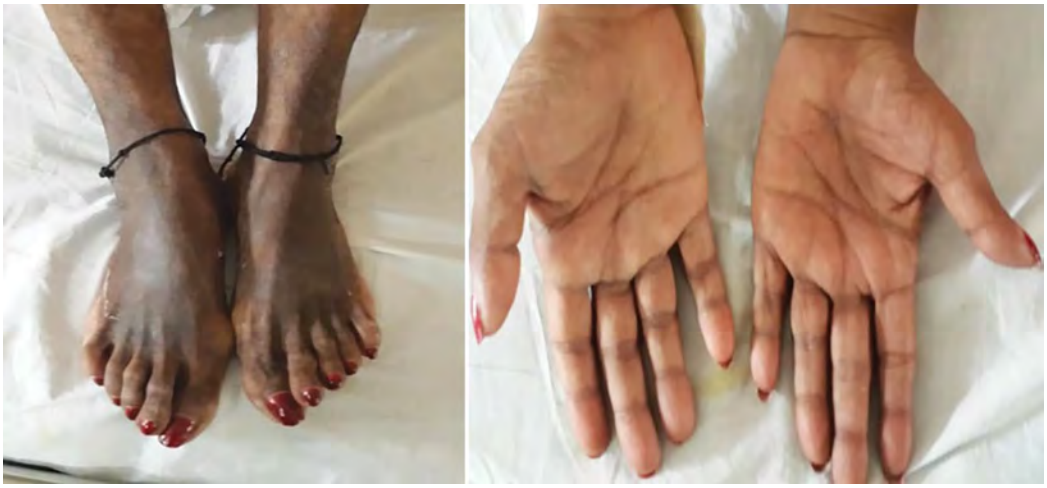
- A thickened or enlarged peripheral nerve with a loss of sensation and/or weakness in the muscles supplied by the nerve.
- The presence of AFB in slit skin smears.

## Treatment

- Medical treatment of leprosy.
- Management of neuropathic pains.

### *Medical Management of Leprosy*

As per WHO recommendations, patients fulfilling the diagnostic criteria should be started on MDT including three drugs (dapsone, rifampicin, and clofazimine) for all leprosy patients irrespective of bacillary load. The duration for paucibacillary leprosy is 6 months, whereas for multibacillary it is 12 months.



**Figs 3A and B:** A 40-year-old female with skin changes in LL secondary to autonomic neuropathy (A) with mononeuritis multiplex—wasting of left hand, and (B) Photo courtesy—Dr Varsha Patil

Table 5 depicts the treatment regimens for various types of leprosy.

*Drug-resistant Leprosy*

Although not very common, drug-resistant leprosy has been documented. WHO recommends the use of second-line medications such as ofloxacin, minocycline, clofazimine, and clarithromycin.[61]

Usually, leprosy presents with predominantly negative symptoms like numbness or anhidrosis, but during typical lepra reactions, neuropathic pains can be particularly predominant. Corticosteroids are the definitive treatment to reduce the impact of nerve damage, and they also help alleviate the neuropathic pains. Symptomatic treatments that can be offered are gabapentin, pregabalin, and duloxetine. Lepra reactions are treated with high doses of corticosteroids over a few weeks to months, and in resistant cases, clofazimine and thalidomide can be used.[51]

### Human Immunodeficiency Virus-related Neuropathy

Among other neurological features of HIV1, peripheral neuropathy is the most common neurological complication, affecting 30–50% of individuals.[62,63] HIV-associated neuropathies may present with varied clinical presentations at different stages of illness. DSPN is the most common, but inflammatory demyelinating neuropathies, progressive polyradiculopathies, mononeuritis multiplex, autonomic neuropathy, and the highly active antiretroviral therapy (HAART)-related neuropathies are encountered from time to time.

*Treatment of Human Immunodeficiency Virus-related Neuropathy*

Human immunodeficiency virus-related neuropathy can be prevented with adequate suppression of viral load and an increasing trend of CD4 count. The evolution of sensory neuropathy after HAART was observed by Centner et al. in 2017.[64] Results indicated that painful symptoms improved after long-term neuro-safe HAART *via* reduction of exposure to HIV-induced oxidative stress. HAART-induced neuropathy, commonly reported with stavudine, didanosine, nevirapine, zalcitabine, and protease inhibitors, requires switching over to newer drugs for effective management of HIV as well as to help prevent the risk of neuropathy. Lamivudine, abacavir, dolutegravir, emtricitabine, and adjusted doses of protease inhibitors are safer in this regard. Neuropathic pain is the most disabling complaint in HIV-related neuropathy, and drugs like antidepressants (tricyclics), anticonvulsants (gabapentin, pregabalin, lamotrigine), and topical analgesics have been successfully used in the treatment of neuropathic pain. HIV-related DSP has a better response from capsaicin 8% cutaneous patch when compared to mononeuropathy, cervical radiculopathy, and postherpetic neuralgia.[65] Other nonpharmacological interventions like hypnosis,[66] dietary supplements like curcumin and tart cherry extracts,[67] and bromelain[68] which increase the antioxidants and reduce neuronal stress are still under investigation but can be used in refractory conditions with caution.

## Drugs/Toxin-induced Neuropathy

Toxic peripheral neuropathies can occur secondarily to environmental, occupational, recreational, and iatrogenic (drug-induced) causes. The most common pattern observed is distal symmetric length-dependent sensory neuropathy along with motor or autonomic neuropathy. Several prescription medicines are known to cause neurotoxicity, like chemotherapy agents and antibiotics such as isoniazid, metronidazole, and nitrofurantoin. Alternative medicine products have been shown to contain heavy metals like lead, mercury, and arsenic, which are known to cause neurotoxicity along with other systemic features. Table 6 presents the important aspects of common drug-induced neuropathies.

## Cranial Neuropathies

Various disease categories such as infections, inflammations, tumors, and infiltrations affect the cranial nerves. The commonly encountered conditions are as follows. Among the infections, the herpes zoster virus affects the facial nerve, causing Bell's palsy, and the seventh and eighth nerves, causing Ramsay Hunt syndrome. In children, diphtheria can result in lower cranial neuropathies, producing dysphagia. Tuberculosis of the nervous system, mainly meningitis, is common, and the basal exudates result in various cranial neuropathies, often predominating in the lower segments. Common inflammations are the Tolosa Hunt syndrome, which results from inflammation at the apex of the orbit. A proportion of such patients have the IgG4 antibodies. Patients respond to corticosteroids but may have a recurrent and prolonged course requiring long-term immunotherapies. Lymphomas, leukemias, other lymphoreticular malignancies, and deposits from other bodily tumors can infiltrate or compress the cranial nerves, resulting in their dysfunction. Cerebrospinal fluid centrifuge examination for abnormal cells and contrast MRI scans help the diagnosis, and the treatment depends upon the primary condition. The optic

**Table 6:** Important aspects of common drug-induced neuropathies

| *Drugs* | *Incidence* | *Site of toxicity* | *Clinical features* | *Treatment* |
|---|---|---|---|---|
| *Chemotherapy drugs* | | | | |
| Cisplatin | 30% of symptomatic neuropathy | Sodium channel abnormalities causing axonal hyperexcitability and repetitive discharges ± DRG | First symptoms appear after 1st month of treatment<br>Dose-dependent toxicity<br>Chronic sensory predominant small fiber neuropathy with burning paresthesia, pain, and tingling | After stopping the drug, autonomic and motor symptoms tend to improve. Sensory symptoms worsen after finishing the chemotherapy—coasting stage. Eventually coming back to baseline[69] |
| Oxaliplatin | 10–20% with modest dose | Sodium channel abnormalities | Neurotoxicity presents as two types—acute and chronic sensory neuropathy<br>Cold-induced sensitivities | Acute neuropathy subsides after stopping the drug, and increases after consecutive dose—Sawtooth pattern of neuropathy[70] |
| Vincristine | Almost all | Microtubular axon transport function abnormalities<br>DRG | Sensory predominant with mild motor weakness (weakness in finger extension first)[71]<br>Sensory ataxia ±[72] | Symptomatic treatment for small fiber neuropathy like gabapentin, pregabalin, and lamotrigine |
| Bortezomib | 30–60% | DRG<br>Small fibers, type C | Along with small fiber neuropathy, bortezomib also presents with severe motor-predominant polyradiculopathy[73] | Symptomatic treatment |
| *Antibiotics* | | | | |
| Metronidazole | 5–6% | Nerve | Sensory predominant reversible length-dependent neuropathy<br>Predominantly negative symptoms—numbness and decreased sensations | Stopping the drug usually reverses neuropathy[74] |
| Isoniazid | 10–20% | Nerve | Starts with tingling numbness and decreased sensation distally followed by a glove and stocking-like pattern | Prevented with pyridoxine prophylaxis. Reverses if stopped with early symptoms[75,76] |
| Dapsone | 1–2% | Motor | Upper limb predominant multiple mononeuropathies[77] | Stop the drug |
| Nitrofurantoin | Incidence is higher in the elderly and patients with renal disease | Sensory nerve<br>Demyelinating | GBS like syndrome<br>Length-dependent sensorimotor polyneuropathy[78,79]<br>Sensory painful DSPN | Most neuropathy related to nitrofurantoin are refractory and have delayed improvement after stopping the drug |
| Linezolid | As high as 80% | Sensory painful small fiber neuropathy | Dose-dependent toxicity. Small fiber burning, pain, and paraesthesia[78,80,81] | The improvement is mostly seen after 6 months of cessation of the drug. Few can be irreversible |
| *Heavy metals* | | | | |
| Lead | 30% | Axonal damage of motor nerves | Acute to subacute form—predominantly motor neuropathy—frequently starts with distal extension weakness in upper limbs<br>Chronic long-term exposure—mild sensory and autonomic neuropathy | Acute neuropathy—chelation is helpful to some extent. Neurotoxic features are not reversible in chronic forms[82,83] |
| Arsenic | | GBS like syndrome | Acute form—GBS-like syndrome, although cranial nerve involvement is rare<br>Chronic form—length-dependent sensory motor axonal neuropathy | Chelation may help with the acute form of neuropathy. Treatment of GBS-like syndrome involves PE or IVIG |
| Mercury | | Peripheral nerve axons<br>CNS | Sensory predominant and ataxia<br>Behavioral changes | Chelation and cessation of exposure |
| Alcohol | | Peripheral nerve | Malnutrition—involves multiple vitamin deficiencies like thiamine and Vit B12, causing sensorimotor peripheral neuropathy<br>Without malnutrition—mild form of distal sensory polyneuropathy | Abstinence improves early symptoms |
| Pyridoxine excess | | DRG/axons | Sensory axonopathy or neuronopathy | |
| Organophosphorus compounds | | Motor > sensory axons | Distal motor weakness, foot drop, cramps, and mild sensory disturbances | Symptomatic management |

