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Teleneurology for Physicians

Satish Khadilkar¹*, Mehul Desai², Darshan Pandya³

Introduction

World Health Organization defines telemedicine as “the provision of health services, where distance is a critical factor, by all healthcare professionals using information and communication technologies to exchange valid information for the diagnosis, treatment, and prevention of diseases and injuries, research and evaluation, and continuing education of healthcare providers, all in the interests of advancing the health of individuals and their communities.”¹⁻⁵ Although telemedicine has been available since the late 18th century, the concept of teleneurology gained momentum with the emergence of the COVID-19 pandemic, with most countries adopting the mandatory practice of social distancing and interruption of public transportation facilities.⁶ In the case of teleneurology, even before the pandemic, the scarcity of tissue plasminogen activator (tPA)—enabled hospital programs had already propelled the development of telesroke networks utilizing Internet technology in the late 1990s and early 2000s.⁷ Closer to home, Bahrani et al. working at AIIMS, New Delhi, had published the results of a randomized control trial in 2017, impressing the potential of telemedicine. Their investigation documented that for outpatients with epilepsy, telephone review was superior to face-to-face review in terms of costs and the number of patients retained in follow-up.⁸,⁹ Although telemedicine has been used for many years in India, the government of India released detailed guidelines for the use of telemedicine in March 2020 to provide healthcare professionals with precise do’s and don’ts of teleconsulting, a detailed discussion of which is beyond the scope of this review.

In countries like India, where there is a shortage of trained medical professionals, telemedicine provides a medium for expert neurological services to remote and underserved areas and reduces the disparity between availability and the need for neurological care.⁶⁻¹⁰ The use of telemedicine in the field of neurology, “teleneurology,” has been gaining impetus in the last few years, especially in the management of conditions such as stroke, epilepsy, Parkinson’s disease, etc., and its scope continues to expand.¹⁰⁻¹⁴

Ways of Delivering Teleneurology

Teleneurology can be used in various forms (Flowchart 1), such as real-time video conferencing, which has been increasingly used with features of media such as WhatsApp or Zoom calling since the emergence of the Internet and the COVID pandemic. Other forms include asynchronous store and forward technology or remote monitoring.²¹⁻²⁰

Telemedicine can be used in neurology for the following purposes.

• Consultations
• Rehabilitation
• Education
• Research

Teleconsultations

The most widespread use, as expected, is for teleconsultations for conditions such as stroke, epilepsy, movement disorders, headache, etc. With experience, telemedicine can provide adequate information for certain areas of neurological assessments like history taking, higher mental function and cranial nerves examinations, power testing, cerebellar and gait examinations, etc.

Flowchart 1: Types of teleneurology
As of 2022, the number of neurologists in India is not enough when faced with the vast population of India. Moreover, a large proportion of them is in metropolitan cities, leaving further smaller numbers to cater to the rural and semi-urban settings. Therefore, a significant proportion of neurological diseases in India are treated by internal medicine physicians and family practitioners.57,58 There is a continuing need for interaction between neurologists and physicians for the exchange of knowledge regarding neurological diseases and therapies. Tele-education provides these avenues, and it is noteworthy that the Indian Association of Neurology, along with the Association of Physicians of India (API), in a joint venture, are currently offering a webinar series that has attracted hundreds of physicians from all over India. Similarly, API and the Indian College of Physicians organize webinar series-educational programs to update physicians all over India by experts in different fields and provide certificate/credit hours. Such joint ventures can be conducted in the virtual world with great ease and with wide benefits to various specialties.

**Flowchart 2: Overview of virtual neurological examination**

Tele-rehabilitation

Rehabilitation is an important part of chronic neurological care, and its role in the totality of the outcomes is being increasingly recognized. Telemedicine provides us with unique opportunities to provide rehabilitation services that are often an integral part of recovery from a neurological disease.51 Telephysiotherapy can be used to instruct caregivers or family members on how to perform physiotherapy in a systematic way and to promote mobilization.52,53 Tele-speech therapy is especially beneficial for poststroke aphasia. Teleoccupational therapy with music therapy, entertainment, and patient meetings with the support group and each other can be very uplifting and encouraging.54,55 Garg and Dhamija, in their study of telerehabilitation among people with Parkinson's disease in India, found barriers at the level of recruitment, adherence issues, and maintenance in implementing a telerehabilitation program.47,56

**Tele-education**

As of 2022, the number of neurologists in India is not enough when faced with the vast population of India. Moreover, a large proportion of them is in metropolitan cities, leaving further smaller numbers to cater to the rural and semi-urban settings. Therefore, a significant proportion of neurological diseases in India are treated by internal medicine physicians and family practitioners. There is a continuing need for interaction between neurologists and physicians for the exchange of knowledge regarding neurological diseases and therapies. Tele-education provides these avenues, and it is noteworthy that the Indian Association of Neurology, along with the Association of Physicians of India (API), in a joint venture, are currently offering a webinar series that has attracted hundreds of physicians from all over India. Similarly, API and the Indian College of Physicians organize webinar series-educational programs to update physicians all over India by experts in different fields and provide certificate/credit hours. Such joint ventures can be conducted in the virtual world with great ease and with wide benefits to various specialties.
Telereaseh
At this point in time, the potential for multicentric work using telemedicine has not been well utilized in India. One of the strengths of the Indian situation is the high numbers of afflicted individuals, and studying them cohesively on uniform platforms can provide much-researched information about therapies, their cost-effectiveness, long-term quality of life, and other related issues. Telereaseh can be used to enhance awareness and applicability of research methodology and reviews of the literature for new and experienced researchers. Online ethics committee meetings can be held for the approval of research topics. Data collection, either telephonically or through video calls via different media, can form the substrate for research projects.59,60 We do hope that some of these get utilized by Indian physicians (Fig. 1).

Practice Points and Pitfalls
From the above discussion, it can be surmised that teleneurology can be utilized by physicians and family practitioners in their daily work as enumerated below61 (Fig. 2).

- To obtain an opinion from a neurologist to guide ongoing treatment.
- Help to arrive at decisions for acute situations, for example, stroke thrombolysis.
- For physicians to follow up on their chronic neurology patients, for example, epilepsy and Parkinson’s disease.
- For physiotherapists to guide and monitor progress.
- Conferences among multiple consultants to formulate action plans.
- Updating one’s knowledge base.5,62

In the future, the scope will extend to telereaseh as well. However, there are some cautions that need to be mentioned. An in-person examination can unearth much more details than is feasible in the online mode, and some neurological cases require that type of examination for diagnostic purposes. This is particularly true for some parts of the neurological examination such as the sensory examination, tendon reflexes, and optic fundi.63 In some instances, the human touch works well for the interaction. A sector of the population cannot relate to or navigate through an electronic consultation. All these factors should also be considered in the broad view of the telesystem.64

![Fig. 1: Tools for telereaseh](image)

![Fig. 2: Practical points and pitfalls of telemedicine](image)
Teleneurology for Physicians

CONCLUSIONS
Teleneurology has been an integral part of the care and clinical practice of neurological patients in recent times. Although teleneurology is being used in the service sector and for updating one’s knowledge base, it is still in its early days. The potential is enormous. Telemedicine can be used by clinicians for tele-education and teleresearch and by patients to obtain teleconsultation or seek information. It is particularly useful in the guidance for acute stroke management, especially with regard to thrombosis. Timely follow-up can be ensured, which can improve compliance and adherence. Teleradiology and telepathology can be used for remote interpretation and second-expert opinion in an out-of-the-box scenario. Despite all this, a comprehensive neurological examination is not possible with teleconsulting, which can lead to difficulties in diagnosis and management, particularly in complex cases. It can never replace in-person consultation as well as all medical interventions; it carries both risks and benefits, requiring randomized controlled trials to compare its efficacy and cost-effectiveness with conventional methods.65

REFERENCES
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Liver Involvement in Individuals with Obesity: A Cross-sectional Study from Western India

Minal Shastri1, Vaishnavi M Rathod2*, Darshankumar M Raval3, Shahin Khan4, Shashwat Mallik5, Dipakkumar L Solanki6

Received: 27 July 2022; Accepted: 23 September 2022

Abstract

Background: Obesity is a largely neglected health problem in developing countries which leads to additional morbidities including nonalcoholic fatty liver disease (NAFLD), one of the most important causes of chronic liver disease. Central obesity is intricately related to the pathogenesis of the NAFLD, which over time could result in a fibrogenic response and end-stage liver disease. We have attempted to study the association of various risk factors and laboratory investigations with the incidence of liver involvement in obese individuals.

Materials and methods: A cross-sectional study of 210 patients was carried out in a tertiary care center in Western India. Patients above 18 years of age with either general or abdominal obesity were included and their history taking and general and systemic examination was done along with laboratory investigations and ultrasonography for visualization any liver involvement.

Results: Age >50 years, female gender, postmenopausal state, sedentary lifestyle, high body mass index (BMI), waist circumference (WC), and neck circumference were all risk factors for liver involvement in obese individuals. Raised C-reactive protein (CRP), serum glutamic-oxaloacetic transaminase (SGOT), triglycerides, low density lipoprotein (LDL), cholesterol, fasting blood sugar (FBS), 2-hour postprandial blood sugar (PP2BS), and low high density lipoprotein (HDL), serum protein, and albumin were significantly associated with liver disease. Patients having high NAFLD fibrosis and BMI, aminotransferase ratio and diabetes (BARD) scores, or Metabolic syndrome (MS) was at a higher risk for liver disease.

Conclusion: Advancing age, postmenopausal females, and lack of physical activity are risk factors for liver disease in obesity. Raised CRP and SGOT along with impaired lipid profile and glycemic control could be used as markers for fatty liver in obese individuals. MS greatly increases the risk of liver involvement in obese individuals.

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Introduction

Overweight and obesity are malnutrition states which harm the health of a person due to abnormal or excessive fat accumulation. People of all ages and socioeconomic statuses are affected by obesity, which is a complex condition influenced by a myriad of social and psychological factors. The worldwide prevalence of obesity has tripled in four decades resulting in an obese population of over 650 million and is associated with more deaths worldwide than in underweight states. Initially restricted to industrialized societies, the obesity epidemic is now widespread even in developing countries which account for about 115 million obese individuals, and yet, it is one of the most neglected health problems. Obesity is more commonly seen in females (15%) as compared to males (11%).

A higher prevalence in higher socioeconomic classes is seen, probably due to unhealthy lifestyles, in contrast to lower socioeconomic classes who are often involved in labor work. Obesity is now recognized as a separate disease on its own which can result in or further aggravate several conditions including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cardiovascular disease, liver dysfunction, respiratory and musculoskeletal disorders, subfertility, psychosocial problems, and certain types of cancer.

Nonalcoholic fatty liver disease (NAFLD) is a commonly encountered health condition that results in chronic liver disease. Due to a rapid increase in the prevalence of obesity, NAFLD is emerging as the most important cause of chronic liver disease in nonalcoholics. In India, prevalence of NAFLD is between 5 and 28%, of which 15–20% is contributed by the obese population. Steatosis is a hallmark feature of NAFLD, which is a result of the imbalance in the rate of fatty acid uptake, de novo fatty acid synthesis, and the rate of oxidation and export of fatty acids (triglycerides and very LDL) from the liver. Sometimes steatosis leads to lipotoxicity, which causes apoptosis, necrosis, generation of oxidative stress, and inflammation which over the long term, activates a fibrogenic response that eventually results in end-stage liver disease. There is a primary association of adipose tissue, namely central obesity, with increased visceral fat and the pathogenesis of NAFLD, as it has more lipolytic potential as compared to subcutaneous fat.

There is a 20% increase in hepatocellular fat with a 1% increase in subcutaneous fat while hepatocellular fat doubles with a 1% increase in intra-abdominal adipose tissue. BMI is a simple index used to classify the nutritional status in adults. BMI and WC are positively associated with the progression of hepatic steatosis. The waist-to-hip ratio (WHR) and waist-to-height ratio are considered to be better indicators of obesity because they do not vary with the changes in body composition due to growth and development and the nonrequirement of population-specific reference tables.

The presence of NAFLD is closely associated with MS and NAFLD is also a strong determinant of the future development of MS. MS is a co-occurrence of several known cardiovascular risk factors including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. 90% of individuals with NAFLD have been found to have at least one risk factor of MS, and 33% have all the features of MS. This study attempts to assess the prevalence and risk factors of liver involvement in obese individuals in and the subgroup of individuals with MS and the severity of liver involvement. Focusing on identifying liver disease in obese patients in the early stages will help us to take measures to slow down disease progression, and reduce morbidity and mortality as there is no definitive treatment for this condition.

Materials and Methods

This was an observational cross-sectional study over a duration of 1 year (2020–2021) carried out in SSG Hospital, Vadodara after taking due approval and clearance from the Scientific Review Committee and Institutional Scientific Review Committee and Institutional Review Board.

*Corresponding Author

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Liver Involvement in Obese Individuals

Ethics Committee for Human Research. A total of 210 patients with obesity (Indian criteria) including those presenting to the General Medicine outpatient department and those admitted to the wards were included. The patients were required to be above 18 years of age with general obesity (BMI) ≥25 kg/m² for both genders; class I- 25–29.9 kg/m², class II- 30–34.9 kg/m², class III- 35–39.9 kg/m², extreme obesity ≥40 kg/m²) or abdominal obesity (WC >90 cm in males and >88.5 cm in females, or WHR > 0.95 in males and >0.80 in females, or neck circumference ≥35.5 cm in males and ≥32 cm in females or the presence of ear lobe crease). Individuals <18 years of age, those with alcoholic liver disease, chronic alcoholics who drink more than the recommended one (for women) or two (for men) drinks a day, or more than seven (for women) or 14 (for men) drinks in a week, those with hepatitis B/hepatitis C/active hepatitis A or E infection, HIV infection, autoimmune or drug-induced hepatitis, genetic liver disease, diabetes mellitus, hypertension or pregnant/postpartum females were excluded from the study.

History taking, thorough general physical examination and systemic examination, were done including demographic data, personal history, drug history, anthropometry (weight, height, WC, hip circumference, neck circumference, ear lobe crease), icterus, pedal edema, and per abdominal examination to assess whether the liver is palpable. Investigations including complete blood count (CBC), differential count, ESR, CRP, urinalysis, lipid profile, fasting (FBS) and 2-hour postprandial blood sugar (PP2BS), serum creatinine, liver function tests, serum protein and albumin, viral markers (HBsAg, HCV, HIV), prothrombin time, and ultrasonography (USG) for liver were also ordered for all patients. The NAFLD fibrosis score and BARD score were calculated for all patients. After collecting history, anthropometry, clinical, biochemical, and radiological data, the correlation between obesity and severity of liver involvement was assessed and analyzed using appropriate statistical methods.

RESULTS

Of the total 210 patients, there were 151 males and 59 females with an average age of 52 years. About 27 out of 86 patients aged ≤50 years had liver disease, while 72 out of 124 patients aged >50 years had liver disease (p < 0.001). A total of 63 out of 151 male patients had liver disease, while 36 out of 59 female patients had liver disease (p < 0.005). Only four patients were symptomatic for liver disease and their symptoms were fatigue (n = 4), abdominal distention (n = 3), and weight gain (n = 2). A total of 54 (25.7%) patients used to take a mixed diet and 156 (74.3%) were purely vegetarian. However, no significant association was observed between the type of diet and liver involvement in our study. While the average calorie intake of participants was 2421.9 Kcal/day, 108 patients had an intake of <2500 Kcal/day and 102 patients had an intake of ≥2500 Kcal/day. However, no significant correlation was seen between calorie intake and liver involvement in our study. Significant associations were found between liver involvement with physical activity and liver involvement with the menopausal state in females (Table 1).

Body mass index (BMI), WC, and neck circumference had a significant association with liver involvement. Out of 151 males, 30 (19.86%) had a WC > 100 cm, whereas out of 59 females, 36 (61%) had a WC > 95 cm. Out of these 36 females, 30 (83.33%) had liver disease. This finding suggests that abdominal obesity in females could be considered as an independent risk factor for NAFLD (Table 2). There were 127 patients (60.5%) having a WHR > 1.05; however, it had no significant correlation with liver disease in our study. Only four patients had signs of liver cell failure including pedal edema (n = 4), ascites (n = 4), and icterus (n = 2). On systemic examination of the abdomen, only two patients had palpable hepatomegaly, no patients had palpable splenomegaly and four patients had signs of free fluid on palpation and percussion.

Table 1: Association of liver involvement with physical activity and menopausal state in females

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Table 2: Association of liver involvement with BMI, WC in males and females, and neck circumference

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<th>Obesity (BMI)</th>
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<table>
<thead>
<tr>
<th>WC (males)</th>
<th>Normal liver</th>
<th>Liver disease</th>
<th>Row total</th>
<th>p &lt; 0.00,001</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;95 cm</td>
<td>41</td>
<td>8</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>95–100 cm</td>
<td>42</td>
<td>30</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>&gt;100 cm</td>
<td>5</td>
<td>25</td>
<td>30</td>
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<td>Column total</td>
<td>88</td>
<td>63</td>
<td>151</td>
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</table>

<table>
<thead>
<tr>
<th>WC (females)</th>
<th>Normal liver</th>
<th>Liver disease</th>
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<tbody>
<tr>
<td>&lt;90 cm</td>
<td>6</td>
<td>2</td>
<td>8</td>
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</tr>
<tr>
<td>90–95 cm</td>
<td>11</td>
<td>4</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>&gt;95 cm</td>
<td>6</td>
<td>30</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>23</td>
<td>36</td>
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<table>
<thead>
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<th>Neck circumference</th>
<th>Normal liver</th>
<th>Liver disease</th>
<th>Row total</th>
<th>p &lt; 0.00,001</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 cm</td>
<td>100</td>
<td>57</td>
<td>157</td>
<td></td>
</tr>
<tr>
<td>≥40 cm</td>
<td>11</td>
<td>42</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
</tbody>
</table>
Liver involvement in obese individuals

17 (8.1%) had raised bilirubin levels, but these parameters did not have a significant association with liver involvement. Of 210 participants, 82 (39.1%) had raised serum glutamic-pyruvic transaminase (SGPT) (ALT) and 145 (69.1%) had raised SGOT (AST) levels. While high SGOT had a significant association with liver disease, no such correlation was found for high SGPT. Triglycerides, HDL, LDL, and cholesterol were all significantly associated with liver disease (Table 3). About 28 out of 105 patients with normal FBS and 46 out of 124 patients with normal PP2BS had liver disease, while 71 out of 105 patients with FBS > 100 mg/dL and 53 out of 86 patients with PP2BS > 140 mg/dL had liver disease. So, impaired glycemic control significantly increases the risk of liver disease in obesity (p < 0.0005). The urinalysis and coagulation profile of all patients revealed no abnormalities. A total of 68 out of 163 patients with normal serum protein and 41 out of 105 patients with normal serum albumin had liver disease, while 31 out of 47 patients with low serum protein (<6 gm/dL) and 58 out of 105 patients with low serum albumin (<3.2 gm/dL) had liver disease. Hence, low serum protein (p < 0.005) and albumin (p < 0.05) have a significant association with liver involvement in our study.

On USG, 99 (47%) patients had liver involvement in the form of mild fatty changes (n = 72) (males = 44, females = 28), mild fatty changes with hepatomegaly (n = 42) (males = 14, females = 28), grade 2 fatty changes (n = 3) (males = 2, females = 1), coarsened liver with free fluid (n = 2) (males = 1, females = 1), and/or splenomegaly (n = 6) (males = 4, females = 2). High NAFLD Fibrosis score and Bard score > 2 are significantly correlated with liver disease in obese patients. Of the total of 210 patients, 40 were suffering from MS and they were more likely to develop liver disease (p < 0.0001) (Table 4).

**Discussion**

Obesity has grown rapidly across the developed world in the last four decades and is now a significant health concern even in developing countries. It is associated with an array of additional health problems of which, NAFLD is a significant contributor to high morbidity and mortality. The prevalence of NAFLD is found to increase with increasing age. Kagansky et al. and Frith et al. found the NAFLD prevalence to exceed 40% in individuals over 70 years of age, similar to the present study in which 58.06% of patients were above 50 years of age. In general, fatty liver is more prevalent in men than women up to the age of 60 years, but beyond menopause, the prevalence of fatty liver rises sharply in women and exceeds that observed in their male counterparts.17 In our study, 36 out of 59 females had liver disease and most of them (67.8%) were postmenopausal. This finding suggests a possible protective role of female hormones during their reproductive years. However, a larger female sample size is needed for accurate analysis. The clinical presentation of NAFLD is mostly asymptomatic, as seen in our study, unlike the typical presentation of alcoholic hepatitis. A high-calorie intake and lack of physical activity in a genetically predisposed individual leads to fatty liver. A similar association between a sedentary lifestyle and liver involvement was found in our study, but the daily calorie intake had no such influence. Fan et al. suggested that higher BMI was an independent, dose-dependent risk factor for

**Table 3**: Association of liver involvement with SGOT, triglycerides, HDL, LDL, and cholesterol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Liver</th>
<th>Liver Disease</th>
<th>Row Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT &lt; 40 IU/mL</td>
<td>43</td>
<td>22</td>
<td>65</td>
<td>0.002,907</td>
</tr>
<tr>
<td>41–80 IU/mL</td>
<td>55</td>
<td>47</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>81–120 IU/mL</td>
<td>9</td>
<td>17</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>&gt;120 IU/mL</td>
<td>4</td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal level</td>
<td>53</td>
<td>12</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>151–200 mg/dL</td>
<td>55</td>
<td>58</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>&gt;200 mg/dL</td>
<td>3</td>
<td>29</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>HDL &lt; 35 mg/dL</td>
<td>4</td>
<td>26</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Normal level</td>
<td>107</td>
<td>73</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>&gt;35 mg/dL</td>
<td>4</td>
<td>26</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>LDL &lt; 40 IU/mL</td>
<td>43</td>
<td>12</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Normal level</td>
<td>110</td>
<td>57</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>&gt;230 mg/dL</td>
<td>1</td>
<td>42</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
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</tbody>
</table>

**Table 4**: Association of liver involvement with NAFLD Fibrosis score, BARD score, and MS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Liver</th>
<th>Liver Disease</th>
<th>Row Total</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD fibrosis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0–F2 (&lt; −1.435)</td>
<td>43</td>
<td>12</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Intermediate score (−1.435–0.675)</td>
<td>43</td>
<td>33</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>F3–F4 (&gt;0.675)</td>
<td>25</td>
<td>54</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>BARD score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 score</td>
<td>11</td>
<td>2</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>&gt;2 score</td>
<td>100</td>
<td>97</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>Presence of MS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individuals with only obesity</td>
<td>104</td>
<td>66</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>Individuals with MS</td>
<td>7</td>
<td>33</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Column total</td>
<td>111</td>
<td>99</td>
<td>210</td>
<td></td>
</tr>
</tbody>
</table>
Liver Involvement in Obese Individuals

the fatty liver which is in concordance with our study.20

Raised CRP levels were significantly associated with liver disease in our study, which is similar to the results of Zimmermann et al.21 Both SGOT and SGPT were significantly associated with fatty liver in obese individuals in the study by Choi et al. but, only SGOT had a significant association in our study.22 We observed a positive association between high levels of triglycerides, LDL, cholesterol, FBS, PP2BS, and low levels of HDL with liver disease in obese individuals, which is similar to the results of Han et al.23 While a low serum protein and albumin were associated with liver involvement in our study, Andersen et al. reported a decreased albumin in obese patients as compared to non-obese individuals even in the absence of fatty liver disease.24 Our study found a significant association between liver involvement and NAFLD Fibrosis and BARD scores, similar to Cichoż-Lach et al.’s findings. Thus, these clinical scoring systems could decrease the requirement for liver biopsies in NAFLD patients.25 Nearly 82.5% of patients with MS had liver disease in our study, which concurs with the findings of Fan et al.26

Limitations

This was a cross-sectional study and hence, follow-up of patients was not done. The patient population was largely limited to Western India and hence, further multicenter studies are required to assess the generalizability of our results. We were limited by the nonavailability of fibroscan which is a more sensitive test for the detection of liver fibrosis.

Conclusion

In the present study of 210 obese individuals, advancing age (>50 years), female gender, especially in the postmenopausal state, and sedentary lifestyle were found to be risk factors for the development of liver disease. The risk of liver disease increases with increasing BMI, WC > 100 cm in males and >95 cm in females, and neck circumference ≥40 cm. Abdominal obesity in women can be considered an independent risk factor for NAFLD. Raised CRP and SGOT could be used as markers for liver disease in obesity.

Triglycerides, LDL, cholesterol, FBS, and PP2BS were positively correlated while HDL, serum protein, and albumin were negatively correlated with liver disease. Mild fatty changes were the most common USG finding in obese individuals with liver involvement. NAFLD Fibrosis score and BARD score had a significant association with liver disease and hence, can be used to noninvasively assess the liver involvement in obese individuals. Those with MS have a very high risk of developing NAFLD. In conclusion, since there is no definitive treatment available for NAFLD at present, recognition, and management of risk factors resulting in a reversal in the early stages is the only treatment option.

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Shahin Khan https://orcid.org/0000-0002-4581-787X
Shashwat Malik https://orcid.org/0000-0002-6557-6794

REFERENCES

Multiorgan Inflammatory Syndrome in Adults MIS-A Post SARS-CoV-2 Infection: A Novel Clinical Enigma

Ashwin Gawas¹, Ramnath P Nevrekar²*, Anar V Khandeparkar³

Accepted: 27 February 2022; Accepted: 02 November 2022

Abstract

Background: Multisystem inflammatory syndrome in adults (MIS-A) is an emergent heterogeneous clinical syndrome seen in the convalescent phase of COVID-19 infection. MIS in children (MIS-C) is a rare but severe post-COVID-19 illness that has been recognized by the WHO and the Centre for Disease Control and Prevention (CDC). It introduced a similar illness in adults based on multiple case series, identified as MIS-A.

Objective: We present four rare cases of multiorbital inflammatory syndrome in adults (MI-A) presented in Goa Medical College (Tertiary Medical Institute). We would like to highlight the diversity of presentation of symptoms with a significant history of previous covid infection, laboratory abnormalities, the clinical course of the disease, treatment strategies, and response and follow-up findings. We seek to highlight the emergence of a serious clinical entity that can be fatal if not diagnosed or treated promptly.

Materials and methods: This was a descriptive study conducted in Goa Medical College from June 2021 to November 2021. A systematic search in the Department of General Medicine, the Department of Medical Records, and data from ICU, ITU, and critical covid wards were collected.

Results and conclusion: A total of four cases fulfilling the criteria for MIS-A as per MMWR (CDC 2020) were included, ranging from the age group of 29–70 years. All had features of severe systemic inflammatory response with multiple organ dysfunction and elevated proinflammatory markers. All four patients had a recent history of (mild) COVID-19 infection. Hence, in the current pandemic scenario, MIS-A should be considered as a possible diagnosis in patients with recent COVID infection presenting with MODS, when the obvious septic cause is excluded through thorough clinical, physical, serological, laboratory, and radiological investigations. However, the presence of a past covid infection may not be an absolute criterion due to mild symptoms of the primary covid infection which usually go unnoticed resulting in non-testing.

INTRODUCTION

The COVID-19 pandemic caused by the SARS-CoV-2 virus has affected over 20.9 Cr people across the world, with India being 2nd in line with over 3.23 Cr after the USA.¹ Diversity in the presentations of the disease has been seen over the last 2 years into the pandemic. MIS-C is a rare but severe post-COVID-19 illness that has been recognized by the WHO and the CDC. A similar upcoming entity was observed for the first time in October 2020. CDC introduced a similar illness in adults based on multiple case series, which has been identified as MIS-A.² The evolving data indicate multifactorial pathogenesis, namely inflammation, nervous system dysfunction, endothelial damage, and thromboembolism as the main pathogenic mechanisms.³ Since many cases of MIS-C have a negative COVID-19 on PCR testing but elevated titers of COVID-19 antibodies, this finding necessitates antibody testing to identify cases in adults as well.

There is a relative paucity of data especially in the Indian scenario as regards MIS-A and hence the present study was aimed to ascertain the clinical profile of these patients.

We present a case series on MI-A from Goa Medical College during the 2nd wave of the pandemic elaborating on the presentation, trend in inflammatory markers, diagnosis, treatment, and follow-up (Table 1).

Materials and Methods

This was a descriptive observational study conducted in Goa Medical College (Apex Medical Institute and Teaching Hospital in Goa, India) from June 2021 to November 2021. Institutional Ethics Committee approval was obtained. A systematic search was made in the Department of Medical Records, records from the ICU and critical care wards. Various data characteristics namely demographic characteristics and underlying condition, initial signs and symptoms, inflammatory markers, 2D ECHO, ECG, HRCT thorax, CT severity score, a pattern of lung involvement, serological evidence, and SARS-CoV-2 history were considered using the algorithm published by the Brighton collaboration.⁵ Cases were studied and selected according to the inclusion and exclusion criteria. After the exclusion of eight suspected cases, we detected four cases where the diagnosis of MIS-A was highly possible.

Patients who fulfilled the working MIS-A case definition (as per MMWR 2020 CDC) used in this report were included, the criteria are as follows:²

- Severe illness requiring hospitalization in a person aged ≥21 years;
- A positive test result for current or previous SARS-CoV-2 infection (nucleic acid, antigen, or antibody) during admission or in the previous 12 weeks;
- Severe dysfunction of one or more extra pulmonary organ systems (hypotension or shock, cardiac dysfunction, arterial or venous thrombosis or thromboembolism, or acute liver injury);
- Laboratory evidence of severe inflammation (elevated C-reactive protein (CRP), ferritin, D-dimer, interleukin-6 (IL-6); and
- Absence of severe respiratory illness (to exclude patients in which inflammation and organ dysfunction might be attributable simply to tissue hypoxia).

Patients were excluded if alternative diagnoses such as bacterial sepsis were identified after a thorough clinical and laboratory workup.

Case 1

A 29-year-old male presented with a high fever and profuse sweating for 5 days associated with vomiting, headache, and generalized weakness. He developed acute dyspnea on day 5 of fever and signs of shock. There was a recent history of mild COVID-19 infection

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2Assistant Professor, Department of Medicine;
3Professor and Head, Department of Medicine, Goa Medical College, Bambolim, Goa, India;
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Table 1: Table showing comparative clinical, lab features, treatment and disease outcomes of MIS-A patients

<table>
<thead>
<tr>
<th>Cases</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/sex</td>
<td>29/M</td>
<td>49/M</td>
<td>70/M</td>
<td>39/F</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Nil</td>
<td>Diabetes for 5 years</td>
<td>Old CVA</td>
<td>nil</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Fever for 5 days, hypotension, vomiting, profuse sweating, generalized weakness, acute dyspnea</td>
<td>Generalized weakness, hypotension, nausea, vomiting</td>
<td>Fever, dyspnea, diarrhea</td>
<td>Bradycardia, hypotension, shock on post-op day 1 of LSCS unexplained by infection, sepsis, operative complication, blood loss, preeclampsia</td>
</tr>
<tr>
<td>Previous SARS-CoV-2 RTPCR/disease severity</td>
<td>Covid +ve 4 weeks prior (mild)</td>
<td>Covid +ve 3 weeks prior (mild)</td>
<td>Covid +ve 3 weeks prior (mild)</td>
<td>Covid +ve 4 weeks prior (mild)</td>
</tr>
<tr>
<td>Current SARS-CoV-2 RTPCR</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>15.8</td>
<td>9.78</td>
<td>8.19</td>
<td>14.80</td>
</tr>
<tr>
<td>TLC (cells/mm³)</td>
<td>16,100</td>
<td>8240</td>
<td>16,500</td>
<td>26,600</td>
</tr>
<tr>
<td>N/L ratio</td>
<td>91/4</td>
<td>74/17</td>
<td>80/8</td>
<td>88/6</td>
</tr>
<tr>
<td>Platelets (cells/mm³)</td>
<td>100,000</td>
<td>2,18,000</td>
<td>60,000</td>
<td>3,30,000</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1</td>
<td>0.5</td>
<td>1.7</td>
<td>0.84</td>
</tr>
<tr>
<td>AST (IU/L) (normal 5–40)</td>
<td>32</td>
<td>88</td>
<td>146</td>
<td>39</td>
</tr>
<tr>
<td>ALT (IU/L) (normal 16–63)</td>
<td>43</td>
<td>110</td>
<td>41</td>
<td>159</td>
</tr>
<tr>
<td>BUN (mg/dL) (normal 7–20)</td>
<td>27</td>
<td>26</td>
<td>14.12</td>
<td>28.00</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.81</td>
<td>0.96</td>
<td>0.82</td>
<td>1.66</td>
</tr>
<tr>
<td>Serum albumin (mg/dL) (N 4–4.7)</td>
<td>3.49</td>
<td>2.1</td>
<td>1.7</td>
<td>2.46</td>
</tr>
<tr>
<td>qSOFA</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D-dimer (ng/mL) (normal 0–200)—At admission</td>
<td>3480</td>
<td>7749</td>
<td>6351</td>
<td>5493</td>
</tr>
<tr>
<td>Ferritin (ng/mL) (normal 23–336)—At admission</td>
<td>2325.1</td>
<td>9876</td>
<td>1069</td>
<td>5386</td>
</tr>
<tr>
<td>Ferritin (ng/mL)—repeat</td>
<td>308</td>
<td>3484</td>
<td>NA</td>
<td>—</td>
</tr>
<tr>
<td>LDH (U/L) (normal 81–234)—Initial</td>
<td>288</td>
<td>482</td>
<td>218</td>
<td>978</td>
</tr>
<tr>
<td>LDH (U/L)—repeat</td>
<td>164</td>
<td>276</td>
<td>NA</td>
<td>—</td>
</tr>
<tr>
<td>Troponin I (ng/L) (normal 0–0.034)</td>
<td>0.107</td>
<td>0.056</td>
<td>2.20</td>
<td>10.2290</td>
</tr>
<tr>
<td>CRP (mg/L) (&lt;10 mg/dL)</td>
<td>890</td>
<td>948</td>
<td>826</td>
<td>760</td>
</tr>
<tr>
<td>Blood and urine cultures</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
</tr>
<tr>
<td>Screening (malaria/dengue/scrub typhus/lepto/chikungunya)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>High resolution CT thorax</td>
<td>Bilateral ground glass opacities (GGO) and extensive areas of consolidation involving bilateral lung parenchyma (predominantly lower lobes)</td>
<td>Bilateral pleural effusion (moderate), GGO, mosaic attenuation, atelectasis in bilateral lower lobes</td>
<td>Multiple areas of GGO septal thickening fibrotic areas in all the lobes of bilateral lungs predominantly in the basal lung parenchyma</td>
<td>—</td>
</tr>
<tr>
<td>2D ECHO (TTE)</td>
<td>Global LV hypokinesia EF 35%, IVC—2 cm dilated and noncollapsing</td>
<td>LVEF 60%, moderate PAH</td>
<td>Mild global hypokinesia, IVC 22% collapsing</td>
<td>Global hypokinesia LVEF 20%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Antibiotics, LMWH, corticosteroids, IVIG, dobutamine, norepinephrine</td>
<td>Antibiotics, LMWH, corticosteroids, IVIG, dobutamine, norepinephrine</td>
<td>Antibiotics, LMWH, corticosteroids, IVIG, adrenaline, corticosteroids, IVIG</td>
<td>Antibiotics, LMWH, corticosteroids, IVIG, dobutamine, norepinephrine</td>
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Contd…
Multiorgan Inflammatory Syndrome in Adults MIS-A Post SARS-CoV-2 Infection

Contd...

