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EDITORIAL

Going Green: Climate Change and Health

Shashank Joshi[1*], Mahika Panandikar[2]

The World population doubled from 4 billion humans to 8 billion humans from 1974 to 2022, and it is unlikely to double again. The population of India has now surpassed China, with around 1.4 billion, and we have also already climbed up to become the world's fifth largest economy. Unfortunately, rapid economic development, urbanization, and modernization bring with them deleterious effects on national health, especially if the population does not take preventive measures to protect themselves. Additionally, economic development incorporates rapid industrial and agricultural advances, all of which impact the environment directly.

Pollution has insidiously crept up in the last few decades, particularly due to practices such as crop burning, industrial and domestic waste, and the use of considerable amounts of pesticides and chemicals in agriculture. The need for clean water, air, and the entire ecosystem has never been as acutely felt as now. Cutting off trees has not only led to the choking lungs of towns and cities but, in the long run, will also create a huge adverse impact on global biodiversity. It will impact the key chains that matter for the continuity of the living being across all species. Deforestation needs an urgent halt, and the conservation of flora and fauna is the key to the future of the human race. Through the invasion of nature and forests, we have hurt the wildlife and disturbed their life chains. COVID-19 is a classic example of how a wildlife virus strain surviving in bats jumped *via* an intermediate host and halted the world.

A study published in the Lancet in 2021 stated that abnormally hot or cold weather states were associated with over 5 million deaths worldwide.[1] This included air pollution due to wildfires, heat strokes, and other conditions caused by changes in normal environmental temperature. Heat waves are associated with an increased risk of hospitalization for cardiac, respiratory, and renal abnormalities.

Air, water, and food are integral to our survival. Unfortunately, they are also carriers of bacterial, viral, and parasitic diseases. Floods, drought, excessive heat, and other complications of climate change are disturbing the precarious balance of nature, giving these pathogens a breeding ground. Malaria, malnutrition, and diarrhea are already major public health problems in India, all of which would be further worsened due to climate change.[2]

Climate change not only affects the physical but also the mental health of individuals. Climate disasters such as tsunamis, earthquakes, and hurricanes lead to massive displacement and destruction of property, which can take a massive toll on one's mental health. Conditions such as droughts and floods are associated with an increased risk of depression, anxiety, and posttraumatic stress disorder, whereas extreme heat can affect mood and anxiety disorders, leading to increased interpersonal violence or suicide risk.[3,4]

It is imperative for humans at an individual level to large government as well as global policymakers to make small but meaningful changes and go green to save ecosystems and rebuild biodiversity.

The Climate Crisis is a health crisis but also a humanitarian crisis. Over 3 billion people live in hotspots vulnerable to climate change. Many of these are in fragile countries in the global south that are affected by conflict, which further limits people's ability to adapt and respond to shock. In addition to this, the individuals in society who are most affected are children, disabled people, and those with predisposing conditions.[5] According to the World Health Organization, in the Greater Horn of Africa, a combination of drought and floods has left 47 million people facing acute hunger and 18 million individuals displaced.

Similarly, the Climate Crisis affects healthcare delivery and access to people worldwide. A study done in the United States showed that health-related costs, including hospital admissions, emergency department visits, and other similar medical expenditures, along with lost wages, totaled $10 billion in 2018 dollars.[6]

Climate disasters have been found to deepen already existing inequalities, as their effects are most felt by individuals of the lower socioeconomic strata as well as those at heightened risk due to comorbidities and chronic illnesses. Not only this, large-scale events such as floods and hurricanes also lead to evacuations and destruction of property and machinery at hospitals and clinics, which is essential for the treatment of individuals. This can affect access to and the quality of healthcare.[7]

An estimated 22.5 million people are said to be displaced annually due to climate-related occurrences, which is believed to increase in the coming years. This adds significant social and mental stresses to communities and individuals outside of the financial burden. Another facet of this problem is the fact that the corporations and individuals who are most to blame will most likely have to deal with the smallest complications. The wealthiest 1% are said to contribute twice the amount of carbon footprint as those in the bottom two-thirds. These are individuals who will most likely not have to suffer the consequences due to better access to healthcare.

Climate agreements are health agreements. The effects of climate change will depend not only on the resilience of our communities but also on the transformational action that we take now to reduce emissions and prevent ourselves from reaching a potentially irreversible tipping point.

The current solutions offered to reduce our carbon footprint are not effective enough. All it does is transfer where the emissions come from. We have historically had more effective options, but patents get bought by oil companies, and the plans never see the light of day.

We must work by combining scientific research with health research to properly understand the impact of climate change on health currently and in the future. This will require funding from governmental as well as nongovernmental agencies.

We must also incorporate environmental goals into our economic ideals. One example of this is the "Blue Economy," which, according to the World Bank, is the "sustainable use of ocean resources for economic growth, improved livelihoods, and jobs while preserving the health of ocean ecosystem." This, along with green energy, is a way in which we must adapt to prevent a hazardous future.

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Health is the ultimate measure of progress on climate change. We will be able to count our success in breaking our fossil fuel addiction in fewer cases of asthma in children and deaths from lung cancer. To avoid catastrophic effects and prevent death and mortality caused by climate change, we must act soon. We, as individuals, as well as larger organizations and nations, must come together to solve this issue and work toward achieving longer, healthier lives on a healing planet.

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ORIGINAL ARTICLE

Performance of CBNAAT on Pleural Biopsies Obtained by Semirigid Thoracoscopy for Diagnosis of Unexplained Pleural Effusion: A Prospective Study from North India

Nazia Mehfooz[1*], Arif R Sheikh[2], Umar H Khan[3], Farhana Siraj[4], Gulnaz Basheer[5], Besina Syed[6], Afshan Shabir[7], Suhail Mantoo[8], Mudasir Qadri[9], Sonaullah Shah[10]

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Abstract

Background: Exudative pleural effusions are commonly encountered in clinical practice, but in about one-fourth of cases, etiology remains elusive after initial evaluation. Medical thoracoscopy with semirigid thoracoscope is a minimally invasive procedure with high diagnostic yield for diagnosing pleural diseases, especially these undiagnosed exudative pleural effusions. In tubercular endemic areas, often, these effusions turn out to be tubercular, but the diagnosis of tubercular pleural effusion is quite challenging due to the paucibacillary nature of the disease. Although culture is the gold standard, it is time-consuming. Cartridge-based nucleic acid amplification test (CBNAAT) is a novel rapid diagnostic test for tuberculosis (TB) and has been recommended as the initial diagnostic test in patients suspected of having extrapulmonary TB (EPTB).

Materials and methods: We conducted a prospective observational study of 50 patients with undiagnosed pleural effusion admitted to our tertiary care hospital. The primary aim of the study is to evaluate the diagnostic performance of CBNAAT on thoracoscopic guided pleural biopsy and compare it with conventional diagnostic techniques like histopathology and conventional culture.

Results: Of 50 undiagnosed pleural effusions, TB (50%) was the most common etiology. The overall diagnostic yield of semirigid thoracoscopy in this study was 74%. Our study showed that CBNAAT of pleural biopsies had a sensitivity of 36% only but a specificity of 100%. The sensitivity of CBNAAT was not far superior to the conventional culture.

Conclusion: Tuberculosis (TB) is a common cause of undiagnosed pleural effusion in our set-up. CBNAAT testing of pleural biopsy, though, is a poor rule-out test for pleural TB, but it may aid in the early diagnosis of such patients.

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Introduction

Exudative pleural effusions are commonly encountered in clinical practice, and the most common causes include tuberculous pleurisy, malignancies and bacterial infections.[1] Despite thorough clinical assessment and detailed pleural fluid analysis, the etiology of 20% of pleural effusions remains undiagnosed and poses a diagnostic challenge to practicing respiratory physicians and pulmonologists across the world.[2] In developing countries with high tuberculosis (TB) burden, often, these patients are empirically started on antitubercular drugs. This practice not only leads to misdiagnosis but also contributes to growing drug-resistant TB cases.

The advent of semirigid thoracoscopy has been a major step forward in these patients with undiagnosed pleural effusions as it not only allows direct visualization of the pleural cavity but also allows us to take pleural biopsies for histopathological and microbiological analysis. The definite diagnosis of tubercular pleurisy still largely depends primarily on characteristic histopathological features or demonstration of positive *Mycobacterium tuberculosis* (MTB) culture in pleural tissue. Currently, molecular detection methods like cartridge-based nucleic acid amplification test (CBNAAT) are being increasingly used for the diagnosis of TB as they not only allow rapid diagnosis but also detect drug resistance to one of the first-line antitubercular drugs, that is, rifampicin. Whereas World Health Organization (WHO) has endorsed the use of CBNAAT in both pulmonary and certain cases of extrapulmonary TB (EPTB), data about its applicability to pleural tissue is limited.[3,4]

We aimed to determine the performance of CBNAAT on pleural biopsies obtained by semirigid thoracoscopy for diagnosis of TB in unexplained exudative pleural effusions in our set-up and compare it with conventional methods (MTB culture and histopathology) for diagnosis of tubercular pleural effusion.

Materials and Methods

Study Design and Patient Selection

It was an observational prospective study conducted at a leading tertiary care hospital in North India from January 2019 to December 2020. Approval to conduct the study was obtained from the Institute's Ethical Committee, and written informed consent was taken from each participant prior to enrollment.

All patients with undiagnosed exudative pleural effusion were included in the study. Undiagnosed pleural effusion was defined as exudative effusion meeting lights criteria where the diagnosis was not achieved by initial pleural fluid analysis, including pleural fluid adenosine deaminase (ADA), CBNAAT, negative acid-fast bacilli (AFB) stain and negative cytology results for malignant cells. Patients who had a contraindication for medical thoracoscopies like bleeding diathesis, clinical instability, severe intractable cough, minimal pleural effusion on presentation, and elderly frail patients were excluded from the study.

Prethoracoscopy Assessment

All the included patients underwent a detailed clinical and laboratory assessment prior to thoracoscopy. Information regarding age, gender, residence, signs and symptoms at presentation, laboratory and imaging findings, and pleural fluid analysis was recorded on a preformed *pro forma*.

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Thoracoscopy Procedure and Sample Preparation

Thoracoscopy was performed by a semirigid thoracoscope after obtaining proper informed consent. The patient was kept in a lateral decubitus position with the affected side upwards, and the entry position was marked with the help of ultrasonography. The procedure was done under conscious sedation by giving intravenous midazolam, and the patient was monitored throughout the procedure with regard to vital parameters. Local anesthesia was infiltrated at the marked entry point. Blunt dissection was done at the site, and an 11 mm plastic trocar was inserted after dilation of the track. Thoracoscope was inserted through the trocar into the pleural cavity, and the whole of the pleural cavity was examined. Thoracoscopic findings were noted. Under direct vision, abnormal or suspicious areas were biopsied. Multiple biopsy pieces were taken in each patient.

Around 4–6, pieces were collected in formalin solution for histopathological examination and Ziehl-Neelson staining. At least two pieces of pleural tissue were collected in two saline tubes for mycobacterial culture and the CBNAAT test. For CBNAAT testing, the biopsy sample was homogenized and then suspended with a phosphate buffer. The tissue homogenate was mixed with the sample reagent in a 1:2 ratio and then subjected to CBNAAT assay as per the manufacturer's instructions. For mycobacterial culture, the tissue homogenate was processed with N-acetyl-cysteine sodium hydroxide for decontamination and then inoculated into conventional Lowenstein–Johnson culture media.

Statistical Analysis

The data was recorded in a Microsoft Excel spreadsheet and then exported to Statistical Package for the Social Sciences software v 22.0. Continuous variables were summarized as mean ± standard deviation (SD) and categorical variables were listed as frequencies and percentages. Student's *t*-test, Chi-squared tests, and exact tests, whichever were appropriate, were used for comparing different variables between tubercular and nontubercular pleural effusions. Chi-squared tests were used to calculate the sensitivity and specificity of CBNAAT and mycobacterial culture using histopathological confirmation as the gold standard.

Results

Baseline Characteristics

A total of 50 patients with undiagnosed pleural effusion underwent thoracoscopy during the study period. Table 1 shows the baseline characteristics of study patients. The mean age of patients was 47.36 years (±SD 19.84). The majority of patients had a rural background. Males constituted 78% of the total study cohort. Patients had predominantly moderate pleural effusion. Table 2 shows computerized tomography (CT) and pleural fluid analysis of the study population. CT chest showed passive collapse in 52.0% of patients, whereas lung mass was seen in 12% of patients. Pleural fluid was straw-colored in maximum patients, with analysis showing a lymphocytic exudative pattern in 21 patients, as shown in Table 2.

Table 1: Baseline characteristics of patients with unexplained pleural effusion

Variable	*Frequency/ mean*	*Percentage/SD*
Demographics		
Age	47.36	19.84
Rural residence	41	82.0
Males	39	78.0
Females	11	22.0
Side of pleural effusion		
Right	24	48.0
Left	26	52.0
Quantity of pleural effusion		
Mild	5	10.0
Moderate	29	58.0
Massive	16	32.0

Table 2: Computerized tomography (CT) and pleural fluid characteristics of patients with unexplained pleural effusion

Variable	*Frequency/ mean*	*Percentage/ SD*
CT findings		
Loculations	13	26.0
Passive collapse	26	52.0
Pleural thickening and/or pleural enhancement	08	16.0
Lung mass	06	12.0
Pleural deposits	01	2.0
Mediastinal lymphadenopathy	09	18.0
Consolidation	06	12.0
Pleural fluid characteristics		
Colour		
Hemorrhagic	16	32
Straw	32	64
Serous	2	4
Analysis		
Mean leucocyte count	928.0	1224.24
Mean protein concentration	4.63	1.02
Mean LDH	504.03	442.49
ADA ≥ 40	12	24.0
L:N ratio ≥ 0.75	21	42.0

Thoracoscopic Findings

The visual findings during thoracoscopy included inflamed and/or edematous pleura, plaques/nodules on parietal pleura, nodules on visceral pleura, sago-grain nodules with edematous pleura, pleural thickening and pleural adhesions as shown in Table 3.

Histopathological examination of pleural biopsies taken during thoracoscopy yielded a diagnosis of TB in 50% of patients, whereas malignancy was seen in 24% of patients, as shown in Table 4.

Sensitivity and Specificity of CBNAAT and Mycobacterial Culture

The performance of CBNAAT and mycobacterial culture was evaluated using

Table 3: Thoracoscopic findings of patients with unexplained pleural effusion

Variable	*Frequency*	*Percentage*
Thoracoscopic findings		
Inflamed and/or, edematous pleura	16	32.0
Plaques/nodules on parietal pleura	37	74.0
Nodules on visceral pleura	3	6.0
Sago-grain nodules with edematous pleura	9	18.0
Pleural thickening	14	28.0
Thin pleural adhesions	26	52.0
Thick pleural adhesions	17	34.0
Others	6	12.0

Table 4: Final diagnosis on histopathology of patients with unexplained pleural effusion

Diagnosis	*Frequency*	*Percentage*
TB	25	50.0
Malignancy	12	24.0
Adenocarcinoma lung	06	12.0
Squamous cell carcinoma	03	6.0
Poorly differentiated carcinoma	02	4.0
Mesothelioma	01	2.0
Nonspecific pleuritis	13	26.0

histopathology as the gold standard. Out of the 25 patients with histopathological evidence of TB, nine patients had positive CBNAAT, and seven patients had positive mycobacterial culture. None of the patients who were diagnosed as having nontubercular effusion had either of these tests positive. Thus, the sensitivity of CBNAAT was 36%, and mycobacterial culture had a sensitivity of 28%, but the specificity of both tests was 100%, as shown in Tables 5 and 6.

Discussion

Semirigid thoracoscopy has revolutionized the diagnostic workup of patients with undiagnosed pleural effusion. Because of its efficacy and safety, it is now considered an integral part of the diagnostic evaluation of patients with recurrent exudative pleural effusion. This study provides important insights into the patient characteristics, laboratory, and imaging findings of patients with undiagnosed pleural effusion undergoing medical thoracoscopy through semirigid thoracoscope and provides important information about the different thoracoscopic findings. Also, the performance of CBNAAT and mycobacterial culture for the diagnosis of TB has been prospectively studied in patients with undiagnosed pleural effusion.

The overall diagnostic yield of the semirigid thoracoscope in our study was 74%. Previous studies from India have shown a yield of 66–97% in patients with undiagnosed pleural effusion undergoing thoracoscopy.[5–8] Other studies from across the world have shown a diagnostic yield of 45–95% in such patients.[9–13] This variability in diagnostic yield could be due to different patient characteristics. Moreover, studies reporting higher diagnostic yields have included nonspecific pleuritis as a benign cause and thus higher yield. We have not included nonspecific pleuritis in the final analysis while calculating the yield, as we considered it nondiagnostic.

In our study, tuberculous pleural effusion was the most common histopathological diagnosis in patients with undiagnosed pleural effusion constituting about 50% of patients. Kannan et al. also reported a prevalence of TB >50% in patients with unexplained pleural effusions.[14] However, most studies done across the globe show malignancy as the most common cause. Hucker et al., from England, have shown that malignancies contribute to around 59% of patients with unexplained pleural effusion.[15] Similarly, Hansen et al. reported the incidence of malignancies being 62% in such patients.[16] This difference in final etiological diagnosis could be explained by two reasons: First, this study was done in an area with a high TB burden with most of the patients belonging to a rural background; and secondly, patients suspected to have malignancy do not undergo invasive investigations in our set up; thus a selection bias favors more TB patients in our set-up.

Cartridge-based nucleic acid amplification test (CBNAAT) is a quantitative real-time polymerase chain reaction assay that has now been recommended as a frontline test for TB in India. CBNAAT has been previously studied for tuberculous pleural effusion by using pleural fluid as a sample; however, its low yield is a major drawback. The preferred specimen for diagnosis of pleural TB is a pleural biopsy, but only a few studies have previously studied the accuracy of CBNAAT of pleural biopsies, and a varied sensitivity ranging from 14 to 84% has been reported.[17–20] Our study showed that CBNAAT of pleural biopsies had a sensitivity of 36% only but a specificity of 100. The lower sensitivity in our study, as compared to a few other studies, could be because of the different selection criteria used in our study. Also, pleural TB is a paucibacillary condition, and hence detection of the pathogen is extremely difficult. Some previous studies have used AFB stain and culture as reference standards and hence higher reported sensitivity. Our results show that the CBNAAT of pleural biopsies is a good rule-in test but not a reliable rule-out test. However, CBNAAT testing of pleural biopsies has a big advantage: results of this test are available within 2–3 hours, and hence it aids in early diagnosis as compared to the conventional culture, which requires at least 2–3 weeks. Given the relatively safe nature of the semirigid thoracoscopy procedure and its high diagnostic yield in cases of undiagnosed pleural effusions, thus it would still be prudent to test biopsy specimens for CBNAAT as it has a high positive predictive value and gives rapid results.

Conventional cultures for mycobacterium TB are often considered the gold standard for diagnosis. However, its application for diagnosis in tubercular pleural effusion is limited. Previous studies using pleural biopsy as a specimen for culture have also reported its lower sensitivity for the diagnosis of tubercular pleural effusion. Sun et al., in their study, have reported a sensitivity of only 16.43% of biopsy mycobacterial culture.[19] Similarly, Gao et al. have reported a sensitivity of 25.93%.[1] Li et al., however, have reported a higher sensitivity of 56.6%.[20] Our study showed that conventional mycobacterial cultures performed on pleural tissue have a sensitivity of 28%, possibly reflecting the paucibacillary nature of tubercular pleurisy.

Our study has its own limitations. A small sample size precludes its use for generalization of the results of the study. Taking histopathological results as a composite reference standard may have its own limitation, as other causes of chronic granulomatous inflammation may be misdiagnosed as TB.

Table 5: Diagnostic value of CBNAAT and on pleural biopsies for the diagnosis of TB in unexplained pleural effusions

Statistic	*Value*	*95% confidence interval (CI)*
Sensitivity	36.00%	17.97–57.48%
Specificity	100.00%	86.28–100.00%
Negative predictive value	60.98%	53.80–67.71%
Negative likelihood ratio	0.64	0.48–0.86
Diagnostic accuracy	68.00%	53.30–80.48%

Table 6: Diagnostic value of the culture of pleural biopsies for the diagnosis of TB in unexplained pleural effusions

Statistic	*Value*	*95% CI*
Sensitivity	28.0%	12.07–49.39%
Specificity	100.0%	86.28–100.0%
Negative predictive value	58.14%	35.53–64.47%

Conclusion

The semirigid thoracoscopy procedure plays a vital role in the diagnostic evaluation of undiagnosed pleural effusion because of its high diagnostic yield and relatively safe nature of this procedure. TB is a common cause of undiagnosed pleural effusion in our set-up, and certain laboratory and imaging findings may favor a diagnosis of tuberculous pleurisy. CBNAAT testing of pleural biopsy is a good rule-in test but not a reliable rule-out test for pleural TB. It may aid in the early diagnosis of such patients and, most importantly, rule out drug resistance simultaneously.

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ORIGINAL ARTICLE

Utility of Chemical Shift Imaging and Diffusion-weighted Images/Apparent Diffusion Coefficient Maps as a Tool for Evaluation of Solid Renal Tumors

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Abstract

Objectives: To study the utility of chemical shift imaging (CSI) and diffusion-weighted images (DWI)/apparent diffusion coefficient (ADC) maps for the evaluation of solid renal tumors.

Methods: Magnetic resonance imaging (MRI) has an equivalent application as computerized tomography (CT) in the characterization of renal masses. It offers a radiation-free imaging technique and has a better soft tissue contrast than CT. Also, MRI is favored in patients with chronic kidney disease. MRI is useful when findings on CT are equivocal. The role of DWI in characterizing solid renal lesions as malignant is encouraging, and DWI can be particularly useful when gadolinium is contraindicated. CSI is useful in differentiating angiomyolipoma (AML) from clear cell (cc) renal cell carcinoma (RCC). We did a cross-sectional study on 24 patients with solid renal masses. MRI of the upper abdomen (from the dome of the diaphragm to the iliac crest) will be done on an MRI machine in our department (1.5T, ACHIEVA, Phillips medical system) using the torso coil.

Result: There was no significant association seen in terms of ADC values and histological subtypes ($\chi^2 = 11.222$, $p = 0.082$). In our study, 50% (one out of two) of AML showed a signal drop, whereas 40% of cases (6 out of 15) of ccRCC and 66% (two out of three) of papillary RCC showed a signal drop.

Conclusion: In this article, we concluded CSI, although a useful tool to look for microscopic fat, can't be used as a reliable marker to rule in cc-carcinoma as both AML and papillary cell carcinoma have microscopic fat. Further, no histological classification can be done on the basis of DWI/ADC images.

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Introduction

Renal neoplasms are common and have varying prognoses depending on the subtype of the tumor. The neoplasm can be benign or malignant, with nearly 85% of solid renal masses being malignant.[1] Malignant masses include renal cell carcinoma (RCC), urothelial carcinoma, lymphoma, and metastasis. Most renal masses are detected incidentally, and only 10% of patients with RCC present with the classical triad of flank pain, hematuria, and palpable mass. RCCs are divided into different histology groups, the most common being clear cell (cc) carcinoma (80%), papillary carcinoma (20%), and chromophobe type (5%).[2] Urothelial cancers take their origin from the epithelium of calyces and renal pelvis, amounting to 7–8% of all renal tumors.[3]

Most RCCs occur in the cortex of the kidney, which is made of the glomerulus, tubular apparatus, and collecting duct. RCCs are divided into different histology groups, the most common being cc-carcinoma (80%), papillary carcinoma (20%), and chromophobe type (5%).[4] Urothelial cancers take their origin from the epithelium of calyces and renal pelvis, amounting to 7–8% of all renal tumors.[5] Lymphomas are generally secondary and are associated with non-Hodgkin's lymphoma. Metastasis commonly comes from the breast, lungs, etc. Benign tumors account for 10% of all renal cortical tumors. It includes mainly angiomyolipoma (AML) and oncocytoma. AML contains adipose tissue, blood vessels, and muscle tissue. It is associated with tuberous sclerosis and lymphangioleiomyomatosis.[6] They account for 2–6% of all resected tumors.[7] Oncocytomas are uncommon and are composed of oncocytes, and they can be multifocal. Renal tumors are frequently detected incidentally and generally at an earlier stage with the use of different modalities.

Magnetic resonance imaging (MRI) now has an equivalent application in computerized tomography (CT) in the characterization of renal masses. It offers a radiation-free imaging technique and has a better soft tissue contrast than CT. Also, MRI is favored in patients with chronic kidney disease.[8] MRI is useful when findings on CT are equivocal.[9] Multiparametric MRI features, including T2 signal, chemical shift imaging (CSI) characteristics, apparent diffusion coefficient (ADC) signal, patterns of early enhancement and de-enhancement, help in the characterization of solid renal tumors.[10] RCC is mildly hypointense on T1 and has a high signal on T2, with ccRCC showing the highest signal on T2 among all RCCs, with hypointense pseudocapsule on T1 (25%) and T2 (60%).

The role of diffusion-weighted images (DWI) in characterizing solid renal lesions as malignant is encouraging, and DWI can be particularly useful when gadolinium is contraindicated or when enhancement is equivocal with lower ADC values in renal neoplasms compared with benign lesions. There are significantly lower ADC values in RCCs compared to oncocytomas and renal tissue. Both papillary RCC (pRCC) and chromophobe RCC demonstrate significantly lower ADC values when compared to ccRCC.

In-phase and opposed-phase imaging or CSI are useful in AML; it shows an Indian ink artifact at its interface with renal parenchyma on the opposed phase. A significant signal intensity (SI) drop (CSI SI index > 25%) in RCC is characteristic of the ccRCC subtype, whereas other RCCs only rarely demonstrate intralesional microscopic fat. RCC demonstrates gross internal fat content from various causes, including osseous metaplasia and engulfing of the renal sinus fat, which is a known pitfall for the diagnosis of AML.[11]

In the year 2015, a study reported that intracellular lipid was detected in 15% of pRCC because of the presence of foaming histiocytes, and T2WI revealed a heterogenous signal. The drop in signal on chemical shift MRI is seen due to intratumoral lipids, which is most commonly seen in ccRCC but also seen in intracellular lipids containing pRCC, that is why the signal drop in opposed phase image is said to be nondiagnostic of AML.[12]

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In the year 2016, a study compared 58 pRCC and 11 fat-poor AML and reported that a drop in SI in pRCC on in-phase images vs the out-phase images was due to the presence of hemosiderin on chemical shift in-phase imaging. This was specific for making a diagnosis of pRCC, and the results showed a sensitivity of 37.9% and specificity of 100%.[13]

In 2017, another research about different characteristics of tumors on multiparametric MRI showed a high SI on T2WI and revealed a drop in signal due to fat on chemical shift MRI, which indicates either AML or ccRCC. Macroscopic fat is seen in AML, whereas central necrosis is seen in ccRCC. However, a low T2 signal indicates ccRCC and lipid-poor AML. If the lesion is hypoenhancing on postcontrast imaging and shows a signal drop on in-phase imaging relative to the opposed phase, it suggests pRCC as it contains hemosiderin. A drop in the opposed phase signal suggests lipid-poor AML.[14]

A study done in 2021 concluded that benign lesions have higher ADC values as compared to malignant lesions, with few exceptions. The study further revealed among RCC, the cc variants have a higher mean ADC value than compared to papillary and chromophobe RCC. The cc-carcinoma also had a higher mean ADC value than the benign renal AML. The study stated that if the mean ADC value in the renal tumors is lower than 1.375, then the lesion is not likely to be cc-carcinoma.[15]

The overall prognosis of RCC depends on the age, tumor, size, histological subtype, and invasion of neighboring tissues, which is why a preoperative radiological assessment of RCC is important and can also be supplemented by confirmatory histopathological examination. Common risk factors of RCC include smoking, hypertension, obesity, and exposure to chemicals like benzene, cadmium, and vinyl chloride.

Aim

To assess the utility of chemical shift images and DWIs as a tool for the evaluation of solid renal tumors.

Methods

Patients who were incidentally diagnosed with renal masses on imaging or referred to us for evaluation of renal masses. The patients who had contraindications to MRI had purely cystic masses, or were claustrophobic were excluded. The sample size for the proposed study was 24.

Magnetic resonance imaging (MRI) of the upper abdomen (from the dome of the diaphragm to the iliac crest) was done on an MRI machine in our department (1.5T, ACHIEVA, Phillips medical system) using the torso coil.

Results

The following observations were made.

Patient Characteristics

About 4.1% of patients each were aged between 21 and 30 years, 31 and 40, and 71 and 80 years, respectively. Only 12.5% of patients were between the age group 41 and 50 years. Around 29.1% of patients were between the age group 51 and 60. A total of 45.8% of patients were between the age of 61 and 70 years.

Pathological Outcome

In the analysis of 24 patients with renal masses, we found that two out of 24 patients had benign tumors, and 22 out of 24 patients had malignant tumors (Fig. 1).

Pathological Subtypes

Of the 24 sampled renal masses, two were benign, and 22 were malignant. Both the benign masses were renal AML. A total of 15 cases of 22 malignant renal masses comprised of ccRCC. Three out of 22 malignant renal masses constituted papillary RCC. One out of 22 cases was of chromophobe RCC, adenocarcinoma [not otherwise specified (NOS)] metastasis, and urothelial carcinoma, respectively.

Benign or malignant	*Subtype*	*Frequency*
Benign	AML	2
Malignant	ccRCC	15
Malignant	Papillary RCC	3
Malignant	Chromophobe RCC	1
Malignant	Adenocarcinoma (NOS)	1
Malignant	Urothelial carcinoma	1
Malignant	Metastasis	1

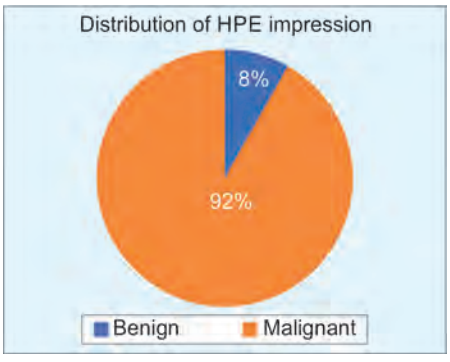


Fig. 1: Showing percentage of benign and malignant masses

Of 24 patients with renal masses assessed, seven did not undergo surgical treatment either due to advanced stage of disease or did not consent to surgery. Of the remaining 17 cases, 75% of patients with low nephrometric scores underwent partial nephrectomy, and 12.5% with moderate nephrometric scores underwent partial nephrectomy (Fig. 2). Radical nephrectomy was the only surgical procedure done in patients with high nephrometric score.

Imaging Outcomes

The diagnostic performance of MRI in predicting histopathological examination (HPE) interpretation was as follows—sensitivity: 100%; specificity: 50%; positive predictive value (PPV): 96%; negative predictive value (NPV): 100%; and diagnostic accuracy: 96%. The two methods agreed in 95.8% of the cases and disagreed in 4.2% of the cases.

The disagreements observed between the two methods were as follows:

- One (4.2%) case classified as benign by HPE interpretation was classified as malignant by MRI Interpretation.
- The two methods agreed in 70.8% of the cases and disagreed in 29.2% of the cases for subtyping renal tumors.
- There was moderate agreement between the two methods, and this agreement was statistically significant.

Nine out of 22 renal masses (37.5%) showed a signal drop on outphase images. Among the subtypes, six out of 15 (40%) ccRCC showed signal drop on outphase images. Two out of three (66%) papillary cell RCCs showed a signal drop on out-phase images. One out of two (50%) AMLs showed a signal drop in out-phase images. One out of three papillary RCC showed a signal drop in in-phase images (Table 1).

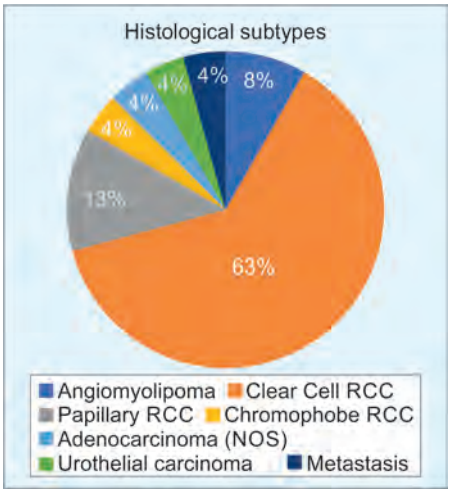


Fig. 2: Pie chart showing the percentage distribution of various subtypes of renal masses

Table 1: Tabulation of pathological renal subtypes with SI drop on CSI

Subtype according to HPE	*SI drop category*				*Fisher's exact test*	
	No signal drop	*Signal drop in outphase images*	*Signal drop inphase images*	*Total*	χ^2	*p-value*
cc	9 (64.3%)	6 (66.7%)	0 (0.0%)	15 (62.5%)	12.260	0.359
Papillary	0 (0.0%)	2 (22.2%)	1 (100.0%)	3 (12.5%)		
AML	1 (7.1%)	1 (11.1%)	0 (0.0%)	2 (8.3%)		
Metastasis	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)		
Urothelial Ca	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)		
Adeno carcinoma	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)		
Chromophobe	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)		
Total	14 (100.0%)	9 (100.0%)	1 (100.0%)	24 (100.0%)		

There was no significant difference between the groups in terms of ADC value ($10^{-3} \times mm^2$) (MRI) ($\chi^2 = 11.222$, $p = 0.082$).

Table 2: Tabulation of pathological renal subtypes with ADC values

ADC value ($10^{-3} \times mm^2$) (MRI)	*Subtype according to HPE*								*Kruskal–Wallis test*	
	Nonspecific	*cc*	*Papillary*	*AML*	*Metastasis*	*Urothelial Cal*	*Adenocarcinoma*	*Chromophobe*	χ^2	*p-value*
Mean (standard deviation)	NaN (NA)	1.29 (0.33)	0.68 (0.38)	1.00 (0.28)	0.89 (NA)	0.94 (NA)	0.40 (NA)	0.80 (NA)	11.222	0.082

Out of 24 renal masses, the ccRCC had the highest ADC value and was lowest for adenocarcinoma NOS. The chromophobe RCC had a higher mean ADC value than the papillary RCC (Table 2).

In our study, we found that the mean ADC value of 1.42 was highest for international society of urological pathology (ISUP) grade I and was lower for grade II ISUP at 1.22 and lowest for grade III at 0.98.

Discussion

Renal tumors consist of a diverse spectrum of histopathological subtypes with variable morphological appearances and are often broadly classified as benign and malignant in order to formulate a treatment for the patient. The surgical approach for the resection of the tumor is quite variable; hence, good cross-sectional imaging provides an accurate preoperative characterization of renal tumors. Ultrasound is usually the first diagnostic modality; however, the results are inconclusive in many cases, and it fails to assess the deeper compartments, retroperitoneal lymphadenopathy, and intravascular invasion. Although multiphase CT has the added advantage of evaluating lesions, metastatic lymph nodes, and variable enhancement patterns, it has a limited role in discriminating between malignant masses or commenting upon the different subtypes of renal tumors. MRI is considered the next diagnostic modality due to its better soft tissue contrast resolution to overcome the aforementioned limitations and to improve the preoperative characterization. Our study aimed at identifying CSI as a tool for CSI.

A total of 24 patients were included in the study over a period of 1 year and 3 months. Most of the patients were diagnosed with renal tumors incidentally on imaging with no clinical suspicion, while others had complaints of hematuria abdominal pain for a significant duration. Out of 24 patients, 21 patients had a single renal mass, while one patient each had two, three, and four renal masses, respectively. Most renal masses in our study were malignant, that is, 22 out of 24, while two out of 24 renal masses turned out to be benign. The most common histological subtype in our study was cc-carcinoma. Both benign tumors in our study were AML.

The patients in our study belonged to the age range of 29–72 years, with the maximum number of patients with renal tumors being in the range of 60–70 years (45.1%). Of the 24 patients included, 14 patients were males, and 10 were females.

Out of 24 renal masses, the majority of the renal masses were malignant. A total of 22 out of 24 renal masses were malignant. The most common is cc-carcinoma, with 15 out of 22 being malignant renal masses. The papillary cell carcinoma was three out of 22 malignant renal masses. One case each was observed of chromophobe cell carcinoma, adenocarcinoma NOS, metastasis, and urothelial carcinoma.

Renal tumors can be subtyped based on the variable morphological feature. Fat-rich renal AMLs and cc-carcinoma are hyperintense on T2-weighted SI; however, the presence of macroscopic fat is more suggestive of AML, which in our study was assessed by observing areas of intratumoral signal drop on spectral attenuated inversion recovery (SPAIR) images compared to T2 images. Among RCC, the microscopic fat is commonly seen in the cc variant of RCC, likely due to the engulfment of renal sinus fat; however, it is not specific, and few cases of papillary cell carcinoma can show microscopic fat due to presence of foamy cells. The microscopic fat is assessed by seeing >20–25% signal drop in out-phase images of CSI as compared to phage images. The papillary renal cell shows a characteristic signal drop in phase images, likely due to hemosiderin. Based on these morphological features, the renal masses were subtyped into various histological subtypes. These were then compared to the results obtained via histopathological examination. The comparison revealed an agreement of 70.8% and disagreement of 29.2%. This was a fair agreement and was statistically significant (Cohen's $\kappa = 0.335$, $p \leq 0.001$). This is in agreement with the study done in 2018 by Van Oosenbrugge et al.

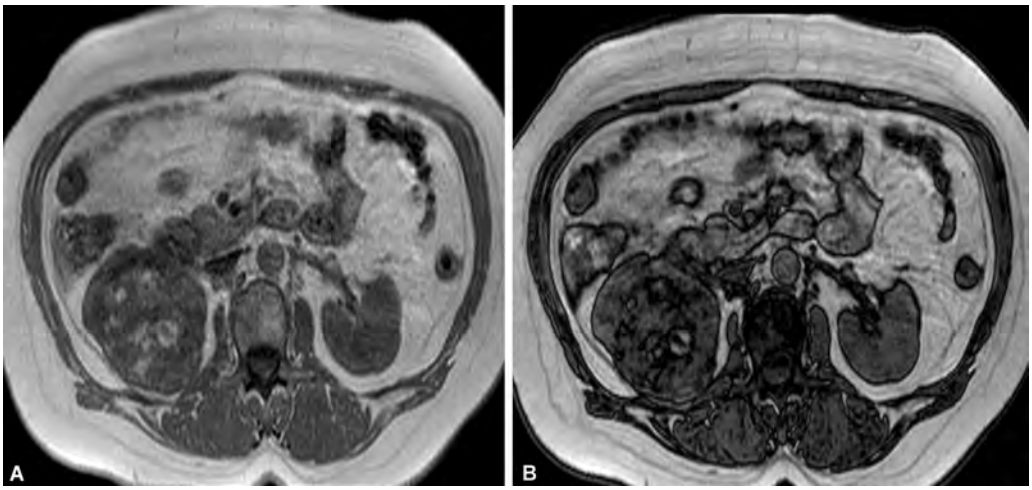
Chemical shift imaging (CSI) is used to look for microscopic fat only, whereas SPAIR and STIR images are used to assess macroscopic fat. CSI is based on the principle that it utilizes the difference of precession frequency in water and fat molecules. Thus, protons in water molecules process at a slightly higher frequency than protons in fat. This difference in frequency is known as the chemical shift effect. This effect is exploited in In phase (IP) and out-phase (OP) imaging in CSI. The difference in phase between the images acquired at different echo times is the basis of OP imaging. The OP images reduce the fatty tissue signal. This results in a signal loss at the fatty-normal tissue interface, leading to the formation of India ink artifact.[16] This is

characteristic of OP images. In our study, we calculated signal drop in all 24 renal tumors by carefully placing the point region of interest (ROI) in the darkest solid portion of renal tumor in OP images and avoiding cystic changes. Similarly, point ROI was placed in the same region, and the signal drop was calculated using the formula SI (IP) – SI (OP) / SI (IP) × 10. Any value >1.5 was considered a signal drop in outphase images, and a negative value was considered a signal drop in in-phase images. In our study, the signal drop value was calculated and compared with histological subtypes and the association was calculated using Fischer's exact test; it was found that there was no significant association between the groups and histopathological subtype ($\chi^2 = 12.260$, $p = 0.359$). However, in our study, 50% (one out of two) of AML showed signal drop (Fig. 3), whereas 40% cases (six out of 15) of ccRCC (Fig. 4) and 66% (two out of three) of papillary RCC showed signal drop (Fig. 5). Only one case in our study showed a signal drop in IP images which was seen in papillary carcinoma which was due to the presence of intratumoral hemorrhage. This was in agreement with the study done by Murray et al. in 2016.[13] No signal drop was seen in the chromophobe RCC, urothelial carcinoma, or metastasis.

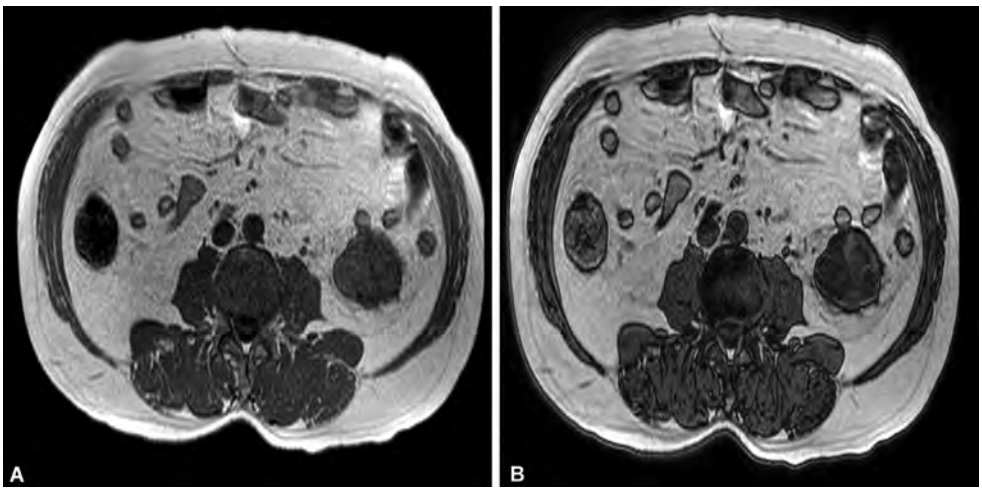
Malignant tumors have high cellular solid components leading to reduced movement of water molecules, thus appearing hyperintense on DWI and hypointense on corresponding ADC images, suggestive of diffusion restriction. In our study, all 24 cases showed diffusion restriction, that is, both benign as well as malignant lesions. The ADC value was calculated using point ROI, carefully placing it on the solid portion of renal tumors and avoiding areas of necrosis and cystic changes. In our study, we found that cc-carcinoma showed the highest mean ADC values compared to the non-cc variant; however, in our study, it was also noted that the mean ADC values of benign AMLs were lower than the cc variant (Figs 6 and 7). There was no significant association seen in terms of ADC values and histological subtypes ($\chi^2 = 11.222$, $p = 0.082$). This was in agreement with the study done in 2021 by de Silva et al. The ADC values were also compared to IUSP grade of malignant renal tumors, and it was found that the mean ADC was highest for the IUSP grade I tumors (1.42) followed by grade II tumors (1.22) and the mean ADC values for ISUP grade III were the lowest (0.98).

Limitations

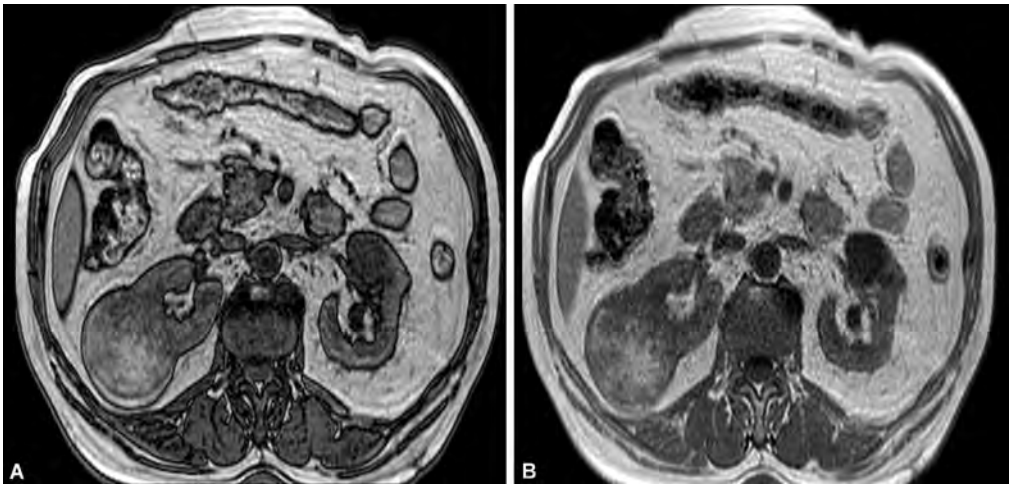
- The major limitation of our study was a small sample size and narrow histopathological spectrum of cases. Very few benign cases were seen during the limited period of the study. As a result, the spectrum of the type of cases included was very narrow. This has been reflected in the final results. Larger studies with greater sample size and wider spectrum are required to confirm the promising results seen with MRI and other advanced sequences.



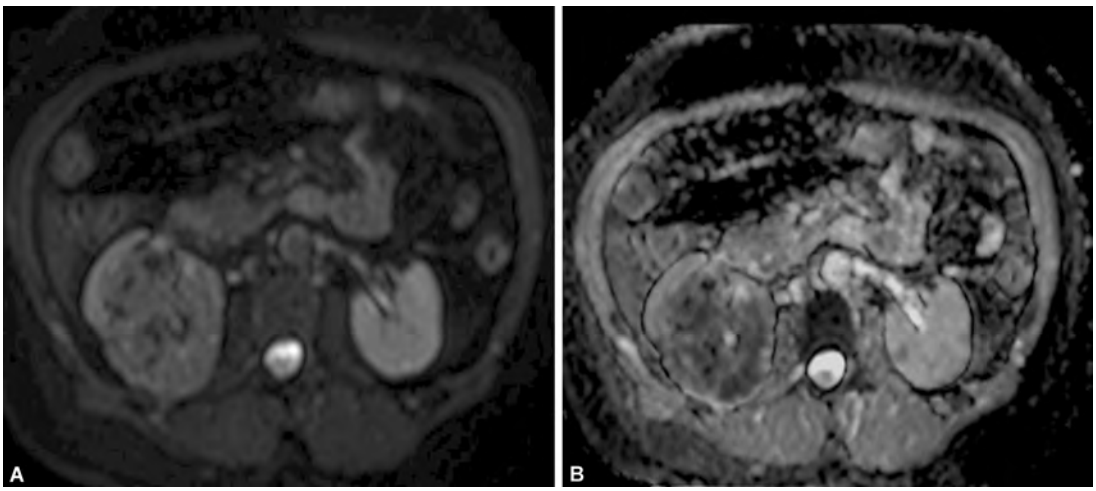
Figs 3A and B: Well-defined partially exophytic mass arising from right kidney showing signal drop on OP images; (B) As compared to IP images; (A) On CSI; pathological outcome—angiomyolipoma



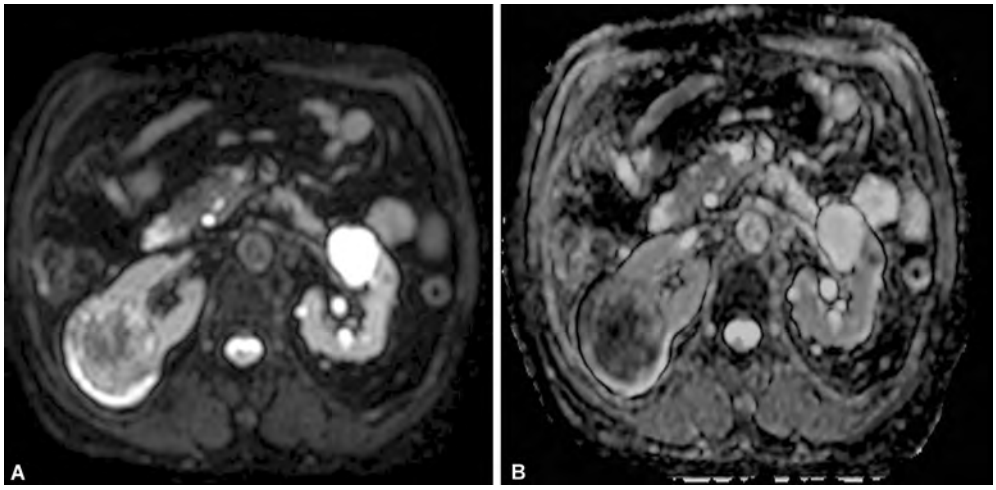
Figs 4A and B: Well-defined partially exophytic mass arising from left kidney showing signal drop on OP images; (B) As compared to IP images; (A) On CSI; pathological outcome—ccRCC



Figs 5A and B: Well-defined partially exophytic mass arising from right kidney showing signal drop on OP images; (B) As compared to IP images; (A) on CSI; pathological outcome—papillary RCC



Figs 6A and B: Well-defined partially exophytic mass arising from right kidney showing diffusion restriction; (A) Represents DWI images; (B) Represents ADC images; pathological outcome—AML



Figs 7A and B: Well-defined partially exophytic mass arising from right kidney showing diffusion restriction; (A) Represents DWI images; (B) Represents ADC images; pathological outcome—papillary RCC

- The other limitation was that only a qualitative assessment of multiple parameters was done. There can be interobserver bias in qualitatively assessing the curve.