**Table 7:** Entrapment neuropathies of upper and lower limbs

| *Nerve entrapped* | *Anatomical site of compression* | *Clinical presentation* | *Treatment* |
|---|---|---|---|
| Upper limbs | | | |
| Long thoracic nerve (C5–C7) | • Middle scalene<br>• Middle and posterior scalene<br>• Second rib and clavicle | Medial winging of the scapula | Thoracic/supraclavicular decompression or combined—within 6–12 months for better results[85] |
| Spinal accessory nerve (C1–C6) | At the jugular foramen—due to tumor<br>In the posterior triangle—due to lymph nodes/intervention | Lateral winging of scapula | Medical management for pain<br>Surgical decompression—resection of fascia[86] |
| Axillary nerve (C5–C6) | Quadrilateral space by posterior humeral circumflex artery | Paresthesias, posterior shoulder pain, weakness of deltoid, and teres minor | Medical management for pain and paresthesias<br>Surgical intervention within 6–12 months of onset[87] |
| Median nerve (C6–T1) | AIN entrapment—pronator teres heads<br>Carpel tunnel syndrome—flexor retinaculum at wrist | AIN—weakness of muscles in deep anterior compartment<br>CTS—dull aching pain at wrist, worsened in night, with paresthesias in later 3.5 fingers | Severe sensorimotor weakness—surgical intervention such as decompression of flexor retinaculum relieves maximum symptoms<br>Mild-moderate weakness—medical management with gabapentin, pregabalin, etc.[88] |
| Ulnar nerve (C8–T1) | Medial epicondyle and olecranon—cubital tunnel syndrome<br>Guyon canal syndrome—palmar carpel ligament | Pain in medial elbow with intermittent numbness in ring finger and little finger with weakness of small muscles of hands | *In situ* decompression, medial epicondylectomy, anterior subcutaneous transposition, intramuscular transposition, and submuscular transposition[89] |
| Radial nerve (C5–T1) | Arcade of Frohse<br>Deep head of supinator muscle | Lateral elbow pain and wrist drop | Decompression surgery—relieving the nerve from arcade of Frohse—good prognosis[90] |
| Lower limbs | | | |
| Sciatic nerve (L4–S3) | • Between piriformis and obturator internus muscle<br>• Ischiofemoral impingement syndrome—compression by quadratus femoris<br>• Proximal hamstring syndrome, compression by hamstring muscles | Posterior thigh and hip pain, ± radicular in nature.<br>Buttock pain aggravated by sitting—compression by piriformis muscle | Most cases—resolve spontaneously<br>Bed rest<br>Analgesics/NSAIDs, physical and behavioral therapy<br>Interventions like chemonucleolysis for refractory leg pain may be tried[91] |
| Lateral femoral cutaneous nerve of thigh (L1–L3) | Most common compression at exit from pelvis | Unilateral pain, paresthesia, and numbness in the lateral or anterolateral thigh, relieved after sitting[92] | Conservative treatment focuses on reduction of the factors that cause or intensify nerve compression, for example avoidance of tight clothing and constrictive belts around the waist<br>Surgical intervention-decompression of nerve at inguinal ligament[92] |
| Peroneal nerve | • Most common compression at fibular head<br>• At exit of lateral leg<br>• At tight tunnel formed by external retinaculum | Foot drop, pain, and numbness of the lateral lower leg and foot dorsum, aggravated by plantar flexion and foot inversion | Timely surgical decompression can treat peroneal entrapment neuropathy, positive correlation between decreased time of surgery, and better outcomes[93] |

nerve, being a part of the central nervous system myelin, is affected by demyelinating diseases such as multiple sclerosis and neuromyelitis optica, and toxic and deficiency diseases such as the B12 deficiency. Toxic amblyopia and methanol toxicity are some common examples in clinical practice.

## Entrapment Neuropathies

Entrapment neuropathies are treatable disorders that are caused by compression of peripheral nerves secondary to passage through narrow anatomical spaces. They are characterized by pain and/or sensorimotor loss. The common pathomechanisms of entrapment neuropathies are as follows[84]:

- Extra- and intraneural ischemia.
- Demyelination and axonal degeneration.
- Neuroinflammation.

These compression neuropathies can be divided based on gradings of peripheral nerve injuries such as neuropraxia (nerve sheath intact but nerve function is temporarily impaired), axonotmesis (nerve fibers are interrupted but connective tissue remains intact), and neurotmesis (most severe type of nerve injury where the nerve fibers and connective tissue are severed). A few of the common entrapment neuropathies are described in Table 7.

## Autonomic Neuropathy

Autonomic neuropathies are a complex group of disorders targeting mainly the autonomic

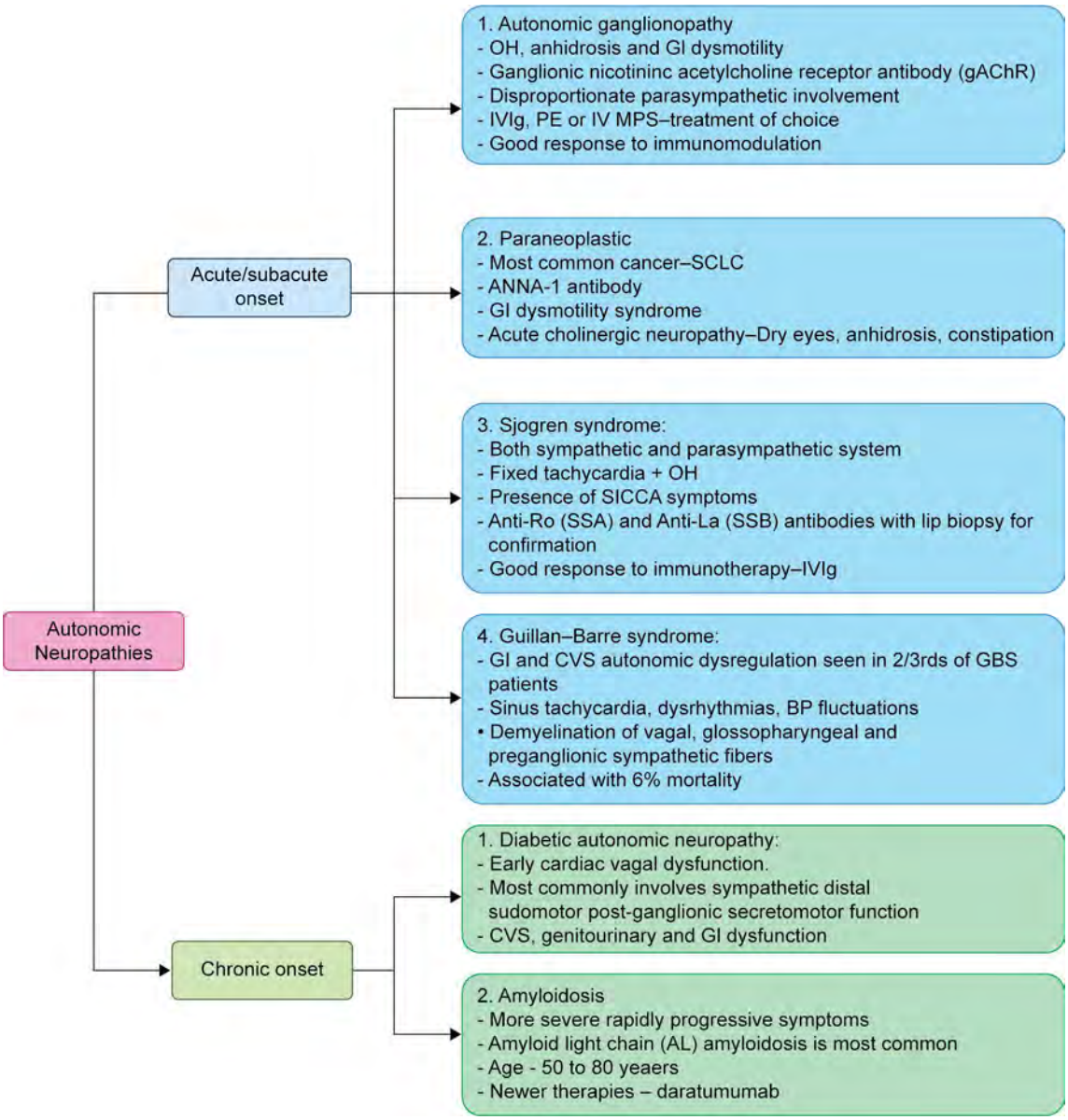



**Fig. 4:** Autonomic neuropathies

fibers, including the parasympathetic and sympathetic systems. They are classified according to temporal course/disease onset (acute/subacute/chronic), etiology (hereditary/acquired), and as per the involvement of the fibers (parasympathetic/sympathetic/generalized).[94] Pertaining to the current article, a few of the most important treatable entities are described briefly in Figure 4.

## Conclusion

As can be surmised from the above discussion, a variety of neuropathic processes have the potential of reversibility, and these need to be rapidly identified and treated for best outcomes. Evaluation of clinical features, coupled with investigations, helps the process of segregation and reaching the diagnosis. Inflammatory, infective, toxic, metabolic, and deficiency neuropathies form the main categories of reversible neuropathies and should be actively looked for for best outcomes.

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## Author Contributions

SVK: concept, design, and review.

JM: literature review and writing the manuscript.

HH: design, manuscript preparation, and review.

RR: concept and review.

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REVIEW ARTICLE

# A Review on Sarcopenia, Cachexia, and Aging

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## Abstract

Sarcopenia and cachexia are two crucial geriatric problems that largely pass unrecognized, and their presence is a harbinger of a bad outcome. With the growing older of the human body, there is a gradual loss of muscle tissue and an increase in fat mass, leading to increased abdominal circumference. Sarcopenia is described as the progressive and generalized loss of skeletal muscle mass, strength, and physical function, leading to reduced workout capacity. It needs to be differentiated from cachexia, wherein the weight loss is because of an underlying sickness like cancer, chronic obstructive pulmonary disease (COPD), and immunodeficiency disorder, leading to loss of fat and muscle tissues, and starvation, which is a reversible situation on proper nutrient supplementation. Skeletal muscle tissue loss due to sarcopenia is resistant to dietary vitamin supplements. Even with many commonalities between these two situations, these are considered separate clinical entities.

Aging may be described as the time-associated deterioration of the physiological functions critical for survival and fertility. The traits of growing older—as distinguished from ailments of growing old (together with cancer and coronary artery disease)—affect all the humans of a species. A massive loss of muscle tissue and strength (sarcopenia), a reduced regenerative capacity, and a compromised physical performance are hallmarks of aging skeletal muscle. It is prudent to outline the distinction between the two conditions within the aging population so that a therapeutic method may be targeted toward the skeletal muscle loss and strength in aged humans. The treatment consists of appetite stimulants, dietary and nutritional supplementation, tailored exercise, and anti-inflammatory drugs. Megestrol acetate, an appetite stimulant, and dronabinol (Marinol), a narcotic drug used to treat nausea and vomiting in patients with cachexia.


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## Introduction

There is a rising percentage of the geriatric population as a result of better medical facilities, such as early diagnosis and treatment by advanced technologies, although the problem of polypharmacy and multiple comorbidities in elderly people is still causing a problem for the treating physician. Skeletal muscle mass is useful in locomotion, metabolism of glucose, and synthesis of protein.[1]

Slow weight reduction is common among older human beings. If there is a loss of 10% or more of body weight between age 50 and old age, it is associated with a 60% increase in mortality compared to those with stable weight.[2] With the aging of the human body, there is a gradual loss of muscle tissue and an increase in fat mass, leading to expanded abdominal circumference. This aging-associated loss of muscles and strength is known as sarcopenia. Sarcopenia is characterized by declining muscle mass, strength, and physical function.[3] It must be differentiated from cachexia, wherein the weight reduction is due to an underlying disease, leading to loss of fat and muscles, and starvation, which is a reversible condition on proper nutrient supplementation. Skeletal muscle mass loss due to sarcopenia is resistant to nutritional supplementation. Failure to differentiate these conditions often causes frustration among the treating geriatric physicians.

### Ancient Elements

As lifespan increased at the beginning toward people who we consider long-lived, the genetics of aging might also become increasingly important. Operational definition of sarcopenia includes: (1) probable sarcopenia is low muscle strength (LMS); (2) confirmed sarcopenia is LMS with low muscle quantity or quality; (3) severe sarcopenia is LMS, low muscle quantity or quality with low physical performance (LPP).[4]

### Cachexia

Cachexia has been described as a lack of lean tissue mass, involving a weight reduction of >5% of body weight in 12 months or less within the presence of persistent inflammation, or as a body mass index (BMI) <20 kg/m$^2$. In addition, three criteria out of the following five are required: reduced muscle power, anorexia, reduced fat-free mass index, fatigue, and increase of inflammatory markers such as C-reactive protein (CRP) or interleukin-6 (IL-6), as well as low hemoglobin or hypoalbuminemia.[5] Cachexia can occur in most major illnesses, including infections, cancer, heart disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and stroke.

### Aging

Aging is defined as a time-associated reduction in the physiological skills that are vital for life. Aging is completely different from the diseases of the elderly (which include most cancers and coronary heart disease), as aging affects all human beings of a species. An enormous reduction in the muscles and strength (sarcopenia), which is associated with reduced regenerative capabilities of muscles and a decrease in overall performance of the body, is characteristically seen during aging.[6] These changes are normally accompanied by impaired muscle metabolism, including mitochondrial disorder and insulin resistance. To decelerate aging, physical exercise is a major counterpoint to age-related reduction in muscle mass, muscle strength, regenerative potential, and muscle metabolism. Exercise and physical activity definitely retard aging at some point and therefore need to be emphasized as part of a lifestyle vital to healthy aging. With advancing aging, motor neurons lose their ability to regenerate, and denervation of some muscle fibers also leads to loss of function.