<table>
<thead>
<tr>
<th>Cases</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospitalization and disease outcome</td>
<td>Recovered and discharged after 16 days</td>
<td>Recovered and discharged after 10 days</td>
<td>Recovered and discharged after 9 days</td>
<td>Expired within 48 hours</td>
</tr>
<tr>
<td></td>
<td>LV function improved to normal after 2 weeks of admission</td>
<td></td>
<td>LV function improved to normal after 3 weeks of admission</td>
<td></td>
</tr>
</tbody>
</table>

chest CT severity score (CTSS 0) 38 days ago and was home quarantined. On examination, he had a fever (105°F), tachypnoea, SPO2 85%, disproportionate tachycardia, signs of shock, and raised JVP. Cardiovascular system (CVS) auscultation revealed an S2 gallop. Nasopharyngeal throat swabs (SARS-CoV-2 PCR) were negative. Laboratory analysis revealed leukocytosis, elevated N/L ratio, lymphopenia, and marked elevation in D-dimer, troponin, ferritin, CRP, procalcitonin, and IL-6. Chest computed tomography (CT) was showing bilateral ground glass opacities (GGO) and findings consistent with pulmonary edema. A 2D ECHO revealed LV global hypokinesia, LVEF 35%, IVC dilated and noncollapsing, mild TR, normal pulmonary hypertension (PA) pressure, LA/LV not dilated. The patient was intubated for ventilator support (pc bipap mode with FiO2 100% and PEEP 8 cms) and isotropic support. Blood, urine, throat, and stool cultures were obtained to exclude possible infectious etiology. Considering sepsis as the primary etiology he was empirically started on meropenem, aztreonam, and azithromycin. The patient had procalcitonin of 6.1 and hence was started empirically on antibiotics azithromycin, cefoperazone, and sulbactam. Chest CT showed multiple areas of GGO septal thickening fibrotic areas in all the lobes of bilateral lungs predominantly in the basal lung parenchyma (CTSS 7/25) all suggestive of previous covid infection. A 2D ECHO revealed mild hypokinesia, IVC nondilated and noncollapsing (collapsibility 22%), LA/LV not dilated. Diagnosis of myocarditis was considered primarily. On the clinical and radiological examination and with the results of basic laboratory tests, we could not find any focus for infection. History of COVID-19 was considered significant in this case and MIS-A was strongly considered as the possible diagnosis. Therefore, dexamethasone 6 mg 8 hourly was started along with intravenous antibiotics: azithromycin, piperacillin, and tazobactam until culture reports were ready. Chest CT showed bilateral pleural effusion (moderate)/GGO mosaic attenuation, atelectasis of bilateral lower lobes. A 2D ECHO revealed normal findings. On the physical, and radiological examination and with the results of basic laboratory tests, we could not find any focus for infection. History of COVID-19 was considered significant in this case and MIS-A was strongly considered as the possible diagnosis. The patient was treated with steroids and LMWH for a period of 5–6 days and the patient showed improvement in clinical signs and symptoms. The patient fully recovered and was discharged after 9 days.

**Case 3**

A 70-year-old male presented to the ER with a fever for 10 days, passing loose motions for 2-day, and acute dyspnoea for 2 days. The patient had a mild COVID-19 infection 20 days prior. The patient was febrile (101°F), SPO2 87%, and had no rhonchi, tachycardia, or shock. There was no obvious clinical focus of infection. Routine infectious screening for malaria, dengue, leptospirosis and scrub typhus were negative. Blood and urine cultures were sterile. Nasopharyngeal swabs (SARS-CoV-2 PCR) yielded negative results. Laboratory analysis revealed leukocytosis, neutrophilia, lymphopenia, elevation in D-dimer, troponin, ferritin, CRP, procalcitonin, and elevation in the liver enzyme (AST/ALT). Chest X-ray didn’t show any signs of pneumonia. Chest CT was normal. The patient was empirically started on antibiotics: azithromycin, piperacillin, and tazobactam until culture reports were ready. Chest CT showed bilateral pleural effusion (moderate)/GGO mosaic attenuation, atelectasis of bilateral lower lobes. A 2D ECHO revealed normal findings. On the physical, and radiological examination and with the results of basic laboratory tests, we could not find any focus for infection. History of COVID-19 was considered significant in this case and MIS-A was strongly considered as the possible diagnosis. The patient was treated with steroids and LMWH for a period of 5–6 days and the patient showed improvement in clinical signs and symptoms. The patient fully recovered and was discharged after 9 days.

**Case 4**

A 39-year-old female G2P1L1 presented with unexplained shock post LSCS. The patient had a mild COVID-19 infection 28 days ago and was in home quarantine. The surgery was uneventful. However, on post-op day 1, the patient developed acute hypotension, fever, rigors, oliguria, and dyspnoea. She had marked tachycardia, shock, bilateral coarse crepits, acute kidney injury, and drowsiness. There was no obvious clinical focus of infection. There was no postpartum hemorrhage, or any other obstetric complication causing shock. The saturation of
the patient deteriorated gradually. The patient was started on noradrenaline infusion and had to be intubated eventually. Nasopharyngeal swab samples (SARS-CoV-2 PCR) yielded negative results. Laboratory analysis revealed leukocytosis, neutrophilia, lymphopenia, elevated liver enzyme (SGOT), serum creatinine and urea with hyperkalemia, elevation in D-dimer, LDH, troponin, ferritin MB, and troponin I. ECHO showed ejection fraction 20%. Routine infectious screening for malaria, dengue, leptospirosis, and scrub typhus was negative. Blood and urine cultures were sterile. USG abdomen and pelvis were unremarkable. Chest X-ray revealed fluffy alveolar shadows. A provisional diagnosis of MI-A-myocarditis was considered. The patient was started on meropenem, targcocid, metronidazole, LMWH, methylprednisolone, and IVIG infusion. However, the patient expired within 48 hours of admission.

**In our case series**, all the patients were tested with SARS-CoV-2 RTPCR at admission and were found to be negative, and all had a recent history of mild COVID-19 in the preceding 3–4 weeks (RTPCR positive for SARS-CoV-2), along with significantly elevated inflammatory markers, varied symptoms and clinical as well as lab evidence of multiorgan dysfunction. On taking a detailed history and performing a thorough clinical examination, laboratory tests, we could not find any obvious focus of infection/septic focus to explain the MODS. We used qSOFA scoring to predict the mortality in these patients. In our observational study, two patients had a score of ≥ 2 suggestive of poor outcome.

The heterogeneity in the presentation of MIS-A is evident by multisystem involvement namely cardiovascular, gastrointestinal, mucocutaneous, and neurological. Severe SARS-CoV-2 infection also causes hyper inflammation and multiorgan system involvement with respiratory failure as the predominant presentation. Contrary to that, MIS-A is associated with a paucity of primary respiratory symptoms, hypoxemia, or radiological abnormalities.

In our series three out of four cases presented with fever and cardiogenic shock with elevated troponin I levels and 2D ECHO revealing evidence of moderate to severe LV dysfunction. All these patients also had highly elevated inflammatory markers and cardiac enzymes with a history of COVID-19 infection in the preceding 4 weeks. A case-based review article of 51 cases of MIS-A showed that cardiovascular involvement is the most frequent finding (82.4%), followed by gastrointestinal manifestations (72.5%) (Bastug et al.). The first case series published by CDC MMWR had 11 patients a total of which seven underwent cardiogenic shock at the time of presentation. Even though there is a plethora of debilitating symptoms, fever, shock, gastrointestinal symptoms such as abdominal pain, diarrhea, headache, myocarditis, and hypotension via capillary leak syndrome are the predominant ones.

All our patients had high levels of inflammatory biomarkers such as CRP, ferritin, LDH, D-dimer, and IL-6. A case-based review revealed the mean level for CRP was 293.7 ± 119.3 mg/L and the mean level for lymphocytes was 999 cell/µL (±119.3), the median level for ferritin was 1265 µg/L (21–100.000) and the median level for D-dimer was 2.8 µg/L (0.35–20). Our study showed a similar profile in the inflammatory markers. D-dimer, ferritin, and LDH were highly elevated in all our patients and showed progressive decline within 72 hours of induction of steroid therapy with or without IVIG.

**Conclusion**

Multisystem inflammatory syndrome in adults (MIS-A) is an emerging clinical complication of SARS-CoV-2 infection, limited understanding of this disease seeks the need for research to systematically define its pathogenesis, presentation, and management protocol according to its severity. Through this case series, we seek to highlight the emergence of a serious clinical entity in adults which can be fatal if not diagnosed or treated promptly. Patients presenting with features of severe sepsis or multiple organ dysfunction, particularly cardiac dysfunction, and myocarditis, with or without a history of COVID-19 in the midst of the pandemic and not responding to the standard sepsis management protocol—MIS-A should be strongly considered as a possible diagnosis and promptly started on steroid therapy with or without IVIG provided the alternative focus of infection is excluded by a thorough clinical, serological, laboratory, and radiological investigations.

The presence of past COVID-19 infection, one of the essential criteria in the working MIS-A case definition (MMWR criteria) used in this report may not be an absolute criterion due to mild symptoms of the infection which usually go unnoticed by the population and they do not seek testing for covid. Antibody titer as diagnostic criteria may also not be reliable due to paucity in the literature on the duration of the antibody titer seen in the sera post-SARS-CoV-2 infection.

**Limitations**

A limited sample size of the study limits extensive insight into the disease due to...
unreported cases, early demise, and lack of awareness among the medical fraternity.

REFERENCES
Ulinastatin Add-on to Standard of Care in Critically Ill COVID-19 Patients: A Multicenter, Retrospective Study

Yatin Mehta1, Kapil Zipre2, Subhal Dixit3, Abdul Ansari4, Chitra Mehta5, Abhijeet Deshmukh6, Sourabh Ambapkar7, Saanvi Ambapkar9, Mukund Joshi9, Ameya Joshi10, Manish Bathija11, Mayur Shah12

ORIGINAL ARTICLE

ABSTRACT

Aim: To assess the impact on 30-day mortality with ulinastatin (ULI) used as add-on to standard care (SOC) compared to SOC alone in coronavirus disease (COVID-19) patients requiring admission to the intensive care unit (ICU).

Materials and methods: In this multicentric, retrospective study, we collected data on clinical, laboratory, and outcome parameters in patients with COVID-19. Thirty-day mortality outcome was compared among patients treated with SOC alone and ULI used as add-on to SOC. Odds ratio (OR) and 95% confidence intervals (CI) were determined to identify the predictors of 30-day mortality.

Results: Ninety-four patients were identified and enrolled in both groups with comparable baseline parameters. On univariate analysis, 30-day mortality was significantly lower in ULI plus SOC group than SOC alone group (36.2 vs 51.1%, OR 0.54, 95% CI 0.30–0.97, p = 0.040). The effect on mortality was more pronounced in patients who did not require intubation (10.9 vs 34.0%, OR 0.24, 95% CI 0.09–0.66, p = 0.006) and with early administration (within 72 hours of admission) of ULI (30.7 vs 57.9%, OR 0.32, 95% CI 0.11–0.91, p = 0.032). On multivariate analysis, only intubation predicted mortality (adjusted OR 10.13, 95% CI 3.77–27.25, p < 0.0001) and the effect of ULI on survival was not significant (adjusted OR 0.58, 95% CI 0.22–1.52, p = 0.270).

Conclusion: Given the limited options for COVID-19 patients treated in ICU, early administration of ULI may be helpful, especially in patients not requiring intubation to improve the outcomes. Further, a large, randomized study is warranted to confirm these findings.

INTRODUCTION

Coronavirus disease has been a devastating pandemic that affected over 270 million people and caused over 5 million deaths around the globe. Immundysregulation has been identified as one of the major mechanisms responsible for organ dysfunction in COVID-19. Uncontrolled inflammatory response leads to severe and critical disease. Immunopathological alterations managed with steroids, interleukin 6 (IL-6) inhibitors, and Janus kinase 1/2 inhibitors have improved survival in hospitalized severely and critically ill patients. However, except for steroids, the availability and affordability of other immunomodulating agents limit their use, and these may not be the first option even in eligible patients. Though steroids and IL-6 inhibitors are proven effective for the treatment of COVID-19, their rampant use has invited opportunistic infections such as mucormycosis.

Ulinastatin is a broad-spectrum serine protease inhibitor that inhibits trypsin, chymotrypsin, thrombin, kallikrein, neutrophil elastase, and cathepsin. It has a significant anti-inflammatory effect with a reduction in inflammatory cytokines such as IL-6, IL-8, IL-4, tumor necrosis factor-α, and inflammatory markers like C-reactive protein (CRP). Additionally, it inhibits apoptosis, improves coagulation disturbances, reduces endothelial dysfunction, and improves tissue perfusion. ULI has a proven role in improving survival in sepsis and acute respiratory distress syndrome (ARDS). A small study of 12 moderate to severe COVID-19 patients reported improved clinical symptoms, oxygenation, and pulmonary lesion resorption after high-dose ULI. During the first wave of COVID-19, the global medical fraternity managed hospitalized severe and critically ill COVID-19 patients on their expertise with multiple treatment options. ULI was also considered as one of the treatment options. In this multicentric, retrospective study, we evaluated the effect of ULI on mortality outcome in COVID-19 patients who required intensive care.

MATERIALS AND METHODS

In this multicenter, retrospective, observational study, patients of COVID-19 who required admission to the ICU were identified from four centers from Gurugram, Mumbai, and Pune. The Institutional Ethical Committee approved the study protocol at each participating center. The study was conducted according to the ethical principles of the Declaration of Helsinki, good clinical practices, and applicable local regulatory guidelines. As this was a retrospective analysis of existing data, informed consent was not necessary and was waived off by the ethical committees.

From the database at each center, we identified the COVID-19 patients who required admission to the ICU and were treated with ULI in addition to existing treatments. Patients admitted between April and December 2020 who had been treated with ULI in addition to the SOC within 7 days of admission and had identifiable hospital outcomes at day 30 of admission were included in the study. For comparison, the control group included the patients who received SOC. The SOC was considered as steroids (dexamethasone/methylprednisolone or hydrocortisone) and other supportive treatments. Patients in the control group with SOC were selected with similar criteria as the ULI group. We matched the two groups for treatment with tocilizumab and
the requirement of intubation. For ULI, we noted the dose per day, day of administration from admission, and duration of therapy.

We collected data on demographic parameters such as age, gender, etc. Clinical parameters on presentation such as fever, cough, breathlessness, and oxygen saturation on admission were recorded. Among treatments, we collected data on tocilizumab and low molecular weight heparin (LMWH) administration. We also recorded hemoglobin (Hb), total leucocyte count (TLC), serum creatinine, total serum bilirubin, liver enzymes, and serum albumin. We also collected data on inflammatory parameters such as CRP, D-dimer, lactate dehydrogenase (LDH), and serum ferritin levels. Duration of ICU and hospital stay (days) was also noted.

The data were captured in a Microsoft Excel sheet and were analyzed with SPSS software version 15. We presented the categorical variables as frequency and percentages. The normality of the continuous variables was checked by plotting histograms. Normally distributed data were presented as mean and standard deviation and were compared using the Student’s t-test. Data that were not normally distributed were presented as median and interquartile range 25–75 (IQR25–75) and were compared with nonparametric Mann–Whitney U test. We assessed predictors of mortality using univariate analysis performed with logistic regression analysis. Adjusted OR with 95% CI was determined using multivariate analysis with multinomial logistic regression. p-value of <0.05 was considered significant for all the comparisons.

**RESULTS**

Between April and December 2020, we identified 94 patients who had received ULI for treatment of COVID-19 and had required ICU admission. We identified an equal number of patients in the SOC group. The data were matched for the treatment with tocilizumab and the need for invasive ventilation. **Table 1** shows the baseline characteristics of these patients. Baseline parameters were comparable in the two groups. The mean age in SOC + ULI group was 59.6 ± 13.7 years, and in SOC alone group was 59.5 ± 13.8 years (p = 0.989). The distribution of gender did not differ in the two groups (p = 0.860). Breathlessness on presentation among patients in the two groups did not differ significantly (p = 0.292). The mean oxygen saturation at baseline was significantly lower in SOC alone group than SOC plus ULI group (88.1 ± 12.9 vs 92.7 ± 5.6, respectively, p = 0.002). All patients in both groups had received steroids as treatment protocol. There were no significant differences in the proportion of patients treated with tocilizumab (p = 0.741), LMWH (p = 1.000), and need for invasive ventilation (p = 0.768). Among laboratory parameters, there were no differences in Hb (p = 0.169), TLC count (p = 0.097), serum creatinine (p = 0.177), serum bilirubin (p = 0.498), alanine transaminases (p = 0.908), and serum albumin (p = 0.622). The median levels of aspartate transaminases were significantly higher in the SOC group than in the SOC + ULI group (51 vs. 32.5 IU/L, respectively, p < 0.0001). Though median levels of serum CRP were higher in SOC + ULI group, it was not significantly different.

**Table 1:** Baseline characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SOC + ULI (n = 94)</th>
<th>SOC alone (n = 94)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>59.6 ± 13.7</td>
<td>59.5 ± 13.8</td>
<td>0.989</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>48 (51.6)</td>
<td>50 (53.2)</td>
<td>0.829</td>
</tr>
<tr>
<td>Male sex</td>
<td>74 (78.7)</td>
<td>73 (77.7)</td>
<td>0.860</td>
</tr>
<tr>
<td>Major symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>69 (73.4)</td>
<td>60 (63.8)</td>
<td>0.157</td>
</tr>
<tr>
<td>Cough</td>
<td>56 (59.6)</td>
<td>47 (50.0)</td>
<td>0.187</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>55 (58.5)</td>
<td>62 (66.0)</td>
<td>0.292</td>
</tr>
<tr>
<td>O2 saturation on admission</td>
<td>92.7 ± 5.6</td>
<td>88.1 ± 12.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>94 (100.0)</td>
<td>94 (100.0)</td>
<td>–</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>24 (25.5)</td>
<td>26 (27.7)</td>
<td>0.741</td>
</tr>
<tr>
<td>LMWH</td>
<td>86 (91.5)</td>
<td>86 (91.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Need of invasive ventilation</td>
<td>39 (41.5)</td>
<td>41 (43.6)</td>
<td>0.768</td>
</tr>
<tr>
<td>Laboratory investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (gm/dL) (n = 90 and 94)</td>
<td>13.0 ± 3.9</td>
<td>12.4 ± 2.3</td>
<td>0.169</td>
</tr>
<tr>
<td>TLC (cells/cmm) (n = 91 and 94)</td>
<td>8570 (5360–12,790)</td>
<td>10,540 (6872.5–13,675)</td>
<td>0.097</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL) (n = 92 and 91)</td>
<td>0.9 (0.7–1.2)</td>
<td>0.8 (0.7–1.2)</td>
<td>0.177</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL) (n = 70 and 81)</td>
<td>0.6 (0.4–0.9)</td>
<td>0.7 (0.4–1.0)</td>
<td>0.498</td>
</tr>
<tr>
<td>Alanine transaminases (IU/L) (n = 86 and 81)</td>
<td>43 (29–69.3)</td>
<td>44 (27.4–80.5)</td>
<td>0.908</td>
</tr>
<tr>
<td>Aspartate transaminase (IU/L) (n = 86 and 81)</td>
<td>32.5 (25–52)</td>
<td>51 (30–85.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum albumin (mg/dL) (n = 56 and 71)</td>
<td>3.3 ± 0.6</td>
<td>3.3 ± 0.5</td>
<td>0.622</td>
</tr>
<tr>
<td>CRP (mg/dL) (n = 74 and 71)</td>
<td>59.7 (29.2–125.3)</td>
<td>24 (11–215.2)</td>
<td>0.327</td>
</tr>
<tr>
<td>D-dimer (µg/mL) (n = 68 and 82)</td>
<td>0.7 (0.3–5.8)</td>
<td>0.9 (0.3–2.5)</td>
<td>0.756</td>
</tr>
<tr>
<td>LDH (IU/L) (n = 75 and 77)</td>
<td>413 (312–611)</td>
<td>463 (345–636.5)</td>
<td>0.200</td>
</tr>
<tr>
<td>Serum ferritin (µg/dL) (n = 69 and 82)</td>
<td>525 (279–774)</td>
<td>504.5 (239.5–884.3)</td>
<td>0.918</td>
</tr>
<tr>
<td>IL-6 (pg/mL) (n = 8 and 54)</td>
<td>115.7 (7–719)</td>
<td>96 (35.6–214.5)</td>
<td>0.900</td>
</tr>
</tbody>
</table>

Number in parentheses against each parameter indicates the available data.
Ulinastatin in Critically Ill COVID-19

As shown in Table 2, the proportion of deaths in SOC + ULI group was significantly lower than SOC alone group (36.2 vs 51.1%, OR 0.54, 95% CI 0.30–0.97, p = 0.040). When stratified by the need for intubation, there was no difference in 30-day mortality outcome in intubated patients (71.8 vs 73.2%, OR 0.93, 95% CI 0.35–2.49, p = 0.890). However, in patients who did not require intubation, 30-day mortality was significantly lower in SOC + ULI group than SOC alone group (10.9 vs 34.0%, OR 0.24, 95% CI 0.09–0.66, p = 0.032). By the need for intubation, no significant effect on 30-day mortality was seen. In those not requiring intubation, six patients who died were only in ULI ≤3 days group.

As shown in Figure 2, the median ICU stay did not differ in the two groups (p = 0.569). However, the median duration of hospital stay was significantly shorter in SOC + ULI group than SOC alone group (10.5 (IQR 25–75: 8–14) days to 12.5 (IQR 25–75: 9–18) days, p = 0.038).

Table 4 shows the predictors of mortality. ULI dose in survivors and non-survivors was 4.2 ± 0.9 and 4.2 ± 0.7 lac units per day, respectively. There was no significant difference in the dose of ULI among survivors and non-survivors. The median duration of ULI administration was 5 days. On univariate analysis, significant predictors of 30-day mortality were age (OR 1.04, 95% CI 1.02–1.07, p = 0.001), intubation (OR 9.22, 95% CI 4.73–18.0, p < 0.0001), TLC counts (OR 1.00, 95% CI 1.00–1.00, p = 0.021), serum creatinine (OR 1.32, 95% CI 1.00–1.74, p = 0.050), D-dimer (OR 1.06, 95% CI 1.01–1.11, p = 0.014), serum LDH (OR 1.002, 95% CI 1.001–1.003, p = 0.001), and serum ferritin (OR 1.001, 95% CI 1.00–1.001, p = 0.045) whereas administration of ULI predicted improved 30-day survival (OR 0.54, 95% CI 0.30–0.97, p = 0.040). On multivariate analysis, only the need of intubation remained a significant predictor of mortality (OR 10.13, 95% CI 3.77–27.25, p < 0.0001), and the effect of ULI on survival was not significant (OR 0.58, 95% CI 0.22–1.52, p = 0.270).

**Discussion**

Immunopathogenesis has been identified as the pathogenic mechanism in the progression of COVID-19 to severe and critical diseases. In the early phase of the COVID-19 pandemic, physicians faced a significant challenge in managing hospitalized critically ill patients. With the understanding of immunopathological alterations similar to that observed in bacterial sepsis, physicians treating critically ill COVID-19 patients relied on all available therapies. Around the globe, drugs directed at inflammation primarily in cancer therapies and immunomodulatory therapies repurposed for use in COVID-19 possess significant anti-inflammatory and immunomodulatory activity that has proven efficacy in sepsis, ARDS, and multi-organ dysfunction. From our clinical experience, we used ULI in some of the ICU-admitted patients as one of the adjunctive therapies in addition to ongoing treatment that included steroids and LMWH.

In comparison to SOC alone, the addition of ULI to SOC showed lower mortality at day 30. Though there are no studies on the use of ULI in COVID-19, previous studies involving critically ill patients with sepsis showed a significant effect on mortality reduction at day 30. Probable mechanisms contributing to lower mortality may include immunomodulatory and anti-inflammatory effects suppressing the cytokine storm and prevention of development of new organ dysfunction.

A case series of 12 patients identified that high-dose ULI improved...
peripheral oxygenation, significantly reduced CRP levels, and resulted in marked resorption of pulmonary lesions. Another case report observed significant improvement in clinical signs and pulmonary functions with ULI use in a patient who did not respond to tocilizumab. Such effects with ULI could be a reason for a shorter hospital stay and possible mortality benefit.

We observed that the benefit of mortality reduction was more pronounced in patients who did not require intubation and those who had received ULI within 72 hours of admission. It indicates that early administration is crucial in considering immunomodulator therapy in critically ill patients. Early immunomodulator treatment in these patients can provide increased benefits. A study from Choudhuri et al. observed lower multiple organ dysfunction syndrome with early administration (<48 hours) of ULI in sepsis patients. Some experts suggest the use of immunomodulators such as steroids right from the day of hospitalization. We observed that invasive ventilation was a significant predictor of mortality. Critically ill COVID-19 patients have significantly higher odds of mortality with invasive mechanical ventilation during the hospital stay. Thus, the need for intubation remains one of the critical factors in mortality prediction. It is important to note that the ULI was used in ICU patients. In our experience, we observe that benefits with ULI can be better in moderate to severe than critically COVID-19 patients.

Our study has several limitations. Being a retrospective study, selection bias cannot be ruled out, and therefore results need to be interpreted with caution. Though we tried to capture major data, we missed the data on comorbid conditions, which may introduce some bias in data analysis and interpretation. As the study involved only patients who required ICU admission, the sample size was limited. Outcomes with the use of ULI in noncritical diseases may be worth studying. There is also missing data on various baseline parameters. Though requiring ICU admission indicates severe and critical disease, we did not assess the pulmonary function objectively and data on disease severity score was lacking. Data regarding the day of administration of tocilizumab and steroids and the day of intubation during the hospitalization could provide more answers as to how survival can be improved in such critically ill patients, which were not analyzed. Also, we did not perform any propensity matching that limits the generalizability of our results. Furthermore, the dose of ULI was on the lower side. A higher dose may provide incremental benefits as reported in previously published case series. Nonetheless, immunomodulators have now been established in the management of COVID-19 patients. ULI may offer a safer and affordable alternative to high-end immunomodulators such as tocilizumab and baricitinib.

**Conclusion**

In conclusion, the use of ULI in addition to SOC involving steroid therapy in critically ill COVID-19 patients may reduce 30-day
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mortality. The survival benefits may be greater with early administration (<72 hours) and non-intubated patients. Given the limitation of retrospective comparison, randomized controlled trials are further needed to delineate the effect of ULI in COVID-19 patients. Based on our experience and results from our study, we suggest that it may be helpful to administer ULI in patients with moderate COVID-19 who require hospitalization to prevent progression to severe disease, preferably within 3 days of admission.

Acknowledgments
We thank Dr Vijay Katekhaye (Director, Quest MedPharma Consultants, Nagpur, India) for his contribution in drafting, editing, and reviewing the manuscript. We also thank Mr. Joby George for his assistance in data assimilation at the Delhi center. We express our gratitude to Urich Pharmaceuticals Pvt. Ltd. for their financial support in medical writing.

References
Usage Pattern of Fixed-dose Combinations at ICMR Network of Rational Use of Medicine Centres across India: Recommendations for Policymakers and Prescribers


Received: 03 August 2022; Accepted: 20 October 2022

Abstract

Aim: Irrational use of medicines is a global problem. In India, one contributing factor is the availability of a large number of fixed-dose combinations (FDCs). To improve rational use and to strengthen policies, it is important to assess the usage patterns and rationality of FDCs.

Methods: This study was conducted as part of a 1-year prospective cross-sectional analysis of prescriptions in the outpatient clinics of broad specialties from 13 tertiary care hospitals across India. Five most commonly prescribed FDCs in each center were analyzed. In addition, all the prescribed FDCs were classified as per the Kokate Committee classification and it was noted whether any of the FDCs were irrational or banned as per the reference lists released by regulatory authorities.

Results: A total of 4,838 prescriptions were analyzed. Of these, 2,093 (43.3%) prescriptions had at least one FDC. These 2,093 prescriptions had 366 different FDCs. Of the 366 FDCs, 241 were rational; 10 were irrational; 14 required further data generation; and the remaining 96 FDCs could not be categorized into any of the above. Vitamins and minerals/supplements, antibacterial for systemic use, and drugs for gastroesophageal reflux disease (GERD) and peptic ulcer were the most used FDCs.

Conclusion: Based on the finding that some prescriptions contained irrational FDCs, it is recommended that a rigorous, regular, and uniform method of evaluation be implemented to approve/ban FDCs and that prescribers be periodically notified about the status of the bans.

Introduction

One of the objectives of healthcare is to maximize benefit and minimize harm to patients. Clinicians could achieve this by incorporating the concept of "rational use of medicines" in their routine clinical practice. The World Health Organization (WHO) defines rational use of medicines as the situation wherein patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community. Irrational use of medicines, however, is not uncommon with the WHO estimating that more than half of all medicines are either prescribed, dispensed, or sold inappropriately. The consequences of irrational use are enormous and include potential loss of effect, increased adverse effects, resulting financial burden, and increased antimicrobial resistance (in the case of antimicrobial agents). All of these could in turn reduce the overall quality of life of patients. Misuse of medicines often leads either to unavailability of resources or renders them expensive for those who are in dire need.

Irrational use of medicines occurs in many ways. One way is with the use of irrational FDCs. FDCs, as defined by the Central Drugs Standard Control Organisation (CDSCO) of India, refer to products containing one or more active ingredients used for a particular indication. FDCs are often used to improve compliance and are justified in certain situations, for example, to improve effect (sulfamethoxazole and trimethoprim), or to decrease antimicrobial resistance.
(antitubercular drugs). However, in India, FDCs of different drug classes and various strengths are widely available and not all of these are rational. To further strengthen the hands of policymakers and to sensitize healthcare professionals and patients regarding the need to use only rational FDCs, there was a need felt to assess the usage of FDCs across India. Although there are a few studies from India which describe FDC usage patterns (especially concerning irrational FDCs), a majority of these were carried out either at a single center or at most by involving a few centers. In order to fill this gap, we present the findings from prescription evaluation research regarding FDC usage conducted in 13 tertiary care hospitals across India. The main purpose was not only to analyze the pattern of commonly used FDCs but also to see whether the prescriptions included (1) any of the FDCs that were banned at some point in time or (2) any of the FDCs that were classified as irrational (by CDSCO).

