# Editorial

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EDITORIAL

Metabolic Karma and Health

Sanjay Kalra

Karma

The Sanskrit word “karma” represents the past, present, and future. A noun that is used to describe actions undertaken in the past, experiences being felt now, as well as destiny that will manifest in the future, karma can be used in multiple ways. “Karma” also refers to predetermination, and can be used to explain the inevitable or non-modifiable aspects of life. Indian philosophy is sometimes criticized for promoting fatalism. Nothing, however, can be further from the truth. The karmic hypothesis actually suggests that one can use present actions to modify the future course of events. This is true not only for actions, but also for beliefs, thoughts, and intentions: the right action, undertaken with the right intention, in the right direction, is bound to lead to the right outcomes, and accomplish desired results.

Health Karma

The concept of karma is engrained in health and illness. The etiology and pathogenesis of illness are the karma of the past; present health status, the karma of the present; and prognosis karma of the future.

Most diseases are caused by or precipitated by inappropriate health-related behavior. The Global Burden of Disease Study suggests that most risk factors of disease can easily be avoided. The same findings emerge from the INTERHEART study, which analyzed the causes of myocardial infarction. Excessive tobacco and alcohol intake, suboptimal exercise, and inadequate fruits/vegetable consumption are examples of karma that lead to coronary artery disease. Other karmas which can precipitate myocardial infarction include uncontrolled lipids, blood pressure, body weight, and hyperglycemia. These four challenges remind one of the chariota or chariot run by four horses. Allegorically, the chariot represents the human body, and the horses, the senses.

Metabolic Karma

This analogy serves as a useful explanation of the work done in the metabolic clinic to manage wayward horses and ensure optimal health. Metabolic karma can be defined as the actions taken, in the past and present, to influence metabolic health, in the present and future. The term “metabolic karma” was first popularized by Thomas et al., and we reiterate our acknowledgment and appreciation for his use of age-old Sanskrit terminology to explain a concept that is backed by modern evidence.

Metabolic karma encompasses various domains, including lifestyle and behavior, as well as the utilization of pharmacotherapy and other interventions. This is similar to the terms metabolic memory and glycemic legacy, which have been used to describe the positive effect of metabolic control on long-term health in persons living with diabetes.

Evidence for Karma

Metabolic karma is an evidence-based concept. Recently the United Kingdom Prospective Diabetes Study (UKPDS) reported a 44-year-long follow-up of their participants. The UKPDS aimed to assess the impact of various glucose-lowering therapies on complications of diabetes. Participants were randomized to receive “conventional” or “intensive” therapy. Timely intensive glycemic control with insulin and sulfonylureas was able to reduce microvascular complications by 26% and mortality by 11%. Similar intervention with metformin accomplished a 25% reduction in mortality and a 31% fall in myocardial infarction, 44 years after intensive control had been instituted for the duration of the study.

This data build upon and strengthen earlier reports from UKPDS, the Steno trial, and others. These trials along with the more recent drug-specific cardiovascular outcome trials have revealed statistically significant improvements in long-term diabetes outcomes with various glucose-lowering strategies and interventions.

All these results reinforce the fact that meaningful improvements can be brought about in diabetes care, using the right strategy, at the right time. The advantages persist long after the “initial” intervention has been completed. This is the phenomenon of metabolic karma, that we work to achieve in our fellow citizens who live with diabetes.

Clinical Relevance

The concept of metabolic karma holds great clinical as well as public health relevance. The evidence base of glycemic legacy can easily be explained to our patients as beneficial metabolic karma, or as equivalents in other languages (metabolic Vipaka). This phrase can be used to encourage proactive health behavior, with regard to both lifestyle and adherence to prescribed medication. It can also be used as a slogan for public awareness campaigns and health care policies, geared towards ensuring diabetes control. In fact, the utility of this slogan is not limited to diabetes; it holds true for all noncommunicable and metabolic diseases. Please join us in our endeavor to improve the metabolic karma, and the health of our countrymen and women.

References

7. UK Prospective Diabetes Study. [last accessed on 2022 Oct 5]. Available from: https://www.dtu.ox.ac.uk/ukpds/
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Antibiotic Susceptibility Pattern of Aerobic Bacterial Pathogen Isolated from Endotracheal Aspirate

Swetha S1, Pramodhini S2*, Umadevi S3, Joshy M Easow4

Received: 11 May 2022; Accepted: 13 August 2022

INTRODUCTION

Ventilator-associated pneumonia accounts for major ICU-acquired infections, which appear following 48 hours of ET intubation.1 It is estimated that around 6 to 10-fold increase in the risk of respiratory tract infections is due to mechanical ventilation.2,3 In mechanically ventilated patients in ICU, pathogens associated with lower respiratory tract infections tend to enhance the risk of VAP or hospital-acquired pneumonia (HAP) and are identified to be the primary cause of mortality.4 Culture analysis of ET aspirate cannot distinguish between infection from colonization, but there is a high tendency of biofilm to grow at the end of the ET device which enhances the infections.5 Moreover, the emergence of bacterial resistance is common among patients in the ICUs. The aim of the study is to identify the common bacterial pathogen isolated from an ET aspirate culture and to analyze their antibiotic sensitivity pattern.

MATERIALS AND METHODS

This prospective analytical study was carried out in a tertiary care hospital for a period of 1 year. All ET aspirate sample sent to the microbiology laboratory was processed and identified by standard biochemical tests and antibiotic sensitivity was by disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI) guidelines.

RESULTS

Of the total 217 samples studied, 39.17% (85) were sterile and 60.82% (132) were culture positive. Among 132 isolated, 53 (40.15%) were Enterobacteriaces, 75 (56.81%) were Enterobacteriaces, and four (3.03%) were Staphylococcus aureus. The predominant organism isolated among Enterobacteriaces was K. pneumoniae 32 (24.24%), followed by Enterobacter aerogenes 10 (7.57%), Escherichia coli six (4.54%), and Citrobacter spp. five (3.78%). Among 75 non-Enterobacteriaces isolated, 48 (36.36%) were A. baumannii followed by P. aeruginosa 27 (20.45%) (Table 1).

The antibiotic-resistant pattern of A. baumannii showed more than 90% of isolates were resistant to meropenem, imipenem, and gentamicin, and most of the isolates were 80% and above resistant to ceftazidime, amikacin ciprofloxacin, and piperacillin-tazobactam. Among Pseudomonas, 100% resistance was shown to ceftazidime (Table 2).

Among K. pneumoniae, 71.88% were resistant to cefotaxime and more than 50% of the isolates were resistant to ciprofloxacin, co-trimoxazole, gentamicin, imipenem, and meropenem. E. aerogenes also exhibited a similar pattern of sensitivity as Klebsiella spp. E. coli showed 83.33% resistance to ciprofloxacin and 100% sensitivity to imipenem.

Table 1: Analysis of isolates from ET aspirate sample

<table>
<thead>
<tr>
<th>Isolates</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>217</td>
<td>100</td>
</tr>
<tr>
<td>Sterile</td>
<td>85</td>
<td>39.17</td>
</tr>
<tr>
<td>Culture positive</td>
<td>132</td>
<td>60.82</td>
</tr>
<tr>
<td>Gram-negative organism</td>
<td>128</td>
<td>96.97</td>
</tr>
<tr>
<td>Enterobacteriaces</td>
<td>53</td>
<td>40.15</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>32</td>
<td>24.24</td>
</tr>
<tr>
<td>E. aerogenes</td>
<td>10</td>
<td>7.57</td>
</tr>
<tr>
<td>E. coli</td>
<td>6</td>
<td>4.54</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>5</td>
<td>3.78</td>
</tr>
<tr>
<td>Non-Enterobacteriaces</td>
<td>75</td>
<td>56.81</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>48</td>
<td>36.36</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>27</td>
<td>20.45</td>
</tr>
<tr>
<td>Gram-positive organism</td>
<td>4</td>
<td>3.03</td>
</tr>
<tr>
<td>S. aureus</td>
<td>4</td>
<td>3.03</td>
</tr>
</tbody>
</table>

1MBBS Student; 2-4Professor, Department of Microbiology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth Deemed to be University, Pillayarkuppam, Puducherry, India; *Corresponding Author

meropenem, piperacillin-tazobactam, and cefoperazone-sulbactam. Of five *Citrobracter* spp. isolates, 80% resistance was shown to amikacin, cefotaxime, ciprofloxacin, and gentamicin (Table 3).

The antibiotic-resistant pattern of *S. aureus* isolated from ET aspirate showed 100% resistance to ampicillin and 25% to erythromycin and clindamycin. All four isolates were sensitive to cotrimoxazole, tetracycline, gentamicin, cefoxitin, linezolid, vancomycin, and teicoplanin (Table 4).

### DISCUSSION

Endotracheal aspirate culture helps in the evaluation of the occurrence of febrile episodes in mechanically ventilated patients and also to assess the patient’s risk to develop VAP. As colonization precedes infection, bacteria isolated and identified by ET aspirate cultures can be a predictor for causative microbial agents once VAP develops. Several studies have demonstrated that ET culture is an additive diagnostic tool along with routine tests in the detection of plausible pneumonia pathogens.

Among several organisms which accounted for causing pneumonia in mechanically ventilated patients, the most commonly studied agents were *Acinetobacter* species, *Pseudomonas* species, *Enterobacteriaceae*, and *S. aureus*. The common problem encountered in other studies is that bacterial pathogens isolated from ET aspirates often tend to be multidrug-resistant organisms. Several studies have demonstrated a higher incidence of multidrug-resistant gram-negative bacteria isolated from the ventilated patients. In the current study, of 217 samples processed, 132 samples (60.82%) were culture positive with gram-negative bacilli being the most predominantly isolated 96.97% (*n* = 128), followed by gram-positive cocci (*n* = 4) which were in accordance with a study by Samal et al., where they have reported predominance of 87.5% gram-negative bacilli compared to our study.

In our study, *A. baumannii* (36.36%) was the predominant isolates from ET aspirate culture followed by *K. pneumoniae* (24.24%) and *P. aeruginosa* (20.45%). Studies have shown the predominance of *A. baumannii* isolated among ET cultures accounting for 39.1%, 16 37.5%, 17 and 46%, 18 concordant to our study. *A. baumannii* appears to be a predominantly emerging nosocomial pathogen in HAP.

The antibiotic susceptibility profile of non-fermenters showed increased resistance to cephalosporins and carbapenem group of drugs. In our study, *A. baumannii* appears to be a multidrug-resistant organism observed to have 80–90% resistance to cephalosporins, aminoglycosides, fluoroquinolones, and carbapenem group of drugs, and around 35% isolates showing sensitivity to piperacillin-tazobactam in concordant to a similar study by Gowda et al. Few other studies have shown resistance of *A. baumannii* similar to our study except that of carbapenems, wherein a study by Ahmad et al. had shown 2.5% sensitivity to imipenem compared to 10% sensitivity in our study.

Among *Enterobacterales*, increased resistance was shown to cephalosporins and fluoroquinolones group of drugs. The second predominantly isolated *Klebsiella* spp. showed maximum resistance to cephalosporins and more than 50% of the isolates showed resistance to ciprofloxacin, aminoglycosides, cotrimoxazole, and carbapenems, and the least resistance was shown to cefoperazone-sulbactam. Studies have shown increased sensitivity of *Enterobacterales* to carbapenems, in contrast, we have reported only 60–65% sensitivity to cefoperazone-sulbactam and 70% sensitivity to carbapenems, which shows the changing trends of sensitivity pattern.

*S. aureus* isolated among four patients was found to be 100% sensitive to tetracycline, co-trimoxazole, gentamicin, cefoxitin,

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linezolid, vancomycin, and teicoplanin, and 100% resistant to ampicillin.

**Conclusion**

In our study, gram-negative bacilli were predominant with *A. baumannii* being the most commonly isolated followed by *K. pneumoniae* and *P. aeruginosa*. We have reported a higher percentage of resistance among the isolated gram-negative bacilli to carbapenems, aminoglycosides, and third-generation cephalosporins, with increased sensitivity to piperacillin-tazobactam and cefoperazone-sulbactam. One of the rising concerns of hospital-acquired respiratory pathogens is the surge of multidrug-resistant organisms. Hence, strict adherence to antibiotic policy and appropriate use of drugs according to the guidelines will save the use of life-saving drugs in near future.

**References**


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Assessment of Prescription Adherence to Secondary Prevention Guideline Recommendations and Patient Adherence to Pharmacotherapy and Lifestyle Modifications in Acute Coronary Syndrome and Chronic Coronary Syndrome Patients

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Abstract
Background: Coronary artery diseases (CADs) contribute to the majority of deaths and disabilities worldwide. People who have suffered an acute myocardial infarction (AMI) are at a higher risk of having a further attack. Hence, prolonged secondary prevention is necessary following index myocardial infarction (MI) for long-term cardiovascular protection as it reduces the morbidity and mortality associated with reinfection, improves the quality of life, and is cost-effective.

Methods: An observational, ambidirectional study was carried out in a tertiary care hospital for 6 months. A total of 200 patients above 18 years of age with a confirmed diagnosis of acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) were included in the study. Prospective data were collected using a self-designed patient profile form and by interviewing patients in the cardiac outpatient department while retrospective data were collected from the medical records department of the hospital.

Results and conclusion: Sex-wise distribution showed that males and females constituted 79% and 21% of the study participants, respectively, while the age-wise distribution revealed that the majority of patients were in the age-group of 60 years and above (63.5%). Hypertension and diabetes mellitus were the most common comorbid conditions, while dyslipidemia was the least observed comorbidity. Prescription adherence to secondary prevention guideline recommendations was studied, which revealed that 26.5% of the prescriptions were adherent to all four guideline recommendations. On evaluating adherence to pharmacotherapy, the maximum proportion of patients demonstrated moderate adherence (45%).

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Introduction
Cardiovascular diseases (CVDs) are the leading causes of morbidity and mortality worldwide. In India, there are about 40 million heart patients and nearly a quarter of all deaths can be attributed to CVDs. CAD and stroke, the main causes of CVDs in India, contribute to 80% of all cardiovascular deaths. 74% of Indians are at risk of developing CVDs, implying that heart diseases are rampant turning into an epidemic in India that necessitates a structured solution.1–3

Coronary artery disease, also known as coronary heart disease (CHD) or ischemic heart disease, is the most prevailing form of CVD. CAD occurs due to the gradual accumulation of plaque along the walls of the arteries supplying blood and oxygen to the myocardium. CAD has a dynamic nature and results in a disease process having prolonged, stable periods (chronic) but may become unstable (acute) at any moment due to acute atherothrombotic events caused by plaque rupture. Based on this, the clinical manifestations of CAD can be classified as ACS or CCS. CAD is a result of atherosclerosis in coronary arteries and can be asymptomatic, whereas ACS refers to a range of conditions associated with a sudden reduction in blood flow and always manifests as a symptom, like unstable angina or MI.4 MI usually referred to in layman’s terms as a heart attack occurs when the blood vessel gets occluded due to plaque, causing an interruption in the blood supply and ultimately leading to the death (necrosis) of the heart muscle cells. The initial treatment for AMI focuses on restoring blood flow to prevent further ischemia and can be achieved through percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. In settings where patients are unable to undergo PCI within 120 minutes of medical contact, fibrinolysis proves to be a significant reperfusion strategy. Most MI patients will require dual antiplatelet therapy (DAPT) for a year, an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin-II receptor blocker (ARB), a β-blocker and a statin, all of which have been associated with a lower risk of cardiovascular death.5–8 Following 12 months of DAPT, the guidelines suggest weighing individual patients’ risk of ischemic events when deciding whether to continue DAPT or switch to single antiplatelet therapy (SAPT).9–10

People who have suffered from an acute attack are amenable to secondary prevention to mitigate the risk of recurrent cardiovascular events. Several studies have proven that secondary prevention can improve outcomes in such patients and could prevent hospitalizations due to reinfections.9 Atherosclerosis being the predominant cause of ACS, its risk factors are often alleviated in the prevention of the disease. Modifiable risk factors like hypertension, diabetes mellitus, dyslipidemia, obesity, cigarette smoking, and sedentary lifestyle are accountable for 90% of cases in men and 94% of cases in women.5,11,12 Secondary prevention focuses on controlling these modifiable risk factors. Adherence to prescribed pharmacotherapies that improve major coronary risk factors (i.e., hypertension, diabetes, dyslipidemia, and obesity) partly aids in the achievement of secondary prevention. Moreover, lifestyle changes (smoking cessation, exercise, and a well-balanced diet) can also be beneficial in this regard, offering independent and additive benefits in reducing cardiovascular morbidity and mortality.13

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The primary objective of secondary prevention following an AMI is to lessen the likelihood of reinfarction, improve the overall quality of life, and decrease morbidity and mortality. To achieve the above objectives, available cardiovascular prevention guidelines unanimously suggest lifestyle interventions including smoking cessation, increased physical activity, maintaining a healthy body mass index, optimal control of risk factors (blood pressure, cholesterol, and glucose control), and optimal use of cardioprotective drugs (antiplatelets, β-blockers, ACE inhibitors/ARBs, and lipid-lowering drugs).

To reap the maximum benefit from secondary prevention recommendations, adherence is crucial and patients must take the prescribed medications. Various studies have demonstrated that adherence to secondary prevention medications after ACS is suboptimal worldwide. Nonadherence to secondary prevention medications has been associated with a relative increase in the risk of hospitalization by 10–40% and a relative increase in mortality by 50–80%. Several factors contribute to low adherence including multiple comorbidities, poor motivation, worry that the medication will do more harm than good, a feeling that their condition is under control, polypharmacy, forgetfulness, limited practical support, fear of adverse effects, lack of education about medications, and cost of medications. Nonadherence to secondary prevention medications can result in poor risk factor control, poor quality of life, increased hospital readmissions, mortality, and higher medical expenses. Thus, it is critical to emphasize the significance of medication adherence in ACS and CCS patients.

Materials and Methods

Study Design and Ethical Approval

An observational, ambidirectional study was conducted in the Cardiology Department of Aditya Birla Memorial Hospital for a period of 6 months after obtaining ethical approval from the Ethics Committee of the hospital.

Study Criteria

- **Source of subjects**: The study was conducted in the Cardiology Department of Aditya Birla Memorial Hospital.
- **Inclusion criteria**
  - **Prospective study**: A total of 60 patients who visited the outpatient department of cardiology of either gender, age ≥18 years, with a confirmed diagnosis of ACS or CCS, and willing to participate in the study were included.
  - **Retrospective study**: Medical records of patients admitted to the cardiology department in the past 6 months were studied and a total of 140 patients of either gender, age ≥18 years, with a confirmed diagnosis of ACS or CCS were enrolled in the study.
- **Exclusion criteria**: Pregnant women and patients diagnosed with congenital heart diseases and malignancies were excluded from the study.
- **Study duration**: The duration of the study was 6 months.

Data Collection, Assessment, and Analysis

Prior to participation in the study, patients were handed the patient information sheet and informed consent was obtained in writing from the patient or his/her relative. All the demographic and clinical information such as age, sex, medical history, details of the revascularization procedures, and secondary prevention medications were collected with the help of a self-designed patient profile form. In addition to the above-mentioned parameters, details regarding adherence to pharmacotherapy, social habits, and lifestyle were obtained in prospective cases. Prescriptions were compared against the standard secondary prevention guideline recommendations and medication adherence was analyzed using the eight-item Morisky Medication Adherence Scale (MMAS-8). This scale includes eight questions, the first seven of which are dichotomous questions (asks for yes/no as a response) that imply adherent or nonadherent behavior. For question 8, a patient can select an answer on a five-point Likert scale specifying how frequently he or she struggles to remember to take all of the prescribed medications. Each “no” response is scored as 1 and each “yes” response is scored as 0 except for question 5, which is scored the opposite way. Total MMAS-8 scores range from 0 to 8, with eight indicating high adherence, seven or six indicating medium adherence, and scores less than six indicating low adherence. Social habits and adherence to lifestyle modifications were also studied. All the gathered data were transcribed into Microsoft Excel and descriptive statistics were used to analyze the results which were then compared to those documented in the literature.

Morisky Medication Adherence Scale-8

The MMAS-8 scale used to assess medication adherence is included below. The patients were asked to answer each question based on their personal experience with their medications.
Assessment of Prescription Adherence and Patient Adherence in ACS and CCS Patients

RESULTS

Demographic Patterns
A total of 200 patients (140 retrospective cases and 60 prospective cases) were enrolled in the study. Subjects were classified into four age-groups—age-group 18–29 years consisted of 1% of patients, age-group 30–44 years consisted of 9% of patients, age-group 45–60 years consisted of 26.5% of patients, and the age-group 60+ years consisted of 63.5% patients. Out of the total subjects enrolled, 79% were males, while 21% were female patients.

Comorbidities
The prevalence of comorbidities in ACS and CCS patients is shown in Figure 1. Hypertension was the most observed comorbid condition in patients. 59.5% of the patients were hypertensive; followed by diabetes mellitus which was observed in 55% of patients. Out of 200, 35.5% of patients had both hypertension and diabetes mellitus. Dyslipidemia was the least observed comorbidity and was observed in only 3.5% of patients; whereas 16% of patients had no comorbidity conditions before hospital admission.

Revascularization Procedure
Out of the 140 retrospective cases studied, 49% of the population had single-vessel disease (SVD), 28% of the population had double-vessel disease (DVD), and 23% of the population had triple-vessel disease (TVD). Out of the total 200 patients, 83% of patients underwent PCI for revascularization whereas 17% underwent CABG. Most patients with TVD needed CABG. About 19% of patients underwent a second revascularization procedure.

Prescription Adherence to Secondary Prevention Guideline Recommendations
Prescription adherence to secondary prevention guideline recommendations was studied. As per recommendations, an ACE-I or ARB, a β-blocker, a statin, and DAPT must be included in the regimen. After DAPT has concluded, lifelong SAPT is indicated. The percentage of prescriptions adherent to individual guideline recommendations is shown in Figure 2 and the cumulative adherence of prescriptions to secondary prevention guideline recommendations is shown in Figure 3.

Prescription Pattern of Antihypertensives
The prescription pattern of antihypertensives is shown in Figure 4. Among the 200 patients enrolled in the study, 10% were not prescribed any antihypertensive medications. The analysis of the prescription pattern revealed that β-blockers were the most prescribed class (67.5% of patients) while calcium channel blockers (CCBs) were the least prescribed class (10.5% of patients) of antihypertensives. 22% of patients were...
prescribed ARBs, 19.5% of patients were prescribed ACE inhibitors, and 33% of patients were prescribed diuretics. Most patients were on 2–3 antihypertensive medications.

**Patient Medication Adherence**

Medication adherence was assessed in 60 outpatients (47 males and 13 females) using the MMAS-8. According to MMAS-8 scoring, 33.33% of patients had high medication adherence, 45% had moderate medication adherence, and 21.66% had low medication adherence (Fig. 5).

Overall, all age-groups revealed moderate adherence to medications. The average MMAS-8 score was 7.37 for those aged 18–29 years, 6.65 for those aged 30–44 years, 6.89 for those aged 45–60 years, and 7.22 for those aged 60 years and above (Fig. 6).

**Adherence to Lifestyle Modifications**

Sixty outpatients were interviewed to assess their adherence to suggested lifestyle changes post-AMI. 87% of patients claimed to be nonalcoholics while 13% were alcoholics (Fig. 7). 84% of patients were nonsmokers, 13% were smokers, and 3% were tobacco chewers (Fig. 8). Of the total patients interviewed, 72% of patients led an active lifestyle while 28% led a sedentary life (Fig. 9).

**Discussion**

Persistent secondary prevention is crucial after the index MI as these patients have an increased risk of having a further attack. Several studies affirm that secondary prevention can improve outcomes in such patients and could reduce the likelihood of recurrent cardiovascular events. It is proved through several studies that males are more prone to CHDs and the low susceptibility of women is often attributed to the cardioprotective effects of estrogen. Similar results were observed in our study. Out of the sample size of 200 patients, 79% were males and 21% were females. Although ACS primarily affects patients over the age of 50, younger patients can also be affected. It has been found through studies that the risk of CAD increases with age. A reason for this is the increase in cholesterol levels and blood pressure with age. Our study showed that the highest proportion of patients was above 60 years of age (63.5%), followed by 45–60 years (26.5%), which is comparable to the already available literature.

Comorbid conditions are very common among CAD patients even in younger age-groups and patients often present with more than one comorbidity. In our study, we found that hypertension and diabetes mellitus were the most observed comorbidities while dyslipidemia was the least observed comorbidity. 35.5% of patients had both hypertension and diabetes mellitus. About 16% of the study population did not have any comorbidities before hospital admission.
We observed that for revascularization, 83% of patients underwent PCI whereas 17% underwent CABG. Approximately 19% of the study population needed a second revascularization procedure. Out of 140 prospective cases, 49% had SVD, 28% had DVD, and 23% had TVD. Emergency CABG was majorly performed in patients with TVD than in those with SVD or DVD. This finding was similar to a study published in JACC conducted by Weintraub et al.21

As per secondary prevention guidelines, the prescription of patients after an AMI must include dual antiplatelets, ACE-I/ARB, β-blockers, and statins—all of which have been found to reduce the risk of mortality and morbidity.5 The guidelines advise weighing the risk of reinfarctions in individual patients when deciding whether to continue DAPT after a year or switch to SAPT.9,10 A study conducted by Solomon et al. concluded that after an AMI, cumulative adherence to secondary prevention guideline recommendations, optimal control of cardiovascular risk factors, and lifestyle interventions were associated with an increased survival rate. They also observed that greater adherence to guidelines was linked to lower mortality and that following any individual guideline recommendation after AMI is associated with modest benefits while complete adherence is associated with the greatest survival benefit.7

Out of the 200 prescriptions assessed in our study, all prescriptions had statins and antiplatelet agents (DAPT 87.5% and SAPT 12.5%), 67.5% of prescriptions had β-blockers, and 41.5% of prescriptions had ACE-I/ARBs. We also observed that atorvastatin was the most prescribed statin, ramipril—the most prescribed ACE-I, telmisartan—the most prescribed ARB, and metoprolol—-the most prescribed β-blocker. The most prescribed combination of DAPT was aspirin + ticagrelor. The results of our study revealed that the cumulative adherence to all four secondary prevention guideline recommendations was 26.5%. A survey conducted by EUROASPIRE also found that the vast majority of CAD patients did not meet the standard of secondary prevention stipulated by the guidelines.13 Our findings were consistent with those of Redfern et al. who revealed that only one-quarter of ACS survivors received optimal secondary prevention in the hospital.22

After analyzing the prescription pattern of antihypertensives, we found that β-blockers were the most widely prescribed class of antihypertensives. Among β-blockers, metoprolol and bisoprolol were the agents of choice. Calcium channel blockers were the least prescribed class.

We used Morisky Medication Adherence Scale-8 to determine medication adherence in outpatients. The results of several studies reveal that medication adherence in CAD patients varies between 30 and 70%.23,24 A study conducted by Kassab et al. to assess patient adherence to secondary prevention pharmacotherapy after ACS concluded that the majority of patients reported moderate adherence (51.1%).25 Similar results were observed in our study. The maximum proportion of patients showed moderate adherence to pharmacotherapy (45%). The average MMAS-8 score was 7.37 in the 18–29 age-group; 6.65 in the 30–44 age-group; 6.89 in the 45–60 age-group, and 7.22 in the 60+ age-group.

We also noted the social habits and lifestyle of 60 outpatients and found that the majority of patients claimed to be nonalcoholics (87%) and nonsmokers (84%). 13% of the patients were alcoholics, 3% of the patients were tobacco chewers, and 13% were cigarette smokers. 72% of the patients led an active life whereas 28% of patients admitted to living a sedentary life.

**STUDY LIMITATIONS**

The following are the study’s inherent limitations:
- The sample size is limited and is not enough to correlate observations or generalize the findings of the study.
- Since most of the data were retrospective, some parameters of the study could not be retrieved from the medical records.
- We did not exclude patients who were ineligible for specific guideline-recommended therapies (i.e., patients with a relative or absolute contraindication to β-blockers or ACE-I or ARBs).
- Our study may be subject to the personal biases of the respondents while answering the questionnaire.
- We could not assess the contributors of nonadherence or determine other preventive measures such as dietary habits or exercise patterns.

**SUMMARY AND CONCLUSION**

Secondary prevention involves preventive care that focuses on early risk stratification and initiation of appropriate treatment to cease the progression of an established disease process. Adherence is a key factor in the effectiveness of pharmacological therapy. Adherence to guideline-recommended treatment, control of cardiovascular risk factors, and lifestyle changes following index MI are critical for improving patient outcomes and preventing hospitalizations due to reinfarctions and other cardiovascular events.

The findings of our study reveal that the percentage of prescriptions adherent to all four secondary prevention guideline recommendations was limited. This might be attributed to our limitation in excluding patients ineligible for specific guideline recommendations. To overcome this problem, a checklist stating the recommendations should be developed and used as a tool to improve adherence to secondary prevention guidelines. At the time of the patient’s discharge post-PCI or CABG or during their follow-up visits, their discharge medications should be compared against this checklist by the clinical pharmacist of the hospital and if there are any deviations from the guideline recommendations, reasons for nonadherence may be stated within the checklist.

Nonadherence to medication is common among CAD patients as it involves chronic therapy. In our study, the prevalence of medication nonadherence in CAD patients
was found to be above 50%. Medication nonadherence is complex and influenced by numerous factors such as demography, socioeconomic conditions, frequency of follow-up, complex treatment regimens, adverse effects of medications, and health literacy. For these reasons, health care providers should not only assess medication adherence but also the reasons for nonadherence, as nonadherence to secondary prevention medications attribute to poor control of cardiovascular risk factors, poor quality of life, increase in hospital readmissions, increase in health care costs, and a higher mortality rate.

Health care professionals play a pivotal role in attaining optimal secondary prevention in CAD patients. Individual-, system-, and population-level barriers from the prescriber as well as the patient’s perspective should be evaluated in future studies.

ACKNOWLEDGMENTS

We show immense gratitude and indebtedness to the cardiology team for their constant help and cooperation throughout our study period. We also extend our heartfelt thanks to our guides for their expertise and assistance throughout all aspects of our study.

REFERENCES


Midterm eGFR Predicts Pregnancy Outcomes: An Observational Study

Anupma Kaul1, Amita Pandey2, Manas R Behera3, Monika Yachha4, Dharmendra Bhaduria5, Manas R Patel6, Ravi Kushwaha7, Narayan Prasad8

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Abstract

Introduction: The hemodynamic adjustments during pregnancy play a pivotal role in sustaining the gestation, however, its clinical connotation on midterm renal hyperfiltration and its consequence on maternal and fetal outcomes need a greater appraisal. The present retrospective study looked into the midterm estimated glomerular filtration rate (eGFR) among pregnant females without overt pieces of evidence of chronic kidney disease (CKD) as a surrogate marker for midterm hyperfiltration and its implication on maternal and fetal outcomes.

Materials and methods: All pregnancies among females aged 18–50 years with available pregestational baseline serum creatinine were included in the study. Maternal renal hyperfiltration was expressed as the highest eGFR, using the creatinine clearance method. Its association with adverse maternal and fetal outcomes was assessed.

Results: A total of 1,045 pregnancies were assessed during the study. According to midterm eGFR, among them, 65% of pregnancies showed midterm eGFR between 120 and 150, however, 4.3% of pregnancies had values more than 150 mL/min per 1.73 m². The risk of poor pregnancy outcome was observed for eGFR levels below and above the reference level of 120–150 mL/min per 1.73 m² (1.97 for values ≥150 mL/min per 1.73 m², and 1.72 for 90–120 mL/min per 1.73 m²). Pregnancies with eGFR between 60 and 90 mL/min per 1.73 m² had odds ratios (ORs) of 5.64.

Conclusion: A distinctive relationship was observed between the midterm eGFR and adverse pregnancy outcomes with the best outcomes for midterm eGFR levels between 120 and 150 mL/min per 1.73 m². Despite no apparent functional renal deterioration, a poor maternal hyperfiltration response may play a crucial impact on poor pregnancy outcomes.

Introduction

The kidney undergoes conspicuous hemodynamic and structural changes to adapt to normal pregnancy. The consequence of the physiological increase in cardiac output together with sodium and water retention results in blood volume expansion with a subsequent fall in systemic vascular resistance.1 Midterm renal hyperfiltration is a well-accepted physiological hemodynamic alteration which occurs in the early part of pregnancy persisting until delivery.2 A poor response to this physiological reciprocation has been incriminated to adverse pregnancy outcomes.3,4 However hyperfiltration phenomenon among nonpregnant states such as obesity and diabetes is considered part of the early phases of kidney disease. Under these circumstances, it is implied as a notable risk factor for the progression of CKD, cardiovascular outcomes, and mortality.5,6 Its existence during pregnancy has been implicated in hemodynamic adaptation rather than glomerular hypertension,7,8 thus a measure of the reserved kidney functions during pregnancy. Nevertheless, poor physiological response in the early stages of CKD poses challenges to pregnancy outcomes and neonatal morbidity.1,9 A careful observation of this subtle change is essential to recognize the underlying unrecognized kidney diseases during pregnancy which happens to be a checkpoint to the diagnosis of CKD.9 Midterm eGFR and its role in predicting pregnancy outcomes have yet not been clear. Park et al. demonstrated a positive correlation between midterm eGFR values below and above 120–150 mL/min per 1.73 m² with adverse pregnancy outcomes.10 A U-shaped temporal association between midterm eGFR and pregnancy complications may suggest a concealed association of endothelial and intrarenal hemodynamic dysfunction. This could perhaps indicate an early kidney disease not overtly evident and in turn, could put the mother at risk along with adverse pregnancy outcomes. None of the so-called traditional risk factors associated with hyperfiltration was seen contributing to the elevation in eGFR.4,11 Estimated GFR is a widely practiced method for assessment of GFRs with its utility both in clinical situations as well as for research, this seems to be much safer in pregnancy situations also. Literature pieces of evidence suggest poor correlations between cystatin C and maternal GFR due to placental production of cystatin C per se.12 It would be worthwhile understanding the link between renal reserve in pregnancy and the role of intrarenal hemodynamic function with obstetric or fetal outcomes among the Indian population. Could it be used as a surrogate marker for masked CKD and poor pregnancy outcomes needs further understanding.