## Pathophysiology of Sarcopenia

There are two types of skeletal muscle fibers: type I fibers are usually resistant to fatigue because of densely packed mitochondria, a rich capillary network, and myoglobin material, while type II fibers are relatively susceptible to fatigue because of higher glycolytic capacity and lower oxidative capacity; however, at the same time, they may carry out excessive-intensity exercising hobby.[7] In sarcopenia,

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there is a decline in length and range of type II muscle fibers associated with infiltration of fatty tissues in the muscle fibers. Sarcopenia is also characterized by reduced functional capacity of the satellite cells, which are primarily involved in the restoration and update of damaging muscle fibers.

Many causes for sarcopenia have been proposed, including factors spanning muscle-specific processes and systemic mediators concerning numerous domains (e.g., inflammation and amino acid dysmetabolism), neurodegenerative processes (α motor neuron), and decreased production of anabolic hormones. Mitochondrial disorder describes the mechanism of aging and sarcopenia. Skeletal muscle tissues have strong reliance on oxidative metabolism, which results in the production of reactive oxygen species (ROS) in mitochondria, triggered by breaks in telomere regions.

## Mitochondrial Dynamics

Exchange of matrix content and proteins between individual mitochondria takes place through the process of fusion and fission. Alteration of these processes hampers mitochondrial functioning in terms of respiration potential, coupling, ROS production, and apoptotic sensitivity. Excessively fragmented mitochondria generally tend to exhibit decreased respiration chain potential, increased ROS production, and increased susceptibility to the release cascades, which will ultimately cause apoptosis.[8] Dysfunctional mitochondria are removed by means of the process of mitophagy, in which a fragmented mitochondrion becomes encapsulated with a double membrane and forms an autophagosome, which ultimately fuses with a lysosome and undergoes hydrolytic lysis.

As age progresses, there is an increase in oxidative damage and reduced antioxidant defense, which results in mitochondrial damage at the neuromuscular junction (NMJ). Neurotransmitter-containing synaptic vesicles are also reduced in number, which slows down transport across the axon. Mitophagy-associated clearance of damaged mitochondria is also reduced, which leads to accumulation of abnormal proteins and mutated mitochondrial DNA. These respiratory-deficient mitochondria lead to a reduction in neuromuscular transmission, decreased capability of the mitochondrial membrane, and release of cytochrome c-like proapoptotic factors.[9]

## Lower Motor Neuron

As the age advances, there is a reduction in motor neurons of the spinal cord and transmission across the NMJ, which leads to a reduction in the strength of muscles and their power. Loss of motor neurons also leads to lateral sprouting of neighboring neurons to innervate muscle fibers, which results in metabolic overburden and hypertrophy of the motor neurons and makes the nerve fibers prone to overload-associated degeneration.[10]

## Sarcopenia and Hormones

Insulin-like growth factor I (IGF-I) is an essential component to increase the muscle mass and strength; it also reduces the degenerative capacity, which leads to enhanced proliferation of satellite cells of muscle fibers. For this purpose, IGF-I may recently be used as an important health biomarker. IGF-I is also related to aerobics and measurements of muscle endurance.[11]

Adjustments within the growth hormone (GH)/IGF-I level cause a decrease within the levels of protein anabolism in skeletal muscle cells and accordingly have a key role in the reduction of skeletal muscles. As age increases, testosterone levels decline, leading to loss of muscle mass and weakening of bone strength, increasing the risk of fracture. Still, patients suffering from loss of muscle mass cannot benefit from GH or testosterone injections, where they are likely to increase the muscle mass because of their side-effect profile.[12]

Increasing age was found to be associated with a state of hypercortisolism, which causes an increase in visceral fat accumulation. A low level of vitamin D is associated with decreased muscle strength. In elderly people, because of insulin resistance, they lack anabolic action, viz., protein synthesis driven *via* insulin, therefore leading to loss of muscle mass. Inflammatory markers and sarcopenia: IL-6, CRP, and tumor necrosis factor (TNF)-α—these inflammatory markers consistently show a negative association with muscle mass, strength, and physical function. Due to a sedentary life in the elderly population, visceral fat increases, which has more glucocorticoid and androgen receptors as compared to subcutaneous fat; therefore, it is hormonally more active. Visceral fat directly correlates with the level of TNF-α and IL-6, which leads to a reduction of skeletal muscle mass. Moreover, high-intensity exercise has shown reduced levels of IL-6 and improvement of muscle mass and performance.[13]

## Interrelation between Exercise, Myokines, and Sarcopenia

Exercise causes the release of cytokines or signaling peptides called myokines, and it also maintains a positive balance between anti- and proinflammatory mediators. Myokines are necessary for whole-body homeostasis and metabolic, cardiovascular, kidney, bone, and hepatic tissue.[14] Myostatin is a negative regulator of skeletal muscle mass; it acts *via* activation of small mothers against decapentaplegic (SMAD) proteins, which results in transcription of catabolic genes and also activates satellite cells and the ubiquitin–proteasome system (UPS).[15]

Follistatin is secreted by the liver and increases with exercise. It binds with myostatin and inhibits it. Decorin also counter-regulates myostatin. Musclin is also released by exercise and is expressed in bone; it inhibits cardiac remodeling after myocardial infarction and modulates muscle mass. Apelin is a positive regulator of mitochondriogenesis, stimulates regenerative properties, and thereby exerts a positive effect on muscle mass. Myonectin turns on protein kinase B (AKT), insulin receptor substrate 1 (IRS-1), and mechanistic target of rapamycin (mTOR), consequently downregulates transcription of autophagy genes, and still has an aerobic shielding effect. Brain-derived neurotrophic factor (BDNF) plays a crucial role in regulating the increase, survival, and preservation of neurons and decreases adipose tissue bulk.[16]

## Sarcopenia Obesity

It is a multifactorial syndrome that is characterized by the cooccurrence of obesity and sarcopenia. Physical inactivity is the most important risk factor for obesity. With advancing age, there is an increase in fat mass and a reduction in muscle mass. Specifically, visceral fat and intramuscular fat tend to increase and lead to intramuscular fat infiltration, leading to a decrease in muscle strength. Visceral fat also increases the proinflammatory adipokines, which have a catabolic effect on muscle fibers.[17]

## Aging Pathophysiology

It is a point of debate whether detrimental effects on muscle physiology are related to age or are a consequence of lifestyle and ailment. Primary aging is related to adjustments in morphological and physiological aspects that occur independent of lifestyle, environmental impacts, or sickness. Changes regarding interactions of aging with environmental factors and sickness are considered secondary aging. Aging is associated with decreases in muscular tissues, muscle strength, and regenerative potential. A high body fat content reduces the muscle mass and strength and is related to insulin resistance, mitochondrial dysfunction, and defective potential of regeneration.

Etiological elements in sarcopenia include enhanced fatty tissues in muscle, insulin resistance, lack of alpha motor neurons, reduced dietary consumption of protein, high IL-6, reduced estrogen or androgen levels, a physical state of no activity, and many others. These modifications are possibly linked to age-related adjustments in the central nervous system and peripheral nervous systems and lead to a reduction in the motoneurons and degradation of NMJ.[18] With aging, there is denervation of single motor nerve fibers (typically fast). After denervation, there is always reinnervation of the remaining motoneurons (usually slow). This reinnervation of muscle fibers leads to conversion and grouping of fiber type.

## Clinical Aspects of Sarcopenia

The most common symptom of sarcopenia is muscle weakness. Other symptoms may include recurrent injuries and fractures due to muscular imbalance, difficulties in ascending stairs, getting from a chair, decreased levels of protein-related hormones, and vitamin D value in blood (<50 nmol/L) (Fig. 1).[19]

## Screening of Patients with Sarcopenia

Screening helps in the early identification of conditions and early detection of patients at risk for muscle decline[20]:

- SARC-F is the most confirmed and adapted screening survey for sarcopenia and has very high specificity to expect sarcopenia. The SARC-F questionnaire consists of self-reporting of strength, help with walking, rise from a chair, climbing stairs, and falls. High scores are associated with deficits in everyday living activities.
- Anthropometric measures—BMI, mid-upper arm muscle circumference (MUAMC/MAMC), and calf circumference (CC). Low muscular tissues may be classified as MUAMC/MAMC <21.1 cm in men and 19.2 cm in women. The cutoff point for measurement of CC of <34 cm in men and 33 cm in women is considered low muscle tissues.
- Muscle strength and performance—hand grip power, chair stand test (chair upward push test), gait pace, timed-up-and-go (TUG) test, and short physical performance battery (SPPB).
- Combined tools—the Ishii screening tool, which includes age, grip energy, and CC, stratified for sex. It has high sensitivity (75.5% for men and 84.9% for women) compared to SARC-F and specificity (92.2%) comparable to SARC-F (93.7%). In evaluation to the SARC-F, the Ishii screening tool gives a more objective risk evaluation of the probability of being sarcopenic. Different combined tools use the presence of two criteria to discover sarcopenia, particularly decreased muscle mass and decreased muscle functionality.

Other combined tools include MSRA-7, MSRA-5, and the finger circle test.

## Diagnostic Tools

Tools used for diagnosis of sarcopenia are computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), muscle biopsy, and other serological markers. Advantages and limitations for various diagnostic tools are tabulated in Table 1.

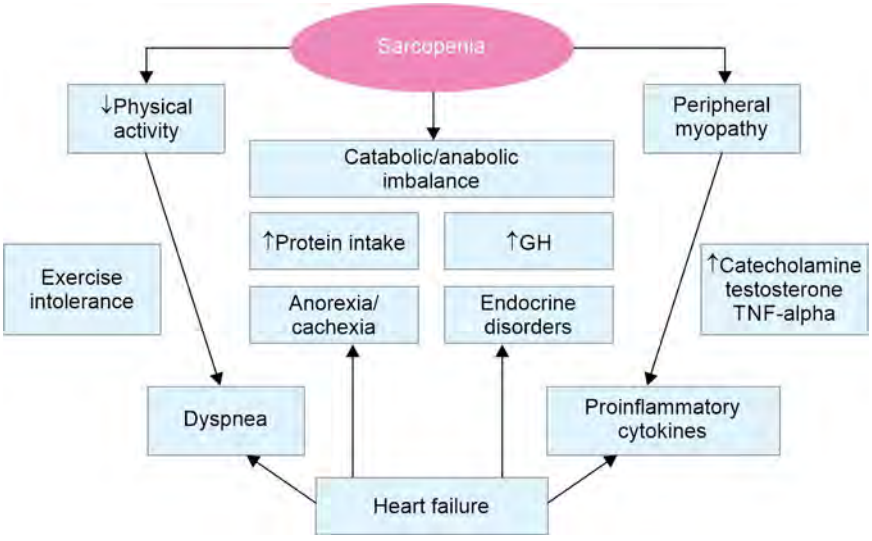


**Fig. 1:** Clinical aspects of sarcopenia

## Diagnostic Criteria

There is no specific test to diagnose sarcopenia, nor is there a gold-standard method for determining whether a patient is sarcopenic.

Three main components used for the diagnosis of sarcopenia are:

- An evaluation of muscle mass: the skeletal muscle index (SMI) was recorded by usage of DEXA. The SMI was calculated as appendicular skeletal lean mass (ALM; the sum of the muscle tissues in both legs and arms) divided by height squared.
- An assessment of muscle power: the handgrip power was evaluated by using a handheld dynamometer. Individuals needed to squeeze the device as hard as they could three times in each hand.
- An assessment of physical ability: the SPPB test was used to assess physical performance. It consisted of three separate assessments—balance, 4 m gait velocity, and chair stand test. A rating between 0 and 4 was assigned for each component (with a maximum of 12 points).[22] The European Working Group on Sarcopenia in Older People (EWGSOP) criteria 2019 for defining sarcopenia and assessment criteria for cachexia are mentioned in Tables 2 and 3. Sarcopenia must be differentiated from cachexia on a clinical and physiological basis. The comparative differences between sarcopenia and cachexia are mentioned in Table 4.

Sarcopenia is defined as low appendicular skeletal muscle mass (ASMM) with reduced strength of muscles or reduced physical performance, while severe sarcopenia is defined as low ASMM with reduced strength of muscles and reduced physical performance.