The FDC research presented here was undertaken as a part of a project initiated in 2019 by the Indian Council of Medical Research (ICMR) which tasked the setting up of rational use of medicines centers (RUMCs) under the National (virtual) Centre for Clinical Pharmacology (NvCCP) in departments of pharmacology of various medical institutions located in different parts of the country to create competency for rational use of medicines. Other activities undertaken in the project include the development and launch of an online course (containing 50 modules) on prescribing skills and prescription evaluation research.

Methods

The study reported here is the secondary data analysis from a prospective observational analysis of prescriptions carried out from August 2019 to August 2020. Thirteen tertiary care institutions across India participated in this study. A common protocol was made available to these centers by the coordinating team from ICMR. All the participating centers obtained approval from their respective Institutional Ethics Committees. Informed consent was obtained from patients whose prescriptions were included (except in centers where a waiver for written informed consent was obtained). Prescriptions were selected based on the following criteria:

Inclusion Criteria

- Prescriptions for patients of any age from outpatient clinics in the participating tertiary care hospitals,
- Prescriptions for both new patients (visiting the department for the first time) and repeat patients (visiting the department more than once either for review or for follow-up).

Exclusion Criteria

- Prescriptions where information from the medical charts regarding clinical features or relevant investigations or provisional diagnosis were not mentioned,
- Prescriptions where information from the medical charts regarding provisional diagnosis or disease is not written or unavailable, and
- The patient was seriously ill and/or was admitted.

Sample Size and Sampling

Each center aimed to collect a minimum of 600 prescriptions from the outpatient clinics as per the WHO guidance document. Prescriptions were analyzed from the departments of general medicine, general surgery, obstetrics & gynecology, pediatrics, dermatology, ophthalmology, otorhinolaryngology, psychiatry, community medicine or general practice. The number of prescriptions analyzed from each department was based on the overall proportion of outpatients seen by these departments.

Primary Data Collection

Patients were contacted after their outpatient consultation in the respective department’s clinic or at the hospital dispensary (pharmacy). All consecutive patient prescriptions fulfilling the inclusion criteria were included till the sample size was achieved. A photocop
copy or photograph of each prescription was collected for digital records. A case record form was used for entering the data extracted from the prescription and the medical chart of the patient. Details such as demographics, signs and symptoms, findings from clinical examination, results of investigations, provisional or definitive diagnosis, and medication details were collected. Care was taken to maintain the confidentiality of patients and physicians. The data collected from all the centers were aggregated and analyzed at a central level. Prescriptions from all levels of healthcare professionals (interns, postgraduates, and faculty) were included. The primary data were analyzed using the WHO prescription indicators and for rationality assessment (and is presently under consideration for peer-review elsewhere). However, the study presented in this paper focuses only on the secondary data and more specifically, the FDC data.

FDC Data (Secondary Data)

Data related to the use of FDCs was captured under a separate template as part of the above prescription research project. All prescriptions were analyzed for the presence of FDCs. The prescribed FDCs were then analyzed to determine how many individual types of FDCs were present (after removing duplicates).

All centers were asked to report the five most commonly prescribed FDC preparations in their respective setting (this was done to understand the usage trend and rationality status of FDCs in outpatient department settings of participating centers). The data sought included details on the usage of irrational and banned FDCs, and additional FDCs that are currently not banned but are similar to banned FDCs. Later, all the individual FDCs were analyzed based on Kokate Committee classification using notifications available on the website of CDSCO (last referred August 2021). This was referred to map all the prescribed FDCs to category A (irrational), category C (rational), and category B (require further data generation). The latest list of category B could not be obtained and hence was not included. FDCs with vitamins/minerals/supplements or micronutrients were considered as category C as 471 FDCs (with vitamins, minerals, or micronutrients) have been recently (in 2020) classified as rational.

The gazette notifications under section 26A of the Drugs and Cosmetics Act, 1940 by the Ministry of Health and Family Welfare and the current list of irrational FDCs under review at the CDSCO website were used as references. FDCs approved by the Drugs Controller General of India (DCGi) and FDCs related to vitamins, minerals, and micronutrients were referred to while checking the approval status.

Brief Background of the Kokate Committee

Prof C. K. Kokate (widely referred to as the Kokate Committee) was appointed for reviewing over 6000 applications pertaining mainly to FDCs that were approved by state licensing authorities but without an approval from CDSCO at the central level. The committee reviewed 5581 FDCs and categorized them as:

- Category A (963)—FDCs which are considered irrational and harmful,
- Category B (1692)—FDCs that require further deliberations,
- Category C (2617)—FDCs which are considered rational.
Results

A total of 13 institutions carried out prescription evaluation research in their respective outpatient clinics from August 2019 to August 2020. The list of participating centers is provided in the Appendix. Data pertaining to analysis other than FDCs (i.e., overall rationality assessment of prescriptions viz., whether each prescription is in line with standard treatment guidelines or not, summary of WHO prescribing indicators, usage of medicines

Table 1: The most common FDCs used across 13 institutions based on category

<table>
<thead>
<tr>
<th>Sl. no.</th>
<th>Category</th>
<th>Frequency of this category (out of 64)</th>
<th>Composition</th>
<th>Number of centers that used the given FDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vitamins, mineral supplements</td>
<td>15</td>
<td>• Different preparations of calcium and cholecalciferol</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Different preparations of multivitamins and minerals or minerals alone</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(excluding above one)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Antibacterials for systemic use</td>
<td>10</td>
<td>• Amoxicillin and clavulanic acid</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Ceftriaxone 1 gm + sulbactam 500 mg</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sulphamethoxazole + trimethoprim</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Drugs for peptic ulcer, GERD with prokinetic and antiemetic</td>
<td>9</td>
<td>• Pantoprazole and domperidone</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Rabeprazole and domperidone</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Omeprazole and domperidone</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Analgesics and antipyretics</td>
<td>7</td>
<td>• Paracetamol and aceclofenac</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Paracetamol and diclofenac</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Paracetamol and tramadol</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Paracetamol and ibuprofen</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Drugs related to respiratory system</td>
<td>5</td>
<td>• Montelukast and levocetirizine</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Formoterol + budesonide (inhalation)</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Drugs related to cardiovascular system</td>
<td>5</td>
<td>• Telmisartan + metoprol succinate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Furosemide + spironolactone</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Spironolactone + torsemide</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Aspirin and clopidogrel</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Atorvastatin and aspirin</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Iron preparations in combination with folic acid</td>
<td>4</td>
<td>Iron and folic acid preparation</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Drugs related to nervous system</td>
<td>2</td>
<td>• Clonazepam + escitalopram</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fluoxetine + olanzapine</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Cough and cold preparations (syrup)</td>
<td>2</td>
<td>• Guaiphenesin + terbutaline + bromhexine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Phenylephrine (5 mg/5 mL) + chlorpheniramine maleate (2 mg/5 mL) + dextromethorphan hydrobromide (10 mg/5 mL)</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>Ear drops</td>
<td>2</td>
<td>• Betamethasone + neomycin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Benzocaine + chlorbutol + paradichlorobenzene + turpentine oil</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>Topical oil</td>
<td>1</td>
<td>G. fragrantissima + C. camphora + eucalyptus globulus + M. spicata + C. deodara</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Antacids</td>
<td>1</td>
<td>Antacid (aluminium hydroxide + magnesium hydroxide + sodium carboxymethyl cellulose + simethicone)</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Oral rehydration salt formulations</td>
<td>1</td>
<td>Oral rehydration solution</td>
<td>1</td>
</tr>
</tbody>
</table>

Total number of frequently used preparations 64
listed in the National List of Essential Medicines (NLEM), pharmacoeconomic analysis, etc., have been analyzed separately and is being peer-reviewed elsewhere.

**FDC Usage across Participating Centers**

A total of 4,838 prescriptions were enrolled/collected from these 13 centers. Of these, 2093 (43.26%) had at least one FDC in them. The average number of FDCs per prescription was 0.76 (standard deviation = 0.4533). The 2093 prescriptions contained 366 individual types of FDCs (after removing duplicate entries).

**Five Commonly Used FDCs in Each Center**

Twelve centers reported the five most frequently prescribed FDCs as per the design. However, one center reported only four FDCs. Thus, there were 64 frequently prescribed FDCs as per the design. There were 29 unique FDCs overall. There were many common FDCs across the centers (e.g., eight centers reported that amoxicillin-clavulanic acid were among the five most common FDCs used by them). After removing these, there were 29 unique FDC preparations (Table 1). Of the 29 frequently used FDCs, 24 were approved by the DCGI while the rest five were not (i.e., namely, (1) syrup guaiphenesin + terbutaline + bromhexine, (2) syrup phenylephrine + chlorpheniramine maleate + dextramethorphan hydrobromide, (3) topical ear drops betamethasone + neomycin, (4) topical ear drops benzocaine + chlorbutol + paradichlorobenzene + turpentine oil, and (5) topical oil preparation Gaultheria fragrantissima + Cinnamomum camphora + Mentha spicata + Cedrus deodara). It is also not known whether these five FDCs are presently under review for approval or have already been approved by any of the state drug controllers.

Another interesting finding is that only five of the 29 commonly prescribed FDCs are mentioned in India’s NLEM 2015. These were amoxicillin-clavulanic acid, sulphonamethoxazole + trimethoprim, formoterol + budesonide, iron and folic acid preparations, and oral rehydration solution salts.

**Usage of Irrational FDCs**

Table 2 summarizes the irrational FDCs among the 366 individual types of FDCs prescribed across the centers. These FDCs were neither approved by DCGI nor were a part of the NLEM 2015.

<table>
<thead>
<tr>
<th>Ban on Hold FDCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among the 366 individual types of FDCs, there were five FDCs whose composition consisted of banned ones. However, none of these medicines were available in the hospital pharmacies or adjoining local pharmacies as observed during physical visits and verification by staff members of the participating centers.</td>
</tr>
</tbody>
</table>

**Classification of FDCs as per the Kokate Committee**

The 366 individual FDCs obtained from the prescriptions were further analyzed based on the Prof Kokate Committee classification. Of the 366, 150 FDCs belonged to category C (rational). Similarly, 91 FDCs with vitamins/minerals and supplements were also grouped in category C. Fourteen FDCs belonged to category D (require further data generation). Five FDCs were in ‘ban on hold’ category and 10 were irrational. The remaining 96 FDCs could not be categorized into any of the above classes. Overall, among the 366 FDC types, 62% were approved by DCGI and 38% were not mentioned in the list.

**Examples of category D FDCs**

Examples of category D FDCs were gabapentin + amitriptyline where phase IV trial data and escitalopram + etizolam for which active postmarketing surveillance data were requested.

**DISCUSSION**

The perceived benefit of FDCs has to be carefully balanced against potential disadvantages including the pharmacoeconomic impact. In the past decade, India has gone through a lot of regulatory, policy, and legal issues with respect to FDCs, as discussed in previous publications. A detailed review of these changes is beyond the scope of this manuscript.

The overall percentage of prescriptions with FDC was slightly higher when compared to another study from central India (43% in the present study vs 38% reported in that study). Overall, multivitamins and minerals constituted the most commonly used FDC category in this study, as against the results of another study conducted in 2017 in the same hospital which found that antibiotics constituted the most frequently prescribed FDC category.

**Table 2**: Usage of FDCs that were classified as irrational by the CDSCO

<table>
<thead>
<tr>
<th>Compositions</th>
<th>Reference12</th>
<th>DCGI approval</th>
<th>NLEM 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ginkgo biloba + piracetam + vinpocetine (60 + 800 + 5 mg)</td>
<td>FDC number 1441</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>2 Levocetirizine + phenylephrine (5 + 10 mg)</td>
<td>FDC number 3235</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>3 Ofloxacin + flavoxate (200 + 200 mg)</td>
<td>FDC number 2282</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>4 Bromhexine + dextromethorphan hydrobromide + ammonium chloride (4 + 5 + 50 mg)</td>
<td>FDC number 2552</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>5 Chloroalazepoxide + clidinium + dicyclomine + rabeprazole (10 + 5 + 2.5 + 10 mg)</td>
<td>FDC number 2268</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>6 Kojic acid dipalmitate + arbutin + octinoxate + mulberry extract + vit E (2, 1.5, 7.5 + 1%)</td>
<td>FDC number 3906</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>7 Cetirizine + paracetamol + phenylephrine (5 + 325 + 10 mg)</td>
<td>FDC number 2633</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>8 Etodolac + paracetamol+ serratiopeptidase (400 + 500 + 15 mg)</td>
<td>FDC number 312</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>9 Propranolol + etizolam (20/20/40 + 0.25/0.5/0.5 mg)</td>
<td>FDC number 1182</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
<tr>
<td>10 Heparin + benzyl nicotinate + sorbic acid I.P. (ointment) (50 IU + 2 + 1.97 mg)</td>
<td>FDC number 3985</td>
<td>Not mentioned in the list</td>
<td>No</td>
</tr>
</tbody>
</table>
reported earlier.\textsuperscript{7} This is to be expected considering the widely prevalent usage of multivitamins and minerals, and the tendency to combine these preparations for human consumption. From a rational use perspective, however, it is rare to have multiple deficiencies of vitamins and minerals concurrently. Individual vitamin supplementation has more scientific backing and may be more cost-effective.

Though we have identified the most frequently used FDCs across the 13 centers involved in this study, it is not possible to comment whether these were prescribed for the indication against which they were originally approved by DCGI. For example, pantoprazole-domperidone is approved for the treatment of GERD (when there is no response to pantoprazole alone). It could not be ascertained whether this indication was adhered to.

Banned FDCs were neither available in the pharmacies of participating hospitals nor with other chemists in nearby localities/towns on physical visits by the team from these centers. The five instances of prescriptions that contained banned FDCs could be due to lack of awareness on the part of the prescriber. The nonavailability of such FDCs in the hospital pharmacies of the participating centers augurs well for appropriate medicines management in our tertiary care hospitals. It is, however, important to continue to maintain constant guard against such combinations while simultaneously making the prescribers aware of such bans. One of the difficulties would be when companies substitute one or more ingredients so that the ban does not apply.\textsuperscript{20} In such cases, it is imperative that Drug and Therapeutics Committees in each hospital review the need for such combinations with a special focus on the substituted ingredients. It would also be good for policymakers to mandate special reviews when such substitution takes place.

All the identified irrational FDCs are currently being reviewed by the CDSCO. However, reviewing these combinations is associated with its own challenges. For some of the FDCs, companies do not provide the indications for which it was proposed, or sometimes the indication list is very exhaustive (especially for FDCs with antibiotics) or broad. Companies also submit data from a few studies to support the superiority of FDCs over individual agents, but the quality of data varies.\textsuperscript{21} Such FDCs, if approved, are permitted only for one or two indications. However, on the ground, these FDCs could be used off-label for other indications. For some FDCs which require prior liver assessment (e.g., diacerein), misuse can cause liver failure and other adverse effects such as diarrhea.\textsuperscript{22} A few such FDCs are available in India, namely, glucosamine + diacerein + sulfasalazine. The potential harm due to the use of such irrational FDCs is difficult to measure and could include more adverse effects, besides being more expensive; especially in India where out-of-pocket expenditure (60% or more in many regions) is the predominant way of availing healthcare.\textsuperscript{23}

Similarly, we have noticed the use of multiple FDCs for the management of chronic illnesses such as diabetes mellitus, hypertension, and cardiovascular illnesses. Management of such conditions needs greater adherence to achieve better clinical outcomes, and FDCs (and/or polypills) have been promoted for their key role in achieving the same.\textsuperscript{24–27} There is a need for data from well-designed studies comparing the advantages and disadvantages of such polypills over individual pills in the Indian population. However, care has to be taken while changing doses and there is a need to minimize medication errors while using FDCs for these indications.\textsuperscript{28} Most of these conditions require combination therapy when either first-line therapy fails or does not result in achieving the target outcomes. However, we do not know whether this was followed for the prescriptions used in this study.

Other commonly encountered preparations in our study included cough and cold medications. Their over-the-counter sale is not strictly regulated.\textsuperscript{29} Several FDCs with Montelukast were encountered despite US Food and Drug Administration’s black box warning associated with it for serious mental health side effects.\textsuperscript{30} Although Montelukast in combination with antihistamines is approved only for rhinitis, chronic urticaria, atopy, allergy associated with asthma, and prevention of seasonal attacks of asthma; many a times these combinations are being prescribed in patients without any documented history of asthma, chronic urticaria, or rhinitis.

Post the Kokate Committee classification, several subcommittees continued to review FDCs of various categories; especially those of category A and category B. Based on these, some FDCs from category B might have been further categorized into either category A/C/D. Since these processes are ongoing, some of these documents are not publicly available. Besides, most of the FDCs reviewed by the Kokate Committee were approved between 1988 and 2012, which means that the FDCs approved after 2012 have not been classified by the Kokate Committee. All these probably explain why we could not map the 96 FDCs featured in our prescription analysis into any of the above classes. Nevertheless, it is important to keep track of such unclassified FDCs and include them formally in future assessments. This would ensure a certain
degree of accountability and contain the pressure to use such combinations.

In India, where there are challenges in both access to healthcare and medicines, as well as excessive use or misuse, the plethora of FDCs adds to the challenge. This is especially the case due to the wide availability of irrational combinations. In the context of difficulties in regulating over-the-counter use of medicines, there is a need for more stringent implementation of existing policies and regulations.

**Conclusion & Recommendations**

Though much has been done by the national authorities in the past few years, much more remains to be done for streamlining the rational use of FDCs. With this in mind, the following recommendations have been placed for policymakers and other stakeholders to consider:

- **Usage of rational FDC**: Monitor the usage of commonly used FDCs to ensure that they are used for an approved indication. The CDGII approval list should be updated on a regular basis to include or modify the indications based on current evidence and guidelines.
- **Ban on hold’ FDCs**: There are different notifications related to banned FDCs and some of the banned FDCs are under review. Even though most of this information is available on the website of CDSCO, a dynamic system is desirable to identify whether all FDCs are completely banned, which ones are under legal review, and which ones are to be used or not to be used until a specific decision is available. A user-friendly system customized to different stakeholders, namely, clinicians, industry personnel, the general public, administrative personnel, etc., needs to be in place.
- **In general, approval of FDCs** should be done with the highest possible scrutiny and by following the policy guidelines for approval of FDCs in India—2013.31
- **FDCs which could be irrational**: Given the rising availability of newer FDCs that could have similar characteristics to banned or irrational FDCs, there is an urgent need for the CDSCO to have a firm, watchful policy for such newer FDCs. Ensuring that the onus is on the pharmaceutical company to conduct studies to generate sufficient evidence and having a stringent review system in place would ensure that there is an optimal filter for entry of such FDCs.

**Limitations**

Following are the limitations of this study:

- It was not possible within this study to verify whether any of the state licensing authorities have approved FDC preparations that were not on the CDGII’s approved FDC list. Besides, many FDCs which we have presumed to be disapproved might be under review at the CDSCO office for approval.
- The Kokate Committee classification is a few years old and a list of category B (FDCs which require further deliberations) could not be accessed. Due to further refinement being currently undertaken under the FDCs section of the CDSCO division, we may have missed any revisions/updates to the original Kokate Committee classification.
- The list of irrational FDCs which we have used is the one which is currently (April–May 2021) being reviewed at CDSCO. We may have missed any other similar previous list.
- Though each center aimed to enroll 600 prescriptions for prescription analysis, few of them could not complete the target due to the COVID-19 pandemic and other issues (such as delays in getting ethical clearances, staff appointment for the project, and other logistics).

**Statement of Ethics**

The study is a part of the ICMR RUMCs prescription research and evaluation project. There are 13 tertiary care centers. Each center has obtained the respective Institutional Human Ethics Committee approval. As part of the project, prescription evaluation and analysis were carried out, and findings pertaining to FDC are reported here.

**Authors’ Contributions**

Study concept: NAK, RK (overall).
FDC research study related: JR, SJC, NAK, RK.
Study design (overall): JR, SJC, PK, CDT, DKB, BS, BM, SKK, RT, HD, SC, NT, CD, PG, RR, SK, RK.
Study design (FDC): NAK, JR, SJC.
Data acquisition and control: RJ, JR, SJC, HRB, PKC, DKB, BM, SKK, RT, HD, SSR, SC, NT, CD, PG, RR, JM, SK, NAK (at respective centers).
Data analysis and interpretation (at respective centers): All coauthors from their respective centers except RK.
Manuscript preparation: JR (first draft).
Manuscript review and inputs: All coauthors.
Manuscript editing and finalization: JR, SJC, NAK, CD, SC, DKB.

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**Appendix**

- Christian Medical College, Vellore, Tamil Nadu, India.
- All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India.
- Vardhaman Mahavir Medical College & Safdarjung Hospital, New Delhi, Delhi, India.
- Christian Medical College & Hospital, Ludhiana, Punjab, India.
- Postgraduate Institute of Medical Education and Research, Chandigarh, Punjab, India.
- Seth Gordhandas Sunderdas Medical College (GSMMC) and the King Edward Memorial (KEM) Hospital, Mumbai, Maharashtra, India.
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Usage Pattern of FDCs at ICMR Network of RUMCs across India

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REFERENCES
**ABSTRACT**

**Aim:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has been causing a global pandemic of Coronavirus (COVID-19) disease in recurring waves. On November 24, 2021, a new SARS-CoV-2 variant (B.1.1.529) was identified in South Africa. We aimed to study the clinical profile, laboratory parameters, complications, and outcomes in patients hospitalized with COVID-19 infection during the third wave in India.

**Materials and methods:** This was a single-center cross-sectional study conducted from 10th January 2022 to 10th February 2022. Data on demographic profile, clinical symptoms, laboratory findings, complications, and clinical outcome was collected and compared between nonsevere and severe cases.

**Results:** A total of 74 patients were included. Four (5.4%) had a severe disease while 70 (94.6%) had a nonsevere disease. The most common symptoms were fever (60.8%), cough (52.7%), and sore throat (45.9%). There was a significant difference between severe and nonsevere groups in terms of symptom duration (p < 0.0412), and time elapsed from symptom onset to hospitalization (p < 0.001). The severe disease group also had significantly higher levels of leukocyte count, C-reactive protein (CRP), D-dimer, ARDS, sepsis, and a higher need for respiratory support (p < 0.001). A total of 70 (94.6%) patients were discharged while four (5.4%) patients succumbed to complications of COVID-19 infection. Complete vaccination against COVID was associated with significantly lower chances of severe disease [odds ratio (OR) 0.083, 95% confidence interval (CI) 0.0080–0.8632].

**Conclusion:** As compared to the previous two waves, the current wave of the pandemic had milder symptoms, less severe disease, and fewer ICU admissions and deaths. Successful completion of vaccination against COVID was associated with significantly lower morbidity and mortality.

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**INTRODUCTION**

COVID-19 was declared a pandemic by WHO on March 11, 2020. Since then, many variants have been identified giving rise to multiple waves in different countries. On 24th November 2021, a new SARS-CoV-2 variant (B.1.1.529) was identified in South Africa. WHO declared the new SARS-CoV-2 variant B.1.1.529 a variant of concern on 26th November 2021 and named it omicron. Owing to its multiple mutations, particularly in the spike protein, there were concerns about high transmissibility, greater binding affinity as well as escape from natural infection or vaccine-induced immune responses. Given its characteristics, it has spread to many more countries worldwide. The first case of Omicron in India was reported on 2nd December 2021 in Kamataka, within ten days of the first case reported by South Africa; indicating its high infectivity and transmissibility. To our knowledge has reported clinical and demographic. Here, we aimed to study the clinical profile, laboratory parameters, complications, and outcomes in patients hospitalized with COVID-19 infection during the third wave.

**MATERIALS AND METHODS**

This was a single-center cross-sectional observational study. It was conducted at a tertiary care hospital on the western coast of India, in Gujarat from 10th January 2022 to 10th February 2022. All adults >18 years of age with laboratory-confirmed RT-PCR positive were included in the study. The cases for which complete data were not available were excluded. The study was conducted after getting approval from the Institutional ethics committee.

The patients having severe dyspnoea, low oxygen saturation (SpO₂ < 93%), respiratory distress, or requiring mechanical ventilation and/or ICU admission were defined as severe cases. The nonsevere disease was defined as patients with mild symptoms and not requiring any respiratory support or ICU admission.

**Data Collection**

The clinical and laboratory data for all included patients was collected from case records. Two study investigators checked the collected data independently. Data abstracted included age, gender, prior history of COVID-19 infection, vaccination history, history of underlying comorbidities (hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, malignancy, etc.), symptoms (fever, cough, dyspnea, backache, myalgia, etc.), vital signs at admission (heart rate, blood pressure, and respiratory rate) and laboratory parameters on admission (CBC, blood glucose level, CRP, D-DIMER, RFT, serum electrolytes, chest X-ray, chest computed tomographic (CT) scans (when indicated)). Details regarding duration from the onset of symptoms to admission, the total length of stay in the hospital, the development of any other complications, and mortality were also recorded.

We also compared the demographic profile, clinical characteristics, and outcomes among patients with severe and nonsevere diseases.

**Statistical Analysis**

All the collected data were entered in a Microsoft excel sheet. The data were analyzed using SPSS software (version 22.0). Continuous variables have been presented as mean ± standard deviation (SD). Categorical variables are expressed as percentages (%). A Chi-square test has been applied to compare categorical variables and an independent t-test applied to compare continuous variables. For all the statistical analyses, p-value < 0.05 was considered statistically significant.

**Results**

A total of 74 patients were included with a mean age of 30.48 ± 16.45 years. Most...
Characteristics and Outcomes of Third wave of the COVID-19

of them (73%) were from the age group of 18–30 years. About 55.4% were females. Only four (5.4%) of these had severe disease while 70 (94.6%) had the nonsevere disease. The mean age of patients with severe disease was significantly higher as compared to that of nonsevere disease (53.25 ± 20.06 years vs 28.73 ± 14.97 years, p = 0.0032). There was a statistically significant difference between severe and nonsevere groups in terms of vaccination history (complete vaccination: severe vs nonsevere disease—1 (25%) vs 56 (78.6%), p = 0.0412) and time elapsed from symptom onset to hospitalization (7.5 ± 1.29 vs 2.85 ± 1.14 days; p ≤ 0.001) (Table 1).

The most common symptoms were fever (60.8%), followed by cough (52.7%), sore throat (45.9%), backache (40.5%), fatigue (40.5%), myalgia (31.1%), headache (25.7%), and rhinorrhea (20.3%). Less common symptoms were nausea/vomiting (9.5%), breathlessness (6.6%), loss of taste/smell (5.4%), and diarrhea (5.4%). A total of 18 (24.3%) patients were asymptomatic who were admitted for other medical or surgical conditions/procedures. These patients were isolated and closely monitored. All patients with severe disease had breathlessness while only 1.4% of those in nonsevere group had breathlessness. The most common comorbidities were diabetes and hypertension seen in 14.9% and 13.5% of patients, respectively, the difference being statistically significant between severe and nonsevere disease groups (100% vs 10%, p ≤ 0.001) (Table 1).

On comparing laboratory values between the two groups (severe vs nonsevere) we found a statistically significant difference in hemoglobin (8.95 ± 2.49 g/dL vs 12.19 ± 2.85 ± 2.24; p < 0.001), WBC count (13.16 ± 2.10 vs 12.19 ± 2.85 ± 2.24; p < 0.001), CRP (87.25 ± 13.94 mg/L vs 5.77 ± 2.5; p < 0.001), D-dimer (2131.5 ± 887.7 vs 480.95 ± 203.1 ng/mL, p < 0.001), RBS (243.3 ± 61.03 vs 140.2 vs 64.5, p = 0.0208), and serum creatinine (2.13 ± 0.89 ± 0.51, p = 0.0049). PaO2 and lung infiltrate were also significantly different (PaO2 74.25 ± 8.66 vs 96.5 ± 2.88; p < 0.001, lung infiltrates 100% vs 1.4%; p < 0.001 in severe and nonsevere groups, respectively) (Table 2).

Complete vaccination against COVID was associated with significantly lower chances of severe disease (OR 0.083, 95% CI 0.0080–0.8632).

All patients with severe disease needed respiratory support in the form of either oxygen through a mask, or noninvasive

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Severe cases (n = 4)</th>
<th>Nonsevere cases (n = 70)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>4 (100%)</td>
<td>41 (58.6%)</td>
<td>0.2609</td>
</tr>
<tr>
<td>Cough</td>
<td>39 (52.7%)</td>
<td>36 (51.4%)</td>
<td>0.6866</td>
</tr>
<tr>
<td>Sore throat</td>
<td>34 (45.9%)</td>
<td>33 (47.1%)</td>
<td>0.7275</td>
</tr>
<tr>
<td>Backache</td>
<td>30 (40.5%)</td>
<td>29 (41.4%)</td>
<td>0.8987</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 (40.5%)</td>
<td>28 (40%)</td>
<td>0.6920</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23 (31.1%)</td>
<td>21 (30%)</td>
<td>0.7755</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (25.7%)</td>
<td>19 (27.1%)</td>
<td>0.5351</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>15 (20.3%)</td>
<td>15 (21.4%)</td>
<td>0.6910</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>7 (9.5%)</td>
<td>7 (10%)</td>
<td>0.5063</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>5 (6.6%)</td>
<td>1 (1.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss of taste/smell</td>
<td>4 (5.4%)</td>
<td>4 (5.7%)</td>
<td>0.6320</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (5.4%)</td>
<td>4 (5.7%)</td>
<td>0.6320</td>
</tr>
</tbody>
</table>

Comorbidity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Severe cases (n = 4)</th>
<th>Nonsevere cases (n = 70)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>10 (25%)</td>
<td>7 (10%)</td>
<td>0.0322</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (14.9%)</td>
<td>7 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>2 (5%)</td>
<td>1 (1.4%)</td>
<td>0.2141</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>5 (12.5%)</td>
<td>5 (7.1%)</td>
<td>0.5799</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (2.7%)</td>
<td>0</td>
<td>0.0471</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (5%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a p value indicates difference between patients with severe and nonsevere disease. p ≤ 0.05 was considered to be statistically significant.
or invasive ventilation while none of the nonsevere group needed respiratory support (p < 0.001). Significantly more patients in the severe as compared to nonsevere group received antiviral (100% vs 14.3%; p = 0.0003) and steroid therapy (75% vs 1.4%; p < 0.001).

About 75% and 50% of patients in the severe group had ARDS and sepsis, respectively while in nonsevere group no instance of ARDS or sepsis was seen (p < 0.001 for both). All those with severe disease succumbed while all those in the other group recovered (Table 3).

### Discussion

This retrospective study described the clinical characteristics and outcomes of patients infected with COVID-19 disease during the third wave in a tertiary care hospital in Western India. A different pattern of clinical characteristics and outcomes was observed in the third wave as compared to the previous two waves of COVID-19 variants. During the study period, 74 patients were diagnosed with COVID-19 disease of which 70 (94.6%) patients had mild disease and only four (5.4%) had severe disease. Around 24.3% of patients were asymptomatic. Similar observations were made by Kim et al. in South Korea and Maslo et al. in South Africa. Infection was more common in previously infected individuals.

**Table 2: Laboratory and radiological findings among hospitalized Covid-19 patients among nonsevere and severe cases**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>Nonsevere cases</th>
<th>Severe cases</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin gm/dL</td>
<td>12–15</td>
<td>12.19 ± 2.36</td>
<td>8.95 ± 2.49</td>
<td>0.0247*</td>
</tr>
<tr>
<td>Leukocyte count x10⁹ (cells/µL)</td>
<td>4–11</td>
<td>5.77 ± 2.5</td>
<td>13.16 ± 2.10</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Platelet count x10⁹</td>
<td>1.5–4</td>
<td>2.81 ± 1.03</td>
<td>1.92 ± 0.80</td>
<td>0.1297</td>
</tr>
<tr>
<td>CRP &lt; 3 mg/L</td>
<td>9.21 ± 16.08</td>
<td>87.25 ± 13.94</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>D-dimer &lt; 500 ng/mL</td>
<td>480.95 ± 203.1</td>
<td>2131.5 ± 887.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ALTT 7–50 U/L</td>
<td>36.13 ± 21.58</td>
<td>38.60 ± 11.72</td>
<td>0.8198</td>
<td></td>
</tr>
<tr>
<td>AST 5–40 U/L</td>
<td>21.20 ± 7.82</td>
<td>32.80 ± 12.81</td>
<td>0.1223</td>
<td></td>
</tr>
<tr>
<td>RBS</td>
<td>140.2 ± 6.54</td>
<td>243.3 ± 61.03</td>
<td>0.0208</td>
<td></td>
</tr>
<tr>
<td>Creatinine 0.5–1.2 mg/dL</td>
<td>0.937 ± 0.51</td>
<td>2.13 ± 1.15</td>
<td>0.0049</td>
<td></td>
</tr>
<tr>
<td>Sodium 135–145 mEq/L</td>
<td>139.3 ± 2.75</td>
<td>136.5 ± 4.95</td>
<td>0.4078</td>
<td></td>
</tr>
<tr>
<td>Potassium 3.5–5.0 mEq/L</td>
<td>4.05 ± 0.21</td>
<td>4.52 ± 0.39</td>
<td>0.1671</td>
<td></td>
</tr>
<tr>
<td>Albumin 3.4–5.4 gm/dL</td>
<td>3.07 ± 0.39</td>
<td>2.81 ± 0.30</td>
<td>0.2174</td>
<td></td>
</tr>
<tr>
<td>PaO₂ 80–100 mm Hg</td>
<td>96.5 ± 2.88</td>
<td>74.25 ± 8.66</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Treatments, complications, and outcome of COVID-19 patients among nonsevere and severe cases**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total (n = 74)</th>
<th>Nonsevere (n = 70)</th>
<th>Severe (n = 4)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory support</td>
<td>4 (5.4%)</td>
<td>0</td>
<td>4 (100%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Oxygen mask</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Noninvasive ventilation (NIV)</td>
<td>2 (2.7%)</td>
<td>0</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>Invasive ventilation</td>
<td>2 (2.7%)</td>
<td>0</td>
<td>2 (50%)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral 14 (18.9%)</td>
<td>10 (14.3%)</td>
<td>4 (100%)</td>
<td>0.0003*</td>
<td></td>
</tr>
<tr>
<td>Antibiotics 74 (100%)</td>
<td>70 (100%)</td>
<td>4 (100%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Steroid therapy 4 (5.4%)</td>
<td>1 (1.4%)</td>
<td>3 (75%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS 3 (4.1%)</td>
<td>0</td>
<td>3 (75%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sepsis 2 (2.7%)</td>
<td>0</td>
<td>2 (50%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>8.29 ± 2.49</td>
<td>7.0 ± 1.15</td>
<td>11.50 ± 1.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge 70 (94.6%)</td>
<td>70 (100%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Death 4 (5.4%)</td>
<td>0</td>
<td>4 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p value indicates difference between patients with severe and non severe disease. p ≤ 0.05 was considered to be statistically significant.