Conclusion

The following conclusions were drawn from the study

- In our study, the majority of the solid renal tumors in our study came out to be malignant (91.6%), and only 8.4% of cases were benign. Most of the renal tumors were diagnosed incidentally on imaging. Among the malignant renal tumors, the most common histological subtype was cc-carcinoma, followed by papillary cell tumor and then chromophobe cell carcinoma.
- Chemical shift imaging (CSI), although a useful tool to look for microscopic fat, can't be used as a reliable marker to rule in cc-carcinoma as both AML and papillary cell carcinoma have microscopic fat.

In our study, we found that there was no relation between the ADC values and the type of renal tumor.

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ORIGINAL ARTICLE

A Study of Relationships between the HbA1c Level and Inflammatory Markers, Neutrophil-to-Lymphocyte Ratio, and Monocyte-to-Lymphocyte Ratio in Controlled and Uncontrolled Type 2 Diabetes Mellitus

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Abstract

Aim and objective: To assess the relationship between glycated hemoglobin (HbA1c) with inflammatory markers, neutrophil-to-lymphocytes ratio (NLR), and monocyte-to-lymphocytes ratio (MLR) in controlled and uncontrolled type 2 diabetes patients.

Materials and methods: This was a hospital-based cross-sectional study conducted at the Department of Medicine, SMS Hospital, and an attached group of hospitals (Jaipur, Rajasthan, India) after informed consent from the Ethics Committee of the institute.

After obtaining informed consent from patients who met the inclusion and exclusion criteria, 200 diabetic patients were included in the study using the simple randomization method. Following a detailed history and diagnosis, vital demographic information, and blood tests were collected from patients via a predesigned preliminary questionnaire. The following blood tests were collected: white blood cell (WBC), Hb, hematocrit (HCT), red cell distribution width (RDW), neutrophils, lymphocytes, HbA1c, blood glucose, NLR ratio, and MLR ratio. Data were entered and analyzed using Statistical Package for the Social Sciences version 22.

Results: The mean age of patients with controlled diabetes mellitus was 54.10 years, while that of patients with uncontrolled diabetes mellitus was 55.3 years. Glycemic control was more in the age group of 51–60 years. Around 54% of males and 46% of females were included in the present study, and no association was found between the two genders with poor and good glycemic control. Around 63.29% of participants with uncontrolled diabetes have an increased NLR, and 61.39% of participants with uncontrolled diabetes have an increased MLR. A strong association was found between the NLR and MLR with the glycemic control.

Conclusion: Uncontrolled diabetes mellitus had a positive association with inflammatory markers, that is, NLR and MLR.

Statement of significance: Diabetes mellitus is the most common metabolic disorder in Asian countries. It leads to many acute and chronic complications in uncontrolled diabetes. Markers like the NLR ratio and MLR ratio are inexpensive and easily available for blood investigation. Hence, these markers are quite useful in differentiating controlled and uncontrolled diabetes and, therefore, useful in predicting blood sugar control in type 2 diabetes mellitus.

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Introduction

Diabetes mellitus is a condition in which blood sugar is too high for a long time due to deficiency or relative deficiency of the hormone insulin, either due to the inability of the pancreas to produce insulin or insufficient insulin production or insufficient action of insulin action. Type II diabetes is increasing worldwide and has reached epidemic proportions in many countries, especially India.[1] Inflammatory processes play an important role before and in the development of type 2 diabetes. Damage to blood vessels by endothelial cells can be affected by hyperglycemia, increased free fat, altered lipoprotein, and high blood pressure. Subclinical inflammation may be associated with cardiovascular risk in patients with diabetes.[2]

Leukocytes and their subtypes, neutrophil-to-lymphocyte (NLR) and monocyte-to-lymphocyte ratios (MLRs), are new markers of inflammation.

The NLR is a new marker of subclinical disease.[3] Many studies have highlighted the increased NLR rate as a result of macrovascular and microvascular complications of diabetes. MLR and NLR are routine investigations, inexpensive, and easy to test. These markers may be quite useful in predicting complications of type 2 diabetes mellitus; hence, the objective of the present study is to find out the relation between glycated hemoglobin (HbA1c) with inflammatory markers, NLR, and MLR in controlled and uncontrolled type 2 diabetes patients.

Aim and Objectives

Evaluation of hematological indices, NLR, and MLR in controlled and uncontrolled T2DM.

Objectives

To assess the relationship between HbA1c with MLR and NLR.

Materials and Methods

This was a hospital-based cross-sectional study conducted at the Department of Medicine, SMS Hospital, and the attached group of hospitals, Jaipur, Rajasthan, India, after approval from the Ethics Committee of the institution.

Inclusion Criteria

- Type 2 diabetes mellitus according to ADA criteria.
- Age 18–70 years.

Exclusion Criteria

- Acute and chronic liver disease.
- Anemic patients.
- Hemoglobinopathies (thalassemia and sickle cell anemia)
- Patients taking drugs causing alteration in HbA1c, for example, aspirin and vitamins E and C.
- Acute infections.
- Chronic inflammatory conditions like inflammatory bowel disease,

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osteoarthritis, rheumatoid arthritis, gout, bronchial asthma, and chronic hepatitis.
- Acute myocardial infarction and cerebral infarction.
- Acute and chronic kidney disease.
- Pregnant.
- Patient not willing to participate in the study

A total of 200 patients with diabetes mellitus were included in the study using simple random techniques after written informed consent from the patients who fulfilled the criteria of inclusion and exclusion. Basic demographic details and blood investigations were collected from the patients by means of a predesigned, pretested questionnaire after a detailed history and clinical examination. Following blood investigation, data were collected: white blood cell (WBC), Hb, hematocrit (HCT), RDW, neutrophils, lymphocytes, HbA1c, blood sugar, NLR ratio, and MLR ratio.

Data were analyzed and summarized as percentage correlation between HbA1c and NLR and MLR in controlled and uncontrolled type 2 diabetes mellitus, analyzed by the Chi-squared test and student's *t*-test. A value of $p < 0.05$ was considered to be statistically significant.

Observation

A total of 200 diabetic patients participated in this study. Table 1 shows the baseline characteristics of the subjects.

In the present study, the majority, that is, 19 participants with controlled diabetes, belonged to the age group between 51 and 60 years, while only four participants belonged to the 24–40 years of age group. The mean age group of participants with controlled diabetes was 54.10 years, with a standard deviation of 9.56 years.

Similarly, 60 participants in the age group of 51–60 years had uncontrolled diabetes, while only 16 participants belonged to the age group of 24–40 years. The mean age group of participants with uncontrolled diabetes was 55.3 years, with a standard deviation of 9.86 years.

A total of 24 males had controlled diabetes, while the majority of them, that is 91 males, had uncontrolled diabetes, and 18 females had controlled diabetes, while the majority of females, that is, 67, had uncontrolled diabetes.

There has been no substantial difference in terms of age and sex distribution between the individuals with controlled and uncontrolled diabetes mellitus (Table 1).

Table 2 shows that only a few participants, that is, 17 with controlled diabetes mellitus, had NLR of >2 while the remaining had a ratio of <2.

Likewise, among 158 participants with uncontrolled diabetes mellitus, 100 patients had an NLR of >2, while only 58 of them had a ratio of <2.

Therefore, the results were determined to be statistically significant ($p = 0.013$) according to the NLR (Table 2).

Table 3 shows that, among 42 participants with controlled diabetes mellitus, 64.29% of them had an MLR of <2, while the remaining had a value of >2.

Similarly, in participants with uncontrolled diabetes mellitus, the majority, that is, 61.39% of them, had an MLR of >2, whereas only 38.61% had a ratio of <2.

So, the results were determined to be statistically significant in terms of MLR ($p = 0.005$).

Discussion

Glycated hemoglobin (HBA1c) is used to measure the long-term glycemic control in diabetic patients but does not predict the ongoing inflammation of diabetic-associated complications accurately.

The NLR is a sign of balance between neutrophil and lymphocyte levels in the body and is an indication of subclinical inflammation. The NLR is a potential marker to determine inflammation in various cardiac and noncardiac disorders. The present study was thereby conducted to find the relationship between the HbA1c level and inflammatory markers like NLR and MLR in controlled and uncontrolled type 2 diabetes mellitus.

In the present study, it was found that the mean age of patients with controlled diabetes mellitus was 54.10 years, while that of patients with uncontrolled diabetes mellitus was 55.3 years.

Glycemic control was more in the age group of 51–60 years. Selvin et al.[4] published an article stating that people diagnosed with diabetes between the ages of 30 and 65 have poorer glycemic control than people

Table 1: Distribution of participants in terms of age group and sex distribution

	Controlled diabetics: HbA1c <7.0		*Uncontrolled diabetics: HbA1c >7.0*		*p-value*
	No.	*%*	*No.*	*%*	
Age distribution					
24–40 years	4	9.52	16	10.13	0.478
41–50 years	10	23.81	24	15.19	
51–60 years	19	45.24	60	37.97	
>60 years	9	21.43	58	36.71	
Total	42	100.00	158	100.00	
Sex					
Male	24	57.14	91	57.59	0.902
Female	18	42.86	67	42.41	
Total	42	100	158	100	

Table 2: Number of participants in controlled and uncontrolled groups on the basis of NLR

NLR >2	*Controlled diabetics: HbA1c <7.0*		*Uncontrolled diabetics: HbA1c >7.0*	
	No.	*%*	*No.*	*%*
Yes	17	40.48	100	63.29
No	25	59.52	58	36.71
Total	42	100.00	158	100.00
p-value (result)		0.013*		

*Significant (if $p < 0.05$)

Table 3: Distribution of participants on the basis of MLR

MLR >2	*Controlled diabetics: HbA1c <7.0*		*Uncontrolled diabetics: HbA1c >7.0*	
	No.	*%*	*No.*	*%*
Yes	15	35.71	97	61.39
No	27	64.29	61	38.61
Total	42	100.00	158	100.00
p-value (result)		0.005*		

*Significant (if $p < 0.05$)

diagnosed at ages 65 and older. Similar results were observed in the study of Shamshirgaran et al.,[5] which concluded that compared with the ≤49 age group, the middle-aged group (50–59 years) and the elderly group (60 years and above) were less likely to have poor blood sugar control. Nanayakkara et al.[6] also published in their article that younger age is associated with poor glycemic control and poor cardiovascular outcomes. Kakade et al.[7] found in their study that there was no difference between the ages of patients with poor and good glycemic control. In our study, we found that 54% of men and 46% of women were included in the study, and there was no study that did not find a relationship between poor control and glycemic control in both genders. A 2002 UK cross-sectional study[8] involving 10,663 people aged 17–98 with type 2 diabetes and another Canadian study[9] involving 5,569 patients also found no association between gender and HbA1c level. In our study, a very significant increase in the NLR was observed in patients with uncontrolled diabetes compared to patients with controlled diabetes. These results are based on Devamsh et al. It is supported by research conducted by Devamsh et al.,[10] who found that the neutrophil ratio was positively correlated with HbA1c and was indicative of poor glycemic control in patients with type 2 diabetes. Increased neutrophil levels were associated with increased HbA1c and poor glycemic control.[11]

Duman et al.[12] found that the neutrophil ratio had a positive relationship with HbA1c ($r = 0.49$, $p < 0.001$). Berberoglu.[13] also found a better neutrophil count in the poor glycemic control group compared to the good glycemic control group. Verma et al.[14] examined the relationship between NLR and HbA1c in patients with type 2 diabetes and concluded that increased NLR was associated with increased HbA1c, and glycemic control was not good. Therefore, in addition to HbA1c, this ratio should be used as an indicator of the level of diabetes control in patients with type 2 diabetes. Mahankali et al.[15] came to similar conclusions as the present study. However, the study conducted by Umarani et al.[16] showed no significant relationship between the NLR and the increasing severity of glucose intolerance. A significant association was found between the MLR and glycemic control in the present study. However, Adnyani[17] concluded that LMR did not show significant differences between the two groups.

Conclusion

Diabetes mellitus is the most common metabolic disorder in Asian countries. It leads to many acute and chronic complications in uncontrolled diabetes. Uncontrolled diabetes mellitus had a positive association with inflammatory markers, that is, NLR and MLR. Moreover, markers like NLR and MLR are inexpensive and easily available for blood investigation. Hence, these markers are quite useful in differentiating controlled and uncontrolled diabetes and, therefore, useful in predicting blood sugar control in diabetes mellitus.

Our study has limitations because the small size of a single institution may not represent the general population.

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ORIGINAL ARTICLE

Clinical Profile of Mucormycosis Patients during Coronavirus Disease 2019 Pandemic: A Retrospective Observational Study

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Abstract

Background: During the coronavirus disease (COVID-19) pandemic, an increased incidence of mucormycosis infection was noted globally, the majority being from India. We aimed to study the clinical profile of the mucormycosis patients during the COVID-19 pandemic admitted at tertiary care centers.

Materials and methods: This is a retrospective record-based observation study conducted at Gandhi Medical College, Bhopal. All suspected or laboratory-proven mucormycosis patients were included. Detailed data on demography, clinical features, risk factors, laboratory/radiological findings, and outcomes were recorded.

Results: A total of 288 patients were enrolled and 121(42%) showed mucormycosis on potassium hydroxide (KOH) mount. The mean age was 51.52 ± 10.88 years, male:female ratio was 2.3:1. Most common symptom was facial swelling/pain and fever. The most common risk factor was COVID-19 infection (78.5%) followed by the presence of diabetes mellitus (DM) (70.8%) out of which 152 (52.8%) patients were previously diagnosed cases and 52 (18%) patients were newly diagnosed, 159 (55.2%) had a history of corticosteroid use, 87 (30.2%) had a history of use of oxygen support and 67 (23.2%) had hypertension. Most patients had invasion limited to sinus (46.5%) but the presence of DM was associated with an increased risk of cerebral invasion. Out of 288 patients admitted with mucormycosis, 31 patients collapsed to death while the remaining 257 patients were discharged from the hospital.

Conclusion: It is observed that during the COVID-19 pandemic, hyperglycemia and inappropriate use of corticosteroids were associated with an increased risk of development of mucormycosis in patients with or without DM. We conclude that regular blood glucose monitoring, adequate glycemic control, and judicious evidence-based use of corticosteroids and immunosuppressants in COVID-19 are recommended to reduce the emergence of mucormycosis in such circumstances.

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Introduction

Despite recent advancements in diagnosis and treatment, mucormycosis remains a dreadful condition with high mortality rates. To be specific, the zygomycetes order mucorales, which contain the filamentous fungi responsible for this disease. After the 2019 appearance of COVID-19 infection, the global incidence of mucormycosis appears to have increased, notably in diabetic patients and patients who took steroids during the coronavirus disease (COVID-19) pandemic. Although it was classified as an opportunistic infection prior to COVID-19, affecting primarily those with compromised immune systems [such as those with diabetes mellitus (DM)], neutropenia, malignancy, chronic renal failure, acquired immunodeficiency syndrome (AIDS), and recipients of organ or hematopoietic stem cell transplants), it can also infect immunocompetent hosts (such as those who have recently undergone trauma).[1]

Patients with associated comorbidities [e.g., DM, chronic obstructive pulmonary disease (COPD)] and immunocompromised conditions [e.g., corticosteroid therapy, ventilation, and intensive care unit (ICU) stay] are prone to develop severe opportunistic infections. Secondary fungal or bacterial infections or coinfections are important challenges that increase the patient's morbidity and mortality.[2]

The second wave of the COVID-19 pandemic has resulted in an increase in the cases of mucormycosis in many countries, the majority from India.[3,4] Rhino-orbito-cerebral mucormycosis (ROCM) is observed to be the most common form of mucormycosis which is acquired by inhaling spores of fungal into the paranasal sinuses. Rather, the use of corticosteroids to modulate immune-related lung damage and reduce mortality in patients with COVID-19, who require respiratory support and additional oxygen support, may predispose the patients to secondary infections that increase the risk of mortality.[5]

Hyperglycemia causes glycosylation of transferrin and ferritin which reduces their iron-binding capacity, thus increasing free iron levels. Raised interleukin-6 levels in COVID-19 further increase free iron levels through increased production of ferritin. In addition, there is upregulation of the expression of glucose regulator protein 78 on endothelium cells and fungal ligand spore coat homolog protein, which facilitates angioinvasion of the fungus, hematogenous dissemination, and tissue necrosis.[6,7]

The use of long-term corticosteroids has traditionally been associated with a high-risk of opportunistic fungal infections. Corticosteroids cause impairment of the function of several immune cells, such as polymorphonuclear leukocytes, T lymphocytes, monocytes, and macrophages.[8]

Materials and Methods

The present study was conducted as a retrospective record-based observational study from case records of all the patients admitted with mucormycosis in Gandhi Medical College and associated Hamidia Hospital, Bhopal, Madhya Pradesh, India.

Detailed history with presenting complaints like facial pain, facial swelling, headache, fever, breathlessness, diminution of vision, altered sensorium, etc., past history or current status of COVID-19 disease, comorbidities like diabetes, hypertension, immunodeficiency disorders, cancers, etc. were obtained. Drug history like the use of steroids, immunosuppressive therapy, chemotherapy, etc. were recorded. Clinical signs and vitals including pulse rate, blood pressure, and oxygen saturation were recorded at baseline. Investigations like hemoglobin, total leukocyte counts, platelet, creatinine, serum electrolytes, and hemoglobin A1c (HbA1c) were recorded. Radiological parameters including computed tomography (CT), magnetic

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resonance imaging (MRI), and endoscopic findings were recorded and based on the invasion of mucormycosis. Staging of the patient was done based on the staging of ROCM (Honavar, Santosh G. Code Mucor).[9] Diagnostic modality used for diagnosing mucormycosis infection was recorded and based upon this patients were categorized as possible mucormycosis, probable mucormycosis, and proven or laboratory-confirmed mucormycosis. Detailed history regarding diagnostic or therapeutic interventions and surgical procedures was recorded. Duration of stay in the hospital treatment history and use of antifungal agents during the stay were noted. Clinical outcomes of the patients were recorded for all the patients in terms of discharge or death.

A total of 288 patients were enrolled in this study including suspected cases based on clinical findings, cases with radiological evidence of invasive fungal infection and potassium hydroxide (KOH), and histopathological examination (HPE)—based lab-confirmed cases of mucormycosis. The suspected patients underwent diagnostic nasal endoscopy, fungal microscopy, culture of the swab collected from the involved part, biopsy and HPE of the involved part, and radiological investigations mainly contrast-enhanced MRI and CT. The patients who were diagnosed underwent thorough history taking, their presentation details, COVID-19 history, imaging findings, comorbidities, management details, and follow-up information were obtained, recorded, and analyzed. Most patients underwent proper surgical debridement along with the administration of liposomal amphotericin. Microscopic visualization of broad ribbon-like aseptate hyphae in sterile body fluids or tissue of a patient is identified as a confirmed case of mucormycosis.[10]

Statistical Analysis

Data were recorded into Microsoft® Excel worksheet 2019 and exported into Statistical Package for the Social Sciences version 21.0 (IBM, United States of America) for statistical analysis. Quantitative data were expressed as median and range.

Results

The study group comprised 288 patients with a mean age group of 51.52 ± 10.88 years and median age of 51 years (range, 18–80 years). Incidence of mucormycosis was maximum in the age group between 51 and 60 years (33.3%) followed by 41–50 years (30.9%). Incidence of mucormycosis in the age-group 31–40 years was 16%, in 61–70 years was 14.2%, and between 71 and 80 years was 4.2%. The incidence was found to be higher in males (69.8%) than females (30.2%).

Amongst all the hospitalized patients majority presented with complaints of facial swelling (41.6%) followed by facial pain (38.19%) and fever (38.19%) followed by headache (31.2%), eye swelling (25%), breathlessness (25%), and altered sensorium (13.8%) (Fig. 1).

The majority had hospital duration between 1 and 10 days (36.1%) followed by 11–20 days (34.7%) and 21–30 days (17%).

Staging of ROCM was done based on invasion of an organism to the nose, sinus, orbit, and cerebrum (Honavar, Santosh G. Code Mucor) revealed that the majority had stage 2 (sinus) (46.5%) followed by stage 3 (orbital) (23.6%) and stage 4 (cerebral) (21.9%). There were 22 (7.6%) patients who had stage 1 (nasal) of mucormycosis. One patient was diagnosed to have pulmonary mucormycosis which was not included in this staging of mucormycosis.

Out of 288 patients, 18 (6.3%) were graded as possible mucormycosis on clinical suspicion, and 149 (51.7%) were graded as probable mucormycosis based on radiological and endoscopic findings. There were 121 (42%) patients with mucormycosis who were proven based on KOH and HPE findings.

A total of 226 patients had present or prior history of COVID-19 infection out of which 161 patients were diabetics. Among these COVID-19-positive patients, 106 (46.9%) had stage 2 (sinus invasion) and 53 (23.5%) patients had stage 3 (orbital invasion) followed by stage 4 (cerebral invasion) in 46 (20.4%), and stage 1 (nasal) in 20 (8.8%) patients. One patient who had COVID-19 infection and DM had pulmonary mucormycosis. The total number of deaths in COVID-19-positive patients was 23 (10.2%) out of which 20 patients had DM and only three patients were nondiabetic (Table 1).

Among 288 patients, 204 patients had DM out of which 152 patients were previously known cases and 52 patients were newly detected to have DM. A total of 88 (43.1%) patients in this group had stage 2 (nasal invasion) followed by 54 (26.5%) patients who had stage 4 (cerebral invasion) and 51 (25%) patients had stage 3 (orbital), and 10 (4.9%) patients had stage 1 (nasal invasion). The total number of deaths in diabetic patients was 27 (13.2%) out of which 19 patients were previously known diabetics and eight were newly detected diabetic patients. A total of 19 patients were neither diabetic nor had COVID-19 infection, among these patients 12 (63.2%) patients had stage 2 mucormycosis and only one death.

Out of 288 patients, 159 (55.2%) patients had a present or prior history of corticosteroid use, 87 (30.2%) patients had a history of use of oxygen support, 67 (23.2%) patients had hypertension, four patients had a past history

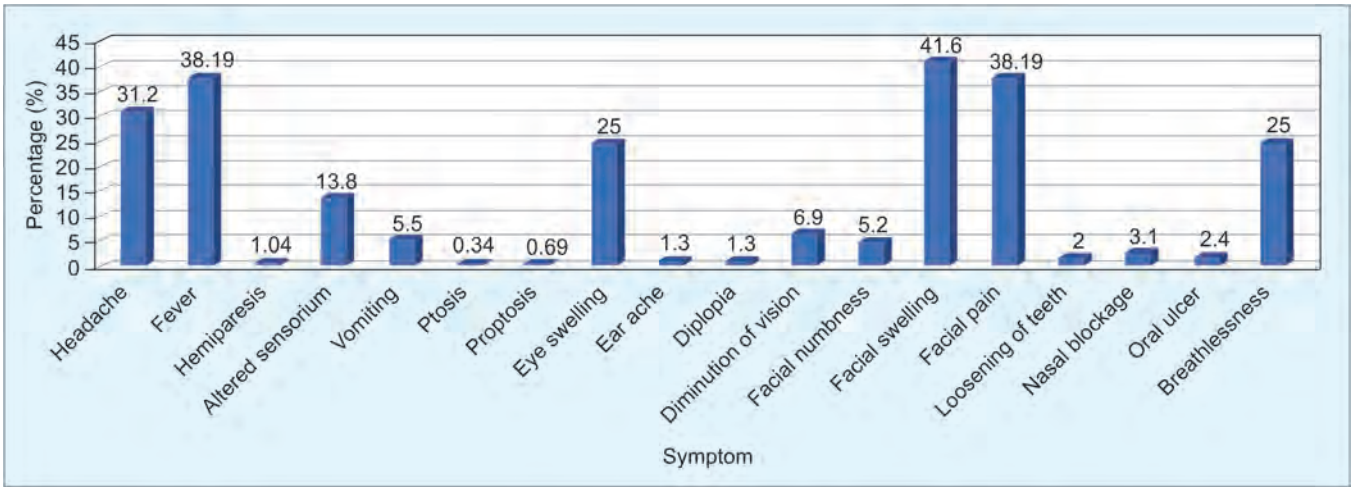

Fig. 1: Distribution of patient according to symptoms

Table 1: Distribution of patients based on history of COVID-19 infection and DM (previously known and newly detected)

		All		*Total COVID-19+*		*COVID-19+ DM+*		*COVID-19+ DM–*		*DM+ COVID-19–*		*Total DM+ (new and old)*		*Previously known DM*		*Newly detected DM*		*COVID-19– DM–*	
Frequency		*N = 288*		*N = 226*		*N = 161*		*N = 65*		*N = 43*		*N = 204*		*N = 152*		*N = 52*		*N = 19*	
Mean age		51.52		51.52		51.52		51.41		51.42		51.52		51.52		51.23		51.18	
		Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%	Value	%
Gender	Male	201	69.8%	158	69.9%	109	67.7%	49	75.4%	32	74.4%	141	69.1%	108	71.1%	33	63.5%	11	57.9%
	Female	87	30.2%	68	30.1%	52	32.3%	16	24.6%	11	25.6%	63	30.9%	44	28.9%	19	36.5%	8	42.1%
Stage of mucormycosis	1 (nasal)	22	7.6	20	8.8%	8	5.0%	12	18.5%	2	4.7%	10	4.9%	5	3.3%	5	9.6%	0	0.0%
	2 (sinus)	134	46.5	106	46.9%	71	44.1%	35	53.8%	17	39.5%	88	43.1%	63	41.4%	25	48.1%	12	63.2%
	3 (orbital)	68	23.6	53	23.5%	40	24.8%	13	20.0%	11	25.6%	51	25.0%	42	27.6%	9	17.3%	3	15.8%
	4 (cerebral)	63	21.9	46	20.4%	41	25.5%	5	7.7%	13	30.2%	54	26.5%	42	27.6%	12	23.1%	4	21.1%
Pulmonary mucormycosis		1	0.34%	1	0.44%	1	0.6%	0	0.0%	0	0.0%	1	0.49%	0	0	1	1.9%	0	0.0%
Outcome	Discharged	257	89.2%	203	89.8%	141	87.6%	62	95.4%	36	83.7%	177	86.8%	133	87.5%	44	84.6%	18	94.7%
	Death	31	10.8%	23	10.2%	20	12.4%	3	4.6%	7	16.3%	27	13.2%	19	12.5%	8	15.4%	1	5.3%

of cerebrovascular accident, three patient had a history of coronary artery disease, three patients had chronic kidney disease, two patients had hypothyroidism, two patients had a history of tuberculosis, one patient was hepatitis B positive, and two patient had arrhythmia.

The majority of the patients underwent functional endoscopic sinus surgery (32.6%) followed by debridement (32.3%) and ocular exenteration (9%). In the present study mortality rate among the patients with mucormycosis was 10.8%.

In the present study, 71 females with mucormycosis had hemoglobin levels <12 gm/dL and 16 female patients had hemoglobin levels ≥12 gm/dL. Among the male population, 164 patients had hemoglobin levels <13 gm/dL, while 37 male patients had hemoglobin levels ≥13 gm/dL. In the current study, the majority of the patients with mucormycosis had a total leukocyte count between 4,000 and 11,000/µL (197) followed by patients with TLC level >11,000/µL. There were nine patients with having TLC count of <4,000/µL in the present study. In this study, the majority of the patients (*n* = 234) had platelet counts in the normal range. While there were 32 patients who had platelet counts <150,000/µL. There were 22 patients who had platelet counts of >450,000/µL in the present study (Table 2).

Among male patients, 25 patients had serum creatinine levels >1.35 mg/dL and among female patients, 18 patients had serum creatinine levels >1.04 mg/dL. Hyponatremia was reported in 110 patients and hypernatremia was reported in four patients. Hyperkalemia was reported in 16 patients whereas 60 patients had hypokalemia in the current study. The majority of the patients had reported hypomagnesemia (82) whereas hypermagnesemia was reported in 15 patients.

The majority of the patients had an HbA1c level of >6.5% while there were 65 patients had an HbA1c level of <5.7%. There were 14 patients having HbA1c levels between 5.7 and 7.4%. This highlights the greater impact of the level of HbA1c on the incidence of mucormycosis. The majority of the patients (*n* = 163) had random blood sugar (RBS) levels between 70 and 200 mg/dL followed by patients with RBS levels >200 mg/dL (121). There were four patients who had RBS levels less than 70 mg/dL. Hypercholesterolemia was reported in 36 patients whereas the majority of the patients (117) reported hypertriglyceridemia with a level of >150 mg/dL.

These observations report a significant impact of DM and uncontrolled blood glucose levels on disease severity and outcome of mucormycosis patients.

Discussion

Mucormycosis is a rare opportunistic fungal infection of class zygomycetes. Before its surge during the second wave of the COVID-19 pandemic, mucormycosis was an opportunistic infection preferentially in immunocompromised conditions like an organ or hematopoietic stem cell transplant patient, patients on immunosuppressants, malignancy, acquired immunodeficiency syndromes and uncontrolled hyperglycemia.[11] Severe acute respiratory syndrome coronavirus 2 pandemic in 2019 was associated with higher mortality in severe cases and due to lack of management guidelines as the disease was new, disproportionate use of corticosteroids and other immunosuppressants like tocilizumab and remdesivir were tried to control the disease severity.[12,13] Excessive use of corticosteroids leads to uncontrolled hyperglycemia and other complications in those with or without DM. Surge of mucormycosis infection was observed in patients with COVID-19 in the second wave in 2021.[14] History of diabetes, use of corticosteroid, and duration of use of corticosteroid during the treatment of COVID-19 were risk factors observed in the patients with mucormycosis.

Limitations

- The present study was retrospective with no comparison group included, and the study was conducted in a single institute. Patients referred to a tertiary care center mostly have the more advanced or refractory disease, and thus may not be demonstrative of the overall patients affected by mucormycosis.
- The present study was conducted as a retrospective observational study; however, a prospective study with follow-up of patients after discharge might have revealed the long-term outcome.

Conclusion

In this retrospective study, we discussed that the sudden increase in mucormycosis infection appeared to be a result of the presence of uncontrolled DM, disproportionate use of corticosteroids which led to an increase in blood glucose and opportunistic fungal infections, and COVID-19 infection associated with cytokine storm, lymphopenia, and endothelial damage. The disease severity and outcome of patients were devastating in patients with DM and uncontrolled hyperglycemia. Strict monitoring and control of blood glucose levels and judicious evidence-based use of corticosteroids, and immunosuppressants in COVID-19 is recommended to reduce the burden of deadly mucormycosis.

Table 2: Analysis of laboratory parameters in mucormycosis patients

Parameters	*n*	*Gender*	*Findings (mean ± standard deviation)*
Hemoglobin in (gm/dL)	288	Male	11.06 ± 1.89
		Female	11.07 ± 1.90
Total leukocytes counts (per µL)	288		10099 ± 5601
Platelet counts in lakhs (per µL)	288		2.73 ± 1.04
HbA1C	147		6.49 ± 3.64
RBS levels	288		205.44 ± 92.69
Creatinine	288	Male	0.94 ± 0.54
		Female	0.94 ± 0.54
Serum sodium levels	250		135.39 ± 33.97
Serum potassium levels	250		3.93 ± 1.20
Serum magnesium levels	135		1.46 ± 0.88
Triglycerides	187		190.07 ± 113.45
Total cholesterol levels	244		150.84 ± 68.94

Compliance with Ethical Standards

Contributors

Badal Gondane, Shailendra Kumar Jain, and Simmi Dube.

Ethical Approval

The study has been approved by the Institutional Ethics Committee and has been performed in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was not required as it was a record-based retrospective observational study.

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ORIGINAL ARTICLE

Clinical and Immunological Profile of Systemic Lupus Erythematosus: A 5-year Retrospective Analysis from Northeast India

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Abstract

Objective: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with a wide range of clinical manifestations having considerable variation in clinical features that are influenced by ethnic, sociocultural, and geographical factors. This disease primarily affects young women aged between 18 and 35 years. The aim of this present study was to delineate the clinical manifestations and immunological patterns of SLE patients from the Northeastern (NE) region of India.

Materials and methods: The study was carried out in a tertiary care hospital from January 2016 to January 2021. Adult patients of age >18 years fulfilling systemic lupus international collaborating clinic criteria (SLICC) for classification of SLE were included in this study. Immunology such as antinuclear antibodies (ANA) and double-stranded deoxyribonucleic acid (dsDNA) were also performed followed by enzyme-linked immunosorbent assay (ELISA).

Results: Over a period of 5 years, 142 patients were recruited for the study, with an overall female-to-male ratio was 9.9:1, a median age at onset of 25 years (interquartile range age 21–32 years) and a mean disease duration was 15.25 months (range 2–60 months). Our study revealed that ANA was positive in 97.18% of patients while anti-dsDNA was positive in 78.68%, indicating that women from this region have higher positivity rates.

Conclusion: Our findings support the notion that SLE is a multisystem disorder that predominantly affects young females, especially during the second and third decades of life. Hematological, mucocutaneous, and renal manifestations are common in our patients. Moreover, pulmonary, cardiovascular, and gastrointestinal (GI) manifestations were understudied in other cohorts, which is one of our study's strengths.

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Introduction

The SLE is a systemic autoimmune rheumatic disease that predominantly affects young females with variable clinical features.[1] It is an immune-mediated disease that causes immune complexes to disrupt the barrier control between innate and adaptive immunity, resulting in inflammatory injury.[2] The etiology of SLE is still not fully understood but widely assumed that multifactorial causes such as genetic susceptibility, hormonal, and environmental factors all play a significant role in the pathophysiology of the disease. The heterogenicity of SLE has been attributed to genetic, environmental, and sociodemographic factors.[3] Several studies have found differences in the prevalence of disease manifestations and outcomes in various ethnic groups, including African Americans, Caucasians, and several Asian populations.[4,5]

A literature review revealed that several articles from India discussed the clinical profile of SLE.[6–12] However, studies based on SLE burden in Northeastern (NE) India are mostly limited to one particular area.[13,14] Due to the unique genetic background and sociocultural factors associated with the NE population, it is hypothesized that distinct demographic, clinical presentations, and immunological features would be encountered in the study. Therefore, we thoroughly investigated the epidemiology of SLE comprehensively in the study population.

Materials and Methods

Study Design and Participants

A 5-year retrospective study of SLE patients from a tertiary care hospital in Meghalaya was conducted from January 2016 to January 2021. Patients satisfying the systemic lupus international collaborating clinic criteria (SLICC) criteria for SLE were included in this study.[15] Patients underwent baseline investigations for biochemical parameters, radiology, and cardiology. Immunological tests such as antinuclear antibodies (ANA) were measured using an immunofluorescence method, antidouble-stranded deoxyribonucleic acid (dsDNA) was measured using an enzyme-linked immunosorbent assay (ELISA), and complement levels (C3, C4) were measured using nephelometry. The disease activity of SLE was assessed by the systemic lupus erythematosus (SLE) disease activity index (SLEDAI) scoring system.

Statistical Analysis

The statistical analyses were performed using Statistical Package for the Social Sciences 17.0 (Chicago, United States of America). The categorical data were tabulated as counts and percentages.

Results

Demographic Characteristics

A total of 142 SLE patients were enrolled in the study. The study cohort comprised 129 females and 13 males. The female-to-male ratio was 9.9:1. SLEDAI was analyzed in all patients at the time of presentation. The percentages of patients with mild, moderate, and severe and very severe disease activity were 4.93, 37.32, 33.1, and 24.65%, respectively (Table 1). Geographically, the patients were from various NE states, with the majority coming from Meghalaya 42.26%, Assam 19.01%, Arunachal Pradesh 14.79%, Nagaland 9.15%, Mizoram 5.64%, Manipur 4.93%, and Tripura 4.22%.

Clinical Characteristics

The most significant clinical manifestations are depicted in Table 2. The most frequent clinical features were constitutional symptoms in 85.91% followed by hematological symptoms

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Table 1: Age distribution, duration of illness, and disease activity score in the systemic lupus erythematosus patients (n = 142)

	Number of cases	*Frequency (%)*
Age-group (years)		
<21	34	23.94
21–25	41	28.87
26–30	26	18.31
31–35	17	11.97
36–40	11	7.75
>40	13	9.15
Sex		
Female	129	91
Male	13	9
SLEDAI score		
1–5 (mild)	7	4.93
6–10 (moderate)	53	37.32
11–19 (high)	47	33.10
>19 (very high)	35	24.65
Duration of illness (months)		
Range	2–60	
Average	15.25	
Median	12	

SLEDAI, systemic lupus erythematosus disease activity index

Table 2: Clinical manifestations of SLE patients at presentation (n = 142)

Manifestation	*Frequency (%)*
Constitutional symptoms: fatigue, malaise, fever, anorexia, and weight loss	122 (85.91)
Hematological	110 (77.46)
Anemia (chronic disease)	94 (66.2)
Thrombocytopenia, normal range (165–415 x 10^3/mm^3)	63 (44.37)
Leukopenia, normal range (3.54–9.06 x 10^3/mm^3)	40 (28.16)
Lymphopenia, normal range (714–4,530/mm^3)	29 (20.42)
Hemolytic anemia	11 (7.74)
Splenomegaly	17 (11.97)
Cutaneous	107 (75.35)
Malar rash	78 (54.92)
Discoid rash	52 (36.62)
Alopecia	64 (45.07)
Photosensitivity	88 (61.97)
Vasculitis rash	28 (19.72)
Musculoskeletal	105 (73.94)
Nonerosive polyarthritis	88 (61.97)
Arthralgia/myalgia	78 (54.93)
Avascular necrosis of bone	2 (1.41)
Renal	96 (67.61)
Proteinuria >500 mg/day, normal range (<150 mg/day)	92 (64.79)
Nephrotic syndrome	56 (39.43)
End-stage renal disease	12 (8.45)
Pulmonary	68 (47.88)
Lupus pneumonitis	8 (5.63)
Pleural effusion	56 (39.44)
Diffuse alveolar hemorrhage	3 (2.11)
GI	64 (45.07)
Nonspecific (nausea, mild pain, and diarrhea)	45 (31.69)
Ascites	30 (21.12)
Abnormal liver enzymes	16 (11.27)
Antral gastritis	26 (18.31)
Neuropsychiatric	49 (34.51)
Headache	39 (27.46)
Altered sensorium	8 (5.63)
Stroke	6 (4.22)
Seizure	5 (3.52)
Cardiovascular	38 (26.76)
Pericardial effusion	27 (19.01)
Heart failure (myocarditis, cardiomyopathies)	11 (7.74)

in 85.24%, cutaneous manifestations occurring in 77.46%, musculoskeletal in 73.94%, renal in 67.61%, pulmonary in 47.88%, gastrointestinal (GI) in 45.07%, neuropsychiatric in 34.51%, and cardiovascular in 26.76% patients.

Among the constitutional symptoms, fatigue remains the most common symptom followed by mild febrile illness, malaise, and generalized weakness. Fever was present in more than half (53.52%) of the patients. Significant weight loss (>10% of the body weight over 6 months) was seen in 14.08% of the patients.

Malar rash was the most common LE-specific cutaneous manifestation, accounting for 54.92%, followed by discoid rash at 36.62%. Among LE nonspecific features, photosensitivity in 61.97% followed by nonscarring diffuse alopecia in 45.07%. The vasculitic rash was seen in 19.72% of the patients. Oral ulcers were seen in this study in 25.35% of the cases.

The most prevalent hematological abnormality was anemia, affecting 85.91% of the patients in the study group with a mean hemoglobin value of 9.5 mg/dL. Autoimmune hemolytic anemia was seen in 7.74% of them. Thrombocytopenia (<150,000/mm^3) was present in 44.37% (n = 63) of the patients and leukopenia (<4,000/mm^3) was present in 28.16%.

Musculoskeletal involvement was one of the common clinical manifestations, present in 73.94% of patients. The most frequent was nonerosive inflammatory polyarthritis similar to rheumatoid arthritis, seen in 61.97% of cases. Generalized myalgia was reported in 54.93% (n = 78) of the patients with one patient showing features of associated inflammatory myositis. Avascular necrosis was distinctly uncommon having been reported in only two patients.

Renal involvement was observed in 67.61% of patients. Proteinuria (>500 mg/24 hours) was found in 64.79% of patients, with 39.43% of patients having nephrotic range proteinuria (24-hour urine protein >3 gm). Renal biopsies were performed on 83 patients and classified as per the International Society of Nephrology and the Renal Pathology Society.[16] Diffuse lupus nephritis (class IV) was the most common histological pattern, seen in 52 patients (74.69%) followed by focal lupus nephritis (class III) in 21 patients (25.3%), mesangial proliferative lupus nephritis (class II) in 10.84%, and membranous lupus nephritis (class V) in 6.02% patients.

Cardiovascular manifestations are common in SLE patients during their course of illness. In the present study, 26.76% of patients had cardiovascular features.

Pericardial effusion was the most common feature reported in 19.01% of patients. Cardiac involvement due to cardiomyopathies, myocarditis and endocarditis was found in 7.74% of patients, all of whom were in severe condition.

Pulmonary involvement was seen in 47.88% of patients, with pleural effusion being the common feature in 39.44%, followed by pneumonitis in 5.63%.

The GI involvement was seen in 45.07% of patients. Amongst the GI manifestations, nonspecific symptoms such as abdominal pain, nausea, and occasional loose motions were the most common at 31.69%, followed by ascites at 21.12%. Abnormal liver enzymes (elevation of aspartate aminotransferase and alanine aminotransferase of more than three times) were observed in 11.27% of patients. Upper GI endoscopy was performed on 32 patients, with 18.31% having antral gastritis and 8.45% having esophageal candidiasis.

Nervous system involvement was seen in 34.51% of patients, with headache being the most common feature (27.46%), followed by acute confusional state (5.63%), stroke (4.22%), and seizure 3.52%. Magnetic resonance imaging (MRI) of the brain was performed in 20 patients, 13 of whom had features suggestive of central nervous system (CNS) vasculitis, two of whom had cerebral atrophy, and five of whom had a normal study.

Autoantibody Data

Regarding the prevalence of various antibodies, ANA was positive in 97.18% of patients. Four patients with negative ANA met more than four ACR criteria for SLE diagnosis. The mean ANA titre was 2236.4 ± 2643.89 (1:40–1:10240). The ANA pattern was mostly coarse speckled in 56. 52% of the 138 patients for whom data on ANA pattern was available. Ds DNA antibodies were found to be positive in 76.76% of the cases. Anti-SSA/Ro were positive in 54.34% ($n = 75$) of patients and anti-SSB/La in 25.36% ($n = 35$). Anti-Sm antibodies were prevalent in 43.28% of the studied population, anti-RNP antibodies in 36.95%, and anti-Ro52/TRIM21 in 34.78% (Table 3).

Table 3: Autoantibody titer and profiles of the patients ($n = 142$)

Autoantibody	*Frequency (%)*
ANA-IFA titer	138 (97.18)
1:80	43 (30.71)
1:160	39 (28.26)
1:320	29 (20.71)
>1:640	25 (17.85)
Anti-dsDNA	109 (76.76)
ANA reflex	
Anti–SSA/Ro60	75 (54.34)
Anti–Ro52/TRIM21	48 (34.78)
Anti–SSB/La	35 (25.36)
Anti–Sm	58 (43.28)
Anti–U1RNP	51 (36.95)
Anti–Rib–P0	38 (27.53)

ANA, antinuclear antibody; dsDNA, double-stranded DNA; IFA, immunofluorescence assay; RibP0, ribosomal P0; SSA, Sjögren's syndrome-related antigen A; SSB, Sjögren's syndrome-related antigen B; SmD1, Smith D1; TRIM21, tripartite motif-containing protein 21; U1RNP, U1-ribonucleoprotein

Discussion

The current study will provide an insight to the demographic, clinical and immunological profiles of SLE patients from Meghalaya, India's NE state. The NE region of India is a unique ethnological, sociocultural, and geographical transition zone between the Indian subcontinent. Epidemiological studies from nearby East/Southeast Asian countries with which the NE region shares ethnic and cultural similarities have documented a significant burden of autoimmune disease and serious organ manifestations, particularly lupus nephritis, which remain prevalent in this region. SLE predominantly affects women in child-bearing age with high female: male ratio in the third to fourth decade which is consistent with our findings. The frequency of occurrence of the lupus manifestations varies greatly between ethnic groups. A few similarities and differences have been observed when comparing this study to other studies from different racial and ethnic groups from different parts of India (Table 4).[17–22]

Table 4: Comparison of clinical features noted in the present study with other Indian studies

Clinical feature	*Present study N = 142 (Northeast India, Meghalaya)*	*Malaviya et al. n = 1,366 (Chennai, Mumbai, Kolkata, and Hyderabad)*	*Kosara et al. n = 48 (South India)*	*Saiga et al. N = 60 (Western India)*	*Agrawal et al. N = 87 (Central India)*	*Santhan et al. N = 100 (Chennai)*	*Kishor et al. N = 40 (Mangaluru)*	*Talukdar et al. N = 147 (Northeast India)*
Fever	53.52%	77%	58.33%	6.7%	82.8%	81%	55%	n.a.
Arthritis	61.97%	85%	64.58%	86.7%	52.9%	61%	33%	46.9%
Alopecia	45.07%	83%	18.75%	65%	10.34%	n.a.	n.a.	67.58%
Photosensitivity	61.97%	48%	27.08%	75%	63.2%	n.a.	7.5%	55.17%
Malar rash	54.92%	58.5%	35.41%	43.3%	71.3%	n.a.	12.5%	46.21%
Renal	67.61%	57%	20.83%	56.7%	69%	44%	58%	58.03%
Pulmonary	47.88%	n.a.	12.5%	11.7%	12.6%	11%	n.a.	n.a.
Cardiovascular	26.76%	22%	n.a.	6.7%	2.3%	29%	n.a.	n.a.
GI	45.07%	1.5%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Neuropsychiatric	34.51%	51%	8.33%	13.3%	4.6%	45%	5%	20%
Hemolytic anemia	7.74%	4%	0.002%	25%	8.1%	29%	7.5%	n.a.
Thrombocytopenia	44.37%	9%	n.a.	33.3%	14.9%	39%	48%	8.55%
Oral ulcer	25.35%	55%	25%	61.7%	42.53%	n.a.	15%	25.52%
ANA	97.18%	97%	64.28%	98.3%	97.7%	100%	n.a.	100%
Anti-dsDNA	76.76%	68%	89.36%	75%	93.9%	45%	43%	62.76%

Mucocutaneous and hematological involvements are the two most common features observed in this study. The cutaneous and hematological manifestations observed in previous reports from Asian cohorts ranged from 52–98 and 26–83.8%, respectively.[23] Photosensitivity and nonscarring alopecia, on the contrary, were found in a significantly higher proportion among SLE patients in NE compared to any other racial group. One possible cause of photosensitivity is the high altitude of the people living here 1,520 meters (4,990 ft) above sea level causing physiological exaggeration. Neuropsychiatric manifestations are found to be less in our study, the reason might have been due to the formal anxiety and depression scales were not used for evaluation, and many subclinical cases of neuropsychiatric symptoms were possibly missed. One notable finding is the high prevalence of GI, pulmonary, and renal involvement. Although GI symptoms can present in nearly half of SLE patients, they are rarely diagnosed due to the difficulty in determining the causes. In comparison to other studies outlined in Table 3, nearly half of the patients in our study had pulmonary involvement. Our study found that up to two-thirds of the patients had renal involvement, outnumbering another study by Malaviya et al., which is one of the largest epidemiology studies from India. Furthermore, pulmonary, cardiovascular and GI manifestations were not well studied in other cohorts, which is one of the strengths of our study.

Cardiovascular manifestations develop in many SLE patients during their illness. Pericarditis and pericardial effusion are the most common findings and most of them remain asymptomatic or have mild clinical symptoms that are detected during echocardiography. Heart failure remains a cause of high morbidity and mortality unless recognized early and adequately treated. Evidence suggests that immune complex deposition, complement activation, and subsequent inflammatory response are responsible for the cardiovascular manifestations of SLE.[24] According to a Cleveland Clinic study, while the frequency of diffuse alveolar hemorrhage (DAH) was found to range from 2 to 5.4%, it resulted in a mortality rate of 92%.[25] In this study, three patients were diagnosed with DAH during their course of illness and improved with active management. Although we lack comparable data, it is possible that we detected clinical signs earlier during the disease course that might have resulted in a better prognosis in our cohort.

Four patients (2.8%) tested negative for ANA and were diagnosed with SLE based on the criteria. Two separate studies by Gladman et al. and Ferreiro et al. reported a prevalence of approximately 5% of SLE cases that were ANA negative at the time of diagnosis.[26,27] This emphasizes the importance of relying on clinical judgment rather than existing criteria for diagnosis and management of SLE.