Assessment of cachexia includes:

- Primary criteria: at least 5% weight loss within 3–6 months for cancer or within 12 months for other chronic disease, or low BMI <20 kg/m$^2$.
- Secondary criteria: reduced muscle strength, fatigue, reduced appetite, low fat-free mass index, anemia, hypoalbuminemia, and increased inflammatory markers.[20] Cachexia includes the primary criterion and three secondary criteria.

## Preventive and Treatment Strategies for Sarcopenia

Preventive strategies targeted at exercise and nutritional interventions are the most effective targets for prevention of sarcopenia and can slow the progression to sarcopenia, improve physical performance, and prevent future loss (Table 5). The newer pharmacologic

**Table 1:** Advantages and limitations for various diagnostic tools for sarcopenia[21]

| *Diagnostic tools* | *Assessment* | *Advantages* | *Limitations* |
|---|---|---|---|
| CT | SMA (skeletal muscle area per centimeter square)<br>SMI ($cm^2/m^2$)<br>MRA (muscle radiation attenuation, HU) | Gold standard for precise measurement of muscle mass | High cost, high radiation exposure |
| MRI | Muscle mass (DTI)<br>Water/fat composition of a muscle<br>Fiber type composition of muscle (31P-MRS) | Gives cross-sectional analysis of muscle quantity and quality and unique insight into the metabolic quality of the muscle | High cost and low availability<br>contraindication—implants results in exclusion of participants |
| DEXA scan | • SMI<br>• ASMM | High reproducibility for body composition<br>Low radiation exposure, highly acceptable | Even this low dose radiation needs to be considered as a limiting factor for routine assessment of body composition, high cost, and low availability |
| Ultrasound | Skeletal muscle architecture and texture:<br>• Thickness<br>• Cross-sectional area<br>• Fascicle length<br>• Pinnation angle | Portable, low costs and risk, and no ionizing radiation is used | Few validation studies have been made and the heterogeneity of methodology and references limits accurate interpretation |
| Muscle biopsy | Type of muscle fiber: type I—being slow twitch fibers and types IIA and IIB, respectively fast twitch oxidative and fast twitch glycolytic fibers | Gives valuable data on muscle quality | The invasive technique poses burden for patients, risk of infection, requires additional infrastructure and knowledge in obtaining, processing, and interpretation of the data |
| BIA | Skeletal muscle mass | Noninvasive, fast, and easy-to-use method for estimating body composition, with moderate acquisition and low maintenance costs, commonly used in clinical practice<br>BIA is validated and useful for determining the body composition at a distinct point of time as well as for monitoring the change of body composition over a longer period of time | Limitations in obese and cachectic patients due to disproportion of body mass and body conductivity and a greater variety of intra- and extracellular water |
| Laboratory assessment | Serum albumin, creatinine kinase, myoglobin, urine or creatinine dilution test, amino acids and micronutrients | | No specific recommendations, references, or cutoff values available for any specific biomarker in order to assess muscle mass or quality |

**Table 2:** EWGSOP criteria 2019 for defining sarcopenia[23]

| *Variable* | *Assessment* | *Reference range* |
|---|---|---|
| Muscle mass | DEXA | SMI = ASMM or appendicular muscle mass/height per meter square [2 standard deviations (SD) below mean of young adults]<br>Men: <20 kg or 7.26 $kg/m^2$; women: <15 kg or 5.5 $kg/m^2$ |
| Muscle strength | Handgrip strength | Men: <27 kg; women: <16 kg |
| | Chair stand test | >15 seconds for five rises |
| Physical performance | SPPB | <8 point score |
| | Gait speed | <0.8 m/second |
| | TUG test | >20 seconds |
| | 400 m walk test | >6 minutes/noncompletion |

Sarcopenia = low ASM + LMS or LPP; Severe sarcopenia = low ASM + LMS and LPP

approach for treatment of sarcopenia is mentioned in Table 6.

## Dietary Strategies

Dietary strategies include adequate protein intake (1–1.5 gm/kg/day), nutrition-rich diet like soybeans, whey, cowpea, lentils, and vitamin D supplementation (50,000 IU per week) (Table 4). Administration of leucine stimulates the synthesis of muscle protein and inhibits the degradation of protein. As per study record, increasing the contents of leucine in the meal accelerates the postprandial muscle protein synthesis *in vivo* in aged men. Calorie restriction (CR) mimetics are bioactive substances obtained from plant sources, herbs, and spices, which mimic the substantial antiaging effects. These CR mimetics include resveratrol, quercetin, epigallocatechin-3-gallate, and nootkatone. Due to insufficient data on antioxidants, currently there is no scientific rationale for using antioxidants in patients with sarcopenia.[24]

## Exercise

To increase muscle strength and improve muscle function, resistance and aerobic exercise are both useful:

- Aerobic exercise: The anabolic response to amino acids and glucose is increased by aerobic exercise in healthy adults, which is useful to prevent muscle loss during aging. Studies have shown that aerobic exercise

**Table 3:** Assessment criteria for cachexia[20]

| *Primary criterion* | *Other criteria* |
|---|---|
| Weight loss of at least 5% in 3–6 months for cancer or in 12 months for other chronic illness<br>OR<br>Low BMI <20 kg/m$^2$ (in absence of data on weight history) | • LMS<br>• Fatigue<br>• Anorexia<br>• Low fat-free mass index<br>• Abnormal biochemistry (anemia, low serum albumin, and increased inflammatory markers) |

CACHEXIA = primary criterion + three of other criteria

helps in the reduction of oxidative damage to skeletal muscle and mitochondrial proteins.
- Resistance exercise: Resistance exercise increases muscle protein synthesis and causes hyperplasia of type 1 and type 2 muscle fibers.

Progressive resistance exercise is considered the best exercise for the prevention of sarcopenia. In this, the participant exercises their muscles against resistance at least 2–3 times a week for 8–12 weeks. Studies have shown that after PRE, participants showed a gain in whole-body muscle mass, as well as strength and gait speed.

**Table 4:** Differences between sarcopenia and cachexia[2]

| | *Sarcopenia* | *Cachexia* |
|---|---|---|
| Definition | Muscle mass <2 SD of young healthy population, decreased muscle function | Weight loss >5% in 6 months |
| Mechanism | Aging | Pathologic |
| Comorbid condition | +/– | +++ |
| Functional limitation | ++ | +++ |
| Inflammation | – | ++ |
| Protein degradation | –/+ | +++ |
| Resting energy expenditure | Decreased | Increased |
| Anorexia | + | ++ |
| Muscle protein synthesis | Increased | Increased |
| Muscle mass, strength, and function | Decreased | Decreased |
| Fat mass | Increased | Decreased |
| Basal metabolic rate and total energy expenditure | Decreased | Increased |
| Insulin resistance | Increased | Increased |

**Table 5:** Dietary strategies for management of sarcopenia[24]

| *Dietary strategies* | *Recommendations* |
|---|---|
| Protein | The total protein intake should be 1–1.5 gm/kg/day |
| Vitamin D supplementation | Doses of 50,000 IU of vitamin D a week are safe |
| Branched chain amino acids—leucine | Leucine administration stimulates muscle protein synthesis and inhibits protein degradation *via* insulin-structured and insulin-unbiased pathways. Recent research record that growing the leucine content of a meal to a stage exceeding 3 gm, increases rate of postprandial muscle protein synthesis *in vivo* in aged men, thereby normalizing the blunted reaction of muscle protein synthesis to meals ingestion |
| CRs and CR mimetics<br>• Resveratrol (found in grapes and red wine)<br>• Quercetin (found in apples, onions, and berries)<br>• Epigallocatechin-3-gallate (found in green tea)<br>• Nootkatone (found in grapefruit) | Reduction in total calorie intake, of about 20% (mild) and 50% (severe) and without malnutrition<br>CR mimetics are bioactive substances from plant sources, herbs, and spices which mimic the substantial antiaging effects that CR has on many laboratory animals and humans |

## Angiotensin-converting Enzyme Inhibitor and Sarcopenia

Angiotensin-converting enzyme inhibitor (ACE-i) improves endothelial function and angiogenesis and reduces inflammation by improving mitochondrial function, enhancing IGF-I levels, promoting skeletal muscle glucose uptake, and suppressing proinflammatory cytokine levels such as IL-6.

## Treatment of Cachexia

There are no specific guidelines for the management of cachexia. The treatment includes appetite stimulants, dietary and nutritional supplementation, adapted exercise, and anti-inflammatory drugs. Megestrol acetate, an appetite stimulant, and dronabinol (Marinol), a narcotic drug used to treat nausea and vomiting in patients with cachexia.

Patient-centered approach for management of sarcopenia includes early identification by SARC-F screening test and intervention by way of exercise.[25] Primary treatment for cachexia includes exercise and adequate intake of protein diet for all chronic hospitalized patients with aggressive resistance exercise. Secondary treatment for cachexia includes resistance exercise, low protein intake, leucine, methyl hydroxy butyrate, and vitamin D3 supplementation as per requirements. Tertiary treatment for cachexia includes physical therapy, occupational therapy, speech therapy for dysphagia, providing adequate protein diet, and treatment of underlying disease.

# Conclusion

As the population is rising, the prevalence of patients with sarcopenia will also rise, leading to more dependency both physical and emotional. The population who are at high risk should be screened for sarcopenia as it prompts early diagnosis and early management. Isolated LMS is defined as probable sarcopenia, while LMS associated with low muscle quantity or quality is called confirmed sarcopenia. When confirmed sarcopenia is combined with LPP, then it is called severe sarcopenia. Increasing awareness among patients and healthcare providers, early detection, and intervention can delay the progression to sarcopenia. Many mechanisms have been proposed for sarcopenia, including mitochondrial dysfunction in skeletal muscles, systemic inflammation, defective amino acid metabolism, neurodegenerative process (α motor neuron), and decreased anabolic hormones. The fields of muscle aging and exercise physiology have synergized

**Table 6:** Newer pharmacologic approach for treatment of sarcopenia the road to future[26]

| *Drug name* | *Target* | *Remark* |
|---|---|---|
| Brimagrumab | Activin receptor type 2B | Thigh muscle volume increased by week 2 and was sustained throughout the treatment period (June 2017, phase 2) |
| Trevogrumab (antibody) | Myostatin | Primary end point of phase 2: percent change in total lean body mass |
| Sarconeos (natural active ingredients) | Proto-oncogene protein c-MAS-1, MAS receptor | Meaningful activity in animal models of muscular dystrophies. Good tolerability profile and no serious adverse events (phase 1) |
| ARM-210 (small molecule) | Ryanodine receptor | Treatment of Becker and limb-girdle muscular dystrophies as well as cachexia |
| TEI-SARM2 | Androgen receptor | Selective androgen receptor modulator |
| *AAV* (gene therapy) | Myostatin | Obtained from a natural source and has potential in the modulation of myostatin expression |
| Peptide of follistatin | Furin, Janus kinase 3, myostatin | Discovery of a myostatin inhibitor therapeutic for the treatment of sarcopenia |
| ATA 842 (antibody) | Myostatin, activin | ATA 842 demonstrated increased muscle mass and muscle strength in the treatment of young and old mice for 4 weeks |
| *AVGN7* (gene therapy) | Activin receptors | Gene expression inhibitors. *AVGN7* contains a gene called *SMAD7*, which stops gene expression for muscle wasting |

to provide vital insights into primary results of aging on muscle and how aging-associated modifications can be attenuated or prevented by way of exercising. Dietary factors and exercise have a major role in prevention and treatment of sarcopenia. However, more trials should be done on drugs targeting the molecular pathway for better and specific treatment strategies.

## Author Contributions

Dr C Nawal and Dr RS Chejara contributed to the concept and design of this expert opinion document. The manuscript draft was developed by Dr A Singh and critically reviewed by all the authors. The manuscript was edited and modified by Dr G Rankawat. All authors have approved the final draft of the manuscript.

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REVIEW ARTICLE

# Transmission of *Mycobacterium Tuberculosis*

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## Abstract

**Introduction:** Tuberculosis (TB) has been a leading killer of mankind since time immemorial. There are four key components in the TB elimination approach. They are known as "Detect–Treat–Prevent–Build". Under the preventive strategy, scaling up of airborne infection control measures is an important step in controlling the global disease burden.