In our study cohort, only four patients (5.4%) had severe disease requiring noninvasive ventilation (NIV) or invasive ventilation and succumbed. All these patients were elderly, had multiple comorbidities, presented late to the hospital after the onset of symptoms, were partially vaccinated or unvaccinated, and had raised inflammatory markers. Similar observations have been made in earlier studies.

### Limitations

The sample size is low and hence may not represent the entire general population. Viral genotyping was not available hence we could not provide genotyping was not available hence we could not provide
not confirm the variant as omicron. The number of patients over the age group of 60 years was only 10.8%, hence, the results may not reflect the actual disease severity in the elderly.

Despite these limitations, this study provides an idea of how the virus behaved in the third wave in India and reports areas of concern for severe disease. The findings can be confirmed with more elaborate data and used to form policies in the future as we still expect more waves of the virus.

**Conclusion**

We found that as compared to the previous two waves, the current wave of the pandemic had milder symptoms, resulting in less severe disease with relatively fewer ICU admissions and fewer deaths. Successful completion of vaccination against COVID was associated with significantly lower morbidity and mortality. Prior history of COVID infection was associated with milder subsequent infection.

**Acknowledgment**

We acknowledge the contribution from Dr Ashish Savani and interns Vidhi Parikh, Krishna Bramhabhatt.

**References**

A Study of Role of Medical Thoracoscopy in Undiagnosed Pleural Effusion

Vishakha Kapadia1*, Savita Jindal2, Pratik Patel3, Sanjay Tripathi4

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ABSTRACT

Aim and objectives:
- To know the diagnostic yield of pleuroscopy (medical thoracoscopy) in cases of pleural effusions which remain undiagnosed after routine initial investigations.
- To notice the different gross pleuroscopic findings during the procedure.
- To observe various histopathological reports of pleural biopsy taken through medical thoracoscopy.
- To know the various complications of pleuroscopy in patients undergoing this procedure.

Materials and methods: A total of 56 patients having undiagnosed pleural effusion were taken for study after informed written consent. All patients underwent medical thoracoscopy. The clinical, demographic, and radiological profile of patients was recorded. Gross pleuroscopic findings and histopathological reports of the pleural biopsy were noted. All patients were observed for any complications that occurred during or after the procedure.

Result: Diagnostic yield of thoracoscopy in the present study was 91.07% (malignant pleural effusion 75% and tuberculous pleuritis 12.5%). Adenocarcinoma was the commonest malignancy in 60.71% of patients amongst malignant pleural effusion in the present study. Very few complications were recorded. The most common postprocedure complication was subcutaneous emphysema (12.5%) followed by pneumothorax (10.78%).

Conclusion: Thoracoscopy gives excellent diagnostic yield in undiagnosed pleural effusion without major complications, and should be utilized wherever feasible.

Introduction

Pleural effusion diagnosis usually starts with detailed clinical history, clinical examination, and chest radiography. Pleural fluid examination for microbiological, biochemical, and cytological analysis after pleural fluid aspiration is done to determine the etiology of pleural effusion. In some cases, a blind biopsy of the pleura might help for the establishment of a diagnosis.

Medical thoracoscopy technique has high sensitivity and specificity and so remains the gold standard for the diagnosis and management of undiagnosed pleural effusion. In 1910 HC Jacobus, the Swedish internist performed this procedure first time for malignant pleural effusion in a 62-year-old woman. In t r o d u c t I o n

Aim and objectives:
- To know the diagnostic yield of pleuroscopy (medical thoracoscopy) in cases of pleural effusions which remain undiagnosed after routine initial investigations.
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Conclusion: Thoracoscopy gives excellent diagnostic yield in undiagnosed pleural effusion without major complications, and should be utilized wherever feasible.

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Materials and Methods

Inclusion Criteria
- All the cases of undiagnosed pleural effusion even after all routine investigations, microbiological, and biochemical testing of pleural fluid after thoracentesis and willing to go for thoracoscopy.
- Hemodynamically stable.

Exclusion Criteria
- Patient is not willing for thoracoscopy.
- Patients who are unfit for thoracoscopy.
- Patients with multiloculated effusion.
- Patients in whom pleural space is likely to be inaccessible easily.
- Patients with honeycomb lung, suspected hydatid cyst, pulmonary arteriovenous aneurysms, and highly vascularized pulmonary lesions.
- Patients with hemodynamic instability.

This is a prospective study conducted at a tertiary care hospital, Ahmedabad to establish the role of medical thoracoscopy in undiagnosed pleural effusion. All the patients of pleural effusion who came to the hospital undergo detailed clinical history including symptoms, addiction, occupation, significant medical, and surgical illness in past, drug intake if any, etc. All the required laboratory hematomatological and radiological investigations were done. Etiological diagnosis of pleural effusion was done by initial pleural fluid examination which includes microscopic and biochemical analysis (sugar, protein, gram stain, ZN stain, and culture, adenosine deaminase—ADA level) and at least three pleural fluid cytology—negative for malignant cells or other definite causes. All undiagnosed pleural effusions after initial and repeated biochemical and cytological analysis were taken for the study.

The procedure and its risk were explained to the patients and relatives. Proper written consent was taken.

Patients were advised to be nil by mouth for at least 6 hours prior to the procedure. Intravenous access was achieved in the upper limb contra lateral to procedure side proper positioning was given with lie down in lateral decubitus position with the affected side facing upward. The patient’s both arms were placed above and below the head. All vital parameters including blood pressure, oxygen level, and electrocardiogram were monitored throughout the procedure continuously. The procedure was carried out under local anesthesia at the desired incision site. Injectable tramadol and midazolam were given to improve the patient’s comfort without compromising respiration.

Usually the port site was at 5th or 6th intercostal space in midaxillary line. Approximately 1–2 cm sized incision was made

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at the selected site and then subcutaneous tissue and muscles were dissected bluntly to reach the pleural space. After reaching the pleural cavity, the insertion of a trocar with a cannula was done through the chest wall. Aspiration of pleural fluid was done and the systemic exploration of the pleura and pleural cavity was done.

Biopsies (2–6 samples) were taken from the abnormal sites with biopsy forceps and sent for histopathological analysis. In case there wasn’t any abnormality grossly seen over the parietal pleura, multiple biopsies were taken from different sites. The procedure ended with the chest tube placement with an underwater seal via the thoracoscope insertion site, after the removal of the port cannula. Chest radiograph was taken 2 hours after the postprocedural period. The patient was monitored for complications, and a detailed record was kept of any complications that occurs.

Pleuroscope used: OLYMPUS EVIS EXERA III CV-190.

### Results (Table 1)

#### Demographic Profile

Out of 56 patients, 45 (80.35%) were male and 11 (19.64%) were female. The mean age of the patients was 52.46 years (ranging from 11 to 82 years). A total of 21 patients (37.5%) were between 61 and 70 years of age, 12 (24.42%) patients in the age group 51–60 years, 8 (14.28%) patients in the age group 31–40 years, 7 (12.5%) patients in the age group 41–50 years, 4 (7.14%) patients in 21–30 years, 2 (3.57%) in the age group 11–20 years and 1 (1.78%) patient each between the age group 71–80 years and more than 80 years of age.

#### Symptomatology

All patients in the study had both dyspnea and cough. A total of 45 patients (80.35%) had dyspnea of Modified Medical Research Council (MMRC) grade 3 and 50 (89.28%) had a dry cough. Seventeen (30.35%) patients had complained of hemoptysis. A history of weight loss was seen in 45 (80.35%) patients. Fever was seen in 47 (83.92%) patients, out of them 43 (76.78%) patients had low-grade and 4 (7.14%) had high-grade fever.

1. A total of 40 (71.42%) patients had anorexia and chest pain along with other symptoms.

#### Comorbidities

A total of 29 (51.78%) patients had comorbidities in the present study. Ten (17.85%) patients had hypertension followed by eight (12.21%) patients who had diabetes type II. Six (10.71%) patients had both systemic hypertension and type II diabetes. Two (3.57%) patients had hypothyroidism and three (5.35%) patients had COPD.

### Table 1: Shows observed results in this study

<table>
<thead>
<tr>
<th>Demographic profile</th>
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<tbody>
<tr>
<td>Age (Mean ± SD)</td>
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<tr>
<td>Range</td>
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<tr>
<td>Gender n (%)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
</tr>
<tr>
<td>Symptomatology n (%)</td>
</tr>
<tr>
<td>Cough</td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Hemoptysis</td>
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<td>Weight loss</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Comorbidities, n (%)</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Thyroid disorders</td>
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<tr>
<td>COPD</td>
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<tr>
<td>Characteristics of pleural effusion, n (%)</td>
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<tr>
<td>Side</td>
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<tr>
<td>Right-sided</td>
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<tr>
<td>Left-sided</td>
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<td>Bilateral</td>
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<td>Amount</td>
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<td>Moderate</td>
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<td>Exudative/transudative</td>
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<tr>
<td>Exudative</td>
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<tr>
<td>Transudative</td>
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<tr>
<td>Thoracoscopic findings, n (%)</td>
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<tr>
<td>Multiple variable nodules</td>
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<tr>
<td>Mass</td>
</tr>
<tr>
<td>Adhesion</td>
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<tr>
<td>Sago grain</td>
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<tr>
<td>Ulcerative</td>
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<tr>
<td>Diagnosis, n (%)</td>
</tr>
<tr>
<td>Malignancy</td>
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<tr>
<td>Adenocarcinoma</td>
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<tr>
<td>Mesothelioma</td>
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<tr>
<td>Small cell Ca</td>
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<td>Squamous cell Ca</td>
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<tr>
<td>Papillary cell Ca</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Acute inflammatory reaction</td>
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<tr>
<td>Complications, n (%)</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
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<tr>
<td>Pneumothorax</td>
</tr>
</tbody>
</table>

#### Addiction

In the present study, 30 (53.57%) patients were smokers. A total of 25 (44.64%) patients had a
Role of Medical Thoracoscopy in Undiagnosed Pleural Effusion

Characteristics of Pleural Effusion

1. A total of 28 (21 male and 7 female) (50%) had right-side pleural effusion. About 23 (19 male and 4 female) (41.07%) patients had left side pleural effusion. Bilateral pleural effusion is present in five (8.92%) males. A total of 45 (80.35%) patients were diagnosed with gross pleural effusion followed by 11 (19.64%) who had moderate pleural effusion. Fifty (89.28%) patients had exudative pleural fluid and six (10.71%) patients had transudative pleural effusion.

2. Twenty-three patients were diagnosed with malignancy and two patients had acute inflammatory reactions among 27 patients who had hemorrhagic effusion.

Out of 29 patients presented with nonhemorrhagic pleural effusion seven (22.58%) and 19 (61.29%) patients had tuberculosis and malignancy, respectively.

Thoracoscopic Findings

Multiple variable-sized nodules over visceral and parietal pleura in 30 (57.27%) patients was the most common thoracoscopic findings followed by mass lesion in 12 (21.42%) patients, adhesions between visceral and parietal pleura were seen in nine (16.07%) patients.

In five (8.92%) patients sago grain appearance was found during thoracoscopy. Ulcerative lesions over the pleural surface were seen in only one (1.78%) patient.

Diagnosis

Out of 56 patients, 51 (91.07%) were diagnosed by medical thoracoscopy. The yield of thoracoscopy in this study is 91.07%.

1. A total of 42 (75%) patients were diagnosed with malignancy among which adenocarcinoma in 34 (60.71%) patients, three (5.35%) patients with mesothelioma, and three (5.35%) small cell carcinoma. One (1.78%) male diagnosed with squamous cell and one (1.78%) carcinoma and papillary cell carcinoma.

2. Seven (12.5%) patients were diagnosed as tuberculous pleuritis followed by two (3.57%) patients who had an acute inflammatory pleural reaction.

3. Five (8.92%) patients remained undiagnosed even after the thoracoscopic procedure and pleural biopsy.

Complications

There were very few complications after the procedure and overall it was found to be safe.

In the present study, 8.92% of patients had a sago grain appearance which is a less commonly observed finding amongst undiagnosed pleural effusion and similar to findings observed by Mehta et al.15 (9.3%).

Adenocarcinoma (60.71%) was proved to be the most common cause of pleural effusion in the current study. Compelling support to the present study is given by Thangajunam et al.21 and Wang et al.18 in which majority of patients (33.33% and 25.92%, respectively) diagnosed with adenocarcinoma.

Tuberculous pleuritis (12.5% of patients) was diagnosed less commonly as compared to malignancy in undiagnosed pleural effusion, which is comparable with the study of Thangakunam et al.21 and Wang et al.18 Tuberculosis can be diagnosed with pleural fluid analysis so thoracoscopy is not required in these patients where there are limited resources.

In a study by Swarnakar et al.3 tuberculosis pleuritis was diagnosed in 44.44% which is not consistent with the present study.

Small cell carcinoma proved to be a cause of pleural effusion in 5.35% of patients. Compare with the study of Wang et al.18 11.11% of patients were diagnosed with small cell carcinoma which is slightly higher than the present study.

In our study, 3.57% of patients with pleural effusion were diagnosed with an acute inflammatory reaction which is comparable with the study of Mohan et al.19 (5.55%). As compared to my study, Wang et al.18 and Swarnakar et al.3 have more patients diagnosed with acute inflammatory reactions in 11.11% and 20% of patients, respectively.

In studies done by Lee et al.29 and Tscheikuna et al.21 diagnostic yield was 96.07% and 95.34%, respectively which is comparable with the present study.

The diagnostic yield of thoracoscopy in a study done by Law et al.22 (78.57%), Mehta et al.15 (76%), Mootha et al.23 (74.28%) is found to be slightly lower than the present study.

In the present study, the most common postprocedure complication was subcutaneous emphysema in 12.5% of patients which is comparable with the study of Law et al.,22 Wang et al.,18 and Prabhu and Narasimhan17 in which subcutaneous emphysema developed after thoracoscopy in 20%, 3.70%, and 4.41% of patients, respectively.

Another less common complication like pneumothorax was seen in 1.47% of the study of Prabhu and Narasimhan17 which is comparable with my study (1.78%).
**Conclusion**

Thoracoscopy provides a positive diagnosis of pleural effusions in whom the diagnosis has not been achieved by initial investigations, and repeated cytological and biochemical analysis of pleural fluid. The major advantage of thoracoscopy is that it gives an opportunity to perform a biopsy on suspicious-looking pleural lesions and nodules on the surface of the lung under direct vision. It is also possible to break down the adhesions with biopsy forceps. In addition, it is possible to carry out chemical pleurodesis at the same time. This procedure has the advantages of visual inspection, high safety, and few complications. The diagnostic yield of thoracoscopy is higher in undiagnosed pleural effusions so this procedure should be carried out in all undiagnosed pleural effusions whenever feasible.

**References**

In T2DM Uncontrolled on DPP4i+Metformin or SGLT2i+Metformin,

Switch Early to

UDAPA-Trio
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TURN TOWARDS IMPROVED CARE

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Ensures Adherence

Abridged Prescribing Information

Indication: It is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

Dosage and Administration: The recommended dose is one tablet daily. Each tablet contains a fixed dose of Dapagliflozin, Sitagliptin and Metformin Hydrochloride.

Adverse Reactions:

- Most common adverse reactions reported are: Dapagliflozin- Female genital mycotic infections, nasopharyngitis, and urinary tract infections. Sitagliptin- Upper respiratory tract infections, nasopharyngitis and headache. Metformin- Diarrhea, nausea/vomiting, flatulence, asthenia, abdominal pain, and headache.

Warnings and Precautions:

- Dapagliflozin: Volume depletion; Ketoacidosis in Patients with Diabetes Mellitus; Urosepsis and Pyelonephritis; Hypoglycaemia; Genital Mycotic infections

- Sitagliptin: General- Sitagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Acute pancreatitis: Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products; Renal impairment; Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions - Stevens-Johnson syndrome; Bullous pemphigoid. Metformin: Lactic acidosis. In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a healthcare professional is recommended.

- Contraindications: Dapagliflozin: Hypersensitivity to the active substance of Dapagliflozin, Sitagliptin & Metformin or to any of the excipients listed. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis). Diabetic pre-coma, Severe renal failure (GFR<30mL/min). Acute conditions with the potential to alter renal function such as: Dehydration, Severe Infection, Shock, Acute or chronic disease which may cause tissue hypoxia such as: Cardiac or respiratory failure, Recent myocardial Infarction, Shock, Hepatic impairment, Acute Alcohol intoxication, Alcoholism

- Use in special population: Pregnant Women: Due to lack of human data, drug should not be used during pregnancy. Lactating Women: It should not be used during breastfeeding. Paediatric Patients: The safety and efficacy of drug has not yet been established. No data are available. Geriatric Patients: In Patients > 65 years, it should be used with caution as age increases.

Additional information is available on request.

Last updated: January 03, 2023
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Post-COVID Syndrome: The Stranger Ghost of Culprit COVID-19

Sudhir Bhandari1, Govind Rankawat2, Shashank Joshi3, Mangesh Tiwaskar4, Anurag lohmrro5, Shiven Bhandari6
Received: 26 November 2022; Accepted: 01 January 2023

ABSTRACT
Background: Post-COVID syndromes are the most abundant sequel of coronavirus disease of 2019 (COVID-19) infection, which affects millions of people around the world. There is a significant difference observed during the acute phase as well as during the post-COVID period between patients hospitalized with (alpha, delta, or omicron) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant. In the present scenario, when most people are vaccinated, COVID-19 disease is less likely, but the remnants of previous COVID-19 infections are still a vast health burden.

Materials and methods: This prospective, observational, comparative, and analytical study included a total of 3,840 COVID-19-infected patients who visited the hospital. We included 1,150 patients of alpha variants, 1,845 patients of delta variants, and 815 patients of omicron variants, from June 2020 to November 2020, March 2021 to July 2021, and January 2022 to May 2022, respectively. All medical data of the study population, including hospital stay and vaccination status, were collected, and all patients were followed up for 6 months of duration. All collected data were compiled and analyzed to compare the post-COVID thrombotic and other events among different variants of COVID-19.

Results: Patients infected during the delta variant are the most symptomatic at onset (higher prevalence of fever, dyspnea, cough, myalgia, headache, or gastrointestinal problems) than those infected with the alpha or omicron variant (p < 0.01). A total of 2,830 patients (7.48%) [1,520 (82.38%) of delta variant, 598 (73.37%) of omicron variant, and 712 (60.34%) of omicron variant] developed post-COVID syndrome during their follow-up period out of 3,220 enrolled patients and the difference was statistically significant when compared among variants (p < 0.05). In this study, the highly prevalent post-COVID syndrome was mucormycosis (1.14%), followed by new-onset diabetes (9.89%), pulmonary fibrosis (7.67%), ischemic heart disease (6.46%), brain stroke (3.29%), and other thromboembolic disorders (2.37%).

Conclusion: COVID-19-associated onset symptoms during the delta variant were more severe and highly prevalent, while neurological symptoms (aguesia and anosmia) were more common during the alpha variant. Patients infected with the delta variant of COVID-19 are more prone to develop post-COVID-associated complications with minimal risk in the omicron variant and intermediate risk in the alpha variant. Long COVID-19 requires specific attention for management, irrespective of the SARS-CoV-2 variant.

INTRODUCTION
The several variants of SARS-CoV-2, such as alpha, beta, gamma, delta, epsilon, zeta, eta, theta, iota, lambda, and more recently, omicron have appeared in the world because of its quick spreading capability. Alpha, beta, gamma, delta, and omicron have been considered the variants of concern, in addition to the Wuhan variants. Post-COVID-19 syndrome is an important dilemma of SARS-CoV-2 infection, which cause a huge burden on healthcare systems worldwide. As per clinical studies, nearly about 60% of COVID-19 survivors will suffer from post-COVID syndrome during the 1st year after the infection. If the patient remains symptomatic after 3 months of diagnosis of COVID-19 and is not diagnosed otherwise, defined as a post-COVID syndrome. Most post-COVID patients have mild symptoms, and they recover early during the course of the disease, especially within months after infection, while some patients suffer from protracted progressive symptoms which adversely impair their daily activities and professional and social life. The most common post-COVID-19 symptoms include fatigue, musculoskeletal pain, dyspnea, and headache, while a few other symptoms, such as anosmia, ageusia, and skin rashes, also exist. The quality of life is usually compromised by the presence of the post-COVID syndrome. As per clinical research studies, post-COVID syndrome will be experienced by many people in the future. It is important to know the association of long COVID-19 with the different variants of SARS-CoV-2. We know that the omicron variant of COVID-19 has been associated with asymptomatic to mild disease with a lower rate of hospitalization compared with delta, but we did not know about long-term complaints of both variants either have similar extent or not. The majority of studies on different designs and populations suggest that the risk of post-COVID syndrome is approximately doubled in the unvaccinated group compared to vaccinated individuals. Antonelli et al. suggest that the omicron variants have a lower risk of developing post-COVID syndrome as compared to delta or any previous variant. Another study suggests that the risk of post-COVID syndrome is lower with the alpha variant but not with the delta or omicron variant of SARS-CoV-2.

We purposed this study to evaluate and compare clinical presentation at the acute phase of the infection as well as during the development of post-COVID-19 syndrome between patients hospitalized with the alpha, delta, and omicron variants of SARS-CoV-2. We also access the difference in the risk of thromboembolic events with emerging variants and vaccination. Thereby, public health policies and vaccination strategies can be planned worldwide for the future management of this pandemic.

MATERIAL AND METHODS
Study Design
The present prospective, observational, comparative, and analytic study was conducted on a total

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of 3,840 COVID-19-positive patients who visited the Outpatient Department (OPD) or Inpatient Department (IPD) of Sawai Man Singh (SMS) Medical College and Attached Hospitals, Jaipur, Rajasthan, India, in different time slots. SMS Medical College and its attached hospitals are the largest COVID-dedicated center in North India, containing 6,000 beds for IPD patients and 700 fully equipped intensive care unit (ICU) beds for the care of COVID-19 patients. This study was approved by the Institutional Ethics Committee of the institution. In this study, we included 1,180 patients of alpha variants from June 2020 to November 2020, 1,845 patients of delta variants from March 2021 to July 2021, and 815 patients of omicron variants from January 2022 to May 2022. These patients underwent serial observations and were monitored for any thrombotic events in their post-COVID periods especially within 6 months of exposure to the SARS-CoV-2 virus.

Data Collection
Diagnosis of COVID-19 was made according to World Health Organization guidelines. The collected medical data include demographics, medical and clinical history, the severity of the disease, duration of hospital stay, and vaccination status. The severity of COVID-19 patients was decided by the guidelines of the Indian Council of Medical Research (ICMR). All included patients of the study groups were successively monitored for any post-COVID thrombotic events for 6 months of duration from the day of exposure. At the time of active COVID-19 infection, data regarding age, gender distribution, clinical symptoms, disease severity, comorbidity, hospital stay, vaccination status, and prior COVID-19 infection among all patients were extracted from the medical records and stored for the study purpose.

All patients in the study group closely followed up at regular intervals to know any unexpected medical events related to post-COVID thrombosis. All patients are continuously monitored for a maximum of 6 months duration. All study populations were asked for symptoms that appeared after recovery from COVID-19 or whether the symptoms persisted at the time of the study. Post-COVID symptoms like dyspnea, fatigue, anosmia, ageusia, hair loss, skin rashes, brain fog, visual problems (e.g., worsening of vision and blurred vision), chest pain, palpitations, diarrhea, cough, and loss of concentration were systematically assessed. Those patients who lost follow-up were excluded from the study group. We used standard diagnostic criteria for confirmation of all post-COVID disorders.

Statistical Analysis
The quantitative data is denominated as mean and standard deviation, while qualitative data as proportions. Chi-squared test and z-score were applied to compare different parameters among different groups. A p-value of <0.05 was considered significant.

Results (Tables 1 and 2)
A total of 3,840 COVID-19-positive patients who visited the COVID care center in the different time slots were included in this study, out of which 1,180 patients were infected in the alpha wave, 1,845 patients were infected in the delta wave, and the remaining 815 patients were infected in the omicron wave of COVID-19 (Fig. 1).

In this study, we try to evaluate the prevalence of post-COVID symptoms among three major variants of COVID-19. There were also some group differences in the length of follow-up time by study group. COVID-19-infected patients were selected for the study group in the range of 30–70 years of age. The mean age of alpha, delta, and omicron variants of COVID-19 was 53.1 years (53.1 ± 12.4), 42.5 years (42.5 ± 11.6), and 48.1 years (48.1 ± 13.2), respectively. The elderly group of patients was more prone to capture infection in the alpha and omicron waves, while the relatively younger age group was affected in the second wave.

Male patients were more prone (60–65%) to develop SARS-CoV-2 infection as compared to female patients (35–40%) among all three major waves. In this study, symptomatic presentation was found to be higher in the delta variant as compared to another two variants. Clinical symptoms like fever, cough, dyspnea, myalgia, headache, anosmia, and ageusia are all found to be significantly higher in the delta variant of COVID-19 as compared to the alpha variant (p < 0.05). Major symptoms of COVID-19, like fever, cough, dyspnea, and headache also found to be higher in the delta variant as compared to the omicron variant.

In this study, we found that the prevalence of underlying chronic medical illness was highest during the alpha variant (46.02%) and lowest during the delta variant of COVID-19 (28.02%), while it was in between for the omicron variant (38.04%) with statistically significant difference (p < 0.05). Most of the patients who visited the hospital were asymptomatic to mild during alpha (83.71%) and omicron (75.42%) variants, while moderate to severe during the delta wave (61.24%). In the alpha wave, most of the infected patients required home-based OPD (42.03%) or IPD treatment (53.05%), while in the delta wave, 29.97% of patients required ICU care, and 54.63% of patients required IPD treatment.

In this study, we found that out of a total of 3,840 patients, 2,830 patients (73.69%) developed post-COVID thrombotic events during their follow-up period. Among three major variants, 82.38% of patients (n = 1520) developed post-COVID thrombotic events during the delta wave, while 73.73% (n = 598) during the omicron wave, and 60.34% (n = 712) during the alpha wave developed post-COVID disorders with a statistically significant difference. The most prevalent post-COVID symptoms were fatigue and muscular pain, which was most prevalent in the delta variant, followed by omicron and alpha variants in decreasing order (p < 0.05).

Discussion
In this study, we evaluate the post-COVID symptoms and their risk factors along the time course of three major variants of COVID-19. This study was carried out to know the actual real-life clinical remnants of COVID-19 disease in the three different major waves. This is a prospective, observational, and comparative study that includes patients who visited hospitals with asymptomatic, mild, moderate, and severe categories as per ICMR guidelines, while critically ill patients were excluded from this study. It is already explained that COVID-19 is a hyper-coagulable state and requires long-term thrombo-prophylaxis. After slowing down the COVID-19 waves, we should focus on post-COVID complications for early diagnosis and treatment. It is necessary of time that how we can improve the quality of life after this great pandemic, especially when post-COVID syndrome persists as a risk factor. The omicron and delta variants of COVID-19 are associated with equally increased risks of post-COVID symptoms when compared to non-infected.

Prevalent rates of most post-COVID-19 thrombotic events up to 6 months after hospitalization by different COVID-19 variants suggest that these events represent a common finding. Although SARS-CoV-2 variants differ in terms of viral load, transmissibility, and potential reinflections, the pathogenic cell-to-cell mechanisms associated with the development of post-COVID-19 fatigue may be similar between all variants.

In this study, we found that male patients were more prone (60–65%) to develop SARS-CoV-2 infection as compared to female patients (35–40%) among all three major waves. Patients infected with delta variants exert most of the symptomatic presentation as compared to the other two alpha and...
Table 1: A comparative analysis of the study population for the post-COVID syndrome

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Alpha wave</th>
<th>Delta wave</th>
<th>Omicron wave</th>
<th>p-value</th>
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<tr>
<td></td>
<td>(N = 1180)</td>
<td>(N = 1845)</td>
<td>(N = 815)</td>
<td></td>
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<tr>
<td></td>
<td>Alpha vs delta variants</td>
<td>Delta vs omicron variants</td>
<td>Alpha vs omicron variant</td>
<td></td>
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<tr>
<td>Median follow-up days (IQR)</td>
<td>182.5–178.176</td>
<td>184–169–188</td>
<td>170–182</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.1 ± 12.4</td>
<td>42.5 ± 11.6</td>
<td>48.1 ± 13.2 &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 708 (60%) Female: 472 (40%)</td>
<td>Male: 1120 (60.70%) Female: 725 (39.30%)</td>
<td>510 (62.58%) 315 (38.65%)</td>
<td>0.5892 0.337 0.1835</td>
</tr>
<tr>
<td>Symptoms at admission</td>
<td>Fever: 602 (51.02%) Cough: 342 (28.98%) Dyspnea: 156 (13.22%) Myalgia: 414 (35.08%) Headache: 390 (33.05%)</td>
<td>Fever: 1349 (73.12%) Cough: 1030 (55.83%) Dyspnea: 522 (28.29%) Myalgia: 810 (43.90%) Headache: 864 (46.83%)</td>
<td>Fever: 518 (63.56%) 328 (40.25%) 274 (33.62%)</td>
<td>&lt;0.001 &lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>GIT symptoms: 119 (10.08%)</td>
<td>GIT symptoms: 219 (11.87%)</td>
<td>GIT symptoms: 113 (13.87%)</td>
<td>0.1187 0.1388 0.0056</td>
</tr>
<tr>
<td>Medical comorbidity</td>
<td>Yes: 543 (46.02%) No: 637 (53.98%)</td>
<td>Yes: 517 (28.02%) No: 1328 (71.89%)</td>
<td>Yes: 310 (38.04%) No: 505 (61.96%)</td>
<td>&lt;0.001 &lt;0.001 0.0004</td>
</tr>
<tr>
<td>Severity of disease</td>
<td>Asymptomatic: 460 (38.98%) Mild: 525 (44.49%) Moderate: 146 (12.37%) Severe: 49 (4.15%)</td>
<td>Asymptomatic: 115 (6.23%) Mild: 604 (32.74%) Moderate: 723 (39.19%) Severe: 403 (21.84%)</td>
<td>Asymptomatic: 139 (17.06%) Mild: 476 (58.40%) Moderate: 168 (20.61%) Severe: 32 (3.93%)</td>
<td>&lt;0.001 &lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>OPD treatment: 496 (42.03%) IPD treatment: 626 (53.05%) ICU treatment: 58 (4.92%)</td>
<td>OPD treatment: 284 (15.39%) IPD treatment: 1008 (54.63%) ICU treatment: 553 (29.97%)</td>
<td>OPD treatment: 214 (26.26%) IPD treatment: 496 (60.86%) ICU treatment: 105 (12.88%)</td>
<td>&lt;0.001 &lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Mean duration of hospital stay (days): 7.9 ± 5.2</td>
<td>Mean duration of hospital stay (days): 12.2 ± 11.5</td>
<td>Mean duration of hospital stay (days): 8.5 ± 6.2</td>
<td>&lt;0.001 &lt;0.001 0.0204</td>
</tr>
<tr>
<td>Vaccination status</td>
<td>Unvaccinated: 1180 (100%) Single dose: 0 Double dose: 0 Triple dose: 0</td>
<td>Unvaccinated: 1120 (60.70%) Single dose: 595 (32.25%) Double dose: 130 (7.05%) Triple dose: 24 (2.94%)</td>
<td>Unvaccinated: 111 (13.62%) Single dose: 524 (64.29%) Double dose: 156 (19.14%) Triple dose: 24 (2.94%)</td>
<td>&lt;0.001 &lt;0.001 &lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Duration of the last dose: &lt;6 months – 1845 (100%) &gt;6 months – 0</td>
<td>Duration of the last dose: &lt;6 months – 583 (71.53%) &gt;6 months – 232 (28.47%)</td>
<td>Duration of the last dose: &lt;6 months – 70 (3.79%) &gt;6 months – 63 (7.73%)</td>
<td>&lt;0.001 &lt;0.001 0.001</td>
</tr>
</tbody>
</table>

omicron variants. Major clinical symptoms of COVID-19, like fever, cough, dyspnea, myalgia, headache, anosmia, and ageusia, are all found to be significantly higher in the delta variant as compared to the alpha variant (p < 0.05). In this study, we found that the prevalence of underlying chronic medical illness was highest during the alpha variant (46.02%) and lowest during the delta variant of COVID-19 (28.02%), while it was in between for the omicron variant (38.04%) with statistically significant difference (p < 0.05). This is also true from the literature that patients with risk factors like comorbid disease are more prone to get an infection with COVID-19 in the first wave of COVID-19.