Materials and Methods

All pregnant females aged 18–50 years attending the obstetrics outpatient department in the Department of Obstetrics and Gynecology in a medical college in Northern India were part of the study. Those pregnancies with available pregestational baseline serum creatinine were included in the study from January 2015 till December 2019. Each participant included in the study had at least one preconception serum creatinine value and her second serum creatinine available during the second trimester. They were regularly followed and an assessment for 24 hours of creatinine clearance was done. Those pregnancies which were multigestational and all pregnancies with known CKD were excluded. The study was approved by the Institutional Ethics Committee and prior informed consent was obtained from all study participants. The eGFR was calculated among all pregnant females during midterm gestation and was further classified based on e-GFR. A 24-hour urine collection for creatinine clearance as a standard for GFR estimation in pregnancy was taken for estimation in the study population.

José V. Ferreras

1,2,3,4,5,6,7,8,9,10,11,12,13


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The study group was categorized into four subgroups of the highest midterm eGFR values obtained during the second trimester of pregnancy classified based on the Park et al. study into:

- 90 (60 ≤ eGFR < 90) mL/min per 1.73 m².
- 120 (90 ≤ eGFR < 120) mL/min per 1.73 m².
- 0–150 (120 ≤ eGFR ≤ 150) mL/min per 1.73 m².
- ≥150 mL/min per 1.73 m².

Details about the participant’s age, weight before pregnancy, outcomes of previous pregnancies, preterm or abortion, height, weight gain during the present pregnancy, and any significant history were noted. The pregnancy was followed up and any complications related to pregnancy including gestational diabetes, hypertension, and preeclampsia were noted. The type of delivery, birth weight, time of delivery, and outcomes of pregnancy were noted.

The method was chosen for midterm GFR—the eGFR values were calculated using 24 hours creatinine clearance method. A dipstick urine albumin test was also noted. This is the calculated GFR.

Midterm eGFR—eGFR values in and around 20 weeks of gestation (second trimester: 14–28 weeks).

Pregnancy outcomes and complications:
- An adverse pregnancy outcome:
- Fetal outcomes—WHO classification⁹:
  - Preterm birth—birth <37 weeks of gestation.
    - Moderate-to-late preterm birth (≥32 and <37 weeks of gestation).
    - Very preterm birth (≥28 and <32 weeks of gestation).
  - Low birth weight—a birth weight of <2.5 kg.
  - Very low birth weight—a birth weight of <1.5 kg.
- The pregnancy outcomes in terms of maternal outcomes—occurrence of preeclampsia, eclampsia, gestational diabetes, or any organ damage.

Preeclampsia
Definition: new onset hypertension at or beyond 20 weeks of gestation with or without proteinuria or/and evidence of end-organ damage.

Gestational Diabetes Mellitus
Definition: any degree of glucose intolerance observed during pregnancy.

Midterm eGFR was calculated as a surrogate marker for midterm hyperfiltration among women without overt evidence of CKD and also evaluated its prognostic significance during gestation. Thus assessment of whether intrarenal hemodynamic dysfunction in pregnancy could contribute to gestational complications.

Statistical Analyses
The data are expressed as mean ± standard deviation (SD). All probabilities were two-tailed and the level of significance was set at 0.05. The student’s t-test was used to compare the significance of the mean and the Chi-square and Fisher’s exact tests were used to compare the proportion between the two groups. All data were analyzed by using SPSS 10 version software.

Univariate and logistic regression analyses were performed to find out the independent risk factors for adverse pregnancy outcomes while assessing the midterm e-GFRs. Their associations were expressed as ORs with a 95% confidence interval (CI) with p <0.05 was considered statistically significant. Data were expressed as mean ± SD for uniformly distributed variables while the median (interquartile range) was applied for non-normal variables. Univariate and multivariate logistic regression analysis was used to evaluate the risk of adverse pregnancy outcomes.

Results
A total of 1,450 deliveries that had a preconceptional serum creatinine available were recorded at a high referral-based medical college. The 1,425 pregnancies had serum creatinine values available during the second trimester. Women with multifetal pregnancy (n = 313) and impaired renal functions during or before gestation (n = 43) were excluded. All pregnancies resulting in delivery during the second trimester (n = 24) were also excluded. A total of 1,045 pregnancies were evaluated for the study. Fifteen (1.4%), 305 (29.1%), 680 (65.0%), and 45 (4.3%) pregnancies observed midterm eGFR levels of 60–90, 90–120, 120–150, and ≥150 mL/min per 1.73 m², respectively.

Relationship between the Midterm eGFR and Baseline to Pregnancy Characteristics (Table 1)

The group with eGFR ≥150 mL/min/1.73 m² was found to be younger. Though they had the lowest baseline body mass index (BMI) yet they showed appropriate weight gain during pregnancy. They were more of primigravida. However, with previous pregnancies, this group did not encounter a history of diabetes or hypertension in past pregnancies. Those pregnancies with an eGFR range of 60–90 mL/min/1.73 m² were seen to have a higher association with a preexisting history of hypertension, diabetes, and gestational diabetes. An inverse relationship was observed between eGFRs and past pregnancy-related complications, that is, their prevalence’s decreased with higher eGFR among the studied population (p < 0.01).

Comparing the baseline eGFR to midterm eGFR among various groups, the baseline eGFR values showed a linear relationship to the gestational eGFR, and this increase of the median eGFR from baseline was appreciated among pregnancies in all subgroups, except for pregnancies with eGFR of 60–90 mL/min/1.73 m². Comparing the net glomerular hyperfiltration based on the difference between preconception serum creatinine and midterm serum creatinine values and the measured GFR between the two point frames, reflected a greater difference as we moved towards higher eGFR. Women with eGFR of 120–150 mL/min per 1.73 m² were shown to have the least chance of hypertension and albuminuria while its incidence was observed to be higher among pregnancies with eGFR values higher and lower than the 120–150 mL/min per 1.73 m².

Relationship between Midterm eGFR and Pregnancy Outcomes (Table 2)
Midterm eGFR value between 120 and 150 mL/min per 1.73 m² was observed to have the least gestational complications both maternal and fetal (preterm birth, low birth weight, and preeclampsia) while adverse pregnancy outcomes were consistently higher among pregnancies with midterm eGFR of 60–90 mL/min per 1.73 m². The risk of fetal complications like preterm and low birth weight was associated with an eGFR range of 90–120 mL/min per 1.73 m² than with 120–150 mL/min per 1.73 m². Despite having eGFR >150 mL/min per 1.73 m² pregnancy outcomes were not good, that is, a higher risk of maternal and fetal complications (preterm birth, low birth weight, and preeclampsia) were observed (Table 3).

Discussion
This is the first Indian study to have shown the association between midterm eGFR and maternal and fetal outcomes. A close relation was observed in midterm eGFR (<120 mL/min per 1.73 m²) to adverse
p​regnancy outcomes. A U-shaped interdependence between eGFR and outcomes suggests that eGFR values <120 mL or >150 mL/min per 1.73 m² had an inferior maternal and fetal outcome. The study suggests a better pregnancy prediction among pregnancies with good maternal renal hyperfiltration evidenced by eGFR. However, poorer pregnancy outcomes among pregnancies with eGFR values <120 mL or >150 mL/min per 1.73 m² could reflect an intrarenal hemodynamic dysfunction perhaps suggesting an early kidney disease.

During the early first weeks after conception, there occurs an increase in eGFR which remains sustained until the end of gestation. Those pregnancies complicated by hypertensive disease show a decline in kidney function. This abnormal maternal renal hyperfiltration response to pregnancy could help in predicting the risk of underlying CKD. Despite the renal functions being normal, the clinical significance of unusual response to maternal renal hyperfiltration could be novel predictors for adverse pregnancy outcomes and give subtle signals for underlying kidney disease.

The observation of a blunted renal response despite normal renal function with adverse pregnancy outcomes has been reflected in various studies. Barai et al. observed that the renal reserve declined with GFR among various stages of CKD from 19.08% in CKD stage I, 15.4% in CKD stage II, 8.9% in CKD stage III, to 6.7% in CKD stage IV, respectively. The U-shaped association seen in our study population could explain the intrarenal hemodynamic dysregulation perhaps among those with lower eGFR thereby initiating a poor adaptive hemodynamic response while among pregnancies with midterm eGFR more than 150 mL/min per 1.73 m² could be reflecting a pathologic increase in GFR suggesting underlying occult disease conditions, such as metabolic syndrome, obesity, endothelial dysfunction, or hypertension thus increasing the propensity risk among mothers due to this hyperfiltration resulting in poor pregnancy outcomes.

The eGFR is considered by far a powerful prognostic factor among patients for adverse clinical outcomes in terms of all-cause mortality, progression to kidney failure, and

Table 1: Midterm eGFR and its association with baseline and pregnancy characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>eGFR 60–90 (n = 15)</th>
<th>eGFR 90–120 (n = 305)</th>
<th>eGFR 120–150 (n = 680)</th>
<th>eGFR ≥150 (n = 45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31 (30–35)</td>
<td>32 (31–37)</td>
<td>28 (26–31)</td>
<td>27 (26–33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.4 (19.2–23.1)</td>
<td>20.7 (19.6–23.2)</td>
<td>20.5 (19.9–23.8)</td>
<td>20.6 (19.4–23.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline serum creatinine (mg/dL)</td>
<td>0.9 (0.7–1.0)</td>
<td>0.8 (0.6–0.8)</td>
<td>0.7 (0.06–0.08)</td>
<td>0.5 (0.4–0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous history of hypertension</td>
<td>6 (40%)</td>
<td>25 (8.3%)</td>
<td>49 (7.6%)</td>
<td>2 (4.4%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gestational age when eGFR measured, week</td>
<td>20 (15–22)</td>
<td>20 (15–24)</td>
<td>20 (16–24)</td>
<td>21 (17–25)</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline eGFR mL/min per 1.73 m²</td>
<td>97.9 (90.1–110.9)</td>
<td>120.1 (110.1–122.2)</td>
<td>127.3 (123.4–134.5)</td>
<td>138 (127.9–139.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2.56 (2.30–3.12)</td>
<td>3.1 (2.73–3.20)</td>
<td>3.20 (2.70–3.32)</td>
<td>3.01 (2.75–3.32)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight gain until delivery (kg)</td>
<td>9.2 (8.5–12.9)</td>
<td>10.7 (9.1–13.2)</td>
<td>10.2 (10.0–14.0)</td>
<td>10.1 (8.3–14.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pregnancy outcomes in past</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fullbirth</td>
<td>11 (73.7%)</td>
<td>266 (87%)</td>
<td>605 (89%)</td>
<td>37 (82.4%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2 (13%)</td>
<td>21 (7%)</td>
<td>41 (6%)</td>
<td>4 (8.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Preterm</td>
<td>2 (13.3%)</td>
<td>18 (6%)</td>
<td>34 (5%)</td>
<td>4 (8.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Midterm eGFR mL/min per 1.73 m²</td>
<td>88.3 (86.1–89.7)</td>
<td>122.4 (1119.5–129.2)</td>
<td>137.8 (129.1–139.9)</td>
<td>169.2 (160.2–172.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midterm serum creatinine (mg/dL)</td>
<td>0.8 (0.7–0.9)</td>
<td>0.6 (0.5–0.7)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.2 (0.1–0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous hypertension (mm Hg) during pregnancy</td>
<td>6 (40%)</td>
<td>27 (9%)</td>
<td>35 (5.2%)</td>
<td>3 (6.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albuminuria (dipsticks)</td>
<td>7 (46.6%)</td>
<td>84 (27.8%)</td>
<td>81 (12%)</td>
<td>5 (11.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes during pregnancy</td>
<td>1 (6.6%)</td>
<td>12 (3.9%)</td>
<td>17 (2.5)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>4 (26.6%)</td>
<td>100 (32.7%)</td>
<td>186 (28.8%)</td>
<td>16 (35.5%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2: Maternofetal outcomes according to midterm eGFR

<table>
<thead>
<tr>
<th>Adverse pregnancy outcomes</th>
<th>eGFR 60–90 (n = 15)</th>
<th>eGFR 90–120 (n = 305)</th>
<th>eGFR 120–150 (n = 680)</th>
<th>eGFR &gt;150 (n = 45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth, &lt;37 weeks</td>
<td>8 (53.3%)</td>
<td>76 (24.9%)</td>
<td>86 (12.6%)</td>
<td>8 (17.7%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Gestational age, week</td>
<td>36 (32–38)</td>
<td>38 (37–39)</td>
<td>38 (37–39)</td>
<td>37 (35–39)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Low birth weight, &lt;2.5 kg</td>
<td>7 (46.6%)</td>
<td>55 (18%)</td>
<td>82 (12.1%)</td>
<td>11 (25.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2.56 (2.30–3.12)</td>
<td>3.1 (2.73–3.20)</td>
<td>3.20 (2.70–3.32)</td>
<td>3.01 (2.75–3.32)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>4 (26.6%)</td>
<td>25 (8.1%)</td>
<td>27 (4%)</td>
<td>3 (6.6%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
cardiovascular events. Literature evidence has shown a strong relationship between preeclampsia, albuminuria, and adverse fetal outcomes. Diabetics are considered to have higher eGFR owing to hyperfiltration which has been conceptualized as the loss of kidney function. The presence and degree of proteinuria have been associated with adverse clinical outcomes even at lower and higher eGFR. Park et al. in their study reflected that higher eGFR could be a representation of an early stage of underlying CKD—an inappropriate response to hemodynamic adaptation. On adjusting for the baseline BMI and gestational weight gain, the interdependence of eGFR to proteinuria outcomes hints at probable dysfunctional hemodynamic response despite hyperfiltration.

This study focuses on the importance of hyperfiltration among pregnancies with no underlying kidney dysfunction suggesting midterm eGFR could be a screening tool to evaluate hemodynamic remodeling during pregnancy and unmasking the occult kidney disease.

The major limitation of the study was its retrospective nature and thus such a study among prospective healthy pregnant women with routine serum creatinine would be promising in validating the above results.

### Conclusions
A distinct U-shaped correlation observed between the midterm eGFR and the maternal and fetal outcomes subordinates the prognostic implication of midterm e-GFR. It holds importance, especially among women who show no obvious clinical evidence of underlying CKD, and therefore the unusual maternal renal hyperfiltration response during pregnancy with its effect on maternal and fetal outcomes could stand as a novel biomarker for assessment of at-risk pregnancies. This seems to be a valuable tool in better fetal and maternal outcomes and unmasking of underlying subclinical kidney diseases.

### References

### Table 3: Risk of adverse pregnancy outcomes in each midterm eGFR subgroup

<table>
<thead>
<tr>
<th>Composite outcome</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &gt;150</td>
<td>1.97</td>
<td>1.34–2.45</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 120–150</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 90–120</td>
<td>1.72</td>
<td>1.30–2.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 60–90</td>
<td>5.64</td>
<td>4.23–12.4</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preterm</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &gt;150</td>
<td>1.93</td>
<td>1.34–2.45</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 120–150</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 90–120</td>
<td>1.71</td>
<td>1.45–2.56</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 60–90</td>
<td>4.09</td>
<td>3.67–9.89</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low birth weight</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>eGFR &gt;150</td>
<td>1.86</td>
<td>1.42–2.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 120–150</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 90–120</td>
<td>1.54</td>
<td>1.37–2.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 60–90</td>
<td>4.67</td>
<td>2.34–5.78</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preeclampsia</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &gt;150</td>
<td>1.85</td>
<td>1.56–3.56</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 120–150</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 90–120</td>
<td>1.96</td>
<td>1.43–3.34</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>eGFR 60–90</td>
<td>5.6</td>
<td>4.2–7.87</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
COVID-19-associated Neurological Manifestations and Complications: An Observational Study

Bhuvaneshwari Rajendran1*, Sridhar N2, Gayathri Ramkumar3

Received: 16 July 2022; Accepted: 13 September 2022

Abstract

Background: Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to one of the deadliest pandemics faced by mankind. The typical manifestation of COVID-19 infection includes respiratory distress. However, we know that the characteristic immunologic pathways of SARS-CoV-2 infection inflict systemic disorders and eventually multi-organ dysfunction in a subgroup of patients. The disease can affect both central and peripheral nervous systems.

Objective: The aim of our study was to describe the wide spectrum of neurological manifestations associated with SARS-CoV-2 infection and its clinical characteristics.

Materials and methods: We conducted a retrospective, single-center, observational study to analyze neurologic manifestations associated with COVID-19 patients from May 2020 to September 2021 at a tertiary care hospital in Chennai, South India.

Results: A total of 80 COVID-19–confirmed patients with neurological disorders were included in our study. The most reported neurological manifestation was altered sensorium (29.6%). Twenty-nine (34.4%) patients were on noninvasive ventilation and a significant number of patients (22) (26.8%) needed invasive ventilation. The mortality rate was 34.1% and the large vessel involvement in stroke patients was 10%.

Conclusion: Neurological issues in COVID-19 patients are relatively common and have the propensity to manifest later as post-acute COVID-19 syndrome.

Introduction

From March 2020, the novel coronavirus, SARS-CoV-2 affected 32,028,825 individuals with 439,529 deaths in India.1 The pandemic threatened the healthcare system with an exponential increase in disease burden across many countries. A high proportion of elderly, immunocompromised, and patients with comorbid clinical conditions was found to have a greater risk of developing severe forms of COVID-19 illness.2 The clinical characteristics of COVID-19 were heterogeneous and data indicated that 40–45% of the COVID-19–positive patients were asymptomatic.3 Reports also pointed out that the young adult population was also affected by exacerbated critical illness and fatality due to COVID-19.4 The global pandemic fuelled an upsurge of life-threatening respiratory complications with evidence strongly suggesting that COVID-19 can also inflict significant neurological impairment. One-third of COVID-19 patients were reported to have neurological disorders.5 In a large multicenter cohort study, the Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) reported the prevalence of neurological manifestations in hospitalized COVID-19 patients.6 A prospective registry (ENERGY) was framed by the European Academy of Neurology in association with the European National Neurological Societies and the Neurocritical Care Society and Research Network for monitoring the COVID-19–related neurological complications including disease progression and long-term outcomes.7 Several published reports emphasize the plausibility of neurological complications even after the recovery from COVID-19. The likelihood of developing long-term effects of COVID-19 including post-acute COVID syndrome, long COVID, and long haulers came to light. The main objective of our study was to describe the clinical spectrum of neurological manifestations associated with COVID-19 and to study the clinical characteristics of COVID-19 patients with neurological complications.

Materials and Methods

We conducted an observational study to collect the neurologic manifestations associated with COVID-19 infection. We retrospectively evaluated patients between May 2020 and September 2021 at a tertiary care hospital in Chennai, South India. Study participants and data collection included patients fulfilling the following criteria: (1) all adult COVID-19–positive patients with neurological symptoms. COVID-19–positive status was confirmed with a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on a nasopharyngeal sample and/or a SARS-CoV-2 serology. (2) When the RT-PCR and serology results were not available on time for some patients, we considered COVID-19 based on the clinical history and the chest computed tomography (CT) scan findings. Exclusion criteria: (1) children aged 18 years or younger. (2) Patients with no diagnosis of COVID-19. (3) Patients in life-threatening conditions where neurological evaluation was not possible. (4) Patients with incomplete data on hospital records. We collected and evaluated patients’ data including demographic details, clinical features, medical intervention, radiological findings, treatment course, and outcome. All neurological manifestations were confirmed by a neurologist. The missing data were collected from patients and their families through telephonic communication and/or direct clinical visits. The neurological presentations were broadly classified into three categories: (1) coagulopathy: cerebrovascular disease—transient ischemic attack, hemorrhage, and ischemic strokes confirmed by clinical symptoms and imaging; (2) encephalopathy comprising altered mental status, seizures, weakness, myoclonus, hemorrhagic encephalitis based on the clinical presentation and laboratories; and (3) autoimmunity: immune-mediated neurological disorders including meningoencephalitis, Guillain–Barré syndrome (GBS), and acute demyelinating encephalomyelitis occurring in the postinfectious period.


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Statistical Analysis
Categorical variables were presented as counts and percentages. Continuous variables were summarized as median and interquartile range (IQR). All the statistical analyses were performed using SPSS software, version 16 (IBM Corp., Armonk, NY, USA).

Results
General Characteristics of COVID-19 Patients with Neurological Disorders
A total of 81 COVID-19-confirmed patients with neurological disorders were included in our study. The demographic and clinical characteristics have been illustrated in Table 1. The median (IQR) age was 66.6 (19–102) years and 52 (64.1%) patients were men. Of these patients, 16 (19.7%) patients had a past history of neurological disease, five (6.1%) patients had a stroke, three (3.7%) patients had a seizure history, and three (3.7%) patients had a neurodegenerative disease. The most reported neurological manifestation was altered sensorium (29.6%) followed by an altered level of consciousness (25.9%) as illustrated in Figure 1. In our study, we observed that majority of patients required oxygen support, 29 (34.4%) patients were on noninvasive ventilation and a significant number of patients (21) (25.9%) needed invasive ventilation. Apart from the oxygen requirement, 49 (60.4%) required intensive care unit (ICU) admission, and these patients were monitored in an isolation ward.

Table 1: Baseline clinical features of COVID-19 patients with neurological disorders

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) years</td>
<td>66.6 (19–102)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52 (64.1)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (35.8)</td>
</tr>
<tr>
<td>Prior neurologic comorbidities</td>
<td></td>
</tr>
<tr>
<td>Previous history of stroke</td>
<td>5 (6.1)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Neurodegenerative disease</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (6.1)</td>
</tr>
<tr>
<td>Oxygen requirement</td>
<td></td>
</tr>
<tr>
<td>Noninvasive ventilation</td>
<td>29 (34.4)</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>21 (25.9)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>49 (60.4)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>27 (33.3)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise indicated; COVID-19, Coronavirus disease 2019; ICU, Intensive care unit; IQR, Interquartile range

We performed routine blood tests, screening CT, and magnetic resonance imaging if warranted. They were transferred to the neurology ward on the improvement of their clinical condition and COVID-19 tested negative. The mortality rate was 33.3% in our study.

Neurologic Manifestations Associated with COVID-19
Encephalopathy
Of the total 81 patients, 35 (43.2%) patients presented with COVID-19-associated encephalopathy. The median age was 71 (19–102) years. The most reported neurological manifestation was seizures followed by altered sensorium (Fig. 2—electroencephalogram (EEG)). Sixteen patients required noninvasive ventilation and seven patients were on mechanical ventilation. Twenty patients were admitted in ICU and the average stay in the hospital was 8 (2–27) days. Death was reported in 10 (28.5%) patients.

Cerebrovascular Disease
Twenty-two (27.1%) COVID-19 patients were diagnosed to have cerebrovascular complications. The median age was 60.5 (28–85) years (Figs 3A and B). The most common neurological manifestation was an altered level of consciousness. Large vessel involvement was detected in eight (10%) patients. Ten patients required noninvasive ventilation and eight patients were on mechanical ventilation. The majority of the patients, 90.0% (20 patients) needed ICU monitoring and the average stay in the hospital was 11.5 (2–51) days. Unfortunately, 12 (54.5%) patients belonging to this group died (Table 2).

Immune-mediated Neurological Disorder
Seventeen (20.9%) patients had immune-mediated neurological disorders (Fig. 4). The median age was 59.5 (30–78) years. Ataxia and focal neurological syndrome were reported high. The average length of stay in the hospital was 6 (0–45) days. Most of the patients were
COVID-19-associated Neurological Manifestations and Complications

Six patients required ICU admission, and six patients required invasive ventilation, three (17.6%) of whom died.

**DISCUSSION**

Although the cardinal feature of coronavirus disease is respiratory involvement, COVID-19 infection also causes vascular and brain injury. Coronavirus is characterized by increased affinity towards angiotensin-converting enzyme 2 receptor (ACE2). ACE2 receptors are also expressed in glial cells in the brain and spinal neurons and in the nasal epithelium. Furthermore, neurotropic potential has been demonstrated in various animal studies. Thus SARS-CoV-2 targets ACE2 receptors and depending upon the expression of ACE2

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**Table 2:** Clinical profile of 75 COVID-19 patients with cerebrovascular disease, encephalopathy, and immune-mediated neurologic disorder

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cerebrovascular disease (n = 22)</th>
<th>COVID-19 encephalopathy (n = 35)</th>
<th>Immune-mediated neurologic disorder (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) years</td>
<td>60.5 (28–85)</td>
<td>71 (19–102)</td>
<td>59.5 (30–78)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 16 (72.7)</td>
<td>22 (62.8)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td>Prior neurologic comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (9)</td>
<td>1 (2.8)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0</td>
<td>3 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Neurodegenerative disease</td>
<td>2 (9)</td>
<td>1 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (13.6)</td>
<td>3 (8.5)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Peripheral limb weakness</td>
<td>2 (9)</td>
<td>0</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Seizures</td>
<td>1 (4.5)</td>
<td>12 (34.2)</td>
<td>2 (11.7)</td>
</tr>
<tr>
<td>Focal neurologic deficit</td>
<td>3 (13.6)</td>
<td>2 (5.7)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>2 (9)</td>
<td>22 (62.8)</td>
<td>0</td>
</tr>
<tr>
<td>Altered level of consciousness</td>
<td>6 (27.2)</td>
<td>7 (20)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1 (4.5)</td>
<td>0</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2 (9)</td>
<td>5 (14.2)</td>
<td>0</td>
</tr>
<tr>
<td>Aphasia</td>
<td>0</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1 (4.5)</td>
<td>0</td>
<td>2 (11.7)</td>
</tr>
<tr>
<td>Stroke characteristics</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Vascular territory</td>
<td>8 (36.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebellar infarct</td>
<td>1 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>5 (22.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>1 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bifrontal</td>
<td>1 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen requirement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninvasive ventilation</td>
<td>10 (45.4)</td>
<td>17 (48.5)</td>
<td>0</td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>8 (36.3)</td>
<td>6 (17.1)</td>
<td>6 (35.2)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>20 (90.9)</td>
<td>21 (60)</td>
<td>6 (35.2)</td>
</tr>
<tr>
<td>Duration of hospital stay, median (IQR) days</td>
<td>11.5 (2–51)</td>
<td>8 (2–27)</td>
<td>6 (0–45)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Death 12 (54.5)</td>
<td>10 (28.5)</td>
<td>3 (17.6)</td>
</tr>
</tbody>
</table>

Data are summarized as n (%); COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; MCA, middle cerebral artery; N/A, Not applicable; PCA, posterior cerebral artery
COVID-19-associated Neurological Manifestations and Complications

receptors in the central nervous system (CNS), the virus can attribute to neuronal tissue injury. The chief route of direct access into the brain is through the blood–brain barrier.8,11 In addition, another mechanism which can lead to brain damage is the retrograde invasion of peripheral nerve terminals. The SARS-CoV-2 virus then gets transmitted through the neural synapses and gains entry to the CNS.8 The detailed discussion of host and virus interaction is beyond the scope of this article. Immune response triggered by COVID-19 leads to the subsequent release of proinflammatory cytokines and chemokines. The surge in cytokines including interleukin-6, T cells, and raised tumor necrosis factor-α contributes to an aberrant coagulation cascade leading to extensive complement activation. This is one of the principal pathological mechanisms for the increased likelihood of cerebrovascular disease, especially thrombotic strokes.12

In our study, the majority of the COVID-19 patients exhibited COVID-19-associated encephalopathy (35/80, 43.8%), followed by cerebrovascular disease (CVD) (22/80, 27.5%) and immune-mediated neurological disorder (16/80, 20%). COVID-19-associated encephalopathy altered sensorium (29.6%) was the most frequently reported neurological presentation in our study. An altered level of consciousness was reported in 25.9% of patients and the patients were older (≥71 years) compared to patients with CVD and immune-mediated neurological disorders. The factors associated with encephalopathy in COVID-19 patients are complex including systemic inflammation, vascular dysfunction, direct neurotropism of SARS-CoV-2, and altered brain homeostasis.13–15 In our study, 18.7% of patients presented with seizures. Impaired consciousness and seizures can occur in patients with severe COVID-19.5,16 The mortality rate was 31.4%. Early recognition and supportive treatment should be adopted to prevent hypoxic insult and subsequent CNS injuries. Cerebrovascular complications and focal neurological deficit were present in 23.4% of COVID-19 patients in our study. Ischemic stroke was present in 19 (86.3%) of the patients with CVD while large vessel involvement was detected in 36.3% of patients. Published studies revealed a high incidence of thromboembolic events in patients with COVID-19; however, the underlying pathology is not completely understood.12,13 Supporting data revealed large vessel involvement and multiple vascular territory involvement in patients with COVID-19.14,15 In our study, patients with cerebrovascular complications had higher mortality (54.5%) while the mortality rate in the study conducted by Yaghi et al. was 63.6%. The patients with CVD had longer hospital stays, 11.5 (2–51) days. Studies have reported that elevated D-dimer levels in COVID-19 patients play a pivotal role in escalating the prothrombotic state and the SARS-CoV-2 induces sepsis leading to a cascade of events linked with hypercoagulability often associated with poor outcomes.16,17 Thrombolytic therapy in patients with ischemic stroke might reduce the potentially devastating adverse outcomes.18 Longitudinal studies evaluating the role of antiplatelets and anticoagulants in COVID-19 patients are mandatory. Immune-mediated neurological disorders of the total 15 patients, five patients had GBS, four had autoimmune encephalitis, three had myositis, two had nephropathy, and one had myelopathy. Neurological disorders in the postinfectious period resulted due to the immunomodulatory effects of the viral infection. Recent research revealed that neurotropism is one of the salient features of coronaviruses.19 The impairment of the nervous system can be through direct entry of SARS-CoV-2 and/or through indirect immune-mediated biological pathways, presenting in the later phase of the disease.20 The pathways involved in the neuroinvasion of the virus are still not defined. A growing body of evidence suggests that SARS-CoV-2 can inflict potential damage to the CNS through an interplay of complex biological pathways.21–23 Most of our patients were treated with intravenous immunoglobulins and the mortality documented was 18.8%. Physicians should be aware of the occurrence of immune-mediated disorders in the postinfectious period. Long-term follow-up of COVID-19 patients is mandatory to rule out immune-mediated neurological disorders. The immune-mediated late response can happen in patients who have not been very ill or without typical respiratory issues and therefore a high index of suspicion is required. Our study has several limitations. This is a single-centered, retrospective study and has an inherent limitation in extracting data from medical records. Further studies are required to evaluate the mechanisms involved in the causation of SARS-CoV-2-related neurological disorders.

Conclusion

In conclusion, the neurological manifestations following COVID-19 infection are diverse. COVID-19-associated encephalopathy and thrombotic vascular events were increasingly reported. Large vessel stroke is frequently associated in the younger adult population. Immune-mediated neurological disorders including GBS and encephalitis can present later in the later course of the disease. Larger prospective studies are needed to study this association and to identify the pathways causing thrombotic embolic events in these patients. Clinicians must be vigilant of neurological complications while screening COVID-19 patients. Multimodality imaging and diagnostic procedures should be performed to mitigate potential life-threatening events. Pulmonary manifestations have been observed as one of the hallmarks of COVID-19. However, neurological complications and sequelae are also recognized in the clinical course of COVID-19.

References

COVID-19-associated Neurological Manifestations and Complications

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Hematological Profile with Peripheral Blood Smear Morphology of Admitted COVID-19 Infected Patients: A Study at a COVID Dedicated Hospital in Kashmir

Jangbhadur Singh Sarna1*, Mehak Shafat2, Afiya Shafi3, Harminder Kour4, Bushra Sahaf5, Azhar Shafi6

Received: 24 March 2022; Revised: 28 July 2022; Accepted: 15 September 2022

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection started in Wuhan, China, and spread to the rest of the world to become a pandemic affecting over 385 million people throughout the world to date. Coronavirus disease 2019 (COVID-19) is primarily started as a respiratory tract infection. Recent studies indicate that it should be regarded as a systemic disease involving multiple systems including the hematopoietic system. Complete blood count and its parameters are important investigative tools in its prognosis. However, very few studies highlight the importance of peripheral blood cell morphology in this disease.

Aim: To study the hematological parameters (complete blood count and peripheral blood film) of COVID-19-positive patients and to compare the hematological parameters of those admitted in intensive care units (ICUs) with those admitted in non-ICUs of the hospitals.

Materials and methods: This retrospective study was carried out at a COVID-19 dedicated tertiary care center over a period of 3 months from July 2020 to September 2020. In our study, all 79 patients had complete blood counts performed at the time of admission. Complete blood count was repeated during the hospital stay for all severe cases. The data which provided information on the age and gender of each patient were obtained from the Laboratory Information System (LIS) of the hospital.

Results: The mean age of our study group was 46.05 years. Out of 79 cases, lymphopenia was seen in 16.5% with five patients presenting with severe lymphopenia (<0.5 × 10⁹/L). All the patients that required ICU care presented with moderate to severe lymphopenia. The patients in the ICU setting showed significant neutrophilia (mean 14.16 ± 10⁹/L) on follow-up complete blood count. Thrombocytopenia was observed in 35.3% of cases. It was observed that the mean neutrophil–lymphocyte ratio was higher in ICU admitted patients as compared to the non-ICU admitted patients. Among the ICU patients, 80% showed a neutrophil–lymphocyte ratio above the baseline cutoff (3.1). A wide array of morphological changes were observed in the peripheral blood smear including toxic-like granules in neutrophils, fetus-like C-shaped nucleus, lymphoplasmacytoid cells, bizarre cells, and apoptotic cells.