**Methods:** This is a narrative review for which we used online databases such as PubMed, Embase, and CINAHL from inception to July 2024. The search terms used include TB, transmission, aerosols, cough, droplet nuclei, Wells–Riley equation, and ultraviolet germicidal irradiation (UVGI). All types of articles were selected.

**Results:** The primary mechanism of transmission of *Mycobacterium tuberculosis* (*M. tb*) is the inhalation of small infected droplet nuclei (1–5 µm in diameter) consisting of a few mycobacteria that have the capacity to reach the alveoli. The transmission dynamics of TB can be influenced by various human, environmental, and pathogenic factors. Several mechanisms such as coughing, sneezing, talking, laughing, singing, and normal tidal breathing can produce droplet nuclei.

**Conclusion:** It is crucial to thoroughly understand the mechanisms of TB transmission for a better understanding of TB dynamics. TB is mainly transmitted by droplet nuclei, and preventive strategies should incorporate this mechanism.


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## Introduction

The term "tuberculosis (TB) transmission" indicates spread of TB bacilli from one person to another. The transmission of TB occurs through the airborne route by inhalation of droplet nuclei. Droplet nuclei are the infectious particles of TB of sizes ranging from 1 to 5 µm. They are produced by numerous aerosol-generating activities such as coughing, sneezing, talking, laughing, singing, and normal tidal breathing. The droplet nuclei are usually produced in patients with laryngeal or pulmonary TB disease.[1,2] The number of droplets produced by one cough episode is 500, and a treatment-naïve pulmonary TB patient generates on average 75,000 droplets per day. This number drops to 25 infectious droplets per day after 2 weeks of appropriate treatment.[2,3] Singing produces a higher percentage of droplet nuclei of up to 2.9 µm diameter than coughing (34.1 vs 26%). Tidal breathing is also an equally important maneuver in TB transmission.[4] In a modeling study, tidal breathing was responsible for almost 90% of the daily aerosolized *Mycobacterium tuberculosis* (*M. tb*) among symptomatic TB patients.[4] Patterson and Wood[5] suggested that the aerosols are produced in the larynx, bronchi, and bronchioles. However, bronchi and bronchiolar aerosols are primarily responsible for TB transmission. Moreover, singing, talking, coughing, and less commonly tidal breathing all produce bronchiolar aerosols. Tidal breathing exclusively produces bronchiolar aerosols. Therefore, TB can be spread even in the absence of coughing.

Wells in 1934 suggested that the small droplet, after emanating from the mouth, fell on the surface and that the rate of fall of the droplet is proportional to its surface area or diameter.[6] If the diameter of the droplets is larger than 1 mm, particles will fall to the surface in 0–6 seconds, but smaller droplets of <0.001 mm will take approximately 16.6 hours. The droplet nuclei in the environment undergo evaporation and become smaller in size, and the rate of this evaporation is proportional to the square of the diameter. These tiny droplets may remain airborne for a longer period and are infectious as they carry *M. tb*.[7] The average half-life of aerosolized TB bacilli is approximately 6 hours. The layer of respiratory secretions protects the droplet nuclei from natural irradiation, oxygen injury, dehydration, and other environmental stresses.[7] These nuclei, on inhalation by contact, can enter the lungs' periphery, establishing infection if they float in the air for a sufficient amount of time. The droplet nuclei on the surface are difficult to reaerosolize, as the viable bacilli are coupled to relatively big, nonrespirable particles that typically impact the relatively resistant upper airways.[8,9] Loudon et al.[3] documented that at 6 hours, 55.8% of the aerosols of *M. tb* (H37Rv) and 13.1–37.5% of the nontubercular mycobacteria survived. Children are usually less infectious due to the paucibacillary nature of the disease, less sputum production, and often have hilar or mediastinal lymphadenopathy, bronchial obstruction, and atelectasis.[10]

## Brief History of Transmission of Tuberculosis

The concept of airborne transmission is not unexplored. Aristotle in 384–322 BC initially recognized the infectious nature of TB and its transmission *via* pernicious air.[11] Hippocrates (470–410 BC) asserted that "consumptives beget consumptives," supporting the idea that TB is inherited.[12] Galen (129–216 AD) stated, "When many sicken and die at once, we must look to a single common cause, the air we breathe."[13] In a seminal research in 1861, Louis Pasteur demonstrated that air was inhabited by microorganisms.[14] All of their statements support the concept of airborne TB transmission. A French military surgeon named Jean-Antoine Villemin (1827–1892) was the first person to demonstrate the transmissibility of TB from patient to animal.[15] In 1882, Koch showed that animals exposed to tubercle bacilli in the air developed a chronic form of TB and those animals exposed to massive doses died shortly.[16] Although Koch did not confirm it experimentally, he suspected the airborne transmission as well, assuming the majority of the cases occurred in the respiratory tracts; the bacilli are usually inhaled with air.[16] In 1899, German bacteriologist and hygienist Flügge laid down the concept of droplet transmission of TB. Moreover, his work led to the recognition of the use of surgical masks to prevent spread of infection by transmissible aerosols.[17] However, the scientific basis of

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droplet nuclei–mediated transmission of TB was based on Wells' research,[18] which showed that not all aerosols fell within a short distance from the source.[19] Flügge's theory did not highlight the role of evaporation. They believed that the size of the aerosols was constant. Loudon and Roberts in the 1960s reported the mechanisms of aerosolization by talking, singing, coughing, and sneezing.[2,20] Riley et al. were credited to first confirm the airborne transmission of TB experimentally in the human-to–guinea pig transmission study where the only contact between them was shared air.[21] They conducted the study on a six-bed TB ward at the Veterans Hospital in Baltimore. These rooms were sealed off from the rest of the hospital. The ward had a precisely calibrated and controlled closed-circuit ventilation system and a sizable animal exposure chamber situated in the system's exhaust duct. Guinea pigs were exposed to air vented from the pilot ward occupied by TB patients. The air in the exposure chamber and the ward that housed the TB patients had the same infectivity, according to earlier research by the same investigators.[22,23] The investigators performed tuberculin tests every month on the entire 150 guinea pigs. An autopsy and a histopathological examination were conducted on the animals showing positive tuberculin conversion. The presence of tubercles depicted through the examination was considered as the basis of the TB diagnosis. Over a period of 2 years, 71 guinea pigs became infected with TB, and over a period of 4 years, 134 guinea pigs contracted TB. The average number of infections contracted in a single month was approximately three (0–10). This study confirmed that transmission of TB infection occurred *via* airborne infection. Additionally, there was a noticeable variation in transmission of infection from TB patients. The author also demonstrated how guinea pigs were shielded from infection by ultraviolet germicidal irradiation (UVGI). The majority of infections were caused by three patients, indicating variability of aerial infectivity of TB patients.[24] Escombe et al.[25] subsequently reproduced the result by Riley. They used the *in vivo* air sampling model to study the airborne transmission of TB in human immunodeficiency virus (HIV)–TB coinfected patients. An animal facility that housed on average 92 guinea pigs was built above a mechanically ventilated HIV–TB ward in Lima, Peru. About 97 patients with pulmonary TB were admitted with a median duration of hospitalization of 11 days, and 42% had positive sputum microscopy results. There was a wide variability in the rate of TB infection as monthly rates of positive tuberculin skin test (TST) among the guinea pigs were 0–53%. The mean number of airborne infectious units or quanta was 8.3 per hour compared to 1.25 quanta per hour in Riley's cohort.

Subclinical TB also contributes to TB transmission. Nguyen et al.[26] conducted a multivariate analysis of data from TB prevalence and TB survey data in Vietnam. The adjusted risk ratio of TST positivity in children living with patients of subclinical TB was 2.26 (95% CI: 1.03–4.96) after adjusting for index smear status. Children aged 6–10 who lived with patients of smear-positive TB (both clinical and subclinical) had a similar elevated risk of TST positivity compared to those living with individuals without TB. Emery et al.[27] estimated the infectiousness of subclinical TB in relation to clinical TB at 1.93 (0.62–6.18, 95% prediction interval). Modeling analysis suggests that subclinical TB can cause 68% of global transmission of TB. Therefore, early diagnosis and treatment should be ensured.

## Factors Related to Transmission of Tuberculosis

Factors related to TB transmission include characteristics of index patients and contacts, characteristics of the bacillus, and environment. Factors related to the index patients include the site of disease, bacillary load, presence of cough, lack of cough etiquette, and anti-TB therapy. Although both pulmonary and laryngeal TB are infectious, patients with laryngeal TB are more contagious compared to patients with pulmonary TB.[28] Patients with cavitary disease on a chest radiograph are at higher risk of transmitting infection, as a 2 cm cavity can contain $10^8$ TB bacilli.[29] The minimum number to become smear-positive is 10,000 bacilli per mL of sputum,[30] whereas culture positivity requires approximately 10–100 live bacilli. Patients with smear-positive pulmonary TB are more susceptible to infection than smear-negative patients, as approximately $10^6$–$10^7$ acid-fast bacilli per mL of sputum are expectorated by smear-positive individuals daily, whereas sputum from smear-negative individuals contains fewer than $10^3$ bacilli per mL.[31,32] van Geuns et al.[31] estimated that among smear- and culture-positive patients, TST reactivity among household contacts (HHCs) and casual contacts was 20.2 and 3.7%, respectively. Among smear-negative and culture-positive patients, the corresponding figures among HHCs and casual contacts were only 1.1 and 0.2%, respectively. Although smear-negative individuals are less contagious, they also contribute to TB transmission.[33] Persistent cough (either spontaneous or induced) may also help in the transmission of TB bacilli. Amount and severity of cough in the source patient are also important, particularly when the patient is not following cough etiquette. Early initiation of effective chemotherapy rapidly makes the person noninfectious.[3,34] According to Styblo's estimation,[35] one untreated smear-positive case leads to approximately 10 secondary infections annually. Unsuspected TB patients in the ward are particularly common in high-TB-burden countries. They may fuel TB transmission in a busy hospital ward. Bates et al.[36] reported unsuspected TB among 13.4% of TB cases in Zambia. In a different study, 13 unsuspected TB patients were admitted, and 46% of them were diagnosed as MDR-TB.[37] In nations with high TB burdens, proactive TB screening must be performed on all inpatients.

### Contacts

The risk factors of infection include closeness, frequency, and duration of exposure. HIV, other T-cell defects, structural lung disease, uncontrolled diabetes, and younger age may increase the risk of infection among the contacts. Among HHCs of smear-positive cases, the TST reactivity rates are 30–50% higher than among age-matched controls. On the contrary, the tuberculin reactivity rate is 5% higher than the community controls in culture-positive and smear-negative cases.[38] Paradkar et al.[39] from India observed that HHCs of adult pulmonary TB (PTB) patients had a higher rate of TB infection. Approximately 71% of 997 HHCs had baseline TST ≥5 mm or interferon-gamma release assay (IGRA) ≥0.35 IU/mL. Certain cough-inducing procedures such as bronchoscopy, endotracheal intubation, sputum induction, and cardiopulmonary resuscitation may also help in TB transmission. Loudon and Spohn[40] recorded the radiological extent, bacteriological status, and cough counts in patients with newly diagnosed and untreated pulmonary TB. The prevalence of tuberculin sensitivity among contacts of index TB patients with far advanced radiological disease was significantly higher compared to contacts of index patients with moderate or mild disease. When the index pulmonary TB patients were positive on microscopy and culture, culture-positive and smear-negative, and both smear and culture-negative, the corresponding prevalence of tuberculin reactivity among HHCs was 44.3, 21.4, and 14.3%, respectively. When the index pulmonary TB patients had mean cough counts of <12, 12–47.9, and >48, the corresponding prevalence of tuberculin reactivity among HHCs was 27.5, 31.8, and

43.9%, respectively. Grzybowski et al.[41] estimated the prevalence of infection among contacts of pulmonary TB patients. The prevalence was variable depending on the bacillary load. An increased risk of infection with increasing age was reported when compared to the general population. The prevalence of infection among smear-positive contacts, culture-positive pulmonary TB in the 0–4 years and ≥40 years age-groups was 29.1 and 61.1%, respectively.