A study by Fernández-de-las-Peñas et al. suggests that all three variants of SARS-CoV-2 have different COVID-19-associated symptoms at the time of hospitalization. The Wuhan variant has predominant symptoms of fever, dyspnea, and gastrointestinal problem, while the delta variant has predominant neurological symptoms (e.g., anosmia, ageusia, and headache). A study in South Korea suggests that delta variants have myalgia more common as compared to other variants. Mattiuzzi et al. reported no differences in COVID onset symptoms among all prevalent variants. However, these authors analyzed web searches of the general population. In fact, altered taste sense (ageusia) and altered smell sense (anosmia) is found to be a useful parameter for...
the clinical categorization of COVID-19 patients from other respiratory tract infection during the pandemic. For example, COVID-19, caused by alpha, delta, and omicron variants, can be differentiated from common flu caused by the influenza virus. Nevertheless, on the basis of flu-like symptoms in SARS-CoV-2, we should not consider it as common flu caused by the influenza virus.

Christensen et al. compared the omicron, alpha, and delta variants of COVID-19 and found that the populations differed significantly in median age, hospital admission rates, maximum respiratory support, vaccination status, and median length of stay. The younger population was more prevalent with the omicron variant as compared to the alpha and delta variants of COVID-19. Studies suggest that patients infected during omicron variants were hospitalized less frequently with lesser medical hospital stays as compared to alpha and delta variants.

Most of the patients who visited the hospital were asymptomatic to mild during the clinical categorization of COVID-19 patients from other respiratory tract infection during the pandemic. For example, COVID-19, caused by alpha, delta, and omicron variants, can be differentiated from common flu caused by the influenza virus.

A meta-analysis suggests that most post-COVID symptoms persist among three different variants of SARS-CoV-2 have different symptomatology. Brain fog is the most prevalent (11–13.5%) and bothersome symptom, was found to be similar among all the three SARS-CoV-2 variants. Myalgic encephalomyelitis/chronic fatigue syndrome with endothelial dysfunction has shared a

Table 2: A comparative analysis of post-COVID symptoms in the delta and omicron variants of SARS-CoV-2 virus

<table>
<thead>
<tr>
<th>Post–COVID symptoms</th>
<th>Alpha variant (N = 1180)</th>
<th>Delta variant (N = 1845)</th>
<th>Omicron variant (N = 815)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alpha vs delta variants</td>
</tr>
<tr>
<td>Number of patients (n)</td>
<td>712 (60.34%)</td>
<td>1520 (82.38%)</td>
<td>598 (73.37%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscular pain</td>
<td>533 (45.17%)</td>
<td>1068 (57.89%)</td>
<td>415 (50.92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>686 (58.14%)</td>
<td>1385 (75.07%)</td>
<td>539 (66.13%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cough</td>
<td>142 (12.03%)</td>
<td>649 (35.18%)</td>
<td>76 (9.33%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Palpitation</td>
<td>214 (18.14%)</td>
<td>227 (12.30%)</td>
<td>33 (4.05%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>83 (7.03%)</td>
<td>518 (28.08%)</td>
<td>50 (6.13%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>248 (21.02%)</td>
<td>520 (28.18%)</td>
<td>79 (9.69%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Depression</td>
<td>201 (17.03%)</td>
<td>370 (20.05%)</td>
<td>75 (9.20%)</td>
<td>0.0384</td>
</tr>
<tr>
<td>Brain fog</td>
<td>142 (12.03%)</td>
<td>207 (11.22%)</td>
<td>108 (13.25%)</td>
<td>0.4122</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>258 (21.86%)</td>
<td>532 (28.83%)</td>
<td>156 (19.14%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>235 (19.92%)</td>
<td>559 (30.30%)</td>
<td>125 (15.34%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Attention disorder</td>
<td>84 (7.12%)</td>
<td>203 (11.00%)</td>
<td>66 (8.10%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Visual problem</td>
<td>71 (6.02%)</td>
<td>126 (6.83%)</td>
<td>35 (4.29%)</td>
<td>0.2937</td>
</tr>
<tr>
<td>Hair loss</td>
<td>353 (29.92%)</td>
<td>722 (39.13%)</td>
<td>226 (27.73%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The presence of post-COVID cough, dyspnea, anxiety, depression, poor concentration, sleep disturbance, attention disorder, and hair loss were significantly higher in delta variant as compared to alpha and omicron variant (p < 0.001). Post-COVID syndrome like pulmonary fibrosis, mucormycosis, ischemic heart disease, brain stroke, and new onset diabetes were found to be significantly higher in delta variant as compared to alpha and omicron variant (p < 0.001).
similar prevalence among all three major variants.24,25

In a United States-based prospective study of 163 patients who were discharged without thrombo-prophylaxis, nearly 2.5% of patients were predisposed to thrombotic events within 30 days of discharge. This includes laboratory-confirmed pulmonary thromboembolism, intracardiac thrombus, thrombosed arteriovenous fistula, and ischemic cerebral vascular accident stroke.26 Other than this, we found that people infected with the delta variant reported a greater number of post-COVID-19 symptoms, particularly dyspnea, cough, fatigue, and few neurological symptoms, than the alpha or omicron variant. Persistent respiratory symptoms like dyspnea and fatigue after COVID-19 infection produced a higher burden on health care.27 As per literature, COVID-19 survivors persistently live with fatigue, persistent dyspnea, and health burden.28Nevertheless, delta variants of COVID-19 were found to be most notorious as it produces the highest-burden and health cost even after their post-COVID period as compared to other variants.

The most prevalent post-COVID syndrome observed in this study was mucormycosis (11.41%), new-onset diabetes (9.89%), pulmonary fibrosis (7.67%), ischemic heart disease (6.46%), brain stroke (3.29%), and other thromboembolic disorders (2.37%) in decreasing order. There are multiple risk factors for coronary artery disease and cerebral vascular disorders, which cumulatively alter the results of the prevalence of these life-threatening events. All post-COVID complications were significantly higher in the delta variant as compared to alpha and omicron variants.

Nalbandian et al. suggest that patients with a high risk for post-acute COVID-19, including those who had a severe illness during acute COVID-19, are most susceptible to complications (for example, the elderly, underlying chronic medical illness, post-transplant and active malignancy), and those with the highest burden of persistent symptoms should be taken on priority for post-COVID follow-up.29

Lund et al. suggest that the absolute risk of severe post-COVID thrombotic events after SARS-CoV-2 infection for asymptomatic and mild patients is low. However, increases in visits to general practitioners and outpatient hospital visits could indicate COVID-19 sequelae.30

Patients who required long-term hospitalization were more prone to develop post-COVID thrombotic events. As per the literature, we know that the delta variant was the most dangerous, and most of the patients were dependent on IPD/ICU treatment for weeks to months, so these patients easily sank into post-COVID thrombosis.

Fernández et al. suggest that the first Wuhan variant had more severe onset symptoms with post-COVID thrombotic events, while the delta variant had more neurological symptoms.20

As per clinical severity, most of the patients with the omicron variant remain asymptomatic to moderate. The University of Liverpool, Liverpool, England31 in their research study, suggests that the omicron variant generally does not infect lung cells efficiently and thus produces less damage to the lungs as compared to delta and other previous variants. Bojkova et al. suggest that the host cell interferon immune response generally does not affect by the omicron variant, which leads to lesser severity as compared to other variants.32 The interferon proteins released from infected cells and signal to the other system cells to resist viral growth; which fight the replication of SARS-CoV-2 and other viruses.33

It is essential to consider post-hospital discharge extended-duration thrombo-prophylaxis with LMWH or oral anticoagulants from a minimum of 2–12 weeks in selected COVID-19 patients with lower bleeding risk and higher thromboembolic risk, including advanced age, stay in the ICU, cancer, a prior history of thrombotic events, thrombophilia, severe immobility, an elevated D-dimer (>2 times ULN).34

**Conclusion**

In the present scenario, when most people got vaccinated, COVID-19 disease infection may be less likely, but the remnants of previous COVID-19 infections still are a vast health burden. COVID-19-associated onset symptoms during the delta variant were more severe and highly prevalent, while neurological symptoms (ageusia, anosmia) were more common during the alpha variant. Patients infected with the delta variant of COVID-19 are more prone to develop post-COVID-associated complications (like pulmonary fibrosis, thromboembolic stroke, ischemic heart disease, subsequent oxygen dependency, new-onset diabetes, etc.) with minimal risk in the omicron variant and intermediate risk in the alpha variant. Post-COVID symptoms were in decreasing order of delta, alpha, and omicron variant of COVID-19 but brain fog and blunting of memory was significant with the omicron variant and matched with the earlier two strains. As a remark, evidence supports that long COVID-19 will require specific management attention independently of the SARS-CoV-2 variant.

**Limitations**

There are several limitations to this study. Certain confounding factors like geographical distribution, age group, comorbidities, and mortality could not be matched because these parameters can significantly influence the long-term outcome of COVID-19. It was a single-center, observation, cross-sectional study, and the possibility of bias couldn’t be ruled out.

**Author Contributions**

S. Bhandari, S. Joshi and G. Rankawat prepared the research questions to design the study. G. Rankawat, A. Lohmror, Shiven Bhandari, and M. Tiwaskar collected and analyzed data for the study. S. Bhandari and G. Rankawat wrote the manuscript. S. Bhandari, M. Tiwaskar, and S. Joshi conducted the quality assessment. The manuscript is critically reviewed by all authors. The final version of the manuscript is read and approved by all authors.

**Availability of Data and Materials**

Available from the corresponding author upon reasonable request.

**References**

Post-COVID Syndrome: The Stranger Ghost of Culprit COVID-19

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Clinical Spectrum of Mercury Poisoning in India: Case-series from a Poison Control Center

Amit Balachandran1, Mohan Jambugulam2, Krupa George3, Srijita Inturi4, Swathi Padankatti5, Anand Alwan6, Sherin Susheel Mathew7, Arun Jose Nellickal8, Anand Zachariah9, Ravikar Ralph10*

Background: Mercury is a naturally occurring heavy metal that finds wide application in industrial and household settings. It exists in three chemical forms which include elemental (Hg⁰), inorganic mercuric (Hg⁺) or mercuric (Hg⁺⁺) salts, and organic compounds. All forms are highly toxic, particularly to the nervous, gastrointestinal, and renal systems. Common circumstances of exposure include recreational substance use, suicide or homicide attempts, occupational hazards, traditional medicines, and endemic food ingestions as witnessed in the public health disasters in Minamata Bay, Japan and in Iraq. Poisoning can result in death or long-term disabilities. Clinical manifestations vary with chemical form, dose, rate, and route of exposure.

Aims and objectives: To summarize the incidence of mercury poisoning encountered at an Indian Poison Control Center and use three cases to highlight the marked variations observed in clinical manifestations and long-term outcomes among poisoned patients based on differences in chemical forms and routes of exposure to mercury.

Materials and methods: A structured retrospective review of the enquiry-database of the Poison Information Center and medical records of patients admitted between August 2019 and August 2021 in a tertiary care referral center was performed. All patients with reported exposure to mercury were identified. We analyzed clinical data and laboratory investigations which included heavy metal (arsenic, mercury, and lead) estimation in whole blood and urine samples. Additionally, selected patients were screened for serum voltage-gated potassium ion channels (VGKC)—contactin-associated protein-like 2 (CASPR2) antibodies. Three cases with a classical presentation were selected for detailed case description.

Results: Twenty-two cases were identified between August 2019 and August 2021. Twenty (91%) were acute exposures while two (9%) were chronic. Of these, three representative cases have been discussed in detail. Case 1 is a 3.5-year-old girl who was brought to the emergency department with suspected elemental-mercury ingestion after biting a thermometer. Clinical examination was unremarkable. Chest and abdominal radiography revealed radiodense material in the stomach. Subsequent serial radiographs documented distal intestinal transit of the radiodense material. The child remained asymptomatic. This case exemplifies the largely nontoxic nature of elemental mercury ingestion as it is usually not absorbed from the gastrointestinal tract. Case 2 is a 27-year-old lady who presented with multiple linear nodules over both upper limbs after receiving a red intravenous injection for anemia. Imaging revealed metallic-density deposits in viscera and bones. Nodular biopsy was suggestive of mercury granulomas. A 24-hour urine mercury levels were elevated. She was advised chelation therapy with oral dimercaptosuccinic acid (DMSA). Case 3 is a 22-year-old lady who presented with acrodynia, neuronomyotonia, tremulousness, postural giddiness, tachycardia, and hypertension for 2 months, associated with intractable, diffuse burning pain over the buttocks and both lower limbs, 1 month after completing a 3-week course of traditional medications for polycystic ovarian syndrome. A 24-hour urine normetanephrine levels and mercury levels were markedly elevated. Serum anti-VGKC antibodies were present. She was treated with glucocorticoids and oral DMSA with a favorable clinical response.

Conclusions: The clinical manifestations of mercury toxicity are highly variable depending on the source, form, and route of mercury exposure and are related to its toxicokinetics.


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area corresponding to the stomach (Fig. 1A). The Poison Control Center was consulted for advice on further management. The treating team was advised to monitor the patient for 24 hours and examine her closely for evolving features of mercury vapor inhalational injury. She remained asymptomatic during this period. Subsequent serial radiographs revealed a distal transit of the radiodense material (Fig. 1B). She was discharged and remained clinically well on ambulatory clinical review.

**Case 2**

A 27-year-old lady from Jharkhand was referred to the clinical toxicology unit of the Poison Control Center for evaluation of incidentally detected metallic-density pulmonary deposits on a routine chest radiograph (Fig. 2). General physical examination was significant for hyperpigmented, firm, non-tender subcutaneous nodules in linear distribution over both upper limbs (Fig. 3A). Systemic examination was unremarkable. Radiographs of the upper limb revealed metallic deposits linearly distributed along the course of veins, corresponding to the location of subcutaneous nodules (Figs 3B and C). Ultrasonography of the nodules revealed multiple hypoechoic lesions of varying sizes with punctate hyperechoic foci within the subcutaneous plane. The left cephalic vein was obliterated by similar punctate hyperechoic foci. Computed tomography of the thorax, abdomen, and pelvis, performed to better characterize the pulmonary deposits and assess their extent, revealed extensive metallic density foci in the lungs, liver, kidneys, bowel, pelvic soft tissues and bones, vertebral bodies, and spinal canal (Fig. 4).

A subcutaneous nodule over the left proximal forearm was biopsied. Histopathological examination showed superficial dermal deposits of opaque spherical globules with associated foreign body-giant cell reaction with mixed inflammatory infiltrates (Fig. 5). There was a clear rim surrounding the globules, indicating a zone of collagen necrosis. These findings were highly suggestive of mercury granuloma. On revisiting the history, the patient recalled that the subcutaneous nodules had appeared 1 week after receiving painful intravenous infusions of a reddish-colored traditional medicine in both hands for anemia following an induced abortion. A region-based literature search indicated that this injection could possibly have been “red mercury,” a mixture of metallic mercury with a red dye, often promoted by scammers as a hematinic, aphrodisiac, and cure for various conditions including abortion. A sample of this compound could not be obtained for laboratory analysis.

Based on a history of possible exposure and clinical, radiological, and histopathological findings, a diagnosis of metallic mercury poisoning was established. This was confirmed by elevated 24-hour urinary mercury levels (585.20 µg/L; normal <3 µg/L). A detailed clinical and laboratory examination for acute and chronic effects of metallic mercury poisoning including neuropathy, nephropathy, and catecholamine excess was negative. The patient was advised periodic assessment. Source control by excision of the mercury granulomata was deemed less useful due to the extensive viscerocutaneous distribution of the deposits.

**Case 3**

A 21-year-old lady from Tamil Nadu presented to the neurology clinic with complaints of burning pain in both hands and progressive peeling off of skin over the fingers and toes bilaterally for 2 months. These symptoms were associated with a continuous, intractable, moderate intensity, diffuse aching or burning pain over the buttocks and both lower limbs which persisted through the day and disturbed sleep. The pain was aggravated by standing or walking and did not entirely subside on lying still. These symptoms started 1 month after the completion of a 3-week course of traditional medications for polycystic ovarian syndrome.

The patient also noticed an involuntary rippling of calf muscles during this period, suggesting myokymia. One month later, she developed postural lightheadedness and tremulousness.

She denied any history suggesting a low mood, suicidal ideation, emotional lability, forgetfulness, confusion, behavioral changes, limb weakness, imbalance, or prominent tremors. There were no loose stools, vomiting, decreased urine output, profuse sweating, or significant weight loss.

General physical examination was significant for tachycardia (heart rate: 140 beats per minute) and hypertension (blood pressure right arm supine: 154/90 mm Hg). She was noted to have warm, moist, and mildly edematous extremities with a pink discoloration of the hands and feet associated with desquamation of both palms (Fig. 6). A diffuse sensitivity was noted on palpating the extremities. Systemic examination was otherwise unremarkable.
Clinical Spectrum of Mercury Poisoning in India

Figs 3A to C: (A) Photograph of the right forearm showing flesh-colored nodules distributed in a linear fashion; (B and C) Plain radiograph of both forearms showing metallic densities distributed linearly, likely corresponding to the course of the veins—anteroposterior (A) and lateral (B) views.

Figs 4A and B: (A and B) Computed tomography scan of lower thorax, abdomen, and pelvis–coronal cuts, showing metallic density deposits in the lung bases, liver, kidneys, spinal canal, and pelvis.

Figs 5A and B: (A) Photomicrograph shows clear spaces in the superficial dermis with displaced dark opaque spherical globules of varying sizes (arrows) surrounded by chronic inflammation (H&E, 4×); (B) Photomicrograph shows clear spaces in the superficial dermis with displaced dark opaque spherical globules of varying sizes (arrows) surrounded by histiocytic palisades admixed with a few neutrophils, lymphocytes, and occasional giant cells (star) (H&E, 40×).
In view of features suggestive of acrodynia (erythema of palms and soles, edema of the hands and feet, diaphoresis, tachycardia, and hypertension), neuropathic pain, myokymia, and a history of possible exposure to mercury through traditional medicines, a clinical diagnosis of inorganic mercury poisoning was considered. The patient was referred to the clinical toxicology unit of the Poison Control Center for further evaluation and management.

A diagnosis of chronic mercury exposure was confirmed by elevated 24-hour urine mercury levels (64.35 μg/L; normal <3 μg/L). The complete blood count, serum electrolytes, liver function tests, and plasma creatinine and urea levels were within normal limits. The patient had significant proteinuria on urinalysis which was quantified to be in the nephrotic range. She did not consent for a renal biopsy. A 24-hour urine normetanephrine levels were elevated (860 μg/24 hours), with a normal 24-hour urine metanephrine level (176 µg/24 hours). An electromyogram confirmed clinical findings of neuromyotonia. A positron emission tomography scan performed to rule out paraneoplastic etiology was negative.

The autoimmune panel was negative for antibodies associated with systemic lupus erythematosus, Sjogren’s syndrome, and antibodies to the voltage-gated potassium channel (VGKC) (CASPR2) were detectable in serum. The patient was treated with tapering weekly doses of intravenous glucocorticoids for 8 weeks and two chelation cycles of oral DMSA for 2 weeks each. A complete resolution of clinical symptoms and a normalizing trend in laboratory parameters were noted at week 4 of therapy (Table 1).

**Discussion**

This case series highlights the varied clinical manifestations of mercury poisoning following exposure to elemental and inorganic forms via the oral and intravenous routes. In the next sections, we discuss sources, toxicokinetics, and clinical manifestations associated with exposure to the three chemical forms of mercury (elemental, inorganic, and organic). We also summarize important aspects of diagnosis and management.

**Elemental Mercury**

Elemental mercury or quicksilver continues to be used in many Indian appliances like thermometers and sphygmomanometers, which constitute one of its most common sources. Historical exposure sources include dental amalgams and mercury-filled syringes. Elemental mercury undergoes negligible absorption from an anatomically and functionally normal gastrointestinal tract. This is exemplified by case 1 where the child did not develop features of mercury toxicity despite radiological evidence of ingestion.

Inhalation represents the primary route of toxicity. Mercury is the only metal that exists in liquid form under standard temperature and pressure. However, it readily vaporizes on exposure to atmospheric conditions. On being inhaled, mercury vapors easily pass alveolar cell barriers. Injections are an unusual source of entry and are usually reported in settings of homicides or deliberate self-harm. Existence in liquid form makes it possible for the metal to be injected subcutaneously, intradermally, intramuscularly, and intravenously.

Following entry into the bloodstream, metallic mercury and its vapors undergo rapid oxidation to mercuric and mercuroous ions which cannot cross the blood–brain barrier and bind to serum proteins to exert cumulative effect. The metal and its vapors, however, readily cross the blood–brain barrier and accumulate in the brain since oxidation to mercury ions is not rapid enough to prevent their considerable uptake by the central nervous system (CNS). Clinical manifestations of elemental mercury poisoning can often be nonspecific and include weakness, generalized pain, anorexia, and weight loss. Acute high-level inhalational exposure to mercury vapors results in cough, fever, shortness of breath, vomiting, and acute gingivitis within hours of exposure. CNS accumulation results in mercurial erethism, a neuropsychiatric syndrome characterized by personality changes, irritability, insomnia, and shyness. Additional neurological manifestations include cognitive impairment, constricted visual fields, coarse postural tremors of outstretched hands (Hatter’s shakes), and other signs of cerebellar dysfunction. Chronic intoxication from low-level exposure to mercury vapors causes a classic triad of tremors, neuropsychiatric disturbances, and gingivostomatitis.

Case 2 highlights clinical consequences of intravenous injection of elemental mercury. Upon subcutaneous, intradermal, or intravenous injection, mercury deposits in capillary-dense areas of the body to cause local and/or systemic effects. Local effects include erythema and indurated nodules and plaques, caused by a foreign body granulomatous reaction or hypersensitivity. The deposited metal oxidizes slowly into mercury ions which exert a toxic systemic effect in the long term.

**Fig. 6:** Photograph of the right hand of a 21-year-old lady (case 3) showing a pinkish discoloration of fingertips and desquamation suggestive of acrodynia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline values</th>
<th>Postchelation cycle 1</th>
<th>Postchelation cycle 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour urine protein (mg)</td>
<td>3440</td>
<td>1200</td>
<td>320</td>
</tr>
<tr>
<td>EMG-NCV</td>
<td>Tibial F-wave after discharges, multiplets in gastrocnemius</td>
<td>Tibial F-wave after discharges</td>
<td>No tibial F-wave after discharges</td>
</tr>
<tr>
<td>Anti-VGKC antibodies (CASPR2)</td>
<td>2+</td>
<td>1+</td>
<td>Negative</td>
</tr>
<tr>
<td>24-hour urine mercury (μg/L)</td>
<td>64.35</td>
<td>38.53</td>
<td>13.13</td>
</tr>
<tr>
<td>24-hour urine normetanephrine (µg/24 hours)</td>
<td>860</td>
<td>270</td>
<td></td>
</tr>
</tbody>
</table>
complications of retained mercury deposits include microscopic pulmonitis, axonopathy, asthenozoospemria, renal impairment, liver toxicity, myocardial granulomatia, and chronic toxic encephalopathy characterized by memory deficits, extrapyramidal signs, cerebellar signs, and emotional lability.41,133

Inorganic Mercury

Inorganic salts of mercury are used in many traditional systems of medicine.2,27 They are usually insoluble, relatively stable, and poorly absorbed.2,28 Following acute ingestion, they exert a caustic effect on gastrointestinal tract mucosa, resulting in manifestations ranging from mild irritation to corrosive injury and hemorrhagic gastroenteritis.2,27 The proximal convoluted tubule is the primary site of deposition of mercury ions and renal excretion predominates.2,28 Acute kidney injury results for a combination of dehydration and direct toxic injury to the proximal convoluted tubules.2,28

Upon subacute or chronic exposure, inorganic mercury can affect multiple organ systems, as exemplified by case 3. Clinical manifestations of chronic exposure arise from inactivation of many biologically active molecules (enzymes and structural and transport proteins) in the internal milieu of the exposed organism.2,3,10 The inactivation is produced by the avid binding of mercury ions to sulfur atoms present in these molecules.2 For instance, mercury inactivates S-adenosylmethionine by binding to its sulfhydryl groups.19 This hinders the activity of catecholamine-O-methyltransferase, a key enzyme involved in the inactivation of catecholamine neurotransmitters like dopamine, norepinephrine, and epinephrine.1,2,20 This results in a catecholamine excess state characterized by tachycardia, hypertension, tremulousness, hyperhidrosis, and postural hypotension21 (as seen in case 3). Mercury also inhibits astrocyte uptake of cysteine, the rate-limiting step in the production of glutathione, a major antioxidant.2,22 This leads to a number of oxidant-induced tissue damage, including neuropathy and degeneration of various structures of the brain. Direct toxic damage to neuronal structures may also occur.2,23

Many other manifestations are a consequence of immune-mediated or hypersensitivity reactions. Immune-mediated injury is triggered by molecular mimicry and immune activation.2,22 T-cell mediated polyclonal B-cell activation causes immune-complex mediated glomerular disease characterized histopathologically as membranous nephropathy, minimal change disease, or focal segmental glomerulosclerosis.23–27 Autoantibodies against the VGKC (CASPR2 antibodies) may be formed, resulting in neuromyotonia.27 Acrodynia or “pink disease,” characterized by painful pink discoloration and peeling of the hands and feet, results from an idiosyncratic hypersensitivity to mercury ions.2

Organic Mercury

Human exposures to organic mercury chiefly occur through the ingestion of fresh- or saltwater fish which concentrate considerable amounts of methyl and dimethyl mercury in their tissues from contaminated water bodies.2 Organomercury compounds are highly lipophilic.2,10,21 They are rapidly absorbed from mucosal surfaces and skin. On entry into the bloodstream, aryl and long-chain alkyl compounds rapidly dissociate to release mercury ions due to an unstable carbon-mercury bond and hence produce toxicity similar to inorganic mercury.2 Short-chain alkyl compounds do not readily dissociate and adhere to sulfhydryl groups of serum proteins.2,28 These compounds easily cross membranes including blood–brain barrier causing predominant CNS effects.2 Methyl mercury vapor is absorbed as rapidly as vapors of elemental mercury. Neurotoxicity is typically delayed and occurs months after exposure.29 Classical neurological symptoms include visual disturbances (scotomata and contracted tubular visual fields), ataxia, dysarthria, hearing loss, paresthesia, and psychiatric symptoms.2,21,10

Diagnosis and Treatment

Given the wide variety of clinical manifestations, a high degree of suspicion is required to diagnose mercury poisoning. Temporal association with a possible exposure source is paramount. However, unique exposure sources like unauthorized medications (cases 2 and 3) render source ascertainment challenging. Exposure to elemental and inorganic mercury is best confirmed by 24-hour urinary estimation.2,31 Urinary mercury concentrations are reliable indicators of long-term exposure while whole-blood levels are of greater value in detecting acute high-level exposures.2,31 Blood and urine levels of mercury may not always correlate with clinical manifestations.2,32 Organomercury compounds are eliminated via the fecal route and urinary estimation is not helpful in these cases.2,31

Treatment includes supportive care, chelation, and occasionally other specific therapies like immunosuppressants.2,3 In case of localized dermal or subcutaneous inoculation, surgical excision may provide good source control.8 This option could not be selected in case 2 due to the widespread extent of the deposits. Supportive care includes stabilization and decontamination. Chelators including a thiol group are preferred (DMS and DMSA) as they compete with indigenous sulfhydryl groups for binding of mercury.2,33 Glucocorticoid therapy is used in immune-mediated manifestations like neuromyotonia and nephrotic syndrome.17,26 Robust clinical evidence on the efficacy of these treatment modalities is currently lacking.

Conclusions

Mercury toxicity can present with a wide variety of clinical manifestations and can often pose a diagnostic challenge. The pathophysiologic mechanisms and clinical features of mercury poisoning vary depending on the form, route, and duration of mercury exposure. Because of the presence of many unconventional exposure sources, mercury exposure is often not suspected, and diagnoses of mercury toxicity may be missed. Clinicians need to be familiar with the multiple clinical features of mercury which will facilitate prompt testing and diagnosis. Many cases may benefit from chelation and other specific therapies.

References

Clinical Spectrum of Mercury Poisoning in India

In hypertensive with CAD, initiate with Tazloc-Beta

Telmisartan 40 mg + Metoprolol Succinate 25 mg / 50 mg PR

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3. Cardio Protection
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7. Preferred in multiple patient profiles
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9. Prescribed as initiation therapy
10. Patient compliance
In patients with hypertension and diabetes,

**Tazloc AM**

Telmisartan 40/80mg + Amlodipine 5mg

For the Detrimental duo... The Distinctive duo...

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1. J. Am Coll Cardiol 2021 Mar; 77 (10) 1300-1301 CV: Cardiovascular
Predicting Short-term Readmission in Hospitalized Patients with Acute Heart Failure: The Use of 6-minute Walk Test at Discharge

Bermio Vijayakumar1, Anusuya Meganathan2, Balamanikandan Paulchamy3, Sharmila Devi Ranganathan4

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ABSTRACT

Background: Hospitalization is an important landmark in the history of heart failure. Patients admitted for acute heart failure have a high chance of readmission. We require predictors which can foresee readmission. Functional capacity assessment by the 6-minute walk test is one such predictor.

Objectives: To compare the mean 6-minute walk distance among acute heart failure patients readmitted within 30 days, those readmitted within 60 days, those readmitted within 90 days, and those not readmitted at 90 days following discharge after the first admission.

Methodology: This is a follow-up study conducted in Madras Medical College from March 2021 to August 2021. The study included patients who were admitted for the first time in their life for acute heart failure. The clinical details were noted, and the patients were managed as per standard protocols. Before discharge, a 6-minute walk test was performed. The patients were followed up at the end of 30, 60, and 90 days.

Results: 25% of the patients had one readmission at the end of 90 days. Majority of readmissions occurred at the end of 30 days. A low 6-minute walk distance at discharge was a significant predictor of readmission at the end of 30 days. A distance of 200 m was a reasonable cutoff in our population. A lower time walked was also a significant predictor of readmission at the end of 30 days. Some other parameters such as a longer duration of stay, a longer duration of intravenous (IV) diuretic requirement, discharge respiratory rate, and lower serum albumin at admission were also significant predictors of readmission at the end of 30 days.

INTRODUCTION

Readmission is an important issue in the management of heart failure.1,2 While the major focus has been on cardiac structural abnormalities, comorbidities, drug therapy, etc., emerging importance is also given to the functional level of the patient. Symptom-based scoring is a subjective method of assessing the functional level while tests such as the 6-minute walk test are objective tests for assessing the same. Very few studies have tested the correlation between a 6-minute walking distance and the risk of readmission for heart failure. Studies have been conducted in patients with chronic heart failure and also in patients with acute heart failure. This study was assigned to test the utility of the 6-minute walk test in predicting the risk of readmission in acute heart failure and to determine a cutoff of 6-minute walking distance which can be applied in practice to predict readmission. The results of this study could be used to prognosticate and hence give adequate importance to a subgroup of people who have a possibility of getting readmitted for the same illness.

AIMS AND OBJECTIVES

To compare the mean 6-minute walk distance among acute heart failure, patients readmitted within 30 days, those readmitted within 60 days, those readmitted within 90 days, and those not readmitted at 90 days following discharge after the first admission and assess the statistical significance.

METHODOLOGY

This was a prospective observational study of 118 consecutive patients admitted in Department of Internal Medicine, Madras Medical College with a diagnosis of acute heart failure with ejection fraction <40%. Study duration was 6 months (from March 2021 to August 2021) for recruitment of study participants and a further 3 months were taken to complete the follow-up (November 2021).