Conclusion: The study highlights that at the time of admission older age, decreased lymphocyte count, and raised neutrophil–lymphocyte ratio were closely associated with ICU admissions. Also, the morphological changes in peripheral blood film reveal atypical changes predominantly in the white blood cell (WBC) lineage.

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Introduction

Severe acute respiratory syndrome coronavirus 2 causing COVID-19 has rapidly evolved from an epidemic outbreak in Wuhan, China into a pandemic infecting over 385 million individuals all over the world to date. Clinically, the COVID-19 infected patients had a varied picture, ranging from an asymptomatic state to those with severe acute respiratory symptoms and multi-organ involvement. As we know that COVID-19 infection manifests as pulmonary infection, recent studies establish that it has a multisystem involvement including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems. On the basis of various studies conducted worldwide, hematological parameters provide clinicians with useful evidence of disease severity and progression. The role of laboratory tests as disease indicators has been well established by ongoing studies, but limited data are available so far. Lymphopenia as a common finding in COVID-19 infected patients can be due to a poor immune response to the virus. A recent meta-analysis has projected the most important laboratory abnormalities observed in patients with COVID-19 infection as lymphopenia, increased value of C-reactive protein, lactate dehydrogenase, erythrocyte sedimentation rate, and D-dimer. The role of the laboratory cannot be limited to mere diagnosis and surveillance, it has far more implications with regard to disease severity and progression.

Aims and Objective

• To study the hematological parameters (complete blood count and blood smear) of COVID-19 infected patients.

• To study and compare hematological parameters of ICU and non-ICU COVID-19 infected patients.

Materials and Methods

The Ethics Committee of SKIMS Medical College & Hospital approved this study along with the approval to exempt patients from informed consent. This study is a retrospective, observational, and cross-sectional study done at a COVID dedicated tertiary care center over a period of 3 months from July to September 2020.

In our study, the 79 patients that had been admitted, had at least one complete blood count performed at the time of admission. Complete blood count was repeated during the hospital stay for all severe cases. The data for analysis were obtained from the LIS, to know the clinical parameters and relevant information about the age and gender of each patient. The patients were separated into two groups; those admitted in ICU and others who were admitted in general or non-ICU.

Inclusion Criteria

All COVID-positive patients proven by reverse transcription polymerase chain reaction (RT-PCR) and admitted during this time were included in our study.

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Exclusion Criteria

- Patients with COVID-19-like symptoms but RT-PCR negative for COVID-19 were excluded from this study.
- Patients with chronic obstructive pulmonary diseases, hematopoietic diseases, liver diseases, and other neoplastic diseases, as well as those on chemotherapy, were excluded from the study.

Statistical Analysis of Data

All the continuous variables of the study statistics like frequency, percentage, mean, and standard deviation (SD) acting as variables of the study were represented by descriptive statistics.

All the vital comparisons were performed by using Student’s t-test for statistical analysis, after confirming the normal distribution of data.

The results were discussed at a 5% level of significance, that is, p-value 0.05 was considered statistically significant. All the data were studied with the help of the statistical software package SPSS v-23.0.

Results

A total of 79 patients were admitted with a mean age of 46.05 years (10–90) which included 46 males and 33 females (Table 1). Only three patients were in the pediatric age-group. Out of the total 79 patients, five required ICU care (6.3%). Older age patients got admitted in ICU care as compared to those admitted in the non-ICU group (mean age 62 years vs 42 years, p-value = 0.003).

On admission, mild leukocytosis was observed in 11 patients (>1 × 10^9/L) while leukopenia (<4 × 10^9/L) in only two patients. Lymphopenia was seen in 13 patients (16.5%) with eight patients presenting with moderate lymphopenia (0.5–1 × 10^9/L) and five patients presenting with severe lymphopenia (<0.5 × 10^9/L). All the patients that required ICU care presented with lymphopenia, with more than 60% of patients having severe lymphopenia.

The data analysis is summarized in Table 2. The mean absolute neutrophil count (ANC) in the non-ICU group and ICU group of patients was 7.5 × 10^9/L and 5.3 × 10^9/L, respectively, at the time of admission. However, the patients in the ICU setting showed significant neutrophilia (mean 14.16 × 10^9/L) on follow-up complete blood count.

The mean platelet count in our study group was 160 × 10^9/L. Thrombocytopenia was observed in 35.3% of cases. When the platelet count was compared between the ICU and non-ICU groups, it was observed that 60% of the ICU patients had thrombocytopenia (20% having severe thrombocytopenia) while only 21% of the non-ICU patients had thrombocytopenia (p-value 0.856).

The neutrophil–lymphocyte ratio was >3.1 in 33 patients (41.7%) as shown in Table 3. The ICU admitted patients as compared to the non-ICU patients had a higher neutrophil–lymphocyte ratio. The neutrophil–lymphocyte ratio above the baseline cutoff (3.1) was observed in 80% of the ICU patients.

Peripheral Blood Film Observations

Giemsa-stained peripheral blood smears were studied to observe any change in the morphology of blood cells in order to highlight the importance of the peripheral smear examination in COVID-19 cases. A wide array of morphological changes were observed as summarized below (Figs 1A–F).

Red blood cells (RBCs): Changes observed in RBC morphology were mainly nonspecific and no specific etiological correlation to the virus could be noted. Normocytic normochromic blood picture to microcytic hypochromic cell was seen.

Neutrophil: Coarse granules (toxic-like granules), hypolobation, hypogranulation, fetus-like C-shaped nuclei (COVID nuclei), and shift to left were seen.

Lymphocyte: Lymphocytopenia, large granular lymphocyte, and variant reactive monocytoid and plasmacytoid forms.

Monocyte: Cytoplasmic vacuolation was prominent.

Platelet: Mild to moderate thrombocytopenia with giant forms.

Other cells: Bizarre cell and apoptotic

Morphological changes observed in the peripheral blood smear cells examined under light microscopy were either due to the virus infecting them or as a consequence of pathogenesis related to COVID-19 infection, this needs further research to evaluate the exact mechanism involved.

Discussion

In our study population, the median age was 46.05 years. The age range in our study was 10–90 years with most of the cases presenting in the 20–65 years age-group (66%). Li et al., in a study conducted on the first 425 cases of COVID-19 in Wuhan, China, observed that the median age of patients was 59 years, with ages ranging from 15 to 89 years. Nath et al., in their study, mentioned that the mean age of patients was 35.85 ± 17.69 years. Out of a total of 79 cases, five patients required ICU admission (6.3%). In our study, older patients were admitted in ICU care as compared to those admitted in non-ICU care with a mean age of 62–42 years, and this difference was statistically relevant (p = 0.003) as depicted in Table 1. Fan et al. mention in their study that patients admitted in ICU care units of the hospital were about a decade older than those admitted in the non-ICU care units of the hospital. It was further observed that 54 years was the median age of ICU care unit patients and 42 years was the median age of non-ICU care unit patients (p = 0.02).

In our study, out of the total cases, 58.2% were males with a sex ratio of 1.31 (M:F) hence showing slight male preponderance. Out of the patients that required ICU care, 80% were males. In the studies conducted by Guan et al.,11 Zhang et al.,12 and Chen et al.,13 the disease incidence was more in males than in females. It was observed in the previous studies conducted on SERS–CoV and MERS that the incidence was more in males as compared to females.14,15 This difference in a lower incidence of females to viral infections could be explained in relation to the protection given X chromosome and sex hormones, which are known to play an important role in innate and adaptive immunity or sex differences may exist in angiotensin-converting enzyme (ACE) 2 receptor as observed in various studies.16–18

The hematological observations at the time of admission revealed mild leukocytosis in 11 patients while only two patients had leukopenia. Studies show mild leukocytosis in a minority of COVID-19 infected patients, irrespective of whether it represents having either neutrophilia or lymphocytosis, or both, and appears to signify bacterial infection or superinfection.5

Lymphopenia was seen in 16.5% with eight patients presenting with moderate lymphopenia (0.5–1 × 10^9/L) and five patients presenting with severe lymphopenia (<0.5 × 10^9/L). All the patients that required ICU care presented with moderate to severe
lymphopenia on admission with 60% of patients in the ICU having severe lymphopenia. Lymphopenia is the most common finding in patients with COVID-19 infection and is believed to represent a defective immune response to the virus. In the study conducted by Huang et al., it was observed that lymphopenia (defined as an absolute lymphocyte count <1.0 × 10⁹/L) was seen in 26 (63%) patients. In another study of 67 COVID-19 patients from Singapore, Fan et al. identified that a lymphocyte count of <0.6 × 10⁹/L was predictive for admission to the ICU.

Lymphopenia in COVID-19 infection can be related to several factors. It has been shown that lymphocytes express the ACE2 receptor on their surface; thus SARS-CoV-2 may infect these cells and subject these cells to lysis. In addition, the cytokine storm leads to markedly increased levels of interleukins and tumor necrosis factor (TNF)—alpha, which further causes...

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Non-ICU admitted patients (n = 74)</th>
<th>ICU admitted patients (n = 5)</th>
<th>p-value</th>
<th>Total (n = 79)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean 42.83 (10–90)</td>
<td>Mean 62.6 (38–80)</td>
<td>0.0032</td>
<td>46.05</td>
<td></td>
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<tr>
<td>Gender</td>
<td>Males 42 (56.7)</td>
<td>4 (80)</td>
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<tr>
<td></td>
<td>Females 32 (43.2)</td>
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<td>33 (41.8)</td>
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<table>
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<tr>
<th>Blood profile at admission</th>
<th>Hb</th>
<th>WBC (×10⁹/L)</th>
<th>ALC (×10⁹/L)</th>
<th>ANC (×10⁹/L)</th>
<th>Platelet count (×10⁹/L)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean 12.92 (2.45)</td>
<td>8.6</td>
<td>1.73</td>
<td>7.5</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>SD 13.96</td>
<td>5.18</td>
<td>0.71</td>
<td>5.34</td>
<td>86</td>
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<td></td>
<td>NO 74</td>
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<table>
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<th>Blood profile during stay</th>
<th>Hb</th>
<th>WBC (×10⁹/L)</th>
<th>ALC (×10⁹/L)</th>
<th>ANC (×10⁹/L)</th>
<th>Platelet count (×10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean 12.86 (1.8)</td>
<td>7.73</td>
<td>0.72</td>
<td>5.4</td>
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<tr>
<td></td>
<td>SD 16.17</td>
<td>3.89</td>
<td>0.57</td>
<td>3.37</td>
<td>68</td>
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<tr>
<td></td>
<td>NO 5</td>
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<td></td>
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</tbody>
</table>

| Table 3: Neutrophil–lymphocyte ratio (NLR) of patients in ICU vs non-ICU |
|-----------------------------|-------------------------|---------------------------------|---------|-------------|
|                             | ICU                      | Non-ICU                         | Total   | p-value     |
| Total no.                   | 5                       | 74                               | 79      | 0.003       |
| Mean NLR                    | 15.67                   | 3.89                            |         |             |
| SD                          | 11.79                   | 4.54                            | 1.73    |             |
| NLR<3.1                     | 1 (20%)                 | 45 (60.9%)                      | 46 (58.3%) | 0.15        |
| NLR>3.1                     | 4 (80%)                 | 29 (39.1%)                      | 33 (41.7%) |             |
Hematological Profile with Peripheral Blood Smear Morphology

It was observed that the mean neutrophil–lymphocyte ratio was higher in ICU admitted patients as compared to the non-ICU patients and this difference was statistically significant. It was further noted that 80% of the ICU patients showed a neutrophil–lymphocyte ratio above the baseline cutoff (=3.1). Qutaiba et al.,31 in their study, mention that neutrophil–lymphocyte ratio was ≥3.1 in 28 patients (25%), with moderate and severe disease. Our findings were in collaboration with those of previous studies on the relationship between neutrophil–lymphocyte ratio in COVID-19 disease.19 Imran et al., in their study, concluded that neutrophil–lymphocyte ratio can act as a warning signal for deterioration in severe COVID-19 infection and can provide an objective basis for early segregation and management of severe COVID-19 pneumonia.32 On analyzing the morphology of peripheral blood cells, we observed a range of morphological changes occurring in the disease, especially in the WBC series. Neutrophil showed coarse granules (toxic-like granules) with hypolobation and hypogranularity in some cases. The most pronounced finding was the presence of fetus-like C-shaped nuclei labeled as COVID nuclei. Shift to left was also seen in many cases. The lymphocytic series showed lymphocytopenia with large granular lymphocyte apoptosis.21–23 Substantial cytokine activation may also be associated with atrophy of lymphoid organs, including the spleen, which further impairs lymphocyte count.24

The mean ANC in the non-ICU group of patients at the time of admission was 7.5 × 10^9/L while the mean ANC group of patients was 5.3 × 10^9/L. However, the patients in the ICU setting showed significant neutrophilia (mean 14.16 × 10^9/L) on follow-up complete blood count. Fan et al., in their study, observed that neutrophilia is common in patients treated in the ICU during hospitalization (11.6 vs 3.5 × 10^9/L). The data suggest that neutrophilia as an expression of the cytokine storm and hyperinflammatory state have an important pathogenetic role in COVID-19 and related infections such as SARS.12–18 Neutrophilia can be due to superimposed bacterial infection.5

Thrombocytopenia was observed in 35.3% of cases in this study (mean platelet count 160 × 10^9/L). It was observed that 60% of the ICU patients had thrombocytopenia (20% had severe thrombocytopenia) while only 21% of the non-ICU patients had thrombocytopenia (p-value 0.856). A meta-analysis of nine studies has revealed that thrombocytopenia is mostly associated with the severity of the COVID-19 disease, a more sizeable drop in platelet counts was noted especially in nonsurvivors.25 Another study data on the SARS outbreak reported thrombocytopenia in 55% of cases and correlated with an increased risk of severe disease.22–24 In a patient with severe infection, thrombocytopenia is identified in up to 57.7% of patients, as compared to 31.6% of patients with less significant COVID-19 symptoms. Mechanisms of thrombocytopenia which have been hypothesized include directly infecting bone marrow cells by the virus along with inhibition of platelet synthesis, platelet destruction by the immune system, and platelet clumping in the lung tissue, resulting in microthrombi and platelet consumption.26–28

Neutrophil–lymphocyte ratio is considered as a biomarker for the assessment of the severity of bacterial infections and in determining the prognosis of patients with pneumonia and tumor. Neutrophil–lymphocyte ratio may serve as a substitute marker of early risk identification in COVID-19 infection. Forget et al.,29 identified in a study that normal neutrophil–lymphocyte ratio values in an adult population in good health are between 0.78 and 3.53. Whereas, Liu et al.,30 in their study, concluded that patients with age ≥50 years having neutrophil–lymphocyte ratio ≥3.13 stand at risk of severe illness, and should get rapid access to the ICU. Neutrophil–lymphocyte ratio was >3.1 in 41.7% of cases in the study. It was observed that the mean neutrophil–lymphocyte ratio was higher in ICU admitted patients as compared to the non-ICU patients and this difference was statistically significant. It was further noted that 80% of the ICU patients showed a neutrophil–lymphocyte ratio above the baseline cutoff (=3.1). Qutaiba et al.,31 in their study, mention that neutrophil–lymphocyte ratio was ≥3.1 in 28 patients (25%), with moderate and severe disease. Our findings were in collaboration with those of previous studies on the relationship between neutrophil–lymphocyte ratio in COVID-19 disease.19 Imran et al., in their study, concluded that neutrophil–lymphocyte ratio can act as a warning signal for deterioration in severe COVID-19 infection and can provide an objective basis for early segregation and management of severe COVID-19 pneumonia.32

On analyzing the morphology of peripheral blood cells, we observed a range of morphological changes occurring in the disease, especially in the WBC series. Neutrophil showed coarse granules (toxic-like granules) with hypolobation and hypogranularity in some cases. The most pronounced finding was the presence of fetus-like C-shaped nuclei labeled as COVID nuclei. Shift to left was also seen in many cases. The lymphocytic series showed lymphocytopenia with large granular

Figs 1A to F: Morphological changes in peripheral blood film, (A) Atypical flower-shaped nucleus in lymphocyte; (B) Fetus-like nucleus in neutrophil (covicyte); (C) Ring-shaped nucleus in neutrophil; (D) Monocyte with vacuolated cytoplasm and pseudopods; (E) Lymphoplasmacytoid lymphocyte; (F) Toxic-like granules in neutrophil
lymphocytes with reactive change in the form of monocytoid and plasmacytoid forms. Cytoplasmic vacuolation was prominent in the monocytic series.

In a study by Singh et al., the authors observed that the morphological abnormalities in peripheral smear included many crowded, dark granules in the cytoplasm of polymorphs (similar to “toxic” granules) changes in nuclear shape were striking, with an increase in a number of band forms along with dyspoietic features, with absent nuclear segmentation, as seen in with pseudo-Pelger–Huët abnormality.  

In two studies done in India, the morphological findings in the peripheral smear of COVID-19 cases included nonspecific changes in RBC lineage, neutrophils with toxic granules, vacuoles, hypolobation, dyspoiesis, lymphocytes with lymphocytopenia, large granular lymphocytes, variant reactive monocytoid and plasmacytoid forms and blastoid forms, monocytes with large bizarre forms, vacuoles, granules, platelets with agglutination and thrombocytopenia. In another study highlighting the changes in peripheral blood smear morphology of COVID-19 infected patients suggests the presence of lymphoplasmacytoid cells as observed in our study. In another recent update, such quantitative and qualitative abnormalities can be implicated to the cytokine storm and hyperinflammation which is an important pathogenic factor in the evolution of COVID-19 pneumonia, possibly in the form of secondary hemophagocytic lymphohistiocytosis, leading to often fatal multi-organ failure with a possibility of relapse.

**Limitations and Conclusion**

In summary, the study highlights that at the time of admission older age, decreased lymphocyte count, and raised neutrophil–lymphocyte ratio were closely associated with ICU admissions. Also, the morphological changes in peripheral blood film reveal atypical changes predominantly in the WBC lineage. Hence it may be assumed from the study that monitoring complete blood count parameters with peripheral blood cell morphology can provide insight into the severity of the disease and these routine laboratory investigations may evolve as useful prognostic tools in COVID-19 disease. However since this was a retrospective study without follow-up, we could not observe changes in the results after treatment.

**References**

15. Liao YC, Liang WG, Chen FW, et al. IL-19 induces proliferation of band forms along with dyspoietic features, shape were striking, with an increase in a number (similar to “toxic” granules) changes in nuclear shape were striking, with an increase in a number of band forms along with dyspoietic features, with absent nuclear segmentation, as seen in with pseudo-Pelger–Huët abnormality.
In uncontrolled T2DM patients on combination OAD's with CV risk or comorbidities, initiate early with Dapaturm-S (Dapagliflozin 5/10 mg + Sitagliptin 50/100 mg) tablets.

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**Turn Towards a Better Life**
Stroke Characteristics as Predictors of New-onset Seizure in Patients with Acute Ischemic Stroke

Augustine Jose1, Minakshi Dhar2*, Mohammad Ajmal3, Latika Mohan4, Yogesh Saxena5, Nowneet K Bhat6

Received: 25 June 2022; Revised: 24 August 2022; Accepted: 14 September 2022

Abstract

Introduction: The current guidelines on diagnosis and management of new-onset seizures in stroke are not well defined, especially in the Indian setting. Our study aims at providing insight into the hospital prevalence risk of new-onset seizures following ischemic stroke and to correlate seizure risk with the characteristics of stroke and other clinical parameters.

Methods: A total of 127 patients were analyzed for the study where we assessed the clinical severity and the imaging severity of stroke using the National Institute of Health Stroke Scale (NIHSS) score and Alberta Stroke Program Early CT (ASPECT) score, respectively. Seizure-related variables including semiology, timing, and details of antiepileptic drugs (AEDs) were assessed under the domain of early and late poststroke seizures (PSSs). All patients were followed for 6 months for the seizure recurrence and change in Barthel index. In statistical analysis, quantitative variables were compared using the independent t-test/Mann–Whitney U test, and qualitative variables were correlated using Chi-square test/Fisher’s exact test. Univariate and multivariate logistic regression was used to find out the significant risk factors of acute symptomatic seizure.

Results: The mean age of the study population was 59.72 years (±14.77), with a male predominance (60.63%). About 78.74% of the cases had an NIHSS score more than or equal to 6.24% had posterior circulation strokes and the rest had anterior circulation strokes. A cortical location of infarct was observed in 62.2% of cases and a subcortical location in 61.4% of cases. The prevalence of early PSSs observed in our study was 10.6%. Of those, 80% had generalized seizures, 13.3% had focal seizures, and 6.67% had focal seizures with secondary generalizations. No patient in the study group had late-onset seizures. Total leukocyte count, serum protein levels, serum uric acid levels, and erythrocyte sedimentation rate (ESR) values were associated with early seizures (p < 0.05).

Conclusion: There was no recurrence of seizures in those who defaulted for AED and one patient had a seizure even on AED. Prophylactic AEDs in stroke patients based on stroke characteristics could not be ascertained, but the sample size was small. Knowing the fact that antiepileptics cause sedation and increase the chance of aspiration, continuing AEDs in patients who develop acute symptomatic seizures should be judged judiciously.

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Introduction

Stoke has been recognized as an important cause of seizures in the elderly population. Seizures, both as a presenting symptom and complication of stroke, are common causes of hospital admission.1 In the elderly population, almost half of all “first ever” seizures observed are caused by stroke.2 PSSs contribute significantly to increased mortality, higher neurological disability, and prolonged hospital stay.3 The clinician should carefully consider the parameters in diagnosing poststroke epilepsy, as this may have a serious psychosocial impact on the patient, with lower health-related quality of life.4

Early research on PSSs used an arbitrary cutoff of 2 weeks between early and late seizures based on latency from the onset of stroke symptoms.5 The International League Against Epilepsy (ILAE) has described a clear distinction between acute symptomatic seizures and unprovoked seizures with new definitions of temporal relationship with the inciting brain insult. “Acute symptomatic seizures” are events that occur in close temporal proximity to an acute brain insult.6 The proposed time interval as per ILAE are those occurring within 7 days of stroke occurrence (i.e., early PSSs). Seizures occurring without evidence of a potential causative condition or those occurring beyond the specified time period for acute symptomatic seizures are defined as “unprovoked seizures.”

Thus, unprovoked seizures in the setting of stroke (late-onset PSSs) are those occurring after 7 days of the onset of stroke symptoms. The risk of poststroke epilepsy described ranges from 2 to 15%. The various risk factors for the development of poststroke epilepsy identified include hemorrhagic etiology, anterior circulation stroke, larger stroke, higher NIHSS score at admission, cortical location of stroke, cortical symptoms, and a younger age of stroke occurrence.7–11 The incidence of PSSs is higher in children often reported close to twice the corresponding rate in adults. This could be due to the different neurophysiological makeup in children and uncommon etiologies of stroke.12

Though PSSs have been described well in the literature over the last three decades, there still is no clear consensus regarding the initiation, duration, and choice of AED therapy in this situation. The European Stroke Organization (ESO) in 2017 provided guidelines for the management of PSSs and epilepsy, adopting the definitions of ILAE. Primary AED prophylaxis is not recommended in the setting of acute ischemic and hemorrhagic strokes. It is interesting to note that ESO does not advise the institution of secondary AED prophylaxis even in cases of acute symptomatic seizures, based upon the observations of low seizure recurrence in acute stroke settings.13

The current guidelines on diagnosis and management of PSSs are not well defined in the Indian setting, which represents a distinct genetic makeup. There is insufficient data in recent literature on this entity, especially from North India, using the latest definitions of acute symptomatic seizures and poststroke epilepsy. The current study aims at providing...
data regarding the risk factors for the onset of new seizures following ischemic stroke in the Indian scenario and describes the correlation of seizure risk with the characteristics of stroke and other clinical parameters. It may contribute to guiding further randomized controlled trials for the efficacy and safety of prophylactic antiepileptic therapy in patients after an ischemic stroke.

Methods

This was an observational study of admitted patients in the stroke division of the Department of Internal Medicine and Neurology at a tertiary care center in Northern India from January 2018 to July 2019. Based on 80% power of study and confidence interval of 95%, the sample size was calculated quoting the risk of seizures in ischemic stroke observed by Bladin et al. which came out to be 8.6%. The formula 4P/L2 was used, where P is the prevalence in %, Q = (100 – P), and L is the precision in %. A minimum of 125 patients of ischemic stroke were decided to be recruited for the study.

The primary inclusion criteria were patients with acute ischemic stroke with age more than or equal to 18 years. Exclusion criteria included: (1) patient who had associated intracranial hemorrhage at presentation; (2) prior history of head injury; (3) patients with other risk factors of seizures—previously recognized epilepsy, intracranial space-occupying lesion, metabolic derangements, use of seizure potentiating drugs, infections, congenital malformations, neurocutaneous syndromes, hypertensive encephalopathy; (4) patients who had undergone neurosurgery; (5) patients who underwent thrombolysis; (6) patients with an inflammatory etiology of stroke—vasculitis and infection. Demographic information including age, sex, and risk factors for stroke was collected along with comorbid conditions. Blood investigations including hematological and biochemical parameters along with 2D transthoracic echocardiography were also obtained. Imaging modalities used for diagnosing acute stroke were a 128 mm computed tomography (CT) scan and 1.5 Tesla magnetic resonance imaging (MRI).

Stroke characteristics were defined as:

- Stroke severity: Clinical stroke severity, using the NIHSS score at admission, was assessed for all patients. NIHSS score has an important application in the decision for thrombolyis as well as the assessment of neurological improvement after thrombolyis. An NIHSS score of less than 6 is generally considered to indicate a minor stroke.14 The ASPECT score was used to judge the severity of stroke on imaging. ASPECT score has been validated for both anterior and posterior circulation strokes.15–17
- Infarct location: Stroke location, including the cortical and subcortical distinction, was assessed using areas in the ASPECT score. Areas M1 to M6 and I were considered cortical areas in the middle cerebral artery territory, while L, C, and IC were considered to be subcortical areas. Anterior (middle cerebral and anterior cerebral arteries) and posterior circulation (vertebral, basilar, and posterior cerebral artery territories) strokes were noted.
- Stroke etiology: TOAST classifications and ASCOD phenotypic (A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other causes, and D for dissection) classification were used.18–20 This was supported by vascular imaging (CT or magnetic resonance angiography and ultrasound Doppler of extracranial vessels), 2D transthoracic echocardiography, and transesophageal echocardiography (for select cases) and workup for prothrombotic conditions.

Seizure-related variables including semiology, timing, and details of AED usage were assessed under the domain of early and late PSSs. Acute symptomatic seizure/early PSS was defined as any form of a seizure occurring within 1 week from the onset of ischemic stroke symptoms. Late-onset PSS/remote PSS was defined as any seizure occurring after 1 week from stroke onset.5

Dyslipidemia was defined as triglycerides >150 mg/dL, total cholesterol >200 mg/dL, and low-density lipoprotein (LDL) >130 mg/dL. This is as per the consensus statement given by the Lipid Association of India.21

All patients were followed up by telephonic interview for any symptomatic seizures and functional status assessment using the modified Barthel index at the 3rd and 6th months. The modified Barthel index of the ADL is a reliable measure for assessing stable stroke patients. In addition, the high validity observed in the telephone interview supports its use in longitudinal studies and large surveys where direct performance evaluation is not feasible or too costly.22

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. The normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then a nonparametric test was used. Quantitative variables were compared using the independent t-test/Mann–Whitney U test (when the datasets were not normally distributed) between the two groups. Qualitative variables were correlated using Chi-square test/Fisher’s exact test. Univariate and multivariate logistic regression was used to find out the significant risk factors of acute symptomatic seizure. A p-value of <0.05 was considered statistically significant. The data were entered in a Microsoft Excel spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 213 consecutive patients of the first-ever acute ischemic stroke were recruited for the study. After exclusion, 127 patients were analyzed with a minimum follow-up duration of 6 months. The major reasons for exclusion were the detection of other probable causes of seizures, in-hospital mortality, and mortality before the completion of the minimum follow-up period. A summary of the process of patient selection is given in Figure 1.

The mean age of the study population was 59.72 years (S.D of ±14.77 years), with a male predominance (60.63%). Among

![Fig. 1: Algorithm showing the summary of patient selection. *These patients were included in the estimation of the prevalence of early seizures but were not analyzed. †All patients had undergone surgery before 7 days from the onset of the stroke](image-url)
127 patients, the major vascular risk factors observed were as follows: 36 (28.35%) were overweight or obese, 55 (43.31%) had significant smoking history, 38 (29.92%) had diabetes mellitus, 53 (41.73%) had dyslipidemia (hypertriglyceridemia was noted in 22.05% cases), 67 (52.7%) were hypertensive, and 11 (8.66%) reported either an ongoing significant alcohol use or a prior history of alcohol intake in cirrhogenic doses. Among the risk factors for an embolic stroke, coronary artery disease was present in 18 (14.71%) cases, and documented atrial fibrillation was found in 11 (8.66%) cases.

The hospital-based prevalence of early PSSs observed in our study was 10.6%. Of those, 80% had generalized seizures, 13.3% had focal seizures, and 6.67% had focal seizures with secondary generalizations. In more than half of the cases (53.2%), the seizure occurred within the first 24 hours of the onset of stroke symptoms. The timing of seizures from the onset of the stroke is shown in Figure 2. Acute symptomatic seizures in all cases were well controlled with AED monotherapy. 80% used levetiracetam and 10% used carbamazepine or phenytoin. Recurrence was noted in one patient who was on AED, even though five patients had left AED on their own. On follow-up, none of the patients showed any signs of drug toxicity or adverse effects.

Characteristics of Stroke

All recruited patients had undergone either a noncontrast CT brain or an MRI. Repeat imaging was not uniformly done in all patients due to variations in the protocol, and was performed, in most cases, following the identification of deterioration in neurological status. The majority of the cases had an NIHSS score of more than or equal to 6 (78.74%). Anterior and posterior circulation strokes were unevenly distributed and posterior circulation strokes (10.24%) represented a small proportion in the current study. A cortical location of infarct was observed in 62.2% of cases and a subcortical location in 61.4% of cases. About 4.42% had ASPECT scores <4, 45.13% had scores between 4 and 7, and 50.44% had scores >7. In terms of etiology of stroke as per TOAST classification were as follows: large artery atherosclerosis (44.09%), cardioembolism (22.05%), acute stroke of undetermined etiology (20.47%), small vessel occlusion (11.81%), and acute stroke of determined etiology (1.57%). With regards to prothrombotic states, 57.14% had secondary polycythemia and 14.29% had antiphospholipid syndrome (APLA), hyperhomocysteinemia, or a history of oral contraceptive usage.