## Environmental Factors

The risk of transmission is determined by the exposure site and ventilation. If contacts are exposed to an infectious TB patient in an enclosed and small space with no cross-ventilation, there will be an increased chance of transmission. A well-ventilated room with a sufficient amount of air change per hour lowers the risk of transmission. Environmental factors, by increasing the concentration of droplet nuclei, may enhance the risk of transmission. The factors that might increase the concentration of droplet nuclei and the enhanced risk of transmission include exposure within a small enclosed space, inadequate ventilation, recirculation of air containing infectious aerosols, and improper sample handling within the laboratory.[42] This explains why TB outbreaks occur in enclosed places such as nursing homes, prisons, urban homeless shelters, aircraft, schools, and bars. Furthermore, several aerosol-generating procedures, such as open abscess irrigation, endotracheal intubation and suctioning, bronchoscopy, and autopsy, have the potential to transmit TB nosocomially.[43–46] Almost, all TB transmission occurs indoors. It has been reported among marijuana and cocaine users also.[47–49] The "shotgunning" drugs, where a person inhales smoke and then exhales into someone else's mouth, have the potential to effectively spread respiratory infections.[50]

## Characteristics of the Bacilli

Various strains of TB bacilli have different transmission potential. Some strains are super-spreaders also. A large outbreak was reported by Valway et al.[51] in a small, rural community with a low-risk population in the USA. In five patients, active TB developed following a brief and casual exposure. The strain in this study differs from other strains in its growth characteristics. Mice administered the Erdman strain of *M. tb* showed approximately 1,000 and 10,000 bacilli per lung after 10 and 20 days, respectively, while mice infected with the virulent strains had approximately 10,000 and 10 million bacilli per lung, respectively.

## Effective Chemotherapy

Effective chemotherapy for TB reduced the risk of transmission of infection markedly. After 2 weeks of appropriate chemotherapy, the number of infectious droplets drops to 25 per day.[52] Brooks et al.[34] demonstrated the efficacy of chemotherapy in 21 patients with pulmonary TB. They discharged the patients after 2 weeks of chemotherapy and measured the risk of new infection among 72 HHCs. The majority of patients were smear and culture-positive (19 patients) and had cavitary disease (16 patients). None of the 72 HHCs who were TST-negative on initial testing converted. There was a rapid drop in bacillary number postchemotherapy. Riley et al. also assessed the impact of drug therapy of index patients on the risk of transmission. In the case of drug-susceptible TB, untreated patients transmitted infection to 29 guinea pigs with 100% infectiousness. However, in the drug therapy group, only one guinea pig contracted infection, indicating a drastic reduction of infectivity by 98%. Similarly, with drug-resistant organisms, treatment reduced infectivity by 23%.[53]

## Nosocomial Transmission of Tuberculosis

The fact that healthcare facilities, particularly in developing countries, have been known to be important locations for TB transmission since time immemorial. There are many examples of institutional outbreaks of drug-susceptible and drug-resistant TB.[54–56] Immunocompromised individuals, such as HIV-positive persons, are particularly vulnerable to contracting TB infection. In developing countries, data on the institutional spread of TB is often lacking due to the nonavailability of molecular epidemiological tools. The crowded indoors, outpatients, lack of triaging facilities, and respiratory isolation are good recipes for nosocomial transmission of TB. Moreover, TB infection prevention and control (IPC) program often remains neglected in resource-poor countries.[57] Using TST and IGRA, a cross-sectional study was conducted on 726 healthcare workers in India who had no prior history of TB. About 50% of the healthcare workers were positive for either of the two tests.[58] The follow-up survey among 216 medical and nursing students revealed the annual risk of infection of 5%, which is higher than the community average, suggesting potential nosocomial transmission.[59] The spread of extensively drug-resistant TB (XDR-TB) in Tugela Ferry, KwaZulu-Natal Province, South Africa, underscores the significance of infection control in preventing the nosocomial spread of TB.[60] There are two important aspects of this incident. The majority of patients had a primary transmission of TB as they are treatment-naïve. If the patient had been hospitalized in the preceding 2 years, hospitalization was a significant risk factor for XDR-TB, with an odds ratio of 3.7.[61] Among 53 XDR-TB patients, 67% had been hospitalized recently. There was a similar strain in 85% of patients. About 71% of XDR-TB cases reported by Gandhi et al.[62] had been exposed to at least one infectious XDR patient while in the hospital. The Tugela Ferry incident had also raised questions about the theory of loss of fitness of resistant strain.

## Mathematical Models of Transmission

A mathematical model of TB transmission was proposed by Riley, who modified the Wells' use of the soper mass balance equation, assuming that the risk of TB from casual contact was much lower than that of measles.[23,63] This equation is known as the Wells–Riley equation.

Equation 1:

$$C = S\,(1 - e^{-Iqpt/Q})$$

Where,

C = Number of new cases.

S = Number of susceptible exposed.

e = Natural logarithm.

I = Number of infectious sources.

q = Number of quanta (infectious doses) generated per unit minute.

p = Human ventilation rate (L/minute).

t = Exposure duration.

Q = Infection-free ventilation (L/second)

When air from the space is exchanged with uncontaminated air.

The Wells–Riley equation suggests that infectious cases, degree of infectivity, susceptible hosts who are exposed, exposure duration, and ventilation rate are important parameters during transmission of TB infection. A uniform virulence of organisms was assumed, as well as susceptibility of the individuals exposed to infection, which further made the base of the equation. So, it was only used in steady-state conditions. The resource-intensive measurement of room ventilation was an additional limitation. The problem of estimating a room's ventilation was solved by Rudnick and Milton, who suggested the use of human-generated indoor carbon dioxide ($CO_2$) levels as a natural tracer gas.[64] This equation can be used in both a steady state and a nonsteady state.

## Variability of Infection

It is a fact that infectiousness is variable. Some individuals are more contagious than others, and the variability may occur over a

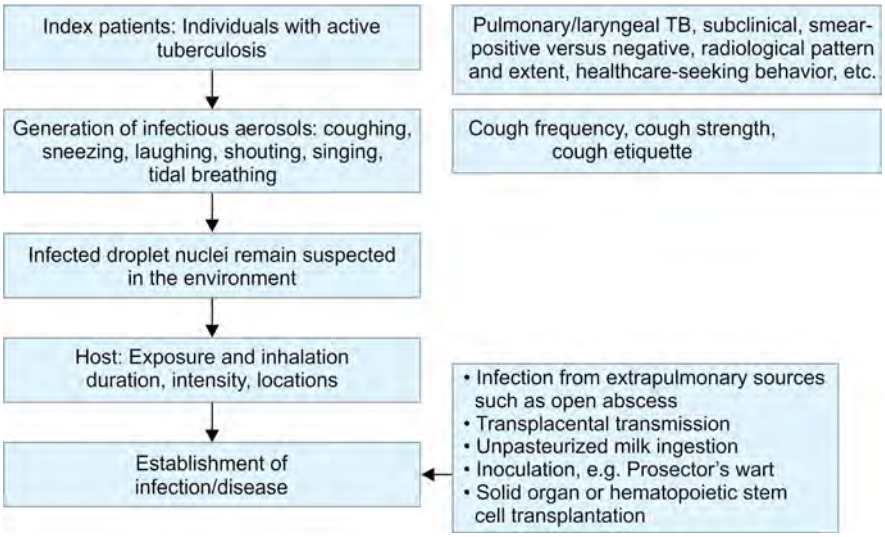


**Fig. 1:** The mode of transmission of TB

period in a patient.[62] The term "quanta" was used by Riley et al. to define the number of infectious airborne particles required to infect a contact. Even one or more airborne particles can establish the infection.[63] In an animal experiment, 63.2% of highly susceptible guinea pigs were exposed to tubercle bacilli available at a concentration that would allow each animal to inhale no more than an average one droplet nucleus. Therefore, the dose that causes 63.2% of exposed subjects to get infected is known as the quantum of infection.[65] The generation of infectious quanta is variable. In one study from the University of California, San Diego Medical Center, the risk of contracting TB infection was high in hospital employees when exposed in a bronchoscopy suite, as 77% of exposed were converted. During bronchoscopy and intubation of the index case, 249 infectious units per hour were generated.[43] The rate of infection aerosols formation was 1.25 quanta per hour in Riley's experiment, clearly suggesting a variability in infectiousness.[53] Melsew et al.[66] reported 9.9% super-spreading events from Victoria, Australia. Radiological extent of pulmonary diseases, bacteriological status, and mean 8-hour overnight cough counts determine the variability in TB transmission. The prevalence of TST sensitivity among contacts of index TB patients with far advanced radiological diseases was significantly higher compared to children who were contacts of index patients with moderate or mild disease radiologically.[40] Similarly, a higher prevalence of reactivity was observed among HHCs when index TB patients had microscopy positivity. When the index pulmonary TB patients were smear and culture-positive, smear-negative culture-positive, and both smear and culture-negative, the corresponding prevalence of TST reactivity among HHCs were 44.3, 21.4, and 14.3%, respectively.

### Other Modes of Transmission

- Congenital *via* transplantation route.
- Inoculation, for example, Prosector's wart.
- Gastrointestinal—bovine TB, heavy inoculums, not due to contamination of foods.
- Other aerosols—laboratory and wound debridement.

Figure 1 shows various modalities of transmission of TB.

## Newer Tool to Detect Infectiousness

Fennelly et al.[67] designed the "cough box" experiment to measure the infectious aerosols released while coughing by TB patients. He was the first to culture *M. tb* using droplet nuclei derived from 38 patients with infectious TB in Kampala, Uganda. In 27.7% of patients with culture-confirmed TB, *M. tb* could be cultured from cough aerosols. After coughing for 10 minutes, a median aerosol colony-forming unit (CFU) (range, 1–701) of 16 was generated. About 96.4% of cultivable particles were in the range of 0.65–4.7 µm in size. Small droplets are therefore the most culturable. Furthermore, small droplets can still form in the absence of evaporation. This study demonstrated a feasible technique for gathering cough aerosols in an environment with limited resources. It also demonstrated that not all patients with infectious TB are transmissible. In patients with pulmonary TB, Jones-López et al.[68] demonstrated that in 45% of cases, smear positivity was associated with aerosol production. Additionally, they found that the only risk associated with a new TB infection was high aerosol production (>10 CFU) (adjusted odds ratio, 4.81; 95% CI: 1.20–19.23). Therefore, among contacts, cough aerosols with high culture positivity are the main predictor of new infection. In future, a widely available, simple, better design, and cost-effective method to measure cough aerosols is required. Cough aerosol sampling measures the patient's aerosol production capacity and is a new study tool that has been proven to correlate better with household transmission. Facemask sampling provides an attractive, sensitive, and noninvasive way of stratifying the most infected individuals.

## Role of Exhaled Breath Carbon Dioxide

Exhaled breath $CO_2$ level can be used as a surrogate for exhaled breath. Exhaled breath by an infected pulmonary TB patient releases infectious particles in the room occupied by the index patient. The only source of $CO_2$ in the room is the exhaled breath, as its $CO_2$ is over 40,000 parts per million, while outside air has about 350 parts per million $CO_2$ content. The vulnerable in the room may develop infection upon inhaling the infected exhaled breath. The "rebreathed air fraction" is defined as the inhaled air that was previously exhaled by someone inside the building. The ambient $CO_2$ concentration depends on the effect of occupancy and ventilation and is a good surrogate for the risk of airborne infection. Richardson et al.[69] used the Rudnick–Milton equation and found that for a classroom of 180 $m^3$, an indoor $CO_2$ concentration of 1,000 parts per million or 12 air changes per hour (ACH) corresponded with a critical rebreathed $CO_2$ fraction of 1.6%. A higher level of median $CO_2$ indicates inadequate ventilation and/or overcrowding, as well as being linked to an increased risk of TB transmission. Nathavitharana et al.[70] reported that the IGRA converters had higher median $CO_2$ levels compared to IGRA nonconverters ($p$ <0.01). Every 100 parts per million rise in median $CO_2$ levels increased the repeat quantitative IGRA result by an odds of 1.81 ($p$ = 0.01).

## Conclusion

A thorough plan is necessary for the two hallmarks of the End TB Strategy, prevention and control of TB infections, while accounting for available resources, cost, and geographical constraints. Understanding the transmission mechanisms and the variables that can impact it would help in taking better infection prevention and maintaining control practices

in the hospital. Healthcare workers should be consistently educated and trained on control and prevention of TB infection, while active TB patients should be properly educated on respiratory hygiene and cough etiquette. Ultimately, a timely and rigorous adoption of prevention and control of TB infection, while accounting for the available resources, should be positively addressed at every level of the health facility.