Inclusion Criteria

All hospitalized patients of both gender who met the criteria of

- Any age.
- First admission for acute heart failure.
- Cardiovascular indication for admission such as cardiogenic shock, acute pulmonary edema, volume overload, and effort intolerance.
- Ejection fraction <40%.
- Comorbidities of systemic hypertension, diabetes mellitus, and dyslipidemia were included.
- Discharge criteria of our study (adapted from American College of Cardiology 2019 guidelines and European Society of Cardiology 2016 guidelines).
  - No dyspnea at rest.
  - No orthopnea and bendopnea.
  - No edema.
  - Jugular venous pressure <8 cm.
  - No symptom recurrence for 24 hours after transitioning from IV diuretic regimen to oral diuretic regimen.
  - Hemodynamically stable for 24 hours before discharge.
  - Stable renal function 24 hours before discharge.
  - Is on evidence-based oral medication.

Exclusion Criteria

- Not willing to participate in the study.
- History of previous admissions for heart failure.
- Noncardiovascular indication for admission.
- Ejection fraction ≥40%.
- Comorbidities of chronic lung diseases, pulmonary hypertension, acute or chronic kidney diseases including cardiorenal syndrome.
- Inability to perform the 6-minute walk test.

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Use of Six-minute Walk Test in Predicting Heart Failure Readmission

Data Collection and Analysis
The patients enrolled in the study had a detailed history and examination documented. Complete blood count, renal function tests, liver function tests, electrocardiograms, and treatment details were recorded. After ruling out contraindications for the 6-minute walk test, the test was conducted on the day of discharge as per the guidelines of the American Thoracic Society 2002 and the 6-minute walk distance noted. Postprocedure vital signs were noted. The patients were followed up till 90 days postdischarge for symptom recurrence and readmission for cardiovascular indication. A repeat 6-minute walk test was performed at the end of 30, 60, and 90 days.

The data collected were entered in the form of a database in Epi Info software. The patients were divided into three categories: readmission at the end of 30 days, readmission at the end of 90 days, and no readmission at the end of 90 days. The mean 6-minute walk distance was calculated in each category and the difference was analyzed statistically using multivariate regression analysis. Correlation was tested with other factors such as the category of heart failure at first admission and vital signs at first admission.

Results

Demographic Details
The study population was 118 patients consisting of 46 males (39%) and 72 females (61%).

Table 1: Age distribution of the study population

<table>
<thead>
<tr>
<th>Age category</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–30 years</td>
<td>4</td>
<td>3.39</td>
</tr>
<tr>
<td>31–40 years</td>
<td>6</td>
<td>5.08</td>
</tr>
<tr>
<td>41–50 years</td>
<td>26</td>
<td>22.03</td>
</tr>
<tr>
<td>51–60 years</td>
<td>40</td>
<td>33.90</td>
</tr>
<tr>
<td>61–70 years</td>
<td>28</td>
<td>23.73</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>14</td>
<td>11.86</td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Readmission details of the study population

<table>
<thead>
<tr>
<th>Group</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not readmitted (A)</td>
<td>84</td>
<td>75</td>
</tr>
<tr>
<td>Readmitted in 30 days (B)</td>
<td>20</td>
<td>17.9</td>
</tr>
<tr>
<td>Readmitted in 60 days</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>Readmitted in 90 days</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>Total</td>
<td>112</td>
<td>100</td>
</tr>
</tbody>
</table>

The age distribution of the study population is shown in Table 1.

About 30.5% of patients were <50 years of age and 69.5% of patients were >50 years of age. The 51–60 years age-group contributed the maximum prevalence (33.9%). The median age of the patients was 58 ± 13.218 years.

Breathlessness, reduced exercise tolerance, and easy fatigability were the most common typical symptoms with which the patients presented during admission, in the order of frequency and similarly, bloated feeling, loss of appetite, and nocturnal cough were the three common atypical symptoms with which the patients presented.

Diabetes mellitus, hypertension, and coronary artery disease were the most common comorbidities in the patients.

Classification of Patients Based on Readmission
Six patients were lost to follow-up. So the final diagnosis included 112 patients. For analysis, the patients were classified into four categories as shown in Table 2.

About 75% of the patients were not readmitted at the end of 90 days. The majority of readmissions were in the first 30 days, contributing 17.9% of the study population.

Comparison of Clinical Data among Various Categories of Patients
The duration of heart failure (if known previously) was not significantly different among the four categories of the study population.

As shown in Table 3, the duration of hospital stay was significantly different between patients who were not readmitted and patients who were readmitted in 30 days. There was no significance between other combinations and no significant difference among all categories overall.

Table 4 shows the comparison of examination findings, laboratory parameters, and treatment details at admission and discharge among various categories of the study population. The following observations were significant:

- Admission room air saturation was significantly different among all categories, specifically between patients who were not readmitted and patients who were readmitted at 90 days, and also between patients who were admitted at 30 days and patients who were readmitted at 90 days.
- Discharge respiratory rate was significantly different among all categories, specifically between patients who were not readmitted and patients who were readmitted at 30 days.
- Discharge room air saturation was significantly different among all categories, specifically between patients who were not readmitted and patients who were readmitted at 90 days.
- There was no significant difference in admission hemoglobin among various groups. But, the hemoglobin of the patients ranged from 8.37 to 13.15 g/mL with a mean of around 10 g/mL, which is in the anemic range as per World Health Organization guidelines.
- Serum albumin alone showed a significant difference among groups, specifically between patients who were not readmitted and patients who were readmitted at 60 days, and between patients readmitted at 30 days and patients who were readmitted at 90 days.
- The duration of IV diuretic was significantly different among all the groups, specifically between patients who were not readmitted and patients who were readmitted at 90 days, and between patients who were admitted at 30 days and patients who were readmitted at 90 days.
- There was no significant difference in admission examination findings, laboratory parameters, and treatment details at admission and discharge among various categories of the study population.

Table 3: Comparison of duration of stay among various categories of the study population

<table>
<thead>
<tr>
<th>Duration of stay in hospital (mean ± standard deviation)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not readmitted (A)</td>
<td>5.62 ± 3.79</td>
</tr>
<tr>
<td>Readmitted in 30 days (B)</td>
<td>8 ± 3.40</td>
</tr>
<tr>
<td>Readmitted in 60 days (C)</td>
<td>7 ± 0</td>
</tr>
<tr>
<td>Readmitted in 90 days (D)</td>
<td>6.50 ± 0.58</td>
</tr>
<tr>
<td>Overall p-value</td>
<td>0.076</td>
</tr>
</tbody>
</table>

Results from the 6-minute Walk Test Performed
The 6-minute walk distance was significantly different among the four categories of patients. The mean 6-minute walk distances in the four groups were 284.222, 153.4, 145.5, and 202.5 m, respectively. The mean 6-minute walk distance was significantly higher in patients who were not readmitted than in the other categories.
Use of Six-minute Walk Test in Predicting Heart Failure Readmission

Table 4: Comparison of examination findings, laboratory parameters, and treatment details at admission and discharge among various categories of the study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Not readmitted</th>
<th>Readmitted within 30 days</th>
<th>Readmitted within 60 days</th>
<th>Readmitted within 90 days</th>
<th>Overall significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission heart rate</td>
<td>95.81 ± 15.79</td>
<td>95.60 ± 15.45</td>
<td>103.50 ± 0.58</td>
<td>102 ± 4.62</td>
<td>0.668</td>
</tr>
<tr>
<td>Admission respiratory rate</td>
<td>21.26 ± 2.62</td>
<td>21.10 ± 1.97</td>
<td>23 ± 3.46</td>
<td>23 ± 1.16</td>
<td>0.295</td>
</tr>
<tr>
<td>Admission SBP</td>
<td>124.81 ± 33.54</td>
<td>132 ± 31.39</td>
<td>95 ± 17.32</td>
<td>135 ± 17.32</td>
<td>0.201</td>
</tr>
<tr>
<td>Admission DBP</td>
<td>79.05 ± 19.25</td>
<td>85 ± 16.05</td>
<td>70 ± 11.55</td>
<td>80 ± 11.55</td>
<td>0.414</td>
</tr>
<tr>
<td>Admission room air saturation</td>
<td>92.33 ± 4.80</td>
<td>92.80 ± 4.40</td>
<td>89.50 ± 5.20</td>
<td>84 ± 6.93</td>
<td>0.006</td>
</tr>
<tr>
<td>Discharge heart rate</td>
<td>79.55 ± 8.06</td>
<td>83 ± 46.59</td>
<td>85 ± 3.46</td>
<td>85 ± 8.08</td>
<td>0.115</td>
</tr>
<tr>
<td>Discharge respiratory rate</td>
<td>18.17 ± 1.03</td>
<td>19.10 ± 0.97</td>
<td>19 ± 1.16</td>
<td>19 ± 1.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Discharge SBP</td>
<td>120.52 ± 13.68</td>
<td>122 ± 7.68</td>
<td>110 ± 0.00</td>
<td>123 ± 15.01</td>
<td>0.369</td>
</tr>
<tr>
<td>Discharge DBP</td>
<td>77.81 ± 9.60</td>
<td>81 ± 5.53</td>
<td>80 ± 0.00</td>
<td>79 ± 10.39</td>
<td>0.532</td>
</tr>
<tr>
<td>Discharge room air saturation</td>
<td>97 ± 1.63</td>
<td>97.10 ± 2.32</td>
<td>96.50 ± 1.73</td>
<td>94 ± 2.31</td>
<td>0.014</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.76 ± 2.39</td>
<td>10.68 ± 1.40</td>
<td>10 ± 0.23</td>
<td>10 ± 0.23</td>
<td>0.826</td>
</tr>
<tr>
<td>Total leucocyte count</td>
<td>10,678.33 ± 3030.42</td>
<td>10,440 ± 2965.49</td>
<td>8854 ± 3979.09</td>
<td>12,200 ± 0.00</td>
<td>0.463</td>
</tr>
<tr>
<td>Platelet count</td>
<td>2.68 ± 0.66</td>
<td>2.75 ± 1.34</td>
<td>2.38 ± 0.05</td>
<td>2.11 ± 0.36</td>
<td>0.450</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>141.69 ± 44.03</td>
<td>155.78 ± 92.87</td>
<td>110 ± 0.00</td>
<td>156 ± 0.00</td>
<td>0.619</td>
</tr>
<tr>
<td>Post prandial blood glucose</td>
<td>194.23 ± 64.45</td>
<td>222.22 ± 112.67</td>
<td>156 ± 0.00</td>
<td>242 ± 0.00</td>
<td>0.338</td>
</tr>
<tr>
<td>Serum urea</td>
<td>44.50 ± 24.40</td>
<td>43.30 ± 17.78</td>
<td>57 ± 26.56</td>
<td>33 ± 5.78</td>
<td>0.533</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.13 ± 0.53</td>
<td>1.31 ± 0.53</td>
<td>1.10 ± 0.23</td>
<td>1.10 ± 0.00</td>
<td>0.551</td>
</tr>
<tr>
<td>Serum AST</td>
<td>38 (28, 46.25)</td>
<td>25.50 (20, 37)</td>
<td>25.50 (19, 32)</td>
<td>33 (24, 42)</td>
<td>0.150</td>
</tr>
<tr>
<td>Serum ALT</td>
<td>38 (30, 45)</td>
<td>26 (15, 34)</td>
<td>29.50 (14, 45)</td>
<td>46.50 (41, 52)</td>
<td>0.386</td>
</tr>
<tr>
<td>Serum total protein</td>
<td>6.14 ± 0.36</td>
<td>5.86 ± 0.75</td>
<td>6.15 ± 0.40</td>
<td>6.25 ± 0.60</td>
<td>0.084</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.64 ± 0.44</td>
<td>3.09 ± 0.48</td>
<td>3.60 ± 0.58</td>
<td>3.90 ± 0.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood bicarbonate</td>
<td>20.51 ± 2.74</td>
<td>20.54 ± 2.70</td>
<td>20 ± 0.00</td>
<td>20 ± 2.31</td>
<td>0.977</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>136.24 ± 5.28</td>
<td>135.60 ± 6.34</td>
<td>136.50 ± 9.82</td>
<td>135 ± 5.77</td>
<td>0.945</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>4.23 ± 0.53</td>
<td>4.10 ± 0.48</td>
<td>3.60 ± 0.58</td>
<td>4.10 ± 0.35</td>
<td>0.108</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>33.02 ± 5.52</td>
<td>32.20 ± 5.97</td>
<td>27.50 ± 2.89</td>
<td>31 ± 5.51</td>
<td>0.226</td>
</tr>
<tr>
<td>Duration of IV inotrope requirement</td>
<td>80 ± 8.53</td>
<td>16 ± 0.88</td>
<td>4 ± 1.50</td>
<td>4 ± 0</td>
<td>0.350</td>
</tr>
<tr>
<td>Duration of IV diuretic requirement</td>
<td>3.02 ± 3.01</td>
<td>5.10 ± 2.02</td>
<td>2.00 ± 2.31</td>
<td>5.50 ± 0.58</td>
<td>0.009</td>
</tr>
<tr>
<td>Dose of IV diuretic requirement</td>
<td>84.32 ± 31.80</td>
<td>98 ± 29.67</td>
<td>80 ± 0.0</td>
<td>80 ± 0.0</td>
<td>0.335</td>
</tr>
</tbody>
</table>

ALT, Alanine transaminase; AST, Aspartate transaminase; DBP, Diastolic blood pressure; SBP, Systolic blood pressure

The 6-minute walk distance performed at discharge and at 30, 60, and 90 days also showed a significant difference between patients who were not readmitted and patients who were readmitted at 30 days (Table 5).

The time walked during the test was significantly different among the four categories (p-value 0.005), especially between patients who were not readmitted and patients who were readmitted at the end of 30 days, and between patients who were not readmitted and who were readmitted at the end of 90 days (Table 6).

The time walked during the test during discharge, at 30, 60, and 90 days were not significantly different. However, there was a decrease in the time walked during the test at the time of readmission (Table 6).

A parameter called walking speed in meters per minute was calculated by dividing the distance covered during the 6-minute walk test in meters by the time walked during the test in minutes.

The walking speed was significantly different between patients who were not readmitted and patients readmitted at 30 days at the 30-day follow-up and at the 60-day follow-up (Table 7).

**Discussion**

The role of 6-minute walk test in heart failure has been applied in two scenarios: (1) in chronic heart failure and (2) in a specific setting such as acute heart failure, cardiac transplant evaluation, postcardiac surgery, etc. Many studies are available validating the 6-minute walk test as a prognostic marker in chronic heart failure. Many have shown positive results while having limitations of vast variation in baseline characteristics including a cutoff of the 6-minute walk distance. An observational study based on National Norwegian Heart Failure Registry by Grundtvig et al. published in 2020 could be a landmark study because this is the largest ever study which used the 6-minute walk test as a prognostic tool in chronic heart failure. The authors have identified 22 independent variables which could prognosticate heart failure, one among them being the 6-minute walk distance.

Very few investigators have tried using the 6-minute walk test in the acute heart failure setting or a related situation. Though a
consensus exists that acute heart failure is a contraindication for performing exercise tests, international studies have been done without issues, even on the day of hospitalization.

All these studies share a few limitations:

- Though hospitalized heart failure patients were the study population, the cause of hospitalization was not mentioned. The patients could have presented with any of the heart failure manifestations such as congestive symptoms, shock, etc.
- Mappangara et al. specifically excluded decompensated heart failure patients.
- So a study with the specific heart failure phenotype would be better to analyze.

### Table 5: The 6-minute walk distance of the various categories of patients during discharge and at the 30-, 60-, and 90-day follow-up

<table>
<thead>
<tr>
<th></th>
<th>Not readmitted (A) (84)</th>
<th>Readmitted in 30 days (B) (20)</th>
<th>Readmitted in 60 days (C) (4)</th>
<th>Readmitted in 90 days (D) (4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 6-minute walk distance</td>
<td>284.222 ± 120.597</td>
<td>153.4 ± 81.99</td>
<td>145.5 ± 98.727</td>
<td>202.5 ± 204.959</td>
<td>A vs B = &lt;0.0001</td>
</tr>
<tr>
<td>during discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A vs C = 0.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A vs D = 0.203</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B vs C = 0.866</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B vs D = 0.413</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C vs D = 0.634</td>
</tr>
<tr>
<td>Mean 6-minute walk distance</td>
<td>309.311 ± 111.097</td>
<td>171.9 ± 64.373</td>
<td>160.5 ± 95.263</td>
<td>197 ± 165.122</td>
<td>A vs B = &lt;0.0001</td>
</tr>
<tr>
<td>at the end of 1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A vs C = 0.0101</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A vs D = 0.0563</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B vs C = 0.7671</td>
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<td>B vs D = 0.5970</td>
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<td></td>
<td>C vs D = 0.7153</td>
</tr>
<tr>
<td>Mean 6-minute walk distance</td>
<td>317.023 ± 106.890</td>
<td>184.6 ± 77.177</td>
<td>162 ± 122.398</td>
<td>203 ± 176.669</td>
<td>A vs B = &lt;0.0001</td>
</tr>
<tr>
<td>at the end of 2 months</td>
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<td>A vs C = 0.006</td>
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<td>A vs D = 0.0461</td>
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<td>B vs C = 0.631</td>
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<td>B vs D = 0.732</td>
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<td>C vs D = 0.716</td>
</tr>
<tr>
<td>Mean 6-minute walk distance</td>
<td>317.049 ± 109.441</td>
<td>193.444 ± 81.502</td>
<td>247 ± 153.575</td>
<td>117 ± 95.840</td>
<td>A vs B = &lt;0.0001</td>
</tr>
<tr>
<td>at the end of 3 months</td>
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<td></td>
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<td>A vs C = 0.222</td>
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<td>A vs D = 0.0006</td>
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<td>B vs C = 0.313</td>
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<td>B vs D = 0.109</td>
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<td>C vs D = 0.201</td>
</tr>
</tbody>
</table>

### Table 6: The time walked during the 6-minute walk test at the 30-, 60-, and 90-day follow-up period

<table>
<thead>
<tr>
<th></th>
<th>Not readmitted (A) (84)</th>
<th>Readmitted in 30 days (B) (20)</th>
<th>Readmitted in 60 days (C) (4)</th>
<th>Readmitted in 90 days (D) (4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time walked during the</td>
<td>328.33 ± 59.23</td>
<td>285 ± 90.29</td>
<td>300 ± 69.28</td>
<td>225 ± 155.89</td>
<td>A vs B = 0.015</td>
</tr>
<tr>
<td>6-minute walk test during</td>
<td></td>
<td></td>
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<td></td>
<td>A vs C = 0.433</td>
</tr>
<tr>
<td>discharge</td>
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<td>A vs D = 0.005</td>
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<td></td>
<td>B vs C = 0.698</td>
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<td></td>
<td>B vs D = 0.122</td>
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<td></td>
<td>C vs D = 0.134</td>
</tr>
<tr>
<td>Time walked during the</td>
<td>340.933 ± 50.142</td>
<td>290.6 ± 77.209</td>
<td>290 ± 80.829</td>
<td>270 ± 103.923</td>
<td>A vs B = 0.0005</td>
</tr>
<tr>
<td>6-minute walk test at the</td>
<td></td>
<td></td>
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<td></td>
<td>A vs C = 0.0567</td>
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<tr>
<td>end of 1 month</td>
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<td></td>
<td>A vs D = 0.0105</td>
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<td></td>
<td>B vs C = 0.989</td>
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<td>B vs D = 0.648</td>
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<td></td>
<td>C vs D = 0.771</td>
</tr>
<tr>
<td>Time walked during the</td>
<td>351.535 ± 29.86</td>
<td>319 ± 83.408</td>
<td>270 ± 103.923</td>
<td>300 ± 69.282</td>
<td>A vs B = 0.0045</td>
</tr>
<tr>
<td>6-minute walk test at the</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A vs C = &lt;0.0001</td>
</tr>
<tr>
<td>end of 2 months</td>
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<td></td>
<td>A vs D = 0.0023</td>
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<td>B vs C = 0.312</td>
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<td>B vs D = 0.675</td>
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<td>C vs D = 0.648</td>
</tr>
<tr>
<td>Time walked during the</td>
<td>347.561 ± 40.66</td>
<td>315.333 ± 75.870</td>
<td>320 ± 46.188</td>
<td>255 ± 121.243</td>
<td>A vs B = 0.0007</td>
</tr>
<tr>
<td>6-minute walk test at the</td>
<td></td>
<td></td>
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<td></td>
<td>A vs C = 0.191</td>
</tr>
<tr>
<td>end of 3 months</td>
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<td></td>
<td>A vs D = 0.0002</td>
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<td>B vs C = 0.908</td>
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<td></td>
<td>B vs D = 0.201</td>
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<td>C vs D = 0.355</td>
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</tbody>
</table>
Use of Six-minute Walk Test in Predicting Heart Failure Readmission

Table 7: The walking speed of the various categories of patients during the 90-day follow-up period

<table>
<thead>
<tr>
<th></th>
<th>Not readmitted (A) (84)</th>
<th>Readmitted in 30 days (B) (20)</th>
<th>Readmitted in 60 days (C) (4)</th>
<th>Readmitted in 90 days (D) (4)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean walking speed during discharge</td>
<td>50.434 ± 17.684</td>
<td>31.469 ± 14.014</td>
<td>26.75 ± 13.568</td>
<td>40 ± 26.943</td>
<td>A vs B = &lt;0.0001</td>
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<td></td>
<td></td>
<td>A vs C = 0.01</td>
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<td></td>
<td>A vs D = 0.263</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B vs C = 0.543</td>
<td></td>
<td></td>
<td>B vs D = 0.352</td>
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<td></td>
<td>C vs D = 0.414</td>
</tr>
<tr>
<td>Mean walking speed at the end of 1 month</td>
<td>53.252 ± 16.399</td>
<td>36.199 ± 9.932</td>
<td>30.886 ± 11.101</td>
<td>37.333 = −22.324</td>
<td>A vs B = &lt;0.0001</td>
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<td></td>
<td></td>
<td>A vs C = 0.0086</td>
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<td></td>
<td>A vs D = 0.065</td>
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<tr>
<td></td>
<td></td>
<td>B vs C = 0.347</td>
<td></td>
<td></td>
<td>B vs D = 0.869</td>
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<td></td>
<td>C vs D = 0.623</td>
</tr>
<tr>
<td>Mean walking speed at the end of 2 months</td>
<td>53.572 ± 16.78</td>
<td>35.851 ± 12.604</td>
<td>31.667 ± 15.011</td>
<td>35.917 ± 27.039</td>
<td>A vs B = &lt;0.0001</td>
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<td></td>
<td>A vs C = 0.012</td>
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<td>A vs D = 0.048</td>
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<tr>
<td></td>
<td></td>
<td>B vs C = 0.561</td>
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<td></td>
<td>B vs D = 0.994</td>
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<td>C vs D = 0.793</td>
</tr>
<tr>
<td>Mean walking speed at the end of 3 months</td>
<td>60.125 ± 16.517</td>
<td>37.194 ± 12.026</td>
<td>43.881 ± 22.462</td>
<td>23.467 ± 11.393</td>
<td>A vs B = &lt;0.0001</td>
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<td></td>
<td>A vs C = 0.0016</td>
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<td>A vs D = &lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td>B vs C = 0.361</td>
<td></td>
<td></td>
<td>B vs D = 0.39</td>
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<td>C vs D = 0.0475</td>
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<td>C vs D = 0.156</td>
</tr>
</tbody>
</table>

all-cause mortality. Heart failure-specific rehospitalization would be a better surrogate to understand the course of the disease.

• The cutoff measured was different in different studies probably due to the differences in demographic characteristics, racial differences, etc., which could not be standardized.

• The treatment details were not studied in any of the studies except by Kommuri et al.

• The standards of treatment have changed over time. So all these studies are not comparable with each other.

• The characteristics of the patients during discharge were not standardized. The probability of discharging an inadequately treated patient was possible.

• The time of performance of the test was not standardized.

• The 6-minute walk test being driven by the motivation of the patient lacked objectivity. This was an inherent disadvantage of the test despite its usefulness.

About 61% of our study population were females and 39% of the study population were males. This is in contrast to majority of the studies. Very few studies have shown a higher prevalence of female heart failure. Even the European Society of Cardiology 2021 guidelines, on mentioning the sex distribution, mention that the female prevalence of heart failure is slightly higher.

The INDia Ukieri Study (INDUS) study from India showed a male:female ratio of 1.9:1. The differences could be due to the definition differences used to define heart failure or due to geographical and lifestyle differences. We mentioned that the incidence of first acute heart failure admission was slightly higher in females with a female:male ratio of 1.6:1.

The median age of the patients was 58 ± 13.218 years, which is similar to most of the studies. The peak incidence was noted in the 51–60 years age-group.

About 25% of the patients were readmitted at the end of 3 months follow-up. The majority of the readmissions occurred at the end of 30 days contributing to 71.4% of the readmitted patients. This finding correlates with nearly all other studies on chronic and acute heart failure, which also show that the majority of the readmissions occur at the end of 30 days.

About 69.6% of the patients had no history of heart failure before admission, 16.1% of patients had a history of heart failure diagnosed <3 months ago, and 14.3% of patients had a heart failure duration of >3 months. Overall, since the number of patients was higher in the newly diagnosed group, the readmission rates were not significantly different among the different durations of heart failure.

Among the other parameters, room air saturation at admission and discharge respiratory rate were significant predictors of readmission.

Considering subgroup analysis, the duration of hospital stay and discharge respiratory rate significantly predicted readmission at the end of 30 days; admission room air saturation and discharge room air saturation predicted readmission at the end of 90 days. None of the other clinical parameters significantly predicted readmission. Ingle et al., McCabe et al., and Lim et al. have identified that systolic blood pressure and heart rate have a predictive value for 30-day readmission. However, Kommuri et al. have concluded that systolic blood pressure, diastolic blood pressure, and heart rate do not have predictive value for 30-day readmission.

Serum albumin was a significant predictor of readmission. Considering subgroups, serum albumin was a significant predictor of readmission at the end of 30 days and serum potassium was a significant predictor of readmission at the end of 60 days. Various studies have shown the utility of various laboratory parameters in predicting heart failure readmission. In these studies, hemoglobin, urea, and sodium were the important predictors of heart failure readmission in the first 30 days. In our study, serum sodium was not a significant predictor of heart failure readmission.
El Iskandarani et al. 15 in a recent meta-analysis, have mentioned that hypoalbuminemia is a significant predictor of long-term and short-term mortality. No other study has considered the utility of this marker. Hypoalbuminemia could be due to congestive hepatomegaly causing hepatic dysfunction.

Similarly, potassium abnormalities have been found to predict hospital mortality in heart failure. 16 In our study, hypokalemia predicted readmission at the end of 30 days, however, the significance could not be relied upon because of the small number of patients who were in that subgroup.

The ejection fraction was not a significant predictor for readmission. Other studies have also shown the same result.

The duration of IV diuretic was significantly different among the different groups of patients. Among the various subgroups, a higher duration of IV diuretic requirement was found to be a significant predictor of readmission at the end of 30 days. Various other studies have observed the proportion of patients taking various cardioprotective and diuretic drugs at discharge 5,8,14 and have also compared the percentages among various subgroups. McCabe et al. 7 have mentioned that persistent congestion is one of the reasons for readmission in heart failure patients. Since we have standardized our criteria to discharge patients only who do not have any symptom or sign of obvious left-sided or right-sided congestion, prolonged duration of IV diuretic requirement may mean a higher degree of congestion the patient may have and not just merely the inadequate decongestive treatment as usually thought of. Also, all the patients were discharged with medications as guided by international and local authority guidelines and every follow-up ensured proper adherence to the drug therapy. So, we did not specifically analyze the effect of medication differences other than diuretics and inotropes, as these two categories of drugs guide acute heart failure management.

The dosage of IV diuretic treatment or the duration of IV vasopressor and inotrope treatment does not significantly predict heart failure readmissions.

The 6-minute walk test in acute heart failure patients

The 6-minute walk distance significantly predicted hospital readmission within 30 days and readmission at the end of 60 days. This finding is in concordance with nearly all studies that tested the utility of the 6-minute walk distance, either in acute heart failure or in chronic heart failure. 5–12,17,18 This answers the primary objective with which this study was undertaken. Even in our population, the 6-minute walk distance was a significant predictor of heart failure at the end of 30 days. Even though the study has shown a sign of the 6-minute walk distance in predicting readmission at the end of 60 days, due to the small number of patients in this category, we feel that this finding may not be clinically significant.

We also analyzed another parameter of the 6-minute walk test, which was the time walked during the test. This parameter was a significant predictor of readmission at the end of 30 days and at the end of 90 days.

One of the limitations quoted in the literature for the 6-minute walk test is that the decision to stop in between the test is a subjective decision taken by the patient. Another school of thought was that it is a more appropriate measure of the daily living and functional capability of the patient.

No other existing study has tested the time walked during the test. We felt that using yet another parameter may add objectivity to the study. The time walked during the test was also a significant predictor of readmission.

We combined both these parameters and used another entity called walking speed in meters per minute. This entity has been recently studied by a few authors. 19,20 The mean walking speed or gait speed of the four categories of the patients was 50.43 m/min, 31.47 m/min, 26.75 m/min, and 40 m/min, respectively. This entity was also able to predict the readmission at the end of 30 days and at the end of 60 days. Hence, this new entity may help in predicting readmission, especially at the end of 30 days.

We also analyzed the trend of these three parameters over the 90 days follow-up period. There was a drop in exercise performance at the particular time they were readmitted. Otherwise, the 6-minute walk distance, time walked during the test, and the walking speed remained stable throughout the 90 days follow-up period. Hence it can be inferred that this test may not be useful as a sole predictor of improvement in survival or quality of life in the short term.

Strengths and Limitations of the Study

This study tried to eliminate the shortcomings of the previous studies in that, this study used standardized criteria for classifying patients and discharging patients. This study also took into consideration of the treatment parameters, which were lacking in most other studies. Also, this was one of the very few heart failure follow-up studies in our part of the country.

This study also had a few limitations such as the very small number of patients in the category of “readmitted within 60 days” and “readmitted within 90 days,” which made a few statistically significant observations to be clinically insignificant. Even larger studies may be needed to further add significance to the observations. We did not specifically include New York Heart Association (NYHA) grading in our analysis because all patients were grade IV NYHA on admission.

CONCLUSION

The 6-minute walk distance predicted readmission at the end of 30 days. The time walked during the 6-minute walk test and a new parameter also had a significant positive predictive value in heart failure readmission. Only a few random clinical, laboratory, and treatment parameters had a significant predictive value in heart failure, and their composite role cannot be ascertained. Follow-up values of the 6-minute walk distance, time walked during the test, and the walking speed were nearly stable over 90 days and do not have a statistically significant prognostic value. We recommend that the 6-minute walk test may be used as a simple bedside clinical test to risk-stratify patients and to intensify treatment measures. Larger studies from many ethnic populations are needed to further strengthen the level of evidence so that it may be incorporated confidently in future heart failure guidelines.

ETHICS STATEMENT

This study was carried out after obtaining Institute Ethics Committee approval of Madras Medical College dated 3rd March 2021. No. 14002021.

REFERENCES

Use of Six-minute Walk Test in Predicting Heart Failure Readmission

The Power and Promise of Angiotensin Receptor Neprilysin Inhibitor (ARNI) in Heart Failure Management: National Consensus Statement


Received: 10 December 2022; Accepted: 30 December 2022

Abstract
Heart failure (HF) is a huge global public health task due to morbidity, mortality, disturbed quality of life, and major economic burden. It is an area of active research and newer treatment strategies are evolving. Recently angiotensin receptor-neprilysin inhibitor (ARNI), a class of drugs (the first agent in this class, Sacubitril–Valsartan), reduces cardiovascular mortality and morbidity in chronic HF patients with reduced left ventricular ejection fraction (LVEF). Positive therapeutic effects have led to a decrease in cardiovascular mortality and HF hospitalizations (HFH), with a favorable safety profile, and have been documented in several clinical studies with an unquestionable survival benefit with ARNI, Sacubitril–Valsartan. This consensus statement of the Indian group of experts in cardiology, nephrology, and diabetes provides a comprehensive review of the power and promise of ARNI in HF management and an evidence-based appraisal of the use of ARNI as an essential treatment strategy for HF patients in clinical practice. Consensus in this review favors an early utility of Sacubitril–Valsartan in patients with HF with reduced EF (HFrEF), regardless of the previous therapy being given. A lower rate of hospitalizations for HF with Sacubitril–Valsartan in HF patients with preserved EF who are phenotypically heterogeneous suggests possible benefits of ARNI in patients having 40–50% of LVEF, frequent subtle systolic dysfunction, and higher hospitalization risk.

Journal of the Association of Physicians of India (2023): 10.5005/japi-11001-0209
The Power and Promise of Angiotensin Receptor Neprilysin Inhibitor

Approach to the Development of Consensus Statement

Across India, a group of experts in cardiology, nephrology, and diabetes participated in a National Meet, wherein they discussed evidence-based latest clinical data on HF assessment and management principles. Postdiscussion on HF treatment strategies, consensus statements on the use of ARNI, and Sacubitril–Valsartan in clinical practice were formulated. All participating 464 experts approved the finalized consensus.