Conclusion

To conclude, we catalogue the clinical and immunological profiles of SLE cases diagnosed in our setup over a 5-year period. Our findings reiterate that clinical manifestations in our SLE cohort are similar to those found in other epidemiological studies in India. However, our patients have a high prevalence of hematological, mucocutaneous and renal manifestations. Owing to its chronicity and potential to cause life-threatening complications, a high degree of clinical suspicion is necessary for SLE diagnosis and management.

Ethical Statement

Ethical clearance was obtained from the Institute Vide letter No. NEIGR/IEC/M10/F5/2020 dated 14th May 2020.

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ORIGINAL ARTICLE

Bibliometric Analysis of the Highly Cited Articles on Biomarker Discovery for Irritable Bowel Syndrome from 1985 to 2023

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Abstract

Background: With an increasing number of patients with irritable bowel syndrome (IBS) and availability of many pharmacological treatment options, there is an urgent need to develop and validate IBS biomarkers for prognostication and selection of patients for treatment and monitoring. The usage of investigations is limited because of its invasive nature, poor patient acceptability, and sampling variability. The bibliometric analysis of biomarker discovery of IBS articles will help in understanding current research trends of biomarkers study of IBS.

Aim: To study the most highly cited articles from literature search on the biomarker for IBS to provide simple educational source.

Study design: A bibliometric literature review—the electronic search by terms and keywords were searched in PubMed databases. The commonly cited article was searched from 1985 to 2023. The total citation number was received from knowledge search engines like Google Scholar. Articles were classified according to number of citations, year of publication, journal name, authors, publications from continents of countries of origin, research hotspots, and article title. The articles written in English and other languages were included in the analysis.

Results: Total number of articles found was 1,449. The mean number of citations per article was 177. The citation count ranged from 24 to 1,191. The articles with citations >30 were included in the study. The majority of articles ($n = 175$) were published between 2016 and 2023. Among the highly cited articles, the most prevalent topic of interest was biomarker discovery. Most of the articles were original articles. The continent of origin for most of the articles was the United States of America ($n = 163$), Europe ($n = 145$), United Kingdom ($n = 23$), Asia ($n = 23$), Australia ($n = 14$), etc.

Conclusion: The analysis of articles on biomarker discovery for IBS will help in understanding the requirement for unmet need for the discovery of biomarker for IBS. The current bibliometric study has highlighted the work of authors with advanced knowledge about discovery of the biomarker for IBS. This study will help to identify the current trends in the biomarker discovery for IBS and help for the further evolution of the field.

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Introduction

In the current era of scientific knowledge publication, there is a digital predatory journal world.[1] Evaluative bibliometrics is a branch of quantitative science that assesses research performance using techniques such as citation analysis.[2] A highly cited article is one that is valued critically, is read extensively, and is utilized to support and defend research. Articles from 1920 to the present can be found in Scopus and other databases, such as Web of Science, which covers articles from 1980 to the present. The journal's contemporary history is covered by Web of Science. The ease of accessibility of articles from PubMed databases has been taken into consideration.[3] To measure the influence of research by looking at how many references an article receives over a period of time is the citation, and it gives the idea about the research value of that article.

Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal (GI) condition marked by irregularities in stool frequency[4] and shape, together with persistent stomach pain. IBS[5–8] affects approximately 11% of adults worldwide and is linked to a lower quality of life and more frequent use of healthcare services and it has a multifactorial underlying pathophysiology that includes altered intestinal permeability (IP), visceral hypersensitivity, microbial dysbiosis, mucosal inflammation, and dietary factors.[9] There is no mortality associated with IBS. IBS patients are classified into subgroups based on their primary bowel habits, which are determined by the consistency and form of their stool—IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with mixed (IBS-M).[10,11] The World Gastroenterology Organization estimates that IBS-D accounts for one-third of patients and IBS-C for up to one-third of cases.[12] IP requires the integrity of the intestinal barrier. The intestinal barrier is the dynamic system acting by humoral signals, and zonulin, acting as physiological modulator, can act as IR dysfunction biomarker. Research is needed to investigate the role of these IP biomarkers and their correlation with other etiological factors in IBS, as the role of zonulin and intestinal fatty acid-binding protein (I-FABP) as IP markers has not been thoroughly studied with large sample sizes to draw specific conclusions. The fundamental pathophysiology of IBS is thought to be caused by IP dysfunction, which is detectable by monitoring the levels of the biomarkers zonulin and I-FABP.[13] Therefore, we considered conducting bibliometric analysis of IBS articles' biomarker discovery, which will aid in the comprehension of IBS with regard to pathogenesis in early course and appropriate treatment decisions.

Aims and Objectives

Aim

To study the most highly cited articles from literature search on the biomarker for IBS to provide simple educational source of knowledge to treating physicians.

Objectives

- To search the most highly cited articles from literature search on biomarker discovery for IBS.
- To do bibliometric analysis with respect to number of citations, year of publication, journal name, authors, publication distribution of leading countries, and article title.

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Study Design

A bibliometric literature review—the electronic search was conducted by search terms and keywords selection "bibliometric analysis and IBS and biomarker or zonulin and I-FABP or zonulin or I-FABP," etc., and their input in PubMed databases. The commonly cited articles were searched from 1985 to 2023. We found total number of articles as 1,449 after initial search. The total citation number was received from knowledge search engines like Google Scholar. Articles were classified according to number of citations, year of publication, journal, authors, publications from which countries, and article title. The articles written in English and other languages were included in the analysis. Articles were analyzed and evaluated quantitatively. As this study was electronic search based, therefore, Ethical Committee approval was not sought.

Statistical Analysis

Statistical analysis was done qualitatively for qualitative data and quantitatively by mathematical tools. The data obtained was entered into the Excel sheet and used for analysis.

Results

The search found the mean number of citations per article to be 177. Citation count ranged from 24 to 1,191. The total number of articles receiving ±100 citations were 105, articles receiving 50–99 citations were 47, and number of articles receiving 30–49 citations was 20 (Fig. 1). The majority of articles (n = 175) were published between 2016 and 2023 (Fig. 2 and Table 1). Most commonly found articles were original articles followed by review and then minireview articles. The continent of origin for most of the articles was the United States of America (n =163), Europe (n = 145), United Kingdom (n = 23), Asia (n = 23), Australia (n = 14) (Fig. 3). The most frequently found journals contributing toward the search were PLOS One and Biochemistry (Fig. 4). Dr Alessio Fasano and Rhiannon MJ Snipe authors were most frequently found authors contributing toward research (Fig. 5).

Table 1: Year wise total number of citations received

S. no.	*Years*	*Total number of citations in PubMed**
1	1985–1995	26
2	1996–2005	80
3	2006–2015	147
4	2016–2023	175

*Citable literature included articles, reviews, editorials, and proceeding papers, etc.

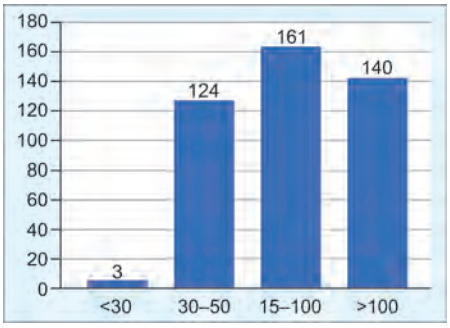

Fig. 1: Number of publications in citation wise

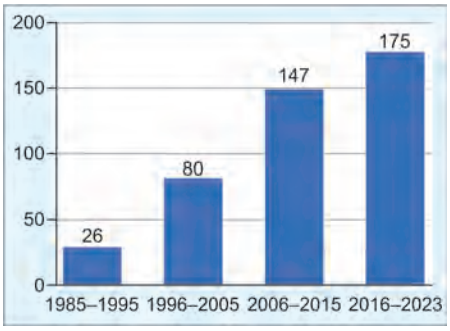

Fig. 2: Number of publications in year wise

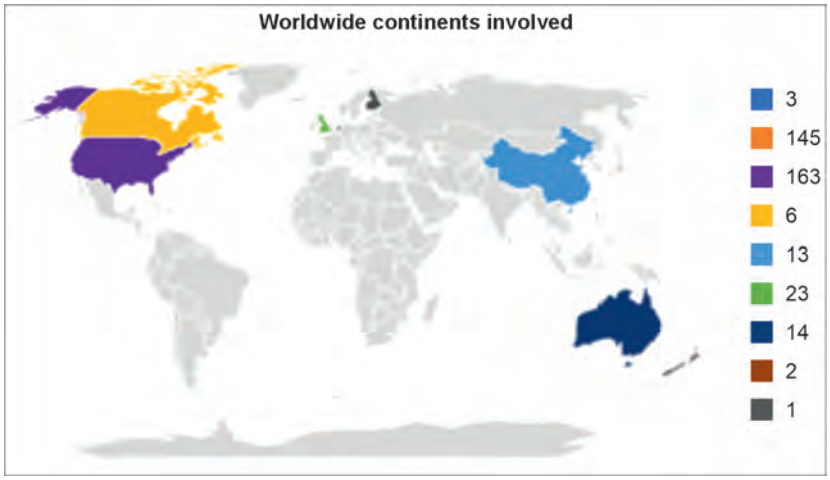

Fig. 3: Continent wise contribution

Discussion

Bibliometrics is a branch of informatics that measures the distribution, relationship, and clustering of the research field by taking the literature system and bibliometric characteristics under consideration as the research object. It is used to assess the credibility, quality, and impact of academic work.[14–16]

The published scientific evidence, which needs to have therapeutic application, is hard to evaluate since it is scattered among multiple sources, including books, journals, conference proceedings, and databases, and is not published in a systematic manner. The current state of the clinicians' knowledge of published research is, therefore, either inadequate or incomplete. By using bibliometric analysis to systematically combine various clinical research types, these problems can be resolved. This study's application can be utilized to apply clinical research knowledge to IBS[14,17] clinical and medical practices. A bibliometric analysis seeks to determine the scholarly impact and characteristics of publications within a particular research field by offering a cross-sectional view to provide insight into the current state of research work. Researchers working on developing research plans to address health issues describing advancements in various specialties and subspecialties may find this analysis to be helpful in providing information. This study will aid in highlighting the authors' contributions to the field of IBS biomarker discovery. The quality, discoveries, and trends[18] in the identification of IBS biomarkers will be identified with the aid of this study.

As far as we are aware, no bibliometric research has been done in the area of IBS biomarker identification. This study is based on the PubMed data collection in an effort to close this knowledge gap. Descriptive statistics were run after pertinent bibliometric data (articles, countries/regions, authors, institutions, journals, references, and keywords) for the IBS research field were retrieved. The majority of the articles, according to the analysis report, were published in developed countries, which suggests that these risk factors have

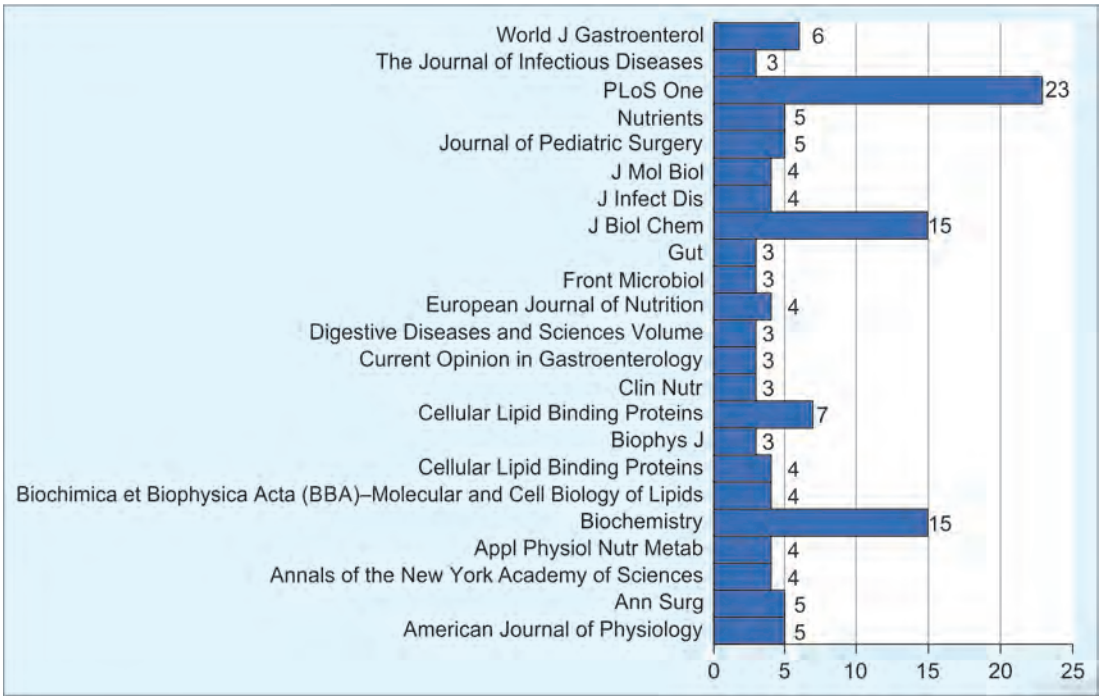

Fig. 4: Most frequently cited journal

Fig. 5: Authors wise contribution

epidemiological roots and may play a role in the pathophysiology of IBS. The majority of the publications in our analysis were released between 2016 and 2023, suggesting that the majority of the major epidemiological appearances of IBS biomarkers are only the tip of the iceberg. To the best of our knowledge, this is the first bibliographic study on the identification of IBS biomarkers. Through this research, we learned about publication trends, IBS distribution, literature related to biomarker discovery, highly cited articles in the field to be identified, bibliometric analysis to evaluate the history and current state of the field, publication distribution of leading nations and institutes, and IBS research hotspots.[19] To the best of our knowledge, no bibliometric system exists that has studied the IBS biomarker discovery.

Limitations

The literature search was done only from PubMed database, which was the limitation of our study. In future studies, databases such as Web of Science, Scopus, etc., can be used along with the analysis tools like Viewscore, etc., to add more updates.

Conclusion

The fundamentals of the IBS biomarker research were covered by our study. Understanding the unmet need for the discovery of a biomarker for IBS can be aided by analyzing the most important articles on the subject. This current bibliometric study highlighted the work of authors who have advanced knowledge about this biomarker discovery for IBS. The field will continue to evolve with the identification of current trends in IBS biomarker discovery. Our results could be useful in conceptualizing research priorities for subsequent studies. It offers insights into various scientific research vantage points that will support the development of evidence-based, individualized medicine practices in IBS.

Authors' Contribution

Conceptualization, data collection, analysis, and draft preparation.

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ORIGINAL ARTICLE

Safety and Efficacy of Golimumab in Indian Patients with Active Spondyloarthritis of Ankylosing Spondylitis or Psoriatic Arthritis: A Multicenter, Noncomparative, Open-Label, Real-World Study

Sundeep Upadhyaya[1], Uma Kumar[2], Srikantiah Chandrashekara[3], Venkataraman Krishnamurthy[4], Syamasis Bandyopadhyay[5], Ajit Surin[6], Liza Rajasekhar[7], Neeraj Jain[8], Ajit Nalawade[9], Sagar Panchal[10*], Nishita Shah[11], Tanuja Korde[12], Jitendra Dixit[13]

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Abstract

Background: The safety and efficacy of tumor necrosis factor-α (TNF-α) inhibitor therapy for most common rheumatological diseases, ankylosing spondylitis (AS), and psoriatic arthritis (PsA) in controlled clinical trials is well-studied. This study evaluated subcutaneous (SC) golimumab in Indian patients with active spondyloarthritis (SpA) of AS or PsA in a real-world setting.

Materials and methods: This phase 4, multicenter, prospective, non-comparative, interventional, 24-week study was performed in patients (age ≥18 years) with active SpA of AS or PsA (NCT03733925). Golimumab 50 mg was given subcutaneously to the patients every 4 weeks. Safety was assessed. The proportion of patients with AS and PsA achieving ≥20% improvement in the Assessment of SpA International Society 20 (ASAS20) criteria and American College of Rheumatology 20 (ACR20) responses, respectively, at weeks 14 and 24 were efficacy endpoints.

Results: Of the 100 patients enrolled (men: 78 [78.0%]; mean age: 36.7 [12.02] years), 94 (94.0%) patients completed the study. Treatment-emergent adverse events with golimumab were observed in 29/100 (29.0%) patients, and nasopharyngitis and upper respiratory tract infection (5.0% each) were the most common (≥5%). Deaths were not reported. At week 14, 74.5% (95% confidence interval [CI]: 59.7; 86.1%) of patients with AS and 84.6% (95% CI: 69.5; 94.1%) of patients with PsA achieved ASAS20 and ACR20 responses, which were sustained at week 24 (ASAS20: 66.0% [95% CI: 50.7, 79.1%]; ACR20: 93.2% [95% CI: 81.3, 98.6%]), respectively.

Conclusion: Golimumab (50 mg) administered subcutaneously was safe and effective in Indian patients with active SpA of AS or PsA during the 24-week study period with no new safety signals.

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Introduction

Spondyloarthritis (SpA) refers to a cluster of rheumatologic disorders that are usually seronegative for the rheumatoid factor and were earlier referred to as seronegative SpA.[1] Ankylosing spondylitis (AS), enteropathic arthritis, psoriatic arthritis (PsA), and reactive arthritis are the different forms of SpAs.[1,2] AS, a common form of SpA, is a chronic inflammatory disease that mostly affects the sacroiliac joints and spine.[1] Whereas PsA, which affects one-third of psoriasis patients, is a chronic immune condition affecting the entheses, nails, sacroiliac joints, axial skeleton, and peripheral joints.[3–7] The frequency of SpA globally varies between 0.20 and 1.61%, with almost similar rates in patients with AS (0.02–0.35%) and PsA (0.01–1%).[8,9] About 0.2% of Asians and 7–9/10,000 Indians have SpA.[8,10] The mainstay of treatment is nonsteroidal anti-inflammatory drugs, followed by conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), leflunomide, or sulfasalazine. Further therapy options in those with the persistent disease are biological (b) DMARDs including tumor necrosis factor-α (TNF-α), interleukin (IL) 17A, and IL-12/23 (skin involvement) inhibitors, and the targeted synthetic (ts) DMARDs (phosphodiesterase-4 and Janus kinase inhibitors).[11–13] Latest AS and PsA management guidelines recommend the use of bDMARDs or tsDMRDs as first-line biological therapy but current practice is to start with TNF-α or IL-17 inhibitors.[11,12]

Golimumab, a fully human immunoglobulin (Ig) G1κ monoclonal antibody, which has potent TNF-α antagonistic activity was licensed in Canada, United States, and Europe in 2009 as the first once-a-month subcutaneous (SC) injection, supplied as a prefilled syringe for injection in 50 and 100 mg doses indicated for AS, rheumatoid arthritis, and PsA.[14,15] In the GO-RAISE and GO-REVEAL randomized phase 3 studies, as well as their open-label 5-year extensions, the clinical efficacy and safety of golimumab SC injections in patients with AS and PsA was established globally.[16–19] To extend these study results, a few real-world observational studies reported SC golimumab to be safe and effective in patients with PsA and AS in clinical practice in other countries.[20–23] However, the real-world evidence to support the effectiveness of golimumab treatment for AS and PsA in India is lacking. This 24-week, postmarketing phase 4 study investigated the safety profile and therapeutic efficacy of SC golimumab in those with active SpA of AS or PsA in real-world clinical settings in India.

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Materials and Methods

Study Design and Patients

This 24-week, multicenter, phase 4, noncomparative, interventional, prospective, single-arm study (NCT03733925) was conducted at nine sites across India between 7th January 2019 and 15th November 2021. For each indication, 50% of patients were registered, consecutively. Adult men or women (aged ≥18 years) with active SpA of AS or PsA prior to the study initiation and no history of tuberculosis, and women who had tested negative for pregnancy were eligible. Confirmed diagnosis of AS per the Modified New York Criteria or PsA per the Classification criteria for PsA (CASPAR), for 6 months at least before the first dosing of the study intervention, and who had poor response to current or previous therapies (but biologic-naive) were eligible for inclusion. Patients who are allergic to human Ig proteins or any golimumab components, or who had a history of active or latent mycobacterial infections (tuberculosis or nontuberculous), or any serious infections including infected joint prosthesis, were excluded. Patients who had, or were anticipated to have any bacterial/viral vaccine (live) during 3 months prior to the administration of the medication, throughout the study, or in the 6 months following the last injection were also excluded. Pregnant or lactating women or those intending to be pregnant were not eligible.

According to the locally approved prescribing information, golimumab 50 mg was administered as an SC injection at week 0 and once monthly thereafter through week 24 using a single-use autoinjector on approximately the same date each month, with or without MTX (up to 25 mg/week) or other nonbiologic DMARDs. This post-marketing study was divided into screening, treatment, and follow-up phases (Fig. 1). The end-of-treatment (EOT) visit (time the last participant completed week 24 visit) and the end-of-study (EOS) visit (conducted in person or telephonically) were carried out 8 weeks post-EOT visit or after the final dose of the treatment, whichever was earlier, to evaluate the adverse events (AEs) observed in the patients.

Ethics Statement

The study was conducted per the New Drugs and Clinical Trials Rules 2019 India, the International Committee on Harmonization Good Clinical Practices, the Drug and Cosmetics Act, the Declaration of Helsinki, and any other applicable regulations (Clinical Trials Registry Number). Ethics committees or institutional review boards at the respective centers of the study approved the study protocol (CNTO148SPD4001). Enrolled patients signed written consent before undergoing any study-related procedures.

Safety

The occurrence of a treatment-emergent AE (TEAE)/serious AE (SAE) (clinical or lab safety event) was the primary endpoint. Hematological, biochemical, and other vital signs investigations were carried out at the physician's discretion and per established clinical practice. The frequency and proportion of AEs were observed for 24 weeks to assess their safety in a regular clinical practice setting. A *post hoc* analysis was performed to determine the prevalence of TEAEs in patients who had either golimumab alone or with MTX.

Efficacy

Efficacy endpoints included the percentage of patients with AS with a 20% improvement in the Assessment of SpA International Society 20 (ASAS20) criteria response, and the percentage of patients with PsA with a 20% improvement in the American College of Rheumatology 20 (ACR20) response criteria, at week 14 and 24. ASAS20 assessed four domains—patient global assessment of disease activity (PtGA) (0 [not active] to 10 [very active] unit numeric rating scale [NRS]), Bath AS functional index (BASFI)] (patient's level of mobility and functional ability on a scale of 0 [easy] to 10 [impossible] unit NRS), total back pain and inflammation from Bath ankylosing spondylitis disease activity index (BASDAI) (0 [none] to 10 [severe] unit NRS). An ACR20 responder is a patient who had ≥20% improvement in swollen joint count (SJC) and tender joint count (TJC), and ≥20% improvement in ≥3 of 5 criteria—patient's assessment of pain, health assessment questionnaire-disability index (HAQ-DI), PtGA, and physician's global assessment of disease activity (PhGA), C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR). *Post hoc* analysis was conducted to assess the responses in patients who received either golimumab alone or MTX with golimumab.

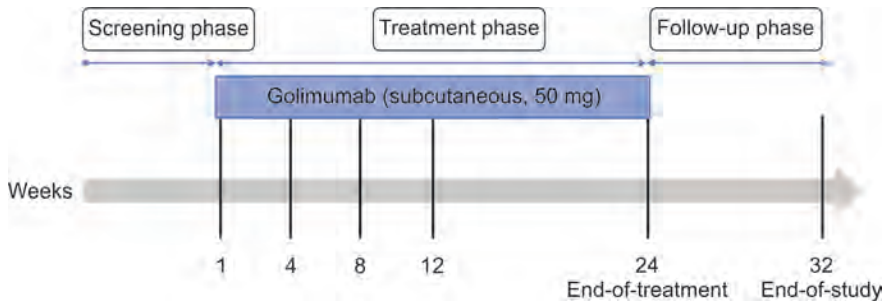

Fig. 1: Study design

Statistical Methods

Overall, 100 patients were enrolled to obtain measurable data. Safety was assessed on the safety analysis set (all patients who were enrolled and had ≥1 dose of the study medication) throughout the study. Medical Dictionary for Regulatory Activities (MedDRA), version 24.0, was used to code the TEAEs by system organ class (SOC) and preferred terms (PT). Efficacy assessments were carried out on the intent to treat (ITT) analysis set (all patients who were enrolled and had ≥1 dose of the study medication and completed week 24 visit). Responses at weeks 14 and 24 were calculated, along with a 95% CI individually for each indication, and were descriptively summarized. Frequencies and percentages were used to summarize categorical variables as appropriate.

Results

Patient Demographics and Disposition

Of the 100 Indian patients (AS: 50 [50.0%]; PsA: 50 [50.0%]) enrolled, 94 (94.0%) patients completed the study treatment while 6 patients (AS: 1 [1.0%]; PsA: 5 [5.0%]) discontinued the treatment. The reasons for discontinuation were adverse events and withdrawal by participants (2 [2.0%] patients each) and loss to follow-up and noncompliance with the study intervention (1 [1.0%] patient each). The mean (standard deviation [SD]) age of patients with AS and PsA was 32.1 (10.09) and 41.4 (12.06) years, respectively, and most were men. All patients received ≥1 dose of golimumab and recommended doses of ≥1 concomitant medication during the study including folic acid (61 [61.0%]) being the most common, followed by MTX (56 [56.0%]) and sulfasalazine (28 [28.0%]) (Table 1). The median (range) number of doses was 7 (2–7; AS: 4–7; PsA: 2–7) injections and 78/100 (78.0%) (AS: 43 [86.0%]; PsA: 35 [70%]) patients received all seven injections.

Safety

Overall, 29/100 (29.0%) patients experienced ≥1 TEAE. Of these the most common TEAEs (reported by ≥2% of patients) were nasopharyngitis and upper respiratory tract infection (RTI) (5.0% each), pyrexia and cough (4.0% each), diarrhea (3.0%), gastritis, dermatitis allergic, arthralgia, and back pain (2.0% each) (Table 2). One (1.0%)

patient-reported each of the remaining TEAEs. The severity of the majority of TEAEs was mild or moderate. TEAEs experienced by 6/100 (6.0%) patients were considered to be attributable to golimumab by the investigator. Overall, 4/100 (4.0%) patients reported SAEs, which included upper RTI, lower RTI (bacterial), abdominal pain, urinary tract infection (UTI), diarrhea, and irritable bowel syndrome (1.0% each). Four serious TEAEs, upper RTI, lower RTI (bacterial), UTI, and diarrhea were observed in 3/100 (3.0%) patients and were considered reasonably related to golimumab per the investigator.

Table 1: Patient demographics and baseline characteristics (safety analysis set)

Characteristics	*AS (n = 50)*	*PsA (n = 50)*	*Total (N = 100)*
Age, year			
Mean (SD)	32.1 (10.09)	41.4 (12.06)	36.7 (12.02)
Sex, *n* (%)			
Men	45 (90.0)	33 (66.0)	78 (78.0)
Women	5.0 (10.0)	17 (34.0)	22 (22.0)
Weight, kg			
Mean (SD)	65.01 (12.27)	69.09 (15.44)	67.05 (14.02)
Concomitant medication (≥25% patients), *n* (%)			
Sulfasalazine	26 (52.0)	2 (4.0)	28 (28.0)
Folic acid	19 (38.0)	42 (84.0)	61 (61.0)
MTX	16 (32.0)	40 (80.0)	56 (56.0)

AS, ankylosing spondylitis; BMI, body mass index; MTX, methotrexate; PsA, psoriatic arthritis; SC, subcutaneous; SD, standard deviation

Among the AS population, 11/50 (22.0%) patients had ≥1 TEAE; upper RTI and nasopharyngitis (4.0%, each) were the most common (>2% patients) among them. All the other TEAEs were reported by 1 (2.0%) patient, each (Table 2). TEAEs experienced by 1/50 (2.0%) patients were considered to be attributable to golimumab by the investigator. Two (4.0%) patients reported SAEs, which included UTI, abdominal pain, and irritable bowel syndrome (2.0% each). None of the TEAEs led to the discontinuation of study medication or participation. In the PsA population, 18/50 (36.0%) patients reported ≥1 TEAEs. Most common among them (reported by >2% of patients) were upper RTI, nasopharyngitis, cough, pyrexia, and diarrhea (6.0% each), and one (2.0%) patient-reported each of the remaining TEAEs (Table 2). TEAEs experienced by 5/50 (10.0%)

Table 2: TEAEs in ≥2% of patients (safety analysis set)

Characteristics, n (%)	*AS (n = 50)*	*PsA (n = 50)*	*Total (N = 100)*
TEAEs	11 (22.0)	18 (36.0)	29 (29.0)
Reasonably related TEAEs[a]	1 (2.0)	5 (10.0)	6 (6.0)
TEAEs leading to death[b]	0	0	0
TEAEs (serious)	2 (4.0)	2 (4.0)	4 (4.0)
Reasonably related TEAEs (serious)	1 (2.0)	2 (4.0)	3 (3.0)
TEAEs leading to discontinuation of study drug	0	2 (4.0)	2 (2.0)
TEAEs leading to termination of study participation	0	1 (2.0)	1 (1.0)
TEAEs of safety events of interest (special situations)	0	0	0
Infections and infestations			
Nasopharyngitis	2 (4.0)	3 (6.0)	5 (5.0)
Upper RTI	2 (4.0)	3 (6.0)	5 (5.0)
Gastrointestinal conditions			
Diarrhea	0	3 (6.0)	3 (3.0)
Gastritis	1 (2.0)	1 (2.0)	2 (2.0)
General and administration site disorders			
Pyrexia	1 (2.0)	3 (6.0)	4 (4.0)
Skin and SC tissue conditions			
Dermatitis allergic	1 (2.0)	1 (2.0)	2 (2.0)
Thoracic, respiratory, and mediastinal conditions			
Cough	1 (2.0)	3 (6.0)	4 (4.0)
Musculoskeletal and connective tissue conditions			
Back pain	1 (2.0)	1 (2.0)	2 (2.0)
Arthralgia	1 (2.0)	1 (2.0)	2 (2.0)
Nervous system conditions			
Headache	1 (2.0)	1 (2.0)	2 (2.0)
Kidney and urinary conditions			
Nephrolithiasis	1 (2.0)	1 (2.0)	2 (2.0)

[a]AE evaluated by the investigator as possibly, probably, or very likely related to study intervention, categorized as reasonably related; [b]AEs leading to death determined based on AE outcome of fatal; AE, adverse event; AS, ankylosing spondylitis; MedDRA, Medical Dictionary for Regulatory Activities; PsA, psoriatic arthritis; PT, preferred term; SAEs, serious adverse events; SC, subcutaneous; SOC, system organ class; TEAE, treatment-emergent adverse event; the population is counted only once for any given event. AEs are coded using MedDRA Version 23.0

patients were considered to be attributable to golimumab by the investigator. Two (4.0%) patients reported SAEs, which included upper RTI, lower RTI (bacterial), and diarrhea (2.0% each). Two (4.0%) patients who reported a TEAE discontinued the study drug and 1 patient (2.0%) the study participation. In both AS and PsA populations, clinically meaningful changes were not observed in physical examination assessments, vital sign measurements, hematology or clinical chemistry parameters, or other safety findings between baseline and week 24. No TEAEs of special interest or ≥3-grade toxicity were observed.

Post hoc analysis revealed 6/33 (18.2%) patients with AS and 4/10 (40.0%) patients with PsA who received golimumab alone, and 5/17 (29.4%) patients with AS and 14/40 (35.0%) patients with PsA on golimumab combined with MTX reported ≥1 TEAE. SAEs were reported in patients with AS on mono and combined therapy with MTX (1 patient each), but in patients with PsA, SAEs were observed only in those who had MTX with golimumab. There were no cases of death reported in this study.

Efficacy

The mean (SD) values of clinical outcome measures in the AS and PsA populations (Table 3) showed a continuous improvement at all postbaseline time points through week 14 and sustained through week 24, indicating a sustained benefit in disease symptoms. Among the patients with AS, 35/47 (74.5% [95% CI: 59.7%; 86.1%]) patients at week 14 and 31/47 (66.0% [95% CI: 50.7%; 79.1%]) patients at week 24 achieved ASAS20 response (Table 4). In patients with PsA, at week 14, 33/44 (84.6% [95% CI: 69.5%; 94.1%]) patients were ACR20 responders and at week 24, a higher percentage of patients (41/44 [93.2%], 95% CI: 81.3%; 98.6%) achieved ACR20 response when compared (Table 4).

During *post hoc* analysis, 12/17 (70.6% [95% CI: 44.0%; 89.7%]) patients with AS who received MTX with golimumab and 19/30 (63.3% [95% CI: 43.9%; 80.1%]) patients who got golimumab alone were ASAS20 responders at week 24. Among patients with PsA, all nine (100% [95% CI: 66.4%; 100%]) patients who received golimumab alone and 32/35 (91.4% [95% CI: 76.9%; 98.2%]) patients who received MTX with golimumab were ACR20 responders at week 24.

Discussion

This open-label, multicenter, interventional, noncomparative, single-arm, phase 4 study demonstrated the safety and efficacy of SC golimumab (50 mg) in adults with active SpA of AS or PsA up to 24 weeks in a real-world clinical setting in India. Response rates reported in this analysis illustrate the advantages of golimumab SC injection in Indian patients with SpA.

Out of the 100 patients enrolled, the majority of patients with AS (90%), as well as PsA (66%) were men, similar to global and real-world studies assessing SC golimumab.[18,19,21–23] The patients in AS and PsA populations were considerably younger than the patients in the reported global and real-world studies.[18,19,21–23] About 80% of the PsA population was on combination therapy (MTX and golimumab), which was considerably greater than that of the global GO-REVEAL study.[19]

The incidence of TEAEs reported in patients with AS in this study was in line with the global study.[18] Comparatively less proportion of patients with AS reported ≥1 TEAE than that of the GO-RAISE global study along with its extension study.[16,18] Nasopharyngitis and upper RTI were the most common reported AEs and consistent with the global study. The SAEs were observed in a few patients with AS (4%), and none of them led to discontinuation of the study medication. A comparatively higher percentage of patients with PsA reported ≥1 TEAE than patients with AS in this study; however, the proportion of events was lower than that reported in the GO-REVEAL global study along with its extension studies.[17,19,24] Upper RTI and nasopharyngitis were most common in the PsA population and were similar to the GO-REVEAL global study findings. AEs and SAEs leading to study medication discontinuation were reported in a very small proportion of patients with PsA (4% each). In the current study, the descriptive analysis showed that the frequency of TEAEs and SAEs was higher in patients with PsA vs AS. No new safety findings were reported in this study. In the *post hoc* analysis, the proportion of patients with AS experiencing TEAEs was higher among those who received golimumab with MTX, while the reverse was observed in patients with PsA. The safety findings of the current study are in line with the global studies suggesting that ethnic differences do not influence safety outcomes. Overall safety findings were consistent with reported real-world evidence of golimumab use in AS or PsA populations in other countries and the studies of other anti-TNF agents in patients with AS and PsA.[20–23,26–32]

Baseline scores of total pain, BASDAI, and PtGA in the AS population were comparable with the global phase 3 GO-RAISE study whereas the BASFI score was numerically higher in this study.[18] Efficacy endpoints, ASAS20, back pain, PtGA, inflammation, and BASFI scores suggested that golimumab-treated patients with AS had clinically significant improvements. In this study, a comparatively higher percentage of patients achieved ASAS20 response at week 24 than in the global study.[18] Efficacy results in the AS population were comparable to those reported in etanercept, infliximab, and adalimumab studies, although no data are available for direct comparisons.[26,33–35] Considerably high baseline scores of CRP levels, ESR, TJC, and SJC scores in the PsA population in this study, suggest severe disease. In patients with high CRP levels and severe spinal inflammation, benefits from anti-TNF treatment have been reported by Rudwaleit et al.[30] Results of ACR20, TJC, SJC, patient's assessment of pain, PtGA, PhGA, ESR, and CRP suggest that patients with PsA showed clinically meaningful improvements when treated with golimumab. A comparatively higher percentage of patients achieved ACR20 response than the GO-REVEAL global study at week 24. Efficacy results in patients with PsA were similar in magnitude to those of the observational real-world study of golimumab in Italy and the previous study of etanercept though data are not available for direct comparisons.[20,36] Substantial responses were observed early in week 4 and were sustained throughout week 24 in both AS and PsA patients. *Post hoc* analysis showed that a numerically higher proportion of patients in AS on combination therapy with MTX achieved an ASAS20 response at week 24 when compared to those on golimumab monotherapy (70.6 vs 63.3%). All patients (100%) with PsA who had golimumab as monotherapy and 91% of those who were on golimumab and MTX combined therapy achieved an ACR20 response. The limitations of the study were small sample size, absence of a control group, open-label study design, and short treatment duration. Furthermore, ACR50/70 response criteria were not assessed in this study.

To conclude, SC golimumab 50 mg was well-tolerated in Indian patients with no new safety findings. The safety profile of golimumab was consistent with the reported randomized-controlled global and real-world studies assessing SC golimumab. Furthermore, sustained, rapid, and meaningful improvements in clinical outcomes of SpA in patients with AS or PsA were observed in this postmarketing phase 4 real-world evidence study assessing the safety and efficacy of SC golimumab 50 mg in Indian clinical settings.

Table 3: Summary of clinical signs and symptoms (ITT analysis set)

Parameter	*SC golimumab 50 mg*
AS	*n = 47*
Patient's global assessment of disease activity	
Baseline score	7.81 (1.21)
Change from baseline	
At week 14	−3.78 (1.97)
At week 24	−4.96 (2.04)
Total back pain	
Baseline score	7.27 (1.59)
Change from baseline	
At week 14	−3.54 (2.00)
At week 24	−4.28 (2.38)
BASFI	
Baseline score	6.66 (1.92)
Change from baseline	
At week 14	−2.92 (2.29)
At week 24	−4.08 (2.15)
Inflammation (from BASDAI)	
Baseline score	6.80 (1.72)
Change from baseline	
At week 14	−3.07 (1.99)
At week 24	−4.31 (2.09)
PsA	*n = 45*
TJC	
Baseline score	9.00 (5.60)
Change from baseline	
At week 14	−3.40 (5.61)
At week 24	−5.40 (5.56)
SJC	
Baseline score	5.50 (4.55)
Change from baseline	
At week 14	−3.40 (3.21)
At week 24	−3.70 (3.63)
Patient's assessment of pain	
Baseline score	6.70 (1.47)
Change from baseline	
At week 14	−2.30 (2.43)
At week 24	−4.10 (2.50)
Patient's global assessment of disease activity	
Baseline score	68.50 (14.60)
Change from baseline	
At week 14	−27.80 (23.23)
At week 24	−40.30 (23.69)
Physician's global assessment of disease activity	
Baseline score	60.60 (14.61)
Change from baseline	
At week 14	−26.90 (23.56)
At week 24	− 38.80 (21.45)
HAQ	
Baseline score	66.40 (18.44)
Change from baseline	
At week 14	−22.20 (25.31)
At week 24	−40.20 (25.37)

Contd…

Contd…

Parameter	*SC golimumab 50 mg*
ESR, mm	
Baseline score	37.30 (33.74)
Change from baseline	
At week 14	−17.40 (32.19)
At week 24	−18.00 (30.28)
CRP, mg/L	
Baseline score	16.42 (21.28)
Change from baseline	
At week 14	−11.61 (22.01)
At week 24	−11.28 (20.69)

Values are expressed in mean (SD); Assessments were made using an NRS (0–10) scale ranging from 0 to 10, where 0 represents productivity not affected at all/no pain and 10 represents productivity affected very much/the worst pain imaginable unless specified; ACR, American College of Rheumatology 20% improvement criteria; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society 20% improvement criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; ITT, Intent to Treat; NRS, numeric rating scale; PsA, psoriatic arthritis; SC, subcutaneous; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count

Table 4: Summary of efficacy findings (ITT analysis set)

Parameter	*SC golimumab 50 mg*			
	AS (n = 47)		*PsA (n = 47)*	
	ASAS20	*95% CI*	*ACR20*	*95% CI*
Improvement from baseline				
Week 4	*n* = 44		*n* = 43	
Patients in response, *n* (%)	15 (34.1)	(20.5, 49.9)	26 (60.5)	(44.4, 75.0)
Week 14	*n* = 47		*n* = 39	
Patients in response, *n* (%)	35 (74.5)	(59.7, 86.1)	33 (84.6)	(69.5, 94.1)
Week 24	*n* = 47		*n* = 44	
Patients in response, *n* (%)	31 (66.0)	(50.7, 79.1)	41 (93.2)	(81.3, 98.6)

ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; ITT, intent to treat; PsA, psoriatic arthritis; SC, subcutaneous

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Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki 1964 and its later amendments.

Disclosures

Sundeep Kumar Upadhyaya serves on the advisory board, and speaker's bureau, and receives travel and scientific meeting expenses from Cipla, Eli Lilly, IPCA, Johnson & Johnson, Novartis, Pfizer, Roche, Torrent, and Zydus. Venkataraman Krishnamurthy serves on the advisory board and/or speaker's bureau and received honoraria from Abbott, Cipla, Eli Lilly, GSK, Johnson & Johnson, Microlabs, Novartis, Pfizer, Pfizer Upjohn, Pulse Pharma, Sun Croslands, and Zydus. Uma Kumar, Srikantiah Chandrashekara, Syamasis Bandyopadhyay, Ajit Surin, Liza Rajasekhar, Neeraj Jain, and Ajit Nalawade have no financial conflicts of interest to disclose. Sagar Panchal, Nishita Shah, Tanuja Korde, and Jitendra Dixit are employees of Johnson & Johnson Private Limited, India, and may own stock or stock options in Johnson & Johnson.

Author Contributions

All authors contributed to data analysis, drafting, or revising of the article, provided final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Sympathetic Neurofunction Testing in Gestational Hypertension and Relationship with Developing Preeclampsia and Eclampsia: Real-world Evidences from Clinical Pharmacology Clinics

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Abstract

Background: Gestational hypertension carries a high-risk for adverse maternal and fetal outcomes, and it can also develop into preeclampsia. A relative decrease in parasympathetic and increase in sympathetic activity has been seen in normal pregnancy which returns to baseline after delivery. The present study aimed to detect any abnormality in sympathetic neurofunction in gestational hypertension and to identify its possible association with the development of preeclampsia/eclampsia.

Methods: A prospective, observational study was carried out among gestational hypertensive patients between 24 and 26 weeks of gestation, who were sent to clinical pharmacology clinics for autonomic neurofunction testing, along with their 24-hour urinary protein testing reports. Preisometric handgrip (IHG) and post-IHG differences in diastolic blood pressure (DBP) were noted. The association between Δ DBP and the development of eclampsia/preeclampsia was probed.

Results: A total of 52 pregnancy-induced hypertension (PIH) participants, both multigravida ($n = 15$) and primigravida ($n = 37$) were included in one arm (PIH arm), and 52 matched (age and gravida) pregnant women, those do not have PIH included in another arm for comparative analysis. On comparing the PIH arm and normal arm, prehand grip DBP ($p \leq 0.0001$), posthand grip DBP, and Δ DBP were significantly higher in the PIH arm. Correlation between Δ DBP and 24 hours' proteinuria was observed in the PIH arm, with a significant positive correlation.

Conclusion: A high-rise in DBP post-IHG exercise is associated with gestational hypertensive mothers and this rise is strongly correlated with the development of preeclampsia and eclampsia, which suggests that addressing sympathetic hyperactivity could be a potential area to target therapeutics while managing gestational hypertension.

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Introduction

Gestational hypertension is a form of high blood pressure (BP) in pregnancy. Gestational hypertension carries a high-risk for adverse maternal and fetal outcomes, and it can also develop into preeclampsia. Pregnancy with high BP and related complications carries a high-risk for maternal and fetal mortality. Around 2–8% of pregnant mothers suffer from preeclampsia.[1] However, the incidence in India is as high as 8–10%.[2] Mothers with preeclampsia have an increased chance of cardiovascular diseases, premature death, type 2 diabetes mellitus, and hypothyroidism.[3] It had been seen that babies of preeclamptic mothers carried an increased risk of cardiovascular and metabolic disorders later in life.[4] High BP (>140/90 mm Hg) developed in pregnancy as measured on two separate occasions at least 4 hours apart after 20 weeks of gestation without proteinuria is defined as gestational hypertension. Whereas BP during pregestational time or before 20 weeks of gestation ≥140/90 mm Hg is defined as chronic hypertension in pregnancy. Preeclampsia is defined as gestational hypertension with proteinuria (300 mg or more per 24-hour urine collection or protein/creatinine ratio of 0.3 or more or dipstick reading of 2+ if other quantitative methods are not available) or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following as thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms.[5] A relative decrease in parasympathetic and an increase in sympathetic activity has been seen in normal pregnancy which returns to baseline after delivery. These changes related to autonomic neurofunction are very crucial for both fetal and maternal health. In the presence of preeclampsia, autonomic neurofunction had shown variable results. However, there exists a dearth of studies looking into autonomic neurofunction activity among pregnant mothers. The present study aimed to detect any abnormality in sympathetic neurofunction in gestational hypertension and to identify its possible association with the development of preeclampsia/eclampsia. The objectives of this study were thus to understand the difference between sympathetic system activity in gestational hypertension and normal pregnancy and to find any association between Δ DBP (measurement of sympathetic nervous system function) and the development of eclampsia/preeclampsia.

Methods

A prospective, observational study was carried out in a few private Clinical Pharmacology Clinics in Eastern India. Permission for the conduct of the study was obtained from the Institutional Ethics

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Committee. Written informed consent was obtained from all the participants consenting to be a part of the study. The study included gestational hypertensive patients between 24 and 26 weeks of gestation, who were sent to clinical pharmacology clinics for autonomic neurofunction testing, along with their 24-hour urinary protein testing reports. Basic demographics and 24-hour urine protein estimation results were noted for all participants. For neurofunction testing, mothers were advised to sit comfortably in chairs with their elbows flexed at 90° and resting on the side table. They were explained about the test procedure. The baseline BP was recorded by the CIRCA PRACTO digital BP monitor. Then they were instructed to grip the handgrip dynamometer using the maximal isometric force of the dominant hand. Measurements were noted three times 2 minutes apart. The maximum value of the three readings was considered the maximal voluntary contraction (MVC). Then a mark was given on the dynamometer at 30% of MVC of the mother and they were again instructed to maintain the sustained grip on the dynamometer up to the mark with uniform intensity till failure due to exhaustion or up to a maximum of 5 minutes. Preisometric handgrip (IHG) and post-IHG differences in diastolic blood pressure (DBP) were noted. As per the requirement for conducting this study, the concerned obstetrician also referred an age and gravida-matched cohort of normotensive pregnant mothers for the same neurofunction testing. Each patient was telephonically followed up by the obstetrician for information on the development of eclampsia or preeclampsia if any, after delivery of each pregnant mother. The association between Δ DBP and the development of eclampsia/preeclampsia was probed.

Data were checked for completeness and statistically analyzed. Descriptive data was represented as mean or percentages as applicable. Where applicable, hypothesis testing and measures of association have been analyzed using suitable statistical tests. Different levels were expressed at a 95% confidence interval. A p-value of <0.05 has been considered statistically significant. All Statistical analysis for various measures was performed using various statistical software packages like Statistical Package for the Social Sciences (SPSS) (Windows version 21.0; SPSS Inc, Chicago, Illinois, United States of America) and Microsoft Excel.

Results

A total of 52 pregnancy-induced hypertension (PIH) participants, both multigravida (n = 15) and primigravida (n = 37) were included in one arm (PIH arm), and 52 matched (age and gravida) pregnant women, those do not have PIH included in another arm for comparative analysis. Comparative analysis between the groups in terms of sociodemographic, comorbidity, laboratory, and clinical data, and their baseline matching was performed as depicted in Table 1.

It was observed that 38.46% (n = 20) of patients have preeclampsia among the PIH group (Fig. 1) and most are primigravida (70%). About 25% (n = 5) of participants developed eclampsia among preeclampsia patients, most being primigravida (80%). The percentage of patients who develop eclampsia among PIH patients was 9.6%. Body mass index (BMI) was in the higher range among preeclampsia patients (27.24 ± 9.23) in comparison to the total population (23.52 ± 2.54) in the PIH arm and the normal group (21.77 ± 2.06).

On comparing the PIH arm and the normal arm, it was observed that parameters like BMI (p = 0.0002), hypothyroidism (p = 0.0159), 24-hour proteinuria ($p \leq 0.0001$), prehand grip DBP ($p \leq 0.0001$), posthand grip DBP ($p \leq 0.0001$) and Δ DBP ($p \leq 0.0001$) are significantly higher in PIH arm. On the contrary, no significant difference was observed in socioeconomic status, lifestyle, tobacco usage, hemoglobin, and fasting blood glucose levels in the PIH arm, when compared to the normal arm. Correlation between Δ DBP and 24 hours' proteinuria was observed in the PIH arm, with a significant positive correlation (R = 0.787, $p \leq 0.00001$) (Fig. 2), signifying high Δ DBP with increasing proteinuria level.