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VIEW POINT

# Ribavirin and IVIG Therapy for Severe hMPV Pneumonia: A Promising Therapeutic Approach for India

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## Abstract

Human metapneumovirus (hMPV) is a leading cause of acute respiratory tract infections (ARTIs), with severe cases predominantly affecting immunocompromised individuals, such as transplant recipients, cancer patients, and those with chronic illnesses. In these high-risk populations, hMPV pneumonia often leads to prolonged hospitalization and elevated mortality rates.

While supportive care remains the cornerstone of hMPV management, targeted therapies are urgently needed. Ribavirin, a broad-spectrum antiviral, combined with intravenous immunoglobulin (IVIG), has shown potential in reducing disease severity and improving outcomes in immunocompromised patients. This manuscript synthesizes the clinical evidence for ribavirin–IVIG therapy, discusses its mechanisms of action, and highlights its relevance in the Indian healthcare context, where respiratory infections impose a significant burden.

Despite its promise, challenges such as high costs, limited awareness among clinicians, and logistical barriers restrict the adoption of ribavirin–IVIG in India. This review emphasizes the need for multicenter trials to establish efficacy, optimize dosing, and evaluate cost effectiveness in resource-limited settings. By addressing these gaps, ribavirin–IVIG therapy could play a transformative role in reducing the morbidity and mortality associated with severe hMPV pneumonia.

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## Introduction

Human metapneumovirus (hMPV), first described in 2001, has emerged as a significant etiological agent of acute respiratory tract infections (ARTIs) worldwide, particularly in vulnerable populations.[1] While the majority of hMPV infections present with mild symptoms, immunocompromised individuals—such as transplant recipients, cancer patients undergoing chemotherapy, and individuals with chronic illnesses—are at increased risk of severe complications. These complications often necessitate prolonged hospital stays and are associated with elevated mortality rates, underscoring the clinical impact of hMPV in high-risk groups.[2]

Despite the substantial burden posed by hMPV, the management of severe cases remains largely supportive, with no universally approved antiviral treatment available. Ribavirin, a broad-spectrum antiviral agent, has shown promise in reducing disease severity when combined with intravenous immunoglobulin (IVIG), which enhances passive immunity. This therapeutic combination has been particularly beneficial in patients with compromised immune systems, as evidenced by case studies and limited clinical trials.[3]

This manuscript aims to provide a comprehensive review of the clinical evidence supporting ribavirin and IVIG as a targeted therapeutic option for severe hMPV pneumonia. It also examines the underlying mechanisms of action and highlights the relevance of this approach within the Indian healthcare context, where respiratory infections remain a leading cause of morbidity and mortality in immunosuppressed populations. By addressing the gaps in current treatment protocols, we aim to underscore the need for tailored therapeutic strategies and the potential for this combination therapy to improve outcomes in resource-constrained settings.

## Clinical Evidence Supporting Ribavirin–IVIG Combination Therapy

The use of ribavirin and IVIG as a therapeutic combination for severe hMPV infections has shown promising results in specific high-risk populations. A notable case report documented the recovery of a 2-year-old child with Burkitt lymphoma and life-threatening hMPV pneumonia following treatment with ribavirin and IVIG after failure of conventional supportive care. This case highlights the potential for targeted antiviral and immunomodulatory therapies to improve outcomes in immunocompromised patients.[4]

In addition, a retrospective multicenter study demonstrated significantly improved survival rates among hematopoietic stem cell transplant recipients who received ribavirin–IVIG therapy compared to those who received only supportive care. This finding underscores the potential role of this combination in reducing mortality in patients at the highest risk for severe hMPV-related complications.[5]

Furthermore, meta-analyses of available evidence have revealed that the ribavirin–IVIG combination can substantially reduce hospitalization duration and mortality in high-risk groups, particularly among immunosuppressed individuals and those with underlying malignancies. These findings collectively support the therapeutic potential of ribavirin and IVIG for managing severe hMPV infections.[6]

## Mechanisms of Action

### Ribavirin

Ribavirin acts as a broad-spectrum antiviral agent by inhibiting viral ribonucleic acid (RNA) polymerase, effectively suppressing hMPV replication. Additionally, ribavirin

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exerts immunomodulatory effects by downregulating proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-10 (IL-10), thereby mitigating the excessive inflammatory responses associated with severe respiratory infections.[7]

### Intravenous Immunoglobulin

Intravenous immunoglobulin provides passive immunity by neutralizing hMPV and supporting antibody-dependent cellular cytotoxicity (ADCC). IVIG enhances the host's ability to clear viral infections, making it particularly effective in immunocompromised patients with diminished endogenous antibody production. The complementary mechanisms of ribavirin and IVIG contribute to their synergistic efficacy in controlling severe hMPV infections.[8]

## Barriers to Implementation in India

### Cost and Accessibility

Ribavirin and IVIG remain prohibitively expensive in many parts of India, posing a significant barrier to their widespread use. Their availability is often limited to tertiary care centers, making them inaccessible to patients in resource-limited settings.

### Lack of Awareness

The use of ribavirin–IVIG for severe hMPV is not widely recognized among Indian clinicians, contributing to its underutilization. Awareness campaigns and training programs are needed to bridge this knowledge gap.

### Evidence Gaps

A lack of robust, large-scale randomized controlled trials (RCTs) specific to Indian populations impedes the development of standardized treatment guidelines. Local studies are crucial to establish the efficacy, optimal dosing, and cost-effectiveness of this combination therapy in the Indian healthcare context.

By addressing these barriers, ribavirin–IVIG therapy could become an integral part of managing severe hMPV pneumonia in India, particularly for high-risk populations.

## Discussion

### Potential Benefits in the Indian Context

India bears a substantial burden of respiratory infections, driven by a high prevalence of comorbidities such as malnutrition, chronic respiratory diseases, and immunosuppressive conditions including cancer and posttransplant immunosuppression. Severe cases of hMPV pneumonia, particularly in these high-risk groups, are associated with significant morbidity and mortality.

Ribavirin and IVIG therapy offers a dual-targeted approach that addresses both the viral burden and the compromised immune response in these populations. Ribavirin's antiviral action directly suppresses hMPV replication, while IVIG provides passive immunity, neutralizing the virus and enhancing immune clearance. Integrating this combination therapy into clinical practice could dramatically improve outcomes for patients with severe hMPV, reducing hospitalization duration and mortality rates. Furthermore, by mitigating disease severity, ribavirin–IVIG therapy has the potential to ease the burden on India's overstrained critical care infrastructure, especially during respiratory infection surges.[9]

### Implementation Challenges

Despite its promise, several barriers hinder the widespread adoption of ribavirin–IVIG therapy in India:

- Cost and accessibility: Ribavirin and IVIG are costly, with availability largely confined to tertiary care hospitals in urban areas. This limits access for patients in rural or resource-limited settings. Government-subsidized healthcare programs, along with partnerships between public health authorities and pharmaceutical manufacturers, could reduce the financial burden on patients and healthcare systems. Local production of ribavirin and IVIG may also help lower costs.
- Awareness and training: Limited awareness among healthcare professionals regarding the use of ribavirin–IVIG for severe hMPV cases is a significant barrier. Evidence-based guidelines and clinician training programs are urgently needed to promote the judicious and effective use of this therapy. Awareness campaigns targeting both tertiary and secondary care centers can bridge this knowledge gap.
- Logistical challenges: Storage, distribution, and administration of ribavirin and IVIG require infrastructure that is often unavailable in smaller healthcare facilities. Strengthening supply chain logistics and ensuring timely availability of these drugs are critical to their successful implementation.

### Research Directions

To integrate ribavirin–IVIG therapy into routine care for severe hMPV pneumonia in India, robust evidence from local clinical trials is essential. Future research should focus on:

- Efficacy: Conducting multicenter RCTs to establish the effectiveness of ribavirin–IVIG therapy in reducing mortality and improving recovery in severe hMPV cases.
- Optimal dosing and timing: Evaluating the most effective dosing regimens and timing of administration to maximize clinical outcomes while minimizing adverse effects.
- Cost-effectiveness: Investigating the economic feasibility of ribavirin–IVIG therapy in resource-constrained settings, including strategies to optimize drug procurement and reduce costs.
- Subpopulation analysis: Assessing the therapy's impact on different patient subgroups, such as pediatric, geriatric, and oncology patients, to develop tailored treatment protocols.

By addressing these research gaps, India can establish evidence-based guidelines for the use of ribavirin and IVIG, paving the way for wider adoption of this promising therapy.

## Conclusion

The combination of ribavirin and IVIG represents a targeted and effective therapy for severe hMPV pneumonia, particularly in immunocompromised populations. While challenges such as cost, awareness, and infrastructure limit its current applicability, strategic interventions can overcome these barriers. Government initiatives, public–private collaborations, and clinician education are critical to making this therapy accessible to those who need it most.

Prioritizing research through multicenter trials and collaborative efforts will strengthen the evidence base, enabling India to integrate ribavirin–IVIG therapy into standard care protocols. By doing so, the country can enhance clinical outcomes, reduce the burden of respiratory infections, and improve the quality of life for vulnerable patients.

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# Calcification at the Level of 12th Dorsal and 1st Lumbar Vertebrae

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A 46-year-old man presented with pain in his left lower limb for the past 2 months. He was taking herbal medications for diabetes, which he had for the past 3 years. He had a history of alcohol dependence for the last 12 years, but recently he was able to overcome his addiction with the help of counseling. He had no history of recurrent abdominal pain and had no complaints of steatorrhea. Clinical examination revealed his body mass index (BMI) was 18 kg/m$^2$, pulse 110 beats per minute, blood pressure 124/78 mm Hg, and absence of icterus. The blood tests showed hemoglobin 11.5 gm/dL, blood sugar (fasting) 440 mg/dL (reference range 60–110), and glycated hemoglobin (HbA1c) 9.5% (good control <6.5), serum calcium 8.9 mg/dL (reference value 8.5–10.5) and vitamin $D_3$ 16 ng/mL (reference range 20–50), serum creatinine 1.2 mg/dL (reference value 0.7–1.4), alanine transaminase 35 U/L (reference range 5–45). For pain in the lower limb, a radiograph of the lumbosacral vertebral spine (Fig. 1) was taken; however, numerous dense calcifications were noted across the 12th dorsal and 1st lumbar vertebrae, more so on the right side. Unenhanced abdominal computed tomography (CT) scans (Figs 2A and B) were obtained. The patient received an oral dosage of 500 mg of metformin twice a day, along with 10 units of human regular insulin delivered *via* subcutaneous injection in the morning and 8 units in the evening. His glucose levels were monitored at regular intervals. In a week's time, the patient's fasting blood glucose level decreased to 110 mg/dL. He was also prescribed calcium supplementation alongside weekly oral administration of vitamin $D_3$ (60,000 IU). Additionally, oral pregabalin at a dosage of 75 mg was administered twice a day.