Introduction

Heart failure (HF), an evolving epidemic, stands as an imperative cause of morbidity and mortality in the growing and aging population.1 Clinical syndrome of HF can be defined as structural and/or functional cardiac abnormalities, objective evidence of pulmonary or systemic congestion, and associated elevated natriuretic peptide levels. HF is divided into three categories based on the LVEF—HFrEF (an LVEF of ≤40%), HFrEF with minimally reduced EF (HFrmEF) (an LVEF of 41–49%), and HFrEF with preserved EF (HfpEF), which has an LVEF of at least 50%. Although there has been significant improvement in the treatment of HF over the past few decades, the prognosis is still poor, with greater rates of mortality, and hospitalization. To further improve its prognosis, new approaches, such as pharmacologic therapy, must be developed.2

The etiology and phenotype of HF differ largely. It presents a multifactorial, systemic disease in which following a cardiac injury—cellular, molecular, structural, and neurohumoral variations can affect the phenotype being present. Subsequently, stimulation of the sympathetic/adrenergic and renin-angiotensin-aldosterone system act as an adaptive mechanism to maintain physiological functioning, which in turn results in volume overload, tachycardia, dyspnea, and further worsening of the cellular function and presents as different, parallel developing clinical signs, and symptoms.3,4

A detailed medical history and physical examination commence assessment for HF along with elevated natriuretic peptides above age and context-specific thresholds and detection of LV systolic dysfunction as measured by echocardiography.5 HFrEF are characterized by ongoing LV dilatation and cardiac remodeling.5 While a diagnosis of HFrEF is challenging, as patients generally have a normal LVEF and near normal chamber dimensions, with some degree of wall hypertrophy and/or increased left atrial (LA) volume.6 Definition of HfpEF has evolved recently in clinical practice. HFP EF patients, they do present with common symptoms of HFrEF, namely fluid retention, reduced exercise tolerance, or limitations in physical activities of daily living.5,8

In some people, HFmEF appears to be a clinical entity midway between HFrEF and HFrEF, while in others, it appears to be more comparable to HFrEF, especially given the high prevalence of ischemic heart disease (IHD) in these patients. Gentler than HFrEF is HFrEF. Patients with HFmEF or HFrEF had a decreased risk of cardiovascular events than patients with HFrEF.9 High mortality and morbidity rates are associated with HF, a significant public health concern. Remodeling of the myocardium is central to the progression of HFrEF and occurs in response to ischemic or nonischemic myocardial injury, in addition to neurohumoral activation. Remodeling consists of changes in cardiac geometry, function, or both reflected by reduced LVEF along with increased LV volumes. Cardiac remodeling is associated with an increased risk of cardiovascular events, such as death and HF-related hospitalization, both of which are crucial targets for HF treatment. Guidelines-directed medical therapies (GDMT) for HFrEF, including β-blockers, angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRA s), have been linked to better outcomes with an increase in LVEF, a decrease in LV volumes, or both.10 In recent decades, there has been a major advancement in the management of HFrEF. Recent pharmacological treatments, such as the ARNI, type 2 sodium-glucose cotransporter (SGLT2) inhibitors, soluble guanylyl cyclase stimulator, cardiac myosin activator, and transcatheter mitral valve repair, mark a significant advancement with a better outlook than base treatments.5

In the prospective comparison of ARNI with ACEI to determine the impact on global mortality and morbidity in HF (PARADIGM-HF) trial, ARNI with Sacubitril–Valsartan reduced the key composite outcome of cardiovascular death or HF hospitalization in comparison to ACEI enalapril. Following this, treatment recommendations advise patients with symptomatic (American College of Cardiology/American Heart Association stage C) HFrEF to switch from ACEI/ARB to ARNI. The benefits of ARNI over ACE inhibition may be related to neprilysin inhibition’s effects on hemodynamics and cardiac remodeling; this increases the levels of biologically active natriuretic peptides and other vasoactive peptides in circulation, which has positive vasodilatory, antifibrotic, and antihypertrophic effects. Neprilysin inhibition lowers central aortic impedance in hypertension (HTN), which is a crucial factor in determining ventricular load and cardiac output. N-terminal pro-B-type natriuretic peptide (NT pro-BNP) and indicators of collagen turnover rapidly decrease with Sacubitril–Valsartan therapy for HFrEF, correlating to the direct effect of neprilysin inhibition on ventricular wall stress and cardiovascular structure, and function.11

Heart failure with reduced ejection fraction (HFrEF) and HFrEF differ both in the development and progression of the disease. For HFrEF, efficient and specific treatment protocols are well established; however, these treatments lack efficacy for HFrEF management.12 Drugs that are helpful in treating people with HFrEF may also be
effective in treating patients with HFmrEF, according to evidence from post hoc and subgroup analyzes of randomized clinical trials and a trial of an SGLT1-SGLT2 inhibitor. In this article, we go through key elements of pharmacological methods that go above and beyond standard therapy for HF patients, and include ARNI.

Prevalence: HTN, HFrEF, and HFpEF

Escalation in the prevalence (Table 1) and incidence of HF correlates to a rising proportion of cardiovascular risk factors. Myriads of associated comorbid conditions worsen the prognosis of HF, with associated several million hospitalizations and a major economic burden worldwide. Worldwide, an estimated 64.3 million people have HF. The prevalence of recognized HF is typically considered to be between 1 and 2% of the general adult population in affluent countries. Because of improved diagnosis and an overall rise in life expectancy, more than half of all HF patients in the general population have a preserved LVEF.

The prevalence of HFmrEF within the overall population of patients with HF is 10–25%. Because of population aging, population growth worldwide, and improved survival following diagnosis, the absolute number of individuals with HF has been rising. In addition to this disease being prevalent in the elderly, an increase in the incidence of obesity and obesity-related comorbidities in younger patients, such as type 2 diabetes, HTN, and atrial fibrillation, corresponds to an increase in the burden of HF in young individuals. At every age group, except for those >74 years, women experience HF at a considerably lower rate than males do. Women appear to have a higher relationship between obesity and incident HFpEF, and as a result, HFpEF is more prevalent in women. Compared to diabetic men, diabetic women exhibit more significant negative LV remodeling and worse outcomes. The same was observed in the Framingham Heart Study as well; in this study, the incidence of HF was increased fivefold in diabetic women and doubled in diabetic males (aged 45–74 years).

Clinical Spectrum

Patients with HF exhibit typical symptoms (such as fatigue, breathlessness, or ankle swelling) and signs (such as peripheral edema, elevated jugular venous pressure, or pulmonary crackles), all of which suggest low cardiac output and/or high intracardiac pressure. HF is defined as the heart’s inability to ensure optimal blood flow, which is necessary for the organs to maintain the metabolic and functional processes (at rest or during stress periods). In this article, we go through key elements of pharmacological methods that go above and beyond standard therapy for HF patients, and include ARNI.

Diagnostic Approach

Congestive HF (CHF) must be diagnosed in the context of objective signs and symptoms of HF, as well as cardiac dysfunction (Fig. 1 and Table 2).

The prevalence of HFmrEF within the overall population of patients with HF is 10–25%.

Diagnostic algorithm for heart failure

Suspected heart failure

- Risk factors
- Symptoms and/or signs
- Abnormal ECG

Heart failure confirmed

Define heart failure phenotype based on LVEF measurement

≤40% (HF:EF)

41–49% HFmrEF

≥50% (HFpEF)

Heart failure unlikely

Determine etiology and commence treatment

Consider other diagnoses

Fig. 1: 2021 ESC guidance for the diagnosis and treatment of acute and chronic HF. Adapted from Eur Heart J 2021;42(36):3599–3726. DOI: 10.1093/eurheartj/ehab368
and a community-based registry define current figures. HF burden, treatment patterns, and long-term outcome data, especially of hospitalized HF patients, are limited in low and middle-income countries (LMICs).

The Trivandrum HF Registry (THFR), which offers 5-year follow-up results and a low attrition rate, is the first structured prospective hospital-based registry of people with HF in India. It is a significant database that closes a gap in the existing research on mortality from HF in LMICs. In 2013, THFR enrolled 1,205 patients in Kerala, India. Acute HF was diagnosed in 7,507 patients overall, with a mean (SD) age of 64.3 (12.9) years and a female gender percentage of 37%. The criteria of the European Society of Cardiology (ESC) were met by the enrolled patients. More than two-thirds (67.5%) showed a decreased EF. GDMT was given to almost one-fourth (28%) of patients with HF and decreased EF. The overall death rate was 7.6%, while the 90-day mortality rate was 11.6%. The THFR study also found that boosting GDMT prescription for HF through focused hospital-based quality improvement activities may increase survival rates both during and after hospitalization in India.18,19

**Table 2:** Recommended diagnostic tests in all patients with suspected chronic HF.14 Adapted from Eur Heart J. 2021;42(36):3599–3726. DOI: 10.1093/eurheartj/ehab368

| Recommendations | Class | Level |...
<table>
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<tbody>
<tr>
<td>BNP/NT pro-BNP</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Transthoracic echocardiography</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Chest radiography (X-ray)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose, and Hba1c, lipids, iron status (TSAT and ferritin)</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; ECG, electrocardiogram; Hba1c, glycated hemoglobin; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; TSAT, transferrin saturation; α, Class of recommendation; B, Level of evidence; References are listed in section 4.2 for this item.

**Scientific Logistics Data with Morbidity and Mortality Reduction in HF (HFrEF, HfPEF)**

For ARNI PARADIGM-HF study, PIONEER-HF study, PROVE-HF study, PARAGON-HF study, PARAMOUNT-HF study, evaluate HF, and meta-analysis data highlights for ARNI.

**PARADIGM-HF Study: Prospective Comparison of ARNI with ACEI to Determine the Impact on Global Mortality and Morbidity in HF**

A randomized, double-blind, and prospective research called PARADIGM-HF compared Sacubitril–Valsartan with enalapril in patients with chronic HF [New York Heart Association (NYHA) functional class II–IV] and reduced EF 40% (n = 8442; age 18 years), Patients were taking a stable dose of α-blocker, an MRA if necessary, and an ACEI or ARB in a dose equivalent to 10 mg/day of enalapril for at least 4 weeks before screening.20 The primary outcome was specified as a composite of hospitalization for HF or death from cardiovascular causes.21

In PARADIGM-HF, when compared to enalapril, patients with HFREF who received Sacubitril–Valsartan had a 20% lower risk of cardiovascular death or hospitalization for HF (the primary endpoint), a 21% lower risk of first hospitalization for HF, and a 16% lower risk of death from any cause (all p < 0.001).22

Benefits of Sacubitril–Valsartan were apparent early in the course of the study and consistent regardless of background therapy, etiology of HFREF, and previous coronary revascularization or β-blocker dose. The advantages of ARNI with respect to cardiovascular mortality were consistent in all relevant subgroups. Sacubitril–Valsartan was superior to enalapril in reducing the risks of death and hospitalization for HF, and the benefit was highly significant and clinically important.20,21

**PIONEER HF Study: Comparison of Sacubitril/Valsalrtan VS Enalapril on Effect on NT pro-BNP in Patients Stabilized from an Acute HF Episode**

When patients with acute decompensated HF (ADHF) were hospitalized, PIONEER-HF evaluated the efficacy and safety of starting Sacubitril–Valsartan therapy as opposed to enalapril therapy after hemodynamic stabilization.23

By the 1st week, it was clear that starting Sacubitril–Valsartan therapy after hemodynamic stabilization caused a higher decrease in the NT pro-BNP than enalapril therapy (Fig. 2). In the Sacubitril–Valsartan group, the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53, whereas, in the enalapril group, it was 0.75 (46.7 vs 25.3%; the ratio of change with Sacubitril–Valsartan vs enalapril, 0.71; 95% confidence interval (CI), 0.63–0.81, and p < 0.001).

PIONEER-HF results supported the in-hospital initiation of Sacubitril–Valsartan in stabilized patients with ADHF and reduced EF, irrespective of prior ACEI/ARB use or prior HF diagnosis.

**PROVE-HF Study: Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling during Sacubitril/Valsalrtan Therapy for HF**

In HFREF patients receiving Sacubitril–Valsartan treatment, PROVE-HF looked at the relationship between NT pro-BNP alterations and long-term changes in markers of cardiac remodeling (measures of cardiac volume and function).10 An improvement in indices of cardiac volume and function at 12 months was weakly but substantially linked with a decrease in NT pro-BNP concentration in this single exploratory group, open-label research of 794 patients with HFREF treated with Sacubitril–Valsartan. At baseline, the median NT pro-BNP concentration was 816 pg/mL, and at 12 months, it was 455 pg/mL (difference, p < 0.001). At 12 months, LVEF increased from 28.2 to 37.8% (94% CI, 8.8–9.9); p < 0.001; LV end-diastolic volume index (LVEDVI) reduced from 86.93 to 74.15 mL/m² (p < 0.001); and LV end-systolic VI (LVESVI) decreased from 61.68 to 45.46 mL/m² (p < 0.001). Significant drops were also seen in LAVI and E/e’ ratio.
The observed reverse cardiac remodeling may offer a molecular explanation for sacubitril-favorable valsartan’s effects in HFrEF patients. Treatment with Sacubitril–Valsartan was connected, in terms of absolute changes in cardiac remodeling parameters, to a mean LVEF increase of 9.4% and clinically significant decreases in LVEDVI and LVESVI at the conclusion of 12 months. The benefits of most HF therapies, including Sacubitril–Valsartan, center on reverse myocardial remodeling, which is manifested by smaller LVs and enhanced function and is linked to a better prognosis.8

PARAGON HF Study: The Prospective Comparison of ARNI with ARB Global Outcomes in HFrEF

With EF of ≥45%, increased natriuretic peptide levels, NYHA class II–IV HF, and structural heart disease, 4,822 patients were randomly randomized to one of two groups using PARAGON-HF. A primary composite outcome of total HFH and cardiovascular death was used to determine which treatment option was given to eligible patients—Sacubitril–Valsartan or Valsartan. We evaluated the primary outcome components, secondary outcomes (such as the change in NYHA class, deteriorating renal function, and change in clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) scale, 0–100, with higher scores indicating reduced symptoms and physical limitations, and safety.8 The primary endpoint was reduced by 13% in the Sacubitril–Valsartan group compared to the valsartan group after a median follow-up of 35 months (relative risk—0.87 and 95%, CI—0.753–1.005, and \( p = 0.058 \)). While there was no improvement in cardiovascular mortality, there was a nonsignificant trend toward a decrease in HFH (Fig. 3).25 There were 690 and 797 total hospitalizations for HF, respectively [rate ratio (RR), 0.85 and 95% CI—0.72–1.00]; the incidence of death from cardiovascular causes was 8.5% in the Sacubitril–Valsartan group and 8.9% in the Valsartan group [hazard ratio (HR), 0.95; 95% CI, 0.79–1.16].8

Secondary outcomes, primarily NYHA class, quality of life, and renal function, all showed improvement. Renal function deteriorated in 1.4 and 2.7%, respectively, of patients in the Sacubitril–Valsartan group and 15.0 and 12.6% of patients in the valsartan group, respectively. In the Sacubitril–Valsartan group, the mean change in the KCCQ clinical summary score at 8 months was 1.0 points higher. There was evidence of heterogeneity among the 12 predetermined subgroups, with Sacubitril–Valsartan showing potential for benefit in patients with lower ejection percent and in female patients.8 The primary outcome of cardiovascular death and hospitalization for HF in the entire study population was missed by the PARAGON-HF trial. In a subgroup analysis, participants with LVEF below the study’s median value of 57% had a substantial drop in HF hospitalization and a significant reduction in RR (HR—0.78% and CI—0.64–0.95%). Results from PARAGON point to the benefits of ARNI in HF patients with structural LV dysfunction resulting in reduced LV systolic function.26 PARAGON thus demonstrated that ARNI is beneficial for patients with LVEF ranging from 40 to as high as 57% (HFmrEF).

PARAMOUNT HF Study: Prospective Comparison of ARNI with ARB on the Management of HFrEF

The PARAMOUNT trial involved patients with NYHA class II–III HF, maintained EF (45% LVEF), and NT pro-BNP levels greater than 400 pg/mL. Participants received treatment for 36 weeks with either Sacubitril–Valsartan titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily. All patients randomly assigned to treatment groups which had a baseline and at least one postbaseline examination were included in the analysis for the primary outcome, which was the change in NT pro-BNP (a measure of LV wall stress) from baseline to 12 weeks.27 After 4 weeks of treatment, Sacubitril–Valsartan administration reduced NT pro-BNP, which reached statistical significance after 12 weeks of treatment (Fig. 4), along with a significant reduction in LA size and an improvement in NYHA class.26 Valsartan baseline, 862 pg/mL (733–1012), 12 weeks, 835 (710–981); ratio Sacubitril–Valsartan/Valsartan, 0.77, 95% CI 0.64–0.92, \( p = 0.005 \). Sacubitril–Valsartan baseline, 783 pg/mL (95% CI 670–914), 12 weeks, This impact persisted for 36 weeks, but the between-group difference was no longer significant since the group receiving valsartan showed a delayed fall in NT pro-BNP.

PARAMOUNT concluded that in patients with HFpEF, Sacubitril–Valsartan reduced NT pro-BNP to a greater extent than valsartan at 12 weeks and was well tolerated.27

EVALUATE HF: Central Aortic Stiffness is Known to be Increased in HF and is a Key Contributor to Pulsatile Load and Wall Stress in the LV

A total of 464 people with HF (NYHA classes I, II, and III) and an EF of 40% or less were included in the multicenter, randomized EVALUATE-HF trial at 85 US sites. This study was done KCCQ to determine if Sacubitril–Valsartan treatment for HFrEF is superior to enalapril in terms of improving central aortic stiffness and cardiac remodeling. A shift in aortic characteristic impedance (Zc), a gauge of central aortic stiffness, from baseline to week 12 was the main result.11

Sacubitril–Valsartan ARNI therapy failed to lower the key study endpoint at 12 weeks. At 12 weeks, there was no discernible difference between individuals receiving Sacubitril–Valsartan vs enalapril in terms of the change in aortic Zc, which is a gauge of central aortic stiffness (~2.9 vs ~0.7 dyne/s/cm5).11

Selected secondary echocardiographic endpoints, such as LVEDVI, LVESVI, LA volume, and the mitral E/e’ ratio, significantly
The Power and Promise of Angiotensin Receptor Neprilysin Inhibitor

Journal of the Association of Physicians of India, Volume 71 Issue 2 (February 2023)

Consensus 1: Based on PARADIGM-HF Study, whether the patient is stable or unstable, we must switch from ARBs and ACEIs to early ARNI intervention in all patients with HFrEF. Stability in HFrEF is an illusion. In PARADIGM-HF Study, 20% of “stable” patients had a primary event during the progression of the trial. Around 50% of these events were deaths and 60% of these deaths were sudden deaths. As ARNI reduces sudden death as well as cardiovascular (CV) death, it has incremental benefits in reducing mortality compared to ACEI.

Consensus 2: Based on PIONEER-HF study, ARNI should be started in all patients with ADHF before discharge once they are off four parenteral inotropes and vasodilators. This strategy is feasible and reduces 8 weeks mortality and rehospitalization rates in patients with HFrEF. This benefit is seen in all groups viz acute decompensated chronic HF and de novo acute HF, irrespective of the presence or absence of background ACEI therapy.

Consensus 3: Reversal of morphological, functional, hemodynamic, biochemical, biomarker, hematological, and cell reprogramming remodeling is well documented in HFrEF and HfPEF with ARNI.

Consensus 4: TRANSITION is a study comparing predischarge and postdischarge treatment initiation with Sacubitril–Valsartan in HF patients with
The Power and Promise of Angiotensin Receptor Neprilysin Inhibitor

Table 3: Selected secondary echocardiographic endpoints in evaluate trial.11 Adapted from JAMA. 2019;322(11):1077–1084. DOI: 10.1001/jama.2019.12843

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sacubitril–Valsartan, Mean (SD)</th>
<th>Enalapril, mean (SD)</th>
<th>Between-group difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12 week</td>
<td>Baseline 12 week</td>
<td></td>
</tr>
<tr>
<td>Aortic Zc, dyne x s/cm²</td>
<td>223.8 (112.7)</td>
<td>218.9 (112.7)</td>
<td>213.2 (102.6)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>34 (10)</td>
<td>36 (10)</td>
<td>33 (10)</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>75.1 (26.1)</td>
<td>70.3 (23.5)</td>
<td>79.1 (25.9)</td>
</tr>
<tr>
<td>LVESVI, mL/m²</td>
<td>50.8 (22.6)</td>
<td>46.3 (20.5)</td>
<td>54.1 (22.6)</td>
</tr>
<tr>
<td>LA volume index, mL/m²</td>
<td>30.4 (9.5)</td>
<td>28.2 (9.0)</td>
<td>29.8 (8.7)</td>
</tr>
<tr>
<td>Mitral E/e’ ratio</td>
<td>13.8 (7.6)</td>
<td>12.3 (5.6)</td>
<td>13.4 (6.8)</td>
</tr>
</tbody>
</table>

reduced ejection-fraction hospitalized for an acute decompensation event. ARNI can be safely initiated in de novo HF patients who are ACEI naive as proved in TRANSITION study. ARNI in such patients, when initiated predischARGE leads to an early reduction in LV dimensions, improvement in LVEF, and also reduction in HS-Trop T levels which in turn reduces mortality and HFH.

Consensus 5: We must try to achieve the target dose of ARNI, which is 200 mg two times a day. This dose has been shown to cause a maximum reduction in mortality in HFH. However, in the PARADIGM-HF trial, all twice daily doses viz 50, 100, and 200 mg showed benefits. The lowest dose showed a 12% reduction in primary composite endpoint compared to the overall trial (20% reduction).

Consensus 6: Angiotensin receptor-neprilysin inhibitor (ARNI) can be safely used even in patients with borderline systolic blood pressure (SBP) after adjusting volume status (by down titrating loop diuretics and stopping all other drugs that can cause low BP but are not helpful in HFrEF viz nitrates, calcium channel blockers, etc.) ARNI in patients with borderline SBP reduces CV death and HFH. Patients who develop hypotension with ACEI have higher mortality than those who develop hypotension with ARNI.

Consensus 7: Hypotension can be easily managed in patients on ARNI therapy by down-titrating loop diuretics, increasing liquid intake judiciously, and stopping all other drugs that can cause hypotension but are not helpful in HFrEF such as nitrates, calcium channel blockers, etc.

Consensus 8: Angiotensin receptor-neprilysin inhibitor (ARNI) reduces the need for device therapy. We recommend that all the foundational pillars of HFrEF therapy, which include ARNI, β-blockers, SGLT2 inhibitors and MRAs should be tried in maximally tolerated dosages for at least 3–6 months, and then the LVEF should be reassessed by three-dimensional echocardiography and/or cardiac magnetic resonance imaging before deciding for cardioverter defibrillator/cardiac resynchronization therapy implant.

Consensus 9: Angiotensin receptor-neprilysin inhibitor (ARNI) reduces the need for Insulin in diabetic patients and also reduces the need for new initiation of Insulin by 29%. ARNI also reduces HbA1C by 0.6– 0.7% gm compared to ACEI. Trivandrum, Kerala, India—the Trivandrum HF study showed that 52% of patients admitted with HF in this registry had diabetes. ARNI reduces CV death by 20%, all-cause mortality by 16% and HFH by 20%, irrespective of glycemic status.

Consensus 10: Angiotensin receptor-neprilysin inhibitor (ARNI) can be given to HFpEF patients to reduce HFH (morbidity). This will mean all patients with signs and symptoms of HF, elevated NT ProBNP, and LVEF from 40 to as high as 57% in men and 60% in women benefit from ARNI (evidence PARAGON and PARAMOUNT study).

Consensus 11: Words of caution and contraindication should be observed in all patients of HFrEF and HFpEF with or without comorbidities, ARNI is contraindicated in patients with a history of angioedema related to previous ACEI or ARB therapy and in patients with concomitant use of ACE inhibitors. Caution is advised to observe for signs and symptoms of angioedema and hypotension. Monitor renal function and potassium in all patients periodically.

Consensus 12: Rarely a few patients, approximately 12–15% of HFrEF and HFpEF, have a contraindication to ARNI. Absolute contraindications include pregnancy and lactation, estimated glomerular filtration rate <30, a history of angioedema, severe hepatic failure, and bilateral renal artery stenosis.

Consensus 13: Hyperkalemia during ARNI therapy can be managed with standard measures such as a strict low-potassium diet, small doses of loop diuretics, potassium-binding resins, and glucose-insulin drips in severe cases. Patisromer will be a revolution in the management of ARNI-inflicted hyperkalemia.

Consensus 14: Angiotensin receptor-neprilysin inhibitor (ARNI) withdrawal may increase all-cause mortality.

Consensus 15: Don’t discontinue ARNI when LVEF improves. Some exceptions may include totally reversible forms of myocardial dysfunction, such as acute myocardial dysfunction in sepsis, COVID-19 myocarditis, and Takatsuho’s cardiomyopathy, etc., but we need more data.

Consensus 16: Low dose ARNI with a low dose of quadruple therapy [comprehensive disease-modifying quadruple therapy (ARNI, β-blocker, MRA, and SGLT2 inhibitor)] may have long-term benefits in those who do not tolerate high dosages. A low dose is still better than no dose.

Consensus 17: Timely meticulous use of ARNI in HF (HFpEF and HFrEF) may delay the need for LV assist device, right ventricular assist device, and biventricular assist device.

Consensus 18: Angiotensin receptor-neprilysin inhibitor (ARNI) intervention in an orderly way in HFrEF may defer the need for a MitralClip to reduce secondary mitral regurgitation (MR). ARNI, by reversal of remodeling, reduces mitral annular dimensions and reduces the quantum of secondary MR.

Consensus 19: Early ARNI Intervention and HFrEF in a protocolized manner may defer the need for a heart transplant.

Consensus 20: Need for protocolization of ARNI and early sequencing with SGLT2 inhibitors, β-blockers, and MRA by maintaining a checklist for escalation or titration of doses will help to prognosticate HF patients. This can be achieved by digital alerts or pharmacovigilance, or reminders by trained physician assistants.

Consensus 21: Need data on early intervention (Time window) of ARNI about its use in the setting of acute MI after percutaneous coronary intervention (PCI), or without PCI may need validation. Prospective ARNI vs ACE inhibitor trial to determine superiority in
reducing HF events after MI (PARADISE-MI) trial\(^a\) should not be interpreted as a defeat for ARNI but as a trial that establishes the safety of ARNI in acute MI settings.

**Consensus 22:** The use of ARNI is now approved by The United States Food and Drug Administration in a protocolized manner in children <18 years of age with HFrEF.

**Consensus 23:** Word of caution to use ARNI in CKD stage III–IV who are prone to hyperkalemia and dehydration.

**Consensus 24:** Euvolemia is of paramount importance for the effective and promising use of ARNI in HF.

**Consensus 25:** Seasonal variation in the dose of ARNI because of its diuretic effect. May need a dose reduction in summer and an increment in dose in winter.

**Consensus 26:** Titrate the dose of ARNI by NT pro-BNP and echo-guided approach combined with clinical parameters such as improvement in NYHA class and systolic BP.

**Consensus 27:** Early up-titration of dosage on every 2 weeks basis of ARNI along improvement in NYHA class and systolic BP and NT pro-BNP is considered to be an a marker of the need for continued intervention.

**Consensus 28:** Reversal of morphological remodeling of LV, mitral annulus, LA, RV, TV, and RA prognosticate sustained benefits.

**Consensus 29:** Angiotensin receptor-neprilysin inhibitor (ARNI) shows a radical reversal of morphological remodeling seen in inflammatory cardiomyopathy such as COVID-19 infected cardiomyopathy, septic cardiomyopathy, Takatsubo’s cardiomyopathy, etc.

**Consensus 30:** Functional/hemodynamic remodeling in the form of reduction of E/E’ and NT pro-BNP is seen with early intervention of ARNI.

**Consensus 31:** Dose titration of ARNI in hypertensive patients is the need of the hour to reduce morbidity and mortality.

**Consensus 32:** The dose of ARNI is variable on the need of the patient and needs monitoring.

**Consensus 33:** Low dose ARNI and SGLT2 inhibitor and bisoprolol and metoprolol, diuretic, MRA, or LD with monitoring of potassium, volume, and BP control need further protocolization. Need further elaboration and validation.

**Consensus 34:** Clinical utility of patiomer in the future may enhance meticulous control of hyperkalemia and may ease and enhance the usefulness of ARNI.

**Consensus 35:** Need for awareness of HF through digital media is essential to reduce morbidity and mortality.

**Consensus 36:** Need for the creation of a mobile/web-based application for physicians, cardiologists, nephrologists, diabetologists, neurologists, intensivists, and pediatricians to enhance the protocolized way of using ARNI.

**Consensus 37:** Need for research on the protocolization of ARNI in HF is recommended.

**Consensus 38:** Need for National Registry for the usefulness of ARNI in HFrEF, HfP EF.

**Consensus 39:** Need for publication on different components of the usefulness of ARNI in journals and textbooks for enhancing scientific, ethical, and legal implications.

**Consensus 40:** Need for continuing medical education on ARNI in HF at National and International forums.

**Conclusion**

It is therefore concluded that the addition of ARNI in the management armamentarium of HFrEF and HfP EF is a revolution in the reversal of cardiac remodeling, thereby having enormous cardiac morbidity and mortality benefits. Its appropriate protocolization is the need of the hour, as mentioned in the above 40 points of National Consensus by cardiologists, nephrologists and diabetologists from India. ARNI (Sacubitril–Valsartan) is therefore considered an iconic molecule in the management of HF.

**National Consensus Group comprising of cardiologists, nephrologists, diabetologists/endocrinologists from India in a national meeting held in New Delhi.**

**References**


Expert Opinion by Clinicians on the Use of Insulin Therapy in People with Hepatic Impairment

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ABSTRACT

People with type 2 diabetes mellitus (T2DM) have a higher risk of developing chronic liver disease (CLD) and its complications. T2DM, obesity, and insulin resistance are all strongly associated with nonalcoholic fatty liver disease (NAFLD). Conversely, people suffering from cirrhosis have reduced glucose tolerance in approximately 60% of cases, diabetes in 20% of cases, and insulin-mediated glucose clearance is lowered by 50% as compared with those who do not have cirrhosis. An exploratory review was conducted using existing published evidence from clinical studies on dosing and titrations of individual insulin formulations in people with CLD to optimize insulin dosage titration for minimizing hypoglycemia risk.

This article discusses current hyperglycemia treatment techniques for patients with CLD as well as the consensus recommendations on insulin use in special populations with T2DM and hepatic impairment. Based on available evidence and expert diabetologists’ recommendations, careful insulin dose titration, customized glycemic targets, and frequent glucose screening are recommended for optimal glycemic management without hypoglycemia in CLD. Long-acting insulin should be avoided or used when short-acting insulin fails to provide adequate glycemic control with raised fasting blood sugar levels. While the patient’s glucose profile is being evaluated, the prandial insulin dose can be lowered by 25% initially. The dose can be titrated based on the patient’s postprandial glycemic expression and whether their food intake meets the Child–Pugh scores A and B categories. Titrating premixed insulins is difficult for patients in class C since their appetite and overall health are constantly compromised and in flux.