Discussion

The pathophysiology of preeclampsia is not clearly understood. Placental dysfunction could play a pivotal role in the development

Table 1: Shows baseline matching, sociodemographic and comorbidity(s), laboratory and clinical characteristics of study participants (n = 104)

Parameters	*PIH arm (n = 52) mean (SD)*	*Matched arm (n = 52) mean (SD)*	*p-value*
Matching criteria			
Age	25.25 (3.75)	25.25 (3.75)	1.0000
Gravida (P/M)	37/15	37/15	1.0000
Sociodemographic criteria/comorbidity			
BMI	23.52 (2.54)	21.77 (2.06)	0.0002
Socioeconomic status (L/M/H)	20/22/10	17/22/13	0.1158
Lifestyle (HW/Wo)	42/10	44/8	0.7961
Tobacco user	7	2	0.1603
Overweight	10	3	0.0721
Hypothyroid	9	1	0.0159
Laboratory criteria			
Hemoglobin (%)	10.69 (0.67)	10.67 (0.76)	0.9024
Fasting blood sugar	88.23 (7.37)	88.27 (7.99)	0.9797
24-hour proteinuria	292.13 (147.32)	183.63 (40.66)	0.0001
Clinical criteria			
Prehandgrip DBP	94.73 (4.12)	68.87 (5.27)	0.0001
Posthandgrip DBP	130.67 (5.95)	90.60 (5.60)	0.0001
Δ DBP	35.94 (4.83)	21.54 (3.21)	0.0001

BMI, body mass index; DBP, diastolic blood pressure; H, high-income group; HW, housewife; L, low-income group; M, multigravida; M, middle-income group; P, primigravida; PIH, pregnancy-induced hypertension; SD, standard deviation; Wo, working; statistic applied Fischer exact test and unpaired t-test, level of significance at 0.05(p); *, means significance

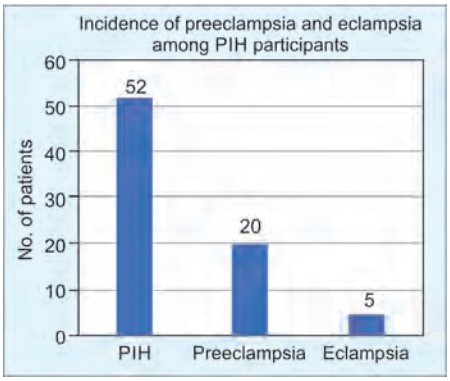

Fig. 1: Incidence of preeclampsia and eclampsia among PIH participants

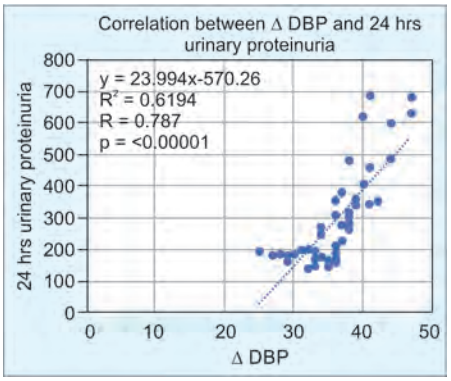

Fig. 2: Association between Δ DBP and 24-hour urinary proteinuria

of preeclampsia.[6] Reduced adaptive capability of the uteroplacental unit vasculature following placental ischemia, and diminished reperfusion are resulted from placental dysfunction. In adaptive physiology modifying cardiovascular function autonomic nervous system (ANS) has a prominent role to play.[7] A relative decrease in parasympathetic and an increase in sympathetic activity has been seen in normal pregnancy which returns to baseline after delivery. These changes related to autonomic neurofunction are crucial to optimizing uteroplacental blood flow.[8,9] In the presence of preeclampsia autonomic neurofunction had shown contradictory results. One heart rate variability study with mothers suffering from preeclampsia had shown increased sympathetic activity and reduced parasympathetic activity.[10] Another prospective observational study by Lakhno depicted a gradual increase in mean sympathovagal balance (LF/HF) with the progredient severity of preeclampsia even when mothers were consuming BP-lowering drugs.[11] Six studies comprising orthostatic tests had shown high sympathetic and low parasympathetic functions in preeclamptic mothers compared to normotensive mothers.[12–17] Two research studies conducted to evaluate changes in biomarkers had reported significantly raised catecholamine levels in preeclampsia mothers when compared to the healthy control group.[18,19] Contrary to these results in five studies where cardiac baroreflex gain was assessed three had shown that mothers with preeclampsia exhibited significant reduction in baroreflex gain but two of them did not show any decline.[20–22] One systematic review on autonomic dysfunction found that dysautonomia was a common feature in preeclamptic mothers which was characterized by elevated sympathetic tone, reduced parasympathetic tone, and reduced baroreflex gain.[23] Preeclampsia mothers have a twofold higher risk of cardiovascular and cerebrovascular disease where cardiac autonomic neuropathy might be responsible.[24]

Isometric exercise produces a potent somatosympathetic reflex. This results in tachycardia, and increased systolic blood pressure (SBP) and DBP. Cardiac output, left ventricular contractility, peripheral vascular resistance, muscle sympathetic nerve activity, and plasma catecholamine levels are also elevated.[25–27] IHG exercise is an important, convenient, and acceptable way to elicit cardiac autonomic function. Ewing et al. depicted a significant correlation between IHG and the DBP rise in both normal and diabetic participants. Impairment of sympathetic function is denoted by a subnormal increase in DBP.[28]

While exercising there is an elevation of lactic acid and adenosine which increase the activity of metaboreceptor afferent fibers and produce a potent reflex by increasing sympathetic nerve activity and elevation of BP.[29] This elevated BP returns to normal levels within 5 minutes of stopping exercise normally. In one study it was found that young normotensive subjects with a history of hypertension in their father and mother there was having significantly higher systolic and DBP responses following isometric exercise.[30] In another study by Krzeminski et al. it was shown that increases in both the systolic and the DBPs with the IHG exercise were significantly high with sympathetic overactivity.[31] Post 5 minutes or at the end of the IHG test, the rise in DBP ≥16 mm Hg is noted as a normal function. If the difference between pre- and post-IHG DBP is <10 mm Hg then there is sympathetic autonomic dysfunction and if it is between 10 mm Hg to 16 mm Hg then there is borderline sympathetic autonomic dysfunction. There is no universal consensus DBP rise measurement suggestive of sympathetic over activity.

In our study, we have found that a high rise in DBP post-IHG exercise is associated with gestational hypertensive mothers and this rise is strongly correlated with the development of preeclampsia and eclampsia, which suggested that addressing sympathetic hyperactivity could be a potential area to target therapeutics while managing gestational hypertension. We need a detailed study to search the potential beneficial effect of drugs like labetalol which also targets hyperactivity of the sympathetic nervous system compared to drugs like nifedipine which cause potential vasodilation leading to reflex tachycardia and indirect further stimulation of already hyperactive sympathetic nervous system.

However, the study is not devoid of limitations. During ANS we could not perform the Valsalva test or deep breathing exercise to check parasympathetic nervous system activity as the COVID-19 pandemic had restricted us from these high-risk respiratory droplet-producing maneuvers which carried the risk of infection to our research participants. Future research should include a battery of parasympathetic nervous system tests to overcome this limitation.

Conclusion

To understand sympathetic ANS activity IHG exercise and DBP change estimation could be a potential tool used in clinical pharmacology clinics which could help obstetricians identify high-risk gestational hypertensive patients and reconcile, review, and provide feedback regarding optimizing therapeutic care.

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ORIGINAL ARTICLE

Impact of Using Global Lung Initiative Race-neutral Equations for Chronic Respiratory Disease in Western India

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Abstract

The Global Lung Initiative (GLI) race-neutral equations are considered to be race agnostic, using inverse probability weight, and have lower limits of normality (LLN) different from the GLI mixed equations.

In this observational study, we analyzed the impact of using GLI equations to interpret spirometry of 1,169 patients with chronic respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), COPD suspects, small airway obstruction, posttubercular lung disease, and preserved ratio with impaired spirometry (PRISm) (46% females, average age 46 years).

Predicted normal and the LLN using GLI equations were significantly higher than those using Indian equations. The GLI race-neutral equations changed the category in 35.17% of males and 42.64% of females compared to Indian equations. The GLI mixed equations categorized a greater percentage of patients to have a mixed ventilatory pattern compared to the GLI race-neutral equations. There was a significant change in the grading of the severity of COPD using Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages based on the percentage of predicted values of FEV1.

Although GLI race-neutral equations have greater concordance with Indian equations than GLI Mixed equations, these substantially overdiagnose abnormal ventilatory patterns on spirometry in adult Indians in western India with chronic respiratory disease. A substantial number of patients with normal or obstructive patterns on spirometry are recategorized to have mixed or restrictive patterns. The use of GLI race-neutral equations increases the severity of airflow limitation in COPD patients. GLI race-neutral predictions for FEV1 result in substantially fewer patients demonstrating postbronchodilator responsiveness (PBDR).

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Introduction

Spirometry is the cornerstone of the diagnosis and management of chronic respiratory disorders. The procedure of performing the investigation has been standardized, and a guideline exists to ensure uniformity.[1] Interpretation of spirometry involves comparing the measured parameters like forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and the ratio of FEV1/FVC with reference predicted values. The reference values are calculated from reference equations and are based not just on age, sex, and height but also on the ethnicity of persons. The importance of ethnicity in determining normal values of lung functions has led to hundreds of equations being published all over the world as respiratory physicians interpret spirometry reports based on equations specific to their patients' country/ ethnicity.[2]

In 2012, the Global Lung Initiative (GLI) reported normative reference values derived from 72 centers in 33 countries. The reference equations were derived for healthy persons aged 3–95 years and were principally for European-Americans, African-Americans, and North and South East Asian populations. At the time, India was highlighted as a particular group in whom further data was needed. A composite equation, an average of the four equations annotated GLI mixed, was provided to facilitate interpretation in individuals not represented by the four ethnic groups. GLI mixed equations have been found to overestimate lung functions in the Indian population and have limited applicability in Indian patients.[3,4]

Although race has been an important determinant of reference values of lung function, there is an ongoing debate about being race-agnostic while predicting normal values of lung function parameters for individuals. The recently published GLI Global equations are a step forward in this direction. The GLI global equations, or the "race-neutral" equations, are derived from the same data points as the GLI equations of 2012. However, the race-neutral equations do not include race as a determinant of predicted lung function. An inverse probability weight was applied to each observation based on the race/ethnicity of the individual within the original data, serving to increase the relative contribution of underrepresented groups.[2,5]

In this study, we evaluated the impact of using GLI race-neutral equations in patients with chronic respiratory disease in Western India. We also evaluated the impact of using these equations in grading the severity of patients with chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.[6] The technical standards on interpretative strategies for routine lung function tests suggest a new criterion for identifying postbronchodilator responsiveness (PBDR) based on GLI equations.[7] We evaluated the impact of this change on identifying PBDR in Indian patients.

Materials and Methods

Study population

We included clinical records of patients who had followed up in our outpatient department at the Department of Pulmonary Medicine and Environmental Pollution Research Centre during the period from January 2020 to January 2023 and performed spirometry as a part of routine clinical evaluation. Clinical records of all patients performing spirometry are stored in our pulmonary function laboratory and include demographic details, history of illness, symptoms during the 3 months preceding the test and examination, and radiographic findings. We included patients aged 18–65 years to compare the Indian equation with other equations. For assessing the impact on PBDR, patients younger than 18 and older than 65 years were also included.

We restricted the study to include patients diagnosed to have one of the

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following conditions—asthma, COPD, preserved ratio with impaired spirometry (PRISm), small airway obstruction (SAO), patients suspected to have COPD, and patients with posttubercular lung disease. Asthma is diagnosed at our center as per the Global Initiative for Asthma (GINA) guidelines, COPD according to GOLD, and patients who have risk factors for COPD and symptoms compatible with COPD with FEV1 of <80% predicted but postbronchodilator FEV1/FVC ratio of >0.7 are labeled to have PRISm.[6,8,9] Patients who have risk factors of COPD and symptoms compatible with COPD, with no other discernible disease, are labeled "suspected COPD," while maximal mid-expiratory flow rates <65% predicted are suggestive of small airway obstruction.[10] The cohort of "posttubercular lung disease" consists of patients who have a history of pulmonary or pleural tuberculosis (TB) and who have persistent respiratory symptoms despite successful treatment of TB.[11,12] Patients with other respiratory disorders, missing records and an exacerbation within preceding 3 months were excluded. The severity of asthma and COPD are graded at our center as per standard protocol. The study was approved by the Institutional Ethics Committee at Seth GS Medical College, and a waiver of consent was granted due to the retrospective nature and absence of direct patient contact.

Spirometry and Reference Equations

Spirometry is performed at our center according to ATS guidelines using the Jaeger MasterScreen machine.[1] Either 5 mg of nebulized salbutamol or 400 µg delivered through a metered dose inhaler is used to assess PBDR. Only acceptable tests as per ATS criteria are reported. We use reference equations for the Indian population for the age group 18–65 years. The European Community for Steel and Coal (ECSC) equations with correction factors incorporated for the Indian population are used for the age group 65–70 years.[13–15]

Four different equations have been formulated by Udwadia et al. to predict normal lung functions in individuals in Western India. There are separate equations for males and females. These have been further subdivided on the basis of age—there are different equations for individuals aged less than and >30 years, respectively. The division based on age is due to the finding that normal lung function values increase till 30 years and decline subsequently. All four equations were analyzed separately in this study.[14]

The predicted values derived from modified ECSC equations, GLI mixed and GLI race-neutral equations, were compared to those calculated using Indian equations. We then assessed the agreement between the interpretation of spirometry using lower limits of normal (LLN) of each equation. The LLN values are based on the fifth percentile value (predicted value minus 1.654 times the standard error of estimate). The GLI mixed and GLI race-neutral predicted values were obtained by using the GLI calculator.[3,16]

Spirometry data were analyzed using Indian, modified ECSC, GLI mixed, and GLI race-neutral equations, and patients classified into one of the four ventilatory patterns—normal if FEV1/FVC and FVC were ≥LLN; obstructive if FEV1/FVC < LLN but FVC ≥ LLN; restrictive if FEV1/FVC ≥ LLN but FVC < LLN and mixed if both FEV1/FVC and FVC < LLN. Although body volumes are mandatory to confirm restriction, FVC < LLN suggests restriction, and for the purpose of this study, we used that guide to classify restriction.[17] Percent of predicted values were used to classify severity as per GOLD criteria.[6]

Statistical Analysis

Categorial and continuous variables are expressed as percentage and mean ± standard deviation, respectively. Data were checked for normality with Shapiro–Wilk and Kolmogorov–Smirnoff tests. Predicted FVC, FEV1, and FEV1/FVC ratio derived from the various equations were compared using analysis of variance (ANOVA) with Tukey's multiple comparisons *post hoc* test for normal data and Kruskal–Wallis test with Dunn's *post hoc* test for skewed distributions. The Chi-squared test was used to compare the ventilatory patterns derived by using the LLN of equations studied. When the expected value in >20% cells was <5, the Fisher exact test for the 4 × 4 contingency table was used. Agreement between measurements was evaluated using *K*-values for nominal variables and using Bland–Altman analysis for continuous variables. Bias and limits of agreement were calculated for Bland-Alman analysis. *K*-values were interpreted as per standard recommendation. Statistical significance was set at $p < 0.05$.[18]

Results

Records of 1,169 patients were analyzed in this study (Table 1). Of these, 928 patients were in the age group of 18–65 years, and their data were used to compare predicted and percent predicted FVC, FEV1/FVC, and FEV1 values. All the patients' records were included to compare PBDR.

Predicted Values

Significant differences were found in the predicted spirometry parameters calculated using the four equations (Table 2). GLI race-neutral and GLI mixed predictions for FVC were higher than Indian equations by 20.5 and 21.9% in males, 24.49 and 25.7% in females aged <30 years, and by 19.12 and 19.7% in males and 19.57 and 20% in females aged between 30 and 65 years, respectively. Predicted values for FEV1 were higher by 24.18 and 24.5% in males and 26.6 and 26.73% in females aged <30 years and by 30.93% in males and 33.5 and 32.95% in females aged between 30 and 65 years. The predicted values calculated by applying correction factors to ECSC equations were closer to the Indian values than the GLI equations. The FEV1/FVC values predicted by the GLI race-neutral and GLI mixed equations were higher by 2.3 and 2.6% in males and 4.76% in females aged <30 years, and by 3.7 and 3.8% in males and 5.06% in females in the 18–65 years age group, respectively.

Percent Predicted Values

Spirometry parameters, expressed as a percentage of predicted values by the equations, had significant differences (ANOVA, $p < 0.01$) (Table 3) except for the FEV1/FVC ratio in males younger than 30 years. Both the GLI equations yielded significant percentages of predicted values compared to the Indian equations.

Lower Limits of Normal

The LLN spirometry parameters calculated from all four equations differed significantly (ANOVA, $p < 0.01$). The LLN calculated using both the GLI equations were significantly higher than the Indian equations for FVC, FEV1, and FEV1/FVC (ANOVA with Tukey's *post hoc* analysis, $p < 0.01$). The LLN calculated using GLI race-neutral equations were significantly lower than GLI mixed equations except those for FEV1/FVC in females younger than 30 years and FEV1 in males younger than 30 years.

Agreement between the Percentage of Predicted Values

The Bland-Altman analysis of agreement of percentages of predicted values calculated using Indian equations with those obtained with the GLI equations and the ECSC equations with a correction factor employed is depicted in Table 4. The agreement was not

Table 1: Baseline characteristics of the study population

Diagnosis	*All; N = 1169*	*COPD*				*PRISm; N = 57*	*COPD suspects; N = 29*	*Asthma*				*SAO; N = 41*	*Post-TB lung disease; N = 237*
		GOLD 1; N = 36	*GOLD 2; N = 127*	*GOLD 3; N = 95*	*GOLD 4; N = 19*			*Intermittent; N = 17*	*Mild persistent; N = 402*	*Moderate persistent; N = 69*	*Severe persistent; N = 40*		
Age, years	46.5 ± 17.4	62 ± 11	60.5 ± 11.3	59.3 ± 11.3	54± 15	58 ± 10.8	69.3 ± 5.8	39.4 ± 13.9	35.9 ± 15.2	38.1 ± 16	46.3 ± 17.6	54 ± 11.7	44.7 ± 14.7
Sex, female (%)	541 (46.2)	3 (8.3)	37 (29.1)	22 (23)	4 (21)	33 (57.8)	12 (41.3)	11 (64.7)	221 (54.9)	35 (50.7)	23 (57.5)	20 (48.7)	120 (50.6)
Height, m	159 ± 9.68	162.6 ± 11.4	160 ± 8	161.2 ± 8.9)	163.4 ± 7.1	157.2 ± 9	155.4 ± 8.5	155 ± 7.8	159.2 ± 10.26	156.9 ± 10	156.7 ± 10.9	156.9 ± 7.6	159 ± 10.2
Weight, kg	56.9 ± 13	55.2± 10.7	56.8 ± 11	54.5 ± 13.7	51.7 ± 14.2	63.3 ± 13.8	59.2 ± 11.2	56.7 ± 14.4	58.8 ± 12.47	56.43 ± 16.4	55.3 ± 15.8	61.6± 11.2	53.5 ± 12.6
Presence of cough (%)	579 (49.5)	9 (25)	66 (52)	46 (48.4)	9 (47.4)	29 (50.8)	11 (37.9)	0	229 (56.9)	47 (68.1)	25 (62.5)	16 (39)	92 (38.8)
Presence of breathlessness (%)	833 (71.3)	16 (44.4)	98 (77)	89 (93.6)	18 (94.7)	47 (82.5)	14 (48.3)	0	303 (75.4)	63 (91.3)	38 (95)	25 (60.97)	122 (51.5)
mMRC grade	1	2	1	2	1	2	1	–	1	1	1	1	1
Presence of allergic rhinitis (%)	264 (22.5)	1 (2.8)	5 (3.93)	3 (3.2)	1 (5.26)	6 (10.5)	0	0	193 (48)	25 (36.2)	11 (27.5)	2 (4.8)	17 (7.17)
History of smoking (%)	216 (18.5)	16 (44.4)	52 (40.94)	47 (49.5)	6 (31.5)	13 (22.8)	10 (34.5)	0	24 (5.97)	4 (5.8)	3 (7.5)	13 (31.7)	27 (11.4)
Biomass fuel smoke exposure (%)	219 (18.7)	2 (5.5)	23 (18.1)	17(17.9)	3 (15.8)	25 (43.8)	12 (41.4)	0	55 (13.68)	13 (18.8)	11 (27.5)	14 (34.1)	43 (18.1)
Dust exposure (%)	101 (8.6)	3 (8.3)	18 (14)	13 (13.7)	3 (15.8)	6 (10.5)	3 (10.3)	0	31 (7.7)	3 (4.35)	9 (22.5)	0	13 (5.49)
Normal chest radiograph (%)	458 (39.2)	11 (30.5)	78 (61.4)	14 (14.7)	5 (26.3)	20 (35)	12 (41.4)	10(58.8)	254 (63.2)	37 (53.6)	14 (35)	23 (56)	33 (13.9)
Normal auscultation (%)	841 (71.9)	27 (75)	25 (19.6)	41 (43)	11 (57)	43 (75)	24 (82.7)	15 (88.2)	350 (87)	52 (75.4)	22 (55)	31 (75.6)	147 (62)
Presence of comorbidities (%)	189 (16.2)	5 (13.8)	27 (21.2)	21 (22)	4 (21)	18 (31.5)	13 (44.8)	2 (11.7)	37 (9.2)	10 (14.4)	5 (12.5)	9 (21.9)	38 (16)
History of pulmonary TB (%)	409 (34.9)	19 (52.7)	56 (44)	43 (43.8)	11 (57)	6 (10.5)	1 (3.4)	1 (5.8)	20 (4.9)	4 (5.7)	6 (15)	5 (12)	237 (100)

satisfactory, with a large bias and wide limits of agreement at a 95% confidence level.

Analysis of Ventilatory Patterns

There were significant differences in the ventilatory patterns as interpreted using the Indian equations compared to the other equations. (Fig. 1 and Table 5) The GLI race-neutral equations categorized 35.17% males and 42.64% females differently compared to the Indian equations. The GLI mixed equations categorized 45.79% males and 57.77% females differently than Indian equations. The differences in categorization were the least with ECSC equations, with the category changing in 24.55% males and 74.57% females compared to Indian equations. Patients with obstructive and normal patterns based on Indian equations were categorized to have mixed or restrictive patterns as per both GLI equations. The GLI mixed equations categorized a greater percentage of patients to have a mixed ventilatory pattern compared to the GLI race-neutral equations.

Analysis of Stages of Chronic Obstructive Pulmonary Disease

There was a significant change in the grading of severity of COPD using GOLD stages based on the percentage of predicted values of FEV1, both in males (Chi-square, $p < 0.001$) and females (Fisher exact test, $p < 0.001$) on switching from Indian to GLI race-neutral equations. The stage increased by using GLI race-neutral equations (Fig. 2).

Postbronchodilator Responsiveness

Applying the new criteria to diagnose PBDR led to a significant decline in the percentage of patients classified to have bronchodilator responsiveness (Chi-squared test, $p < 0.001$). In patients with asthma, the patients with PBDR decreased from 38 to 30% when the new criteria were applied (Fig. 3).

Discussion

This study demonstrated that the GLI equations lead to substantially higher predictions for spirometry parameters compared to Indian equations. The LLN using these equations are substantially higher, leading to significantly different categorization of ventilatory abnormality patterns in patients with chronic respiratory disease.

Table 2: Comparison of predicted spirometry parameters using Indian, ECSC, and two GLI equations

	Indian equations			*GLI race-neutral*			*GLI mixed*			*ECSC*		
	Mean ± SD	*95% CI*	*Median (IQR)*	*Mean ± SD*	*95% CI*	*Median (IQR)*	*Mean ± SD*	*95% CI*	*Median (IQR)*	*Mean ± SD*	*95% CI*	*Median (IQR)*
Males <30 years												
FVC, L*	3.65 ± 0.46+#	3.55–3.76	3.75 (0.59)	4.4 ± 0.59	4.27–4.53	4.51 (0.79)	4.45 ± 0.53	4.33–4.57	4.53 (0.70)	3.62 ± 0.36	3.54–3.7	3.65 (0.44)
FEV1, L*	3.06 ± 0.34+#^	2.98–3.14	3.11 (0.44)	3.8 ± 0.46	3.69–3.9	3.87 (0.63)	3.81 ± 0.42	3.72–3.91	3.88 (0.57)	3.53 ± 0.35	3.46–3.61	3.59 (0.46)
FEV1/FVC ratio*+	0.84 ± 0.02#^	0.836–0.843	0.838 (0.02)	0.86 ± 0.012	0.859–0.864	0.862 (0.014)	0.862 ± 0.011	0.859–0.864	0.86 (0.017)	0.829 ± 0.006	0.827–0.83	0.829 (0.01)
Males ≥30 years												
FVC, L*	3.19 ± 0.46+#^	3.14–3.24	3.2 (0.6)	3.8 ± 0.54	3.75–3.86	3.78 (0.717)	3.82 ± 0.50	3.77–3.88	3.79 (0.69)	3.52 ± 0.37	3.48–3.56	3.5 (0.49)
FEV1, L*	2.36 ± 0.37+#^	2.32–2.39	2.33 (0.54)	3.09 ± 0.45	3.04–3.13	3.03 (0.65)	3.09 ± 0.42	3.05–3.14	3.0 (0.6)	2.74 ± 0.4	2.70–2.78	2.72 (0.59)
FEV1/FVC ratio*	0.778 ± 0.026+#	0.775–0.781	0.776 (0.038)	0.807 ± 0.018	0.805–0.809	0.805 (0.025)	0.808 ± 0.02	0.806–0.809	0.806 (0.027)	0.78 ± 0.018	0.779–0.783	0.778 (0.032)
Females <30 years												
FVC, L*	2.49 ± 0.2+#^	2.45–2.53	2.51 (0.28)	3.10 ± 0.35	3.03–3.17	3.11 (0.5)	3.13 ± 0.31	3.07–3.19	3.14 (0.45)	2.9 ± 0.26	2.85–2.95	2.89 (0.41)
FEV1, L*	2.17 ± 0.17+#^	2.14–2.2	2.17 (0.26)	2.74 ± 0.28	2.69–2.8	2.74 (0.44)	2.75 ± 0.25	2.71–2.81	2.75 (0.39)	2.53 ± 0.23	2.48–2.57	2.52 (0.37)
FEV1/FVC ratio*	0.84 ± 0.007+#	0.844–0.847	0.844 (0.01)	0.88 ± 0.01	0.883–0.888	0.884 (0.20)	0.88 ± 0.01	0.881–0.886	0.88 (0.021)	0.845 ± 0.006	0.843–0.846	0.845 (0.011)
Females ≥30 years												
FVC, L*	2.35 ± 0.29+#	2.33–2.38	2.33 (0.44)	2.81 ± 0.36	2.77–2.84	2.77 (0.526)	2.82 ± 0.33	2.79–2.85	2.79 (0.49)	2.34 ± 0.35	2.30–2.37	2.32 (0.50)
FEV1, L*+	1.76 ± 0.24#^	1.73–1.78	1.73 (0.36)	2.35 ± 0.31	2.31–2.38	2.31 (0.47)	2.34 ± 0.29	2.31–2.37	2.32 (0.44)	1.99 ± 0.32	1.96–2.03	1.98 (0.47)
FEV1/FVC ratio*+	0.79 ± 0.21#^	0.76–0.84	0.79 (0.03)	0.83 ± 0.02	0.830–0.833	0.829 (0.03)	0.83 ± 0.02	0.828–0.832	0.82 (0.03)	0.804 ± 0.02	0.802–0.806	0.804 (0.032)

*ANOVA $p < 0.001$; +Indian equations compared with GLI race-neutral equations; #Indian equations with GLI mixed equations; ^Indian equations with ECSC equations with correction factor applied

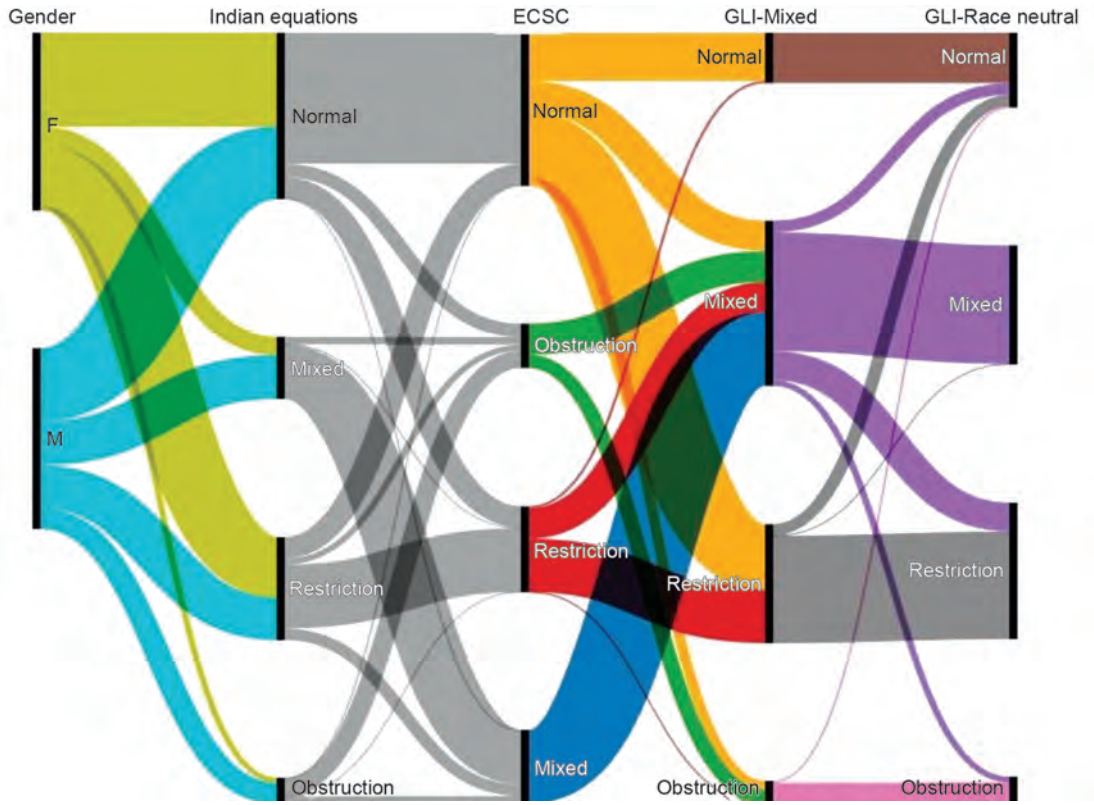

Fig. 1: Alluvial plot depicting change in the classification of ventilatory limitation using the different equations

Table 3: Comparison of measured spirometry values expressed as percent predicted using Indian, ECSC, and two GLI equations

	Indian equations			*GLI race-neutral*			*GLI mixed*			*ECSC*		
	Mean ± SD	*95% CI*	*Median (IQR)*	*Mean ± SD*	*95% CI*	*Median (IQR)*	*Mean ± SD*	*95% CI*	*Median (IQR)*	*Mean ± SD*	*95% CI*	*Median (IQR)*
Males <30 years												
FVC, L*	92.36 ± 23.16+#	87.18–97.5	93.8 (29.75)	76.63 ± 19.05	72.36–80.89	78.19 (24.81)	75.66 ± 18.96	71.42–79.91	77.69 (22.9)	94.23 ± 27.88	87.98–100.47	98.15 (36.1)
FEV1, L*	87.48 ± 24.3+#^	82.04–92.93	93.29	70.49 ± 19.4	66.14–74.83	74.37 (29)	70.15 ± 19.5	65.78–74.52	74.48 (30.6)	75.82 ± 21.41	71.03–80.62	81 (29.77)
FEV1/FVC, percentage	93.64 ± 17.15	89.8–97.48	95.17 (20.43)	91.25 ± 16.67	87.52–94.99	93.41 (19.78)	91.17 ± 16.63	87.4–94.89	93.2 (19.95)	94.78 ± 17.29	90.91–98.66	96.66 (19.37)
Males ≥30 years												
FVC, L*	75.03 ± 21.2+#^	72.86–77.19	73.97 (29.11)	62.8 ± 17.7	60.99–64.62	62.28 (23.93)	62.38 ± 17.58	60.59–64.18	61.95 (24)	68.7 ± 23.58	66.3–71.1	66.17 (31.38)
FEV1, L*	71.4 0 ±26.59+#^	68.7–74.1	71.2 (37.4)	54.4 ± 20.4	52.34–56.5	54.25 (29.2)	54.2 ± 20.34	52.14–56.28	54.14 (28.88)	61.2 ± 22.8	58.9–63.5	60.9 (32.7)
FEV1/FVC, percentage*	88.09 ± 17.33#	86.32–89.86	89.52 (22.93)	84.87 ± 16.77	83.2–86.59	86.46 (22.87)	84.88 ± 16.74	83.17–86.59	88.36 (22.55)	87.8 ± 17.28	86.04–89.57	89.23 (23.35)
Females <30 years												
FVC, L*	93.3 ± 20.3+#^	89.23–97.37	95.25 (24.71)	75.33 ± 16.35	72.06–78.61	76.37 (21)	74.5 ± 16.12	71.27–77.73	75.39 (20.3)	76.9 ± 17.39	76.95–83.92	83.43 (21.2)
FEV1, L*	87.43 ± 22.5+#^	82.91–91.94	89.06 (32.49)	69.47 ± 17.86	65.89–73.06	69.61 (27.32)	69.03 ± 17.73	65.47–72.59	69.94 (26.03)	75.35 ± 19.27	71.48–79.21	76.59 (27.47)
FEV1/FVC, percentage*	96.13 ± 10.93+#	93.93–98.31	97.06 (13.53)	91.74 ± 10.37	89.66–93.82	93.27 (12.6)	91.96 ± 10.37	89.89–94.04	93.3 (12.19)	96.16 ± 10.96	93.96–98.36	97.07 (13.61)
Females ≥30 years												
FVC, L*	75.5 ± 22.11+#	73.28–77.76	75.85 (32.89)	63.2 ± 18.19	61.36–65.05	63.43 (27.79)	62.85 ± 18.07	61.02–64.68	62.83 (28.01)	76.04 ± 21.16	73.89–78.17	76.18 (32.48)
FEV1, L*	76.46 ± 26.6+#^	73.77–79.15	77.37 (40.54)	57.14 ± 19.7	55.14–59.13	57.41 (30.84)	57.26 ± 19.72	55.27–59.26	58.07 (30.64)	67.5 ± 22.78	65.20–69.81	68.06 (35.55)
FEV1/FVC, percentage*	93.2 ± 14.94+#	91.68–94.71	94.93 (18.93)	89.59 ± 14.4	88.13–91.05	91.4 (14.4)	89.77 ± 14.41	88.31–91.23	91.45 (18.5)	92.68 ± 14.86	91.18–94.18	94.54 (19.2)

*ANOVA, $p < 0.001$; +Indian equations compared with GLI race-neutral equations; #Indian equations with GLI mixed questions; ^Indian equations with ECSC equations with a correction factor applied

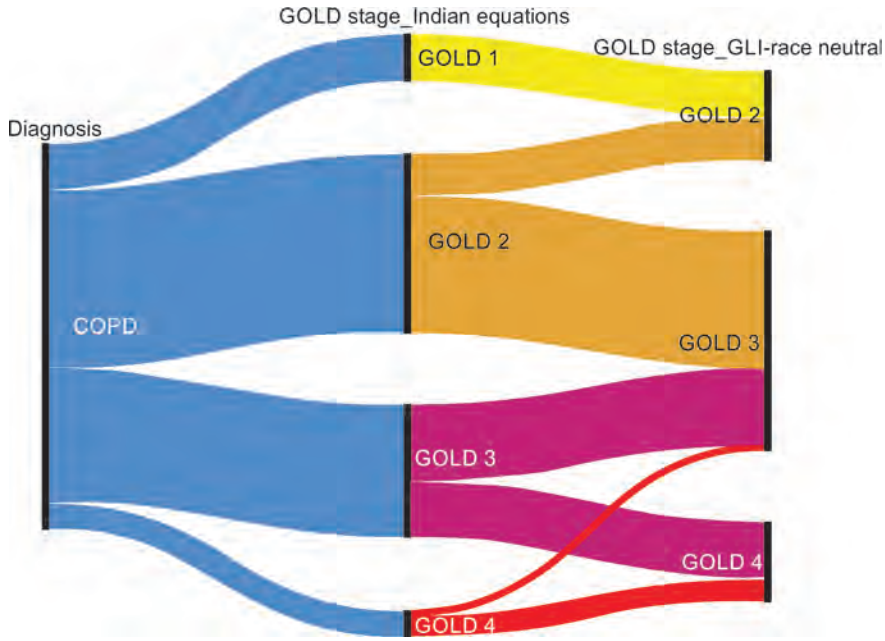

Fig. 2: Alluvial plot depicting a change in GOLD staging on switching to the GLI equations from the Indian equations for FEV 1% predicted values

The GLI race-neutral and GLI Mixed equations are based on the same data points as the original GLI equations.[2] There was a paucity of Indian data during the derivation of the GLI equations of 2012. While the GLI mixed equations are an average of the groups studied in the GLI initiative, inverse probability weight has been applied to derive the GLI race-neutral equations. GLI mixed equations were evaluated in patients from North India and were found to have clinically unacceptable differences in the categorization of ventilatory abnormalities. Although the predicted values for the two GLI equations may not differ substantially, there is a significant difference in the LLN of both equations, contributing to a significant difference in the classification of ventilatory patterns when using these equations. Recent guidelines recommend the use of GLI race-neutral equations for interpreting spirometry.[5,7]

We examined the GLI race-neutral equations for their suitability for diagnosing ventilatory abnormalities. The GLI race-

Table 4: Bland–Altman analysis of agreement for percent predicted values of spirometry parameters between Indian, ECSC, and two GLI equations

	Datasets compared	*Bias (SD)*	*95% limits of agreement*
Males <30 years			
FVC (%predicted)	Indian and GLI race-neutral	15.74 (4.272)	7.363–24.11
	Indian and GLI mixed	16.70 (4.552)	7.773–25.62
	Indian and ECSC	−1.862 (14.89)	−31.05–27.32
FEV1 (% predicted)	Indian and GLI race-neutral	16.99 (5.089)	7.018–26.97
	Indian and GLI mixed	17.33 (4.910)	7.704–26.95
	Indian and ECSC	11.66 (3.371)	5.051–18.26
FEV1/FVC ratio (% predicted)	Indian and GLI race-neutral	2.390 (0.7888)	0.8438–3.936
	Indian and GLI mixed	2.475 (1.094)	0.3303–4.619
	Indian and ECSC	−1.140 (1.721)	−4.513–2.234
Males ≥ 30 years			
FVC (%predicted)	Indian and GLI race-neutral	12.22 (3.561)	5.243–19.20
	Indian and GLI mixed	12.64 (3.907)	4.983–20.3
	Indian and ECSC	6.3 (13.61)	−20.37–32.97
FEV1 (% predicted)	Indian and GLI race-neutral	16.98 (6.321)	4.587–29.37
	Indian and GLI mixed	17.19 (6.488)	4.478–29.91
	Indian and ECSC	12.64 (47.18)	−79.84–105.1
FEV1/FVC ratio (% predicted)	Indian and GLI race-neutral	3.183 (1.175)	0.8802–5.485
	Indian and GLI mixed	3.244 (1.291)	0.7129–5.775
	Indian and ECSC	0.2886 (1.573)	−2.795–3.372
Females < 30 years			
FVC (%predicted)	Indian and GLI race-neutral	17.97 (4.87)	8.45–27.49
	Indian and GLI mixed	18.80 (4.463)	10.05–27.55
	Indian and ECSC	12.87 (4.224)	4.59–21.15
FEV1 (% predicted)	Indian and GLI race-neutral	17.95 (5.205)	7.750–28.15
	Indian and GLI mixed	18.39 (4.96)	8.672–28.12
	Indian and ECSC	12.08 (3.562)	5.101–19.06
FEV1/FVC ratio (% predicted)	Indian and GLI race-neutral	4.383 (0.8576)	2.702–6.064
	Indian and GLI mixed	4.157 (0.7911)	2.607–5.708
	Indian and ECSC	−0.03670 (0.2792)	−0.5839–0.5105
Females ≥30 years			
FVC (%predicted)	Indian and GLI race-neutral	12.32 (4.173)	4.139–20.50
	Indian and GLI mixed	10.19 (7.459)	−4.432–24.81
	Indian and ECSC	−0.5102 (4.265)	−8.870–7.849
FEV1 (% predicted)	Indian and GLI race-neutral	19.32 (7.066)	5.474–33.17
	Indian and GLI mixed	16.68 (9.104)	−1.163–34.53
	Indian and ECSC	8.955 (4.898)	−0.6449–18.56
FEV1/FVC ratio (% predicted)	Indian and GLI race-neutral	3.607 (0.9268)	1.791–5.424
	Indian and GLI mixed	3.425 (0.8281)	1.802–5.048
	Indian and ECSC	0.5163 (0.3793)	−0.2271–1.260

neutral equations categorized ventilatory patterns with greater concordance with Indian equations than the GLI mixed equations, but the difference was still too large to gain clinical acceptability. The difference in the LLN led to patients with normal or obstructive pattern spirometry being classified as having mixed or restrictive patterns with GLI equations. This happened more often with the GLI mixed than with GLI race-neutral equations.

The Bland–Altman analysis revealed limited agreement of GLI equations with Indian equations, with wide limits of agreement and large biases for both males and females across the age groups. Spirometry relies on predicted values for interpretation. Although LLN are used to define the ventilatory pattern, and percentages of predicted values may not be statistically accurate outside of the 20–40 years age group, these percentages find use in clinical medicine.[19] From the severity classification of COPD as per GOLD guidelines to scoring the body mass index, obstruction, dyspnea, and exercise capacity index for COPD prognostication, from a lower percentage of predicted FEV1 predicting exacerbations of asthma to diagnosing PRISm based on a low percentage of predicted FEV1, percentages of predicted values are important in clinical practice. Hence, using the correct equations to calculate predicted values is of primary interest.[8,9,20]

Ethnicity has been an important determinant of predicted values. Living conditions, exposure to pollution, prematurity, and many other factors may affect lung function. Since ethnicity has been found to be associated with socioeconomic determinants, including living conditions

Table 5: Comparisons of patterns of abnormality on spirometry interpreted using Indian, ECSC, and two GLI equations

Pattern of abnormality	*Indian*	*GLI race-neutral*	*GLI mixed*	*ECSC*
Males of <30 years				
Normal	49 (62.03)	28 (35.44)	22 (27.85)	51 (64.56)
Obstructive	14 (17.72)	10 (12.66)	11 (13.92)	12 (15.19)
Restrictive	11 (13.92)	29 (36.71)	27 (34.18)	10 (12.66)
Mixed	5 (6.33)	12 (15.19)	19 (24.05)	6 (7.59)
Concordance with Indian equations		53 (67.09)$	44 (55.69) $	69 (87.34)
K of agreement		0.5278	0.4011	0.7699
Males of ≥30 years				
Normal	138 (37)	58 (15.55)	39 (10.46)	112 (30.03)
Obstructive	41 (10.99)	24 (6.43)	19 (5.09)	46 (12.33)
Restrictive	98 (26.27)	134 (35.92)	108 (28.95)	115 (30.83)
Mixed	96 (25.74)	157 (42.09)	207 (55.5)	100 (26.81)
Concordance with Indian equations		240 (64.34)*	201 (53.88)$	272 (72.92)*
K of agreement		0.5133	0.3742	0.6267
Females < 30 years				
Normal	75 (76.53)	34 (34.69)	26 (26.53)	57 (58.16)
Obstructive	6 (6.12)	12 (12.24)	11 (11.22)	10 (10.20)
Restrictive	14 (14.29)	34 (34.69)	31 (31.63)	22 (22.45)
Mixed	3 (3.06)	18 (18.37)	30 (30.61)	9 (9.18)
Concordance with Indian equations		50 (51.02)$	37 (37.75)$	75 (76.5)$
K of agreement		0.2709	0.154	0.543
Females ≥30 years				
Normal	180 (47.62)	76 (20.11)	43 (11.38)	188 (49.74)
Obstructive	8 (2.12)	29 (7.67)	22 (5.82)	49 (12.96)
Restrictive	143 (37.83)	162 (42.86)	146 (38.62)	75 (19.84)
Mixed	47 (12.43)	111 (29.37)	167 (44.18)	66 (17.46)
Concordance with Indian equations		223 (58.99)$	164 (43.38)$	280 (74.07)$
K of agreement		0.4175	0.2386	0.6093

$Fisher exact test, $p < 0.05$; *Chi-squared test, $p < 0.0$

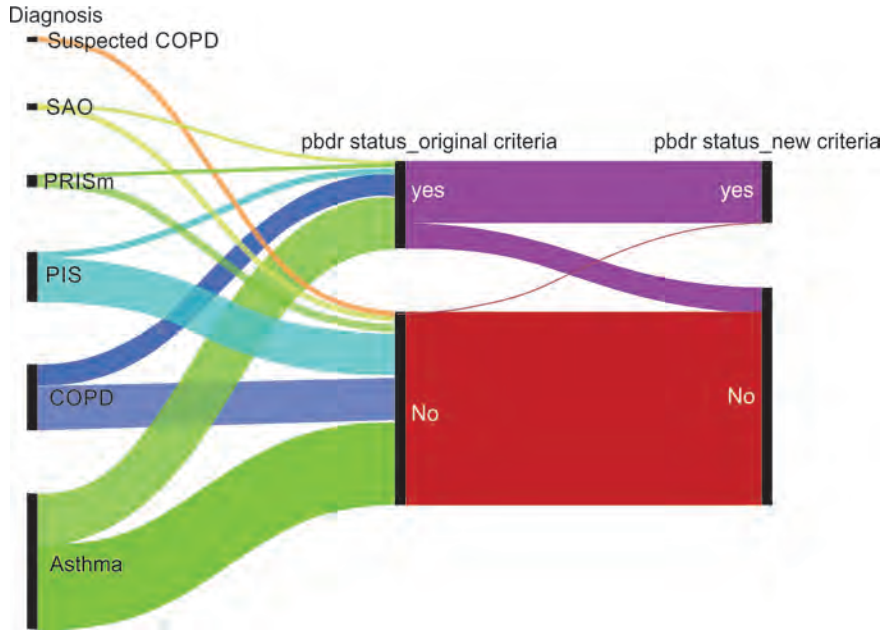

Fig. 3: Alluvial plot depicting the change in postbronchodilator status on using the new criterion

and access to healthcare, it may be premature to conclude whether it is ethnicity or the multitude of socioeconomic factors that determine normal lung functions. Therefore, whether an Indian-origin person living in the same socioeconomic and demographic conditions as a Caucasian person and with the same height and age will have the same lung function has to be determined. While the GLI equations have not incorporated data from the Indian population, various correction factors have been suggested for using Caucasian equations in the Indian population. However, this approach has not been found to be appropriate. This study demonstrated limited agreement between Indian equations and ECSC equations using a correction factor.

Postbronchodilator responsiveness (PBDR) is important clinically for the diagnosis of asthma, and the persistence of PBDR, despite treatment, is an independent predictor of asthma exacerbations. The use of the new criteria for diagnosing PBDR led to a lesser number of patients being diagnosed with bronchodilator responsiveness. Considering the higher FEV1 values predicted using GLI race-neutral equations, this may be due to a larger denominator while assessing PBDR. However,

the clinical significance of switching to the new criteria needs further evaluation.

To the best of our knowledge, this is the first study evaluating the use of GLI race-neutral equations in western India. Although the applicability of GLI mixed equations has been studied in the north Indian population, the difference in the LLN calculated by the two GLI equations and the subsequent change in categorization of the ventilatory patterns add to the significance of this study. A limitation of the current study is that it was a single-center study conducted at a tertiary care institute in an urbanized setting.

The current study shows that using the GLI race-neutral equations instead of Indian equations would almost halve the number of patients diagnosed with normal spirometry. It would substantially increase the number of patients diagnosed with restrictive or mixed patterns. The use of these equations would increase the GOLD stage of a significant number of COPD patients. This has clinical implications for diagnosing and prognostication.

This study has demonstrated that even the GLI race-neutral equations, with substantially LLN, may misclassify Indian patients with chronic respiratory disease. However, whether this disparity is due to ethnicity or other confounding factors, including socioeconomic conditions, remains to be determined. Therefore, the applicability of these GLI race-neutral equations in Indian individuals with environmental and socioeconomic conditions matching their Caucasian counterparts shall have to be evaluated in a separate study. Till this issue is addressed and studied, it may be better to use Indian prediction equations while interpreting the spirometry of individuals of Indian descent, not just in India but anywhere in the world. However, for individuals of Indian ethnicity living in Caucasian environmental and socioeconomic conditions, this approach will mandate greater clinical inputs in decision-making to prevent incorrect categorization of abnormal spirometry values as normal merely due to the lower predicted values of Indian equations.