**Fig. 2:** Incidence of early seizure within different time intervals after the stroke onset

**Table 1:** Comparison of baseline characteristics of patients with and without early PSS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with early PSS (N = 15)</th>
<th>Patients without early PSS (N = 112)</th>
<th>p-value</th>
<th>Univariate analysis: p-value; OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Age (in years; mean)</td>
<td>61.13 ± 13.37</td>
<td>59.54 ± 15</td>
<td>0.697</td>
<td>–</td>
</tr>
<tr>
<td>Age groups(years)</td>
<td></td>
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<tr>
<td>≤30</td>
<td>0 (0.00%)</td>
<td>6 (5.36%)</td>
<td>0.308</td>
<td>0.662; 0.786 (0.267–2.315)</td>
</tr>
<tr>
<td>31–40</td>
<td>2 (13.33%)</td>
<td>7 (6.25%)</td>
<td>0.292</td>
<td></td>
</tr>
<tr>
<td>41–50</td>
<td>0 (0.00%)</td>
<td>15 (13.39%)</td>
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<td></td>
</tr>
<tr>
<td>51–60</td>
<td>6 (40.00%)</td>
<td>25 (22.32%)</td>
<td>0.553</td>
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</tr>
<tr>
<td>61–70</td>
<td>3 (20.00%)</td>
<td>34 (30.36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71–80</td>
<td>4 (26.67%)</td>
<td>20 (17.86%)</td>
<td>0.332</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>0 (0.00%)</td>
<td>5 (4.46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (60.00%)</td>
<td>68 (60.71%)</td>
<td>0.958</td>
<td>0.958; 0.971 (0.323–2.917)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (40.00%)</td>
<td>44 (39.29%)</td>
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<tr>
<td>Comorbidities/Risk</td>
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<td></td>
</tr>
<tr>
<td>DM</td>
<td>5 (33.33%)</td>
<td>33 (29.46%)</td>
<td>0.759</td>
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<td>Overweight</td>
<td>3 (20.00%)</td>
<td>33 (29.46%)</td>
<td>0.553</td>
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<tr>
<td>HTN</td>
<td>6 (40.00%)</td>
<td>61 (54.46%)</td>
<td>0.292</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (6.67%)</td>
<td>10 (8.93%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Carotid AD</td>
<td>3 (20.00%)</td>
<td>15 (13.39%)</td>
<td>0.446</td>
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<td>Dyslipidemia</td>
<td>8 (53.33%)</td>
<td>45 (40.18%)</td>
<td>0.332</td>
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<tr>
<td>Chronic smoking</td>
<td>6 (40.00%)</td>
<td>49 (43.75%)</td>
<td>0.783</td>
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<tr>
<td>Alcohol use</td>
<td>2 (13.33%)</td>
<td>9 (8.04%)</td>
<td>0.618</td>
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<tr>
<td>Prothrombotic state</td>
<td>1 (6.67%)</td>
<td>6 (5.36%)</td>
<td>0.332</td>
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<td>Hemogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>13 (10.77–13.57)</td>
<td>13.15 (12.04–14.39)</td>
<td>0.331</td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>12.48 (9.69–15.15)</td>
<td>10.23 (8.80–12.46)</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>Platelet count (lakhs)</td>
<td>2.64 (1.91–3.90)</td>
<td>2.48 (1.89–2.91)</td>
<td>0.638</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>6.85 (6.49–7.32)</td>
<td>7.4 (6.9–7.67)</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9 (3.300–4.075)</td>
<td>4 (3.740–4.380)</td>
<td>0.135</td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>7.9 (5.550–9.275)</td>
<td>6.1 (4.750–7.550)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>Lipid fraction levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>192 (150–249)</td>
<td>184 (154–210)</td>
<td>0.259</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>121 (100.250–187.750)</td>
<td>105 (90–138)</td>
<td>0.181</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>120 (92–156)</td>
<td>113 (94.500–132)</td>
<td>0.515</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>38 (32.250–42)</td>
<td>38 (34–42)</td>
<td>0.675</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>36 (33–41.500)</td>
<td>32 (25.500–36)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>CRP levels</td>
<td>2.45 (1.395–3.200)</td>
<td>1.48 (0.520–2.600)</td>
<td>0.059</td>
<td></td>
</tr>
</tbody>
</table>

Bold values are significant.
## Table 2: Comparison of stroke characteristics in patients with early PSS and patients without early PSS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with acute symptomatic seizure (N = 15)</th>
<th>Patients without acute symptomatic seizure (N = 112)</th>
<th>p-value</th>
<th>Univariate analysis: p-value; OR (95% CI)</th>
<th>Multivariate analysis: p-value; OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score at admission</td>
<td>8 (6.250–10)</td>
<td>8 (6–10)</td>
<td>0.400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score ≥6</td>
<td>12 (80.00%)</td>
<td>88 (78.57%)</td>
<td>1.000</td>
<td>0.899; 1.091 (0.285–4.180)</td>
<td></td>
</tr>
<tr>
<td>mRS score at admission</td>
<td>5 (4–5)</td>
<td>5 (4–5)</td>
<td>0.855</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPECT score</td>
<td>7 (7–8.250)</td>
<td>7 (6–8)</td>
<td>0.674</td>
<td>0.334; 0.355 (0.043–2.902)</td>
<td></td>
</tr>
<tr>
<td>ASPECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>0 (0.00%)</td>
<td>5 (5.00%)</td>
<td>0.709</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–7</td>
<td>7 (53.85%)</td>
<td>50 (50.00%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7</td>
<td>6 (46.15%)</td>
<td>45 (45.00%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical location of stroke</td>
<td>12 (80.00%)</td>
<td>67 (59.82%)</td>
<td>0.163</td>
<td>0.142; 2.687 (0.717–10.060)</td>
<td></td>
</tr>
<tr>
<td>TOAST classes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>3 (20.00%)</td>
<td>53 (47.32%)</td>
<td>0.209</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>ASOPE</td>
<td>0 (0.00%)</td>
<td>2 (1.79%)</td>
<td>0.540; 3.057 (0.021–49.470)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASUE</td>
<td>6 (40.00%)</td>
<td>20 (17.86%)</td>
<td>0.022; 4.847 (1.249–22.053)</td>
<td>0.030; 4.735 (1.160–22.576)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>4 (26.67%)</td>
<td>24 (21.43%)</td>
<td>0.170; 2.808 (0.635–13.443)</td>
<td>0.185; 2.814 (0.602–14.342)</td>
<td></td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>2 (13.33%)</td>
<td>13 (11.61%)</td>
<td>0.255; 2.831 (0.434–16.143)</td>
<td>0.251; 3.086 (0.418–20.317)</td>
<td></td>
</tr>
<tr>
<td>ASCO classes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A0</td>
<td>19 (16.96%)</td>
<td>4 (26.67%)</td>
<td>0.211</td>
<td>1.000</td>
<td>–</td>
</tr>
<tr>
<td>A1</td>
<td>38 (33.93%)</td>
<td>3 (20.00%)</td>
<td></td>
<td>0.222; 0.394 (0.081–1.779)</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>15 (13.39%)</td>
<td>0 (0.00%)</td>
<td>0.112; 0.140 (0.001–1.470)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>1 (0.89%)</td>
<td>0 (0.00%)</td>
<td>0.835; 1.444 (0.009–32.330)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>20 (17.86%)</td>
<td>4 (26.67%)</td>
<td>0.946; 0.951 (0.216–4.186)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>5 (4.46%)</td>
<td>1 (6.67%)</td>
<td>0.876; 1.182 (0.103–8.449)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>0 (0.00%)</td>
<td>1 (6.67%)</td>
<td>0.102; 13.00 (0.59–2034.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1</td>
<td>1 (0.89%)</td>
<td>0 (0.00%)</td>
<td>0.835; 1.444 (0.009–32.330)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>5 (4.46%)</td>
<td>1 (6.67%)</td>
<td>0.876; 1.182 (0.103–8.449)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>8 (7.14%)</td>
<td>1 (6.67%)</td>
<td>0.791; 0.765 (0.069–5.033)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>8 (5.250–8.750)</td>
<td>6 (5–7)</td>
<td>0.049</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barthel index at 3 months</td>
<td>65 (56.25–73.75)</td>
<td>70 (65–80)</td>
<td>0.079</td>
<td>0.121; 0.962 (0.916–1.010)</td>
<td>–</td>
</tr>
<tr>
<td>Barthel index at 6 months</td>
<td>70 (61.25–82.50)</td>
<td>80 (70–85)</td>
<td>0.132</td>
<td>0.106; 0.963 (0.921–1.008)</td>
<td></td>
</tr>
<tr>
<td>Change in Barthel index</td>
<td>5 (1.25–8.75)</td>
<td>5 (5–7.50)</td>
<td>0.759</td>
<td>0.623; 0.967 (0.848–1.104)</td>
<td></td>
</tr>
</tbody>
</table>

Bold values are significant; mRS, modified Rankin Score
Acute Symptomatic Seizures

The hospital prevalence of early PSSs observed in our study was 10.6%. Of those, 80% had generalized seizures, 13.3% had focal seizures, and 6.67% had focal seizures with secondary generalizations. The most common semiology observed was a generalized seizure. In more than half of the cases (53.2%), the seizure occurred within the first 24 hours of the onset of the stroke symptoms. The timing of seizures from the onset of the stroke is shown in Figure 2. Acute symptomatic seizures in all cases were well controlled with AED monotherapy. 80% used levetiracetam and 10% used carbamazepine or phenytoin. The recurrence was noted in one patient who was on AED, even though five patients had left AED on their own. On follow-up, none of the patients showed any signs of drug toxicity or adverse effects.

Comparison of baseline and stroke characteristics of those who had early seizures with those who did not have early seizures have been listed in Tables 1 and 2. A few important observations were made on comparing the seizure and non-seizure groups, though only one variable showed a predictive association in multivariate analysis. Total leukocyte count, serum uric acid levels, and ESR values were significantly higher in the early PSS group compared to the non-seizure group. Patients with early seizures were found to have a longer hospital stay (6 ± 1 days), p < 0.05. In the TOAST etiological classification, the acute stroke of undetermined etiology was found to have a significant association with the occurrence of early seizure in both univariate and multivariate analysis.

Discussion

The incidences of early PSSs observed in this study were 10.6%. The most common semiology observed was a generalized seizure in contrast to the previous data. More than half of the cases had seizure occurrence in the first 24 hours of stroke and a subsequent peak was noted from 3 to 7 days. The time period limiting the recognition of acute symptomatic seizures after stroke has been 2 weeks or 1 week in most studies. Breitweg et al., however, used a duration of 48 hours for the same classification. The current definitions distinguishing early PSSs and poststroke epilepsy have been in place since 2014, and hence we may find a difference in the incidence of both entities in literature before and after this time point. Though epileptic seizures put the brain at a pathological and enduring risk of further seizure activity, acute symptomatic seizures are not recognized as epilepsy as they have shown a lower risk of subsequent occurrence of unprovoked seizures. Patients with early seizures were found to have a significantly longer duration of hospital stay in this study, reflecting the contribution of seizures to increased morbidity in the acute phase.

Patients with acute symptomatic seizures were found to have significantly higher levels of total leukocyte counts, ESR, and uric acid levels. These may reflect the compromised hydration status of the patient, postictal state, and possibly, also a proinflammatory background. Elevation of C-reactive protein (CRP) levels has been reported in a major proportion of patients with acute ischemic stroke, probably pointing to the inflammatory response to stroke, neuronal injury, and infections which may occur concurrently. CRP response has been found also to have a positive correlation with infarct volume on CT imaging. den Hertog et al. found an independent association of raised CRP levels with poor stroke outcome (mRS >2) and death at 3 months. Though median CRP levels were higher in the early seizure group in the current study, the difference was not statistically significant. Compared to previous studies, the current study did not reveal any significant association between early seizures and stroke characteristics like the volume of infarct, NIHSS score, and cortical location of infarct. One important consideration to be made here is the skewed distribution of stroke severity in the current study, with a much smaller proportion of minor strokes. The etiology of ischemic stroke did not have an influence on seizure occurrence. Acute symptomatic seizures did not have any significant association with both stroke outcomes in the acute phase and functional status at follow-up. There was no significant difference in the change in the Barthel index from 3 to 6 months between the two groups. There was no independent predictive association found in this aspect probably due to the contribution of stroke severity to the functional outcome.

Though current guidelines recommend discontinuation of antiepileptics after the acute stroke period, due to regional differences in practice, almost all patients in the cohort continued drug therapy, except five who were treatment defaulters. This might have affected the incidence of remote PSSs. Though the numbers are not statistically significant enough to be analyzed, observation of individual cases shows that there was no recurrence among this small proportion of defaulters. In fact, one patient who had a remote recurrence of seizures following acute symptomatic seizures was already on drug therapy.

Conclusion

The incidence of acute symptomatic seizures following ischemic stroke was 10.6%. The most common semiology observed was generalized seizures. Most early seizures occurred within 24 hours of stroke onset. Patients with acute symptomatic seizures were found to have significantly higher levels of total leukocyte counts, ESR, and uric acid levels. CRP levels were higher in patients with seizures, but the observation was not statistically significant. Indices of stroke severity (NIHSS and ASPECT score) and etiology of stroke did not have an independent association with acute symptomatic seizures. Change in functional levels in the two groups did not show a difference. There was no recurrence of seizures in those who defaulted for AED and one patient had a seizure even on AED. Also, the possible impact of AEDs on cognition and stroke recovery needs to be balanced prior to a decision of continuing AED.

Limitation

The sample size in this study may not be adequate to make a definitive conclusion, however, this study has revealed that antiepileptics should not be randomly prescribed in stroke patients based on one symptomatic seizure. Larger multicentric studies are required to assess the morbidity burden attributed to early PSSs.

Ethics Approval No

Institutional Ethics Committee approval has been taken via letter no. AIIMS/IEC/18/105.

Acknowledgments

We acknowledge Dr Nidhi Kaelay for helping in data collection. We also acknowledge the patient’s advisors for their contribution.

References


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Prof. Dr. Mangesh Tiwaskar
Editor-in-Chief, JAPI
A Study on Clinical Profile of Hemifacial Spasm in India and the Therapeutic Response to Botulinum Toxin Type A Injection as well as Pre and Postinjection Quality of Life

Amar Kumar Misra1, Joydeep Mukherjee2, Sanjay Kumar3, Gautam Guha4, Bijendra Mohanty5, Pideno S Ngullie6, Akash Manna7, Tapashya Nanda8, Amit Kumar Das9, Kamlesh Tiwari10

Received: 11 August 2022; Accepted: 17 September 2022

ABSTRACT

Background: Hemifacial spasm (HFS) is a distressing, involuntary, irregular tonic-clonic contraction of the facial muscles innervated by the seventh cranial nerve. It affects the quality of life. Botulinum toxin is a preferred symptomatic treatment option for the condition. However, there is a lack of study in the Indian scenario. Therefore, we observed the demographic profile, clinical spectrum, therapeutic response, and adverse effects of botulinum toxin and assessed the quality of life in the pre and postinjection phases in our subjects with HFS.

Materials and methods: The study design is a prospective open-label observational study. Consecutive cases of HFS were selected from the general neurology outpatient department (OPD) and movement disorder clinic of a medical college hospital in Eastern India. Clinical and relevant neuroimaging studies excluded mimickers and secondary causes of HFS. Institutional Ethics Committee’s permission was obtained. Informed consent was taken from patients before botulinum toxin injection. The pre and postinjection assessment tools were spasm rate for a specific period of time, quantification of facial asymmetry, widening palpebral fissure by visual analog scale, Jankovic disability rating scale, HFS-7 scale, and videography.

Results: A total of 250 cases of HFS (F:M = 138:112) were studied. The mean age of presentation was 47 years. The mean dose of botulinum toxin injection was 24.2 units per patient. The mean duration of improvement was 4 months. The spasm frequency was decreased by 90%, and the facial asymmetry was improved by 86%. The improvement in quality of life was 86%. Local adverse effects are seen in 10.4% of cases, and all were reversible.

Conclusion: This is one of the largest studies on the effects of botulinum toxin in subjects with HFS in the Indian population. Periodic injection of botulinum toxin is a safe and effective therapy for subjects with HFS. There is a significant improvement in the quality of life following botulinum toxin therapy in subjects with HFS. Adverse effects were local, mild, well-tolerated, and reversible.

ORIGINAL ARTICLE

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INTRODUCTION

Hemifacial spasm is a disorder of the facial nerve manifested by the involuntary synkinetic movement of the facial muscles on the affected side with minimal facial weakness.1 Although initially, the nature of the facial nerve disorder was controversial, it is now accepted that it is an irritated lesion which is often found to be an aberrantly placed artery compressing the nerve.2,3

The pathophysiology is believed to be focal demyelination at the compression site of the facial nerve at the root exit zone. Demyelinated axons may undergo spontaneous ectopic excitation or activation of the adjacent nerve fibers by ephaptic transmission.4

The condition adversely affects a patient’s ability to communicate via facial expression, produces psychological alteration from substantial disfigurement, intermittent visual disturbances, excessive tearing, difficulty in driving, impaired reading, facial paresthesia, as well as hearing of clicking sound or ticking sound.5 Besides this, in long-standing untreated cases of HFS, there may be fixed contracture of the facial muscles on the affected side.

Because HFS rarely remits spontaneously, most patients need to continue treatment for many years, if not throughout their life.6 Thus, recognizing the condition at the earlier phase of illness and treating it to the best possible extent is essential from a therapeutic and esthetic point of view.

Several pharmacological agents like carbamazepine, phenytoin, baclofen, clonazepam, and gabapentin have been used with limited efficacy in 15–25% cases.7,8

Over the last 30 years, microvascular decompression surgery has been the most effective treatment of HFS, with a success rate of up to 90%.9 However, surgery carries a recurrence rate of up to 25% over the next 2 years.10 In addition, microvascular decompression surgery is not widely practiced as it needs a great deal of expertise, and postoperative bleeding is one of the most dangerous complications.7

Botulinum toxin type A, a potent biological chemodenervating agent, acts at the neuromuscular junction by blocking the presynaptic release of acetylcholine. Besides this, the action of botulinum toxin type A is reversible and dose-dependent. Many studies have shown an excellent response to botulinum toxin in sufferers of HFS.11,12 Hence, botulinum toxin type A is now widely regarded as the treatment of choice for the condition.13,14 However, there is a lack of Indian studies on the therapeutic responses of botulinum toxin type A in cases of HFS.15

Many studies have been performed to assess the response of therapy and subsequent quality of life in sufferers of HFS treated with botulinum toxin type A. Health-related quality of life is determined by the subjective assessment of the impact of the disease or treatment across the psychological, physical, and social domains of functioning of the individuals.15

Indian studies are very few about the response to botulinum toxin type A treatment and assessment of the quality of life of these patients. Singh et al. observed that patients with HFS suffered from significant impairment of quality of life compared to control.16 Botulinum toxin type A injections are effective with a benefit rate of 76–100% and have a relatively low incidence of side

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effects, particularly ptosis and diplopia, but have to be repeated every 3–6 months.12,13 The objective of the present study is to observe the demographic profile, the clinical spectrum of cases of HFS, therapeutic response, adverse effects, and quality of life following treatment with botulinum toxin type A.

**Materials and Methods**

The present study was carried out from April 2017 to March 2022 in the movement disorder clinic and botulinum toxin clinic of Nil Ratan Sircar Medical College and Hospital which is a neurology teaching hospital in Eastern India. Subjects with a possible diagnosis of HFS who are referred from general neurology OPD and private neurologist were enlisted. Consecutive cases of HFS were seen by a competent neurologist with expertise in movement disorders.

Detailed history and neurological findings were recorded in a semi-structured questionnaire. Great care was exercised to exclude mimickers of HFS such as epilepsy partialis continua, blepharospasm, hemifacial tic, hemifacial myokymia, functional facial spasm, facial myoclonus, hemimasticatory spasm, oromandibular dystonia, and postfacial palsy synkinesis following aberrant regeneration of the facial nerve.

The presence of the “other Babinsky sign” and synchronous contraction of the upper and lower facial muscles were specific to HFS. The clinical red flag category in the diagnosis of HFS was tonic rather than clonic, unilateral facial spasm lasting for more than 3 seconds, and spastic paretic hemifacial contracture. The absence of red flag signs, provocative manoeuvres, and home videos was considered to facilitate a precise initial diagnosis.

Secondary cases of HFS were excluded by clinical red flags, relevant electrophysiology studies, and neuroimaging procedures (mostly plain and contrast magnetic resonance imaging (MRI) of the brain, constructive interference in steady state (CISS) sequence, and MR angiography of the brain in selected cases). Radiological investigations could not be performed as all cases of HF are because of financial constraints. In addition, patients were excluded if they had coagulation disorders, a history of known hypersensitivity to botulinum toxin, pregnancy, or aminoglycoside therapy.

The Ethical Committee of the Nil Ratan Sircar Medical College approved the study. The methodology, expected benefit, and possible adverse effects were explained to individuals who intended to take botulinum toxin type A injection. Informed consent was obtained from every subject before the injection.

Following the injection, patients were asked to note the latency of onset of action, peak effect, duration of improvement, adverse effects (if any), and improvement of quality of life in a daily diary. Latency of onset of action was defined as the time gap between the injection and the first sign of progress, measured in days. Peak effect was referred to as the maximum benefit obtained from the injection, and it was assessed from the patient’s perception, review of diary, and interview with family members. We define the duration of improvement as the time between the initial observation of improvement by the patient and the recurrence of symptoms severe enough to bring the patient for any injection. The duration of improvement was measured in weeks or months. The pre and postinjection assessment tool was spasm rate over an extended period (in our case, 5 minutes), quantification of facial asymmetry, and widening of palpebral fissure by visual analog scale reported in percentage (0–100%), severity of spasm as well as the quality of life by Jankovic disability rating scale (0–4), and the HFS-7 scale for quality of life. Besides this, a video recording of the abnormal movement for half an hour before and 2 weeks after the botulinum toxin type A injection was taken for objective assessment.

The Jankovic rating scale is described as 0 = normal, 1 = mild disability and no functional impairment, 2 = moderate disability with no functional impairment, 3 = moderate disability with functional impairment, 4 = incapacitated. The change of one grade of disability in the rating scale will be considered significant.

The HFS-7 scale is depicted as 1 = had difficulty in driving, 2 = had difficulty in reading, 3 = had difficulty in watching television or movie, 4 = feeling depressed, 5 = avoiding eye contact, 6 = felt embarrassed about having the condition, 7 = failed to read about others reaction to you. Each parameter is a score on a five-point scale ranging from zero = “never” to four = “always” for the assessment of the quality of life.19

The site of botulinum toxin type A injection is anatomically important and consequential to the effectiveness of therapy, the site selection was made after close and careful observation of the abnormal facial movements. We injected botulinum toxin type A intramuscularly at four sides into the orbicularis oculi around the eyes, one point at levatoralac nasi, two sites of orbicularis oris, one point at mentalis, and three injection points at the platysma band.

One hundred unit vial of freeze-dried botulinum toxin type A (prepared by Alargan International) is reconstituted with 1 mL of 0.9% normal saline solution to yield toxin in 10 units per 0.1 mL.

The dose of the botulinum toxin type A was individualized based on clinical judgment of severity, location of spasm of facial muscles, and prevalent reports in the literature. Then, using an appropriate sterile technique, the toxin was injected at selected sites using a 1 mL tuberculin syringe with a 24-gauge needle.

The range of botulinum toxin type A dosage in the platysma band was 10–20 units, and the distance between the injection sites was always kept at 1.5 cm. The patients were assessed in the postinjection phase using the same assessment tools at the specified intervals of 2 weeks, 4 weeks, 12 weeks, and 16 weeks. Adverse effect (if any) was noted in the postinjection follow-up session. Postinjection videography was taken 2 weeks after the injection procedure.

**Results**

A total of 250 cases of HFS were seen in the movement disorder clinic during the study period. Of them, 138 were women, and 112 cases were men, with an F:M ratio of 1.25:1. The mean age of presentation was 47 years (range from 5 to 87 years). The mean duration of symptoms before treatment with toxin was 1 year (range being 6 months to 2 years). There was no positive family history of HFS in our cases. The left side of the HFS was more common than that of the right, the ratio being 140:109. We found a single case of bilateral HFS. Exacerbating factors for HFS like talking and exposure to sunlight have been observed in 12 and 20 cases effectively.

We observed five cases of HFS associated with structural pathology. These were cerebellopontine angle acoustic neuroma, arachnoid cyst, and epidermoid cyst, as well as dolicoectatic basilar artery and vertebral artery ectasia. The neuroimaging findings done in 100 cases of HFS revealed neurovascular conflict in 50 cases, structural pathology in five, and normal results in 45.

A total of 250 injection sessions were analyzed in the present study. The mean dose of botulinum toxin type A injection per patient was 24.2 units (10 to 50 units). Side effects were observed in 6% of the total injection sessions.

Twenty percent of patients (n = 50) were erratic after the initial two follow-up sessions. The onset of action was 1–2 weeks following the injection, and the peak effect appeared 3 weeks after the injection. The average duration of activity in our study was 4 months. There was no case of primary failure. Diminution of the number of spasms was found in 90% (n = 225) cases. Widening
of palpebral fissure includes improving facial symmetry in 86% ($n = 215$) of cases (Fig. 1).

The mean baseline score in the pre-injection phase is 3.06 ± 0.91, and the mean post-injection is 1.2 ± 0.92. The mean difference is worth 1.86 ± 1.04, which is highly significant ($p < 0.001$) – the improvement in the quality of life following the treatment of reference by utilizing the HSF-7 score. The Jankovic score was calculated to be 2.96. The mean HFS-7 score in the pre-injection phase was 20.64. Paired sample $t$-test was used to compare the score of the patients before and after treatment. By using the Jancovic score, 48% of patients ($n = 120$) showed improvement in 2 weeks of follow-up ($p < 0.01$, $t = 6.725$), which increased to 80% ($n = 200$) in 4 weeks ($p < 0.01$, $t = 11.134$). The improvement came down to 58% in the 12th week of follow-up; however, sustained improvement was noticed in 70% ($n = 140$) of cases in the 16th week of follow-up. Using the HSF score, it was observed that 60% ($n = 150$) of patients for improvement in quality of life in the 2nd week of follow-up. At the same time, the maximum number of patients showing improvement was the 4th week of follow-up. At the 12th week of follow-up, 48% of patients maintained the same improvement in their quality of life. In comparison, 22% of patients exhibited mild deterioration of quality of life compared to the previous benefit obtained earlier.

Adverse effects were seen in 12% ($n = 30$) of cases, and there were mild improvements over 2–16 weeks. No idiosyncratic reaction was noticed in our series. The adverse effect profile was in the form of mild true ptosis in 12 cases, pseudoptosis in four cases, watering from the eye in two cases, mild facial weakness in eight cases, drooping the angle of the mouth, and leakage of food materials, especially the liquid, was seen in two cases. In addition, two patients reported repeated biting of the inner aspect of the cheek on the affected side in the post-injection phase. We have not observed any long-term side-effects in the entire study period.

**DISCUSSION**

Hemifacial spasm is a painless but distressing condition and usually develops in middle age between the 4th and 5th decades of life or later. The disease is typically symptomatic of an irritating lesion (mass lesion or aneurysm) in the vicinity of the facial nerve in the form of an aberrantly placed artery, touching or pulsating the nerve.

Our study represents one of the largest groups of patients in Indian studies. We found that HFS is the most common in the 5th decade of life, and it is female dominating. One study reported that young HFS (at or below 30 years of age) comprises 6.5% of total cases, most of which are due to neurovascular compression.20

Most cases of HFS are sporadic, though occasional familial cases have been described suggesting that some patients are genetically predisposed to develop HFS.21 In our series, positive family history was lacking in all cases. We have one subject who presented with bilateral HFS (0.4%). Bilateral HFS is occasionally reported, and its prevalence in clinic-based series is from 0.6–5%.22

A group of patients reported exacerbating factors. These were talking ($n = 12$) and exposure to sunlight ($n = 20$). This finding has also been observed in a previous study.23 The exact etiology of exacerbation of HFS with talking is not known. We know that the motor system does not function in isolation and requires the constant flow of sensory information to produce the appropriate movement. The sensory system is also organized in a hierarchical fashion and provides appropriate sensory information to each level of the motor system. Talking involves the movement of lower facial muscles. We hypothesize that there may be an increase in the excitation of motor fibers of the facial nerve induced by kinesthetic sensation from the lower facial muscles while talking by an ephaptic transmission because of focal demyelination. The usual duration of botulinum toxin type A varies from 4 to 6 months, and in our series, the average duration of action was 4 months. Following injection, we have observed a decrease in spasms and widening palpebral fissure in 90% ($n = 225$) and 86%.

The onset, peak of action, and duration of clinical benefit following botulinum toxin type A in our series are comparable to other previous studies. The pre-mean Jancovic score in our study population of the baseline is 2.96. The highest percentage of patients (56%) scored three. Bastola et al. observed a mean Jankovic score of 3.18 in their study.23 Using the disability score and HFS-7 score, the maximum effect of improved quality of life was in the 4th week of follow-up in our series.

The benefits of toxin therapy gradually increased as the number of patients experiencing improvement in the quality of life declined at 12 weeks and 16 weeks. This might indicate retreatment of the patient's condition after 12 weeks from the first injection. Batisti et al. observed that the mean latency of appearance of action following action was around 7.1 days, while the mean effect of duration was 3.1 months.24

In our study, 60% of patients with HFS-7 score and 48% of patients with Jankovic score had begun to improve in the 2nd week of follow-up. However, 20% of the individual
were erratic after the initial two follow-ups. This group of individuals was communicated through telephone, and most have expressed economic restraint and a shortage of human resources for nonattendance. Complications are related to the location of the injection and the amount of toxin injected. The side-effect of true ptosis is due to the spread of the toxin to the levator palpebrae superioris which should be differentiated from pseudoptosis due to eyelid edema. Abolishing the spasm with botulinum toxin type A leads to changes in the local fluid dynamics and tissue fluid accumulation within the eyelids giving rise to pseudoptosis. The complications are usually mild and resolved within 1–2 weeks.

**Limitation**

This is an unblinded study. There was erratic attendance of a group of patients in the follow-up session.

**Conclusion**

This is one of the largest studies on the uses of botulinum toxin type A in the case of HFS reported so far from India. Botulinum toxin provides excellent therapeutic efficacy in controlling HFS in our series. We have not found any case of primary failure following botulinum toxin type A injection. Definite improvement in quality of life following botulinum toxin type A injection has been observed in many cases. Temporary side-effects do occur but are of a mild degree and reversible. Dropout has been observed in a group of subjects and is mostly related to economic restraints.

**Acknowledgments**

We are thankful to Mr Sanjay Talukdar and Professor Dr Debashish Sanyal for carrying out the statistical analysis. We sincerely thank our DM neurology PTDs of this institution for helping the present study.

**References**

Study of Inflammatory Markers in Chronic Obstructive Pulmonary Disease

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Abstract

Introduction: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the sudden worsening of symptoms of COPD like shortness of breath, increased quantity and color of sputum, and systemic inflammation, and has a significant impact on survival. Biomarkers such as high-sensitivity C-reactive protein (hsCRP) and procalcitonin have been studied in AECOPD patients as prognostic markers. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two new inflammatory markers and play a significant role in prognosis in patients with AECOPD. NLR and PLR are easily available and cost-effective markers and have the potential for helping in the risk stratification of hospitalized AECOPD patients.

Aim: Study of inflammatory markers in COPD and their correlation with clinical outcome.

Methods: A prospective observational comparative study was conducted on 100 patients of COPD at the Department of General Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, and all necessary investigations were done.

Results: A total of 100 patients of COPD were taken, 50 patients were in a stable state (controls) and the same number of patients were in an acute exacerbation state (cases). Mean levels of NLR, hsCRP, and procalcitonin in cases were significantly higher as compared to controls whereas levels of PLR in cases and controls were comparable with no significant difference between them. Levels of both of these inflammatory markers (NLR and PLR) were positively correlated with levels of hsCRP and levels of procalcitonin. Of the total 50 patients, 23 (56.00%) patients needed mechanical ventilation and 11 (22%) needed inotropic support. Only 6 out of 50 patients (12.00%) died. Levels of NLR and PLR were positively correlated with the duration of hospitalization. Levels of NLR and PLR were not significantly associated with the need of mechanical ventilation whereas levels of PLR were significantly higher in patients who required mechanical ventilation.

Conclusion: Levels of NLR were raised in patients with AECOPD (cases) than stable state COPD patients (controls). So levels of NLR can be used as a marker to predict acute exacerbation and there was a positive correlation of NLR and PLR with levels of hsCRP and procalcitonin.

Introduction

Chronic obstructive pulmonary disease is characterized by persistent airflow limitation which is progressive and associated with chronic inflammation in the airway and alveoli to noxious particles or gases.¹ COPD is among the four leading causes of death.²

Chronic obstructive pulmonary disease is a chronic inflammatory disease of the airway, primarily associated with smoke exposure.³,⁴ Exposure to inhaled pollutants, mainly cigarette smoke is thought to cause chronic inflammation seen in COPD via the activation of structural and inflammatory cells within the lungs. These cells release chemotactic mediators which recruit more inflammatory cells into the lung parenchyma triggering a state of chronic inflammation, which causes structural changes in the airway, airway obstruction, and symptoms related to breathing.⁵ There are pieces of evidence that COPD is a systemic inflammatory disease, in which there is systemic inflammation and extrapulmonary manifestations are commonly present.⁶

Systemic inflammation may also worsen comorbid diseases, such as coronary artery disease, cardiac failure, osteopenia and bone mineralization disorders, anemia, lung malignancies, depressed mood, and hyperglycemia.⁷

Acute exacerbation of chronic obstructive pulmonary disease is a sudden deterioration of symptoms of COPD like shortness of breath, quantity and color of sputum, and increased systemic inflammation, and has a significant impact on survival.⁸ It may be triggered by an infection with bacteria or viruses or by environmental pollutants.⁹,¹⁰

Biomarkers such as hsCRP and procalcitonin have been studied in AECOPD patients as prognostic markers.¹¹ NLR and PLR are two new inflammatory markers and play an important role in the prognosis of a number of diseases including ischemic heart diseases, pneumonia, acute pulmonary embolism, and AECOPD. NLR and PLR are readily available and inexpensive markers and have the potential for helping in the risk stratification of hospitalized AECOPD patients, especially in resource-limited situations, and improving patient outcomes with timely intervention. NLR and PLR are considerably higher in AECOPD patients as compared to stable-state COPD patients and NLR is more sensitive than PLR in predicting acute exacerbation.¹²–¹⁴

In a cross-sectional study by Kurtipek et al.,¹⁵ they also concluded that NLR and PLR can be used as markers of AECOPD as mean values of NLR and PLR were appreciably higher in patients with AECOPD than stable patients with COPD.

Yao et al.¹⁶ also observed that levels of NLR and PLR were remarkably higher in AECOPD patients who did not survive compared to patients who survived. The combination of NLR, PLR, and CRP increased the prognostic sensitivity. They concluded that NLR may be an easily available and convenient prognostic marker for institutional mortality in patients with AECOPD.

A retrospective study by Teng et al.¹⁷ assessed the levels of NLR for intensive care unit (ICU) occupancy, mechanical ventilation, and 28-day mortality. Raised NLR was shown to be an independent risk factor for the frequency of requiring invasive mechanical ventilation in cases of AECOPD. However, the area under the curve (AUC) of NLR for anticipating ICU occupancy is 0.676 demonstrating low accuracy as an independent predictor. Therefore as per this study NLR cannot be used to predict ICU admission in cases of AECOPD.
Tugba and Ozturk also concluded that blood counts routinely measured in day-to-day practice (especially NLR) can be helpful to anticipate infections caused by bacteria in patients with acute exacerbations of COPD.

A retrospective study by In et al. also noted a negative correlation of NLR with forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), indicating higher NLR levels with increasing severity of COPD and they concluded that NLR could be used as a predictor for exacerbation in COPD and to estimate the severity of inflammation.

**Methods**

This was a prospective observational comparative study in which we recruited 100 patients with COPD, from the Department of General Medicine at Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi. Every patient was subjected to detailed history and clinical examination and relevant investigations including complete blood count, kidney function test, liver function test, hsCRP, procalcitonin, electrocardiogram, chest X-ray, and pulmonary function test. NLR, PLR, hsCRP, and procalcitonin levels were measured in patients admitted with AECOPD within 24 hours of admission and in patients with a stable state on an outpatient basis.

**Inclusion Criteria**

- Patients of COPD diagnosed on the basis of GOLD guidelines.
- Adult >40 years of age, both male and female.

**Exclusion Criteria**

- Patients with bronchiectasis, pulmonary tuberculosis, and bronchial asthma.
- Myocardial infarction or stroke in the last 3 months.
- Collagen vascular disorders.
- Malignancies.
- Inflammatory bowel disease.
- Patients with a history of treatments with steroids in the last 3 months.
- Patients who are unable to perform spirometry.