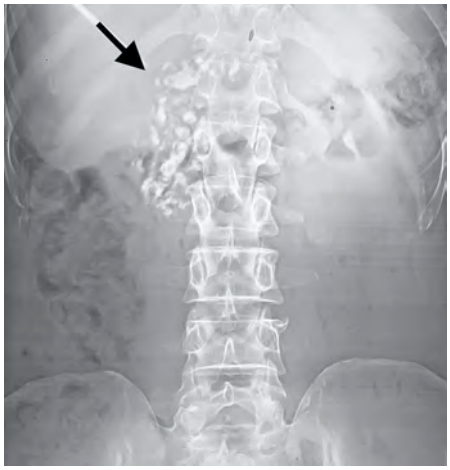
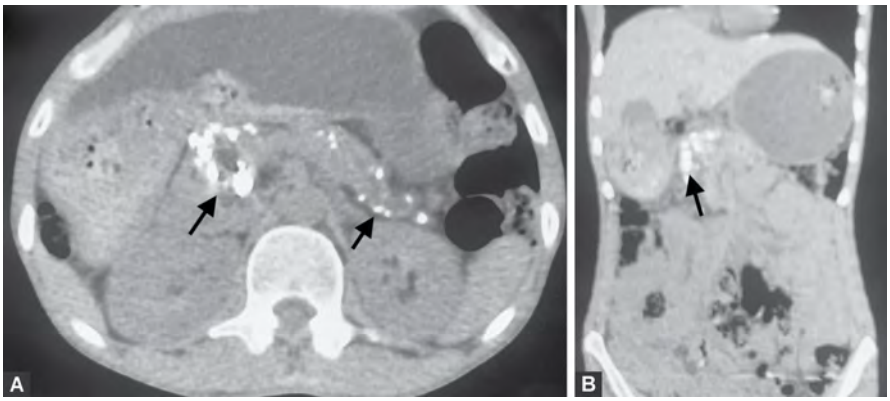


**Fig. 1:** An abdominal radiograph reveals calcifications across D12 and L1 vertebrae (black arrow)

Calcifications across dorsolumbar vertebrae (Fig. 1) identified on radiograph may indicate a variety of conditions, such as pancreatic calcification, splenic artery calcification, cholelithiasis in the common bile duct, and contrast retention within a duodenal diverticulum. The calcification of splenic artery atherosclerosis and pancreatitis resemble each other closely; nevertheless, splenic artery calcification has a characteristic tram-track appearance.[1] Abdominal CT scans (Figs 2A and B) resolved the ambiguities, showing diffuse parenchymal calcifications within the pancreas; they were profusely present in the head of the pancreas, while they were sparse in the body and the tail, indicating chronic pancreatitis. In this particular case, the predominant etiology of chronic pancreatitis is chronic alcohol consumption. The patient's low BMI, vitamin D deficiency and borderline serum calcium levels indicate possible nutritional deficiency. Intense pain in the lower limb could be a sign of diabetic neuropathy, which may worsen with uncontrolled blood sugar levels. A symptom indicating exocrine insufficiency, steatorrhea, may not be detected until >90% of the pancreatic parenchyma is lost.[2] Although abdominal pain is a predominant symptom of chronic pancreatitis, a subset of patients, approximately 10%, may experience a painless course.[3] Endocrine insufficiency, brought on by a loss of insulin and islet cell mass, manifests as diabetes called pancreatic diabetes or type 3c diabetes. This kind of diabetes differs from type 1 and type 2 diabetes as there is loss of counter-regulatory hormones, besides pancreatic exocrine insufficiency. Metformin alone will suffice in management of type 3c diabetes, when HbA1c is <8.0%, or else insulin has to be added to metformin with frequent checks for blood due to significant fluctuations in blood glucose levels. In individuals with




**Figs 2A and B:** Black arrows show numerous pancreatic calcifications over the head and a few in the body and tail in axial and coronal views of a noncontrast CT scan, respectively

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chronic alcoholic pancreatitis, the lifetime prevalence of diabetes mellitus is 80% and the corresponding insulin demand is 50%.[4] Despite the fact that Ewald and Bretzel[5] developed diagnostic guidelines for type 3c diabetes mellitus, this is not widely recognized.

Recognition of type 3c diabetes is crucial for tailoring the treatment approach, as there is a decline in pancreatic function (both endocrine and exocrine) and the loss of counter-regulatory hormones, leading to hyperglycemia with wide swings in blood glucose levels.

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# Can We Make Continuing Medical Education and Continuing Professional Development More Interesting for Healthcare Professionals?

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## Introduction

Continuing medical education (CME) and continuing professional development (CPD) play a crucial role in ensuring healthcare professionals remain up to date with the latest advancements, improve their clinical skills, and ultimately provide the best care to their patients.[1,2] Clinicians, whether they are doctors or other healthcare professionals, have clear expectations from CME programs. Since these programs play a vital role in their professional development, it is essential that CME activities meet their needs and provide value.

## Clinicians' Expectation from Continuing Medical Education/Continuing Professional Development

Clinicians expect CME/CPD programs to provide current, evidence-based information on medical advancements, emerging treatments, and evolving guidelines relevant to their specialty, such as cardiology, oncology, or pediatrics, or their practice setting, including hospitals or private practices. They seek practical insights, case studies, and real-life clinical scenarios that help solve complex cases and improve patient care. Additionally, they demand transparency and independence in CME/CPD programs, particularly those sponsored by pharmaceutical companies. Full disclosure of conflicts of interest, a clear distinction between education and product promotion, and unbiased, scientifically driven content focused on patient care are essential.

Accreditation by reputable organizations and medical educational institutes is highly valued, as it ensures high-quality standards and official recognition for licensing and certification. Given their demanding schedules, clinicians prefer flexible learning formats like online courses, webinars, and on-demand content, along with blended learning models that integrate live and digital education. Mobile-friendly platforms further enhance accessibility, allowing seamless learning anytime, anywhere.

Engagement is another critical factor, as clinicians appreciate interactive elements such as discussions, case-based learning, quizzes, and group activities, which improve knowledge retention compared to passive lectures. They also expect CME/CPD programs to be personalized and specialty-specific, catering to their unique learning needs based on specialty, experience level, and practice setting. Customizable modules and tailored learning pathways ensure relevance and applicability. The credibility of faculty also plays a crucial role, as clinicians seek to learn from renowned experts, thought leaders, and key opinion leaders (KOLs) whose expertise enhances the program's trustworthiness.

One challenge that educators and organizations face is making these educational programs engaging, interactive, and relevant enough to captivate busy healthcare professionals who already juggle demanding schedules. While traditional methods of CME/CPD, such as lectures and written materials, remain valuable, there is a growing recognition that healthcare professionals need more dynamic, engaging, and meaningful learning experiences.

## Let's Make Continuing Medical Education/ Continuing Professional Development More Effective

To make CME/CPD more effective, shifting toward interactive and engaging content is crucial.[3] Traditional CME/CPD programs often involve passive learning, where healthcare professionals listen to lectures or watch presentations. While informative, this does not always capture the attention or interest of busy clinicians who are accustomed to dynamic environments requiring quick thinking and decision-making. Incorporating case-based learning, where real-life clinical cases are presented for discussion, makes learning more practical and relevant. Gamification, which introduces elements such as quizzes, points, and levels, enhances engagement and reinforces learning through repetition and friendly competition. Interactive webinars and workshops featuring Q&A sessions, polls, and real-time discussions allow clinicians to interact with the content actively.

Tailoring content to clinicians' specific needs and interests is another way to improve CME/CPD programs. Offering educational content that aligns with their professional goals, clinical interests, and practice needs prevents disengagement. Personalized learning paths allow clinicians to choose modules relevant to their specialty, experience, and areas of interest. Modular programs help break content into smaller, focused sections, allowing professionals to select the most relevant topics. Peer learning fosters a sense of community and shared purpose, enhancing the overall learning experience.

The advancement of digital technologies has made it easier to deliver engaging, interactive, and accessible CME/CPD programs. Healthcare professionals increasingly rely on smartphones, tablets, and computers to access learning materials. Mobile learning platforms provide content that can be accessed anytime, anywhere, making education convenient even for those with limited time. Virtual reality (VR) and augmented reality (AR) introduce immersive, hands-on experiences that allow clinicians to practice procedures and diagnoses in a controlled, risk-free setting. Digital platforms facilitate peer interaction, allowing healthcare professionals to discuss treatments, share questions, and stay updated on trends, creating a more social learning environment.

Making learning relevant to real-world practice is essential for engagement. CME and CPD programs should focus on current challenges and innovations, addressing issues clinicians face daily. Each session should provide practical tools, guidelines, and strategies that can be immediately applied in clinical settings. Multidisciplinary collaboration enriches CME/CPD by encouraging teamwork and shared learning across specialties. For example, programs designed for both doctors and nurses can improve communication and efficiency in healthcare settings.

Healthcare professionals often struggle with time constraints, making shorter, focused learning sessions more appealing. Breaking down learning into bite-sized segments allows for easier engagement and better retention. On-demand content enables clinicians to learn at their own pace, revisiting materials as needed. Using diverse formats, such as audio lectures,

infographics, and interactive charts, enhances comprehension and quick absorption of information.

Introducing a reward system can further motivate clinicians to engage with CME programs. Certificates, badges, or accredited credits provide tangible proof of participation and achievement, encouraging continued learning. Gamified elements, such as earning points, levels, and badges, add a competitive and fun aspect to learning, increasing motivation. Additional rewards, such as exclusive content or expert consultations, provide further incentives.

Gathering feedback and continuously improving CME/CPD programs ensures their relevance and effectiveness. Regular participant feedback helps refine program content, structure, and delivery, aligning them with clinicians' needs. Keeping CME and CPD programs updated with the latest medical research, best practices, and emerging health challenges ensures they remain impactful and useful.

## Guidelines to Refer for Continuing Medical Education/Continuing Professional Development

There are several important guidelines and best practices to follow when designing, implementing, and evaluating CME/CPD programs.[4–7] These guidelines ensure that educational activities are of high quality, ethical, scientifically rigorous, and effective in enhancing medical practice. The National Medical Commission "Ethics and Medical Registration Board" (EMRB) proposed The Registered Medical Practitioner (Professional Conduct) Regulations in 2022 for public opinion. Accreditation by the Accreditation Council for Continuing Medical Education (ACCME) in the US or equivalent bodies in other countries, such as the European Accreditation Council for Continuing Medical Education (EACCME), and the Royal College of Physicians and Surgeons of Canada, guarantees that programs meet standards for educational quality and scientific accuracy.

## Conclusion

Clinicians expect CME/CPD programs to be relevant, evidence-based, and applicable to their practice. They want educational content that directly addresses their daily clinical challenges, is presented by credible experts, and is free from bias. Flexibility, interactivity, and opportunities for networking and feedback are also crucial to the overall learning experience. By meeting these expectations, CME/CPD providers can ensure that clinicians not only gain valuable knowledge but also enhance their ability to deliver the highest standard of patient care. CME and CPD are critical components of a healthcare professional's lifelong learning journey. Making these programs more interesting and engaging requires a shift toward interactive, personalized, and accessible formats. By incorporating technology, focusing on practical applications, providing engagement opportunities, and offering short, focused sessions, CME/CPD providers can create impactful learning experiences. Ultimately, improving CME/CPD benefits healthcare professionals by keeping them informed and motivated, while also enhancing patient care and healthcare outcomes. As the medical field continues to advance, continuing education must evolve accordingly to ensure clinicians remain proficient in the latest knowledge and best practices.

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# Letter to Editor in Response to Article "Clinical Phenotypes and Disease-specific Health-related Quality of Life in Patients of Chronic Obstructive Pulmonary Disease. J Assoc Physicians India 2025;73(3):36–39."

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We read with interest an article titled "Clinical Phenotypes and Disease-specific Health-related Quality of Life in Patients of Chronic Obstructive Pulmonary Disease" published in JAPI.[1] We have the following comments to offer:

- The main focus of the present study is based on clinical phenotypes of chronic obstructive pulmonary disease (COPD). The authors have mentioned phenotypes as nonsmoker, nonexacerbator (NEP), exacerbator (EP), and asthma-COPD overlap (ACO). Except for the ACO phenotype, which has been mentioned in the GOLD guidelines,[2] the source of the rest of the phenotypes has not been mentioned by the authors. The Spanish guideline (GesEPOC)[3] mentions COPD phenotypes as nonexacerbator, mixed COPD-asthma, exacerbator with emphysema, and exacerbator with chronic bronchitis. Although there are some similarities between phenotypes mentioned by the authors and the Spanish guidelines, the authors have not provided any reference to the Spanish guidelines in the present study. Moreover, these Spanish guidelines have never been followed widely. The basis of mentioning these phenotypes needs to be elaborated by the authors.
- The study mentions use of the modified Medical Research Council (mMRC) dyspnea scale to assess health-related quality of life (HRQoL) in COPD patients,[4] but the data for the same has neither been mentioned in the text nor in tables. Given that dyspnea severity is an important determinant of COPD-related disability, the reason for noninclusion of data about mMRC grading needs comments from the authors.
- In the results and discussion, the study reports significant improvements in spirometry values ($FEV_1$, FVC, and $FEV_1$/FVC ratio) after 3 months of treatment in all the phenotypes. However, the data presented in tables show no statistically significant improvement in these parameters for most groups, except for a marginal improvement in the ACO group.
- In the present study, the authors have used "standard treatment" for all the phenotypes, whereas in COPD, the

treatment is based on the combined COPD assessment, which includes four groups as per the GOLD guidelines.[5] The rationale for using standard treatment needs to be elaborated by the authors.

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