Conclusion

Global Lung Initiative (GLI) race-neutral equations have greater concordance with Indian equations than GLI mixed equations and yet substantially overdiagnose abnormal ventilatory patterns on spirometry in adult Indians in western India with chronic respiratory disease. Patients with normal or obstructive patterns on spirometry are recategorized to have mixed or restrictive patterns in a substantial number of cases. Using GLI race-neutral equations increases the grade of severity of airflow limitation in COPD patients. The use of GLI race-neutral predictions for FEV1 leads to substantially fewer patients demonstrating PBDR.

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ORIGINAL ARTICLE

A Study on Neurological Manifestations in Coronavirus Disease 2019 Patients Admitted to a Tertiary Care Hospital

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Abstract

Aim: The coronavirus disease 2019 (COVID-19) is considered a pandemic by the World Health Organization (WHO). Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, the involvement of other organs needs to be explored. Thus, this study is undertaken to analyze the neurological manifestations in patients with COVID-19 infection.

To analyze the neurological manifestations in patients with COVID-19 infection.

Materials and methods: All COVID-19-positive patients who got neurology referrals from March 2020 to June 2021 were included in the study. Laboratory confirmation of COVID-19 infection was done by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of throat swabs in patients who present with symptoms suggestive of COVID-19. Demographic characteristics, neurological complaints, comorbid conditions, neurological examination, and requisite investigations were analyzed.

Results: Among 160 patients, 107 (67%) were men, and the mean age was 61 years. Comorbidities included diabetes mellitus (51%) of subjects followed by hypertension (28%), chronic kidney disease (10%), and coronary artery disease (5%). Considering the COVID-19 severity, 28.75% had mild; 8.75% had moderate; and 62.5% had severe disease. The most common neurological symptoms included altered sensorium (62.5%), focal neurological symptoms (29.4%), anosmia (13.1%), headache (10.6%), and seizures (7.5%). The most prevalent neurological signs and/or syndromes were acute encephalopathy (62.5%), stroke (21.3%%), and mucormycosis (12.5%). The mortality rate in our study population was 16.3%, encephalopathy being the most common cause.

Conclusion: In our study, encephalopathy was the major cause of morbidity and mortality among the COVID-19-related neurological manifestations. Encephalopathy was most seen in severe COVID-19 infection and was associated with increased neutrophil-to-lymphocyte (NL) ratio raised inflammatory markers. Stroke constituted 29.4% of the neurology referrals in COVID-19 patients confirming COVID-19 infection predisposes to thrombotic events. We found an increased incidence of Mucormycosis in COVID-19 patients, but early debridement and timely treatment with antifungal medications had reduced the mortality.

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Introduction

In December 2019, cases of viral pneumonia began to rise in the city of Wuhan, which is located in the providence of Hubei, China. In March 2020, the outbreak was described as a pandemic by the World Health Organization (WHO).[1] The causative virus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a ribonucleic acid (RNA) virus from the *Coronaviridae* family. The same family of viruses was responsible for SARS in 2002 and Middle East Respiratory Syndrome (MERS) in 2012.[2] What makes the current virus more dreaded than SARS and MERS? Although the basic number of reproductions is high (2–3.5), the most crucial factor in transmission is the high level of virus in the upper respiratory tract.[3] While SARS-CoV-2 is known to cause substantial pulmonary disease, clinicians have observed many extrapulmonary manifestations of COVID-19 such as hematological, hepatobiliary, neurological, ophthalmic, dermatological, and renal.[4,5]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2002) and MERS coronavirus (2012) are known for neurotropism.[6] SARS-CoV-2 was also described to invade the nervous system and cause the neurological manifestations. SARS-CoV-2 can cause multisystem manifestations by using angiotensin-converting enzyme 2 (ACE2) as a receptor which is present in multiple human organs, including the nervous system. Neurological manifestations that are described with coronavirus disease 2019 (COVID-19) infection are headache, myalgia, anosmia, ageusia or dysgeusia, dizziness, seizure, altered sensorium cerebrovascular disease, etc.

This study is undertaken to analyze the neurological manifestations in SARS-CoV-2 infected patients.

Material and Methods

Study Design

This study was a single-center, descriptive study conducted at our tertiary care hospital from March 2020 to June 2021.

Study Population

All COVID-19-positive patients who got neurology referrals during the period were included in the study. Laboratory confirmation of COVID-19 infection was done by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of throat swabs in patients who had symptoms suggestive of COVID-19.

Methodology

Institutional Ethics Committee clearance was obtained prior to starting of the study. Patients were included in the study after obtaining written informed consent from the patient and or attendees. A proforma was prepared which included demographic characteristics, neurological complaints, comorbid conditions, neurological examination, and requisite investigations. We have divided the patients into three categories according to COVID-19 severity, which is defined by the Ministry of Health and Family Welfare, India. Mild disease, positive for COVID-19 but no pneumonia or hypoxia. Moderate disease, patients with pneumonia with oxygen saturation (SPO_2) > 90% on room air. Severe disease, pneumonia plus any one of the following—SPO_2 < 90% on room

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air, respiratory rate >30/minute, or severe respiratory distress.

Statistical Analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean ± standard deviation (SD) (min–max) and results on categorical measurements are presented in numbers (%). Significance is assessed at a 5% level of significance. Student *t*-test (two-tailed, independent) has been used to find the significance of study parameters on a continuous scale between two groups (intergroup analysis) on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance. The Chi-squared/Fisher exact test has been used to find the significance of study parameters on a categorical scale between two or more groups in, a nonparametric setting for qualitative data analysis. The Fisher exact test is used when cell samples are very small.

Significant Figures

+: Suggestive significance (p-value of $0.05 < p < 0.10$).

*: Moderately significant (p-value of $0.01 < p \leq 0.05$).

**: Strongly significant (p-value of $p \leq 0.01$).

Statistical Software

The statistical software namely Statistical Packages for the Social Sciences 22.0, and R environment version 3.2.2 was used for the analysis of the data, and Microsoft Word and Excel were used to generate graphs, tables, etc.

Results

Of the total 160 patients, the mean age was 61.47 ± 14.07 years; 107(67%) were males and 53 (33%) were females. Among the neurological symptoms, altered sensorium was the most common symptom and it was present in (n = 100; 62.5%) of patients followed by focal neurological symptoms in (n = 47; 29.4%), anosmia (n = 21; 13.1%), headache (n = 17; 10.6%), seizures (n = 12; 7.5%), loss of taste (n = 4; 2.5%), unsteadiness of gait (n = 3; 1.9%), numbness and paresthesias (n = 3; 1.9%), involuntary movements (n = 2; 1.3%). There was no statistical significance observed in neurological symptoms in relation to gender.

Diabetes mellitus was the most common comorbid condition observed in this study which was present in (n = 80; 51%) of subjects followed by hypertension (n = 45; 28%), chronic kidney disease(n = 16; 10%), coronary artery disease in (n = 8; 5%). Considering the COVID-19 severity, 28.8% (n = 46) had mild; 13.1% (n = 21) had moderate; 58.1% (n = 93) had severe disease.

In this study, increased neutrophil-to-lymphocyte (NL) ratio and C-reactive protein (CRP) were associated with severe disease with a significant p-value ($p < 0.001$*). The most prevalent neurological signs and/or syndromes were acute encephalopathy (n = 100; 62.5%), stroke (n = 34; 21.3%), mucormycosis (n = 20; 12.5%), bleeding (n = 3; 3.1%), cerebral venous thrombosis (n = 1; 0.6%), Guillain–Barre syndrome (GBS) (n = 1; 0.6%), and acute disseminated encephalomyelitis (ADEM) (n = 1; 0.6%).

Encephalopathy was noted in 62.5% of subjects, which could be multifactorial, causes were hypoxia, metabolic changes, and sepsis, or could be COVID-19-related itself. Hypoxia was observed in 54.4%, Sepsis was observed in 21.9%%, and dyselectrolytemia was observed in 43.2% of the study population. Around 38 patients had cerebrovascular disease out of which 34 had an ischemic stroke [22 had left malignant middle cerebral artery (MCA) territory infarct; 10 had right MCA territory infarct and two had posterior circulation stroke] and three patients had an intracerebral hemorrhage, one patient had cerebral venous thrombosis (superior sagittal sinus and transverse sinus). Three patients had an inhospital stroke and were thrombolysis with alteplase as they presented with symptoms in the window period. Postinfectious immune-mediated manifestations such as ADEM, GBS, myositis, and movement disorder were seen only in 2.4% of COVID-19 patients.

Out of 160 patients, 134 (83.7%) were discharged and 26 (16.3%) patients expired. Among 26 patients with mortality, 25 (96.2%) patients had encephalopathy with a significant p-value ($p < 0.001$), and one patient had mucormycosis. Around 28% of the study population with severe disease had mortality, however, it did not reach statistical significance

Discussion

Coronavirus disease 2019 (COVID-19)—related neurological problems can be divided into three groups—those caused directly by the virus, those caused by an immune response against the virus, and those caused by the systemic reaction/homeostatic imbalance.[7] Neurological problems affect between 36 and 45% of patients, and they are more common in those who have a serious illness.[8,9]

In about 4% of COVID-19 patients, neurological problems are the leading cause of death.[10] Multiorgan failure, severe systemic disease, and sepsis can cause encephalopathy, delirium, skeletal muscle damage, and neuropathies in some people.

In the present study, the mean age was 61.47 ± 14.07 years; 67% were males and 33% were females which was similar to most other studies.[11,12] Increasing age and male gender were associated with severe COVID-19 infection in our study. In a meta-analysis by Yassin et al.,[11] mean age was 50.3 years and 53% were males. Richardson et al.[12] reported mean age was 63 years and 39.7% were females. According to the Mao et al.[8] study, the mean age of 52.7 years, and 40.7% were males.

Diabetes mellitus, hypertension, chronic kidney disease (CKD), and cardiovascular disease were the common comorbid conditions observed in 50, 28.1, 11.3, and 5%, respectively in the present study, and were associated with severe disease, but did not reach statistical significance.

Hu et al.[13] studies described diabetes mellitus (7.7%), hypertension (15.7%), cardiovascular disease (4.7%), and malignancy were the associated comorbid conditions noted in their study. Richardson et al.[12] study reported hypertension, obesity, and diabetes mellitus were the most common comorbid conditions described in their study. Romero-Sánchez et al.[10] study observed that the presence of comorbidities such as obesity, hypertension, CKD, diabetes mellitus, heart disease, and dyslipidemia was associated with severe COVID-19 infection.

Our study reported patients with severe infection and mortality had elevated NL ratio and inflammatory markers similar to Mao et al.[8] In the present study, among the neurological symptoms altered sensorium was the most common symptom observed in 62.5% of patients in contrast to other studies. Encephalopathy was most seen in severe COVID-19 infection and was associated with increased NL ratio raised inflammatory markers. Yassin et al.[11] and Chou et al.[14] reported encephalopathy in 9.4 and 49% of subjects respectively. Romero-Sánchez et al.[10] study observed encephalopathy in 19.6% of subjects, especially in severe infection and statistically associated with older age, lymphocytopenia, and higher CK levels.

In our study, cerebrovascular disease was the second common neurological manifestation noted in 24.1% of subjects and was not associated with increased NL ratio, inflammatory markers, severe disease, and mortality in contrast to other studies.

Yassin et al.[11] Romero-Sánchez et al.,[10] and Chou et al.[14] reported cerebrovascular disease in 2.5, 1.7, and 6% of patients, respectively, and found the presence of neurological signs or syndrome was associated with increased mortality. Strokes could be caused by vascular endothelial dysfunction caused by dysregulated immune response and direct viral invasion, as well as an aberrant inflammatory and hypercoagulable state caused by immunosuppression.[15]

Headache was the most common neurological symptom reported in several studies. Lechien et al.[16] and Liguori et al.[17] reported headaches in 70.3 and 38.3% of patients, respectively.

Several studies reported that anosmia and dysgeusia were about 5–55% prevalent among confirmed cases of COVID-19 infection. Our study showed that anosmia and dysgeusia were associated with less severe disease.

Seizures were noted in 7.5% of patients in the present study in contrast to Romero-Sánchez et al.[10]study, which reported seizures in 0.7% of subjects. Of 160 patients with COVID-19 infection, one patient (0.6%) developed an acute motor axonal neuropathy (AMAN) variant of GBS. The patient was treated with intravenous immunoglobulin and was subsequently discharged with improvement in power. Toscano et al.,[18] also reported an incidence of 0.4% for GBS. Dysimmune response has been considered the important mechanism of GBS in patients with COVID-19 infection

Our study reported mucormycosis in 20 patients. Of 20 patients, 11 were males and the median age was 52 years. Nearly, 12 patients were diabetic, and eight patients received systemic corticosteroid treatment for moderate to severe disease suggesting that patients with diabetes and COVID-19 receiving corticosteroids might be particularly susceptible to the development of COVID-19-associated mucormycosis. All patients underwent debridement and received antifungals.

Strengths

Large sample size of patients.

Limitations

The present study was undertaken inhospital-admitted patients, so minor symptoms that do not need admission might be missed. Detailed neurological examination was not done because of the highly infective nature of the illness. Imaging of the brain was not possible in some patients because of critical illness and difficulty in shifting the patient because of hemodynamic instability. The cerebrospinal fluid (CSF) examination was not done in most of the encephalopathy patients to detect SARS-CoV-2 in CSF. Electroencephalogram and nerve conduction studies were also not done in most of the required patients.

Conclusion

In our study, encephalopathy was the major cause of morbidity and mortality among the COVID-19-related neurological manifestations. Encephalopathy was most seen in severe COVID-19 infection and was associated with increased NL ratio raised inflammatory markers. Stroke constituted 29.4% of the neurology referrals in COVID-19 patients confirming COVID-19 infection predisposes to thrombotic events. We found an increased incidence of mucormycosis in COVID-19 patients, but early debridement and timely treatment with antifungal medications had reduced the mortality.

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REVIEW ARTICLE

Defeating the Silent Enemy: Antimicrobial Resistance Looming as the Next Global Pandemic

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Abstract

Antibiotics are the magic bullets that have saved millions worldwide. Enormous and irresponsible use of antibiotics has led to resistance to antibiotics, which is a matter of global health concern. The superbugs are responsible for life-threatening infections, treatment failure, and high mortality worldwide. The urgent healthcare threat caused by antimicrobial resistance (AMR) to nonfermenting gram-negative bacteria is being increasingly acknowledged worldwide. Antibiotic resistance found in organisms in hospital settings is now increasingly found in the community. Although antimicrobial stewardship requiring a multidisciplinary approach is developing rapidly at the hospital level, it needs more attention at the community level. New therapeutics are certainly required, but the major challenge is rapidly identifying resistant infections and tailoring treatment. This review highlights the crisis that reflects the current scenario of AMR, common resistant pathogens, and the major challenges in the fight against AMR. It also discusses potential methods and strategies to address the intricacies of antibiotic resistance.

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Introduction and Background

One of the greatest threats humankind faces in the 21st century is the global spread of antimicrobial-resistant organisms (Fig. 1) and antibiotic-resistant genes.[1] The intrinsic resistance, acquired resistance, genetic alteration, and DNA transfer are the potential factors contributing to the molecular mechanism of antibiotic resistance.[2] However, in clinical practice, the excessive utilization of antibiotics and negligent prescription by healthcare practitioners have emerged as the key factors contributing to the emergence of antibiotic resistance.[3]

Recently, the World Health Organization (WHO) has identified antimicrobial resistance (AMR) as a significant global public health concern, ranking it among the top 10 threats. It is projected that by 2050, the rise in infections caused by antibiotic-resistant organisms could result in the loss of approximately 10 million lives annually, imposing a staggering economic burden of around $100 trillion on the global economy.[4,5]

The spread of multidrug-resistant (MDR) pathogens, that is, resistance to almost all types of medicines, is a huge public health problem worldwide.[6] Microbial agents developing resistance to various antibiotics can lead to treatment failure. This leads to long illnesses, longer hospital stays, more prescriptions of higher antibiotics that are expensive and even hazardous at times, higher mortality, and an increased chance of more people being affected in the community. Individuals with organ transplants, chemotherapies, and surgeries are at risk of being compromised without proper antibiotics to treat infections with resistant microorganisms.[4]

Antimicrobial Resistance: Global and Indian Scenario

The WHO has issued a warning about the escalating global antibiotic resistance crisis. It is alarming to note that over 70% of the pathogenic bacteria are believed to have developed resistance to at least one commercially available antibiotic.[4] This resistance is prevalent among common pathogens in most countries, affecting >33% of the population. In many countries, approximately 35% of common human infections are resistant to the currently available antibiotics. The situation is even more dire in low- and middle-income countries (LMICs), where the resistance rates for certain antibiotic-bacterium combinations can reach as high as 80–90%. This concerning trend highlights the urgent need for effective strategies to combat antibiotic resistance worldwide.[6]

Low- and middle-income countries (LMICs) are disproportionately impacted by antibiotic resistance due to various factors such as the rampant misuse of antibiotics, agricultural use of antibiotic use, poor quality of drugs, inadequate surveillance, substandard healthcare, malnutrition, infections that are chronic and recurring, and the inability to afford more effective

Fig. 1: Global burden of AMR

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drugs due to high cost. This global issue not only leads to increased mortality rates but also places a significant economic burden on these countries.[4] The classification of antibiotic resistance threats into four sections, as outlined in Table 1, is documented in the Center for Disease Control report released on 13th November 2019.[7]

In 2019, the primary pathogens linked to fatalities caused by resistance were *Escherichia coli* (*E. coli*), followed by *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae (K. pneumoniae)*, *Streptococcus pneumoniae (S. pneumoniae)*, *Acinetobacter baumannii* (*A. baumannii*), and *Pseudomonas aeruginosa* (*P. aeruginosa*). These pathogens were accountable for a staggering 929,000 (ranging from 660,000 to 1,270,000) deaths attributed to AMR, as well as 3.57 million (ranging from 2.62 to 4.78 million) deaths associated with AMR. Notably, methicillin-resistant *S. aureus* (MRSA) alone accounted for over 100,000 deaths due to AMR, while the remaining pathogens caused between 50,000 and 100,000 deaths each.[8]

In India, the issue of antibiotic resistance has emerged as a significant problem with devastating consequences. Annually, it claims the lives of 700,000 individuals, surpassing the combined death toll of cancer and road traffic accidents. It is predicted that this number will rise to a staggering 10 million by 2050. India has earned the unfortunate title of being the global hub of antibiotic resistance. The accessible bacterial genome sequences reveal the existence of approximately 20,000 potential resistance genes across nearly 400 different types. As the effectiveness of antibiotics continues to decline, a growing number of illnesses, such as salmonellosis, tuberculosis, gonorrhea, and pneumonia, are becoming increasingly difficult to treat.[3]

Common Pathogens Showing AMR

As per the WHO and the scientific literature, there are many microbes that are resistant to drugs, as shown in Fig. 2.[5]

Methicillin-resistant *S. aureus* (MRSA) is widely recognized as the primary example of AMR prior to the emergence of carbapenem-resistant organisms (CPO) and vancomycin-resistant enterococci (VRE) that have become significant pathogens in recent years. Management for multidrug resistance presents challenges and carries the potential risk of transferring vancomycin resistance genes to other gram-positive organisms.[9]

The World Health Organization (WHO) has recently released a list of antibiotic-resistant pathogens that are of utmost priority. These pathogens are collectively known as ESKAPE pathogens and include Enterococcus spp, *S. aureus*, *K. pneumoniae, A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp. The purpose of this list is to provide guidance and direction for the development of novel antibiotics. ESKAPE pathogens exhibit a significant level of resistance to drugs and have the ability to evade various therapeutic methods. Their ability to form biofilms on surfaces further enhances their resistance to drugs. These pathogens are responsible for causing nosocomial infections, which have alarmingly high mortality rates.[7,9–11]

The urgent healthcare threat posed by nonfermenting gram-negative bacteria and their resistance to antimicrobial agents is being increasingly acknowledged worldwide.[12] Approximately, 40–70% of AMR cases globally are attributed to infections caused by CPOs. The most common types of CPOs include carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *A. baumannii*, and carbapenem-resistant *P. aeruginosa*.[9]

Carbapenem resistance in Enterobacterales is primarily caused by carbapenemases, including New Delhi metallo-β-lactamase (MBL) (NDM), and oxacillinase-48 like (OXA-48-like) VIM, IMP, and KPC.[13] As per the ICMR, the carbapenem resistance rates is up to 30% for *E.coli* and 50% for *K. pneumonia*.[14] NDM is a variant of MBL that possesses the capability to break down a wide range of β-lactam antibiotics, including carbapenems. These carbapenems are crucial antimicrobials used to combat severe infections caused by various gram-negative bacteria. The prevalence of NDM-positive strains is higher in South Asia, the Balkans, North Africa, and the Middle East.[15] The *blaNDM* gene, which is easily transmitted among various gram-negative organisms, makes NDM-1 a significant concern. This resistance determinant has rapidly spread to numerous countries within a short period of time, making it one of the most dreaded determinants of resistance worldwide.[16]

Numerous NDM-1 variants have emerged in Enterobacteriaceae, Vibrionaceae, and other nonfermenters through substitutions of single and double amino acid residues at various positions. NDM-1 is the predominant variant, while NDM-2, NDM-3, NDM-4, and NDM-5 are considered minor variants that have been identified globally. NDM-1 producers can be found scattered across the

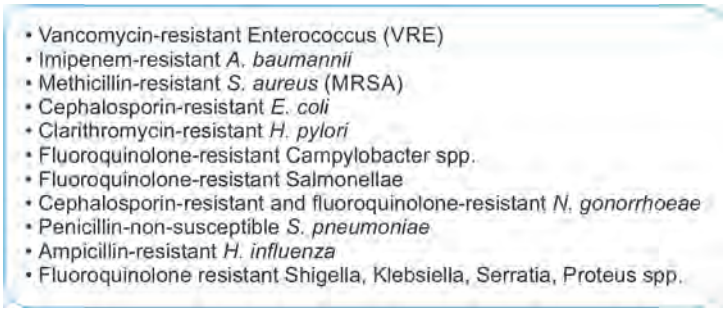

Fig. 2: Common resistant pathogens

Table 1: Categories of threats due to antibiotic resistance

Urgent threats	*Serious threats*	*Concerning threats*	*Watch list*
• Carbapenem-resistant *Acinetobacter.* • Carbapenem-resistant Enterobacterales. • Drug-resistant *Neisseria gonorrhoeae.* • *Candida auris.* • *C. difficile.*	• Drug-resistant *Campylobacter.* • Drug-resistant *Candida* ESBL-producing Enterobacterales, VRE, MDR *P. aeruginosa.* • MRSA. • Drug-resistant *Salmonella typhi.* • Drug-resistant nontyphoidal *Salmonella.* • Drug-resistant *S. pneumoniae.* • Drug-resistant *Shigella.* • Drug-resistant tuberculosis.	• Erythromycin-resistant group I: *Streptococcus.* • Clindamycin-resistant group II: *Streptococcus.*	• Azole-resistant *A. fumigatus.* • Drug-resistant *B. pertussis.* • Drug-resistant *M. genitalium.*

world, with the Asian continent serving as the primary reservoir. China and India account for approximately 58.2% of the NDM-1 variant cases. The highest prevalence of NDM variants is observed in *K. pneumoniae* and *E. coli*.[17] *Elizabethkingia* spp. is a significant contributor to nosocomial acquired bacteremia/sepsis and meningitis in India. Its occurrence is associated with several risk factors, including the irrational and prolonged use of broad-spectrum antibiotics, preexisting comorbidities, and the presence of indwelling catheters and venous line insertion.[18]

Community-acquired Infections at High: a Need to Ponder

Community-acquired infections (CAIs) encompass a broad range of diseases. Individuals with CAI have the potential to introduce harmful microorganisms into the hospital setting, thereby becoming a source of disease outbreaks. Influenza viruses, enteric pathogens, and MDR bacteria are the primary culprits behind CAIs, resulting in increased rates of hospitalization and mortality. While MDR bacteria are commonly associated with hospital-acquired infections, their transmission within the community can significantly impact the morbidity and mortality rates among vulnerable populations.[19] Numerous gram-negative bacteria are accountable for the occurrence of CAIs. The widespread transmission of MDR bacteria poses a significant risk to public health, demanding immediate and proactive measures to be taken.[20]

The excessive utilization of antibiotics in both human and animal healthcare systems is a significant contributing factor to the emergence of MDR in CAIs. Antibiotic consumption by animals through their food can result in antibiotic resistance, even in humans. Additionally, the lack of proper treatment guidelines and the over-prescription of antibiotics by healthcare workers and veterinarians contribute to the increase in antibiotic resistance. Furthermore, the low cost, widespread availability, and irrational use of antibiotics further aggravate the issue of antibiotic resistance.[7]

The development of resistance to a specific antibiotic can occur at any given time, and it can be attributed to either natural selection pressure or the inappropriate use of antibiotics. Another factor that contributes to the emergence of drug resistance is the food chain. The use of similar classes or types of antibiotics in agriculture, human treatment, and livestock or dairy farms has resulted in the spread of antibiotic resistance through the transmission of resistant traits. The excessive use of antimicrobial agents in human, animal, and agricultural settings leads to environmental contamination, particularly in water bodies. Additionally, the disposal of large quantities of biocide-based products into soil or water bodies can have a detrimental impact on the environment and increase the prevalence of resistance traits among microorganisms. As a consequence, common antibiotics are becoming less effective in treating various diseases, leading to prolonged treatment, increased medical costs, and even mortality in some cases.[7]

Patient Dies in the Intensive Care Unit, but the Infection Begins in the Community

Intensive care units (ICUs) are often called "the hub" of infections.[21] Patients are exposed not only to the native flora of the hospital but also to the flora of other individuals who are unwell.[22] Gram-positive organisms such as MRSA, VRE, penicillin-resistant *Pneumococcus*, and *Clostridium difficile* (*C. difficile)* are more commonly found in Western countries. However, in India, gram-negative bacteria like *A. baumannii*, extended-spectrum β-lactamase, and metallo-β lactamase-producing organisms such as *E. coli* and *K. pneumoniae* are more prevalent. This shift in dominant bacteria highlights the difference in infection patterns between Western countries and India. Additionally, the presence of antibiotic resistance in hospital settings is now increasingly observed in community settings as well, as indicated in Fig. 3.[20]

Certain strains of bacteria, such as MRSA and extended-spectrum β-lactamase (ESBL)—producing *E. coli*, possess the ability to sustain their MDR phenotype and disseminate within the community. This phenomenon is primarily attributed to the presence of supplementary genetic material that counterbalances the fitness drawbacks associated with the expression of antibacterial resistance genes.[20]

Challenges of Managing Antimicrobial Resistance

The global cost of AMR is exorbitant and varies significantly from country to country. Low-income nations would bear a greater burden compared to the rest of the world. AMR has the potential to result in reduced productivity due to illness and premature mortality, disproportionately affecting the underprivileged population on a global scale.[23]

The fight against AMR in numerous LMICs is confronted with significant obstacles, including a substantial burden of infectious diseases, poverty, inadequate governance, health systems, and limited awareness.[24] The challenges posed by MDR organisms are manifold. They not only jeopardize the efficacy of therapeutics but also make individuals with compromised immune systems vulnerable. Moreover, MDR organisms can prolong illnesses, result in exorbitant medical expenses, and contribute to increased mortality rates.[25,26] No recent advancements have been made in the development of new classes of antibiotics to combat microbial infections. The absence of effective antibiotics is anticipated to result in a higher global mortality rate from MDR bacteria compared to the combined fatalities caused by diabetes and cancer.[27] The crisis of antibiotic resistance is further exacerbated by environmental pollution caused by pharmaceutical waste and waste from livestock and hospitals.[28]

Antimicrobial resistance (AMR) can be attributed to several factors, including the easy availability of medicines without prescription in pharmacies, self-medication practices, and the absence of laboratory services for proper testing of cultures and antibiotic susceptibility. Additionally, the different

- **MRSA** – A significant MDR bacterium that has effectively shifted from being solely associated with healthcare settings to becoming prevalent in the general population.
- **VRE** – High prevalence of strains in the community requires either an ongoing incoming supply of VRE into the shared community gut microbiome through the food chain, or a high level of antibiotic pressure.
- **Enterobacteriaceae producing extended spectrum β-lactamases** – Widespread resistance in community-associated Enterobacteriaceae isolates mediated by extended spectrum β-lactamases (ESBL).
- **Carbapenemase-producing Enterobacteriaceae** – Resistant to most antibiotics with poor clinical outcomes and the public health threat requiring urgent and aggressive action.
- **Carbapenem-resistant *A. baumannii* (CRAB)** – Intrinsically resistant to several antibiotic classes and carbapenem resistance is through acquisition of carbapenemases such as IMP-like carbapenemases and/or oxacillinases (OXA).
- **Multi-drug resistant *P. aeruginosa*** – Acquires additional antibiotic resistance quite readily and rapidly following exposure to antibiotics.

Fig. 3: Antibiotic-resistant organisms typically found in hospital settings, now also seen in community settings

approaches taken by doctors, such as the fear of missing a bacterial infection or the need to cover for a secondary bacterial infection, along with outdated knowledge of antibiotic guidelines, contribute to the problem. The inappropriate and empirical use of antibiotics, the unnecessary simultaneous use of multiple antibiotics, and the failure to de-escalate antibiotics when not required further worsen the situation. Regulatory issues, such as the lack of strict policy implementation and control by regulatory authorities, differing perceptions among key stakeholders, and ethical challenges faced by healthcare professionals, also play a role. Furthermore, unethical commercial practices that encourage the sale of antibiotics in large quantities and the use of antibiotics by nonmedical and informal healthcare providers contribute to the rise of AMR.[28]

It is imperative to enhance the healthcare systems by implementing robust measures to tackle these challenges. This includes formulating effective regulations to combat the usage of unauthorized antimicrobials, promoting antimicrobial stewardship, creating treatment guidelines for prevalent infections, launching public awareness campaigns to encourage healthier health-seeking behaviors, investing in research and development of vaccines and newer drugs, enhancing water, sanitation, and hygiene practices to prevent common infections, and implementing diagnostic tests for early detection and treatment of infections in order to mitigate the current rise of AMR.[24] Figure 4 describes the important factors that have the potential to greatly contribute to the global battle against AMR.[29]

It is imperative to have collective action, sustain political momentum, and establish robust multisectoral collaboration and partnerships among all stakeholders globally to address the issue of AMR. This comprehensive approach should involve healthcare providers, patients, government and nongovernment agencies, researchers, public health practitioners, hospital administrations, pharmaceutical companies, policymakers, and leaders in the agriculture industry.[23]

Guidelines on Antibiotic Usage

Clinical practice guidelines have the potential to enhance the quality of care through improving decision-making processes and the prescription of antibiotics. These guidelines offer a consistent and methodical approach to administering suitable treatments for particular infectious disease syndromes and infections caused by specific microorganisms. In regions where there is a scarcity of laboratory resources and specialized expertise, these guidelines can be especially valuable.[30,31]

Infectious Diseases Society of America 2023: Empiric Therapy in General

The selection of treatment should be determined by considering the probable pathogens, the probable origin of the infection, the seriousness of the illness, and also the patient-specific factors like significant immune deficiency and long-standing kidney disease.

When determining the appropriate empiric treatment for a patient, it is crucial to take into account the previous organisms identified from the patient and the associated antimicrobial susceptibility testing (AST) data within the last 12 months, if available. Additionally, the patient's exposure to antibiotics in the past 30 days and the local AST patterns should also be considered.

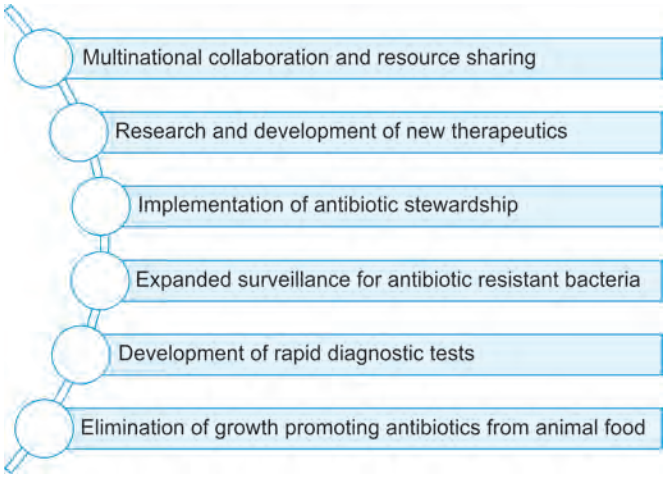

Fig. 4: Factors contributing to the global battle against AMR

Decisions must be further made by considering the pathogen's identity and AST profile, as well as identifying any significant β-lactamase genes.

The current treatment plan needs to be modified by introducing an active regimen for the entire duration of the treatment course, right from the initiation of active therapy, especially if the AST results suggest the presence of an agent that may not be effective.[32]

Infectious Diseases Society of America 2023: Duration of Therapy

- There should be no variation observed in infections caused by organisms with resistant and susceptible phenotypes.
- It is crucial to take into account significant host factors that are associated with immune status, the ability to achieve source control, and the overall response to therapy.
- Transitioning to oral therapy should take into account the susceptibility to a suitable oral medication, if the patient's hemodynamic condition is stable, if adequate measures for source control have been achieved, and if there are no concerns regarding inadequate absorption in the intestines.[32]

Rational Antibiotic Use as per the Indian Council of Medical Research, India

- Make a clinical diagnosis.
- Restrict the administration of empirical antibiotics to only those patients who are critically ill.
- Know the causative organisms
- Consider the potential resistant patterns when selecting a suitable antibiotic.
- Deescalation or modification of empiric broad-spectrum antibiotics is determined by the culture and antimicrobial susceptibility reports, as well as the patient's current condition.
- Discontinue the use of antibiotics in clinical scenarios such as rhino sinusitis, viral pharyngitis, and bronchitis. Also, refrain from prescribing antibiotics for noninfectious cardiopulmonary syndromes that are misdiagnosed as pneumonia, as well as for skin and soft tissue infections such as subcutaneous abscesses and lower extremity stasis dermatitis. Furthermore, avoid treating asymptomatic bacteriuria and pyuria, including in catheterized patients. It is also important to consider the possibility of microbial colonization and culture contamination, as well as low-grade fever when deciding whether or not to administer antibiotics

- Limit the treatment duration.
- Enhance pharcokinetic-pharmacodynamic parameters: Administer loading doses as required, monitor therapeutic drug levels for both toxicity and effectiveness and optimize drug administration or infusion.[33]

The guidelines for antibiotic prescription in ICUs in India are shown in Table 2.[34]

Curtailing Antimicrobial Resistance: Multidisciplinary Approach to Antibiotic Stewardship Program

Given the escalating global issue of AMR, it is becoming imperative not only to seek out novel antimicrobial agents but also to devise effective strategies aimed at diminishing the emergence and prevalence of resistance. Additionally, countering the rapid development of antibiotic resistance by pathogenic microorganisms is of utmost significance.[4] Efforts must be coordinated globally to address the AMR crisis effectively. The objective of the "one health" approach

Table 2: Guidelines for prescribing antibiotics in the ICU in India

Community-acquired pneumonia (CAP)	• Individualize antibiotic therapy to cover commonly implicated organisms (ESBL-producing *Enterobacteriaceae*, *Pseudomonas*, or MRSA). • Promptly start empirical therapy (combination) that targets the common causative organisms in patients with CAP who require ICU admission. Ideally, this therapy should be initiated within the 1st hour after obtaining the necessary microbiologic samples. • If there are no risk factors for *P. aeruginosa* infection, it is recommended to use a nonpseudomonal β-lactam (ceftriaxone, cefotaxime, or amoxicillin-clavulanic acid) in combination with a macrolide (either clarithromycin or azithromycin). • For patients allergic to penicillin and do not have any clinical suspicion of tuberculosis, the recommended treatment options include respiratory fluoroquinolones such as moxifloxacin, levofloxacin, or ciprofloxacin, along with aztreonam. • *P. aeruginosa*: Antibiotics with activity against both pneumococcal and pseudomonal infections, that is, cefoperazone, cefoperazone-sulbactam, ceftazidime piperacillin-tazobactam, meropenem, imipenem, and cefepime. Combination therapy may be considered by adding aminoglycosides or antipseudomonal fluoroquinolones such as ciprofloxacin. • MRSA: Empiric addition of either vancomycin or teicoplanin is recommended; linezolid is a suitable alternative for patients who are intolerant to vancomycin, those with vancomycin-resistant *S. aureus* (VRSA), or individuals with renal failure. • The potential danger of anaerobic infection can be addressed by using antibiotics that have an anaerobic activity, such as clindamycin, moxifloxacin, or amoxicillin-clavulanate. • If there is an indication, carbapenems or piperacillin-tazobactam can be used as empirical therapy for anaerobes. Duration of antibiotic therapy: • CAP requiring ICU admission: 7–10 days. • CAP due to *Pseudomonas/*or aspiration pneumonia: 14 days. • Necrotizing pneumonia due to GNB, MRSA, or anaerobes: 14–21 days. • The duration of treatment should be tailored to the specific causative organism, the patient's response to treatment, the severity of the disease, and any associated complications.
Ventilator-associated pneumonia (VAP)	• In ICUs where the prevalence of MRSA is <15%, the resistance of gram-negative organisms is <10%, and the risk of MDR pathogens is not high, it is recommended to use a single antibiotic that is effective against both MSSA and *Pseudomonas*, rather than a combination antibiotic. • In cases at high risk of MDR pathogens or in an ICU setting with a significant prevalence of MRSA (>15%) and resistant gram-negative organisms (>10%), it is crucial to administer a treatment that targets MRSA and includes at least two agents that are effective against gram-negative organisms, including *P. aeruginosa*. • It is recommended to use two agents that are effective against gram-negative organisms, including *P. aeruginosa,* in ICU, where the prevalence of resistant gram-negative organisms is high (>15%) but the risk of MDR pathogens is low, and the prevalence of MRSA is <10%. • Colistin is not advised for regular use as an initial treatment. However, it can be considered in cases where there is a significant occurrence of CRE, surpassing 20%. • Empirical antibiotic regimen not to include coverage for atypical organisms routinely. • If the ongoing empirical antibiotics regimen for VAP does not include carbapenems (imipenem or meropenem) or piperacillin-tazobactam, metronidazole, or clindamycin should be added to the regimen for patients with risk factors for anaerobic organisms. • The unconventional approach is to use a combination of antibiotics, including fluoroquinolones (moxifloxacin or levofloxacin) or macrolides (clarithromycin or azithromycin). Duration of therapy: • VAP with positive clinical response to therapy: Short course for 7–8 days. • Consider a prolonged duration, that is, 14 days of antibiotic treatment in cases of VAP caused by NF-GNBs or linked to severe immunodeficiency, structural lung disease, empyema, lung abscess, necrotizing pneumonia, and inappropriate initial antimicrobial therapy.
Catheter-related bloodstream infections (CRBSI)	• An effective antibiotic regimen should encompass treatment for both gram-negative and gram-positive bacteria. • Vancomycin or teicoplanin are the preferred first line drugs for empiric treatment of CRBSI caused by MRSA and MR-CONS. In case of intolerance or contraindications, linezolid and daptomycin can be considered as alternative treatment options. • To ensure comprehensive treatment for gram-negative bacilli, it is recommended to include either a fourth generation cephalosporin, a carbapenem, or a combination of β-lactam/β-lactamase inhibitors with or without the addition of an aminoglycoside. • For the management of suspected central line-associated candidaemia, it is recommended to use either echinocandin or fluconazole as empirical antifungal agents. Duration of therapy • Uncomplicated cases of *S. aureus* CRBSI and infective endocarditis require a minimum of 2 weeks of treatment. • Complicated cases of the same infections may require a longer treatment period of 4 - 6 weeks. • Gram-negative CRBSI typically needs a minimum of 7 days of treatment, while CONS bacteremia can be treated for 5–7 days. • In cases of suspected fungal CRBSI, it is recommended to administer antifungal therapy for a minimum of 14 days.

Contd…

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Sepsis of the urinary and urogenital systems	• The initial option for addressing ESBL-producing gram-negative organisms includes β-lactam in combination with a β-lactamase inhibitor, aminoglycosides, or carbapenems. • It is not recommended to use antibiotics targeting gram-positive organisms as the initial empirical regimen for UTI. • Antifungals should be considered as part of the empirical treatment in suitable clinical scenarios.
Abdominal infections	• It is not recommended to routinely use prophylactic antibiotics for the prevention of pancreatic infection after acute pancreatitis, regardless of its severity. • Selection of an appropriate antibiotic regimen for infected pancreatic necrosis should be based on local microbiological data, susceptibility patterns, the pharmacokinetic properties of antibiotics, and the patient's previous antibiotic exposure. • Empirical therapy for treatment-naïve patients presenting with infected pancreatic necrosis should include the administration of piperacillin-tazobactam, carbapenems, or cefoperazone-sulbactam. • In patients who are not showing a response or have already been exposed to piperacillin-tazobactam, cefoperazone-sulbactam, or carbapenems, it is recommended to include colistin in the empirical treatment regimen. • The duration of antibiotic therapy should be determined based on the clinical, laboratory, and radiological parameters.
Central nervous system infections	CAIs like meningitis: • Recommended empirical antibiotics consist of a third generation cephalosporin, preferably ceftriaxone, in combination with vancomycin. • If the individual is >50 years old, it is recommended to include ampicillin or amoxicillin in the treatment regimen. • Chloramphenicol and vancomycin are the preferred antibiotics when β-lactams are contraindicated; cotrimoxazole should be considered an additional treatment option if the patient is over 50 years old. • An alternative regimen could involve the use of either ciprofloxacin or aztreonam in combination with vancomycin. If the patient is > 50 years old, cotrimoxazole may be added to the treatment plan. • Recommended duration of antibiotics varies depending on the suspected or isolated organisms. For *S. pneumonia*, it is 10–14 days; in the case of *S. agalactiae*, the duration is extended to 14–21 days. For *N. meningitides* or *H. influenza*, a 7-day course is sufficient; however, for aerobic gram-negative bacilli, it is recommended to continue antibiotics for 21 days; in the case of *Listeria monocytogenes*, a minimum of 21 days is required; if no microorganism is identified, a duration of at least 10–14 days is recommended. Nosocomial infections like meningitis: • Empirical antibiotics of choice are vancomycin + cefepime, ceftazidime, or meropenem. • Colistin may be administered if there is a high occurrence of CRE or drug-resistant acinetobacter in the particular unit/department. • If β-lactams are not recommended due to contraindications, it is advised to substitute it with either ciprofloxacin or aztreonam. • If the infection shows inadequate response to suitable systemic antibiotics either clinically or microbiologically, intraventricular/intrathecal antibiotics should be considered.
Skin and soft-tissue infections (SSTI)	• For the treatment of moderate nonpurulent SSTI, the recommended initial options are IV penicillin or clindamycin. • Severe nonpurulent SSTI can be effectively treated by combining piperacillin-tazobactam with medications that provide coverage for MRSA, such as teicoplanin, vancomycin, daptomycin, or linezolid. • Severe purulent SSTI will need incision and drainage, followed by the administration of empiric antibiotics like piperacillin-tazobactam, along with coverage for MRSA using teicoplanin, daptomycin, vancomycin, or linezolid. • Treatment for monomicrobial necrotizing infection caused by *S. pyogenes* or *Clostridial* species would need a combination of penicillin and clindamycin. • Treatment for polymicrobial necrotizing fasciitis involves a combination of piperacillin-tazobactam, fluoroquinolone, and clindamycin. • Severe nonpurulent SSTIs necessitate a minimum of 5 days of antibiotic treatment; in cases of severe SSTIs accompanied by organ dysfunction, a prolonged course of antibiotics lasting 2–3 weeks is recommended.
Unknown cause for sepsis	• It is recommended to administer a combination of ceftriaxone and either doxycycline or a macrolide as empirical antimicrobial therapy to treat community-acquired sepsis of unknown origin in the ICU. • It is recommended to administer empirical antimicrobial therapy with a combination of a β-lactam/β-lactamase inhibitor with either a fluoroquinolone or an aminoglycoside to treat nosocomial sepsis of unknown origin in the ICU. • Duration of treatment is usually 7–10 days, although in cases where patients exhibit a slow response, longer courses may be recommended.

is to attain optimal health outcomes for all, encompassing humans, animals, plants, and the environment. This necessitates the implementation of strategies to prevent the misuse of existing antimicrobials, halt the transmission of infections, and eradicate their inappropriate use.[3]

Despite the rapid development of antimicrobial stewardship (AMS) in hospitals, there is a need for greater attention toward antibiotic prescription in ambulatory care and antibiotic exposure in the community. This necessitates not just a change in the behavior of prescribers but also a shift in the public perception of the risks and benefits associated with antibiotics. The implementation of rapid diagnostic tests to promptly identify MDR organisms can effectively reduce the unnecessary use of broad-spectrum antibiotics.[20]

A comprehensive approach is necessary for AMS, involving a collaboration between an infectious disease physician, a microbiologist, and hospital administration to ensure logistical and financial support. It is essential for all hospitals to establish an AMS program that includes the ICUs. As part of this program, it is recommended to conduct a prospective audit of antibiotic use and consider preauthorization whenever possible, providing feedback to the treating team. However, the use of antibiotic cycling as a method within the AMS program should

be avoided. Additionally, strategies should be implemented to facilitate the timely transition from intravenous to oral antibiotic therapy, aiming to reduce healthcare costs and the length of hospital stays. Antibiotic deescalation, which involves switching from broad-spectrum antimicrobials to narrower spectrum options, is also recommended in the ICU setting to minimize the emergence of MDR bacteria and healthcare expenses.[34]

The Three Clearly Communicated Goals of Antimicrobial Stewardship Programs

It is crucial to adopt a cost-effective approach that minimizes the potential risks of adverse events caused by antibiotic misuse to optimize the chances of achieving favorable clinical results in patients undergoing antibiotic treatment. Additionally, it is essential to extend the lifespan of existing antibiotics by reducing the selective pressure that fuels the emergence of resistant pathogens, particularly the ESKAPE bacteria.[27]

The multifaceted approach involving policymakers, the healthcare industry, healthcare professionals, the agricultural sector, and individual patients, if appropriately executed, can successfully tackle and potentially diminish the prevalence of MDR-related infections and fatalities globally.[35]

Conclusion

Antimicrobial resistance (AMR) is a significant problem globally that leads to death and economic burden both in hospitals and communities. While the ICU has traditionally been seen as the main source of MDR, there has been a noticeable shift towards nursing homes, general wards, and the community. The increase in MDR bacteria has resulted in the spread of resistance genes among different bacterial species. The widespread use of antibiotics in humans and animals has created selective pressure, leading to the emergence of resistant strains. The effectiveness of commonly used antibiotics is diminishing due to unnecessary overuse. This poses a serious threat to clinical treatment and emphasizes the need for greater attention to control the rising AMR and preserve the efficacy of available antibiotics. Strengthening efforts to control and prevent the spread of antibiotic-resistant bacteria, including improved infection control practices and appropriate antibiotic use, is crucial. The combination therapies of current antibiotics and antibiotic adjuvants are considered to be one of the solutions to address the emerging AMR phenomenon. It is also crucial to consistently monitor the trends of antibiotic resistance in order to assess the efficacy of interventions and detect any emerging patterns of resistance.

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REVIEW ARTICLE

A Review of Olmesartan-based Therapy in Targeting Effective Blood Pressure Control and Achieving Blood Pressure Goals

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Abstract

For >3 decades now, angiotensin receptor blockers (ARB) have been used in the management of hypertension (HTN) and HTN-related cardiovascular (CV) diseases. Olmesartan medoxomil (OLM) is an angiotensin II type 1 (AT1) receptor antagonist (or blocker) that binds tightly to the AT1 receptor with long-lasting efficacy over the 24-hour period and safety demonstrated in several trials. It is well tolerated and effective in reducing blood pressure (BP) in mono and combination therapy with thiazide diuretics or calcium channel blockers across a wide range of patient subgroups. The effectiveness and safety of OLM-based combination therapies have good and tolerable profiles with high adherence in the fixed single-pill formulation. Consistent antihypertensive efficacy and good tolerability when used as monotherapy or as a combined therapy make OLM a valuable treatment option for adults with HTN. In this review, we discuss the important clinical implications of OLM as an optimal choice as monotherapy and combination therapy in managing patients with HTN.