All the patients of AECOPD admitted to the hospital were followed up for the clinical outcome, which was assessed by:

- Duration of hospitalization.
- Need for mechanical ventilation.
- Need for ionotropic support.
- Mortality.

**Statistical Analysis**

The presentation of the categorical variables was done in the form of number and percentage (%). On the contrary, the quantitative data were presented as means ± standard deviation (SD) and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov–Smirnov test. In the cases in which the data were not normal, we used nonparametric tests. The following statistical tests were applied to the results:

- The comparison of the variables which were quantitative and not normally distributed in nature was analyzed using Mann–Whitney U test (for two groups) and independent t-test was used for the comparison of normally distributed data between two groups.
- The comparison of the variables which were qualitative in nature was analyzed using Chi-square test.
- The receiver operating characteristic (ROC) curve was used to find the cutoff point of NLR, PLR, hsCRP (mg/L), and procalcitonin (ng/mL) for predicting AECOPD.
- Spearman’s rank correlation coefficient was used for the correlation of NLR, PLR, hsCRP (mg/L), and procalcitonin (ng/mL) with each other and the correlation of NLR, PLR with duration of hospitalization (days).

The data entry was done in the Microsoft Excel spreadsheet and the final analysis was done with the help of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0. For statistical significance, p-value of less than 0.05 was considered statistically significant.

**Results and Observations**

Out of 100 patients, 50 were in a stable state and 50 patients were in an acute exacerbation state. On statistical analysis, distribution of age and sex were comparable in cases and controls with no significant difference between them.

A significant difference was seen between anthropometric parameters weight (kg), height, and body mass index (BMI), which were considerably higher in the control group as compared to patients with acute exacerbation and spirometry parameters FEV1 (%), FVC (%), FEV1/FVC were also considerably higher in controls than cases.

In our study, mean levels of NLR, hsCRP (mg/L), and procalcitonin (ng/mL) were considerably higher in cases as compared to controls whereas no significant difference was observed in mean levels of PLR between cases and controls (Table 1).

In our study, mean levels of NLR and PLR were positively correlated with hsCRP (mg/L) and with procalcitonin (ng/mL); however, this correlation was statistically not significant (Table 2).

A nonsignificant positive correlation was seen between the duration of hospitalization (days) and PLR whereas PLR was significantly correlated with the duration of hospitalization (Table 3).

The mean level of PLR in patients who needed mechanical ventilation was significantly higher as compared to patients who did not require mechanical ventilation. The mean level of NLR in patients who needed mechanical ventilation was also higher as compared to patients who did not require mechanical ventilation; however, it

<table>
<thead>
<tr>
<th>Variable (mean ± SD)</th>
<th>Cases</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>60.1 ± 9.23</td>
<td>57.34 ± 8.74</td>
<td>0.128†</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (38%)</td>
<td>19 (38%)</td>
<td>1‡</td>
</tr>
<tr>
<td>Male</td>
<td>31 (62%)</td>
<td>31 (62%)</td>
<td>1‡</td>
</tr>
<tr>
<td><strong>Anthropometric parameter (mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.96 ± 4.72</td>
<td>61.66 ± 4.86</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.4 ± 5.81</td>
<td>169.64 ± 5.67</td>
<td>0.0006†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.8 ± 1.17</td>
<td>21.41 ± 0.96</td>
<td>0.005†</td>
</tr>
<tr>
<td><strong>PFT parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>39.14 ± 5.4</td>
<td>48.22 ± 4.12</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>79.72 ± 10.86</td>
<td>88.84 ± 8.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Inflammatory marker</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLR (mean ± SD)</td>
<td>6.76 ± 3</td>
<td>5.07 ± 0.97</td>
<td>0.0002‡</td>
</tr>
<tr>
<td>PLR (mean ± SD)</td>
<td>140.99 ± 64.89</td>
<td>125.48 ± 60.7</td>
<td>0.368‡</td>
</tr>
<tr>
<td>hsCRP (mean ± SD)</td>
<td>2.66 ± 1.63</td>
<td>0.99 ± 0.55</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>PCT (mean ± SD)</td>
<td>1.46 ± 0.64</td>
<td>0.62 ± 0.43</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

*Denotes independent test; †Denotes Mann–Whitney test; ††Denotes Chi-square test.
was statistically not significant. Mean levels of NLR and PLR in the patient who required inotropic support or who died were higher as compared to patients who did not require inotropic support or who survived; however, the difference was statistically not significant (Table 4).

In our study, we observed that the value of AUC for ROC of NLR was higher as compared to PLR but lower than procalcitonin and hsCRP to anticipate acute exacerbation in a patient with COPD. Procalcitonin (ng/mL) had the highest discriminatory power to anticipate acute exacerbation in patients with COPD followed by hsCRP and NLR and the discriminatory power of PLR is nonsignificant (Table 5).

Table 2: Correlation of NLR and PLR with hsCRP and procalcitonin

<table>
<thead>
<tr>
<th>Variable</th>
<th>hsCRP (mg/L)</th>
<th>Procalcitonin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.047</td>
<td>0.187</td>
</tr>
<tr>
<td>p-value</td>
<td>0.745</td>
<td>0.193</td>
</tr>
<tr>
<td>PLR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.201</td>
<td>0.097</td>
</tr>
<tr>
<td>p-value</td>
<td>0.162</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Table 3: Correlation of NLR and PLR with the duration of hospitalization

<table>
<thead>
<tr>
<th>Variables</th>
<th>NLR</th>
<th>PLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospitalization (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.254</td>
<td>0.377</td>
</tr>
<tr>
<td>p-value</td>
<td>0.076</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Table 4: Association of NLR and PLR with clinical outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mechanical ventilation</th>
<th>Inotropic support</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not required</td>
<td>Required</td>
<td>p-value</td>
</tr>
<tr>
<td>NLR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.719</td>
<td>0.552</td>
<td>0.062</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.062</td>
<td>0.0592</td>
<td>0.246</td>
</tr>
<tr>
<td>95% confidence interval (CI)</td>
<td>0.620–0.804</td>
<td>0.449–0.652</td>
<td>0.629–0.811</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0005</td>
<td>0.3775</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cutoff</td>
<td>&gt;6.1111</td>
<td>&gt;107.2464</td>
<td>&gt;2.5</td>
</tr>
</tbody>
</table>

In our study, 50 patients of age >40 years, either male or female of COPD admitted with acute exacerbation, and 50 cases of age >40 years, either male or female of stable COPD were included in the study.

The mean age (years) in cases was 60.1 ± 9.23 and in controls was 57.34 ± 8.74 with no significant difference between them on statistical analysis and the distribution of gender was also comparable between cases and controls.

The mean levels of weight (kg), height (cm), and BMI (kg/m²) in controls were considerably higher as compared to cases. Lee et al. also observed a negative correlation of NLR with BMI and FEV1. NLR more than 2.8, low BMI, and low FEV1 were predictors of hospitalization due to respiratory symptoms in patients with AECOPD.

Association of NLR and PLR with AECOPD

In our study, the mean value of NLR was significantly higher in cases than in controls whereas no remarkable difference was seen in PLR between cases and controls. Kurtipek et al. also observed that mean NLR and PLR levels were considerably higher in patients with acute exacerbation as compared to stable state COPD. Tugba and Ozturk also concluded that NLR and PLR and monocyte-to-lymphocyte ratio values were significantly higher in the exacerbation group. Similarly, Lee et al., Yousef and Alkhiary, and Bilir et al. also reported that levels of NLR were considerably higher in the exacerbated COPD group compared to the stable COPD group.

Association of NLR and PLR with hsCRP and Procalcitonin

In our study, the mean of hsCRP (mg/L) and procalcitonin (ng/mL) in cases was significantly higher as compared to controls. We also observed a positive correlation between NLR and PLR and hsCRP (mg/L) and procalcitonin; however, it was statistically not significant. Yao et al. also observed that NLR levels were positively correlated with serum CRP levels. Whereas there was no linear correlation between PLR and serum CRP levels noted. In a study by Tugba and Ozturk, all subjects were divided into two groups, patients with NLR less than 3.03 and patients with NLR more than 3.03. Patients in both groups were compared in terms of exacerbation rate, CRP, and procalcitonin values. It was noticed that exacerbation rate and procalcitonin levels were found considerably higher in the NLR than in the 3.03 group. However, there was no considerable difference between the two groups in terms of CRP values. In et al. also observed that there was a considerable positive correlation between NLR and CRP levels in patients with AECOPD. Bilir et al. also noticed that there was a good degree of positive correlation between CRP and NLR in both the stable group and the exacerbation group. They concluded that NLR and CRP levels were higher in stable patients of COPD than in healthy persons.
and their values further rise with the severity of the COPD. In another study, Hedhliabir et al.\textsuperscript{23} also noticed that NLR and PLR were positively correlated with serum CRP levels in AECOPD patients.

**Association of NLR and PLR with Clinical Outcome**

In our study, clinical outcome was assessed by four parameters: duration of hospitalization, need for mechanical ventilation, need for inotropic support, and mortality. Of the total 50 patients, 23 (56.00\%) patients needed mechanical ventilation and 11 (22\%) needed inotropic support. Only 6 out of 50 patients (12.00\%) died. The mean value of the duration of hospitalization (days) of the study subjects was 8.68 ± 2.7 days.

A nonsignificant positive correlation was appreciated between the duration of hospitalization (days) with NLR whereas PLR was significantly correlated with the duration of hospitalization. Lee et al.\textsuperscript{20} also evaluated the correlation of NLR with predictors for hospitalization due to respiratory symptoms by multivariate logistic regression. They observed that NLR more than 2.8, low BMI, and low FEV1 were predictors of hospitalization due to respiratory symptoms. Hedhliabir et al.\textsuperscript{23} also observed that patients who had higher NLR and PLR had a longer duration of hospitalization and were associated with poor clinical outcomes.

There was no association between NLR and the need for mechanical ventilation, need for inotropic support, and mortality. In contrast to this, Yao et al.\textsuperscript{16} observed in AECOPD patients that levels of NLR and PLR were considerably higher among patients who died as compared to patients who survived, and in another study, Kumar et al.\textsuperscript{24} noticed that PLR ≥ 235 was significantly associated with 90-day mortality and, in another study, Yao et al.\textsuperscript{16} observed that PLR was considerably higher among patients who did not survive as compared to patients who survived AECOPD.

**NLR, PLR, hsCRP, and Procalcitonin as a Predictor of Acute Exacerbation in Patients with COPD**

In our study, we noticed that the value of AUC for ROC to predict acute exacerbation in patients with COPD was highest for procalcitonin followed by hsCRP, NLR, and least for PLR. So procalcitonin had the highest discriminatory power to predict AECOPD followed by hsCRP and NLR and the discriminatory power of PLR was nonsignificant. Kurtipek et al.\textsuperscript{15} also demonstrated that ROC analysis for predicting AECOPD showed a significantly more AUC of NLR compared to PLR and they concluded that levels of NLR and PLR were higher in AECOPD and NLR is a better predictor of AECOPD than PLR. However, Youssef and Alkhairy\textsuperscript{21} and Bullent et al.\textsuperscript{22} observed that the AUC of ROC was higher for NLR levels than CRP levels to predict AECOPD.

**Limitations of Study**

- In our study, the number of cases of COPD was small, therefore, the statistical power of the study was low.
- We did not compare the different stages of COPD, so the severity of COPD was not considered in our study.
- We did not include healthy controls, instead, stable-state COPD patients were taken as controls.
- We did not study the association of NLR and PLR with other inflammatory markers like erythrocyte sedimentation rate, interleukin 6, and tumor necrosis factor-alpha.

**Conclusion**

Thus we concluded that the levels of NLR were raised in patients with AECOPD than in stable-state COPD patients. So levels of NLR can be used as a marker of acute exacerbation. Levels of NLR and PLR positively correlated with s. hsCRP and s. procalcitonin levels. Procalcitonin had the highest discriminatory power to predict AECOPD followed by hsCRP, NLR, and PLR. Levels of both of these inflammatory markers (NLR and PLR) were positively correlated with the duration of hospitalization in patients with AECOPD. Levels of NLR and PLR were not significantly associated with the need for inotropic support and mortality, levels of NLR were also not significantly associated with the need for mechanical ventilation whereas levels of PLR were significantly higher in patients who required mechanical ventilation.

**References**


In T2DM Across Continuum,

Start with

Glycomet-GP 1/2

Metformin Hydrochloride 500 mg SR + Glimepiride 1/2 mg

In T2DM MANAGEMENT

Across Comorbidities

Hyper tension

ASCVD & CHF

Across Ages

Young

Elderly

>90 Years

Across Stages

Newly Diagnosed

Early Stage

Long Duration

Across Complications

Nephropathy

Neuropathy/Diabetic Foot

Reliopathy

BMI

Underweight

Normal

Overweight

Obese

Prascribing information


Metformin hydrochloride (USP) as extended-release form 500 mg and glimepiride (USP) as extended-release form 1.25 mg.

Your reliable healthcare partner


Journal of the Association of Physicians of India, Volume 70 Issue 12 (December 2022) 53
UDAPA
Dapagliflozin 5mg & 10mg

The most extensively studied Indian dapagliflozin
Assured control all day long with dosing made easy

Bioequivalent to Vildagliptin 50 mg BID

Therapeutically equivalent to Vildagliptin 50 mg BID

No changes in liver enzyme (SGOT & SGPT) and serum bilirubin

24 hr DPP4 inhibition

**Jalra-OD**

Vildagliptin 100mg SR (Sustained Release)

Every 24 hours.

**Dosage and Administration:**

1. **DOSAGE:** It is recommended that the initial dose of 50 mg be given to the patient. The dose may be increased to 100 mg if required. The maximum daily dose should not exceed 200 mg.

2. **DURATION OF TREATMENT:** The treatment should be continued as long as the patient remains clinically stable on the drug.

3. **CONTRAINDICATIONS:** Jalra-OD should not be used in patients with known hypersensitivity to vildagliptin.

4. **PRECAUTIONS:**
   - Monitor blood glucose levels closely in patients with diabetes mellitus.
   - Patients with renal impairment or hepatic disease may require a lower dose.
   - Patients with history of gallbladder disease may require further investigation.

5. **ADVERSE REACTIONS:** The most common side effects reported with Jalra-OD use are:
   - Nausea
   - Diarrhea
   - Headache
   - Flatulence

6. **OVERDOSAGE:** Symptoms of overdose include hypoglycemia, which may be treated with glucose or intravenous glucose.

7. **INTERACTIONS:** Patients taking Jalra-OD should be advised to report if they are taking any other medications.

8. **PREGNANCY:** Jalra-OD is category C. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

9. **LACTATION:** It is unknown if Jalra-OD is excreted in breast milk. Caution is advised in breastfeeding mothers.

10. **STORAGE:** Store at room temperature and protect from light.

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Metformin Hydrochloride Sustained Release Tablets 250mg/350mg/500mg

The Gold Standard Metformin

Now Approved in Prediabetes

Overweight patients with IGT* and/or IFG*

Increased HbA1C

Still progressing towards T2DM despite lifestyle changes for 3 to 6 months

PCOS Patients with Prediabetes, Women with History of GDM

Abnormal FSH and LH levels, or abnormal BMI

Glycomet-S.R. is contraindicated in patients with known hypersensitivity, renal impairment (estimated glomerular filtration rate <30 mL/min), severe liver disease, sugar patients, and those with abnormal liver function tests. It is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min).

*AF-012: Oral Glucose Tolerance Test intervention study in pre-diabetic patients of type 2 diabetes mellitus, randomized controlled trial for the intervention group. The intervention was抽提的：300 mg/day of Metformin for 6 months. The control group received placebo for 6 months. The intervention group showed a significant decrease in fasting plasma glucose, HbA1c, and body weight compared to the control group. The intervention group also showed a significant increase in insulin sensitivity. The control group showed no significant changes in any of the above parameters.

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Page 55
LEADERS IN DIABETES CARE

In Drug-naïve T2DM patient

**UDAPA-M**
Dapagliflozin 5mg/10mg + Metformin Extended Release Tablets (500mg/1000mg)

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*English, Hindi, Bengali, Gujarati, Marathi, Punjabi, Tamil, Assamese, Kannada, Malayalam, Oriya and Telugu.
Pulmonary Involvement in Systemic Lupus Erythematosus Patients in a Tertiary Care Hospital

Dibyayanam Sahu1, Sandip Saha2, Sharmistha Bhattacherjee3, Saikat Datta4*, Smarajit Banik5

Received: 24 December 2021; Revised: 23 August 2022; Accepted: 14 September 2022

ABSTRACT

Introduction: In half of the individuals with systemic lupus erythematosus (SLE), over the course of the disease, pulmonary involvement occurs frequently and is one of the parts in the array of presenting symptoms. But the published research and information on SLE have historically concentrated on renal, central nervous system (CNS), and dermatological manifestations, while the pulmonary effects of SLE have received very less attention.

Objective: To know the extent and pattern of pulmonary involvement in SLE patients in a tertiary care hospital.

Materials and methods: A cross-sectional observational study was conducted among 70 diagnosed SLE [who fulfilled the revised American College of Rheumatology (ACR) criteria for the classification of SLE] patients attending a tertiary care center. Seventy diagnosed SLE patients who met the updated ACR criteria for the classification of SLE and were enrolled in a tertiary care facility in West Bengal participated in a cross-sectional observational study. After informed consent, clinical examinations, general survey, respiratory examination, cardiovascular examination, and relevant investigations (chest X-ray, pulmonary function test, echocardiography and electrocardiography, and high-resolution computed tomography (HRCT)/chest computed tomography (CT) scan) were performed.

Results: The majority of the study subjects belonged to the 21–30 years of age-group (45.7%) and were females. Most of the study subjects were naive as they were newly diagnosed. Among the chief presenting complaints, the most common was cough followed by dyspnea and pleuritic chest pain. Chest X-rays showed pleural pathology in 37% of study subjects and pulmonary function tests were found to have a restrictive pattern in 4.3%. Echocardiography documented that 19.6% had pulmonary artery hypertension. HRCT revealed that 19.4% of subjects had definitive findings of interstitial lung diseases (ILD).

Conclusion: A substantial contributor to morbidity and death, SLE is a potentially fatal, commonly debilitating autoimmune illness with pulmonary symptoms. Cough was the most common presenting complaint, and the most common radiological abnormality detected was pleural effusion. Spirometry revealed, as expected, a restrictive pattern in most of the cases. Around 29% of cases revealed features suggestive of or confirmatory evidence for intestinal lung disease. As a whole, the prevalence of lung involvement in SLE in the study was 67%.

But this being a study with only 70 participants, a further longitudinal is recommended to study disease activity correlation with the incidence of early pulmonary involvement in SLE disease course.

INTRODUCTION

The archetypal autoimmune illness, SLE, is identified by the generation of autoantibodies to components of cell nuclei in association with diverse clinical manifestations accompanying almost all organs. Several of its clinical manifestations are a result of host cell death by autoantibodies or the accumulation of antigen-antibody complexes in the capillaries of visceral tissues. It is a complex disease with variable presentations and prognosis characterized by remissions and flares.

In SLE, pulmonary involvement is significant, affects 50% of patients during the course of the disease, and accounts for 4–5% of the patient’s presenting symptoms.

The common pulmonary manifestations of SLE include pleuritis, pneumonia, pulmonary arterial hypertension (PAH), pleural effusion, ILD, acute lupus pneumonitis, diffuse alveolar hemorrhage, shrinking lung syndrome, etc.

The population being evaluated, the referral patterns to the unit where patients are studied, and the tools used to identify pulmonary involvement all affect the frequency of pulmonary manifestations in SLE. The paucity of diagnostic facilities, like the detection of serological markers along with the relative lack of sensitization among the medical fraternity, has led to the under-estimation of the caseload in the Indian scenario.

While the published literature and available material on SLE have traditionally focused on renal, CNS, and cutaneous manifestations, the pulmonary consequences of SLE have been relatively under-evaluated. In view of the growing numbers of SLE patients being recognized in this subcontinent, the current study was planned with the aim to generate information regarding pulmonary involvement in SLE patients in a tertiary care hospital, Darjeeling district, West Bengal, with the hope that the results shall lead to better understanding and a more robust database on the topic of pulmonary manifestations in SLE.

OBJECTIVES

The objective of the study was to know the extent and pattern of pulmonary involvement in SLE patients in a tertiary care hospital in West Bengal.

MATERIALS AND METHODS

A cross-sectional observational study was conducted among the diagnosed SLE patients attending the outdoor and indoor wards of general medicine of our tertiary care hospital from April 2015 to March 2016. All patients attending outpatient departments or admitted to wards during the period who fulfilled the revised ACR criteria for the classification of SLE were included in the study. Pregnant women, smokers, and patients with a known history of asthma, chronic obstructive pulmonary disease, rheumatic heart disease, or cardiomyopathy were excluded from the study.

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A sample size of 70 was calculated using the formula \( N = \frac{(Zα^2PQ)}{L^2} \), where \( P \) was the anticipated proportion of pulmonary manifestations in SLE patients (23.68%), \( Q \) was \( 100 - P \), \( Zα \) was 1.96 at 95% confidence interval (CI), and \( L \) was allowable error 10%.

Seventy consecutive study subjects who fulfilled the inclusion and exclusion criteria were taken from the outdoor and indoor facilities of the tertiary care hospital. Data were collected using a semi-structured schedule which consisted of sections for history taking, clinical examinations, general survey, respiratory examination, cardiovascular examination, and relevant investigations (chest X-ray, pulmonary function test, echocardiography and electrocardiography, and HRCT/chest CT scan). The duration of the disease at enrolment was determined by counting the time between the doctor’s diagnosis and the first study visit.

After receiving informed consent, all eligible study participants were questioned in accordance with the aforementioned procedure, and a full clinical examination, including a systemic and general examination, was carried out. This was followed by chest X-ray, pulmonary function test using a spirometer, echocardiography (ruling out thoracic 2D echocardiography), and computed tomography if needed.

Pulmonary Function Test

In accordance with the recommendations, lung function tests were carried out using a portable vitalograph spirometer (CHESTAC-8800, Japan). According to the manufacturer’s recommended practices, calibration was performed using a 3-l calibration syringe at least twice daily, before and after the spirometric readings.

The following lung function tests were performed: forced vital capacity (FVC, l), forced expiratory volume in one second (FEV1, l), peak expiratory flow, forced expiratory flow at 25% of FVC (FEV1/FVC), forced expiratory flow at 50% of FVC (FEV1/FVC), and forced expiratory flow at 75% of FVC (FEV1/FEV2). FEV1 was also calculated as a proportion of FVC.

Values between 80% and 120% of the expected value were considered normal. Predicted values for a given patient were derived by utilizing the patient’s age and height in the relevant regression equation. Individual measurement values that were below the fifth percentile were regarded as abnormal. FEV1/FVC ratios typically range from 0.75 to 0.80, while older age does cause this value to decline slightly.

### Data Analysis

After checking for consistency and completeness, the data collected were entered and subsequently analyzed using SPSS v20. The data were then presented using principles of descriptive statistics and categorical outcome variables were tested by using Chi-square test.

#### Ethical Issues

The study protocol was submitted to the Institutional Ethics Committee and their permission was obtained, before data collection. The proposed method of the study was explained to the participants and his/her family/guardian and informed consent was obtained. The participant and their respective family/guardian were assured of the confidentiality and anonymity of the data collected.

### Results

Table 1 shows that the majority of the study subjects belonged to the 21–30 years of age-group (45.7%) followed by 40.0% and 14.3% in the ≤20 years of age-group and 31–45 years of age-group, respectively. The mean age of the study subjects was 23.37 (SD ± 6.9) years. There was a female preponderance and the majority of the study subjects were female (91.4%). The majority of the study subjects were newly diagnosed (32.9%) and among the rest, 47% were being diagnosed as having SLE in less than 3 years. Mean duration of disease 2 (SD ± 2.2) years.

Most of the study subjects were treatment-naive as they were newly diagnosed, but among others, 23% was taking hydroxychloroquine (HCQ) and prednisolone whereas 17% had been taking cyclophosphamide in addition to HCQ and steroid. Among the chief presenting complaints, the most common were cough (44.3%) followed by dyspnea and pleuritic chest pain (11% each) (Table 2).

Chest X-rays showed pleural pathology in 37% of study subjects and interstitial patterns (reticular, reticulonodular pattern, pleural thickening, and interlobar septal thickening) in 8.6% of study subjects. Pulmonary function tests were found to be normal in 81% of patients, an obstructive pattern was seen in 4%, and a restrictive pattern was seen in 4.3% of patients (Table 3).

About 81% of study subjects had a normal axis in electrocardiography whereas 10% had a right axis and 9% had a left axis deviation.

### Table 1: Sociodemographic variables of the study population (n = 70)

<table>
<thead>
<tr>
<th>Socio-demographic variable</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>28</td>
<td>40.0</td>
</tr>
<tr>
<td>21–30</td>
<td>32</td>
<td>45.7</td>
</tr>
<tr>
<td>31–45</td>
<td>10</td>
<td>14.3</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>8.6</td>
</tr>
<tr>
<td>Female</td>
<td>64</td>
<td>91.4</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100.0</td>
</tr>
</tbody>
</table>

### Table 2: Disease characteristics in the study population (n = 70)

<table>
<thead>
<tr>
<th>Disease characteristics</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>23</td>
<td>32.9</td>
</tr>
<tr>
<td>1–3 years</td>
<td>33</td>
<td>47.1</td>
</tr>
<tr>
<td>&gt;3 years</td>
<td>14</td>
<td>20.0</td>
</tr>
<tr>
<td>On treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>30</td>
<td>42.9</td>
</tr>
<tr>
<td>HCQ only</td>
<td>10</td>
<td>14.3</td>
</tr>
<tr>
<td>HCQ + PRED</td>
<td>16</td>
<td>22.9</td>
</tr>
<tr>
<td>HCQ + PRED + CYCLO</td>
<td>12</td>
<td>17.1</td>
</tr>
<tr>
<td>HCQ + MYCO + PRED</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Presenting complaints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>44.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>15.7</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>11</td>
<td>15.7</td>
</tr>
<tr>
<td>Nonpleuritic chest pain</td>
<td>9</td>
<td>12.9</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>8</td>
<td>11.4</td>
</tr>
<tr>
<td>JVP (elevated)</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>Clubbing</td>
<td>5</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100.0</td>
</tr>
</tbody>
</table>

HCQ, Hydroxychloroquine; PRED, Prednisolone; CYCLO, Cyclophosphamide; MYCO, Mycophenolate mofetil
Pulmonary Involvement in SLE Patients in a Tertiary Care Hospital

Systemic lupus erythematosus’s pulmonary manifestations can exhibit a wide range of symptoms and are frequently challenging to distinguish from other diseases. The present study was carried out on 70 patients of SLE recruited from both outdoor and indoor facilities of the tertiary care hospital from April 2015 to March 2016.

Age and Gender
Systemic lupus erythematosus predominantly affects women of childbearing age with an incidence rate reported to be 6–10 times higher in women than in men. This ratio is known to decline before puberty and late in adult life, although a female predominance remains. This effect of age and sex on the incidence and prevalence rates of SLE suggests a role for hormonal factors in its pathogenesis.

With a reported incidence rate of 6–10 times higher in women than in males, SLE mostly affects women of reproductive age. Although there is still a female majority, it is known that this ratio declines before puberty and toward the end of adult life.9 This relationship between sex, age, and the incidence and prevalence of SLE shows that hormonal variables may play a role in the development of the disease.

The mean age of the study subjects in the present study was 23.37 ± 6.99 (ranging from 13 to 45 years). The female-to-male ratio in the study was approximately 10:1. Omar and Suzan showed comparable age and sex distribution in their study.6 However, a Greek study found no differences between men and women in the mean age, mean age at diagnosis, disease duration, or follow-up time. Raynaud’s phenomenon and malar rash were more common in women, while serositis and discoid lesions were more common in young males.9

Table 3: Investigation findings among the study population (n = 70)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR-PA findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>33</td>
<td>47.1</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>26</td>
<td>37.1</td>
</tr>
<tr>
<td>Reticular, reticulonodular pattern, pleural thickening, interlobar septal thickening</td>
<td>6</td>
<td>8.6</td>
</tr>
<tr>
<td>Bronchiectasis and other nonspecific findings</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Airspace consolidation</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>57</td>
<td>81.4</td>
</tr>
<tr>
<td>Restrictive pattern</td>
<td>10</td>
<td>14.3</td>
</tr>
<tr>
<td>Obstructive pattern</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>ECHO-2D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>57</td>
<td>81.4</td>
</tr>
<tr>
<td>PAH</td>
<td>13</td>
<td>19.6</td>
</tr>
<tr>
<td>HRCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>41</td>
<td>58.0</td>
</tr>
<tr>
<td>Definitive of ILD</td>
<td>14</td>
<td>19.4</td>
</tr>
<tr>
<td>Probability of ILD</td>
<td>7</td>
<td>9.7</td>
</tr>
<tr>
<td>Shrinking lung syndrome</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Consolidation</td>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

High-resolution computed tomography revealed that 14 subjects (19.4%) were having definitive findings of ILD whereas seven (9.7%) were having findings likely of ILD. Among the rest, 41 had normal findings. Other findings were shrinking lung syndrome (3.2%) and consolidation (6.5%). Overall, the prevalence of pulmonary involvement in patients of SLE in the present study was 67% (Table 3).

**Discussion**

Systemic lupus erythematosus’s pulmonary manifestations can exhibit a wide range of symptoms and are frequently challenging to distinguish from other diseases. The present study was carried out on 70 patients of SLE recruited from both outdoor and indoor facilities of the tertiary care hospital from April 2015 to March 2016.

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<td>100</td>
</tr>
</tbody>
</table>

Echocardiography documented that 19.6% had pulmonary artery hypertension.

High-resolution computed tomography revealed that 14 subjects (19.4%) were having definitive findings of ILD whereas seven (9.7%) were having findings likely of ILD. Among the rest, 41 had normal findings. Other findings were shrinking lung syndrome (3.2%) and consolidation (6.5%). Overall, the prevalence of pulmonary involvement in patients of SLE in the present study was 67% (Table 3).

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With a reported incidence rate of 6–10 times higher in women than in males, SLE mostly affects women of reproductive age. Although there is still a female majority, it is known that this ratio declines before puberty and toward the end of adult life.9 This relationship between sex, age, and the incidence and prevalence of SLE shows that hormonal variables may play a role in the development of the disease.

The mean age of the study subjects in the present study was 23.37 ± 6.99 (ranging from 13 to 45 years). The female-to-male ratio in the study was approximately 10:1. Omar and Suzan showed comparable age and sex distribution in their study.6 However, a Greek study found no differences between men and women in the mean age, mean age at diagnosis, disease duration, or follow-up time. Raynaud’s phenomenon and malar rash were more common in women, while serositis and discoid lesions were more common in young males.9

**Disease Characteristics**

**Duration**
The disease duration ranged between newly diagnosed 1 and 9 years with a mean of 2 (SD ± 2.2) years. An Egyptian study by Mohammad et al.10 had 50 female patients of SLE; their mean age was 24.2 ± 7.4 (age range 15–51 years) and a mean disease duration of 28.4 ± 26.5 (range 2–120 months) which was similar to our study.

In the present study, the majority of the study subjects were treatment-naive as they were newly diagnosed, but among others, 23% were taking HCQ and prednisolone whereas 17% had been taking cyclophosphamide in addition to HCQ and steroids. This is similar to the study by Habib et al.11

**Presenting Symptoms**
Pulmonary involvement is common in SLE, occurring in up to 93% of autopsy series, and can be manifested as pleuritic chest pain with or without pleural effusion.12 The initial signs of SLE itself or lung involvement are frequent pleurisy, coughing, and/or dyspnea.13 Pleural effusions in SLE are often bilateral (50%), exudative, and characterized by an elevation in pleural fluid lactate dehydrogenase. Patients may also report cough, dyspnea, and fever.14 In the present study, cough was present in 44%, dyspnea in 15%, pleuritic chest pain in 15%, nonpleuritic chest pain in 9%, hemoptysis in 11%, engorged jugular venous pressure (JVP) in 6%, and clubbing in 7%. This is in contrast to the study by Omar and Suzan where pleuritic chest pain was present in 50%, dyspnea in 49%, cough in 34%, and hemoptysis in 5%.8

**Prevalence of Lung Involvement**
Depending on the standards used to diagnose lung abnormalities, the reported prevalence of pulmonary involvement in SLE ranges from 14 to 100%.15 In the present study, pulmonary affection was present in 47 (67%) study subjects. Badui et al. performed a study on 100 patients of SLE and reported a prevalence of 7% of pleural effusions in patients with SLE.16 Other Indian studies have reported the prevalence of pulmonary involvement in SLE from 8 to 58%.17–19

Despite the fact that ILD is less frequent in SLE than in other systemic autoimmune rheumatic illnesses like rheumatoid arthritis (such as scleroderma and anti-synthetase syndrome). The estimated prevalence of SLE-associated ILD across studies has been observed to be between 3 and 9%.1 In the present study, 19.4% of subjects showed definitive findings of ILD whereas 9.7% had findings likely of ILD. Systemic sclerosis and SLE are two connective tissue diseases that are frequently linked to PAH. Estimates for the prevalence of PAH in SLE range from 0.5 to 17.5%. Numerous processes, including vasculitis, *in situ* thrombosis, and interstitial pulmonary...
fibrosis, which raises pulmonary vascular resistance and may result in right heart failure, are involved in the pathogenesis of PAH. Our study showed that 13 (19.6%) of the study samples had PAH (pulmonary arterial systolic pressure >45 mm Hg and elevated triglycerides). This figure was relatively less than that documented by Omar and Suzan. A meta-analysis showed that the pooled prevalence of pulmonary hypertension in SLE was 8% (95% CI 5–12%). Subgroup analyses showed that SLE patients of different genders, ages, geographies, years of publication, and diagnostic techniques had significantly variable PAH prevalence rates.  