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Overview

Angiotensin receptor blockers (ARBs) are widely regarded as the optimal first-line choice for initiating and maintaining hypertension (HTN) treatment, supported by numerous randomized controlled studies. Many International and Indian guidelines recommend ARBs for initiation and maintenance treatment of HTN either as mono or combination therapy.[1–4] ARB in combination therapy along with calcium-channel blocker (CCB) or diuretic is recommended when the goal/or target blood pressure (BP) is not achieved, where its use is preferred in single-pill combinations (SPCs).[2] ARBs in dual combination with a diuretic or a dihydropyridine CCB have the advantage of pharmacodynamic properties of two classes of antihypertensive drugs with significant BP lowering efficacy, good tolerability, and adherence to therapy. A triple combination therapy with an ARB, CCB, and a diuretic may be needed to achieve the recommended BP targets in patients with difficult-to-treat HTN and those not well controlled on dual therapy.[5]

Olmesartan Medoxomil: an Effective ARB

Olmesartan medoxomil (OLM) is a highly effective ARB that has demonstrated its efficacy in the treatment of HTN.[6] It exhibits a strong affinity and prolonged binding to the angiotensin II type 1 (AT1) subtype receptors, resulting in a long-lasting competitive inhibition of angiotensin II. This characteristic has significant clinical implications.[7] OLM also displays a high degree of insurmountability and greater affinity to type 1 receptor compared to other ARBs.[8]

Olmesartan medoxomil (OLM) is quickly absorbed when taken orally and undergoes metabolism to become active. It reaches steady-state levels with once-daily dosing within a span of 3–5 days. The bioavailability of OLM is ~26%, and it reaches its maximum concentration within 1–2 hours. Unlike other ARBs like losartan, telmisartan, valsartan, and eprosartan, the bioavailability of OLM is not affected by food (Table 1).[8,9]

Compared to other ARBs, a more homogeneous and sustained control of BP over 24 hours with OLM has a consistent buffering effect on BP variability that helps prevent cardiovascular (CV) complications with uncontrolled HTN and short-term BP fluctuations.[1] OLM, in addition to effectively reducing BP, delays the onset of microalbuminuria and decreases the occurrence of nonfatal CV events.[12] OLM has vasoprotective properties with a positive impact on endothelial dysfunction and inflammation and reduction of vascular hypertrophy, reduction in thickness of carotid intima-media and volume of atherosclerotic plaque, and reversal of vascular remodeling.[13–15]

Clinical Use of OLM Either Alone or in Combination

Olmesartan medoxomil (OLM) is a highly efficacious and well-received therapeutic choice for management of HTN that may be used as monotherapy and in combination with other antihypertensive agents.[8]

Olmesartan Medoxomil Monotherapy

Clinical studies have shown OLM is a well-received treatment option that is suitable for both individuals newly diagnosed with HTN and those whose BP is not satisfactorily managed with other antihypertensive therapies.

A total of >10,000 subject data from trials like WINOVER, OLMEBEST, and Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) established the efficacy and tolerability of OLM monotherapy.

The WINOVER study conducted by Kumbla et al. was an open-label, noncomparative, multicentric, real-world postmarketing observational study. It involved a total of 8,940 Indian adults with HTN who were treated with OLM 20/40 mg once daily for a duration of 6 months. A statistically significant reduction in both systolic and diastolic BP (DBP) was reported from day 15 to the end of the study period ($p < 0.0001$), with an increase in the number of responders to systolic BP (SBP) and DBP. OLM in both doses, that is, 20 and 40 mg, was effective and well tolerated, with no serious adverse events in newly diagnosed patients with inadequate BP control.[16]

The OLMEBEST study, conducted in nine European countries and involving 463 centers, was a prospective, partially randomized, double-blind study. The study included 2,306 adult patients aged between 18 and 75 years who had mild to moderate essential HTN with sitting DBP between

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90 and <110 mm Hg. The process of gradually titrating the dosage of OLM (up to a maximum of 40 mg/day) was found to be effective and well-tolerated in patients who had not responded adequately to a lower dose of OLM (20 mg) as a single therapy option.[17]

The ROADMAP study was an observational study conducted over an average period of 3.3 years that included 1,758 participants (placebo arm: 877; OLM arm: 881). Administration of OLM medoxomil (40 mg) was found to effectively postpone the development of microalbuminuria in individuals with type 2 diabetes and normoalbuminuria.[18]

In a multicenter, randomized, double-blind trial by Oparil et al., the antihypertensive efficacy of once-daily OLM (20 mg) was compared to the starting doses of other ARBs such as 50 mg of losartan, 80 mg of valsartan, and 150 mg of irbesartan in patients with essential HTN (n = 588 patients with ambulatory BP monitoring: cuff DBP of ≥100 and ≤115 mm Hg and mean daytime DBP of ≥90 and <120 mm Hg). The study found that the starting dose of OLM was more effective than the starting doses of the other ARBs. The reduction in 24-hour mean SBP and DBP with OLM (20 mg) was greater vs 50 mg of losartan, 80 mg of valsartan, and 150 mg of irbesartan (Fig. 1).[19]

In a comparative study among 60 patients with stage 1 HTN who were randomly assigned to receive OLM (20 mg), telmisartan (40 mg), or losartan (50 mg) in an open-label, parallel-group design, the efficacy of OLM in reducing BP was found to be highest. BP assessments were carried out at 2-week intervals over a period of 3 months. OLM was found to be significantly more effective than telmisartan and losartan in reducing SBP (p < 0.0001). Also, the reduction in DBP achieved with OLM was significantly superior to that observed with losartan (Fig. 2). OLM was also found to significantly decrease lipid parameters (serum triglycerides, total cholesterol, and low-density lipoprotein-cholesterol) compared to Losartan.[20]

In a study conducted by Nakayama et al., an open-label crossover trial showed that OLM had a significantly higher efficacy than telmisartan in reducing systolic, diastolic, and mean BP. OLM also demonstrated a significant reduction in both daytime and nighttime mean BP levels compared to telmisartan. OLM also exhibited a significant decrease in inflammatory markers, such as serum IL-6 and hs-CRP, when compared to telmisartan.[21]

Ono et al. carried out a retrospective analysis of medical records of patients diagnosed with chronic kidney disease (serum creatinine <3 mg/dL and urinary protein of 0.3–3.5 gm/gm creatine) who received treatment with ARBs. OLM, compared to other ARBs such as losartan, valsartan, and telmisartan, showed a greater reduction in BP and protein loss in patients with nondiabetic chronic renal failure. This beneficial effect of OLM may contribute to the preservation of renal function over time.[22]

Telmisartan has been associated with a frequent occurrence of myalgia and elevated creatine phosphokinase levels, whereas such adverse events are extremely rare with OLM. The dissimilarity in lipophilicity and activation

Table 1: Pharmacological and pharmacokinetic properties of ARBs[10,11]

Properties	*Olmesartan*	*Losartan*	*Telmisartan*	*Valsartan*	*Irbesartan*	*Candesartan*	*Eprosartan*
AT1 affinity vs AT2	12,500-fold	1,500-fold	3,000-fold	20,000-fold	8,500-fold	10,000-fold	1,000-fold
Half-life (in hours)	13	6–9	24	6	11–15	9	20
Time to BP effect (weeks)	1–2	3–6	4	4	2	2–4	2–3
Food interactions	No	10% decrease in bioavailability	6–20% decrease in bioavailability	≈ 50% decrease in AUC (NS)	No	No	Delayed absorption (NS)
Drug interactions	None	Rifampin; fluconazole	Digoxin	None	None	None	None
Dose in hepatic impairment	No change	↓Initial dosage	Use with caution	No change	No change	↓The initial dosage in moderate impairment	No change

AT1, angiotensin type 1 receptor; AT2, angiotensin type *2* receptor; AUC, area under the curve; NS, not significant

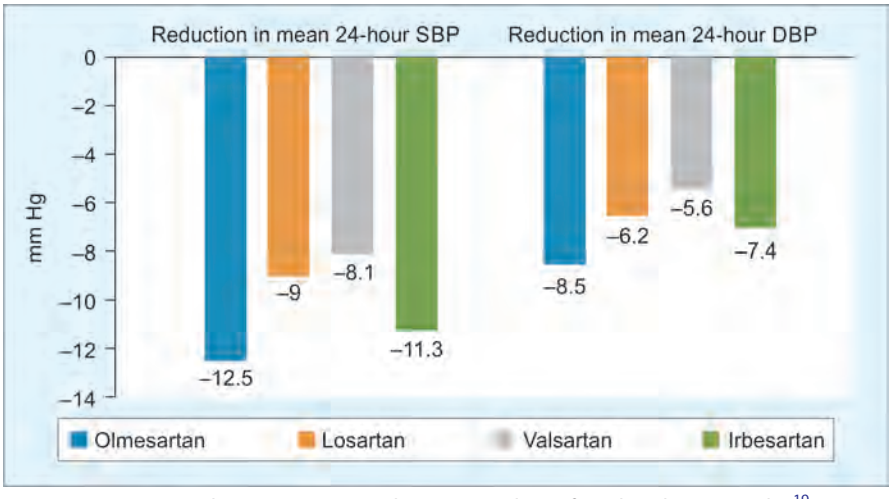

Fig. 1: OLM vs ARBs: reduction in mean 24-hour SBP and DBP from baseline to week 8[19]

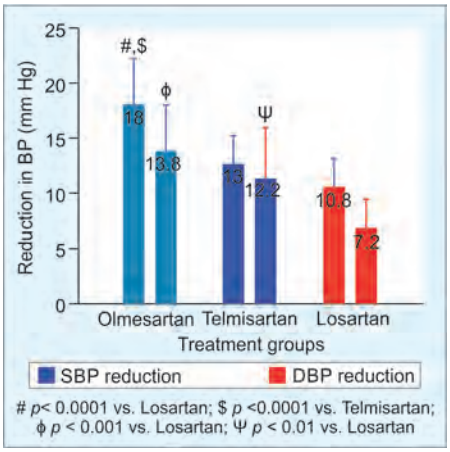

Fig. 2: Comparison of reduction in SBP and DBP with OLM vs telmisartan and losartan after 12 weeks[20]

of peroxisome proliferator-activated receptor γ receptors might explain the development of this reaction specifically with telmisartan but not with OLM.[23]

Olmesartan Medoxomil-based Combination Therapy

No severe drug conflicts have been reported among ARB, CCB, and diuretics when used together, as they have different pharmacological pathways. Therefore, these medications are recommended for patients with moderate-to-severe HTN and for those who do not achieve BP goals with monotherapy.[24] Multiple clinical trials have demonstrated the clinical efficacy and safety of combination therapies of OLM formulated in a single pill, which has a good tolerability profile with patients adhering well to the prescribed treatment regimen.[7]

Dual Combination of Olmesartan Medoxomil and Amlodipine

The combination of OLM and amlodipine has been proven to be safe and effective in attaining and sustaining optimal BP control throughout a 24-hour period. This combination has also been associated with a decrease in BP variability among patients suffering from moderate-to-severe HTN not effectively managed with a single medication.[25]

In an open-label, randomized, multicenter study conducted by Lin et al., the efficacy and safety of OLM and amlodipine in fixed-dose combination (FDC) (20/5 mg) were compared to doubling the dose of amlodipine to 10 mg in patients who did not respond well to amlodipine monotherapy (5 mg daily for at least 2 weeks). The study found that the reduction in both office and ambulatory BP was greater with OLM plus amlodipine FDC compared to the double dose of amlodipine. About 67.1% vs 54.9% of patients had well-controlled BP with OLM and amlodipine FDC vs double doses of amlodipine, respectively ($p = 0.117$) after 8 weeks of treatment.[26]

Dual Combination of Olmesartan Medoxomil and Hydrochlorothiazide

In a study conducted by Chrysant et al., a randomized, double-blind, factorial design was used to investigate the effectiveness of different combinations of OLM (10, 20, or 40 mg/day) and hydrochlorothiazide (HCTZ) (12.5 or 25 mg/day). The study included 502 patients who were not able to control their BP with either OLM or HCTZ alone. The baseline mean seated DBP (SeDBP) ranged from 100 to 115 mm Hg. The results showed that the combination of OLM and HCTZ resulted in greater reductions in both SeDBP and seated SBP (SeSBP) compared to monotherapy with either component. At week 8, the mean reduction from baseline in trough SeSBP/SeDBP was 20.1/16.4 mm Hg with OLM/HCTZ (20/12.5 mg) and 26.8/21.9 mm Hg with OLM/HCTZ (40/25 mg), while the reduction with placebo was only 3.3/8.2 mm Hg.[27]

Triple combination of Olmesartan Medoxomil plus Amlodipine plus HCTZ

The addition of HCTZ to various dose combinations of OLM/AML is well tolerated and enhances the management of BP by significantly reducing DBP and SBP, as well as significantly increasing the attainment of the BP threshold in patients with moderate-to-severe HTN.[28] The SPC of OLM/AML/HCTZ proves to be effective in lowering BP and successfully attaining and sustaining target BP control in patients with HTN who are undergoing treatment and have uncontrolled BP despite dual combination therapy.[29,30]

The TRINITY study, a multicenter, randomized, double-blind, parallel-group study by Oparil et al., aimed to compare the effectiveness of triple combination therapy with OLM, AML, and HCTZ vs the dual combinations in patients with moderate-to-severe HTN (SeSBP of ≥140/100 or ≥160/90 mm Hg) demonstrated the superiority of the triple combination treatment. The specific triple combination used was OLM 40 mg + AML 10 mg + HCTZ 25 mg, which was compared to dual combinations of the individual components, including OLM 40 mg/AML 10 mg in FDC, OLM 40 mg/HCTZ 25 mg in FDC, and AML 10 mg + HCTZ 25 mg. Patients receiving the triple combination treatment had a significantly higher proportion of achieving their BP targets compared to those on the dual combinations at week 12 ($p < 0.001$) (Fig. 3). All patients had good tolerance to all treatments.[31]

Olmesartan medoxomil (OLM) demonstrates effective results in reducing and stabilizing BP either independently or in combination with other antihypertensive medications. Its combination with ALM or HCTZ yields superior outcomes in BP management (Table 2) while maintaining a favorable level of tolerability.[8]

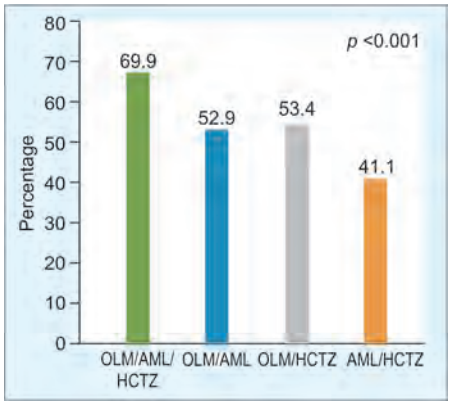

Fig. 3: Patients reaching the BP target (<140/90 mm Hg) at week 12; OLM, olmesartan; AML, amlodipine; HCTZ, hydrochlorothiazide[31]

Table 2: Olmesartan use in patients with HTN

Treatment	*Dose*	*Potential use by patient characteristics*	*Benefits*
Monotherapy OLM[16]	20 and 40 mg	• Stage 1 HTN/newly diagnosed HTN. • BP not adequately controlled with other anti-HTN agents.	24-hour BP control and target organ protection (cardiorenal) beyond BP-lowering effects
Dual therapy OLM AML[26,32–34]	20/5 and 40/10 mg	• Hypertensive patients >50 years of age not controlled with monotherapy. • HTN with T2DM.	More effective BP reduction with lower incidence of side effects like edema vs monotherapy with a high dosage of AML
OLM with HCTZ[27,35,36]	20/12.5, 40/12.5, and 40/25 mg	• Hypertensive patients <50 years of age not controlled with monotherapy. • Initial therapy for those requiring large reductions in BP to achieve goal BP.	High degree of clinical efficacy combined with good tolerability
Triple therapy OLM + ALM + HCTZ[31,37]	40/10/25, 40/10/12.5, 40/5/25, 40/5/12.5, and 20/5/12.5 mg	Inadequately controlled HTN on high-dose dual combination of OLM/AML	Greater proportion of seated and ambulatory BP reduction and improved achievement of BP targets

Conclusion

Olmesartan medoxomil (OLM), an angiotensin II receptor antagonist, demonstrates strong efficacy in reducing and stabilizing BP. Unlike other ARBs, OLM is available as a standalone treatment as well as in combination with AML and/or HCTZ in dual and triple single-pill formulations. The rationale behind combining an ARB with a CCB and a diuretic lies in their complementary mechanisms of action. By targeting both renin-dependent and renin-independent pathways, this combination approach may lead to additional BP reduction, improved tolerability, and decreased BP variability. When used in conjunction with HCTZ or amlodipine, OLM exhibits superior BP control and a lower incidence of adverse events. Its reliable efficacy and tolerability contribute to high adherence rates. Notably, OLM's high potency does not result in increased adverse events or other tolerability concerns, even among vulnerable populations, namely those with comorbidities like type 2 diabetes mellitus (T2DM). Consequently, OLM-based treatment strategies are suitable for a wide range of patient subgroups, with clinical trial data supporting its use as both monotherapy and combination therapy in hypertensive patients. Additionally, OLM has been shown to reduce vascular microinflammation in individuals with essential HTN, further contributing to its beneficial CV effects.

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REVIEW ARTICLE

The 5 Ws of Ambulatory Blood Pressure Monitoring

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Abstract

Blood pressure (BP) measurement is affected by multiple variables which influence clinical management decisions and patient outcomes. Around 24-hour ambulatory blood pressure monitoring (ABPM) avoids incorrect diagnosis of hypertension (HT), and unnecessary treatment and provides the best prediction of cardiovascular (CV) risk. Clinically important phenotypes of HT such as masked HT (masked HT), white coat HT (white coat HT), and nocturnal HT (nocturnal HT) may be missed by not incorporating ambulatory BP monitoring in practice. However, lack of device availability, operational difficulties, and cost remain barriers to its widespread acceptance in India. In this review, we discuss the when, what, who, why, and where (5Ws) relevant to ABPM measurement.

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Introduction

Hypertension (HT) is a leading cause of morbidity and mortality worldwide.

Recent data shows that since 1990 the number of people with HT worldwide has doubled.[1] The Fourth National Family Health Survey evaluated HT in a large population base (n = 799,228) of India and reported HT in 14% of men aged 15–54 years and 9% of women aged 15–49 years with an overall prevalence of 11%.[2] The Fourth District Level Household Survey screened adults >18 years for HT (n = 1320,555) and reported HT in 27% of men and 20% of women with an overall prevalence of 25%.[2] Search for an ideal blood pressure (BP) measurement technique has been the Achilles heel for HT.

When did Ambulatory Blood Pressure Monitoring Start?

Approximately, 300 years ago, Reverend Stephen Hales first measured, direct intraarterial BP in a horse.[3] The 1800s saw the development of sphygmographic devices to measure BP noninvasively in humans.[4] Over the years, evidence favored that BP is a continuous variable and needs to be done outside the clinician's office. The first report of BP measurement outside the clinic came almost a century ago.[5] AT Hinman et al. and Sokolow et al. are credited with the development of the initial semiautomatic ambulatory blood pressure monitoring (ABPM) in 1962.[6] Earlier subjects had to manually inflate BP cuff and Korotkoff sounds were recorded on a tape recorder. Their data showed that BP was variable during the day, correlated poorly with clinic measurements, and predicted risk and cardiovascular (CV) complications of HT.[7,8]

What are the Principles and Techniques of Ambulatory Blood Pressure Monitoring?

Ambulatory blood pressure monitoring (ABPM) devices should be validated independently according to internationally accepted protocols. The International Society of Hypertension and the European Society of Hypertension (ESH) have endorsed preferred and validated devices for ABPM.9 HT Canada accepts gold and silver level devices as accurate for ABPM.10 ESH gives guidance on the steps of ABPM.11 The ABPM device should be in working condition with annual maintenance. The individual has explained the device's function and procedure and is asked to carry out his usual daily activities. The use of a nondominant arm and an appropriate cuff size is recommended. A test measurement is done. It is advised to remain still with arms relaxed at each measurement, not to drive, and preferably avoid showering. A monitoring form is provided to record sleeping times, drug intake, or any symptoms and explains how to switch off the monitor in case of malfunctioning. The measurements are done every 20–30 minutes during the awake period and asleep period. The monitor is removed after 24 hours. A minimum of 20 valid awake and seven asleep readings should be recorded and at least 70% of the expected 24-hour readings should be valid. The readings are interpreted as shown in Table 1.[11] The ABPM data is reported on a single page showing a BP plot of 24 hours with normal bands defining an individual's sleep and awake time intervals and a summary of BP and heart rate during the 24 hours (Fig. 1).

The other significant aspect of BP is a marked circadian pattern, with a normal drop of >10% observed from the awake to the asleep period (dipping pattern). This is recorded in the ABPM report and provides a piece of important prognostic information depending on the type of dipping pattern Table 2.[11–13]

Who Needs Ambulatory Blood Pressure Monitoring?

Ambulatory blood pressure monitoring (ABPM) has utility in both the initial diagnosis and treatment of HT. ABPM is the gold standard for diagnosing HT, detecting white coat HT, masked HT, nocturnal HT, and nondippers. It also helps to detect BP fluctuations in autonomic dysfunction, and symptomatic hypotension, confirming the diagnosis of resistant HT, BP variability, morning surge, and ambulatory arterial stiffness index. Monitoring the effects of antihypertensive medications and long-term control could be done with ABPM. It may be repeated in high-risk populations such as

Table 1: Thresholds for diagnosis of HT by Ambulatory BP monitor

24-hour average	≥ 130/80 mm Hg	Primary criterion
Awake (daytime) average	≥135/85 mm Hg	Daytime HT
Asleep (nighttime) average	≥120/70 mm Hg	Nighttime HT

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[redacted]

Confirmed

Sentinel ABP Report

Patient ID:	[redacted]	Patient name:	[redacted]
Date of birth:	[redacted]	Gender:	Female
Height:		Weight:	
BMI:		BSA:	
Physician:		Ward/Dept:	

Medications **Indications (reason for test)**

Recording information

Start:	24/01/2022 13:13:00	Ambulatory Arterial Stiffness Index (AASI):	0.51
End:	25/01/2022 13:10:00	Morning Surge Index (MSI):	28.97
Duration:	23:57:00	Comfort mode max. pressure:	170
Successful readings:	37 (92.50%)	Child mode:	Disabled
Systolic > limits:	67.57%	Serial number:	90227-005451
Diastolic > limits:	54.05%		

Overall summary - Successful: 92.50% (37 of 40), Avg.: 142/79 mmHg

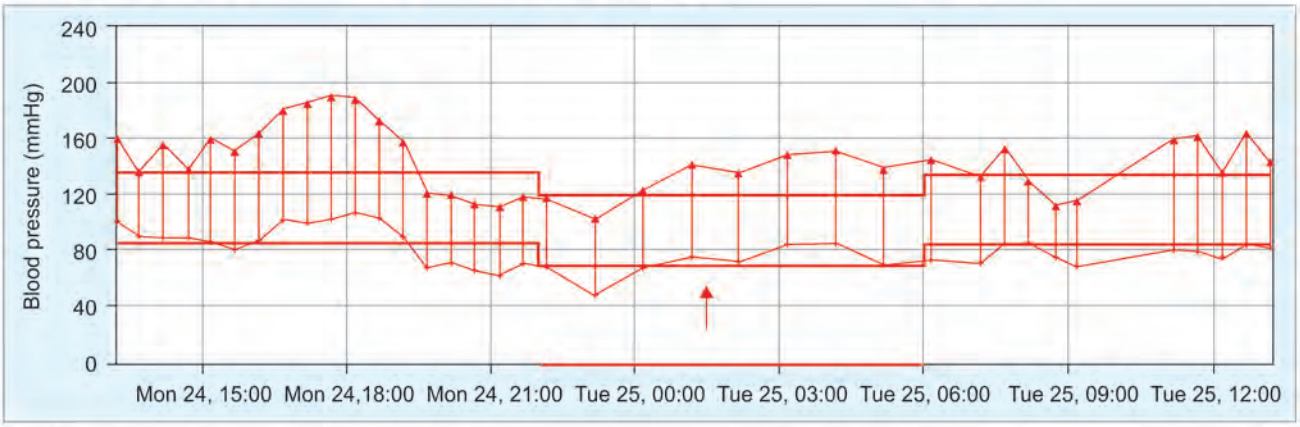
	Hourly avg.	Std. dev.	Min.	Max.	Dipping
Systolic (mmHg)	142	23.38	103 (23:10 Mon)	191 (17:40 Mon)	10.39 %
Diastolic (mmHg)	79	13.06	48 (23:10 Mon)	107 (18:10 Mon)	14.43 %
MAP (mmHg)	101	16.20	69	143	13.23 %
Pulse pressure (mmHg)	63	13.50	37	89	
Heart rate (BPM)	66	6.55	57	84	
Systolic > limits	67.57%	Diastolic > limits	54.05%	AASI: 0.51	MSI: 28.97

Wake periods summary - Successful: 90.63% (29 of 32), Normal values: 135/85 mmHg, Avg.: 147/83 mmHg

	Hourly avg.	Std. dev.	Min.	Max.
Systolic (mmHg)	147	24.06	112 (21:10 Mon)	191 (17:40 Mon)
Diastolic (mmHg)	83	12.29	62 (21:10 Mon)	107 (18:10 Mon)
MAP (mmHg)	105	15.99	80	143
Pulse pressure (mmHg)	64	14.84	37	89
Heart rate (BPM)	65	6.21	57	84
Systolic > 135 mmHg	65.52%	Diastolic > 85 mmHg		51.72%

Sleep periods summary - Successful: 100.00% (8 of 8), Normal values: 120/70 mmHg, Avg.: 133/72 mmHg

	Hourly avg.	Std. dev.	Min.	Max.
Systolic (mmHg)	133	16.87	103 (23:10 Mon)	152 (04:10 Tue)
Diastolic (mmHg)	72	11.90	48 (23:10 Mon)	86 (04:10 Tue)
MAP (mmHg)	92	12.23	69	105
Pulse pressure (mmHg)	61	6.89	49	69
Heart rate (BPM)	69	6.74	61	79
Systolic > 120 mmHg	75.00%	Diastolic > 70 mmHg		62.50%



Findings:

SPACELABS HEALTHCARE Spacelabs ABP version 10.0.2.7852 Generated on Wed 26 Jan 2022 13:18:59 Signed by Tech on 26/01/2022 13:18:54

Fig. 1: A sample of an Ambulatory BP monitor report of a hypertensive individual using a validated device. The arrow in the graph shows a dipping pattern

Table 2: Asleep BP dip (systolic and/or diastolic) compared with awake BP

BP dip (%)	*Dipping pattern*
<0%	Reverse dipper
0–10%	Nondipper
10–20%	Normal dipper
>20%	Extreme dippers

difficult HT, presence of target organ damage, high CV risk and to confirm the efficacy of treatment of nocturnal HT. In uncontrolled HT, it may be performed every 2–3 months until a normal 24-hour profile, and in controlled HT, might be done annually.[11,14]

Why is it Important to Monitor Ambulatory BP?

The readings of ABPM mirror the normal routine environment of an individual and are thus more likely to reflect a true BP profile. A systematic review revealed that office BP and home BP lacked sensitivity and specificity to be recommended as a single diagnostic test for HT.[15] Moreover, ABPM offered appropriate targeting of drug treatment around the diagnostic threshold.[15] Short-term BP variability, early morning surge, and nocturnal dipping are best ascertained by ABPM. Numerous target organ damage parameters like cognitive impairment in left ventricular mass, coronary artery stenosis, microvascular disease, and arterial stiffness have also been best correlated with ABPM.[16]

Where does Ambulatory Blood Pressure Monitoring Stand in India?

The Indian guidelines on HT-IV advise a daytime threshold of >135/85 mm Hg and a 24-hour mean of >130/80 mm Hg for diagnosis of HT by ABPM.[17] The India ABPM Study was a large multicentric study that analyzed office blood pressure measurement (OBPM) and ABPM data from 27,472 subjects.[18] Results showed that the mean OBPM values were higher than daytime ABPM values ($p < 0.001$) in all age-groups.[18] The prevalence of masked HT is 23% and white coat HT is 12% as per this study.[18] This data points to a significant need to incorporate ABPM in the diagnosis and optimal management of HT.

Unfortunately, ABPM is a highly underutilized modality among physicians in India and the diagnosis of masked HT and white coat HT is missed in the routine office BP measurements.[19] In a cross-sectional, observational, questionnaire-based survey by Hiremath et al. conducted at a cardiology conference (n = 260), it was reported that 72% of physicians used ABPM in < 5% of their patients, and 40% of them considered the use of ABPM in only 1% of patients.[20] The HOPE Asia network study reported that the use of ABPM in primary care settings is currently not an option in many Asian regions and it is used almost exclusively at referral centers.[16] Feasibility is limited mainly by the lack of device availability in primary care. Other barriers to its acceptance are cost, patient discomfort, and operational difficulties. Considering the benefit of avoiding misdiagnosis and mistreatment, preventing serious CV morbidity, the non-invasive nature, and the ease of procedure, there is an imminent need for the more widespread utility of ABPM in India.

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REVIEW ARTICLE

Hepatic Decompensation in Patients with Chronic Liver Disease: Exploring the Role of Vitamin D Deficiency as a Prognostic Marker

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Abstract

Introduction: Although the function of vitamin D as a regulator of calcium and bone metabolism is well recognized, its role as an immunomodulator, regulator of cellular differentiation, and anti-inflammatory and antifibrotic actions is being increasingly noted. It is estimated that one-third of liver cirrhosis patients are vitamin D deficient. It has been reported that as liver disease progresses, the incidence of vitamin D deficiency rises. Several clinical implications of vitamin D levels have been proposed, including as a prognostic marker for the assessment of mortality in liver cirrhosis.

Aim: To analyze the link between levels of vitamin D and decompensation of liver cirrhosis.

Materials and methods: This observational, cross-sectional study was conducted on 100 patients with liver cirrhosis admitted at Goa Medical College, a tertiary care government hospital in Goa, from March 2020 to February 2022. Demographic profile, history, and examination findings were recorded, and biochemical analysis included vitamin D levels. Child-Pugh (CP) and Model for End-Stage Liver Disease (MELD) scores were calculated, and based on these, patients were grouped into classes of disease severity. Data was interpreted using Statistical Package for the Social Sciences (SPSS) version 22.

Results: Mean age of the study population was 50 ± 9 years, with a 96% male predominance. Mean levels of vitamin D were 12.13, with a standard deviation (SD) of 7.38. Significant differences were noted between different classes of CP score (CPS). A vitamin D deficient state was noted in 93.3% CP class C group and 0% of class A group. A statistically significant association was demonstrated between low levels of vitamin D and CP class severity of liver dysfunction as well as MELD scores.

Conclusion: This study confirms a high prevalence of vitamin D deficiency among patients with liver cirrhosis concurrent with the results of similar studies done earlier. More importantly, with increasing severity of hepatic decompensation as measured by CPS and MELD, vitamin D concentrations reduce.

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Introduction

Vitamin D is a crucial hormonal regulator of bone metabolism. There is a complex alliance between serum calcium, phosphate, vitamin D, and parathyroid hormone (PTH) levels and liver cirrhosis and its consequences on the musculoskeletal system labeled as "hepatic osteodystrophy," which may contribute to the risk of fractures and morbidity. In addition to this function, the pleiotropic effects of vitamin D on cellular proliferation, differentiation, and immunomodulation are being increasingly recognized.

Functions of vitamin D includes[1]:

Extrahepatic Functions

- Calcium and bone homeostasis: Increased calcium and phosphate absorption in the small intestine and decreased PTH synthesis.
- Innate and adaptive immunity.
- Pancreatic and adipocyte function: Inversely affects body mass index, reduces metabolic syndrome, activates transcription of insulin genes, and improves insulin sensitivity in type 2 diabetes mellitus (DM).
- Cancer: Reduction in colorectal carcinoma and risk of NHL.

Hepatic

- Inhibition of *in vitro* hepatitis C virus (HCV) replication.
- Improvement of liver histology in nonalcoholic fatty liver disease (NAFLD).
- Prevention of liver fibrosis.
- Decreased risk of acute rejection post hepatic transplantation.
- Improved sustained virological response rates in HCV.

Vitamin D in the human body is mainly derived by dermal biosynthesis of cholecalciferol utilizing the ultraviolet B component of sunlight. Vitamin D_3 is also provided by dietary sources, including fish, eggs, and fortified foods, which undergoes absorption in the intestines aided by biliary acids and transported into circulation by chylomicrons.[2–4] Vitamin D_3 can be stored in adipocytes. Vitamin D binding protein (DBP) or albumin act as a transport protein and bind vitamin D and transfer it to the liver for 25-hydroxylation.[2] 25-hydroxy vitamin D (calcidiol) subsequently gets transported to the kidney, whereby enzymatic hydroxylation is converted to 1,25-dihydroxy vitamin D, that is, calcitriol, the most biologically active form of vitamin D. Serum calcium and phosphate levels regulate calcitriol production. Calcitriol is also bound to DBP and activates vitamin D receptors (VDR) which are expressed in several body tissues, including the liver, lymphocytes, pancreas, and gastrointestinal tract.

The 25-hydroxy vitamin D is the predominant blood metabolite with a half-life of 2–3 weeks. 25-hydroxy vitamin D is used for measuring vitamin D levels as it reflects the total quantity of vitamin D, including diet, dermal synthesis, plus conversion from fatty acids in the liver. 25-hydroxy vitamin D concentration is the most reliable Vitamin D status indicator.[5] Calcitriol has a half-life of approximately 4 hours. Eventually, 25-hydroxylase, most abundant in the kidney and intestine, catabolizes calcitriol into an inactive metabolite which is excreted in bile.[6] The regulation of expression of >200 genes by vitamin D regulators (VDR) makes it highly influential in processes of cellular proliferation, differentiation, apoptosis, immunomodulation, and angiogenesis.[7] Vitamin D insufficiency is defined as a 25-hydroxy vitamin D level <30 ng/mL and deficiency as levels <20 ng/mL.[8]

Vitamin D plays a pivotal role in various chronic diseases, including infections, DM, cardiovascular diseases, and some cancers.[9–12] It is estimated that about one-third of liver cirrhotics are vitamin D deficient.[4] Heuman

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et al. exhibited that vitamin D deficiency was more severe in cirrhotics with Child Pugh C than in A or B classes.[13] Various mechanisms may be responsible for vitamin D deficiency in chronic liver disease (CLD), such as malnutrition as, anorexia due to chronic illnesses, reduced dietary intake, low sunlight exposure, low intestinal vitamin D absorption, and reduced levels of albumin and DBP.[14–16] Poor oral intake stems from several factors, including an altered sense of taste, satiety caused by massive ascites, increased serum leptin concentration, fatigue, and low-grade encephalopathy. Fat malabsorption occurs due to the depletion of bile salts in cirrhotics, impaired small bowel motility due to bacterial overgrowth, and portal hypertension. Fat malabsorption induces fat-soluble vitamin deficiency as well as undernourishment. Also crucial is the impaired hepatic vitamin D hydroxylation leading to lowered synthesis of active hormone, while catabolism is increased.[17] Rapid transition from carbohydrates to fat stores for metabolism results in altered pattern of fuel consumption in advanced liver disease, similar to starvation.[18-20]

Previously, most of the research on vitamin D in CLD was concentrated on the evaluation of osteoporosis, skeletal demineralization, endocrine disorders, and osteomalacia in patients with hepatic insufficiency.[21,22] However, the focus has shifted, over the past decades, toward implications vitamin D may exert on the pathophysiology and progression of CLD. In developed nations, the most frequent cause of CLD is NAFLD, and nearly 30% of NAFLD have nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis.[23] The brunt of the progression of NAFLD to NASH falls on insulin resistance-mediated metabolic syndrome.[24] Optimal vitamin D status enhances the metabolism of proinsulin into insulin resulting in reduced insulin resistance.[25,26] Studies have demonstrated that patients with chronic hepatitis C using vitamin D oral supplements respond better to therapy and relapse rates are minimized.[25,26] As vitamin D mitigates the necro inflammatory process in chronic hepatitis C and inhibits the development of liver fibrosis, its deficiency may result in fibrosis progression and, subsequently, liver cirrhosis.[27,28] Skinner RK demonstrated high prevalence of vitamin D deficiency in patients with primary biliary cirrhosis (PBC) with an inverse relationship between Vitamin D levels and advanced liver disease.[29,30]

Autoimmune hepatitis (AIH) patients have lower vitamin D levels, and related genetic influences such as polymorphisms of VDR may be responsible for susceptibility to AIH.[31,32] Autier et al.[31] and Stokes et al.[41] studied deficiency of vitamin D in patients with alcoholic liver disease (ALD) in 2014, with results of both favoring hypovitaminosis D in the study population.

Several clinical implications of vitamin D levels have been proposed, including as a predictive marker of mortality related to cirrhosis, as a noninvasive pointer of fibrosis of the liver in chronic hepatitis C, and as a marker of adverse outcomes of hepatocellular carcinoma (HCC).[33,34] The conceivable advantage of supplementation of vitamin D to prevent the development of liver fibrosis in chronic hepatitis C, as well as expanding the same to the entire population of CLD patients, regardless of the presence of skeletal disease, has been suggested.[35] Lim et al. proposed regular monitoring of vitamin D levels in CLD patients and therapeutic replacement if values are lower than 30 ng/mL.[35] The Endocrine Society clinical practice guidelines endorse screening high-risk individuals, such as those with CLD, for vitamin D deficiency and advocate supplementation when such deficiency is noted. Despite that, the currently recommended screening indications are limited to only hepatic failure and do not include the entire range of liver diseases. International liver study associations suggest supplementation with fat-soluble vitamins, including vitamin D, along with calcium in all patients with cholestatic liver disease.[36]

Chronic liver disease (CLD), particularly alcoholic liver disease, is highly prevalent in the state of Goa in India and contributes majorly to the burden on the existing health care system. This study was designed to have a better understanding of the prevalence of vitamin D deficiency among hospitalized patients of liver cirrhosis and its association with decompensation, contemplating prospective research on the utility of nutritional supplementation in the reduction of disease burden and hospital stay.

Aim of the Study

To analyze the association of vitamin D levels and hepatic decompensation in patients with liver cirrhosis.

Materials and Methods

Study Design and Duration

This is an observational, cross-sectional, hospital-based study.

Study Area

The study was conducted at Goa Medical College, a tertiary care government hospital in the state of Goa, initiated in March 2020 and concluded in February 2022.

Institutional Ethics Committee approval (IEC-GMC/July-19) was obtained preceding the commencement of the study.

Inclusion Criteria

A total of 100 adult patients with liver cirrhosis diagnosed radiologically along with clinical and biochemical abnormalities admitted to general medical wards were selected.

Exclusion Criteria

Patients on medications that can affect vitamin D levels, such as calcium, vitamin D supplements, antiepileptics, and steroids or bisphosphonates, were excluded. Also excluded were patients with chronic illnesses, which can influence calcium and vitamin D levels, such as chronic kidney disease and known systemic malignancy.

A universal sampling method was used, and consequently, all the patients admitted fulfilling the inclusion criteria during the study period were included as the study population.

All study participants were enrolled after informed consent.

Analysis

A thorough demographic profile was obtained, and comprehensive history along with a complete examination was performed and noted. Blood samples were collected and assessed for complete blood count, blood biochemistry profile encompassing kidney function tests, liver function tests, fasting blood sugar level, serum albumin level, prothrombin time and international normalized ratio (INR), calcium, phosphate levels, and serum 25-hydroxy vitamin D levels. Ascitic fluid analysis was performed in patients with clinically significant ascites. Data collated also included grading of hepatic encephalopathy based on West Haven criteria and liver disease severity scores of the Model for End-Stage Liver Disease (MELD) and Child-Pugh score (CPS). As per standard guidelines, patients were categorized into classes based on the status of vitamin D levels, such as deficiency with <20 ng/mL, insufficiency with levels between 21 and 29 ng/mL, and sufficiency with levels exceeding 30 ng/mL.

Using the CP score, study participants were divided into three classes, A, B, and C. (A) CPS score 5–6, (B) score 7–9, and (C) score 10–15. Utilizing the MELD score, categories were framed as ≥40, 30–39, 20–29, 10–19, and ≤9. Applying West Haven criteria, hepatic encephalopathy of grades 2, 3, and 4 was categorized as overt hepatic encephalopathy.

Statistical Analysis

Data was incorporated into Microsoft Excel and analyzed using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago, United States of America). Descriptive statistics, including mean and standard deviation

(SD) for continuous variables, frequencies, and percentages, were determined for categorical variables. Using the Chi-squared test for categorical variables, the association between the variables was assessed. Pie charts and bar diagrams were utilized for the visual representation of the analyzed data. The level of significance was set at 0.05.

Results

The baseline characteristics of the study population are described and tabulated. Around 96% of the study population was composed of males, and 4% were females. The mean age of the population was 49.68 ± 9.92 years (Table 1). Only 17% of participants had DM, and 12% were hypertensive. About 83% of patients had a history of alcohol abuse (Table 2).

On clinical evaluation, 82% of participants were in hepatic encephalopathy, and 52% had overt hepatic encephalopathy (Fig. 1). The ascitic fluid analysis demonstrated evidence of spontaneous bacterial peritonitis in 16% of the study population. Hematological and biochemical parameters of the study population were assessed and tabulated (Tables 3 and 4).

Table 1: Age distribution of study subjects (N = 100)

Age (years)	*No.*	*Percent*
≤40	19	19.0
41–50	39	39.0
51–60	28	28.0
>60	14	14.0
Mean (SD)	49.68 (9.92)	
Range	32–81	

Table 2: Distribution of study subjects related to the total duration of alcohol intake (*N* = 100)

Duration (years)	*No.*	*Percent*
0–5	18	18.0
6–10	39	39.0
11–15	17	17.0
>15	26	26.0
Mean (SD)	12.45 (8.55)	
Range	0–40	

Table 3: Hematological parameters of study population (*N* = 100)

Parameter	*Mean (SD)*	*Range*
Hemoglobin (Hb)	9.12 (2.41)	3.5–15.9
Total count	10973 (6065)	2500–30300
Platelet count	1.169 (0.711)	0.20–5.50
Packed cell volume	26.39 (6.84)	10.0–45.0

Serum levels of vitamin D ranged from 2.1 to 34.0 ng/mL. Mean levels of vitamin D were 12.13, with an SD of 7.38. The mean INR was 2.07 ± 1.21 (range 0.90–10.0) (Table 4). Vitamin D deficiency was documented in 84% of patients under study, 13% had insufficient levels, and only 3% had sufficient levels of vitamin D (Fig. 2). CP class A comprised 7%, class B of 18%, and 75% of patients under study belonged to class C (Fig. 3). MELD score of ≤9 was noted in 7% of subjects and 36% had MELD scores ≥30 (Fig. 4).

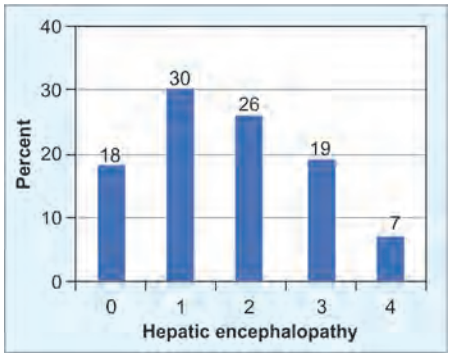

Fig. 1: Distribution of hepatic encephalopathy

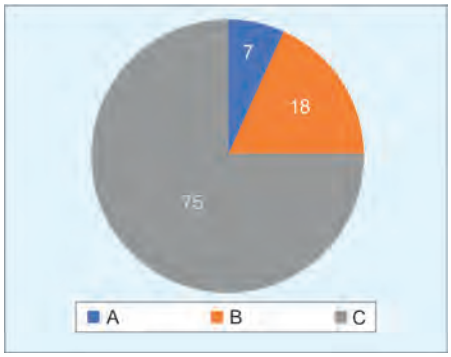

Fig. 2: Distribution of vitamin D

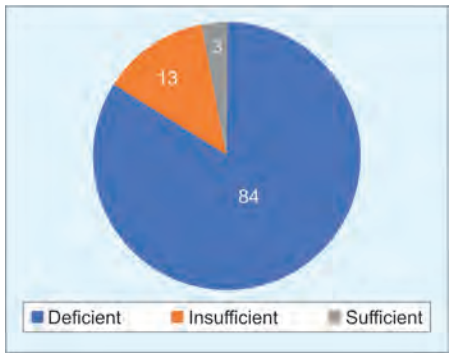

Fig. 3: Distribution of CPS

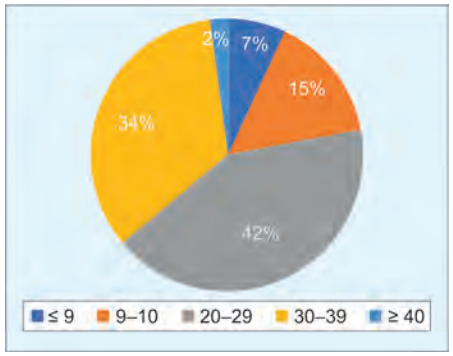

Fig. 4: Distribution of study subjects according to MELD (*N* = 100)

Table 4: Biochemical parameters of study population (*N* = 100)

Parameter	*Mean (SD)*	*Range*
Total bilirubin	6.96 (6.21)	0.3–29.1
Direct bilirubin	3.99 (3.91)	0.1–15.0
Serum glutamic pyruvic transaminase	46.66 (33.42)	7–180
Serum glutamic oxaloacetic transaminase	102.59 (84.23)	9–679
Alkaline phosphatase	121.75 (78.47)	35–722
Total protein	6.39 (1.04)	3.40–9.10
Albumin	2.23 (0.63)	1.20–4.10
Globulin	4.15 (1.03)	2.10–7.00
Serum creatinine	1.55 (1.36)	0.30–8.40
Partial thromboplastin time	22.45 (9.21)	10.2–60.0
Percutaneous transhepatic cholangiography	13.34 (0.75)	11.0–14.0
INR	2.07 (1.21)	0.90–10.0
Fasting blood sugar	94.51 (26.69)	70–232
Postprandial blood sugar	128.69 (43.59)	82–296
Glycated Hb	5.14 (1.23)	3.50–10.4
Vitamin D	12.13 (7.38)	2.1–34.0
Calcium	7.76 (0.85)	5.70–11.20
Phosphate	3.53 (1.45)	0.70–10.20
Uric acid	5.63 (2.57)	1.60–13.90
Potassium	3.80 (0.84)	2.10–13.90
Sodium	129.76 (8.42)	109–160

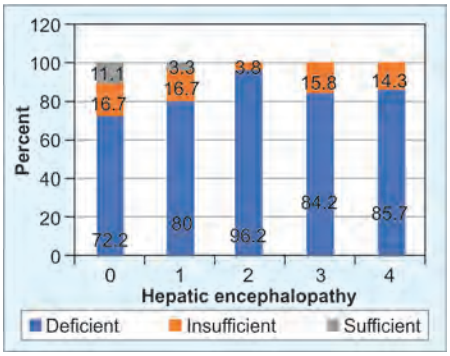

Fig. 5: Vitamin D and CPS; Chi-squared test, *p*-value of <0.001, significant

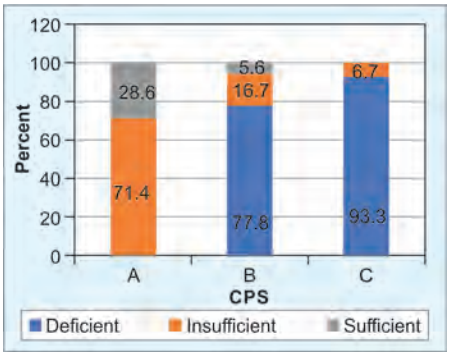

Fig. 6: Vitamin D and hepatic encephalopathy; Chi-squared test, *p*-value = 0.375, not significant

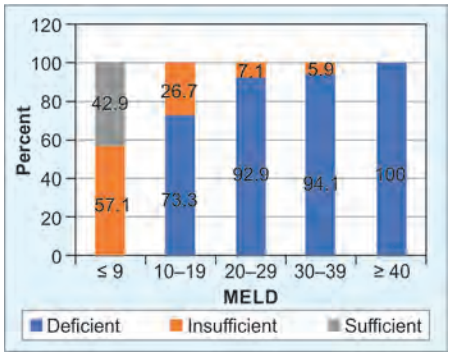

Fig. 7: Vitamin D and MELD; Chi-squared test, *p*-value of <0.001, significant

Around 93.3% of the CP class C group had a vitamin D deficiency state, 6.7% had vitamin D insufficiency, and none had sufficient levels of vitamin D (Fig. 5). A MELD score of 20–29 was documented in 42% of the study population, among which 92.2% had vitamin D deficiency state, in comparison, none of the subjects with MELD score ≤9 was vitamin D deficient whereas 94.1% in the MELD score category of 30–39 were noted to have vitamin D deficiency.

After statistical analysis, based on the results of the Chi-squared test, it was observed that the association between hepatic encephalopathy and serum vitamin D levels was not significant, with a *p*-value of 0.375 which is greater than of α-value (Fig. 6). However, there was compelling link documented between vitamin D levels and CP class severity of hepatic decompensation with a significant *p*-value of <0.001 (Fig. 5). Chi-squared test results also indicated powerful relationship between vitamin D levels and MELD score registering a statistically significant *p*-value of <0.001 (Fig. 7).

Discussion

The foremost finding of our study is the demonstration of a consistent occurrence of vitamin D deficiency among patients with decompensated liver cirrhosis, needing hospital admission. The mean level of vitamin D in the study cohort was 12.13 ng/mL, indicating poor stores of vitamin D among patients with liver cirrhosis. Deficient vitamin D levels were found in 84% of patients evaluated. A North Indian study conducted by Kumar et al. in 2017 revealed vitamin D inadequacy in 80% of the liver cirrhosis group, with 51.85% being vitamin D deficient.[37] Similarly, George et al. demonstrated vitamin D deficiency in 90% of liver cirrhotics in a study conducted at KEM, Mumbai in 2009.[38]

In a retrospective study by Vidot in 2017, 165 patients suffering from CLD were evaluated, and vitamin D deficiency was noted in 29.7% of the study population. However, these were patients with CLD who were assessed for liver transplantation as per routine comprehensive evaluation for suitability for transplantation.[39] In the same study, the mean age of the study group was 53 ± 8 years, and the population was predominantly male, which is comparable with our study wherein the mean age was 50 ± 9 years with a 96% male preponderance. Sufficient stores of vitamin D were noted only in 3% of cohorts. Jamil et al. studied vitamin D levels in 125 patients with liver cirrhosis and found deficient levels in 34% and sufficient levels in a mere 12%. Zhao et al.[40] conducted a study of 365 cases of chronic hepatitis B with liver cirrhosis and illustrated significant vitamin D deficiency with a mean vitamin D level of 4.67 ± 2.76 ng/mL in the cirrhosis group.

Our results also demonstrate that vitamin D levels are lower in the patient subgroup with overt hepatic encephalopathy compared to the nonovert hepatic encephalopathy group. This association, however, was not demonstrated to be statistically significant ($p = 0.375$). These findings are dissimilar to most data on vitamin D research in cirrhosis. This discrepancy could be due to the selection of only those patients needing hospital admission, mainly for hepatic encephalopathy in the study group. In contrast, a contemporary study in 2019 by Yousif et al. demonstrated that serum vitamin D values were significantly lower in hepatic encephalopathy (HE) and spontaneous bacterial peritonitis (SBP) groups and lower in high-grade HE than in low-grade ($p < 0.001$). Notwithstanding, vitamin D values of <7.1 ng/mL in SBP and <0.6 ng/mL in HE could predict mortality with high sensitivity and specificity.[41]

Regarding the correlation between the grade of hepatic dysfunction and vitamin D, we found significant differences between different classes of CPSs. A vitamin D deficient state was noted in the 93.3% CP class C group against only 6.7% with insufficiency and none with sufficient levels. In comparison, none in CP class A were vitamin D deficient, and 28.6% were vitamin D sufficient. Using the Chi-squared test for univariate analysis, this association between vitamin D levels and CP class severity of hepatic dysfunction was statistically considerable, with a *p*-value of <0.001. Indeed, several research reports show that low levels of serum vitamin D predict unfavorable outcomes in CLD. Stokes et al.[42] identified low vitamin D levels as an independent pointer of survival in 65 patients, mainly with alcohol-related liver cirrhosis; 82% were with advanced CP stage B or C with median vitamin D of 8.8 ng/mL (5.3–14.1). Kumar et al.[37] also concluded that the prevalence of deficiency and insufficiency of vitamin D escalated with rising scores of CP and MELD, and this result was irrespective of the etiology of CLD.

A higher MELD score was demonstrated to be associated with more severe vitamin D deficiency states, with a statistically significant *p*-value (<0.001). This result is in parallel to the findings of research by Khan et al. in Jammu and Kashmir, India, on vitamin D status in CLD.[43] Vidot et al. also noted a strongly negative correlation between MELD score and vitamin D levels ($p < 0.0001$).[39] In contrast, Kitson et al.[44] did not observe a significant link between levels of vitamin D and liver cirrhosis in patients with HCV; however, only 15% of the study population had cirrhosis and was in the compensated stage. Bankuti et al.[45] also delineated a significant interrelation between vitamin D status and the severity of liver dysfunction in a study with 75 patients with liver cirrhosis, with 14% in CP class C. This was a prospective study wherein patients were periodically monitored up till the stage of either liver decompensation or death. Finkelmier et al.[46] examined the role of vitamin D status in a prospective study to determine its link to prognosis in a study group comprising 200 patients with HCC. Patients with severe vitamin D deficiency displayed an elevated risk for mortality. On analysis, considerably low vitamin D values

were autonomously linked with high mortality in addition to higher MELD scores and α-fetoprotein levels. Jha et al. also reported an 84.31% prevalence of vitamin D deficiency in decompensated liver cirrhosis in a prospective study conducted in Eastern India.[47] Thus, it is evident that the majority of contemporary research data on patients with cirrhosis confirm a higher prevalence of deficiency of vitamin D. Results of our study, too, concur with these findings.

An important limitation of this study is its observational and cross-sectional design. The findings obtained are considerable; however, they do not establish a causal relationship between vitamin D deficiency and hepatic decompensation. This causal link can be further evaluated by a prospective study design with a larger sample size, which will also play a role in the determination of the long-term effects of vitamin D on the progression of CLD.

Conclusion

Vitamin D deficiency is common in patients with CLD and cirrhosis. More importantly, vitamin D concentrations reduce with increasing severity of hepatic decompensation as measured by CPS and MELD. More work is needed to firmly establish if this association is causal, which will have a pathbreaking effect on the contemporary management of liver cirrhosis and its complications.

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POINT OF VIEW

Doctors, FIRs, and Arrest in Alleged Medical Negligence Cases in India: Demystifying the Legal Tenability

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Abstract

The relationship between a doctor and a patient is a contract, retaining the essential elements of the tort. Modern medical practice has evolved alongside the court of law to regulate the conduct of doctors and hospitals to reduce litigations of medical negligence. Lately, Indian patients have become more aware of their rights and the Consumer Protection Act. This awareness encourages patients to litigate and seek the help of redressal forums to mitigate their loss/injury in cases of medical negligence. Though there is a rise in complaints of medical negligence filed against doctors and hospitals, these allegations are often frivolous.

The specter of litigation constantly looms over medical practitioners, who frequently struggle to defend themselves in a court of law, causing undue anxiety and anguish. Thus, a doctor can be considered the second victim in a medical negligence case. Lack of awareness regarding their legal rights and pertinent laws coupled with contradictory actions of the law enforcement agencies while handling alleged medical negligence cases worsens a doctor's trepidation. Hence, this article attempts to raise awareness among medical professionals, which will thereby allay undue fear while facing an allegation.

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Introduction

The relationship between a doctor and a patient is a contract, retaining the essential elements of the tort. Ever since the inclusion of the medical profession under the purview of the Consumer Protection Act, there has been increasing awareness among patients of their legal rights and options, leading to a steady increase in allegations of medical negligence in India. This awareness pits patients against doctors with medical negligence litigations seeking the help of various redressal forums to mitigate their loss/injury. Though there is a rise in cases filed against doctors and hospitals for medical negligence, often allegations are frivolous or vexatious.[1]

Doctors often struggle to defend themselves against such litigations and must additionally deal with the anxiety and uncertainty of the legal procedures. Thus, a doctor can be considered the second victim in a medical negligence case.[2] According to the National Crime Record Bureau (NCRB), between 2017 and 2021, over 900 criminal cases were registered against doctors, and this surge in allegations of criminal negligence has spread fear among doctors. Table 1 shows the outcomes of the police investigations in these cases. There are numerous factors that influence the outcome of a case of alleged medical negligence, and doctors are often ignorant of these. Such ignorance can be attributed to a lack of awareness among medical professionals about their legal rights and relevant laws, coupled with contradictory actions of law enforcement agencies in relation to the guidelines issued for handling alleged medical (criminal) negligence cases.

Table 1: Details of the cases disposed of by the police as per NCRB

Death due to medical negligence / *Year*	*2017*	*2018*	*2019*	*2020*	*2021*
No. of cases registered in the year	198	218	210	133	142
No. of pending cases from the previous year	107	145	158	155	140
Total no. of cases investigated in the year	305	363	368	289	282
Total cases where investigation completed by the police	162	224	212	147	159
Chargesheeting rate for the year (%)	64.8	62.9	50.9	41.5	49.7

Riddle of Doctor, Damage/Death of Patient and First Information Report

A first information report (FIR) is registered by the police upon receiving any complaint. If the death of a patient results from alleged medical negligence, the aggrieved next of kin can request the police to register an FIR, which is registered either under Section 304 (punishment for culpable homicide not amounting to murder) or 304-A (causing death by negligence) of Indian Penal Code (IPC). However, there have been instances where doctors have been booked under Section 302 (punishment for murder) IPC as well. While these are cognizable offences, Section 302 and 304 IPC are nonbailable, whereas 304-A IPC is a bailable offence.

The Supreme Court (SC) of India has clarified through its judgment in 2013 that registration of FIR is mandatory under Section 154 of the Code of Criminal Procedure (CrPC) if the information discloses the commission of a cognizable offence and no preliminary inquiry is permissible in such a situation. However, in case of alleged medical negligence, a preliminary inquiry may be conducted only to ascertain whether a cognizable offence is disclosed or not. If the inquiry discloses the commission of a cognizable offence, then FIR must be registered. In those cases where preliminary inquiry ends in closing the complaint, a copy of the entry of such closure must be supplied to the first informant forthwith and not later than one week. It must disclose reasons in brief for closing the complaint and not proceeding further.[3] The SC has also instructed that to invoke Section 304 IPC, essential elements need to

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be fulfilled, that is, "death of the person must have been caused, such death must have been caused by the act of the accused by causing bodily injury, there must be an intention on the part of the accused to cause death or to cause such bodily injury which is likely to cause death, or there must be knowledge on the part of the accused that the bodily injury is such that it is likely to cause death." The SC also observed that "no conviction ought to take place unless such intention or knowledge can from the evidence be concluded to have really existed."[4]

In early 2022, in Rajasthan, after a patient died due to postpartum hemorrhage, the concerned obstetrician was booked under Section 302 IPC, leading to her committing suicide. The Government of Rajasthan thereafter developed guidelines that made it mandatory to seek the medical board's opinion, and only if there is enough evidence to suggest that the doctor is grossly negligent FIR can be registered.[5]

Framing of Charges and Issuing Summons by Trial Court

In 2015, the Gujarat High Court observed that "the framing of a charge by the trial court is not an empty formality. The court, at the stage of framing of charge, has to apply its mind and see to it that no prejudice is caused to the accused on account of framing of improper charge. At the same time, it also needs to be stated that the charge has to be framed on the basis of the materials collected by the investigating agency in the form of the chargesheet. The investigating agency also owes a responsibility to see that the appropriate sections are applied to have regard to the nature of the accusation and other materials on record."[6]

In a recent case, the Punjab and Haryana High Court had held that when a police complaint had been made regarding the allegations of medical negligence, and when it was disclosed to the Magistrate, "the Magistrate was well within his powers to hold an enquiry in terms of Section 202 CrPC to satisfy himself as to the genuineness of the allegations and could have also called for the police report regarding the action taken on the said complaint, if any. Therefore, in cases where the allegations and the preliminary evidence lead in support of those allegations are hazy, the court can, and in fact should, hold a preliminary enquiry in the manner that it deems fit before proceeding to summon an accused."[7]

Arrest of Doctors for Alleged Medical (Criminal) Negligence

The SC, in the landmark 2005 Jacob Mathew case judgment, made it very clear that "a doctor accused of rashness or negligence may not be arrested in a routine manner (simply because a charge has been levelled against him). Unless his arrest is necessary for furthering the investigation or for collecting evidence or unless the investigation officer feels satisfied that the doctor proceeded against would not make himself available to face the prosecution unless arrested, the arrest may be withheld." The SC also observed that instructions need to be framed for guarding doctors from malicious proceedings based on certain guidelines in consultation with the Medical Council of India [later superseded by the National Medical Commission (NMC)] by the State Governments and/or the Government of India. Following this, many states in India have formulated a medical board to process complaints of alleged criminal negligence against doctors.[8]

Additionally, in 2021, NMC published a new set of guidelines for protecting doctors from vexatious/frivolous complaints. This guideline will implement an expedited enquiry process at two levels: the district medical board and the state medical board. There is also an additional procedure proposed for the police before arresting a doctor; that is, if the police officer feels that a doctor needs to be arrested, then the factual position of the case needs to be placed in front of the concerned Superintendent of police or Deputy Commissioner of police. Only after obtaining their approval can the doctor be arrested.[9] Unfortunately, these guidelines have not yet been adopted by the appropriate authority and hence lack legal tenability. Once adopted and appropriate directions given by the concerned authority, these guidelines may prove effective and hold valid for practical purposes.

CrPC to the Rescue

Section 482 CrPC (Saving of Inherent Power of High Court)

Doctors can approach the respective high courts if they feel a false FIR was registered or false charges were framed against them in alleged medical negligence cases. We have seen numerous cases (Daljit Singh case, Dr Jayshree Ingole case and Dr Mohammad Azam case, to name a few) where the FIRs, criminal proceedings and/or summons have been quashed by the high courts.[10–12] Thus, this section could be used as a defence by the medical fraternity if they feel that they are being harassed without any prima facie evidence and/or by breach of guidelines issued thereof.

Section 197 CrPC (Prosecution of Judges and Public Servants)

Regarding the prosecution of a doctor working in government service, SC has held that as per Section 197 (Subsection 1) CrPC, prior sanction from the competent authority is required for prosecuting any public servant for the alleged offences directly and reasonably connected with his official duty.[13] Notably, in Dr Manorama Tiwari's case, SC has held that doctors were discharging their public duties while performing surgery in a government hospital; hence, prosecution was not maintainable without sanction from the State Government.[14]

Counter-filing of a Case against the Police

In 2014, SC observed that filing false charges of offence by the police would constitute an offence under Section 211 IPC. However, in case of initiating proceedings against the police, the provisions laid down in Sections 195 and 340 CrPC should be adhered to.[15]

Conclusion

Figure 1 depicts the various legal provisions, remedial measures, and SC guidelines available to safeguard doctors/hospitals. However, despite these, it is disheartening to note that many criminal cases are being registered against doctors without following the SC guidelines. This could be attributed to the lack of awareness among both law enforcement agencies and doctors, which is a major obstacle to preventing undesirable consequences. It is crucial to raise awareness among doctors regarding the remedial measures available to them during such criminal proceedings, and it is equally important not to lose hope during such a stressful period.

Kindly find the brief facts about the legal cases cited in this article in Annexure 1.

Recommendations

For Doctors/Healthcare Institutions

Increasing Awareness

- Micro-level: Periodic educational sessions on current legal issues affecting medical practice and doctors' rights for healthcare providers within institutions.
- Macro-level: Regular awareness programs on legal aspects of healthcare (including various laws and guidelines related to the

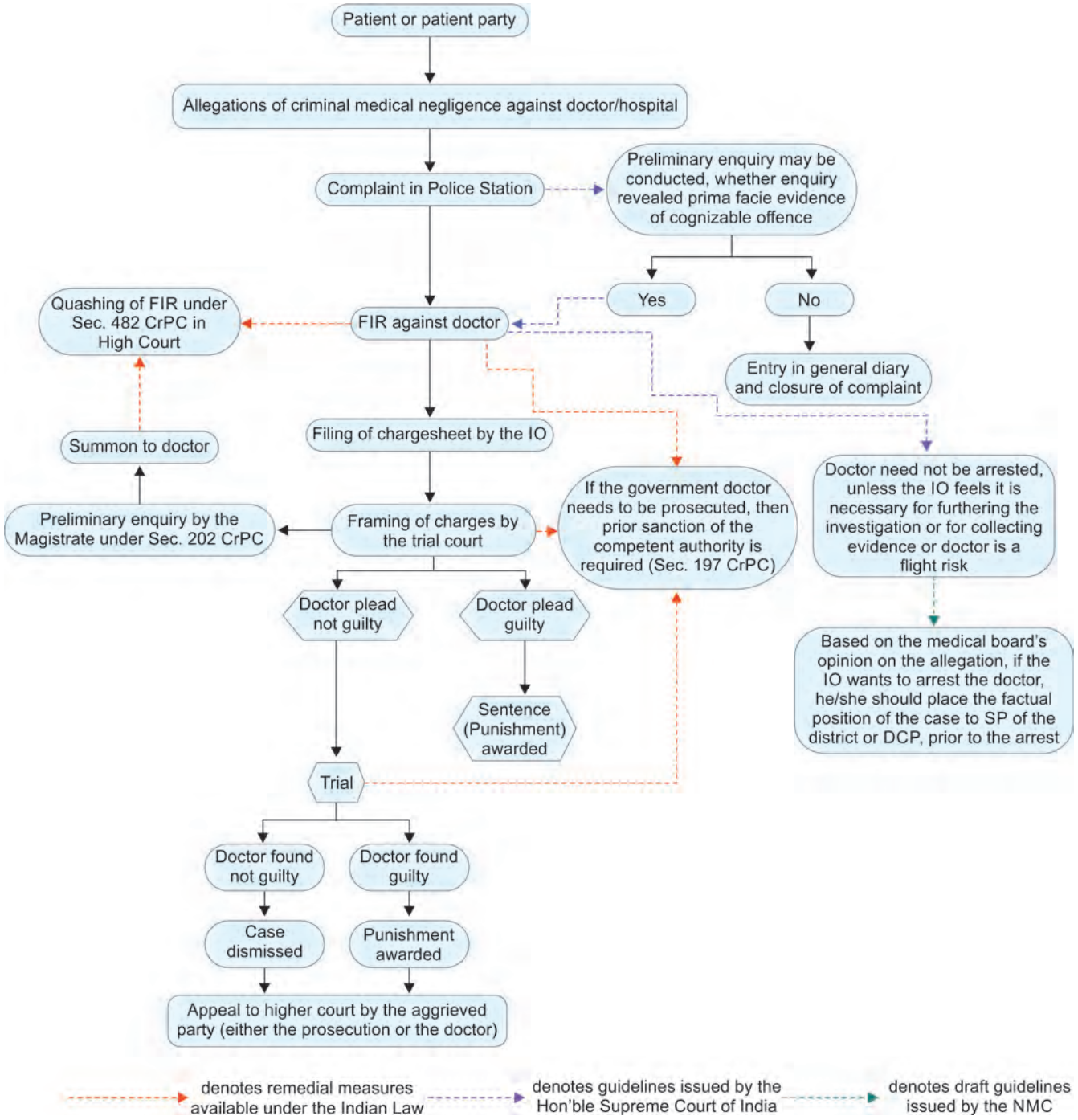

Fig. 1: It depicts the various options available for doctors to avoid harassment in criminal proceedings against them in an alleged medical negligence case (IO, investigating officer; SP, Superintendent of Police; DCP, District Commissioner of Police)

investigation of alleged medical negligence) at the district, state, and national levels.

Setting up Helplines

Helplines could be set up by various professional bodies of medical specialties, Indian Medical Association (IMA) (at national, state and district levels), state medical councils and the NMC for healthcare providers to get timely advice from medicolegal experts on various medicolegal issues associated with Medical Practice.

Establishing Grievance Redressal Cells

Grievance redressal cells could be established by IMA at district, state and national levels and state medical councils to help avoid harassment of doctors.

Medical Indemnity Insurance and Legal Support

- Inform the insurance company about any allegation or legal notice seeking compensation for alleged medical negligence as soon as it is received.
- Seek assistance from the insurance company/lawyer to file a reply to the consumer commission or to a legal notice.

- Prioritize responding to consumer commissions within the allotted time frame; otherwise, the case may go on an ex-parte basis.

Seek Help

To seek out professional or peer support to help cope with the stress brought on by legal disputes and battles related to medical practice.

Seek Assistance from Professional Medicolegal Experts

- To draft a reply to the legal notice from a lawyer/letter received from the police/ honorable courts/consumer commission/ medical council or any other competent authority in accordance with the law of the land (after perusal of patients' medical records and other relevant documents).
- To draft a statement for doctors when the police call doctors to give a statement.
- Collate necessary medical literature and other relevant scientific data to plan a defence during the legal battle.
- To help when confronted with an ethical and legal dilemma.

For Law Enforcement Agencies and Others

Increasing Awareness

- Micro-level: Periodic educational sessions on updates and guidelines for handling medicolegal cases in every police training school, law school, Bar Council, and Judicial Academy.
- Macro-level: Regular awareness programs on updates and directives issued by various authorities concerned and honorable courts in handling various issues against doctors and healthcare Institutions (including various laws and guidelines related to the investigation of alleged medical negligence) at the district, state, and national levels.

Setting up Helplines

Helplines could be set up at the district level for the investigating officers under the supervision of the Superintendent of Police with a quarterly review to assess and streamline the process and to avoid any deviations from the protocol established to handle various medicolegal cases.

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14. Dr Manorama Tiwari & Ors. vs Surendra Nath Rai (2016) 1 SCC 594.
15. Perumal vs Janaki (2014) 1 SCR 591.

Annexure 1: This segment contains brief facts about the legal cases cited in this article

Lalita Kumari vs State of Uttar Pradesh and others (2013)

This case dealt with the kidnapping of a young girl, and the station officer delayed filing an FIR until the Superintendent of Police had been notified. The Court was asked whether "a police officer is bound to register a FIR upon receiving any information relating to the commission of a cognizable offence under Section 154 of the CrPC, 1973" (in short, "the Code"). Or does the police officer have the authority to conduct a "preliminary inquiry" to ascertain the accuracy of such information before registering it? When the issue was submitted to a constitutional bench of five SC justices, they determined that filing an FIR was required if the information revealed an act of a crime that might be a cognizable offence. Suppose the information obtained does not reveal a cognizable offence but rather suggests the need for a preliminary investigation to determine whether or not a cognizable offence has occurred. A list of cases where preliminary inquiries may be performed was laid out by the court. This includes marital and family conflicts, commercial crimes, medical negligence, corruption, etc.

Mahadev Prasad Kaushik vs State of Uttar Pradesh and another (2008)

The complainant's father, Buddha Ram, was experiencing bodily pain, so the complainant brought him to the appellant's clinic for treatment. The complainant claims that Buddha Ram had treatment from the appellant, who gave him three injections. In 30 minutes, Buddha Ram passed away. The complainant went on to the Police Station to file a report against the appellant, but the police declined to register a case. So, he made a request to the Mathura Court of Additional Judicial Magistrate III. The learned Magistrate issued an order in accordance with subsection (3) of Section 156 CrPC, and the Police Authorities were instructed to conduct an inquiry. According to the aforementioned directive, the police conducted the investigation and, in a final report presented under Section 169 of the CrPC, said that the appellant, in this case, had not broken any laws. Under sections 304, 504 and 506 of the IPC, the trial court issued the summons. The learned Magistrate said that eyewitness testimony backed up the complainant's assertion. The court also took notice of press reports claiming that Dr Mahadev's clinic was shut down as a result of directives issued by the district collector and chief medical officer. Additionally, it was claimed that Dr Mahadev kept illicit substances and dangerous injections in his clinic. The learned Magistrate concluded that there was enough evidence to bring the accused to the stand and hear his side of the story. Disappointed by the aforementioned ruling, the appellant filed a revision petition, which the High Court rejected. The SC opined that the purpose or knowledge with which the conduct that caused the death was committed is the most crucial factor in a case involving this offence (304 IPC). The doctor's prosecution was quashed (504 and 506 IPC) because it was ill-founded, and the 304 IPC was misguided given the circumstances. Only the appellant-accused might get a process from the learned Magistrate for a crime covered by Section 304A of the IPC. The appeal is accordingly allowed to the extent indicated above.

Hanif Usmanbhai Kalva and others vs State of Gujarat (2015)

The first informant is an animal rights activist. The first informant and his colleagues, who are also animal activists, intercepted a truck allegedly carrying bullocks for the purpose of slaughter. In the process, the first informant and his colleagues were allegedly attacked and assaulted by the applicants herein. It is the case of the prosecution that the applicants herein, armed with sticks and swords, inflicted injuries on the heads of three persons. The learned advocate, appearing on behalf of the applicants, vehemently submitted that, in the first place, the police should not have filed a chargesheet with section 307 IPC as one of the main offences alleged to have been committed by the applicants. The High Court has observed that "the framing of a charge by the trial court is not an empty formality. The Court, at the stage of framing of charge, has to apply its mind and see to it that no prejudice is caused to the accused on account of framing of improper charge. At the same time, it also needs to be stated that the charge has to be framed on the basis of the materials collected by the investigating agency in the form of the chargesheet. The investigating agency also has a responsibility to see that the appropriate sections are applied having regard to the nature of the accusation and other materials on record."

Dr DL Budwal vs Gurpreet Kaur (2022)

A quashing of complaints filed under Sections 326, 304-A, 447, 504, and 506 IPC is requested in the current petition under Section 482 of the CrPC. According, to the case's short facts, Jagdeep Singh, the son of complainant Gurpreet Kaur, allegedly suffered an eye injury while playing at home. The complainant's kid's condition did not improve despite the medication given, so she continued to visit the petitioner's hospital. Each time, she made the same assurances that her son would get well and continued the therapy. Jagdeep Singh was taken to Akal Eye Hospital, but there was no improvement. There, the doctor informed her that her son's eye had suffered irreparable damage. She then went to many hospitals in Jalandhar and Amritsar for treatment, but because of the petitioner's incompetence, her son's eye was irreparably injured, necessitating the implantation of an artificial right eye. The complainant was intimidated and verbally abused when she went to the petitioner's hospital to express her concerns about her son's damaged eye. The petitioner's attorney claims that the summoning order was issued mechanically under Section 304-A IPC without any thought or consideration of the fact that Jagdeep Singh, whose eye was permanently damaged, has not passed away. Since no such death has occurred, the petitioner would not be called in for questioning under Section 304-A IPC, the attorney claims. Without considering how a crime under Section 304-A IPC was established in the absence of death, the Magistrate merely passed the summons order automatically by referring to the evidentiary lead. Therefore, the Court can and, in fact, hold a preliminary inquiry in the way it sees appropriate before moving to call an alleged accused in circumstances where the accusations and the circumstantial evidence supporting those accusations are questionable. That is the main goal of Section 202 CrPC. The complaint and summons order are thus quashed in the interest of justice.

Jacob Mathew vs State of Punjab and another (2005)

An FIR was filed under Section 304A/34 IPC in response to the claim that the informant's late father, Jiwan Lal Sharma, had passed away as a result of the negligent actions of these particular physicians and nurses. The patient, who was admitted as a patient to a private ward of the CMC Hospital, Ludhiana, had breathing problems. The patient's attendant got in touch with the on-call nurse, but the doctor's visit apparently took 20–25 minutes longer. The patient was examined by the appellant and another physician. When the oxygen cylinder was connected, the breathing problems got worse since it turned out that the cylinder was empty. There wasn't another oxygen cylinder in the room. Vijay Sharma went to the adjoining room and brought a gas cylinder. However, there was no arrangement to make the gas cylinder functional, and 5–7 minutes were wasted in between. By this time, another doctor came who declared that the patient was dead. In this case, the SC has laid down guidelines to be followed by the investigating agency in a case of alleged criminal medical negligence.

Daljit Singh Gujral and others vs Jagjit Singh Arora and others (2014)

The wife of the complaint was brought into the respondent hospital's intensive care unit. However, when her condition deteriorated, she was sent to PGI, Chandigarh. The complaint claimed that because the respondent hospital engaged untrained doctors, proper treatment was not given in the ICU. Furthermore, the hospital altered the record to clear itself of any wrongdoing after discovering that a medical negligence lawsuit had been brought against them. It was argued that because the patient's death was not expressly indicated in the complaint, the court's decision in the case was made based on the presumption that the patient had passed away. Later, the court amended this version, stating that the patient was on the verge of passing away.

Dr Jayshree Ujwal Ingole vs State of Maharashtra and another (2017)

After being hurt in a car accident, a hemophiliac patient was taken to the hospital. The patient complained of stomach discomfort while receiving emergency medical attention. When a surgeon (the appellant) arrived, she asked for a physician's consultation after being contacted. The surgeon did not, however, remain at the hospital to await the physician's arrival. In addition, the physician never showed up at the medical facility. The emergency medical officer learned that the patient had passed away the following morning, but a physician was still not available. All of the medical professionals who treated the dead were accused of a criminal negligence case. The SC said that it is true that she did not wait for the physician to come, but it can be assumed that she would have expected that the physician would come soon. Hence, it is impossible to conclude that the appellant was guilty of criminal negligence, given the facts and circumstances of this particular instance. It is, at best, a judgement error.

Dr Mohammad Azam Hasin vs State of Uttar Pradesh (2019)

The deceased had been admitted to the hospital of the accused after the former met with an accident and remained hospitalized for about 23 days. As he had been treated, he was about to be discharged from the hospital. The team caring for the patient included Dr Hasin (unit in charge). When Dr Adil, a junior resident, and a nurse arrived to remove the chest tube, the patient immediately passed away as a result of the blood that was oozing out freely. A first information complaint was made against Dr Adil Mahmud Ali only by the deceased's brother. According to the postmortem, septicemic shock was opined as the cause of death. Dr Hasin, the applicant (accused), was not the subject of any allegations. Following an inquiry, the police filed a case under Section 304A of the IPC against both physicians, and the learned Chief Judicial Magistrate took cognizance. The high court quashed Dr Hasin's summons order as well as the whole criminal investigation.

Amal Kumar Jha vs State of Chhattisgarh and another (2016)

The patient, Runiabai, underwent surgery at the Patthalgaon Hospital, where the appellant holds the in-charge post, and was thereafter discharged. Dr AM Gupta was contacted since she was throwing up, and he sent one Aklu Ram to treat her. She later passed away after being taken to Patthalgaon's Primary Health Centre (PHC). Dr AM Gupta and the appellant were the subjects of an FIR and a Chargesheet under Section 304-A IPC from the police. The argument is that the applicant did not supply the official vehicle to transport the patient from PHC to the district hospital. On the grounds that prior sanction was necessary and that they could not be prosecuted without it, they pleaded for the motion for discharge under Section 197 of the CrPC. The appellant could not have been prosecuted without approval from the proper authorities as provided in the CrPC, the SC said in its ruling.

Dr Manorama Tiwari and others vs Surendra Nath Rai (2016)

The daughter of respondent Surendra Nath Rai, Ms Tapsi Rai, age 14, underwent surgery at the Maharani Government Hospital in Jagdalpur, Bastar. The appellants, Dr (Smt) Manorama Tiwari, Dr BR Kawdo, and Dr Pradeep Pandey carried out the procedure that was required as a result of the patient's abdominal pain. The respondent's consent to operate was obtained prior to beginning the procedure. However, even after the procedure, the patient's health did not get better, and on the same day, she passed away. After more than five months had passed, the respondent filed an FIR at the Jagdalpur Police Station against Dr Manorama Tiwari and Dr Pradeep Pandey under Section 304A of the IPC. Under the District Magistrate's orders, an investigation into the respondent's complaint took place, and the results indicate that the surgeons were negligent. However, a second investigation was later conducted at the government's request, and the Joint Controller of Health Services for Bastar filed his report, concluding that the surgeons had not been negligent. The complainant (respondent), who made charges of the commission of murder against the appellants, filed a criminal complaint before the Chief Judicial Magistrate in Jagdalpur, although it seems that the police did not submit a chargesheet. The aforementioned incident was filed as a criminal complaint. The appellants filed a motion claiming that Section 197 of the Criminal Procedure Code does not permit prosecution of them without a sanction. The Magistrate refused the application, and the appellants filed a criminal appeal in response. The high court did not provide relief, and the appeal was dismissed. Hence, an appeal was made to the SC, which opined, " As such, the criminal prosecution of the appellants initiated by the respondent (complainant) is not maintainable without the sanction from the State Government."

Perumal vs Janaki (2014)

The case of the appellant herein in his complaint is that though Nagal alleged an offence of cheating against the appellant, which led to the pregnancy of Nagal, such an offence was not proved against him. Upon the registration of Crime No.18/08, Nagal was subjected to a medical examination. She was not found to be pregnant. Dr Geetha, who examined Nagal, categorically opined that Nagal was not found to be pregnant on the date of the examination, which took place 6 days after the registration of the FIR. In spite of the definite medical opinion that Nagal was not pregnant, the respondent chose to file a chargesheet with an allegation that Nagal became pregnant. Therefore, according to the appellant, the chargesheet was filed with a deliberate false statement by the respondent herein. Irrespective of the fact whether the offence disclosed by the complaint of the appellant herein is an offence falling either under Section 193 or 211 of the IPC, Section 195 of the CrPC declares that no court shall take cognizance of either of the abovementioned two offences except in the manner specified under Section 195 of the CrPC. Under Section 340 (1) of the CrPC, it is stipulated that whenever it appears that any one of the offences mentioned in clause (b) of Subsection (1) of Section 195 appears to have been committed in or in relation to a proceeding before a court, that court either on an application made to it or otherwise make a complaint thereof in writing to the competent Magistrate after following the procedure mentioned under Section 340 of the CrPC.

The Mystery of Green Eyes

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Clinical Image

A 27-year-old female with no known comorbidities presented to casualty with fever and loose stools for 7 days followed by shortness of breath and reduced urine output for 1 day. On examination, she was conscious-oriented. She had tachycardia, hypotension [blood pressure (BP) 72/56 mm Hg], and 82% saturation on room air. She was started on intravenous (IV) fluids, and oxygen support and was catheterized. Her BP did not improve and her urine output was nil despite adequate fluid resuscitation. She was started on inotropes and was intubated in view of worsening sensorium and respiratory distress. Her arterial blood gas showed severe metabolic acidosis following which she was started on continuous renal replacement therapy. Endotracheal (ET) secretions grew Aspergillus fumigatus and stool rapid biofire revealed *Shigella dysenteriae* as well as vibrio. On day 18, the cornea of both eyes developed ulcers with greenish discoloration (Figs 1 and 2). A clinical diagnosis of exposure keratitis was made and pus from the corneal ulcer was sent for microbiological examination. Culture of the same revealed Pseudomonas aeruginosa (*P. aeruginosa*). The patient was treated with antibiotic and lubricant eyedrops. The greenish discoloration of the ulcers in our patient was due to pyocyanin, a blue–green phenazine pigment produced by 90–95% of *P. aeruginosa*.[1] The expression of virulence factors in *P. aeruginosa* is enhanced by pigment synthesis, especially pyocyanin.[2] In addition, pyocyanin-producing strains are more virulent and more resistant to many drugs than nonpyocyanin-producing ones.[3]

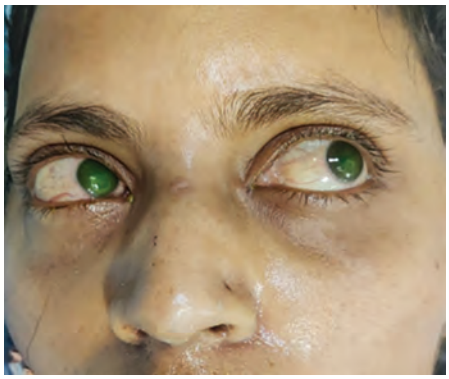

Fig. 1: Greenish ulcerated lesions on both cornea: Exposure keratitis

Fig. 2: *Pseudomonas aeruginosa* causing green ulcers on both cornea

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CASE REPORT

Legionella Serositis: A Rare Presentation

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Abstract

Background: *Legionella* has a higher prevalence in India than in the world. Legionaries' disease most commonly involves the lungs but because of increased awareness, extrapulmonary manifestations are also being diagnosed more frequently.

Case description: We present a case of a young female with acute onset of fever and chest pain. On initial investigation, an electrocardiogram (ECG) reported widespread pulse rate (PR) depression suggestive of pericarditis which was confirmed by ECG. High-resolution computed tomography (HRCT) thorax suggested mild bilateral pleural effusion with normal lung parenchyma. elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) added to the diagnosis of serositis. Serological study for atypical organisms was remarkable for positive immunoglobulin M (IgM) for *Legionella*. She was treated with a high dose of steroids and azithromycin successfully.

Conclusion: Isolated extrapulmonary presentation of legionaries disease is often overlooked and is common. So it should be always included in the diagnostic armamentarium as treatment is highly efficacious if started early.

Journal of the Association of Physicians of India (2024): 10.59556/japi.72.0361

Introduction

In July 1976, nearly 221 people were affected by pneumonia from people attending an American Legion convention in Philadelphia, out of which 34 were fatal. The cause of this outbreak couldn't be found despite a thorough investigation. According to epidemiological studies suggested that this was an airborne infection and originated from one convection hotel. After 6 months a gram-negative bacilli was discovered to be the cause of this outbreak which was named *Legionella pneumophila* (*L. pneumophila*) because of its association with an outbreak at the American Legion convention and this disease was named Legionnaires' disease.[1]

Globally a meta-analysis done by Graham et al. reported the mean incidence of community-acquired pneumonia (CAP) was 46.7/100,000 population from which the proportion of *Legionella* was 4.6%.[2]

In Northern India an epidemiological study done by Para et al., in 2018 reported that the mean proportion of *Legionella* was 17.5% among CAP, in this study urinary antigen test (UAT) was used for the detection of *Legionella*.[3] In 2000 a study done by Chaudhary et al. revealed that among CAP 15% of cases were positive for *Legionella* immunoglobulin M (IgM) antibody.[4] Thus, the prevalence of *Legionella* is higher in India as compared to overall world prevalence.

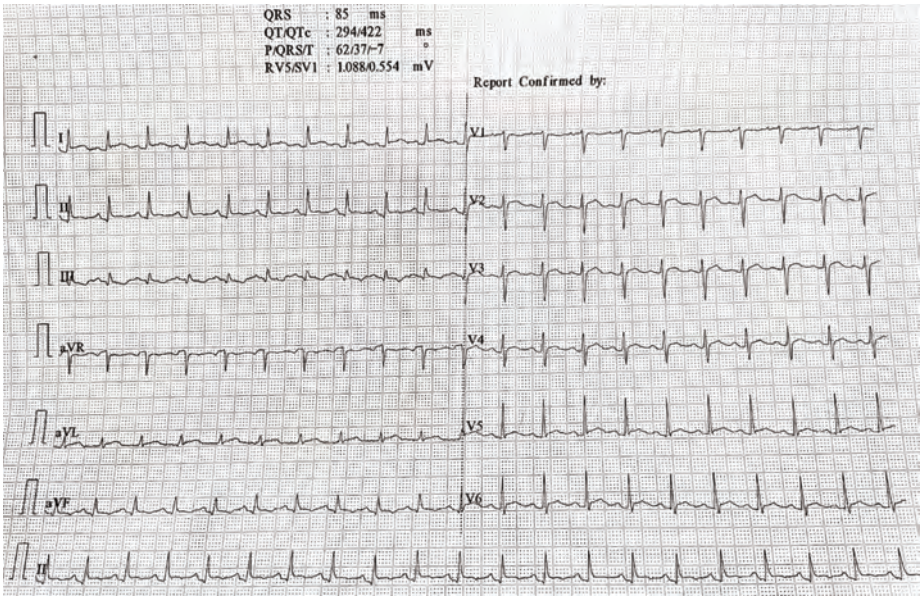

Fig. 1: ECG showing PR depression

Case Description

A 48-year-old female developed an insidious onset of fever associated with chest pain for 2 days. The patient was relatively asymptomatic before 2 days then she developed a moderate fever which was insidious in onset, continuous and was not associated with chills, rigors, and perspiration. She also developed insidious onset and moderately intense chest pain which started from the base of the neck and then involved the upper chest. Chest pain did not vary with any change in position, deep inspiration or expiration. Chest pain was associated with palpitation.

There were no complaints of increased perspiration, breathlessness, cough, headache, abdominal pain, joint pain, rash, burning micturition, burning sensation in eyes, decreased vision, dizziness, or pedal edema.

There was no past history of any chronic illness, trauma, or travel outside the city in the last 6 months.

Their family history was unremarkable.

She consumes a vegetarian diet and has normal bowel and bladder movements. She does not have any addiction.

Examination

On initial examination, she was conscious, cooperative, and well-oriented. Her blood pressure was 128/76 mm Hg. Her pulse was 124/minute, respiratory rate was 18/minute, and oxygen saturation was 98% on room air. Inspection, palpation and percussion of the chest were normal. On auscultation, there were no abnormal sounds or decreased air entry in any region. Examination of other systems was unremarkable.

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Investigation

On the day of admission, her hemoglobin was 10.6 mg/dL, WBC 13,200 /mL (86% neutrophils, 09% lymphocytes), and platelets 300,000/mL. Her CRP was 134 mg/L, ESR 27 mm, creatinine phosphokinase MB—123 IU/L and procalcitonin (PCT) was 0.599 ng/mL. Her arterial blood gas analysis showed mild metabolic acidosis with pH 7.34, bicarbonate 16.1, partial pressure of carbon dioxide 29.7, and partial pressure of oxygen 82. Her liver and renal function were normal except for high globulin levels—4.05 gm/dL. Her chest X-ray was normal. Her electrocardiogram (ECG) was positive for generalised PR depression (Fig. 1). Her ECG revealed mild circumferential effusion (10 mm) of pericardial effusion and dilated inferior vana cava (IVC) (21 mm) and showed reduced respiratory variation. Her high-resolution computed tomography (HRCT) thorax showed left-side mild pleural effusion and minimal right-sided pleural effusion with normal lung parenchyma (Fig. 2). Her anti nuclear antibody (ANA) was negative. She reported negative for influenza A target RNA, H1N1—2009 target, H3N2 target, and influenza B target RNA by reverse

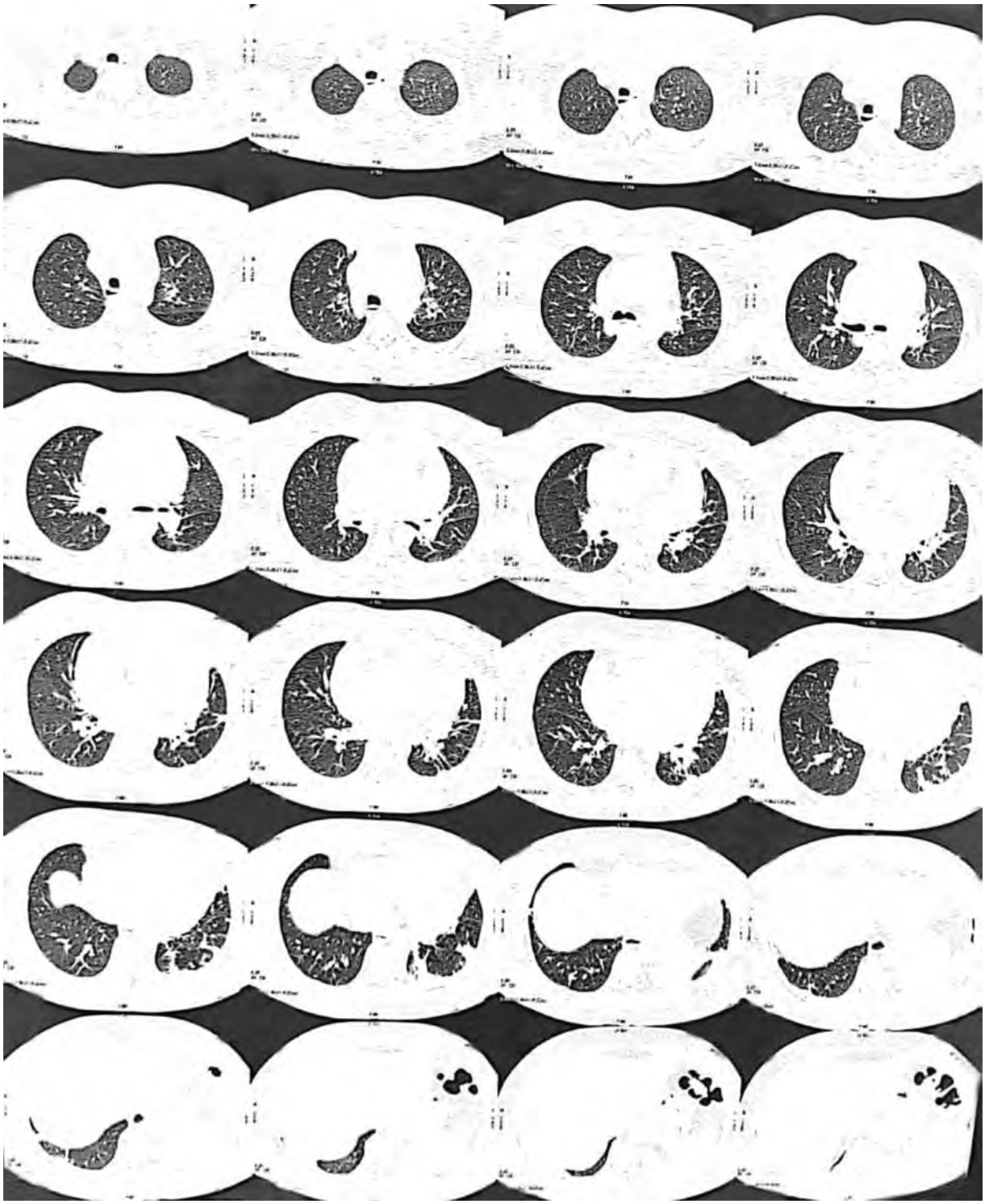

Fig. 2: HRCT thorax with normal lung parenchyma and minimal pleural effusion

transcription polymerase chain reaction (RT-PCR). She also reported negative for COVID-19 by RT-PCR. She reported positive for *Legionella* IgM antibody by immunofluorescence (IF) of atypical pneumonia panel.

Treatment

She was treated with a high dose of non-steroidal anti-inflammatory drugs-tablet (NSAIDS-T). Aspirin 600 mg 6 hourly and antibiotics tablet. Azithromycin 500 mg/day and injection meropenem 1 gm 8 hourly for 5 days. After 5 days she was asymptomatic. Her ESR reduced to 18, but her CRP was still 132. She was discharged with tablet ibuprofen 400 mg 8 hourly and other supportive medication. On follow-up after 15 days of discharge, she was completely and her medication successfully weaned off.

Discussion

We are documenting a case of a young immunocompetent female presented with isolated *Legionella* serositis. The most common presentation of legionaries' disease is pneumonitis but it also has many extrapulmonary manifestations. Common extrapulmonary manifestation includes myocarditis, encephalitis, colitis, pancreatitis, hepatitis, interstitial nephritis, and arthritis. Isolated extrapulmonary involvement of legionaries' disease is rare and there is only one case of isolated *Legionella* pericarditis that has been reported in adult patients which resulted in multiorgan failure.[5]

Diagnosis of *Legionella* can be challenging because of the variety of presenting symptoms, lack of suspicion, and lack of availability of affordable efficacious tests. The incubation period for LD is variable (2–14 days); the symptoms of legionnaire's disease (LD) include—fever at >38.8°C (most common up to 100%), cough (up to 92%), chills (15–77%), dyspnea (up to 56%), neurological abnormalities (38–53%), myalgia or arthralgia, loose stools, chest pain, headache, and nausea or vomiting in descending order.[6–9]

Nowadays 97% of cases of *Legionella* are diagnosed by a UAT but it recognizes only *L. pneumophila* serogroup one which is responsible for 50–80% of Legionaries disease. Buffered charcoal yeast extract medium (BYCE) media with antibiotics, can identify all species and serogroups of *Legionella* with high sensitivity and specificity. Molecular tests such as PCR, loop mediated isothermal amplification (LAMP), and direct fluorescent antibodies are other tests for the detection of *Legionella*.[10] In our settings we did not have culture media, we used serum IF for IgM for *Legionella*.

Treatment of Legionnaires disease should include antibiotics that achieve therapeutic concentrations within macrophages, such as the fluoroquinolones, macrolide, and cyclin families. Azithromycin or levofloxacin are frequently used for *Legionella*. Most patients with *L. pneumonia* require 7–14 days of treatment. Disseminated legionellosis may require a longer duration of therapy, which is not well defined. Immunocompromised patients with cutaneous legionellosis usually require 3 weeks of treatment.[11]

Conclusion

Extrapulmonary manifestation of *Legionella* is highly overlooked. Our case is an example of the importance of early diagnosis and treatment of Legionaries' disease to prevent complications. It is concluded from our case report that extrapulmonary legionaries should be included in our diagnostic armamentarium specially in high prevalence areas like India.

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CASE REPORT

Triple Trouble

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Abstract

We present a case of a 24-year-old female recently diagnosed with acute leukemia who came with complaints of fever for 14 days, progressive lower limb weakness, and multiple episodes of vomiting in the last 1 day. In nerve conduction studies, a diagnosis of Guillain–Barré syndrome (GBS) was established.

Fever with thrombocytopenia workup revealed a positive dengue nonstructural protein 1 (NS1) and immunoglobulin M (IgM) report. Immunophenotyping confirmed pre-B acute lymphoblastic leukemia (ALL). As leukemia is an immunocompromised state, the peripheral nervous system vulnerability is increased, or infection could precipitate an immune neuropathy.

About 10% of adult ALL presents with central nervous system (CNS) leukemias; a higher incidence is seen in mature B ALL. There is some evidence to suggest immunosuppression secondary to intensive chemotherapy (vincristine-induced dying back neuropathy), which was not started in our case.

This rare combination in a short period of time with a worsening situation paralyzed the line of management. Few reports described GBS in patients with dengue in adults. The association of Guillan-Barre syndrome and ALL could be coincidental or has a pathophysiological basis and is under basic investigation.