A decrease in diffusing capacity has historically been associated with a restricted pattern of lung illness in patients with SLE, including those with and without respiratory symptoms and abnormal chest X-rays. In the present study, pulmonary function tests revealed restrictive patterns (FEV1/FVC >80% but reduced FEV1 and FVC) in 14.3% of the study population. Studies by Habib et al. and Fenlon et al. have documented restrictive patterns in 21.4% and 20% of the participants, respectively.  

**Conclusion**

Systemic lupus erythematosus is a multiorgan autoimmune disease with a potentially serious, frequently debilitating, and typically waxing and waning course. SLE may be complicated by pulmonary illness, which also contributes significantly to morbidity and mortality. In the present study, around 67% of the patients revealed pulmonary involvement in some form or the other. Cough was the most common presenting complaint followed by dyspnea and pleuritic chest pain. Pleural effusion was the most common radiological abnormality detected. Apart from being normal, the restrictive pattern of lung disease was the most common spirometry finding. A little less than a third of cases revealed features suggestive of or confirmatory evidence for intestinal lung disease. But this being a study with only 70 subjects, a further longitudinal study might be needed to study disease activity correlation with the incidence of early pulmonary involvement in SLE disease course.

**References**

Percutaneous Coronary Intervention in Anomalously arising Coronary Arteries

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Abstract

Objective: Anomalous origin of coronary arteries (ACA) is rare. The objective of this communication is to describe the difficulties in angiographic recognition and challenges in percutaneous management.

Methods: The material for this retrospective study was provided by contributing interventional cardiologists practicing in tertiary care centers.

Results: From 2010 to 2019, 27 patients underwent percutaneous coronary intervention (PCI) for ACA. Four groups were encountered including anomalous origin from opposite sinus (left anomalous coronary artery from opposite sinus (L-ACAOS, n = 5), right anomalous coronary artery from opposite sinus (R-ACAOS n = 4)), origin of left circumflex from right sinus (n = 12), and origin of right coronary artery from posterior sinus (n = 6). The selection of a guiding catheter is the crucial step and a wide range of accessories was required to achieve an excellent outcome. Radial access may have an advantage in R-ACAOS, although the majority had a successful procedure from the femoral approach.

Conclusion: Percutaneous management of patients with anomalous coronary arteries is challenging but can be accomplished with an excellent immediate outcome.

Introduction

Anomalous origin of coronary artery is rare but is frequent enough to warrant the attention of all invasive cardiologists. Failure to identify the ACA can lead to an inadequate diagnosis, prolonged procedure, repeated catheterization, and may result in serious complications, particularly during acute coronary syndrome (ACS) or acute myocardial infarction.

Anatomically 87% of anomalies are anomalies of origin or distribution and the remaining are coronary fistula.1 The reported prevalence of ACA originating from opposite sinus (ACAOS) is 1.7% and is divided into L-ACAOS and R-ACAOS.2 Recent publications reported a prevalence of ACA of 0.8 and 0.87%, respectively, in a retrospective analysis of coronary angiographic database.3,4 The ACAOS can be associated with angina, myocardial infarction (MI), arrhythmias, sudden cardiac death (SCD),5 or can be complicated by atherosclerosis and present with the acute or chronic coronary syndrome. The present series analyzes the difficulties in the recognition and management of ACA in a real-world scenario.

Methods

The material for this retrospective study (years 2010–2019) was collected from participating interventional cardiologists from their practice in tertiary care centers.

ACA was defined as a coronary artery arising from the inappropriate/opposite sinus which can either be an anomalous left coronary artery from the right sinus or an anomalous right coronary artery from the left sinus.6,7 Clinical, angiographic, and PCI data of 27 patients were analyzed in four groups:

- Anomalous origin of right coronary artery (RCA) from posterior sinus (n = 6, serial 1–6).
- Anomalous origin of left circumflex (LCX) from right coronary sinus (n = 12, serial 7–18).
- Anomalous origin of left coronary artery (LCA) from right sinus (n = 5, serial 19–23).
- Anomalous origin of RCA from left coronary sinus (n = 4, serial 24–27).

Results

The results of 27 patients who underwent PCI are discussed in their respective groups, Tables 1 to 3, and Figures 1 and 2.

Group I: Six male patients aged 40–59 years presented with either non-ST elevation (NSTE), ACS (3), unstable angina (2), or stable angina (1). Left ventricular ejection fraction (LVEF) ranged between 40 and 60%. All had angiography and staged PCI from femoral access.

Angiography was completed using 6F Amplatzter (ART) or AL1, although multiple catheters were often required. The contrast volume for the diagnostic procedure averaged 155 (120–210) mL and for PCI 180 (130–200) mL. The procedure time for angiography and PCI averaged 90 and 100 minutes, respectively. XB3 proved guide catheter (GC) of choice and buddy wire support was needed in one-third. Pre and postdilatation, drug-eluting stent (DES), and antithrombotic use were as per the established protocols.

Group II (Table 1): Twelve patients with anomalous LCX from right sinus (male 8) aged 42–66 years presented with NSTE ACS (6), STEMI (2), stable (3), or unstable angina (1). Femoral access was used for both diagnostic and PCI procedures either staged (10) or in the same sitting (2). ACA was cannulated using either JR3.5, 4, ART1, multipurpose (MP), or AL1 catheter.

Three distinct variants have been described:8

- Type I: Separate ostia for RCA and LCX artery within right sinus of Valsalva (n = 6).
- Type II: Common/adjacent ostia in right sinus (n = 6).
- Type III: Anomalous LCX arising as a branch of the proximal RCA (n = 0).

The site of the lesion was proximal/retroaortic (6), ostial (2), and distal (4). AL1 or XB3 were the most frequently used GC. Buddy wire support and wiring of RCA were needed in five cases.

In case 1, the guide cannulation was extremely challenging. Multiple GC (JR3.5, 4, AR1, XB3, and MP1) failed to engage the RCA ostium which was ultimately done using a 6F right coronary bypass (RCB) diagnostic catheter. This catheter was placed around the LCX ostia and exchanged for a...
### Table 1: Group II—clinical, angiographic, and procedural data

<table>
<thead>
<tr>
<th>Sl. no., Year</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnostic</th>
<th>Guide catheter</th>
<th>Angiographic data</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lesion</td>
<td>Wire</td>
</tr>
<tr>
<td>7, 2010</td>
<td>42</td>
<td>M</td>
<td>2, 6F MP</td>
<td>5, 6F AL1</td>
<td>I</td>
<td>3 mm</td>
</tr>
<tr>
<td>8, 2011</td>
<td>60</td>
<td>F</td>
<td>3, 6F</td>
<td>2, 6F JL4</td>
<td>I</td>
<td>3 mm</td>
</tr>
<tr>
<td>9, 2012</td>
<td>48</td>
<td>M</td>
<td>2, 6F</td>
<td>3, 6F XB3</td>
<td>II</td>
<td>3 mm</td>
</tr>
<tr>
<td>10, 2012</td>
<td>58</td>
<td>F</td>
<td>3, 6F MP</td>
<td>2, 6F AL1</td>
<td>II</td>
<td>2.75 mm</td>
</tr>
<tr>
<td>11, 2013</td>
<td>46</td>
<td>M</td>
<td>2, 6F</td>
<td>2, 6F AL1</td>
<td>I</td>
<td>3 mm</td>
</tr>
<tr>
<td>12, 2013</td>
<td>55</td>
<td>F</td>
<td>3, 6F AR2</td>
<td>2, 6F XB3</td>
<td>I</td>
<td>2.5 mm</td>
</tr>
<tr>
<td>13, 2014</td>
<td>63</td>
<td>M</td>
<td>2, 6F JR</td>
<td>2, 6F XB3</td>
<td>II</td>
<td>2.75 mm</td>
</tr>
<tr>
<td>14, 2016</td>
<td>49</td>
<td>M</td>
<td>1, 6F JR</td>
<td>2, 6F AL1</td>
<td>II</td>
<td>3 mm</td>
</tr>
<tr>
<td>15, 2017</td>
<td>58</td>
<td>F</td>
<td>3, 6F</td>
<td>2, 6F</td>
<td>II</td>
<td>3 mm</td>
</tr>
<tr>
<td>16, 2018</td>
<td>51</td>
<td>M</td>
<td>2, 6F MP</td>
<td>1, 6F XB3</td>
<td>I</td>
<td>3 mm</td>
</tr>
<tr>
<td>17, 2018</td>
<td>50</td>
<td>M</td>
<td>3, 6F AL1</td>
<td>1, 6F AL1</td>
<td>I</td>
<td>2.5 mm</td>
</tr>
<tr>
<td>18, 2018</td>
<td>66</td>
<td>M</td>
<td>3, 6F</td>
<td>2, 6F AL1</td>
<td>I</td>
<td>3 mm</td>
</tr>
</tbody>
</table>

**BMW,** Balanced middleweight

### Table 2: Group III—clinical, angiographic, and procedural data

<table>
<thead>
<tr>
<th>Sl. no., year, age, sex</th>
<th>Diagnostic numbers tried, cannulation, contrast volume</th>
<th>Guide catheter numbers tried, cannulation, contrast volume</th>
<th>Access</th>
<th>Angiographic data</th>
<th>Others</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Lesion, Wire, Stent</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19, 2010, 52, M</td>
<td>4, 6F AR1, 200</td>
<td>1, 6F AR1, 150</td>
<td>Radial</td>
<td>3 mm, mid-LCX, 90%</td>
<td>BMW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20, 2012, 57, M</td>
<td>1, 6F Tiger, 70</td>
<td>1, 6F MP, 110</td>
<td></td>
<td>3 mm, total at mid-LCX</td>
<td>Whisper MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21, 2013, 63, M</td>
<td>3, 6F JR 3.5, 150</td>
<td>1, JR3.5, 130</td>
<td></td>
<td>3.0 mm, mid-LCX, 80%</td>
<td>BMW</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22, 2014, 40, M</td>
<td>1, 6F Tiger, 80</td>
<td>2, 6F MP, 120</td>
<td></td>
<td>2.75 mm, distal LCX, 99%</td>
<td>Whisper MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23, 2015, 66, F</td>
<td>3, 6F AR1, 110</td>
<td>1,6F MP, 120</td>
<td></td>
<td>3.0 mm, mid LCX, 90%</td>
<td>Whisper MS</td>
</tr>
</tbody>
</table>

**Cases 19, 21, and 23 had common ostia; MP, Multipurpose; BMS, Bare metal stent; Others as in text**

### Table 3: Group IV—clinical, angiographic, and procedural data

<table>
<thead>
<tr>
<th>Sl. no., year, age, sex</th>
<th>Guide catheter numbers tried, cannulation, contrast volume</th>
<th>Access</th>
<th>Angiographic data</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lesion, Wire, Stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24, 2012, 61, M*</td>
<td>3, 6F XB3, 280</td>
<td>Radial</td>
<td>3 mm, mid-RCA, 99%</td>
<td>Whisper MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25, 2015, 45, M*</td>
<td>3, 6F XB3, 180</td>
<td>Radial</td>
<td>2.75 mm, mid-RCA, 99%</td>
<td>Fielder FC, Whisper MS (buddy wire)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26, 2016, 74, M*</td>
<td>3, 6F AL1, 150</td>
<td>Radial</td>
<td>3.0 mm, mid-RCA, 99%</td>
<td>BMW, grand slam (buddy wire)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27, 2017, 76, F*</td>
<td>3, 6F XB3, 200</td>
<td>Radial</td>
<td>3.5 mm, mid-RCA, 99%</td>
<td>WhisperMS, Fielder FC (buddy wire)</td>
</tr>
</tbody>
</table>

**Cases referred after the failure of PCI from femoral access using multiple guides; ††Sirolimus eluting stent (Pronova); Abbreviations are as in text or previous tables**
PCI in Anomalously arising Coronary Arteries

6F AL after introducing a 0.014" coronary long wire in the LCX (Fig. 1A). PCI with DES resulted in excellent antegrade flow (Fig. 1B). Antithrombotic protocol was used as per established guidelines.

Group III (Table 3): This group comprised five patients (NSTE ACS 2, inferior wall ST elevation (STE) MI 1, and stable angina 2) with LVEF ranging between 35 and 60%. Both procedures were performed in a single sitting by radial access in two and the remaining had staged intervention. Femoral access was used in two patients referred from other centers after failed PCI and in one with a planned procedure. The contrast volume utilized for diagnostic angiography averaged 102 (70–200) mL with an average procedure time of 70 (40–120) minutes. Vessel cannulation was feasible either by AR1, Tiger, or JR1. The RCA, LAD, and LCX originated from the same/single ostia in the right sinus in three cases and from separate ostium in the right sinus in the remaining. Figure 2 documents the anomalous origin of left coronary system from right sinus (L-ACOS). All three (LAD, LCX, and RCA) arise from common ostia in right sinus with occlusion of LCX (panel A) and restoration of flow after PCI (panel B). The contrast utilized for PCI averaged 118 (110–170) mL with an average procedure time of 90 (80–120) minutes. The GC of choice was 6F multipurpose followed by JR or AR. The PCI was performed for stenosis/occlusion of LCX in all and additionally of RCA in two.

Group IV: This group included four patients (post-thrombolysis for anterior wall STEMI 1, NSTE ACS 1, and stable angina 2) with LVEF on echocardiography ranging from 40 to 60%. All patients had staged procedures. Three patients were referred from other centers after a failed attempt at PCI from femoral access. PCI was performed from radial access in these and also in one where we had to switch to radial.

**DISCUSSION**

This large series includes all major subsets of ACA and focuses on real-world challenges. There are no standardized guidelines to select a diagnostic catheter and the choice is dictated by the anatomy of the ACA and the operator’s experience and preferences. High contrast requirement, prolonged fluoroscopy time, and use of multiple catheters to confirm the diagnosis observed in this study are consistent with earlier reports.9,10

It is essential to plan the PCI procedure, which can be technically demanding. In majority (85%), PCI was performed as a staged procedure to minimize contrast volume and be better prepared with the hardware. In ACS patients, a single-stage procedure was performed. CTA was performed in six patients and helps in accurate imaging of the ACA origin and course of the vessel, detecting high-risk features, and assessing stent status during follow-up.

Femoral access was used in 78%, a practice frequent in the reported literature. Radial site use has been reported.11 We utilized the radial approach during ACS in L-ACAOS (group III) and in R-ACAOS (group IV) referred after a failed procedure from the femoral route. It is beneficial to involve an experienced colleague who is familiar with new devices and techniques including a guide liner.12 A suitable GC provides adequate stability, coaxial alignment, and
backup support, and proper selection is crucial for successful PCI.13

The four distinct variants of ACA seen in this study will be discussed separately.

**Group I: Anomalous origin of RCA from posterior sinus**

Anomalous RCA from the posterior sinus is exceedingly rare and is 0.24% among coronary artery anomalies.1 The origin of RCA from posterior (noncoronary) sinus has ranged between 2 and 5% in series describing the anomalous origin of RCA.14,15 Femoral access was utilized as in a previous study9 whereas radial using Tiger catheter proved a default approach.15 Cannulation of posteriorly directed RCA ostium was feasible by AR2, AL1, or MP diagnostic catheter. Anomalous RCA should be suspected if an experienced operator is not able to cannulate the vessel in a reasonable time. A systematic approach is recommended to facilitate a rapid diagnosis.16 VB3 GC with buddy wire provided the best coaxial support although multiple guides were often required an experience similar to an earlier communication.9

**Group II: LCX from right sinus**

This anomaly is one of the most common variants with a prevalence of 0.18–0.67%. Acute presentation with NSTE-ACS, STEMI, or unstable angina was higher as in an earlier report.10 There can be several clues to suspect anomalous CX. The suspicion usually arises when contrast injection into LCA reveals an unusually long, non-branching proximal segment and a non-perfused lateral wall. Contrast injection into RCA may also fail to opacify the anomalous CX or demonstrate collateral vessels to the lateral wall. Another clue to anomalous CX with retroaortoc course is a “dot sign” just posterior and to the left of the aortic root demonstrated on left ventriculography.17

Three distinct variants of ostium are described with 50% incidence of type I and 25% each of II and III.8 In this series, six cases each had type I and II pattern. GCs which provided excellent support for type I were AL1, J1L, or XB3 whereas EBU, XB3, or AL1 were used for type II. The XB or EBU guide provided strong backup support in both types. Guide catheters JR, AR, or AL in type I and JR or AR in type II or III have been successfully used.8,12,18 Double wire technique (one wire in RCA) helped in anchoring and stabilizing guiding catheters in right coronary sinus and enabled passage of another wire in anomalous LCX. Successful PCI in this variety has been reported.8,10,18

**Group III: Origin of L-ACAOS**

Left-ACAOS is less frequent than right but can cause SCD given the amount of myocardium it supplies. The incidence of anomalous left main coronary artery (LMCA) arising from the right sinus is 0.017% with interarterial course being considered malignant.1 This anomaly should be suspected when there is a failure to visualize left coronary vessels from left sinus.

Percutaneous coronary intervention in this subset is difficult and time-consuming, and the outcome depends on ostial configuration, exit angulation from the aorta, course, and lesion location. Vessel cannulation was achieved by JR, AR, or Tiger and all had retroaortic course. The procedure was mostly performed for lesions in LCX or RCA (Table 2). The femoral approach was utilized in the majority and radial in two patients with STEMI. Radial access has been used in a similar scenario.12 PCI in L-ACAOS is reported for lesions in LMCA, LAD, LCX, or RCA. Common ostia for both right and left coronary arteries were frequently observed in this study although wide variations have been reported. In right sinus, LMCA and RCA can arise from two separate ostia (Fig. 2). All three vessels can arise as trifurcation and are considered as a single coronary artery. The guide used was either MP, AR1, or JR1. A variety of GCs, JR, AR, AL, MP, or Eric Cohen right have been used for successful intervention.19

**Group IV: Anomalous origin of R-ACAOS**

Anomalous origin of RCA arising from the left coronary sinus is rare.2 The R-ACAOS vessel originates from an orifice anterior to the LM ostium in the left sinus and courses between the aorta and pulmonary artery, before reaching the right atrioventricular groove. This anomaly is suspected when the RCA ostium is not visualized in the right sinus and collateral vessels are absent. Selective RCA cannulation is difficult due to variations in the ostial location, its slit-like orifice, and odd angulation. A four-step approach involving right and left coronary sinus angiogram, biplane left ventriculography, and aortography is suggested to facilitate rapid diagnosis.20

Percutaneous coronary intervention was the most demanding but could be successfully accomplished with radial access. XB3 or AL1 provided the coaxial support and stability although on an average three guiding were tried (Table 3). The experience demonstrates the successful use of left GC for intervening in R-ACAOS originating from the left cusp. Buddy wire, extra support wire, and balloon anchoring were required to ensure stability and facilitate stent delivery. Various strategies including the use of oversized AR, undersized JL, XB3, Laya, left bypass catheter, Ikari right, MP, Voda, EBU, SF Launcher, Heart rail, and guide liner have been utilized with favorable outcomes. The guide can be decided by four variants identified by the anatomical landmarks.21 This approach may reduce contrast, radiation exposure, and time. Intravascular ultrasound has been utilized in cases with a partial intramural course and proximal intramural stenosis.

This series summarizes the experience of PCI in diverse variants of ACA presenting with chronic or ACSs. PCI is challenging but can be accomplished successfully with experience and a wide range of accessories.

**Limitations:** This study represents real-world data and suffers from limitations inherent to the collection of retrospective material. There is no standardized protocol and follow-up information is scanty.

**References**

PCI in Anomalously arising Coronary Arteries


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1. J. Am Coll Cardiol 2021 Mar, 77 (10) 1300-1301 CV. Cardiovascular
An Expert Group Consensus Statement on “Approach and Management of Prediabetes in India”

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Received: 15 July 2022; Accepted: 06 October 2022

ABSTRACT

The prevalence of prediabetes, a forerunner of diabetes, is very high, and its conversion to diabetes is also more rapid among Asian Indians. Prediabetes also predisposes to the development of macrovascular and to a lesser extent of microvascular complications of diabetes. In a large community-based epidemiological study, the Indian Council of Medical Research–India Diabetes (ICMR–INDIAB), data reported an overall prevalence of prediabetes of 10.3%, derived from 15 Indian states. This shows that the diabetes epidemic is far from over as many of them may soon convert to diabetes. Prediabetes, however, should not be considered a path to diabetes rather it should be a window of opportunity for the prevention of diabetes. This early screening, detection, and treatment of prediabetes should be made a national priority. Several countries have introduced lifestyle programs to prevent diabetes and, when indicated, pharmacological intervention with metformin as well. This consensus statement outlines the approaches to screening and lifestyle and pharmacological management of prediabetes in Asian Indians.

Prevalence of Prediabetes

Prediabetes is rising at an alarming rate in India even exceeding cases of diabetes in most states suggesting that in the near future large pool of the population could develop T2D. The prevalence of IGT worldwide in 2021 was found to be 541 million, or 10.6%, whereas, the prevalence of IFG worldwide was found to be 319 million adults, or 6.2%, according to IDF 10th edition (Table 2). The phased ICMR–INDIAB study was initiated that estimated the prevalence of prediabetes (IFG and/or IGT) and diabetes in India. The overall prevalence of prediabetes was reported at 10.3% in 15 states studied using WHO criteria. The range of prevalence was 6.0% in Mizoram to 14.7% in Tripura (Fig. 1). The prevalence of isolated IFG was 6.5% which was twice as higher as that of isolated IGT (2.8%) in all states except for Bihar, Manipur, and Meghalaya. If the ADA fasting glucose cutoff point of 100 mg/dL was used, the number of isolated IFG would increase to 20.8% and that of prediabetes to 24.7%. Male gender, obesity, age, family history of diabetes, and hypertension were independent risk factors for diabetes in both urban and rural areas.

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A recent article by Kumar et al. stated a general prevalence of prediabetes/diabetes as 8.4 and 12.3% among adolescent girls and boys in India, respectively. Further, it was also demonstrated in the study that a person's subscapular skinfold thickness and body mass index (BMI) were positively associated with prediabetes/diabetes.15

**Pathophysiology of Prediabetes**

The pathophysiological defects that underlie T2D are also present in the prediabetes stage. In the prediabetes stage of IGT, significant abnormalities in insulin action and secretion are frequently visible. The transition from normal glucose tolerance (NGT) to prediabetes, as demonstrated by longitudinal research by Weyer et al., was accompanied with an increase in body weight, an increase in insulin resistance, and a decrease in endogenous insulin production (β-cell dysfunction).16

The study also showed that increased weight gain, insulin resistance, and β-cell dysfunction were associated with the transition from prediabetes to T2DM. The main finding of the longitudinal observation was that β-cell failure and insulin resistance do not develop one after the other but rather concurrently. Loss of β-cell volume, increased lipolysis, decreased endogenous levels of glucagon-like peptide 1 (GLP-1), a poor incretin action, inadequate postprandial control of glucagon secretion, and perhaps hepatic glucose overproduction are further abnormalities in the prediabetic condition. The present disadvantages of prediabetes are made worse by the proinflammatory cytokine's abnormal expression (Fig. 2).17,18

### Risk Factors

The typical risk factors for the onset of prediabetes is as shown in Figure 3.19 Age, 2-hour plasma glucose, positive family history of diabetes, high glycated hemoglobin (HbA1c), inactivity, and poor high-density lipoprotein (HDL) are the common risk factors for the transition from NGT to dysglycemia, according to a 10-year follow-up of the Chennai Urban Rural Epidemiology Study (CURES). The same study also demonstrated that in those with NGT, sedentary lifestyles and low HDL cholesterol predicted the onset of prediabetes (but not diabetes). On the contrary, people with NGT were more likely to develop diabetes if their family had a history of the disease. As a result, it can be claimed that environmental variables like physical inactivity are associated to the development of prediabetes, but a combination of genetic and environmental factors may be responsible for the later development of diabetes. Therefore, to have the greatest benefit in this population, efforts to prevent diabetes would need to start before the onset of prediabetes.20

**Recommended goal**

A yearly diabetes development monitoring program should also screen for and treat modifiable CVD risk factors such as hypertension, dyslipidemia, smoking, and alcohol use.

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**Table 1: Diagnostic criteria for defining prediabetes**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>ADA</th>
<th>WHO</th>
<th>IDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>Prediabetes</td>
<td>Intermediate hyperglycemia</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>IGT*</td>
<td>140–199 mg/dL (7.8–11.0 mmol/L)</td>
<td>110–125 mg/dL (6.1–6.9 mmol/L)</td>
<td>ND</td>
</tr>
<tr>
<td>IFG**</td>
<td>100–125 mg/dL (5.6–6.9 mmol/L)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>HbA1c</td>
<td>39–47 mmol/mol (5.7–6.4%)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*IGT is assessed using the 2-hour plasma glucose during a 75 gm oral glucose tolerance test; **IFG is assessed based on the FPG level; ADA, American Diabetes Association; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; IDF, International Diabetes Federation; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; ND, Not defined; WHO, World Health Organization
Progression of Prediabetes to Diabetes

Asian Indians experience a rapid conversion from normoglycemia to dysglycemia and have one of the highest incidence rates of diabetes. This is related to the “Asian Indian” phenotype, which is distinguished by greater susceptibility to diabetes, hyperinsulinemia, and levels of total and visceral fat that are higher than those of white Caucasians with comparable BMIs. With a BMI of >23 kg/m² and a waist circumference of 85 cm for males and 80 cm for females, the development of diabetes is accelerated in Asian Indians. Therefore, it is crucial to recognize the circumstances as soon as possible and take proactive preventative actions.

The incidence rates of diabetes, prediabetes, and “any dysglycemia” were found to be 22.2, 29.5, and 51.7 per 1,000 person-years, respectively, in a 10-year follow-up of the CURES. About 19.4% of NGT patients developed diabetes, whereas 25.7% developed prediabetes, for a total conversion rate to dysglycemia of 45.1%. In this cohort, there were 78.9 new cases of diabetes per 1,000 person-years among those with prediabetes.

In both rural and urban areas, diabetes and prediabetes are becoming more common, according to the Secular TRends in DiabEtes in India (STRiDE-I) study. It was stated that all areas had higher rates of prediabetes and diabetes, but only towns and peri-urban villages had higher rates. There was a rise in abdominal obesity among rural villagers as well.

In comparison to rates reported in small, isolated, and homogenous populations like the Pima Indians (87.3 per 1,000 person-years), the Micronesian population of Nauru (62.8 per 1,000 person-years), and Native Americans in the Strong Heart Study (66.1 per 1,000 person-years), the rate of conversion from prediabetes to diabetes in the CURES follow-up is one of the highest reported in a large country (49.0 per 1,000 person-years) (Fig. 4).

It can be suggested that there has already been significant β-cell loss and disease progression by the time prediabetes develops because the incidence of T2D among people with NGT reported in the CURES follow-up was 22.2 per 1,000 person-years, which is significantly lower than the rates seen in people with prediabetes.

Kristian and Gottwald-Hostalek reported a linear fall in β-cell function and approximately 50% β-cell function is lost at diagnosis of prediabetes. Stameiz et al. demonstrated that independent of age, obesity, insulin sensitivity, or family history, Asian Indians with mild dysglycemia showed noticeably impaired β-cell function. NGT had the greatest levels of the major indicator of β-cell function, the unadjusted mean of oral disposition index (DIo), compared to patients with more severe diseases (IFG plus IGT and diabetes). IFG and IGT had 25 and 23%, respectively, larger homeostasis model assessments of insulin resistance (HOMA-IR) compared to NGT (both p = 0.0001) (Fig. 5).

Another study investigated the link between incident diabetes with IGT and DIo obtained from an oral glucose tolerance test in Asian Indian males. The development of incident diabetes

### Table 2: Estimated total number of adults with IGT and impaired fasting glucose in 2021 and 2045

<table>
<thead>
<tr>
<th>Particulars</th>
<th>2021</th>
<th>2045</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>541 million</td>
<td>730 million</td>
</tr>
<tr>
<td>IFG</td>
<td>319 million</td>
<td>441 million</td>
</tr>
</tbody>
</table>

IGT, Impaired glucose tolerance; IFG, Impaired fasting glucose

### Table 3: The MDRF Indian Diabetes Risk Score

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;35 (reference)</td>
<td>0</td>
</tr>
<tr>
<td>35–49</td>
<td>20</td>
</tr>
<tr>
<td>≥50</td>
<td>30</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td></td>
</tr>
<tr>
<td>Waist ≤80 cm (female), &lt;90 (male) (reference)</td>
<td>0</td>
</tr>
<tr>
<td>Waist ≥80–89 cm (female), ≥90–99 cm (male)</td>
<td>10</td>
</tr>
<tr>
<td>Waist ≥90 cm (female), ≥100 cm (male)</td>
<td>20</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>Exercise (regular) + strenuous work (reference)</td>
<td>0</td>
</tr>
<tr>
<td>Exercise (regular) or strenuous work</td>
<td>20</td>
</tr>
<tr>
<td>No exercise and sedentary work</td>
<td>30</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td></td>
</tr>
<tr>
<td>No family history (reference)</td>
<td>0</td>
</tr>
<tr>
<td>Either parent</td>
<td>10</td>
</tr>
<tr>
<td>Both parents</td>
<td>20</td>
</tr>
</tbody>
</table>

Hypertension or on hypertension medicine |   |
Overweight-BMI >25 kg/m² |   |
Physical inactivity |   |
Family history of diabetes |   |
Excess abdominal fat |   |
HDL, High-density lipoproteins; TG, Triglyceride
Statement on “Approach and Management of Prediabetes in India”

Biomarkers of Prediabetes

The gradually rising glucose levels appear rather late in the course of T2D development, by which time the β-cell function may already be significantly diminished. Therefore, it is essential to find more accurate and sensitive biomarkers that can anticipate the onset of dysglycemia early on when β-cell function is essentially at its peak. Some of these biomarkers are discussed below:

**Clinical relevance of biomarkers**

- Help identify people with significant diabetes risk.
- May help to identify subjects at risk of developing macro and microvascular complications.
- Can be added to conventional risk variables and improve the power of prediction.

**Adiponectin**

Adiponectin is derived from adipose tissues and has anti-inflammatory, antiatherogenic, and insulin-sensitizing effects. Adiponectin has been identified as an independent predictor of diabetes in a preliminary investigation of Asian Indians. A low level of adiponectin was strongly predictive of the onset of diabetes and significantly correlated with HbA1c. Independent of racial or gender variations, adiponectin levels are inversely related to the likelihood of incident prediabetes and are directly correlated with insulin sensitivity and indirectly correlated with insulin secretion. The area under the curve was demonstrated to be improved by the addition of adiponectin to HbA1c, however, the predictive power of HbA1c alone was not improved by the addition of interleukin-6 (IL-6).

**Retinol-binding Protein 4 (RBP4)**

The novel adipokine RBP4, which is released by adipocytes and hepatocytes, is the particular transport protein for retinol (vitamin A) in the blood. A favorable correlation exists between RBP4 levels and metabolic risk factors such as BMI, waist circumference, hypertension, and lipid markers. Concentrations of RBP4 are significantly correlated with prediabetes.

**Gamma-glutamyl Transferase (GGT) and Alanine Transaminase (ALT)**

Particularly when fasting, the liver is crucial in the regulation of blood glucose levels. T2DM is more common when there has been liver damage, which is indicated by an increase in blood ALT or GGT levels.

After adjusting for potential confounders known to affect circulating GGT, such as alcohol consumption and insulin resistance, a 2-year prospective, randomized, controlled primary prevention study of diabetes among Asian Indians revealed that higher concentrations of GGT were significantly associated with an increased risk of developing diabetes.

**Leptin**

Leptin is a crucial hormone that controls energy intake and expenditure by regulating appetite and glucose metabolism. It is largely secreted by adipocytes, and the amount of circulating leptin is directly correlated with the overall amount of body fat. In addition to atherosclerosis, hypertension, and coronary vascular disease, leptin insufficiency or resistance causes uncontrolled eating, obesity, and diabetes mellitus. Leptin levels are considerably greater in patients with diabetes than in those without (p = 0.001) in both males and females, according to a cross-sectional observation research by Diwan et al.

**Inflammatory Markers**

An ideal degree of inflammation is necessary for enhancing immunity, and inflammation plays a crucial role in human health. However, there are a number of metabolic illnesses like T2D, obesity, CVD, etc. that are linked to chronic inflammation.

Serum IL-6 levels were shown to be considerably higher in the IFG population compared with the normoglycemic population in an Indian patient research by Upadhyaya et al. (2.00 ± 0.14 pg/mL vs 1.77 ± 0.23 pg/mL).
p = 0.05). The increase was statistically significant when compared between the hyperglycemic and normoglycemic populations (2.84 ± 0.62 pg/mL vs 1.77 ± 0.23 pg/mL, p = 0.01). However, IFG and hyperglycemic groups did not significantly differ from one another.17

A study by Deepa et al. showed that in Asian Indians, inflammatory markers such as IL-6, C-reactive protein, and vascular adhesion molecule 1 increase as the degree of glucose intolerance increases.18

Complications of Prediabetes

The risk of CVD events including myocardial infarction, stroke, or CV death is increased by prediabetes.18 The mean carotid intimal medium thickness (IMT) values in the CURES participants with glucose intolerance were substantially higher than those in the subjects with NGT (NGT 0.69 ± 0.12 mm, IGT 0.75 ± 0.16 mm, newly diagnosed diabetes 0.79 ± 0.19 mm, and known diabetes (0.87 ± 0.24 mm, p = 0.001) (Fig. 6). Even after correcting for age and gender, regression analysis revealed a linear increase in mean IMT values with increasing severity of glucose intolerance.39

The prevalence rates of coronary artery disease (CAD) were 9.1, 14.9, and 21.4% in people with NGT, IGT, and diabetes, respectively, as studied in the Chennai Urban Population Study (CUPS). As compared to NGT, subjects with IGT had a $\frac{3}{5}$% additional risk of CAD (Fig. 7).40

According to the Multi-Ethnic Study of Atherosclerosis (MESA), prediabetes is linked to a prevalence of undiagnosed myocardial infarction that is approximately three times greater than that of NGT (3.5 vs 1.4%). Following multiple risk factor adjustments, those with IFG had higher risks of an undetected myocardial infarction than those with NGT [odds ratio (OR): 1.60 (95% confidence interval (CI): 1.0–2.5); p = 0.048].41

In addition to established T2D, prediabetes has also been associated to retinopathy, neuropathy, and nephropathy, however, these conditions typically manifest in milder forms. Retinopathy is thought to affect 8–12% of adults with prediabetes. Peripheral neuropathy affects 11–25% of those with prediabetes, and neuropathic pain affects 13–21% of them. In a study by Bahar et al., it was discovered that 15.5% of prediabetic participants had microalbuminuria (p = 0.005). The prevalence of diabetic kidney disease in prediabetics ranged from 4.5 to 26.0% across the papers examined by Branda et al.42–45

Management of Prediabetes

Preventing the onset of diabetes and its effects, and reducing the complications of prediabetes itself are the guiding ideas underlying the treatment of prediabetes. It may be possible to understand potential actions that could halt prediabetes from developing into diabetes by raising knowledge and risk classification of people with the condition. It should be attempted in every way to bring prediabetes to a normal glucose condition. The most effective strategy for managing prediabetes is lifestyle modification. Pharmacological treatment comes next, and in cases of severe obesity, bariatric surgery may be an option.46–48

Lifestyle Intervention

Dietary changes, exercise, and quitting smoking and drinking, among other lifestyle interventions, are included. Despite their relatively low BMI and highly insulin-resistant features, the Indian Diabetes Prevention Program (IDPP) intervention research conducted among Asian Indians showed that it was able to prevent diabetes in participants with IGT utilizing lifestyle change. Each subject was advised to change their diet to consume fewer calories overall, fewer refined carbohydrates and fats (20 gm/day), avoid sugar, and consume more fiber-rich foods. They were also encouraged to engage in physical activity for at least 30 minutes each day, including occupational- and transportation-related physical activity. Following a 3-year follow-up, lifestyle changes significantly lower the chance of developing diabetes by 28.5%.48,49

Preventing the development of diabetes also requires a sustained impact of lifestyle changes. The ongoing positive benefits of lifestyle modification have been investigated in the Indian SMS diabetes prevention trial. The study’s findings showed that after a 2-year text messaging period, the effects of lifestyle adjustments in lowering the incidence of diabetes are maintained for an additional 3 years. Text messaging offers the advantages of little disturbance to patients’ lives, convenience of delivery, relatively high retention rates, cheap cost, and continuous benefits in support of lifestyle modifications.50 The relative risk reduction for the incidence of diabetes in major diabetes prevention trials is demonstrated in Figure 8.

The Da Qing Diabetes Prevention Study, the United States DPP, and the Finnish Diabetes Prevention Study (DPS), these three large studies on diabetes prevention have all demonstrated positive effects of lifestyle changes.

The goal of the DPP study was a 6-month weight decrease of more than 7%. Dietary solutions focused on lowering energy consumption and limiting fat intake to 25% of total energy. The subjects were given access to structured meal programs and meal replacement products. A goal of more than 150 minutes per week of moderate-intensity exercise was established, and twice-weekly supervised exercise sessions were made available. Although encouraged, lifestyle physical activity did not count against the 150 minutes per week of physical activity objective (e.g., taking the stairs instead of the elevator).51 It is imperative that physical activity be included in daily life.

After a 3-year follow-up, the study indicated a 58% risk decrease with lifestyle modifications. The study also found that the chance of having diabetes decreased by 16% for every kg of weight lost.52

In the Da Qing trial, which compared diet, exercise, and diet combined with exercise to a control group receiving no therapy, it was discovered that each lifestyle choice decreased the risk of acquiring diabetes by 31–46%.53

The cumulative incidence of T2D in the intervention group in the Finnish DPS research was 11% compared to 23% in the control group after 4 years of active intervention. There was a 58% decrease in the prevalence of diabetes overall.54

A moderate-intensity exercise, just 150 minutes per week of brisk walking, has
been found to enhance insulin sensitivity and reduce belly fat in adolescents and young adults, and people with prediabetes. An exercise program intended to prevent diabetes may also incorporate resistance training in addition to aerobic exercise. It is also recommended to avoid spending too much time sitting down because doing so is linked to somewhat lower postprandial glucose levels.\(^5\)

**Recommendations to prevent T2D in those with prediabetes**
- 6–8 hours daily sleep
- Diet
  - Important factors to control:
    - Attempts to lose 5–10% of body weight if overweight or obese
    - Maintaining the ideal body weight, right from the time of pregnancy, counting and watching calories
    - Refined food grains, juices, and trans fat should be limited
    - Saturated fats and simple sugars should be limited
    - Ample quantity of fiber be included in all the meals
  - Important to individualize the percent of calories from fat and carbohydrate based on clinical goals for each individual
- Regular exercise
  - Brisk walking, swimming, dancing, cycling, or outdoor sports that can give exercise to your body should be done every day
  - Exercise should be performed for 30 minutes 5 days a week
  - It is necessary to walk around generally at least five times every week to keep your mobility
  - Yoga is a promising adjunct along with exercise

**Pharmacological Intervention**

Recommendation: The threshold for the action of pharmacological therapy should be based upon:
- Severity of the hyperglycemia
- Self-perception of severity
- Susceptibility of a person like those subjects who are more susceptible to worsening of dysglycemia, developing diabetes, developing CV complications, or having positive family history should be treated differently than less susceptible patients
- Support from the system like economic support to the patient

**Metformin in Prediabetes**

The management of prediabetes has been researched using a variety of antidiabetic and non-antidiabetic medications, such as anti-obesity medications. The only pharmaceutical now indicated for the prevention or delaying of T2D is metformin. Large, randomized clinical trials have provided evidence that metformin is effective in preventing diabetes, particularly in younger, heavier patients. Additionally, metformin has a strong safety record, with positive benefits on lipid levels and BMI.\(^5\)

It is proposed that the role of metformin in clinical practice can be divided into the following:
- Primary prevention of diabetes when metformin is given from the perspective of diabetes prevention.
- Secondary prevention of prediabetes when metformin is given in prediabetes patients.
- Primordial prevention of vascular ill health when metformin is given to all prediabetes patients to prevent vascular complications.

Thus, to simplify, the following terminologies are suggested to support the role of metformin in the management of prediabetes: glycemic hygiene, vascular hygiene, and vasculometabolic hygiene.

The ADA and IDF recommend individuals with any form of prediabetes (IGT, IFG, or IFG + IGT) to avoid diabetes gradually by changing their lifestyles in addition to taking metformin when their risk is still high. The Diabetes Community Lifestyle Improvement Program (D-CLIP) was a randomized controlled, diabetes prevention trial in overweight/obese Asian Indian adults with IGT, IFG, or IFG + IGT. The U.S. DPP lifestyle recommendation was given to those who were eligible for it for 6 months, along with a step-by-step addition of metformin (500 mg, twice daily), for those who were at the highest risk of developing diabetes after 4 months of follow-up. About 34.9% of control individuals and 25.7% of intervention participants acquired diabetes over the 3-year follow-up period \((p = 0.014)\); the relative risk decrease was 32% (95% CI: 7–50) (Fig. 9).

Although there was variation by type of prediabetes (IFG, 76.5%; IGT, 83.0%; and IFG, 51.3%), the majority of patients (72.0%) needed metformin in addition to a healthy lifestyle. The D-CLIP trial demonstrated that adding metformin gradually to lifestyle counseling is a successful strategy for avoiding or delaying the onset of diabetes in persons with prediabetes.\(^5\)

In the IDPP trial, metformin was effective in reducing the progression rate of IGT to diabetes in the Asian Indian population at a much smaller dose (500 mg/day) as compared to DPP (1700 mg/day). As per ADA 2022, metformin therapy for the prevention of T2D should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m\(^2\), those aged <60 years, and women with prior gestational diabetes mellitus.\(^4\)

**Current Guideline Recommendations on the Use of Metformin in Diabetes Prevention (Table 4)**

- Place of metformin in prediabetes\(^5\)
  - Metformin therapy for the prevention of T2D should be considered in those with prediabetes, especially with
    - BMI >35 kg/m\(^2\)
    - Age 60 years
    - Women with prior gestational diabetes mellitus
  - Metformin may reduce the risk of T2D in subjects with IGT
  - Use metformin 250–850 mg/day where lifestyle intervention is insufficiently effective in reducing body weight and improving glucose tolerance

---

![Fig. 8: Relative risk reduction for incidence of diabetes in major diabetes prevention trials\(^{49,50,57}\)](image-8)

![Fig. 9: Cumulative incidence of diabetes by study arm in the D-CLIP trial from baseline to year 3\(^{57}\)](image-9)
Statement on "Approach and Management of Prediabetes in India"

Other drugs like inhibitors of pancreatic lipase (orlistat), peroxisome proliferator-activated receptor-γ agonists (pioglitazone), α-glucosidase inhibitors (acarbose), meglitinides (nateglinide), and GLP-1 receptor agonists (liraglutide) have also demonstrated benefits.64–66 The results of important landmark trials are summarized in Table 5.

### Surgical Intervention

Another efficient method of treating prediabetes is bariatric surgery. It is recommended for individuals whose BMI is greater than 32.5 kg/m² with comorbidity or greater than 37.5 kg/m² without comorbidity and who are unable to reduce weight under medical supervision. Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, sleeve gastrectomy, and duodenal switch with biliopancreatic diversion are among the frequently performed procedures.46

Bariatric surgery is linked to sustained weight loss and a significant drop in the incidence of diabetes at the 2- and 10-year mark in patients who are morbidly obese. Additionally, the research that is now available suggests that bariatric surgery offers more long-lasting glycemic control than rigorous medication therapy. Additionally, gastric bypass has been shown to reduce visceral fat, including hepatic and pancreatic fat, and to specifically restore pancreatic cell activity, curing the primary abnormalities in diabetes.47

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Summary of recommendations relating to metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICMR (India, 2018)58</td>
<td>People with prediabetes failing to achieve any benefit on lifestyle modifications after 6 months may be initiated on oral anti-diabetic agents (OADs): Metformin in younger individuals with one or more additional risk factors for diabetes regardless of BMI, if overweight/obese and having IFG + IGT or IFG + HbA1c &gt;5.7%, addition of metformin (500 mg, twice daily) after 6 months of follow-up is recommended.</td>
</tr>
<tr>
<td>RSSDI (India, 2020)59</td>
<td>People with prediabetes failing to achieve any benefit on lifestyle modifications after 6 months may be initiated on oral anti-diabetic agents (OADs): Metformin in younger individuals with one or more additional risk factors for diabetes regardless of BMI, if overweight/obese and having IFG + IGT or IFG + HbA1c &gt;5.7%, addition of metformin (500 mg, twice daily) after 6 months of follow-up is recommended.</td>
</tr>
<tr>
<td>ADA (USA 2022)55</td>
<td>Metformin therapy for prevention of T2D should be considered in adults with prediabetes, as typified by the Diabetes Prevention Program, especially those aged 25–59 years with BMI ≥35 kg/m², higher fasting plasma glucose (e.g., ≥110 mg/dL), and higher A1C (e.g., ≥6.0%), and in women with prior gestational diabetes mellitus. Monitor vitamin B12 periodically, especially where anemia or peripheral neuropathy is present.</td>
</tr>
<tr>
<td>ALAD (Latin America, 2011)60</td>
<td>First step is lifestyle management; if not sufficient and/or in additional risk factors, pharmacological treatment (e.g., metformin) is recommended.</td>
</tr>
<tr>
<td>CDA (Canada, 2013)61</td>
<td>Implement intensive lifestyle intervention to prevent T2D; metformin may reduce the risk of T2D in subjects with IGT.</td>
</tr>
<tr>
<td>IDF (Global, 2006)62</td>
<td>Use metformin 250–850 mg/day where lifestyle intervention is insufficiently effective in reducing body weight and improving glucose tolerance.</td>
</tr>
<tr>
<td>Malaysian Endocrine &amp; Metabolic Society (MEMS guidelines 2009)56</td>
<td>Metformin to be considered in patients with additional risk factors or if lifestyle change alone is not sufficient.</td>
</tr>
</tbody>
</table>

### Table 5: Overview of recommendations relating to the use of metformin for the prevention or delay of T2D from selected guidelines with international influence

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP-NIDDM64</td>
<td>Acarbose (100 mg TID) vs placebo</td>
<td>3.3 years</td>
<td>Incidence of T2D was 32% in the therapy group and 42% in the placebo group. Acarbose caused increased flatulence and diarrhea.</td>
</tr>
<tr>
<td>Voglibose for prevention of DM65</td>
<td>Voglibose (0.2 mg TID) vs placebo</td>
<td>48 weeks</td>
<td>5.6% T2D incidence in treatment group vs 12.0% in placebo.</td>
</tr>
<tr>
<td>CANOE trial66</td>
<td>Rosiglitazone (2 mg) + metformin (500 mg) twice daily vs placebo</td>
<td>Median 3.9 years</td>
<td>In patients with IGT, rosiglitazone plus metformin at half the recommended dose were very successful in preventing diabetes and restoring NGT.</td>
</tr>
<tr>
<td>IDPP-267</td>
<td>Pioglitazone (30 mg) vs placebo</td>
<td>3 years</td>
<td>The cumulative incidence of diabetes was 29.8% with pioglitazone and 31.6% with placebo.</td>
</tr>
<tr>
<td>Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication68</td>
<td>15 mg/day ramipril vs placebo and 8 mg/day. Rosiglitazone vs placebo</td>
<td>3 years</td>
<td>Neither ramipril (15.7 vs 16.0%) nor rosiglitazone (15.0 vs 16.8%) decreased the risk of the cardiorenal composite outcome in comparison to placebo. The prevention of the renal component was independently linked to the prevention of diabetes.</td>
</tr>
</tbody>
</table>

Canoe: Canadian Normoglycemia Outcomes Evaluation; IGT: Impaired glucose tolerance; T2D: Type 2 diabetes.

Creating a Holistic Prediabetes Management Plan

The management of prediabetes should be multidimensional. It should not only include lifestyle interventions and pharmacotherapy but also psychological support and education programs.69 A population-based study in urban India reported an increasing prevalence of depression with increasing grades of glucose intolerance which highlights the need for early assessment of psychological factors influencing prediabetes.70 Education programs can be an efficient way of providing education and support to individuals with prediabetes. It could bring significant improvement in knowledge, attitude, and practice. These programs can also help in increasing psychological strength and motivating...
people to change their behavior, and improving quality of life and self-management skills.\(^7^1\)

However, in India, prediabetes education is an underused tool for the prevention of diabetes. Thus, the need of the hour is nationwide prediabetes education and dissemination of knowledge and action plan.

**Role of Telemedicine in Prediabetes**

Successful lifestyle intervention programs require intensive involvement with the patients. An inexpensive style of delivering educational advice about lifestyle modification is mobile phone messaging.\(^7^2\)

In a study from Southeast Asia, researchers looked at whether T2D in Indian Asian men with IGT could be reduced via mobile messaging. According to this study of 8,741 individuals, those who got text messages with advice and encouragement to change their lifestyles had a lower overall incidence of T2D than the controls.\(^7^2\)

The Ministry of Health and Family Welfare, Government of India, has also initiated and executed a mDiabetes program called mHealth Project, a commissioned study to test the feasibility of using mobile technology to reach a large number of people to improve their lifestyle and health-seeking behavior. This evidence positively exhibited the acceptability and feasibility of mHealth in a large population to improve health-seeking behavior by disseminating knowledge regarding diabetes and a healthy lifestyle.\(^7^3\)

Diabetes digital health offers an effective solution for changing the Indian primary health care environment. It interconnects multiple contributors of diabetes care including clinicians, patients, diabetes educators, nurses, and caregivers via smartphones and other communication devices.\(^7^4\)

Telemedicine is one such platform that utilizes information and communication technologies for the delivery of health care services where distance is a very important issue. In India, it has been widely used to create awareness about diabetes prevention among urban and rural populations.\(^7^4\)

An excellent example of how telemedicine may be used effectively to bring diabetes health care and prevention to neglected rural communities in India is the Chunampet Rural Diabetes Prevention Project.\(^7^5\) In Trivandrum, South India, at the Jothydev’s Diabetes Research Center, a telemedicine-based follow-up program known as the Diabetes Tele Management System was first established in 1998. It gives patients and the multidisciplinary diabetes team a live, interactive platform for two-way contact over the phone, the internet, or a secure website at predetermined intervals for an indefinite amount of time.\(^7^6\)

### Bridging the Gap

All general practitioners, physicians, and specialists are aware of prediabetes. However, there seems to be a gap between awareness and adoption of prevention strategies due to a lack of communication. The only solution to bridge the gap is to communicate, share the information, sensitize the stakeholders, and support sensible, rational, and pragmatic action. This is possible through shared decision-making, that is, information should be shared between the person living with diabetes and the physician and caregiver. The purpose of this is to identify reasonable options that best fit and address the situation of the patient. Physicians should be empowered to give the right advice. Peer-to-peer shared decision-making is also needed.

### CONCLUSION

Prediabetes is rising at an alarming rate in the Indian population. Thus, the time is right to develop a proactive approach to prediabetes. Keeping this in view, a consensus was developed on prevalence, risk factors, biomarkers, and interventions for prediabetes. This consensus on early detection and management will help in reducing the progression of prediabetes to diabetes and associated complications. It will also help in increasing awareness for screening and risk stratification of individuals with prediabetes which may guide physicians to understand potential interventions.

### SUMMARY

- Prediabetes is a precursor of T2D.
- The conversion rate from prediabetes to T2D is very high among Asian Indians.
- Individuals with clinical risk factors for prediabetes can be screened using the IDRS screening tool.
- The risk for macrovascular disease starts at the stage of prediabetes as it increases the risk of CVD events, myocardial infarction, stroke, and CV death.
- Prediabetes has been also linked with retinopathy, neuropathy, and nephropathy.
- Biomarkers help in identifying people with a high risk of developing diabetes.
- Identification and aggressive treatment of prediabetes are mandatory.
- Lifestyle intervention is the key to the management of prediabetes.
- Metformin is the only pharmacologic agent recommended for the prevention or postponement of T2D.
- Large, randomized clinical trials have provided evidence that metformin is effective in preventing diabetes, particularly in younger and obese patients.
- The pleiotropic benefits of metformin beyond glycemic control play an important role in the long-term management of dysglycemia.
- Bariatric surgery is another effective way of treating prediabetes, but this is recommended for those with morbid obesity.
- Future requirements:
  - Development of structured prediabetes education programs.
  - Bridging the gap between awareness and adoption of lifestyle and pharmacological treatment when indicated.
- Telemedicine can be an effective tool.

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### AUTHORSHIP

All named authors take the responsibility for the integrity of the work as a whole and have given their approval for this version to be published. The contents published herein represent the views and do not necessarily represent the views or opinions of USV Pvt. Ltd. and/or its affiliates. The details published herein and intended for discrimination of educational, academic, and/or research purposes and are not intended as a substitute for professional medical advice, diagnosis, or treatment.

### COMPLIANCE WITH ETHICS GUIDELINES

This article is based on available literature and previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Yoga and the Need of Its Integration in Modern Medicine

Gouranga Santra*

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Abstract

Introduction: Growing evidences of the health benefits of yoga are available in the literature. But physicians are not aware of it.

Methodology: Databases like PubMed, PubMed Central, Google Scholar, and Scopus are searched for the articles on preventive, therapeutic, and rehabilitation potential of yoga. Scientific evidences available are analyzed and incorporated into the article.

Result: Yoga provides relief from stress, anxiety, depression, and obsessive thoughts. It promotes better sleep. It relieves psychosomatic disorders. Yoga helps to cope with post-traumatic stress disorder (PTSD). Pranayama appears to alter autonomic responses by breath-holding that increases vagal tone and decreases sympathetic discharge and causes relaxation. Yoga increases GABAergic activity that has an anxiolytic effect. Yoga reduces stress-induced cortisol release and reduces hyperglycemia. Yoga reduces seizure frequencies, prevents rapid cognitive decline in Alzheimer’s disease, and helps in poststroke rehabilitation. Reduction of blood pressure and heart rate are seen with yoga. Yoga increases heart rate variability (HRV) and reduces health consequences of allostatic overload. Pranayama improves the vital capacity of lungs. Yoga improves musculoskeletal flexibility and enhances the ability of sustained isotonic muscle contraction. Yoga is proved to be a viable adjunct of drug therapy for depression and anxiety. It is a promising alternative to psychoanalysis and cognitive behavior therapy. Yoga prevents lifestyle disorders.

Conclusion: Yoga is safe and affordable. Integration of yoga in modern medicine needs intensification because of its various health-promoting, disease-preventing, therapeutic, and rehabilitative effects.

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Introduction

Yoga is usually thought of as a form of physical exercise. But it has a deeply meditative and spiritual part also. Mind control with meditation was the target of ancient Indian rishis (sages) who used to practice yoga long back. Postures and breathing exercises help the mind to be still for meditation. Though a part of yoga is physical, in the main it is mental. Health professionals and researchers of modern medicine are not aware of the principles of yoga. It is essential to know the basic principles of yoga before we proceed to know its role in health and disease.

Samkhya philosophy of Kapil Muni described dualism of “Purusha” and “Prakriti.” “Purusha” is the eternal consciousness and “Prakriti” is worldly. Separating “Purusha” from “Prakriti” is the goal of yoga. In the yoga sutra (aphorisms) of Patanjali (Raja yoga) concept of God is brought which exists as perfect consciousness. Yoga is a union with pure consciousness. “Purusha” of Samkhya and yoga darshan (philosophy) correspond to “atman” (soul) of Vedanta. Yoga disconnects “atman” from body and mind. Body, mind, and intellect are parts of “Prakriti.”

Raja yoga has eight limbs (Ashtanga yoga) as described by Patanjali. Yama (universal ethics), niyama (individual ethics), asana (physical postures), pranayama (breath control), pratyahara (control of senses), dharana (concentration), dhyana (meditation), and samadhi (pure consciousness/union of self with the object of meditation). Concentration, meditation, and samadhi are defined in different ways. For concentration on a visual object, the mind is focused on it. For meditation, the focused part is refined and narrowed down. Ultimately only view remains, no sense of effort of viewing presents and this state is called samadhi. In other words, meditation is a deeper thought on a specific aspect of an idea in which the mind is concentrated. Gradually the external senses decrease and ultimately disappear during samadhi. By concentrating on one object other thoughts are removed and in the end, this single thought can also be removed. Then pure consciousness is reached and it is samadhi. This is the union with “atman” or “Purusha” in spirituality.

Yoga is thought to have an immense role in modern medicine but integrative medicine is in a state of infancy. The emerging need is to create awareness among health care professionals about the benefits of yoga as an adjunct to allopathic treatment. By definition, health is not merely the absence of disease but is a complete physical, mental, and social well-being. Yoga helps in the improvement of all these aspects. Collaboration of modern medicine with yoga is the need of time considering the role of yoga in health prevention, promotion, cure, rehabilitation, and palliation.

Because of the popularity of yoga, it is being practiced by individuals throughout the world for perceived health benefits. But a gap exists in awareness of the health benefits of yoga among clinicians and little consideration is given to its integration into conventional health care. A large-scale survey (n = 31,044) in USA revealed that individuals are using yoga to self-manage mental health and musculoskeletal problems. So, it is reasonable for health care professionals to evaluate the clinical evidences of the benefits of yoga and, as appropriate, integrate it into conventional treatment plans.

Purpose of This Review

This review is for highlighting the evidences of health-related benefits of yoga which will dictate the need for intensification of its collaboration with modern medicine.

Methodology

Databases like PubMed, PubMed Central, Google Scholar, and Scopus are searched for articles regarding the preventive, therapeutic, and rehabilitation potential of yoga. Keywords searched are yoga, meditation, pranayama, stress, anxiety, depression, psychiatry, neurology, cardiovascular, musculoskeletal, diabetes, hypertension, cortisol, parasymphathetic, immunology, cancer, etc. Searching was done with combinations of keywords like yoga and stress, yoga and neurology, pranayama and parasympathetic, etc. Only peer-reviewed articles are screened. Recent articles are preferred. Articles only on spiritual aspects are excluded.
are ignored. As the numbers of studies are numerous, individual details and tabulation are not practicable. Only a few articles are cited in the text. Articles with similar content are not cited redundantly.

**Results**

Different studies revealed a promising role of Yoga in modern medicine. Benefits are found in psychiatry, neurology, diabetes, and endocrine, musculoskeletal, and cardiovascular systems.

**Psychology and Psychiatry**

Yoga decreases stress, anxiety, depressive symptoms, and obsessive thoughts. It promotes better sleep and boosts alertness, positive thinking, catharsis, and enthusiasm. Yoga helps in better perception, attention, and cognition. Supporting community in a yoga group eases loneliness and promotes group healing. Yoga helps social adjustment. Yoga helps to relieve psychosomatic disorders which are precipitated by stress like irritable bowel syndrome, functional dyspepsia, anorexia nervosa, and hyperventilation syndrome. Yoga helps to cope with PTSD and enhances resilience. Yoga meditation is an excellent alternative of psychoanalysis and cognitive behavior therapy. Yoga is proved to be a viable alternative or adjunct to antidepressants and anxiolytics. Yoga in prenatal depression can help to avoid or minimize medication-related toxic effects on the fetus. Yoga helps to reduce substance abuse and criminal activities also.

Meditation-induced neurochemical changes like increased parasympathetic activity, decreased locus coeruleus firing of noradrenaline, and increased GABAergic drive produce an anxiolytic effect. The increased levels of endorphins and arginine vasopressin also contribute to the anxiolytic effects. Pranayama by breath-holding increases vagal tone and decreases sympathetic discharge, and helps in relaxation.

Yoga practice improves mood as it increases thalamic gamma-aminobutyric acid (GABA) in major depressive disorders and it also reduces stress-induced cortisol levels which have a neurotoxic effect on the hippocampus. Yoga improves neurocognitive levels which have a neurotoxic effect on the hippocampus. Many psychiatric disorders like depression, anxiety, and PTSD have low parasympathetic activity. Pranayama with controlled breathing is thus beneficial in these disorders.

**Neurological**

Numerous studies have been performed for assessing the role of yoga in neurological disorders. Organic neurological disorders are benefitted by stress reduction, cognitive effect of meditation, and different postures and exercises coping with mobility limitations. Decreased frequency of seizure is found in epileptic patients with drug resistance. It is likely to be due to the reduction of stress, as stress can precipitate a seizure episode. Yoga helps as an additional supplement in refractory epilepsy and improves the quality of life.

Yoga helps stroke prevention and poststroke rehabilitation. It helps in risk reduction of carotid atherosclerosis, hypertension, diabetes, and coronary artery disease which are risk factors for stroke. Specific yoga postures and exercise improve balance, mobility, and quality of life in poststroke patients. Yoga has a positive impact on poststroke depression and anxiety. Yoga improves mobility and reduces fatigueability, depression, and anxiety in multiple sclerosis patients.

Yoga meditation decreases cognitive and memory decline in Alzheimer’s disease. Stress-induced cortisol level has toxic effects on hippocampal cells. Hypercortisolemia in Alzheimer’s disease causes clinical deterioration of the disease. Regular meditation through stress reduction and reduction of serum cortisol and allostatic load benefits Alzheimer’s patients.

Yoga helps in the improvement of fibromyalgia symptoms like pain, fatigue, stiffness, sleep deprivation, and depression. Participants in yoga use to cope pain with adaptive pain strategies like problem-solving, acceptance, relaxation, and activity engagement rather than maladaptive strategies like confrontation, self-isolation, disengagement, and catastrophe.

Yoga helps peripheral nervous system disorders like diabetic neuropathy with an increase in nerve conduction velocity. Yoga improves carpal tunnel syndrome symptoms, enhances grip strength, reduces pain, and improves Phalen’s sign.

Yoga causes functional improvement and enhances the quality of life in Parkinson’s disease. Yoga also improves tension headache, migraine, and spinal cord injury patients.

Morphological and functional neuroimaging studies have shown that meditation usually results in increased gray matter volume in the insula and hippocampus, increased activation of the prefrontal cortex, and enhanced functional connectivity in default neural networks. Changes are maximum in insula indicating its important role across meditative processes. Insula is central in interoceptive body awareness. Higher interoceptive awareness is associated with an increased ability of effective stress coping. Yoga practice is found to reduce right amygdala volume. Amygdala triggers a person’s fight-or-flight response. Right amygdala deals with negative emotions.

**Musculoskeletal**

Yoga enhances muscle strength, tone, muscle mass, and the ability of sustained isometric muscle contraction. Yoga improves the balance and flexibility of joints. Posture helps in stretching and strengthening of muscles. Stretching relieves low back pain. It eases arthritis symptoms, reduces pain, and increases range of motion. Yoga reduces inflammation across a multitude of chronic disorders including heart disease, cancer, and rheumatoid arthritis. Yoga has an immunomodulatory effect due to changes in pro or anti-inflammatory cytokines.

**Cardiovascular**

Yoga causes a reduction in blood pressure and heart rate. Body mass reduction and favorable lipid profile are other benefits of yoga. Yoga practice helps cardiovascular risk factor modification like quitting smoking, alcohol intake, and tobacco chewing. It prevents the development and progression of coronary atherosclerosis. It decreases the number of angina episodes and the need for revascularization. Yoga also helps the regression of lesions in angiography. It helps in the rehabilitation of cardiovascular ailments. Yoga improves functional capacity, quality of life, and cardiovascular outcomes in cardiovascular diseases. Practice of yoga leads to the reduction of oxidative stress. Yoga reduces the need of pharmacological therapies and their side effects.

The transdiagnostic approach of yoga focuses on core processes in pathogenesis rather than discrete diagnoses. Depression, anxiety, PTSD, epilepsy, hypertension, and cardiovascular diseases are all associated with decreased parasympathetic activity and increased sympathetic activity, which are
Yoga and the Need of its Integration in Modern Medicine

common pathways of these disorders. Low parasympathetic activity is also associated with decreased activity in the GABA system in the brain in depression, PTSD, anxiety, and epilepsy. Yoga causes a reduction of stress and restores autonomic balance and increases GABAergic drive. Vagal-GABA theory provides an explanation of the transdiagnostic potential of yoga-based therapy.38

Heart rate variability (time interval between heartbeats) decreases during stress, anxiety, and depression. Parasympathetic stimulation slows the heart rate and increases HRV to restore homeostasis after stress passes. Yoga increases vagal tone and HRV and thus reduces cardiovascular morbidity.39

Allostatics is a biological mechanism with changes in the internal milieu that protects the body from internal and external stresses maintaining homeostasis. It is regulated by the lateral hypothalamus-driven autonomic response, neuroendocrine response (via hypothalamus-pituitary-adrenal axis), and medial basal hypothalamus-related inflammatory response. In presence of chronic stress, persistent overactivity of allostatic system (allostatic load) leads to health disorders. Meditation reduces the allostatic load.40 Epigenetic pathway may have a role in the maintenance of allostatic but needs further research.41

Respiratory Efficacy
Pranayama strengthens respiratory muscles and improves vital capacity in healthy persons, asthmatics, and chronic smokers.

Diabetes Mellitus and Endocrine Effect
Yoga prevents stress-aggravated hyperglycemia. Meditation modulates cortisol levels and reduces blood sugar in diabetic patients. Cortisol homeostasis is important for cognitive and affective functions through cortisol-sensitive brain regions including the hippocampus and prefrontal cortex. Though yoga practice is not of high calorie consuming; asanas, pranayama, and controlled lifestyle help to control body weight.

Others
Antenatal yoga helps in better pregnancy outcomes. Yoga helps in palliation by maintaining physical and mental fitness in oncologic issues and terminal illnesses.42

Surgery
The effectiveness of meditation has been recognized for relieving preoperative anxiety and fear of surgery. Meditation relieves stress, reduces pain perception, and improves sleep, headache, and vomiting during the postoperative recovery phase even after major cardiac surgery like coronary artery bypass grafting.43

Risks of Yoga Practice
In yoga practice, excessive muscle tension or ligament stretch can lead to strain and sprain. But adverse effects are mostly of a mild or transient nature.44

Discussion
The first mention of yoga is seen in the ancient Indian text Rig Veda. It comes from the Sanskrit word “yuj,” which means “union.” Yoga was practiced in northern India even over 5000 years ago. Swami Vivekananda introduced Raja yoga of Patanjali to the West in the 19th century. Hatha yoga is now very popular and commonly followed in the West. The popularity of yoga leads to global recognition and observance of International Yoga Day on 21st June annually since 2015 following its inception in the United Nations general assembly in 2014.

The traditional practice of yoga was focused on personal enlightenment. Recently its physical and mental benefits are also recognized. Three components of yoga with immense health benefits include asana (physical posture), pranayama, and meditation. Spiritual realization may help but is not essential for health benefits. The benefit comes partly from physical effects and mostly from mental relaxation. Yoga causes the removal of stressful thoughts by the concentration of the mind on one idea. The prolonged practice of yoga increases the concentration power of the mind, which is the root cause of academic excellence, newer invention, and greater intuition.