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Introduction

Acute lymphoblastic leukemia (ALL), a malignant clone arising from hematopoietic progenitors commonly seen in children (3–4 years), usually presents with short duration of complaints. Survival rates are lower in adults (35% 5-year survival). Central nervous system (CNS) symptoms are mostly due to meningeal infiltration, particularly seen in mature B-cell ALL. ALL results from an abnormal immune response to infection in a person with genetic risk factors, as explained by the delayed infection hypothesis. Diagnosis established on immunophenotyping. Guillain–Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy involving the peripheral nervous system. The disorder can be life-threatening, with about 15% developing weakness of the respiratory muscles needing mechanical ventilation. Intravenous immunoglobulin (IVIg), or plasmapheresis, is the line of treatment. Dengue fever is an arboviral disease with a wide spectrum of manifestations, ranging from benign self-limited course to severe life-threatening illness in the form of dengue hemorrhagic fever/dengue shock syndrome.

Case Report

We are presenting a case of a 24-year-old female recently diagnosed with ALL who came with complaints of fever for 14 days, progressive ascending lower limbs weakness and multiple episodes of vomiting and headache for 1 day.

On general examination, the patient was afebrile with blood pressure = 140/90 mm Hg, pulse rate = 120/minute, oxygen saturation = 98% on room air; pallor was present. A neurological examination showed the patient was conscious and oriented with Glasgow Coma Scale (GCS) of 15. Bilateral lower limb power was 0/5 and upper limb power was 3/5, and plantars were mute bilaterally. Dysarthria and dysphagia were present. Per abdomen examination showed hepatosplenomegaly. The rest of the systemic examination was normal.

Fundoscopy revealed no evidence of papilledema, electrocardiogram showed sinus tachycardia, chest X-ray was normal, and ultrasonography of the abdomen pelvis revealed hepatosplenomegaly.

Investigations on the day of admission showed hemoglobin to be 11.8 gm/dL, platelet 23000/cumm, and the total leucocytic count was 2.49 lacs/cumm with 85% blasts cells. Liver functin tests revealed mild transaminitis with renal function tests, and serum potassium was 3.7 mmol/L. A second serum potassium was done on day 2, which was 4.2 mmol/L. A fever workup showed dengue nonstructural protein 1 (NS1) and a positive immunoglobulin M (IgM) report. Immunophenotyping confirmed pre-B ALL.

Magnetic resonance imaging (MRI) of the brain with whole spine screening plain with contrast was done to rule out intracranial bleeding; no abnormality was detected. Nerve conduction studies showed the acute motor-sensory axonal neuropathy variant of GBS with decreased compound muscle action potentials in motor nerve studies, along with >50% reduction of normal sensory nerve action potential amplitude in sural and median nerves. Cerebrspinal fluid studies could not be done due to severe thrombocytopenia.

The neurologist advised to start plasmapheresis in view of quadriparesis. The hematooncologist advised withholding plasmapheresis as they suspected blast infiltration of the spinal cord, and the patient's condition had started deteriorating. The patient was started on dexamethasone and allopurinol. The patient developed zero power in all extremities and shallow breathing with persistent fever spikes. Her GCS was E1V1M1. Arterial blood gas was suggestive of respiratory acidosis, and the patient was intubated and planned for IVIg therapy, but it couldn't be started because of hemodynamic instability. Despite multiple blood transfusions, blood investigations revealed marked anemia with thrombocytopenia and associated granulocytopenia, which finally resulted in extensive hemorrhagic shock. The patient succumbed to death on the 5th day of admission. This rare combination in a short period of time with a worsening situation paralyzed the line of management.

Discussion

As leukemia is an immunocompromised peripheral nervous system, vulnerability could be increased, or infection could precipitate an immune neuropathy.

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Acute lymphoblastic leukemia (ALL), a malignant clone arising from hematopoietic progenitors commonly seen in children (3–4 years), usually presents with short duration of complaints.[1]

About 10% of adult ALL presents with CNS leukemias; higher incidence is seen in mature B ALL.

The association of GBS with ALL may be attributed to many factors. The peripheral nervous system vulnerability is increased in lymphoproliferative disorders. Immune neuropathy is triggered by infections that trigger immune neuropathy. GBS may result as a result of neoplasms of the immune system in a manner similar to some viral infections. There is some evidence to suggest immunosuppression secondary to intensive chemotherapy (vincristine-induced dying back neuropathy), which was not started in our case.[2]

Survival rates are lower in adults (35% 5-year survival). CNS symptoms are mostly due to meningeal infiltration, particularly seen in mature B-cell ALL. ALL results from an abnormal immune response to infection in a person with genetic risk factors. The disorder can be life-threatening during the acute phase, with about 15% developing weakness of the respiratory muscles needing mechanical ventilation. IVIg/plasmapheresis is the line of treatment.

Banerjee et al. presented a case with symmetrical polyradiculopathy 6 months prior to the onset of ALL.[3] Levison et al. study showed that out of 2,414 patients, 49 cases had GBS and had a recent diagnosis of cancer. An odds ratio of 3.6 with a 95% confidence interval of 2.6–5.1 for GBS was highest for cancers of lymphatic and hemopoietic tissue [odds ratio (OR) 7.2], respiratory tract (OR 5.6) prostate, and other male genital organs, cancers, and breast (OR 5) cancer.[4]

Bhushan et al.'s study showed intensive chemotherapy caused immunosuppression, some viral infections, and neoplasms of immune systems may also trigger acute inflammatory demyelinating polyneuropathy.[5]

Rajeshwari et al. and Vembu et al. reported three cases in ALL B type had AMAN variant. Most cases were during induction therapy except two, and onset was within 3–5 weeks of therapy.[6,7]

Despite being the most common malignancy, chronic lymphocytic leukemia has been associated with GBS in only three reported cases in studies conducted by Lorenz de Haas and Powles et al.[8,9]

One study found that MRI had 100% detection of cases of neoplastic meningitis due to solid tumors, but B-cell ALL26 detection was 44%. The false-negative rate of MRI was 60–65%, and the false-positive rate was 10%. Therefore, MRI as a diagnostic tool has limitations. A normal MRI imaging does not prove the absence of occult CNS disease in the cases of ALL.[10]

Leukapheresis removes the circulating blasts quickly to alleviate symptoms; chemotherapy would take 24–48 hours to attain the same effect as studied by Karren and Lu et al.[11,12] Therapeutic leukapheresis has also been used prophylactically in patients with leukemia with high blast counts to decrease the risk of tumor lysis syndrome. Chemotherapy, once initiated, leads to rapid cell death and hyperuricemia, consequently resulting in acute renal failure.[13]

Hemodynamically unstable patients, sepsis, and allergy to albumin or fresh frozen plasma are the major contraindications to plasmapheresis. Patients with hypotension, active bleeding, bronchial obstruction and anemia are also some contraindications.[14]

Dalugama et al. have noted that immune attacks on myelin and axons with cytokines such as tumor necrosis factor, interleukins, and complements participating in the immune response are due to molecular mimicry.

Guillain–Barré Syndrome (GBS) associated with dengue fever is the most common peripheral nervous system complication. It is usually seen during the recovery phase of the illness. A wide spectrum of clinical manifestations are documented, ranging from mild motor weakness to quadriparesis with respiratory weakness.[15–17]

The incidence of neurological manifestations is 1–5% in dengue infections. Encephalitis, encephalopathy, mononeuropathies, myelitis, aseptic meningitis, GBS, and intracranial hemorrhage are some of the neurological manifestations. Although rare, GBS has been reported as a neurological manifestation of dengue infection. Verma et al. and Carod et al., in their studies, concluded that dengue fever was associated with widespread neurological complications, including GBS, which was seen in three cases out of 26 cases.[18,19]

Fragoso et al. described 10 cases of GBS with dengue fever. Neurological manifestations in this case series were frequently severe, but recovery was mostly complete.[13] In a study by Dalugama et al., about seven cases of GBS associated with positive dengue serology were discussed, and he stressed the need for screening for dengue infection, especially in endemic areas in patients presenting with acute flaccid paralysis, though GBS was rare as a neurological sequel following the infection. Neurological complications are reported to occur in 0.5–6% of cases with dengue fever. Dengue as an antecedent infection in GBS was uncommon about 10 years back; however, several authors have described GBS in dengue since the majority of these were children and a few cases of postdengue GBS in adults.

Ramzan et al. observed in their study that there was a delay in platelet recovery in ALL patients with dengue as compared to cases of dengue without ALL.[16]

Conclusion

In conclusion, it appears that GBS in ALL is a rare occurrence; a high index of suspicion or differentiation from other neuropathies is needed. Screening for dengue infection is indeed necessary, especially in endemic areas in patients presenting with acute flaccid paralysis. Electrophysiological studies guide the correct diagnosis. All three presenting together is very rare indeed. The differentiation is important to initiate timely immunomodulatory therapies for GBS.

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CASE REPORT

Pulmonary Radiological Manifestations of Paraquat Poisoning: A Pictorial Essay

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Abstract

Paraquat (1,1′-dimethyl-4,4′-dipyridylium) is a liquid herbicide, linked to both accidental and intentional ingestion, which can result in severe and frequently lethal poisoning. It has been known to cause injury to the lungs, kidneys, and liver. We retrospectively reviewed five cases over the last 4 years with a history of paraquat ingestion. The time duration between ingestion and high-resolution computed tomography (HRCT) was assessed. HRCT chest scan was variable, ranging from 4 to 18 days postexposure. The follow-up of the patients was also reviewed.

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Introduction

Paraquat is a widely available and used herbicide in the Indian subcontinent. Paraquat kills weeds by preventing the conversion of nicotinamide adenine dinucleotide phosphate to nicotinamide adenine dinucleotide phosphate hydrogen during photosynthesis and the formation of reactive oxygen species.[1,2]

Paraquat poisoning has both local and systemic symptoms. The most prevalent symptom in a 17-patient Indian series was vomiting (100% of the incidence), altered sensorium (59%), oral ulceration or dysphagia (53%), dyspnea (41%), and loose stools (24%).[3] Paraquat can cause multiorgan failure, renal and hepatic failure, pulmonary edema and fibrosis, cardiac failure, shock, and convulsions. The hallmark of paraquat poisoning is lung involvement in the form of extensive alveolitis and eventual pulmonary fibrosis.[4]

Although paraquat poisoning has been widely reported throughout the world, literature from India describes only a small number of radiograph-based case reports.

The aim of this pictorial essay is to describe the radiological manifestations of lung damage on cross-sectional imaging caused by paraquat ingestion with a focus on the progressive changes over time associated with this condition.

Most of the patients in our case series were farmers and were exposed to paraquat accidentally during spraying. Hence, the exact amount of exposure to paraquat could not be quantified.

Materials and Methods

We retrospectively reviewed the lung abnormalities in five patients with a history of paraquat ingestion/inhalation on high-resolution computed tomography (HRCT) chest examinations, done at our hospital over a period of 4 years.

The CT scan was assessed specifically for the pattern and distribution of pulmonary abnormalities, the presence of architectural distortion, honeycombing, bronchial dilatation, pleural effusion, and significant mediastinal lymphadenopathy (>1 cm in SAD, short axis diameter). CT scans of patients were obtained 4–18 days (mean, 11 days) after ingestion.

All CT scans were obtained with a 64-slice multidetector CT machine (Ingenuity CT, Philips). Thin-section scans with a slice thickness of 1 mm were obtained. The scanning parameters were 120 kVp and 100 mA. The display fields of view included the entire chest without targeting. Both mediastinal (width, 350; level, 60) and lung window (width, 1,600; level, −600) images were obtained. All scans were obtained with the patient in the supine position and at the end inspiration.

Case Report/Results

Case 1

A 22-year-old male presented to the emergency department (ED) with h/o paraquat ingestion 1 day back. On presentation, the patient complained of shortness of breath (SOB), bilateral chest pain, and episodes of vomiting. The vitals were normal. His oral mucosa was congested and edematous. Both lung fields revealed bilateral decreased breath sounds on auscultation. Examination revealed diffuse crepitus over the anterior and lateral chest walls. The patient underwent a frontal chest radiograph (Fig. 1) in emergency at the time of presentation which revealed prominent bronchovascular markings in bilateral lung fields, however, no focal lung parenchymal lesion was appreciated. Serial frontal chest radiographs were done on days 4 and 7 (Figs 2 and 3). As the condition of the patient

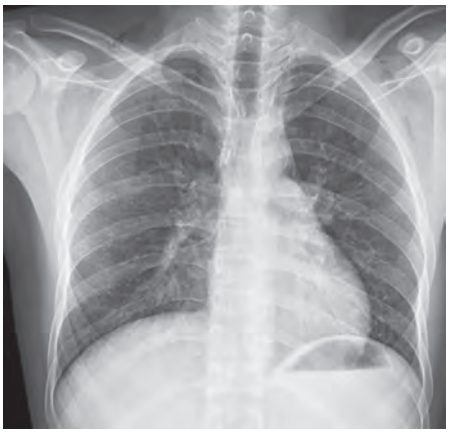

Fig. 1: Day 1—frontal chest radiograph showing prominent bronchovascular markings in bilateral lung fields

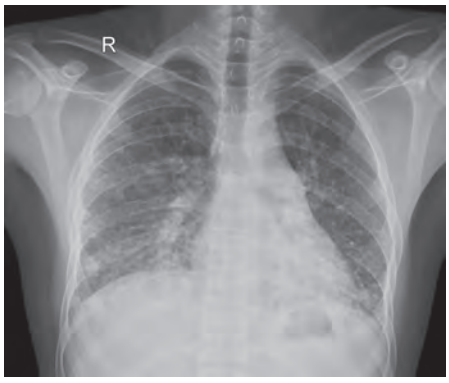

Fig. 2: Day 4—frontal chest radiograph showing ill-defined reticular and nodular opacities in bilateral lung fields with patchy inhomogeneous radio-opacities in the right lower lung zone

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deteriorated on the 7th day, an HRCT chest was planned (Fig. 4) and (Tables 1 to 4).

Case 2

A 23-year-old young male presented to the ED with h/o paraquat ingestion 1 day back. On presentation, the patient complained of oliguria, palpitations, and mild SOB. On examination, the vitals were normal. On 3rd day after admission, the patient complained of sudden onset SOB and bilateral chest pain. Serial frontal chest radiographs were done at the time of presentation, days 4 and 7.

High-resolution computed tomography (HRCT) chest was performed 4 days postingestion of paraquat which revealed pneumomediastinum with diffuse bilateral subcutaneous emphysema. Diffuse ground glass opacities (GGOs) with interlobular septal thickening in bilateral lung fields were also seen (Figs 5 to 8) and (Tables 1 to 4).

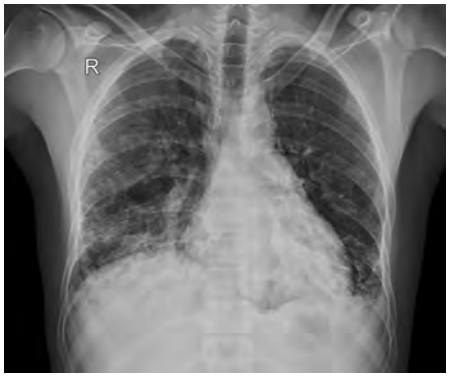

Fig. 3: Day 7—frontal chest radiograph showing an increase in the coarse reticular and nodular opacities in bilateral lung fields with patchy inhomogeneous radio-opacities in the right lower lung zone. Minimal pneumomediastinum is seen

Case 3

A 27-year-old young male presented to the ED with h/o paraquat ingestion 4 days back. On presentation, the patient complained of SOB. Liver function tests and renal function tests were deranged. The patient underwent serial frontal chest radiographs at the time of presentation and 8 days postpresentation. HRCT chest was done 4 days postingestion due to a complaint of severe SOB (Figs 9 to 11) and (Tables 1 to 4).

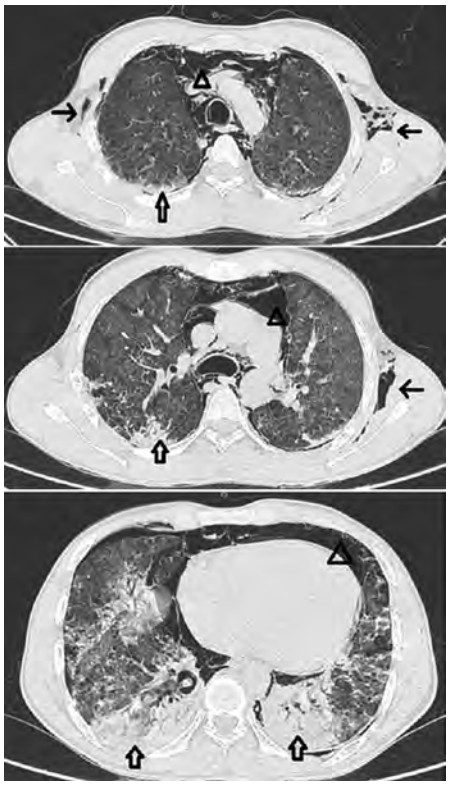

Fig. 4: High-resolution computed tomography (HRCT) chest was performed 8 days postingestion of paraquat which revealed diffuse inter and intralobular septal thickening with superimposed GGOs in bilateral lung fields. Multiple patches of consolidation, predominantly in the dependent portion in bilateral upper, lower lobes, and right middle lobes were noted. Minimal bilateral pneumothorax with extensive pneumomediastinum and subcutaneous emphysema were also seen

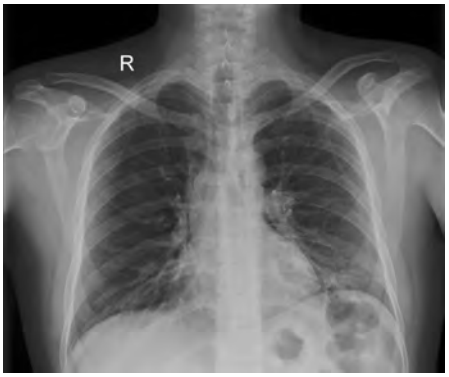

Fig. 5: Day 1—frontal chest radiograph showing mildly increased reticulations in the bilateral lower lung zones

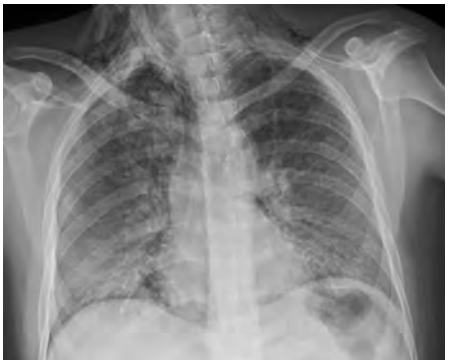

Fig. 6: Day 4—frontal chest radiograph showing increased reticular opacities in bilateral lung fields, predominantly in bilateral lower lung zones. Pneumomediastinum and subcutaneous emphysema are noted

Table 1: Summary of liver function tests of the patients

Case number	*Age/gender*	*Serum glutamic-oxaloacetic transaminase (IU/L)*	*Serum glutamic-pyruvic transaminase (IU/L)*	*Total serum bilirubin (mg/dL)*	*Alkaline phosphatase (IU/L)*	*Total serum protein (gram%)*	*Albumin (gm/dL)*
1	22/M	156	371	13.4	433	4.7	3.1
2	23/M	278	159	19.5	1001	6.5	2.6
3	27/M	314	278	13.5	512	6.2	2.3
4	38/F	56	98	0.4	350	6.0	3.5
5	35/M	176	551	0.7	251	5.6	3.2

Table 2: Summary of renal function tests of the patients

Case number	*Age/gender*	*Sodium (mEq/L)*	*Potassium (mEq/L)*	*Chloride (mEq/L)*	*Urea (mg/dL)*	*Creatinine (mg/dL)*
1	22/M	146	6.2	103	52	1.2
2	23/M	136	3.9	96	171	2.2
3	27/M	147	4.6	99	189	2.6
4	38/F	132	4.5	98	35	0.8
5	35/M	135	3.1	98	81	1.5

Table 3: Summary of hematological parameters of the patients

Case number	*Age/gender*	*Hemoglobin (gram%)*	*Total leukocyte count ($\times 10^9$/L)*	*Differential leukocyte count (N/L/M/E/B)*	*Total RBC count ($\times 10^{12}$/L)*	*Platelets ($\times 10^9$/L)*	*Packed cell volume (%)*
1	22/M	15.7	7.7	70/25/3/2/0	6.20	256	47
2	23/M	12.6	25.7	86/10/2/2/0	4.57	319	35.7
3	27/M	14	4.91	81/14/3/2/0	4.78	187	40.9
4	38/F	11.8	18.4	81.5/10.7/0/0/0	5.69	544	39.1
5	35/M	15.1	15.93	86.3/5.8/0/0.1/0.1	5.03	250	44.2

Table 4: Summary of the radiological findings and outcome of the patients

Case number	*Age/gender*	*Clinical findings*	*HRCT done on day (postexposure)*	*Summary of radiological findings*	*Cause of death*	*Outcome (survival/ death)*
1	22/M	Dyspnea, chest pain, and vomiting	8 days	Septal thickening, consolidation, pneumomediastinum, and pneumothorax	Cardiorespiratory failure	Death
2	23/M	Oliguria Mild dyspnea Palpitation	4 days	Pneumomediastinum, ground glass haze, and septal thickening	Cardiac arrest and sepsis	Death
3	27/M	Dyspnea Oral mucosal ulcers Deranged RFT and LFT	4 days	Ground glass opacifications, consolidation, minimal bilateral, and pleural effusion	Cardiorespiratory failure	Death
4	38/F	Dyspnea Tachycardia Absent DTR	18 days	Diffuse GGOs with apical predominance, consolidation, areas of bronchiectasis, and bronchiectasis	Septic shock	Death
5	35/M	Dyspnea Tachycardia	7 days	Multiple focal areas of fibrosis with cystic lucencies	–	Survival

RFT, renal function test; LFT, liver function test; DTR, deep tendon reflexes

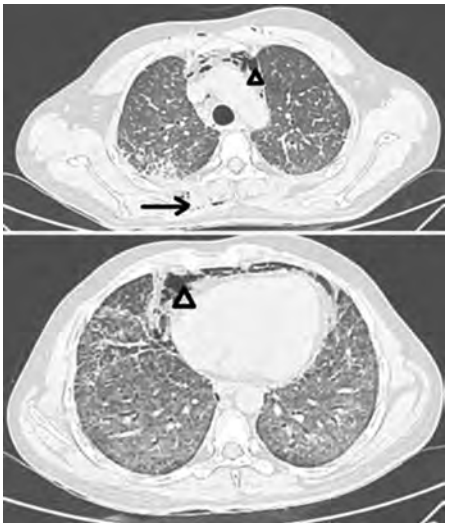

Fig. 7: High-resolution computed tomography (HRCT) chest was performed 4 days postingestion of paraquat which revealed pneumomediastinum with diffuse bilateral subcutaneous emphysema. Diffuse GGOs with interlobular septal thickening in bilateral lung fields were also seen

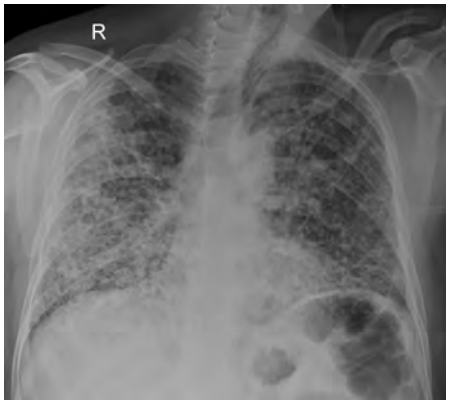

Fig. 8: Day 7—frontal chest radiograph showing markedly increased reticular and nodular opacities in bilateral lung fields with patchy ill-defined inhomogeneous radio-opacities scattered in bilateral lung fields

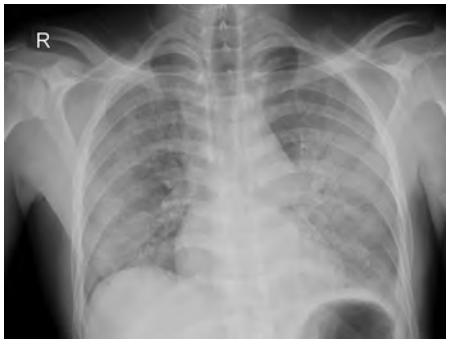

Fig. 9: Day 4—frontal chest radiograph showing diffuse haziness in bilateral lung fields with increased reticular opacities in B/L lower lung zones

Case 4

A 38-year-old female presented to the ED with h/o paraquat ingestion 4 days back. On presentation, the patient complained of SOB and had tachycardia. Decontamination treatment was given in the ED, and he was admitted to the intensive care unit for observation and further evaluation. However, the patient could not be weaned off from non-rebreathing mask (NRM) even after 14 days of admission. HRCT chest was done 18 days after ingestion of the paraquat (Figs 12 and 13) and (Tables 1 to 4).

Case 5

A 35-year-old male presented to the ED with h/o paraquat ingestion 5 days back. On presentation, the patient complained of SOB. On examination, he had tachycardia. A frontal chest radiograph was done at the time of admission. HRCT chest was done 7 days postingestion (Figs 14 and 15) and (Tables 1 to 4).

Discussion

Acute paraquat self-poisoning is a significant problem in the Indian subcontinent.[5] The most frequent routes of exposure to paraquat are ingestion or through direct skin contact.

It is thought that the production of superoxide ions is what causes paraquat to cause lung damage. By directly interacting

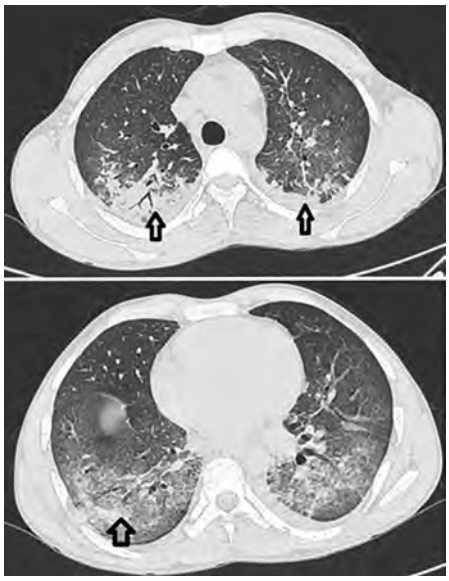

Fig. 10: High-resolution computed tomography (HRCT) chest was performed 4 days postingestion of paraquat which revealed patchy areas of GGOs and consolidation in apicoposterior segment of bilateral upper lobes and bilateral lower lobes with minimal bilateral pleural effusion

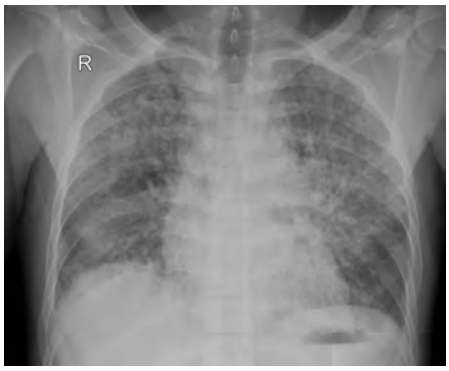

Fig. 11: Day 8—frontal chest radiograph showing markedly increased reticulonodular opacities in B/L lung fields

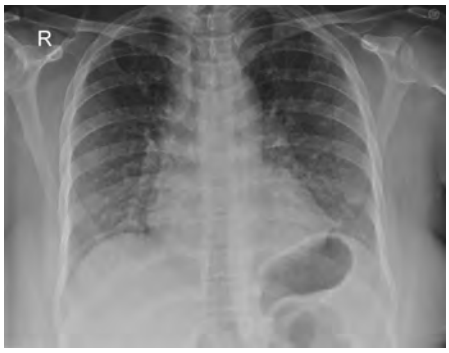

Fig. 12: Day 4—frontal chest radiograph showing increased reticulonodular opacities in B/L lower lung zones

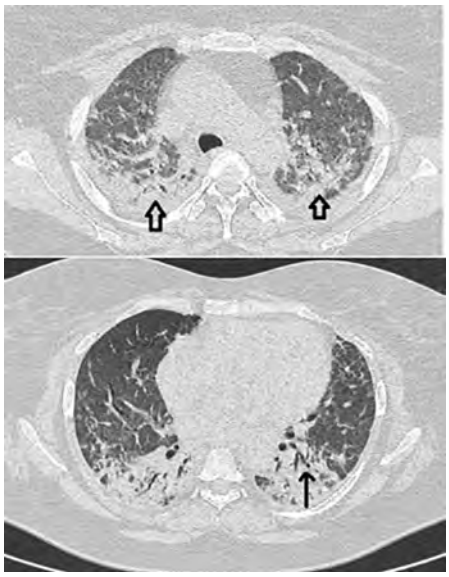

Fig. 13: High-resolution computed tomography (HRCT) chest was performed 18 days postingestion of paraquat which revealed diffuse GGOs with apical predominance coalescing to form patches of consolidation in subpleural and posterior dependent portions of bilateral lung fields with areas of bronchiectasis and bronchiolectasis

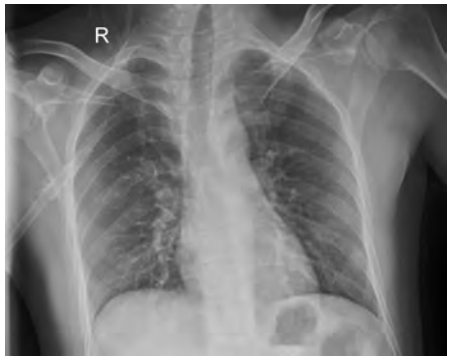

Fig. 14: Day 1—frontal chest radiograph showing mildly increased bronchovascular markings in B/L lower lung zones

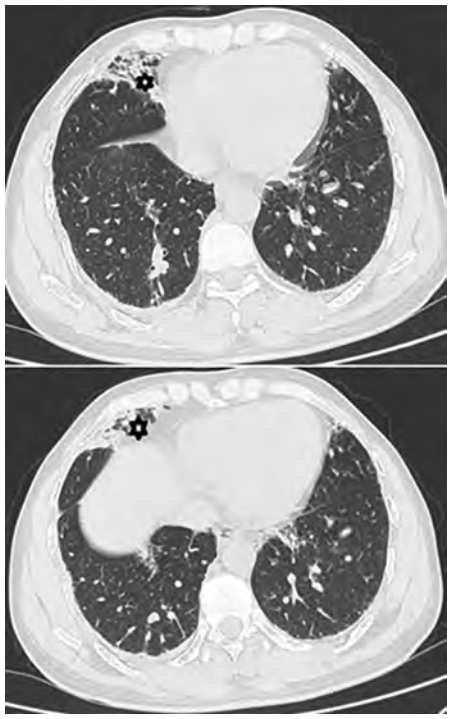

Fig. 15: High-resolution computed tomography (HRCT) chest was performed 7 days postingestion of paraquat which revealed multiple focal areas of fibrosis with cystic lucencies involving the medial segment of right middle lobe (RML), lingula, and posterobasal segment of right lower lobe (RLL) as described

with the lipids found in cell membranes, superoxide ions cause tissue damage and endothelium, and epithelial cell damage and death. Acute alveolitis can also result from paraquat intoxication.[6]

Irrespective of the mode of exposure, paraquat quickly spreads, with the lungs, and kidneys having the highest concentration.[2]

Involvement of the lung in the form of diffuse alveolitis and subsequent pulmonary fibrosis is the hallmark of paraquat poisoning. Acute respiratory distress syndrome because of paraquat usually appears 24–48 hours after ingestion.[4]

Alveolar wall thickening caused by edema, bleeding, and inflammatory cells is one of the early aberrant signs of paraquat poisoning in the lung. A significant amount of fibrin and fluid are present in several of the alveoli.[7]

Various studies have found that certain imaging findings and complications in patients with paraquat poisoning can predict mortality, including the presence of GGOs, interstitial pulmonary fibrosis, and mediastinal emphysema. As described by Zhou et al., pneumomediastinum, which is often caused by paraquat's corrosive effects on the esophagus, is also a specific predictor of mortality, especially if it develops within 8 days of poisoning. The passage also outlines possible mechanisms by which pneumomediastinum can occur, such as fibrosis and alveolar rupture, repeated gastric lavage, esophageal damage from vomiting, or damage from mechanical ventilation.[8] In our study, out of the five cases, two patients had pneumomediastinum and none of them survived.

Pulmonary fibrosis usually begins 7 days or more after paraquat poisoning. Pulmonary fibrosis and microcyst development are reported late aberrant findings of paraquat toxicity (often >2 weeks after paraquat overdose). The lung structure is entirely disorganized and replaced by many small (0.5–2.0 mm in diameter) cysts lined by fibrous tissue.[9]

In our study, the predominant finding within the first 7 days was diffuse inter and intralobular septal thickening with

superimposed areas of GGOs. The initial areas of GGOs changed into areas of consolidation associated with bronchiectasis. A surprising finding in the present study was that the CT pattern 7 days or more after paraquat poisoning showed focal areas of fibrosis with interspersed areas of cystic lucencies. The findings were in accordance with the findings given in the literature.

Severely poisoned patients usually die of circulatory collapse quickly, although if the clinical course is prolonged, pulmonary fibrosis can develop. In our study, out of the five cases, only one survived.

There is no specific remedy available to treat paraquat poisoning. However, several initial measures such as gastric lavage, the administration of adsorbents, and antioxidants like vitamins C and E are attempted. Additionally, free radical scavengers such as Nacetyl cysteine have also been used to treat paraquat poisoning. Hemodialysis is a treatment option for patients who experience acute kidney injury due to paraquat poisoning.[10]

Conclusion

To the best of our knowledge, this is one of the first case series from north India describing the HRCT chest findings in paraquat poisoning. Most of the existing literature is associated with describing the plain radiographic findings. Our study aims to add to the already existing radiographic knowledge about lung findings in paraquat poisoning by describing the HRCT chest findings.

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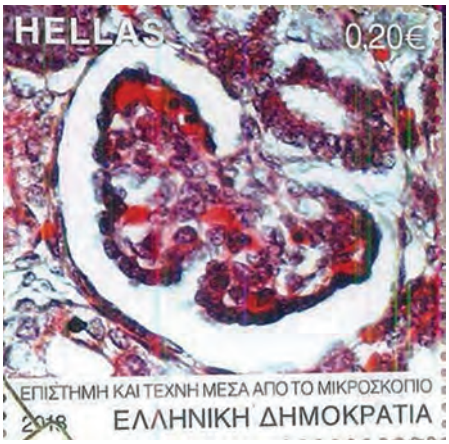
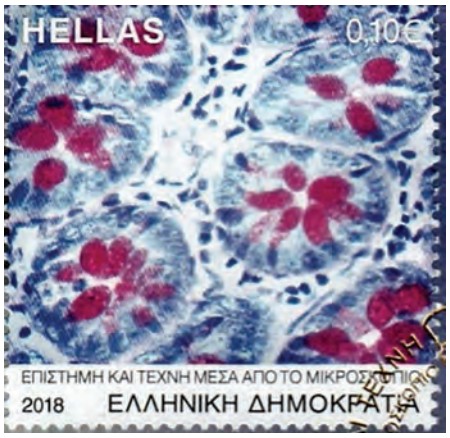
Art under the Microscope

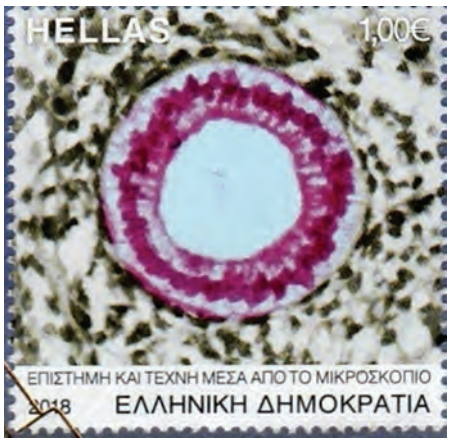
Jayant Pai-Dhungat[1], Aparna Verma[2]



"Captive butterfly;" hematoxylin and eosin-stained section of renal corpuscle ×200 Greece, 2018



"Flower of our inner world;" section of intestinal glands stained with periodic acid-Shiff stain ×200; Greece, 2018



"Wreath;" hematoxylin and eosin-stained section of the fetal lung (tubular phase); Greece, 2018

"The playful deer;" hematoxylin and eosin-stained section of the spermatic duct; Greece, 2018

"Double heart;" hematoxylin and eosin-stained section of renal tubules ×200; Greece, 2018

In March 2018, Greece issued five commemorative stamps that show a beautiful mélange of art and science. Images are, however, genuine views captured through light microscopy of stained human tissue during histopathological examination. Many will remember having drawn such diagrams in their histology and pathology journals during their medical school years. The microscopic images are photographed beautifully by Dr Maria Lambropaulou. She is an Associate Professor of Histology–embryology at the Medical Department of the Democritus University of Thrace, Greece.

A pathologist has a very important and crucial role in diagnosing the material sent to them. The histopathological report determines the clinical course of action and prognosis. Histopathologists spend long hours observing under the microscope. Their Job can be boring sometimes, but at times, they often come across alluring images in the microscope and an amazing world of cells, which suddenly and unintentionally form images of scenes that are as beautiful as any painting hanging in the gallery. Identification of these artistic features under the microscope reflects the analytic training of an experienced pathologist and the ability to recognize common and unusual patterns. Such surreal beauty is found hiding in the tiny world of cells.

Careful examination of the stamps will reveal a golden rim fancy microscope as a cancellation mark in the lower corners. The theme of microscopic art is gaining popularity, and presently, several countries have issued stamps on this subject.

The art forms, however, bring forward the usual question: does art imitate life, or does life imitate art? There can be no doubt that nature is the greatest inspiration for art and beauty. Preparations observed under the microscope contain a wealth of information. The aim of the researcher is to correlate the cellular structure with the structure and functioning of the organism and, ultimately, with the miracle of life. The esthetic quality of the images has led many scientists to stand in their artistic nature.

[1]Professor of Medicine (Retd), Department of Medicine, Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital; Honorable Physician, Bhatia Hospital, Mumbai, Maharashtra; [2]Family Physician, Bengaluru, Karnataka, India

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Inappropriate Use of Steroids in Superficial Dermatophytosis: An Uncommon Case of Erythroderma

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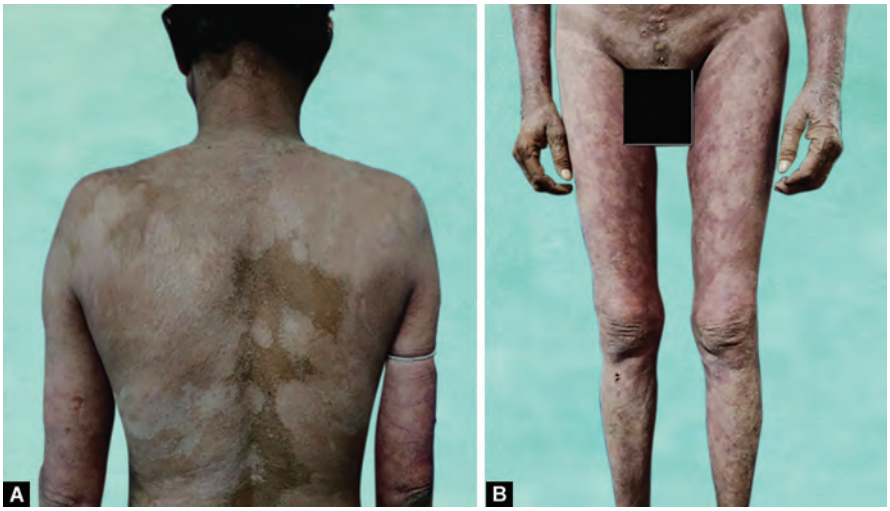
[1,4]Second-year Postgraduate; [2]Senior Professor and HOD; [3]Assistant Professor; [5]Senior Resident, Department of Dermatology, Rabindranath Tagore Medical College, Udaipur, Rajasthan, India

Sir,

Erythroderma is a dermatological emergency presenting with generalized erythema and scaling involving >90% of the body surface.[1] There are various causes of erythroderma, such as psoriasis, atopic dermatitis, phytophotodermatitis, pityriasis rubra pilaris, pemphigus foliaceus, cutaneous T-cell lymphoma, and drug eruptions.[2] However, erythroderma induced by dermatophytosis is encountered rarely. We, here, describe a case of erythroderma developed secondary to extensive dermatophytosis.

A 55-year-old male presented to the skin outpatient department with complaints of extensive redness and scaling all over his body. He was otherwise healthy and not on any medications. The itchy skin eruption appeared 1 year back in the groin and gradually spread to other body areas in a span of 1 year. A cutaneous examination showed generalized erythema superimposed with fine, whitish-grey scales that coalesced over multiple areas (Figs 1A and B). Systemic and laboratory evaluation was normal, indicating the absence of any concealed systemic illness. He took treatment from multiple practitioners over time and recalled initial partial symptomatic relief only to aggravate later on. Documentation of his past treatments highlighted the repeated use of potent topical/oral steroids either alone or in combination with topical antifungal agents. Skin scrapings for potassium hydroxide (KOH) examination were taken from multiple sites. KOH mount microscopy revealed the presence of numerous hyaline, long, septate, branched, and hyphae. Correlation of the clinical presentation, findings of KOH mount microscopy, and repeated use of topical/oral steroids established the diagnosis of steroid-modified dermatophytosis-associated erythroderma. He was treated with oral itraconazole 100 mg twice a day and clotrimazole 1 w/w% cream for 3 months. The patient was followed up regularly every 2 weeks. The complete resolution of the symptoms was achieved after 12 weeks of the mentioned antifungal therapy.



Figs 1A and B: A cutaneous examination showed generalized erythema superimposed with fine, whitish-grey scales that coalesced over back and lower extremities

Tinea incognito/steroid-modified tinea is the name given to a fungal skin infection when the clinical appearance has been altered by inappropriate treatment, usually a topical steroid cream.[3] According to recent studies, rampant use of topical steroids (especially class 1 clobetasol) in cases of tinea has led to the emergence of a new variant, *Trichophyton indotineae*, which is universally resistant to terbinafine.[3]

In our experience, we have observed that the usual tendency of general health practitioners who come across cases of dermatophytosis is to prescribe the topical combination therapy of potent topical corticosteroids/antibiotics with or without topical antifungals. With such inappropriate therapies for dermatophytosis, patients get initial symptomatic relief. These topical steroid combinations are easily sold over the counter without any prescriptions, and patients keep applying such medications regularly by themselves to compound the matter further. This has led to a current epidemic-like situation of tinea, which is causing great distress not only to the patients but also adds to the difficulties of treating dermatologists.

The purpose of sharing this case is to highlight the problems caused by the injudicious use of topical/oral steroids in the management of dermatophytosis, leading to unusual forms of tinea such as erythroderma (as in our case) and treatment-resistant variants of dermatophytes.

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Early Gestational Diabetes Mellitus: An Update

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We have attentively reviewed the recent article authored by Hannah et al., "Early Gestational Diabetes Mellitus: An Update," published in JAPI volume 71, issue 9, September 2023, and we concur with the authors' perspective on the benefits of early screening and treatment for early gestational diabetes mellitus (eGDM). This viewpoint is substantiated by extensive support from various study groups.

Our primary advocacy is for the establishment of universal early pregnancy screening protocols for eGDM. The exclusive reliance on screening high-risk groups may inadvertently omit cases characterized by incomplete medical histories, individuals with poor documentation, and those residing in underprivileged and poorly educated communities, where awareness and record-keeping are limited. These factors are particularly pronounced in semirural and rural areas within the country.

Allow us to illustrate this stance with a case we reported several years ago.[1] A 29-year-old Asian woman, professionally a nurse in Nepal, presented during her first pregnancy at 6 weeks gestation. She lacked a pertinent medical history but had a strong family predisposition to type 2 diabetes. Apprehensive about her glycemic status, we conducted a 75 gm oral glucose tolerance test (OGTT). The fasting plasma glucose measured 6.3 mmol/L, with a 2-hour value of 8.1 mmol/L, leading to a diagnosis of gestational diabetes

mellitus. Regrettably, her first pregnancy was terminated by abortion at 10 weeks. 8 weeks postabortion; her 75 gm OGTT yielded normal results. During her subsequent pregnancy, we performed a 75 gm OGTT at 6 weeks gestation, revealing a fasting value of 5.7 mmol/L and a 2-hour value of 10 mmol/L. Glycated hemoglobin (HbA1c) done at the time was 6.6%. Once more, the diagnosis of gestational diabetes mellitus was considered, and insulin therapy was initiated. At 37 weeks, the pregnancy encountered complications due to premature rupture of membranes, necessitating an emergency cesarean section. Fortunately, a live and healthy female infant weighing 2850 gm was delivered, and the neonatal course remained uneventful. The patient's plasma glucose levels returned to normal the following morning, allowing us to cease insulin injections.[1]

Gestational diabetes mellitus (GDM) is typically diagnosed after 24 weeks of gestation, and screening and diagnostic approaches exhibit notable variability across medical specialties and global regions. Contentious issues encompass whether to perform screening at all, the choice between universal and risk-based screening, the optimal timing of screening, the preferred screening methods (e.g., fasting plasma glucose, random plasma glucose, glucose challenge test), diagnostic criteria (one or two-step procedures, 75 vs 100 gm glucose load, the necessity of one or two abnormal values for diagnosis), and the appropriate cut-off values.[2]

The updated American College of Obstetricians and Gynecologists guidelines for gestational diabetes endorse early screening for specific categories of pregnant women. These categories include those with a bodymass index of 25 (or 23 in Asian Americans), physical inactivity, a family history of diabetes, previous pregnancies involving GDM or macrosomia, hypertension, low high-density lipoprotein cholesterol, high fasting triglycerides, polycystic ovary syndrome, insulin resistance-related conditions, elevated HbA1C levels, and cardiovascular disease.[3]

Current guidelines recommend routine screening for GDM at 24–28 weeks of pregnancy, with early screening offered to those considered high-risk. However, risk stratification may not always be helpful for those who would benefit from early screening, especially in non-Western settings. Akinyemi et al. conducted a study and concluded that their study did not yield conclusive evidence to advocate for universal GDM screening in all pregnant women. Those diagnosed before the 24–28-week period of universal screening typically exhibits substantial risk factors for GDM, making them suitable candidates for risk-factor-based screening.[4]

The International Federation of Gynecology and Obstetrics has issued guidance endorsing universal early pregnancy screening for eGDM. Their recommendation is for all pregnant women to undergo hyperglycemia testing during pregnancy using a one-step procedure. The Federation of Gynecology and Obstetrics further encourages countries and their member associations to adopt and promote strategies to facilitate this approach.[5]

The Diabetes in Pregnancy Study Group of India (DIPSI) was among the pioneers in recommending universal screening of all pregnant women during the first trimester of pregnancy.[6] Given the high prevalence of hyperglycemia in pregnancy in India, it becomes imperative for all pregnant women to undergo screening. DIPSI advocates a simple, cost-effective, and feasible one-step procedure involving a 75 gm glucose challenge, enabling the diagnosis of GDM.[6]

In regions like India, burdened with a high incidence of hyperglycemia during pregnancy, findings from the Towards a Better Outcomes in Gestational Diabetes Mellitus (ToBOGM) study underscore the significance of early screening at the outset of pregnancy, followed by tailored interventions for identified eGDM cases.[7]

Nonetheless, specific diagnostic tests or threshold recommendations for diagnosing eGDM are currently absent. The ToBOGM study also demonstrates the substantial advantages of early identification and treatment of eGDM, particularly for those identified and treated before the 14-week gestational mark. The momentum for screening GDM at the onset of pregnancy is rapidly gaining ground,[7] though we emphasize the importance of universal screening to encompass patients considered nonhigh-risk, given the common prevalence of language barriers, poor medical history documentation, and inadequate medical records, especially in developing and resource-constrained nations to avoid missing.

In Nigeria, Africa, Nwali et al.performed a cross-sectional comparison between universal and selective risk factor-based screening for GDM among 400 antenatal care clients at Alex-Ekwueme Federal University Teaching Hospital Abakaliki. Selective risk factor-based screening missed 31.11% of patients with GDM when compared to universal screening with one step 75 gm OGTT. They conclude the recommendation of universal screening for GDM using the one-step 75 gm OGTT for pregnant women.[8] In this study, all the participants had 75 gm OGTT at 24–28 weeks of gestation and had risk factors; using this criterion, they missed 31.11% of patients with GDM. We wonder if the same could be true for eGDM if we only select patients with high-risk factors for screening.

It is worth noting that our patient, a nurse by profession, effectively communicated her concerns and provided a high-risk history for potential eGDM. This underscores the importance of proactive patient engagement in the diagnostic process, particularly in cases of early gestational diabetes mellitus, which has been associated with adverse pregnancy outcomes.[1]

In conclusion, the evidence and experiences we have presented support the call for universal early pregnancy screening for eGDM. Early identification and intervention, especially in high-risk cases, hold the potential to improve pregnancy outcomes. Nevertheless, considering the challenges faced by non-high-risk patients in terms of language barriers, medical history documentation, medical record-keeping, and unequal health facility access in resource-deprived countries, universal screening at the onset of pregnancy can be a pivotal approach to prevent missed eGDM cases and enhance overall pregnancy outcomes. A larger multicentre study could be an answer to substantiate this further.

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