Sages invented different yoga for spiritual realization or for the ways of life to follow, as shown in Table 1. Raja yoga is considered as the science of spirituality.1 It includes physical conditioning and meditation for the realization of perfect awareness. Jnana yoga is the enlightenment of the mind about reality through the study of philosophy and meditation. Realization of oneness of all (Advaita philosophy) relieves the narrowness of the mind and causes relaxation, prevents depression from worldly desires, and brings empathy. Bhakti yoga is the devotional path of dualism. The attitude of love softens emotions and tranquilizes the mind. Bhakti yoga diminishes self-identity and thus reduces stress, anxiety, fear, and worry. Karma yoga is work without attachment. It promotes pleasure in work without thoughts of success and failure. It causes a loss of sense of individuality and thus reduces stress. Hatha yoga improves physical fitness by stretching and balancing. It includes asana, mudra (hand gesture), and pranayama. In Hatha yoga, Pradipika, 30% of texts are related to meditation. Different schools of yoga (Hatha yoga) developed subsequently like Sudarshan Kriya yoga, Kundalini yoga, Iyengar yoga, Bikram yoga, Vinyasa yoga, Jivamukti yoga, etc. The physical intensity and spiritual focus vary across different forms of yoga. Jnana yoga and karma yoga are relatively difficult.

<table>
<thead>
<tr>
<th>Types</th>
<th>Definition/Description</th>
<th>Effects on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raja yoga (Ashtanga yoga)</td>
<td>Based on the yoga philosophy of Patanjali. Eight limbed paths: yama, niyama, asana, pranayama, and pratyahara—these five are external aids, remaining three are internal aids—dharana, dhyana, and samadhi</td>
<td>Body and mind</td>
</tr>
<tr>
<td>Jnana yoga (Jnana &gt; knowledge)</td>
<td>Path of knowledge through the study of philosophy and meditation and ultimate self-realization</td>
<td>Predominantly mind</td>
</tr>
<tr>
<td>Bhakti yoga (Bhakti &gt; devotion)</td>
<td>It is love for love's sake and union through love and devotion, and ultimate self-realization of oneness with everything</td>
<td>Predominantly mind</td>
</tr>
<tr>
<td>Karma yoga (Karma &gt; work)</td>
<td>Path of selfless action without being attached personally to its consequences. Selfless dedication to duty reduces individuality and related stress</td>
<td></td>
</tr>
</tbody>
</table>
Yoga and the Need of its Integration in Modern Medicine

Table 2: Different systems and diseases influenced by yoga

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Systems</th>
<th>Diseases having beneficial role of yoga</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Psychiatric</td>
<td>Stress, anxiety, depression, OCD, PTSD</td>
</tr>
<tr>
<td>2.</td>
<td>Neurological</td>
<td>Stroke, Alzheimer's disease, MS, CTS, diabetic neuropathy, seizure, tension headache</td>
</tr>
<tr>
<td>3.</td>
<td>Musculoskeletal</td>
<td>Fibromyalgia, low back pain, arthritis</td>
</tr>
<tr>
<td>4.</td>
<td>Cardiovascular</td>
<td>Coronary artery disease, atherosclerosis, hypertension</td>
</tr>
<tr>
<td>5.</td>
<td>Diabetes and endocrine</td>
<td>Type 2 diabetes mellitus, hypercortisolemia, obesity</td>
</tr>
<tr>
<td>6.</td>
<td>Respiratory</td>
<td>Asthma, COPD, hyperventilation syndrome</td>
</tr>
<tr>
<td>7.</td>
<td>GI system</td>
<td>Functional dyspepsia, irritable bowel syndrome</td>
</tr>
</tbody>
</table>

CVA, cerebrovascular accident; CVD, cardiovascular disease; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; MS, multiple sclerosis

Table 3: Different roles of yoga

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Roles</th>
<th>Diseases/Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Preventive</td>
<td>Type 2 diabetes mellitus, CVD, CVA</td>
</tr>
<tr>
<td>2.</td>
<td>Promotive</td>
<td>Attention, memory, cognition/muscle strength, tone, balance/vital capacity of lung</td>
</tr>
<tr>
<td>3.</td>
<td>Curative or adjunctive therapy</td>
<td>Stress, anxiety, depression, OCD, seizure, tension headache, PTSD</td>
</tr>
<tr>
<td>4.</td>
<td>Rehabilitation</td>
<td>CVA, Alzheimer's disease, MS, spinal cord injury</td>
</tr>
<tr>
<td>5.</td>
<td>Palliation</td>
<td>Cancer, terminal illness</td>
</tr>
<tr>
<td>6.</td>
<td>Social well-being</td>
<td>Isolation, loneliness, lack of social support, social phobia</td>
</tr>
</tbody>
</table>

CVA, cerebrovascular accident; CVD, cardiovascular disease; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; MS, multiple sclerosis

Yoga is a noninvasive means of managing medical disorders. It is evident from different studies that yoga helps to cope with different medical disorders, especially as an adjunct to conventional treatment, as shown in Table 2. The roles of yoga in health include prevention, promotion, cure, rehabilitation, palliation, and social well-being, as shown in Table 3.

Studies revealed different benefits of yoga across a range of medical disorders. However, socialization, break of routine, placebo effect, and self-efficacy also contribute to the perceived effects of yoga. Numerous studies are done but have inadequacies in design and are of short duration without adequate follow-up. The scarcity of randomized control trials, heterogeneity of yoga interventions, poor control of confounders, and small sample size leads to low-quality evidence. The heterogeneity of yoga practices leads to interpretative confusion. Blinding of outcome assessors, adequate control group, randomization, and larger samples are required for conclusive evidence. Randomized control trials comparing the efficacy of different styles of yoga will be of great value. The spiritual connection may have some negative effects on its compatibility. Physical capabilities are also important for its applicability.

Eight limbs of yoga were developed to be used together and studying them in isolation is difficult. But the tendency is seen for studying the component parts of yoga for health benefits, such as postures, breathing, and meditation. Differences in approaches create problems in the standardization of yoga practices for clinical research. Optimization of intensity and duration of yoga is also essential.

Despite the absence of good scientific evidence and the prevalence of shortcomings of the studies, the practice of yoga seems to be promising. So, the need is to continue research on its health benefits. It is revealed that yoga as an adjunct therapy in an integrated fashion is acceptable to people of India but more awareness of it is required along with the availability of its trained supervision and guidance.45

CONCLUSION

Yoga brings balance to the physical, mental, social, and spiritual dimensions of an individual. It is a highly promising, safe, noninvasive, feasible, and affordable practice applicable at individual and community levels. Considering the health benefits of yoga and its safety and affordability, the intensification of the collaboration of yoga in modern medicine is a high priority.

Key Messages
- By concentrating the mind on a single idea, yoga removes stressful thoughts.
- Yoga is a promising alternative of psychoanalysis and cognitive behavior therapy.
- Asanas (postures) help in stretching and balancing of the musculoskeletal system.
- Pranayama enhances parasympathetic activity and thus helps for relaxation.
- Yoga has transdiagnostic potential and reduces the allostatic load of chronic stress.
- Yoga has a socialization effect.
- Yoga can be used as an adjunct in conventional patient care.

References


Amyloidoma Presenting as Compressive Myelopathy

Vikramsimha Reddy Yerasi, Bimal Prasad Padhy, Radhakrishna Hari

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BACKGROUND

Spinal cord compression is a common clinical problem that one comes across in daily practice. Among nontraumatic causes, compression secondary to degenerative spine disease (cervical spondylosis) or benign/malignant tumors, infective granulomas or abscesses, osteoporotic vertebral collapse, cystic lesions, and congenital or acquired craniovertebral junction anomalies predominate. This problem is sometimes complicated by the fact that some of the infective lesions like tuberculosis, may follow a protracted course mimicking malignancy. Sometimes the clinical finding of a monoparesis involving one limb may mislead the physician in the localization of the lesion as to whether it is upper motor or lower motor type. Such presentation often occurs when the subject is examined during the early course of the illness. When the localization is improper, the subject tends to get over-investigated in an attempt to arrive at a proper diagnosis. Other puzzling initial presenting symptoms are many, for example, isolated bladder symptoms like urgency or hesitancy, gait ataxia alone, or an isolated Lhermitte's phenomenon.

CASE DESCRIPTION

History dates back to nearly 4 years. At the time of initial presentation to our hospital, this 59-year-old lady developed numbness of both feet nearly 1 month before, difficulty in walking about 20 days before, and abdominal numbness which appeared a week back. The numbness of the feet started insidiously ascending from the soles to the dorsum of both feet simultaneously, within 4–5 days. Later she noticed difficulty in walking particularly through narrow passages, sometimes swaying to either side, but there were no falls. The walking had become very much slowed down. She also had difficulty standing with her eyes closed to offer prayers in her puja room.

The numbness of the abdomen was very disturbing for her affecting the upper abdomen more on the left side, making it difficult for her to sleep on the left side. She sought two physician consultations for abdominal numbness, underwent an ultrasound examination of the abdomen, and later computerized tomographic scan of the abdomen which did not reveal any pathology. There was no bladder or bowel symptom, stiffness of the lower limbs, and no cotton wool sensation of the feet. There were no falls, no neck pain, and there were no upper limb and cranial nerve symptoms. She was prescribed B complex injections by her physician which, however, did not improve her symptoms.

There were no comorbidities in the form of diabetes, thyroid disease, hypertension, or any heart disease.

On examination at our facility, she was normally built, with no external evidence of any systemic disease in the form of pallor, lymphadenopathy, edema, or hepatosplenomegaly. Her neurological examination showed normal cranial nerve function and normal motor system examination with flexor plantar responses. There was exteroceptive sensory impairment by 40% below the costal margins bilaterally and also loss of proprioception at the toes. There was gait ataxia on tandem walking and Romberg sign was positive.

The investigatory workup showed a normal hematocrit, erythrocyte sedimentation rate of 25 mm/1st hour, serum creatinine 0.91 mg/dL, random blood glucose 126 mg/dL, thyroid stimulating hormone 2.55 μIU/dL, and serum B12 level of >2000 ng/mL. A nerve conduction study performed on all four limbs was nearly normal except for mild carpal tunnel syndrome at the right wrist. An X-ray of the thoracolumbar spine showed mild scoliosis to the right side associated with spondylotic changes in the form of marginal osteophytes and end plate

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sclerosis (Fig. 1). There was no destruction of the vertebral bodies in the visualized part of the spine at and below D4 vertebra. MRI of the spine showed collapsed D3 vertebral body with prevertebral, paravertebral, and anterior epidural collection from D2 to D4 levels causing cord edema and compression of the spinal cord (Figs 2 and 3). The disk spaces were well preserved both above and below the D3 vertebra. The radiologist opined it as an infective lesion probably of tuberculous etiology, in view of the site, lesion morphology, and the gradually evolving clinical picture.

She was started on a four-drug HRZE antituberculous regimen. In view of the neurological deficit, surgical decompression was planned, but the patient refused surgery and opted for medical treatment. She was lost to follow-up for nearly 2 months and was taking antitubercular medication at a nearby government dispensary (category I HRZE regimen). She returned to our facility after 2 months as there was a new development in form of stiffness of both lower limbs. The gait ataxia was persisting and additionally, she had mild spasticity and hyperreflexia in both lower limbs. There was no change in the MRI appearance of the lesion on repeat scanning. She had also developed mild hypertension and diabetes in the meantime. This time she underwent surgery, D3 laminectomy, and D2–D4 sublaminar hook with rod fixation, and a tissue biopsy specimen from the lesion was sent for histopathological examination. Under the microscope, the tissue showed amorphous eosinophilic material (Fig. 4) suggestive of amyloid (Figs 5 and 6) and foreign body giant cells apart from cartilage and bony trabeculae. There was a dense lymphoplasmacytic infiltrate in the adjacent stroma. There was no caseation or granuloma formation to suggest tuberculous pathology. The pathologist opined that the histology was suggestive of AL amyloidosis and wanted us to consider plasma cell dyscrasias in the differential diagnosis. She was advised further testing with serum protein electrophoresis to confirm the same.

The patient underwent serum protein electrophoresis subsequently. The total serum protein was 7.1 gm/dl. Serum albumen was 3.9 gm/dL. There was a dense paraprotein band at the cathodal end of gamma globulin at the IgG kappa zone. Serum and urinary protein immunofixation electrophoresis, which was also performed as the suspicion of plasma cell dyscrasia was high, suggested IgG kappa monoclonal gammopathy. The serum free light chain assay revealed kappa of 46.25 mg/L (normal: 3.3–19.4), lambda 15.55 mg/L (normal: 5.7–26.3), and the ratio was 2.97 (0.26–1.65).

In view of the possibility of plasmacytoma and the absence of tuberculous disease on histopathology of the tissue from the site, the antituberculous treatment was stopped and she was referred to a cancer institute. At that institute, she underwent bone marrow aspiration and biopsy along with immunohistochemistry, which suggested only reactive lymphocytosis in the marrow; no evidence of plasma cell malignancy. She returned to our hospital 15 days later with a diagnosis of “no myeloma” and with an advice...
to continue antituberculous treatment as tuberculosis disease elsewhere in the body can also produce secondary amyloidosis. She was restarted on antituberculous treatment and continued for another 9 months, but this time only rifampicin + isoniazid was given. We repeated the serum protein electrophoresis and free light chain studies 9 months later, at the end of treatment. The values had shown an improvement. IgG levels and β₂ microglobulin were normal. Serum light chain assay showed kappa of 36.0 mg/L, lambda of 13.0 mg/L, and the kappa:lambda ratio was 2.76.

Rheumatoid factor and antinuclear antibodies were negative and she did not have any symptoms referable to connective tissue disorders.

The patient had completed antituberculous treatment course and is on only vitamin and calcium supplements apart from medicines for diabetes and hypertension. She is able to walk independently and does her daily chores, and is on regular follow-up once in 3–4 months for control of diabetes and hypertension. Her abdominal nummous had decreased significantly but is still present on focused clinical examination. There were no follow-ups in the COVID-19 pandemic season. As the pandemic is getting better, she came twice for review in the past 6 months, and an MRI scan was done to assess the current situation (Fig. 7). The mass had grown anteriorly into posterior mediastinum and was close to the trachea. The medical oncologist reviewed the case and suggested irradiation to the amyloidoma, if she develops any symptoms of compression and respiratory involvement.

**Discussion**

This case poses two important problems. Early identification of myelopathy is sometimes difficult when the presenting symptoms are atypical as was seen in this patient. Secondly, the diagnosis may continue to evolve as the disease unfolds itself, along with extensive and invasive diagnostic (and therapeutic) procedures. Is it AL (amyloid light chain) amyloidosis or is it amyloidosis secondary to tuberculosis of the vertebral body? Both conditions have different lines of treatment.

Though tuberculosis affects the spine as is commonly seen in our country, the exact site of pathology can vary. It commonly affects the intervertebral disk spaces and the adjacent bone, but less commonly it can involve the vertebral body or even the posterior elements initially. In the vertebral body, the anterior subchondral bone is the most common site of initial involvement.

**AL amyloidosis (otherwise called primary amyloidosis)** is the most common form of systemic amyloidosis and is due to the accumulation of amyloid produced by plasma cells in the bone marrow or at extramullary sites. It may be associated with plasma cell dyscrasias. Amyloid is a systemic disease and generally involves tissues like kidney, heart, liver, spleen, tongue, and nerves (but the brain is never involved), and the symptoms depend on the organ affected. Nephrotic syndrome (28%), heart failure (17%), malabsorption syndrome, autonomic neuropathy, or macroglossia are the presenting features. Isolated amyloid deposits (amyloidomas: solitary or multiple) in the spine are uncommon and when they occur, have a predilection for the thoracic spine. When there is no associated myeloproliferative disease or systemic amyloidosis, the prognosis of primary amyloidoma is excellent. Recent treatment strategies have resulted in improved survival and sparing of vital organ function. Sometimes treatment with bortezomib and dexamethasone may be necessary and the surgical option of spine stabilization becomes mandatory when there is a significant neurological deficit as illustrated in the present case and also as described by Terzi et al. Localized forms of AL amyloidosis like carpal tunnel syndrome, non-purpuric skin lesions, genitourinary forms—do not require systemic therapy. They can be managed with local therapy like limited surgery or radiation, or may be left alone if not producing symptoms. Systemic amyloidosis requires treatment on lines similar to multiple myeloma. Combination of corticosteroids and proteasome inhibitors or immunomodulatory drugs or monoclonal antibodies for induction aimed at reducing the burden of the disease, followed by autologous hemopoietic cell transplantation for consolidating the treatment, should be the line of management for symptomatic systemic amyloidosis as per the recent guidelines.

AA (secondary) amyloidosis is a secondary reaction to chronic inflammation such as rheumatoid arthritis, chronic granulomatous infection, or cancer, which generally affects
the kidneys though other structures can also be affected. Effective treatment of the underlying disease can result in amelioration of the symptoms, though such effective treatment may not be possible for many such systemic diseases.

**Conclusions**

Sometimes myelopathies have atypical initial presentations which can mislead the clinician. Follow-up and revision of diagnosis are necessary as and when new symptoms arise and/or when the initial symptoms are not responding to the treatment. Histopathology is the final confirmation of the condition. As can be seen in this patient rare conditions always require tissue diagnosis for taking up a definite line of management and for prognostication. Though localized forms of AL amyloidosis are sometimes found in clinical practice-involving neurological or other systems, initial presentation as an amyloidoma causing spinal cord compression is very rare.

**References**

Upper Thigh Lump: Atypical Presentation of Tuberculosis

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A 54-year-old male, presented with a gradually increasing swelling over the right lateral aspect of the thigh of size 30 × 20 cm over a 3 months duration (Fig. 1). There was no history of fever, weight loss, decreased appetite, back pain, hip pain, or pain at any other site. There was no history of trauma. The patient was diagnosed with HIV-2 and was taking some antiretroviral therapy for 3 years and was recently put on dolutegravir/lamivudine/tenofovir. The swelling was non-tender, soft in consistency with smooth borders, and had no fluctuation. Other general and systemic examinations were normal. Biochemistry, complete blood count, X-ray chest, and abdominal sonography were normal. The last CD4 count was 337 and the viral load was less than 100 copies/mL in May 2019.

In view of asymptomatic swelling over the lateral aspect of the right thigh, clinical diagnoses like lipoma, spontaneous hematoma, hemangioma, or other benign tumors were entertained. Fine needle aspiration cytology of swelling was asked but the patient was lost to follow-up. He visited us after 2 months with a CT scan of the thigh and abdomen (Fig. 2). It shows spondylitis involving the L3-L4 vertebra and right psoas abscess extending to the right thigh in the subcutaneous plane (Fig. 2).

Orthopedic surgeon asked for MRI spine (Fig. 3) which shows tuberculous spine with minimal collection (Fig. 4), hence advised for conservative management.

One liter of thick pus was drained from the thigh abscess. GeneXpert report of pus shows rifampicin-sensitive acid-fast bacilli so an antituberculous drug (HRZE) was started.

Discussion

There are very few case reports in the literature for cold abscesses in the thigh. Agrawal and Jain from Jabalpur reported a primary cold abscess in the hip in an 11-month-old child. de Araújo et al. discussed various presentations of tuberculosis of the spine but abscess trickling to the thigh is not described. Cold abscess was not entertained before CT/MRI report by any physician. This makes a case interesting and an eye-opener for clinicians. In case of an immune-compromised patient, tuberculosis may always be kept in mind as a differential diagnosis.

References


Fig. 1: Upper thigh lump

Fig. 2: CT abdomen-pelvis s/o psoas abscess

Fig. 3: MRI spine s/o tuberculous spine

Fig. 4: One liter of thick pus drained

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A 14-year-old girl presented with progressive thickening of skin involving the entire body over the last 2 years. There was a past history of Raynaud’s phenomenon. Binding down of skin was present over the body with reduced chest expansion. There was diffuse hyperpigmentation with mask-like face, ironing of the forehead skin, positive Ingram's sign, microstomia, dental overcrowding, and sclerodactyly with atrophic changes (Figs 1 and 2). The hair and mucosa were normal. Anti-nuclear antibody and antitopoisomerase-1 (anti-Scl-70) titers were strongly positive. X-ray of the hand showed acro-osteolysis in all fingers (Fig. 3). CT chest showed minimal subpleural fibrosis in the anterior segment of the bilateral upper lobe. Skin biopsy was suggestive of systemic sclerosis (Fig. 4). Proximal diffuse sclerosis, sclerodactyly, restrictive lung disease, raised anti-SCL-70 titer, and histopathology favored the diagnosis of juvenile systemic sclerosis (JSS) as per the preliminary classification criteria. She was started on cyclophosphamide, mycophenolate mofetil, hydroxychloroquine, and is currently on treatment with gradual improvement.

Scleroderma is a chronic multisystem connective tissue disease of unknown etiology and can present as localized scleroderma or systemic sclerosis. The annual incidence of JSS is 1/million and less than 5% are present under 16 years. Differential diagnoses include systemic lupus erythematosus, polymyositis, and dermatomyositis. These should be differentiated by their particular clinical features, skin biopsy, and specific antibody positivity. Treatment includes antifibrotic medication, immunosuppressive agents, and vasodilators. Autologous hemopoietic stem cell transplantation can be considered for nonresponders. The mortality rate at 5 years is 6–15% and commonly occurs due to involvement of cardiac, renal, and pulmonary system.

Fig. 1: Mask-like face, loss of facial lines, thin lips, sparse hair, breaking of nose, ironing of the forehead skin, positive Ingram's sign (inability of downward retraction of the lower eyelid), and dental abnormality with reduced mouth opening

Fig. 2: Tightening and thickening of the skin of bilateral hands, sclerodactyly with atrophic changes in distal phalanges of all fingers

**Acknowledgments**

We would like to acknowledge Dr Vishwanath (pediatric pulmonologist), Dr Khulood (pediatric rheumatologist), Dr Farzana (dermatologist) for helping and giving their valuable inputs in the management of the case. We would like to thank our Medical Director for giving us permission to publish the manuscript.

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Juvenile Systemic Sclerosis: A Rare Phenomenon

REFERENCES


Fig. 3: X-ray of the right hand showing acro-osteolysis (resorption of the distal phalanges) in all fingers with periarticular osteoporosis

Fig. 4: Skin biopsy suggestive of systemic sclerosis
Frederick Sanger: Winner of Two Nobel Prizes

J V Pai-Dhungat

Frederick Sanger (1918–2013) an English molecular biologist was born in Gloucestershire, England. He graduated from Cambridge in 1939 and earned his PhD in biochemistry in 1943. Sanger’s interest always remained in finding out the exact structure of the amino acid chain in a protein molecule. From 1951, until his retirement in 1983, he remained a researcher for the MRC.

Sanger joined biochemist Albert Chibnall’s team of scientists who were studying the amino groups of the pancreatic hormone insulin, which was isolated earlier, but needed to be used more effectively to treat diabetes.

After 8 years of hard work, Sanger succeeded in elucidating a complete structure of bovine insulin in 1954. It was a stunning achievement. Using the new technique of paper chromatography by Martin and Synge he was able to sequence the amino acids of each chain. Sanger deduced that the complete structure was two chains—one of a phenylalanine chain (21 amino acids) and the other a glycine chain (30 amino acids) held together by two sulfur atoms. He received the 1958 Nobel Prize in Chemistry for determining the structure of the insulin molecule. His work made it possible for other researchers to identify various other important molecules.

Sanger pioneered procedures for sequencing radioactive labeled proteins between 1956 and 1962. He moved to the MRC Laboratory of Molecular Biology in Cambridge in 1958.

Sanger’s interest switched to nucleic acids and he began RNA sequencing using radioactive methods, and the first RNA was fully sequenced in 1967 with t-RNA being successfully sequenced by 1970, Sanger was ready to tackle DNA sequencing. He devised a new DNA sequencing methodology, using acrylamide gel by “read off” methods for sequencing single-stranded DNA of a bacteriophage. Sanger’s group had derived most of the DNA sequence of bacteriophage, the first complete genome to be sequenced; consisting of 5375 nucleotides in 1977. He was awarded the Nobel Prize in Chemistry second time in 1980, this time sharing it with Paul Berg and Walter Gilbert for determining the amino acid sequences of DNA.

He rejected knighthood as he did not want to be addressed as “Sir” but, later accepted the order of Merit in 1986. Frederick Sanger died in 2013 aged 83 years.

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The Big picture of diabetes management across a broad patient population

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Cutaneous Manifestations in Neuroarsenosis

Priyanka Vikas Kashyap¹, Anshul Singh²
¹Assistant Professor; ²Senior Resident, Department of Neurology, All India Institute of Medical Sciences (AIIMS), Bhopal, Madhya Pradesh, India

A 34-year-old male with a background history of psoriasis on intermittent Ayurvedic medicines since the last 3 years, last intake was 3.5 months due to a flare of skin lesions, the patient’s skin lesions responded and he discontinued after 1.5 months of intake. He developed insidious onset progressive quadriparesis since the last 2 months with features of motor, sensory, and autonomic involvement. On examination, the patient had a white transverse line over the finger and toe nails which was non-blanching, and no depression was noted over the nails probably the Mees’ lines (Figs 1A and B), skin examination revealed multiple small hypopigmented spots over the trunk region probably raindrop pigmentation (Fig. 2). Motor system examination showed evidence of peripheral neuropathy. The toxin screen showed an elevated level of serum arsenic 75 μg/L (normal range <35), the patient was not affordable for urine arsenic level hence deferred. The patient was treated symptomatically as his weakness was improving. The patient was explained regarding possible etiology being Ayurvedic medication and to avoid it in the future.

The differential of Mees’ lines includes toxicity due to arsenic¹ and thallium, heart failure,² and renal failure.

Skin and nail inspection is crucial in neurological examination and good knowledge on different patterns of nail and skin changes³ clench the diagnosis without costly investigations. Raindrop appearance in arsenosis may be an indicator of skin malignancy like Bowen’s disease, squamous cell carcinoma, and basal cell carcinoma. Arsenic is a carcinogen and long-duration exposure is more related to it.

REFERENCES

Fallacies of Mantoux in the Diagnosis of Latent Tuberculosis

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Dear Editor,

Prevention of tuberculosis (TB) disease by treatment of latent tuberculosis infection (LTBI) is a crucial constituent of the National Strategic Plan for Tuberculosis Elimination 2017–2025 in India by 2025.

The Mantoux test dates back to 1890 when it was first demonstrated by Robert Koch. Charles Mantoux, in 1912, first described the intradermal technique as it is used today.¹ What is amusing is that even after a hundred years of research, deliberations, and scientific advancements, Mantoux is still the cornerstone of diagnosing LTBI, especially in developing countries like India, despite all its fallacies.

The authors list down seven points as to why should India look beyond Mantoux as a diagnosing test for LTBI and invest in the development of a test which is (importantly) affordable apart from being accurate.

- The standardized dose of Mantoux in India is 5 tuberculin units (TU) (0.1 mL). PPD RT 23 with Tween 80 of strength 1 and 2 TU are standardized tuberculins available, any deviation from these standard tuberculins (many of which are available in the market) leads to an over/underestimation of the size of the induration and hence a faulty interpretation.

- The correct technique of injection produces a pale, discrete elevation of the skin (a wheal) 6–10 mm in diameter at the site of the inoculation.² In India, this test is almost always administered by laboratory technicians whose style of inoculation of the intradermal injection can vastly influence the results of the test.

- The results are interpreted 48–72 hours after the administration of the test dose, which requires the patient to return back to the laboratory. Here, the onus lies on the follow-up by the patient which is frequently not made.

- The interpretation of the test is dependent on the presence or absence of induration (not erythema) which is determined by palpation (not inspection). For the sake of standardization, the diameter of the induration is measured in millimeters transversely to the long axis of the forearm.³ A failure to read the results in the specified form can lead to an over/underestimation of the size of the induration and hence a faulty interpretation.

- There is no uniformity as far as the size of the induration required for a positive test result is concerned. Different sizes are indicated for different patient populations leading to confusion and fallacies (Table 1).⁴

- The sensitivity and specificity of this investigation are low which gives rise
Correspondence

Table 1: Cut-offs for a positive TST for different patient populations

<table>
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<th>TST reaction</th>
<th>&gt;5 mm</th>
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<td>Category</td>
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- People living with HIV
- Household contacts of a case of TB
- Patients with chest radiographic opacities consistent with old healed infection
- Recipients of organ transplant
- Immunosuppression of any other cause
- People who have recently (less than 5 years) migrated from countries with a high prevalence of TB
- People addicted to the use of injectable drugs
- People either living in or employed at centers which have a high risk of transmission of TB (e.g., prisons, nursing homes, shelters for the homeless and for the aged, and hospitals)
- Personnel working in laboratories handling mycobacterium
- Children aged less than 4 years or in contact with adults in high-risk categories
- People who do not have any known risk factors for TB infection

TST, tuberculin skin testing

Anaphylaxis to Commonly Used Drug Oral Pantoprazole

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1Senior Professor and Unit Head; 2–4Resident 2nd Year, Department of Medicine, Government Medical College, Kota, Rajasthan, India

A 64-year-old nonalcoholic nonsmoker Hindu housewife female came to the emergency department with main complaints of knee and shoulder joint pain. The patient was attended by an orthopedic resident with a provisional diagnosis of osteoarthritis and received intramuscular injection diclofenac sodium 75 mg. The patient also took an oral capsule of pantoprazole 40 mg. She was under observation in emergency when she suddenly became restless and developed rashes and itching all over her body associated with profuse sweating, dizziness, and shortness of breath. She was attended by a medicine resident in the emergency department and on examination, her pulse rate was 120/min low in volume regular rhythm extremities cold, SBP was 80 mm Hg, respiratory rate was 22/min, SpO2 was 80% room air, and random blood sugar was 122 mg/dL. She was conscious-oriented, irritable, and had generalized erythema over her body. No pallor, cyanosis, icterus, clubbing or lymphadenopathy was present. Other systemic examination within normal limits (WNL). ECG showed sinus tachycardia only. The patient was diagnosed with drug-induced anaphylaxis (DIA) either due to oral pantoprazole or intramuscular diclofenac and managed with high flow oxygen at a rate of 10 L/min, intravenous normal saline drip, intramuscular 0.5 mL 1:1000 dilution (1 mg/mL) adrenaline, 200 mg of intravenous hydrocortisone sodium succinate. She became comfortable after 20–30 minutes with relief in symptoms of itching, rashes, and shortness of breath and her vitals got stable with a blood pressure of 120/80, pulse rate of 86 bpm good volume, SpO2 of 98% room air, respiratory rate of 18/min, and was shifted to general medicine ward.

On detailed history, the patient told that she had two episodes of itching and rashes after ingestion of an oral capsule of pantoprazole, first episode occurred 3-year back when the patient developed urticaria and dizziness 20 minutes after the dose without breathlessness and sweating at that time, her husband gave oral tab levocetirizine 10 mg with relief of symptoms after an hour at home. After this episode, she never took this medicine in the last 3 years, though she was taking tab diclofenac/etoricoxib off and on for joint pains during this period. The second episode occurred 10 days back when the patient went to the dispensary and ignorantly took this medicine as prescribed, patient developed itching, rashes, and dizziness which got relieved by oral levocetirizine within 2 hours. In her family, her husband was aware of the allergic reaction to oral pantoprazole capsule but this time the patient was brought...
Correspondence

Laboratory parameters were Hb 12.5 gm/dL, TLC 11,700/cumm, DLC 81/14/4/0.9/0.1, PLT 363, blood urea 32 mg/dL, creatinine 0.8 mg/dL, total bilirubin 1.2 mg/dL, direct 0.5 mg/dL, indirect 0.7 mg/dL, SGOT 34 IU/L, SGPT 45 IU/L, ALP 86 U/L, CRP <6, and RA factor was nonreactive. X-ray of the chest and ultrasonography of the whole abdomen were WNL.

To indirectly confirm pantoprazole anaphylaxis, we ruled out diclofenac hypersensitivity which is more common. The patient was given tablet diclofenac in the ward with all emergency measures ready at hand and the patient did not show any untoward effect. With this, the patient was discharged the next day in vitally stable condition with the final diagnosis of anaphylactic hypersensitivity to pantoprazole.

**Discussion**

Proton pump inhibitors (PPIs) are commonly co-prescribed and overused agents not only by treating doctors but also by patients themselves many times in apprehension. Though PPIs are believed to be very safe, sober, and effective drugs they too can have some minor side effects such as nausea, abdominal pain, constipation, diarrhea, headache, and skin rashes. Sometimes even an innocent drug can show a dreaded reaction in an individual. Anaphylactic shock is such rare adverse reaction of PPI.

Gupta et al reported two cases of anaphylaxis due to oral pantoprazole 40 mg in 38 and 32 years old females with periorbital edema, urticaria, pruritus, nausea, vomiting, and difficulty in breathing 20–30 minutes after ingestion. Alolabi and Liem demonstrated pantoprazole hypersensitivity in a 39-year-old female who had symptoms of angioedema, pruritus, pyrexia, vomiting, and diarrhea after drug intake by epicutaneous testing of pantoprazole which yielded a positive reaction with a wheal diameter of 10 mm. Kakode and Kakode also noted adverse drug reaction by pantoprazole three times in a patient, out of which initial two episodes were due to oral pantoprazole leading to rashes and itching 2 months apart which were relieved by antihistaminic drugs, while the third episode occurred 3 months later to intravenous pantoprazole leading to anaphylactic shock.

Causality assessment of adverse drug reaction in our patient was done by Naranjo’s algorithm for causality assessment, which indicated it to be a “probable” side effect with a score of +8.

Antibiotics followed by analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) and others are the common culprit drugs for DIA. Diclofenac sodium has lower rates of adverse reactions than any of the other comparative NSAIDs. In our case also a clear history of reaction to oral pantoprazole and witnessing no reaction to diclofenac salt in the ward confirms the anaphylactic reaction to be because of pantoprazole only though we did not do cutaneous testing as the husband of the patient did not give consent and it was not worth of testing this at risk of life.

**Conclusion**

Drug-induced anaphylaxis is an unanticipated severe allergic reaction. To negate this, the patient and their relatives should be educated and made aware to avoid further exposure to such noxious drugs. Interrogation of drug allergy should be a routine in the history taking of every patient. Furthermore, proper documentation of allergic reactions to a drug should be highlighted in their medical papers to avoid catastrophic events.

**References**

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<td>Olmesartan</td>
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