INTRODUCTION

Chronic Liver Disease

As the 10th leading cause of morbidity and mortality worldwide, it is evident that CLD eventually leads to cirrhosis and/or liver cancer, a serious public health concern. Viral hepatitis (chronic hepatitis B virus (HBV) and hepatitis C virus (HCV)), NAFLD, and alcoholic liver disease are the main causes of CLD.1 The data from the Global Burden of Disease study (between 2012 and 2017) indicated that liver disease claims 2.14 million lives each year and liver disease-related fatalities have increased by 11.4% (16.0% increase in liver cancer deaths and 8.7% increase in cirrhosis deaths).1 A meta-analysis by Younossi et al. estimated that the global prevalence of metabolic comorbidities associated with NAFLD included obesity (51.34%), T2DM (22.31%), hyperlipidemia (69.16%), hypertension (39.34%), and metabolic syndrome (42.54%).2 The NAFLD prevalence has increased along with rising global trends in obesity, T2DM, and metabolic syndrome.2,3

Diabetes

According to the International Diabetes Federation, Diabetes Atlas 2021 (10th edition), 537 million adults (20–79 years) have diabetes and three out of four people with diabetes reside in low- and middle-income countries.4 Diabetes affected 90 million people (1 in 11) in Southeast Asia in the year 2021, which is expected to rise to 113 million by 2030.4 Diabetes was associated with 6.7 million fatalities worldwide in 2021, that is, one death every 5 seconds, with 747,000 deaths in Southeast Asia.4 Diabetes—A Risk Factor in People with Hepatic Impairment

Diabetes and CLD have a well-established relationship. According to existing literature, people with T2DM are significantly more likely than the general population to progress to advanced CLD and experience related complications, such as abnormal liver enzymes, NAFLD, cirrhosis, hepatocellular cancer, and acute liver failure.5,6 Diabetes occurring as a complication of cirrhosis is known as hepatogenous diabetes, which can only be diagnosed after the onset of liver disease.5,6 Insulin resistance, obesity, and T2DM are all strongly associated with NAFLD.7 Globally, NAFLD incidence and prevalence are increasing, imposing a huge clinical and economic burden, in addition to poor patient-reported outcomes.2,8 Cirrhosis and diabetes have a contentious relationship with underlying insulin resistance being the main pathophysiological defect. People with cirrhosis showed impaired glucose tolerance in 60% of cases and diabetes in 20% of cases, as well as a 50% reduction in insulin-mediated glucose disposal.5

In people with diabetes, CLD-related mortality was seen to be increasing.9 Kim et al. analyzed the National Vital Statistics System database to understand the trends in CLD-related mortality in people with diabetes (n = 48,761) in the United States alone and demonstrated that between 2007 and 2017, the mortality rate in people with NAFLD and acute liver disease increased by 11.6 and 1.4%, respectively.5 The age-standardized prevalence of suspected fibrosis (15.7–24.6%) and suspected cirrhosis (8.5–11.4%) was highest among people with diabetes and prediabetes in the 2017–2018 National Health and Nutrition Examination Survey, which included 4,207 people with normal glucose, prediabetes (glicated hemoglobin (HbA1c) = 5.7–6.4%), and diabetes (HbA1c = 6.5%).10 Thus, it has been recommended that people with diabetes should be screened for NAFLD and NAFLD-related fibrosis.10

Glycogen deposition, steatosis, NASH, fibrosis, cirrhosis, biliary disease, cholelithiasis, 4

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Expert Opinion on Insulins’ Dose Adjustment in Hepatic Impairment

Cholecytitis, and complications of diabetes medication are part of the spectrum of liver diseases that occur because of diabetes mellitus (cholestatic and necro-inflammatory liver disease).11

New-onset Diabetes after Transplantation (NODAT)
One of the clinically important complications of solid organ transplantation (particularly liver, kidney, or heart recipients) is the development of NODAT or post-transplantation diabetes mellitus (PTDM),12 which is mainly associated with metabolic disorders and considerably affects the quality of life and increases mortality.13,14 The incidence of NODAT varies depending upon the criteria used to diagnose diabetes after transplantation. PTDM affects 20–40% of liver transplant recipients and 10–20% of kidney transplant recipients.15 The risk factors for developing NODAT or post-liver transplantation diabetes mellitus (PLTDM) and diabetes are similar, and also influenced by the administration of specific drugs following organ transplantation.12,13,14 The diagnosis of NODAT/PLTDM also depends on the need for insulin/antidiabetic drugs 1 month after liver transplant.12

Based on published evidence from clinical trials, an exploratory review-analysis was undertaken on the dosage and titration of various insulin preparations in people with CLD, with some focus on newer insulin analogs because of their unaltered pharmacokinetics (PK) and low risk of hypoglycemia in CLD situations. Thus, this article summarizes the current therapies for managing hyperglycemia in people with CLD as well as consensus on recommendations on insulin use in special populations with T2DM and hepatic impairment.

Association of Diabetes with Liver Disease
The onset of diabetes in cirrhotic patients signals the progression of their disease and may even possibly cause liver failure.11 Diabetes management in people with CLD (or cirrhosis) can be challenging particularly those with Child–Pugh class C score, and these individuals should be differentiated from those without CLD by distinguishing characteristics.6,16,17

Altered Drug Metabolism including Oral Antidiabetic Drugs (OADs) in the Liver
Chronic liver disease is marked by a variety of metabolic changes, the majority of which are catabolic.18 The metabolism of certain drugs may be noticeably affected in liver disease.19 Hepatic blood flow may be impaired in disease-states and may impact the activity of drug-metabolizing enzymes and plasma protein production.17,19,20 Liver disease does affect the PK of certain drugs, notably those metabolized by the cytochromes P450 enzyme system, necessitating dosage adjustments or titration.17,20

Reduced gluconeogenesis ability, resulting in lower hepatic glucose output and decreased hepatic insulin breakdown, may minimize the requirement in people with decompensated liver disease. In contrast, people with impaired hepatic function may require more insulin to compensate for their insulin resistance.7

Cirrhosis has been associated with severe peripheral hyperinsulinism,21 which was caused by a higher rate of insulin secretion as well as a significant reduction in insulin hepatic clearance. Insulin uptake in the cirrhotic liver was investigated by Nygren et al. in six people with alcoholic liver cirrhosis (Laennec’s cirrhosis) and 10 people (control) with other conditions.22 They discovered that the average hepatic insulin uptake was 13.5%, which was significantly lower (p < 0.001) than in the control group (51.5%). This conclusion implies that the cirrhotic liver takes less insulin from portal blood than the noncirrhotic liver, and it supports the findings of other researchers who estimated hepatic insulin uptake using the relationship between insulin and C-peptide in peripheral venous blood.22 A case study in four patients with cirrhosis and poorly controlled T2DM suggested that the continuous subcutaneous insulin infusion helped regulate blood glucose levels in these patients and to reduce the daily dose of insulin.23

The therapy of T2DM in cirrhosis individuals is difficult due to the need for precise adjustment based on the extent of liver function impairment, as well as a lack of a summary of the limited data available.24 Many antidiabetic agents are contraindicated or must be used with caution in those with liver disease.7 Due to reduced liver metabolism and longer drug half-life, some OADs may cause cholestatic jaundice and severe hypoglycemia.16

Glucose Intolerance, Insulin Resistance, and Hypoglycemia
Chronic liver disease is often associated with glucose intolerance (especially after an oral glucose load) and increased insulin resistance, affecting endogenous glucose production, oxidative and nonoxidative glucose disposal, lipolysis, and lipid oxidation.17,18,25 Glucose intolerance affects 60–80% of people with liver disease, and nearly 20% develop diabetes.11,26

Beta-blocker therapy has beneficial effects in patients with cirrhosis, mainly to prevent variceal hemorrhage.27 Use of nonselective beta-blockers such as propranolol may seriously impair glucose recovery from insulin-mediated hypoglycemia.27

The cause of insulin resistance, which leads to impaired glucose tolerance or diabetes mellitus, remains uncertain.18 The existence of liver disease (unless it is decompensated) has a limited effect on the management of diabetes. Hypoglycemia should be regularly monitored in people with decompensated liver disease.7

Cirrhosis and HCV infection doubles the risk of T2DM compared to HBV infection.25 HCV infection triggers glucose intolerance in people with cirrhosis.25 Insulin resistance has been associated with the presence of serum HCV core, the severity of hepatic fibrosis, and decreased expression of hepatic insulin receptor substrates in people with HCV infection.25

Defective glucose storage can lead to malnutrition in people with CLD.18 Lifestyle modification can be recommended in people with mild/moderate hyperglycemia and compensated liver disease; however, stringent dietary restrictions should be avoided at all costs because it could lead to malnutrition.16

Lactic Acidosis in Decompensated Liver Disease
In cirrhosis, sepsis, hemorrhage, or hypoperfusion, increased lactate production due to poor utilization and hepatic metabolism can lead to lactate accumulation and clinically severe lactic acidosis (serum lactic acid ≥5 mmol/L; normal lactate concentration = 2.0 mmol/L).27,28 Metformin is not recommended for people with hepatic insufficiency since it increases the risk of lactic acidosis.28

Acidosis has several effects on insulin sensitivity and resistance. High doses of insulin and dextrose treatment can worsen lactic acidosis, according to one case study in a patient (18-year-old female) with Mauriac syndrome (glycogenic hepatopathy with poorly managed diabetes mellitus).29

Malnutrition
The severity of malnutrition has been associated with the progression of liver disease.30 Since the liver is involved in nutritional metabolism, energy balance, and many other physiological functions, malnutrition is a well-known consequence of CLD reported in 65–90% in different studies.17,30,31 Malnutrition in liver disease can be caused by reduced dietary/nutrient intake, alterations in drug metabolism, and drug-induced malnutrition.31

Hypokalemia, hypomagnesemia, hypophosphatemia, and hypoglycemia are
the most common and possibly lifethreatening anomalies observed in individuals with acute liver failure. Protein restriction may worsen hepatic encephalopathy by increasing endogenous protein catabolism, whereas a higher protein intake appears to protect against problems such as hepatic encephalopathy.31 Severe hypoalbuminemia and ascites are common in people with severe hepatic dysfunction.13,32

Butt et al. found a statistically significant (p < 0.05) association between nutritional status and the Child–Pugh stage of hepatic cirrhosis.30 People in Child–Pugh class C showed significantly lower mean values of body mass index (BMI), triceps skin–old thickness, mid-arm muscle circumference, serum albumin, average daily food intake, and prolonged prothrombin time.30

There is currently no standardized treatment or evidence-based nutritional interventions for malnutrition that can be used to reduce malnutrition in people with CLD and acute liver failure and hence improve their prognosis.31 About half of the population with T2DM and CLD are malnourished; lifestyle adjustments (diet, weight loss, exercises, abstaining from alcohol) may help in improving overall health.7

Insulin and insulin analogs are the only effective and safest therapy options available in persons with T2DM and CLD if OADs, lifestyle, and diet interventions are insufficient; nonetheless, people should be warned about signs of hypoglycemia.7

Insulin Requirement

Many clinicians are cautious to prescribe OADs, especially metformin, to people with T2DM and CLD.16 Incretin-based treatments, such as DPP-4 inhibitors and GLP-1 receptor agonists, are promising choices for treating NAFLD/NASH, however, there is insufficient evidence from a major clinical trial.35 Since its discovery and early clinical use in the 1920s, insulin therapy has transformed the treatment of both T1DM and T2DM. Following that, many types of insulin were developed, ranging from human insulin (H1) to analog insulin, rapid-acting insulin to long-acting insulin.31 Insulin requirement depends on whether there is a reduction in gluconeogenesis or insulin resistance.15

Recommendations and Dose Modification of Insulin in Hepatic Impairment

A multidisciplinary approach and expert opinion for glycemic targets and dose modifications of different antidiabetic agents may help people with diabetes and CLD maintain a good quality of care or life.7,17 Diabetes treatment centers should include a liver examination for staging and treatment of individuals with NAFLD, NASH, or cirrhosis.3 A rise in NAFLD awareness among health care professionals and caregivers of individuals with diabetes could help identify patients at risk of liver fibrosis/cirrhosis and prevent complications.3

To treat hyperglycemia, most diabetic patients, including those with liver cirrhosis, need to take oral diabetes medications and/or insulin.34 A systematic review conducted by Tang et al. compared the efficacy of anti-diabetic agents (ADAs) on NAFLD in patients with T2DM. The study showed evidence that the combination therapy with insulin/metformin for 3–7 months improved hepatic fat content.35 There are other oral agents like pioglitazone, SGLT2i, and GLP1-RA that have shown benefits in NAFLD in those with diabetes.35 Further discussion on oral agents is beyond the scope of this review.

Although clinical studies on insulin-treated people with diabetes having CLD are limited, insulin therapy can be administered at any stage of hepatic impairment.7 Progressive breakthroughs in the techniques for protraction or prolongation of insulin activity have spurred the growth of basal insulin therapy to establish this desired profile in patients.36 Insulin should be initiated if the patients do not respond to OADs alone or in combination, or if they have hepatic failure.37 When the blood glucose levels are >180 mg/dL or in critically ill people, basal or short-acting insulins could be used to overcome glucose fluctuations and improve glycemic levels.38

Insulin, preferably short-acting insulins, is the first-line treatment for diabetes in people with liver diseases such as cirrhosis or chronic hepatitis51 and chronic liver failure.11,17 Short-term intensive insulin treatment is preferred for new-onset diabetes mellitus patients who have HbA1c >9% or in kidney transplant recipients.39,40

Basal insulin therapy has progressed over time from first-generation analogs (glargine U-100, detemir) to second-generation analogs (glargine U-300, degludec) to ultra-long-acting formulations (icodec).38 The Research Society for the Study of Diabetes in India-Endocrine Society of India Consensus Group recommends the use of rapid-acting insulin analogs (insulin aspart or lispro) to attain targeted glycemic levels with a low risk of hypoglycemia in T2DM individuals with hepatic impairment.38 When compared to neutral protamine Hagedorn insulin or premixed insulins, evidence suggests that basal insulin analogs such as glargine, detemir, and degludec are effective and safe, with a lower risk of hypoglycemia and weight gain.38

The insulin dose should be titrated to the requirements to reduce the risk of hypoglycemia. Newer insulin analogs may be chosen as their PK is unaltered and possesses a low risk of hypoglycemia.13 Insulin therapy is usually initiated with basal insulin added to OADs and then switched to either insulin alone as a twice-daily fixed mixture regimen or a basal-bolus regimen, depending on the individual’s condition.7

Management of PTDM requires a multifaceted customized approach along with the step-wise approach recommended for T2DM.41 In patients with PTDM, the choice between insulin and OADs depends on many factors including the severity of hyperglycemia.40 In cases of early posttransplant period or life-threatening emergencies, intravenous insulin should be administered to stabilize the patient’s condition before switching to subcutaneous insulin or OADs.15,41 Insulin (alone or in combination with OADs) continues to be the treatment of choice in the hospital setting for managing hyperglycemia, PTDM, and preexisting diabetes/diabetes.12,40–42 Patients with poor glycemic control can continue insulin after discharge from the hospital with frequent self-monitoring of blood glucose (SMBG) to titrate insulin doses and to determine if it can be switched to OADs if glucose levels are achieved.12,42

Individualized insulin therapy is desirable based on the risk of hypoglycemia, comorbid conditions, functionality, costing, and in special populations.38

The next section discusses the evidence available for initiating insulin therapy in people with diabetes and CLD.

Available Evidence on Insulin Therapy in CLD

The prescribing information of selected insulin preparations (basal, prandial, and premixed insulins) for dose modification based on the PK/pharmacodynamic (PD) profile in hepatic impairment is presented in Table 1.

Basal Insulins

Insulin Detemir

Insulin detemir (Levemir®) can be used in hepatic impairment. The efficacy of insulin detemir was studied in two patients with significant hypertriglyceridemia and established NAFLD.33

Insulin detemir reversibly binds to serum albumin, making it hepatoselective insulin. The albumin–insulin molecule cannot pass through the capillary endothelial cell barrier to reach peripheral adipocytes, whereas the albumin–detemir molecule can freely pass...
through the liver sinusoids. This allows it to have a higher impact on hepatocytes than on other tissues in the body.43

Less hepatic exposure to insulin may limit the efficacy of hepatoselective insulin in NAFLD. Several factors affecting hepatocytes cause hyperglycemia because insulin stimulates the liver to store glucose in the form of glycogen while also turning off gluconeogenesis.43

Insulin detemir is hepatoselective insulin with less efficacy in achieving glycemic control. It could be due to hyperglyceridemia, which could reduce the efficacy of detemir or the consequences of lipid infiltration into the hepatic parenchyma. Patients may need high insulin doses resulting in weight gain.43

**Insulin Degludec**

In comparison to insulin glargine, insulin degludec is a new generation ultra-long basal insulin that allows for slow and continuous absorption, resulting in a flat action profile and four times lesser glycemic variability.44 Because of the longer duration of action (>42 hours), once-daily dose scheduling becomes more flexible.

In a study conducted by Kupčová et al., a total of 24 subjects were assigned to one of four groups (n = 6) based on whether they had a normal liver function or stable hepatic impairment.44

**Biphasic Insulin Aspart**

In participants with hepatic impairment.44

**Coformulation of insulin degludec and insulin aspart**

In people with CLD.

There is no published evidence available for insulin glargine in people with CLD.

**Prandial Insulin Aspart**

Insulin aspart is absorbed into the blood faster than HI following subcutaneous injection, resulting in a higher maximum concentration ($C_{max}$). This is because insulin aspart hexamers dissociate more quickly.45

Holmes et al. examined the effects of obesity, renal impairment, and hepatic impairment on the PK of insulin aspart.
Of 65 patients enrolled in the study, a total of 24 patients (males = 15; females = 9) with hepatic impairment (with or without ascites), BMI ≥19 but ≤38 kg/m², and fasting blood sugar <8.33 mmol/L were categorized by Child–Pugh score (Table 2).45

Hepatic impairment or BMI had no significant effects on PK parameters with respect to the Child–Pugh Score.45 There was no clinically relevant effect of HI on the PK of insulin aspart in normal hepatic function or mild/moderate/severely compromised hepatic function.45

**Insulin Lispro**

Gentile et al. compared lispro, a fast-acting insulin analog, to regular human insulin (RHI) in people with T2DM and compensated CLD in a 12 + 12-week cross-over trial.16 A total of 108 people with T2DM (with fasting blood glucose between 6.7 and 8.9 mmol/L and postprandial values over 10 mmol/L during the last 3 months) and CLD (only Child–Pugh’s score stage A or B) were randomly assigned to insulin lispro or RHI treatment. People with Child–Pugh score stage C were included in this study because of their catabolic status, increased insulin resistance, and low BMI.16

This study demonstrated that in people with compensated CLD and T2DM who did not respond to lifestyle changes, lispro was significantly more effective than RHI at improving glucose control and that glucose fluctuations were higher under RHI than lispro. The insulin concentrations before and after a standard meal, the incremental area under concentration, and the glycemia are well-controlled. Lispro reduced early postprandial glucose levels and late postprandial glycaemia rates, suggesting that it is a potential therapeutic option for persons with T2DM and compensated CLD.16

**Insulin Glulisine**

There is no published evidence available for insulin glulisine in people with diabetes and CLD.

**Premixed Insulins**

There is no published evidence from clinical trials available for premixed insulins in CLD.

When a basal insulin analog is insufficient to maintain glycemic control, the clinicians may use one of two approaches (1) a basal-bolus approach, which includes separate bolus insulin injections but requires titration of two different insulin formulations, or (2) switch to premixed insulins, which provide better glycemic control than basal insulin, but may be associated with lower fasting plasma glucose and HbA1c levels.36

Coformulation of insulin degludec and insulin aspart (IDegAsp) was studied in the general population and people with hepatic impairment, and it was found that no interim control is achieved with the insulin aspart component, while the flat and stable control is achieved with insulin degludec which is the basal component of the coformulation.34–46

The IDegAsp has unique prandial as well as basal glucose-lowering actions in steady-state. It is both safe and effective in people with diabetes who have hepatic insufficiency. Because the PK of insulin degludec or insulin aspart is unaltered, this coformulation can be safely used in people with diabetes and hepatic impairment.34–46

**Glycemic Markers and Glycemic Targets for People with CLD**

Composite glycemic control indicators are recommended to bridge the gap between distinct glycemic control markers (Table 3).17 The first challenge is to establish an accurate diagnosis and determine the disease severity.

Composite parameters are also available; however, they are more useful in theory than in practice.

There are very few guidelines for maintaining glycemic targets in people with CLD. Because most medicines are metabolized by the liver, pharmacological options for management, as well as concerns about hypoglycemia and malnutrition must be carefully considered. Individualized glycemic targets must be used to address these concerns. Composite parameters should be closely monitored because HbA1c values may be erroneously low.

**Clinician’s Expert Opinion**

A clinician may face a variety of challenges when treating people with liver disease, particularly if there is insulin resistance triggered by a decrease in hepatocyte number, inflammation, or fibrosis. The two major issues to consider are (1) reduced insulin clearance by the liver and (2) hyperinsulinemia as a result of the systemic clearing process. Because there is a need to balance the risk of hyperglycemia, this form of classification is a very useful tool for the management of people with CLD who are on insulin therapy.

**The Expert Panel and Methodology Followed**

Based on clinical evidence from published literature, prescribing information on insulin preparations with dose modification recommendations, developed after due consideration of the PK/PD profile of insulins in hepatic impairment, and the clinical experience of the clinicians, clinicians including diabetologists and endocrinologists (henceforth experts) provided their opinion on the use of insulin regimen in people with CLD and diabetes.

- Dr Purvi Chawla, MBBS, MS (Pharm. Sci. USA); PG D. Diabetology (UK) (Consultant Diabetologist and Director—Clinical Research at Lina Diabetes Care, Mumbai, Maharashtra, India).
- Dr M Shunmugavelu, MD (Consultant Diabetologist, Trichy Diabetes Speciality Center, Tiruchirappalli, Tamil Nadu, India).
- Dr Shalini Jaggi, MBBS, Post Graduate Diploma in Endocrinology (Consultant

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**Table 2:** Stages of CLD based on Child–Pugh Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Stages of chronic liver disease</th>
<th>Child–Pugh score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well-compensated disease</td>
<td>5–6</td>
</tr>
<tr>
<td>B</td>
<td>Significant functional compromise</td>
<td>7–9</td>
</tr>
<tr>
<td>C</td>
<td>Decompensated disease</td>
<td>10–15</td>
</tr>
</tbody>
</table>

**Table 3:** Glycemic control monitoring tools in patients with CLD and diabetes

<table>
<thead>
<tr>
<th>Glycated proteins</th>
<th>Most clinicians do not use glycate proteins (fructosamine and glycated albumin) very often, and they also do not interpret them very well. Glycated protein levels are affected by changes in protein metabolism and liver cirrhosis. Liver disease and dietary intake influence 1,5-anhydroglucitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-monitoring of blood glucose (SMBG)</td>
<td>Frequent and repeated SMBG may reflect short-term glycemic control</td>
</tr>
<tr>
<td>Continuous glucose monitoring (CGM)</td>
<td>CGM is highly recommended in specific cases. CGM directs the treatment approach and insulin dosage adjustments</td>
</tr>
</tbody>
</table>

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**Table 3 (Continued):** Glycemic control monitoring tools in patients with CLD and diabetes

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>HbA1c values in people with CLD are often deceptively low, and interpretation should be done with caution due to the risk of hemolysis, anemia, hypersplenism, and blood loss, as well as the effect of alcohol use. A lower diagnostic threshold is needed in people with CLD</th>
</tr>
</thead>
</table>

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**Table 2 (Continued):** Stages of CLD based on Child–Pugh Classification

<table>
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<tr>
<th>Class</th>
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<td>10–15</td>
</tr>
</tbody>
</table>
Diabeticologist, Lifecare Diabetes Centre, New Delhi, Delhi, India).
- Dr A J Asirvatham, MD, D. Diab (Consultant Diabeticologist, Arthur Asirvatham Hospital, Madurai, Tamil Nadu, India).
- Dr Debasis Basu, MD (Medical Director, Heaious Global Private Limited, Kolkata, West Bengal, India).
- Dr Tejas Shah, MBBS (Consultant Diabetologist, IVA Specialty Clinic & Diabes Care Centre, Mumbai, Maharashtra, India).
- Dr Faraz Farishta, MBBS, DNB (Consultant Endocrinologist, FSEndocrinology & Diabetic Center, Hyderabad, Telangana, India).
- Dr Ashok Kumar Das, MD, PhD (Consultant Endocrinologist, Pondicherry Institute of Medical Science, Puducherry, India).

To extract the required published data, a literature search was conducted using PubMed, which included randomized and non-randomized clinical trials, case reports, evidence-based reviews, epidemiological studies, expert opinion, recommended treatment guidelines, and regulatory acts.

On 26th November 2021, the preliminary findings were presented at the 15th National Insulin and Incretin Summit in Bengaluru, India. The Diabetes Research Society (Dia Aid) convened the summit, which was funded by Novo Nordisk in Bengaluru, India. The Indian expert group reviewed the evidence available for basal, prandial, or premixed insulins for the treatment of people with diabetes and comorbid CLD (cirrhosis, NAFLD, liver failure, etc.). The Child–Pugh class A, B, or C were used to classify the stages of CLD for the proposed recommendation (Tables 2 and 4).

After extensive deliberations during the summit, the expert panel reviewed and developed the consensus document on optimal dose adjustments with antidiabetic drugs in people with T2DM and concomitant CLD. The experts’ recommendations were consolidated and appraised to compile the final proposed consensus opinion on the use of insulin, appropriate doses, and titration in people with CLD.

### Dosing and Titration of Insulins in CLD

For individuals with decompensated liver disease (Child–Pugh class C), insulin therapy should ideally start in a hospital setting. According to the expert’s recommendations, insulin dosages in each stage of CLD can be estimated using the following criteria based on body weight and CLD stage (Child–Pugh score) (Table 5).

#### Titration of Basal Insulins in CLD

Insulin detemir has not been thoroughly studied in CLD individuals. The efficacy of insulin detemir has only been evaluated in two people, therefore, there is little evidence, and it indicates that this insulin is less effective in attaining glycemic control in these individuals. There is no reported evidence of insulin glargine in CLD individuals.

Only insulin degludec was evaluated for its efficacy and tolerability profile in CLD individuals, as well as its PK/PD profile. Insulin degludec was studied in 24 patients who were classified as having CLD stages A, B, and C. However, there is a need for large clinical trials with large sample sizes and extensive follow-up periods. The total daily dose should be reduced by 10–12% if the patient’s nutritional status is good.

Dose reduction or long-acting insulin are not recommended for individuals with CLD class C because they will be in a semi-conscious or unconscious state or on dialysis, and even if long-acting insulin is given or the patient becomes mildly hypoglycemic. It will be difficult to manage unless the patient has live continuous glucose monitoring (CGM) to judge how much insulin is broken down, so it is preferable to use short-acting insulin with a 25 or 50% dose reduction. Basal insulin also prevents the breakdown of glycogen stored in the liver, which is a significant risk factor. Because there is no glycogen stored in a liver failure, long-acting insulin may not be as effective as it would be in a healthy individual or mildly liver-compromised state. Therefore, long-acting insulin should be avoided or used only when short-acting insulin fails to achieve glycemic control. Premix insulins should not be avoided, especially if the patient’s condition has improved from class C to A.

#### Titration of Prandial Insulins in CLD

The prandial insulin dose can be reduced by 25% initially while the patient’s glucose condition has improved from class C to A.

---

**Table 4:** Child–Pugh score parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt;34 (&lt;2)</td>
<td>34–50 (2–3)</td>
<td>&gt;50 (&gt;3)</td>
</tr>
<tr>
<td>Serum albumin (mg/dL)</td>
<td>&gt;35</td>
<td>28–35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
<td>1.71–2.20</td>
<td>&gt;2.20</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Suppressed with medication</td>
<td>Refractory</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>Grades I–II (or suppressed with medication)</td>
<td>Grades III–IV (or refractory)</td>
</tr>
</tbody>
</table>

Child–Pugh A = 5–6 points; Child–Pugh B = 7–9 points; Child–Pugh C = 10 or more points.

**Table 5:** Dosing and titration of basal, prandial, and premixed insulins in people with CLD and diabetes

<table>
<thead>
<tr>
<th>Class</th>
<th>Stages of chronic liver disease</th>
<th>Child–Pugh score</th>
<th>Total dose estimation of insulin in CLD</th>
<th>Titrations of basal insulin in CLD</th>
<th>Titrations of prandial insulin in CLD</th>
<th>Titrations of premixed insulin in CLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (U/kg/day)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Well-compensated disease</td>
<td>5–6</td>
<td>As in healthy individual</td>
<td>25–30% dose reduction</td>
<td>25–30% dose reduction</td>
<td>No change</td>
</tr>
<tr>
<td>B</td>
<td>Significant functional compromise</td>
<td>7–9</td>
<td>25–30% dose reduction</td>
<td>50% dose reduction</td>
<td>30–50% dose reduction with glucose monitoring</td>
<td>Consider biochemical parameters</td>
</tr>
<tr>
<td>C</td>
<td>Decompensated disease</td>
<td>10–15</td>
<td>Individualized</td>
<td>Not Recommended</td>
<td>Individualized</td>
<td>Avoid premixed insulin for initiation</td>
</tr>
<tr>
<td>Preferred choice of insulin</td>
<td></td>
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</tr>
</tbody>
</table>

CLD, Chronic liver disease; PK, Pharmacokinetics; TDD, Total daily dose; U, Unit
profile is being monitored. The dose can be titrated based on the patient’s postprandial glycemic expression and whether the patient’s food intake is adequate with reference to Child–Pugh scores A and B categories.

**Titration of Premixed Insulins in CLD**

People with CLD in classes A and B can receive premixed insulin. It could be continued if the patient with decompensated disease (class C) is already on premixed insulin and his or her condition is under control without hypoglycemia. In these instances (individual in class C), titrating premixed insulin is challenging because the patient’s appetite and general state may be constantly compromised and unstable.

**Glycemic Targets and Blood Glucose Monitoring in CLD**

The cause of low HbA1c values in the individual with CLD could be because of the reduced lifespan of all insulins, hypersplenism, as well as gastrointestinal fat loss, and gastrointestinal hemorrhage leading to acute blood loss. It is challenging since the values of serum fructosamine and HbA1c are influenced by serum albumin levels. Clinicians frequently use SMBG and CGM values (rather than HbA1c values) as glycemic targets, and frequent glucose screening are recommended for optimal glycemic control without hypoglycemia in CLD.

**ACKNOWLEDGMENTS**

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**REFERENCES**

Iron Deficiency Anemia as a Potential Risk Factor for Unprovoked DVT in Young Patients: A Case Series

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Abstract
Deep vein thrombosis (DVT) is a serious and potentially life-threatening condition due to the occurrence of pulmonary embolism (PEs) in the acute phase. DVT can be provoked or unprovoked. Provoked DVT can be associated with transient or persistent causes. Iron deficiency anemia (IDA) with reactive thrombocytosis can act as a prothrombotic condition. We present two case reports of lower limb DVT which was associated with moderate anemia. Association between IDA and thrombosis has been reviewed.

Introduction
Deep vein thrombosis (DVT) is a potentially life-threatening condition because of PEs, which occur in the acute phase. DVT can involve both the upper as well as lower extremities, but upper extremity DVT is not very common with limited data and it only accounts for 3% of all venous thrombosis. It is classified as proximal DVT of the lower extremity when popliteal, femoral, or iliac veins are affected and distal DVT of the lower extremity when veins of the calves and lower leg are affected. The incidence of VTE ranges between 1 and 2 per 1,000 persons per year in the general population, while in the elder age group (>85 years) incidence reported is 8 per 1,000 persons per year.1

Proximal DVT is common and is more prone to lead to PE. Patients who have undergone major general or orthopedic surgery, and major trauma are at higher risk for developing DVT, so its early identification will reduce the risk of severe morbidity and mortality.

Deep vein thrombosis (DVT) can be classified either as provoked or unprovoked. Venous thromboembolism (VTE) which is not associated with any environmental risk factor is defined as unprovoked VTE. Hereditary thrombophilia, male gender, or older age are some non-environmental risk factors, whereas a thrombotic event caused by an environmental or an acquired known risk factor for VTE is known as provoked DVT. Hereditary thrombophilia, male gender, or older age are some non-environmental risk factors, whereas a thrombotic event caused by an environmental or an acquired known risk factor for VTE is known as provoked DVT. It can be caused by persistent or transient risk factors. Any transient risk factor is expected to resolve after the thromboembolism event, and it affects the duration of treatment and prognosis for recurrence. The risk of recurrence after stopping the therapy is usually lower as compared to VTE provoked by persistent risk factors. Active malignancy, obesity, congestive heart failure, and varicose veins are some examples of persistent risk factors for provoked DVT. Transient-provoked risk factors include immobilization, hip or lower limb injury leading to immobility, estrogen therapy, trauma or surgery, pregnancy, postpartum period, long-distance travel, and any foreign object or device (like central venous access).1,2

Stasis of blood flow, hypercoagulability, and endothelial injury are the common causes of thrombus formation. Stasis of blood flow is often caused by prolonged bed rest, general anesthesia, lower limb paralysis, or varicose veins of the lower limb. In this report, we describe a series of cases with DVT which were unprovoked and no cause could be found despite a detailed workup.1

Case 1
A 35-year-old previously healthy woman presented to our emergency unit with a history of worsening left lower limb swelling associated with pain and tightness for 3 days. The patient denied any recent surgery or trauma history, prolonged immobilization, long-haul air travel, or smoking. She denied any recent insect or animal bites. There was no history suggestive of SLE or other autoimmune diseases. Her past history was only significant for prior cesarean sections 6 years ago and it was uneventful. On examination, she was conscious, oriented to time, place and person, and vitally stable with pulse rate—102/min, BP—120/72 mm Hg, and mild pallor. Her left lower limb was swollen up to mid-thigh with pitting edema. Local temperature was raised along with tenderness. Systemic examination was normal. Lower limb venous doppler was suggestive of left common femoral vein, superficial femoral vein, deep femoral vein, and popliteal vein noncompressible and prominent with echogenic intraluminal foci on greyscale suggestive of thrombus. The note was also made of subcutaneous edema and skin thickening with features suggestive of left lower limb proximal DVT with cellulitis. On investigation, hemoglobin was 7.1 g/dL, mean corpuscular volume (MCV)—72, mean corpuscular hemoglobin (MCH)—20, mean corpuscular hemoglobin concentration (MCHC)—28.4, total leucocyte count—12,400 (N71, L20), platelets—2.58 L, liver and renal profile were normal. D-dimer—4396 ng/mL, iron study showed serum iron 34 µg/dL (60–150), TIBC—438 (250–400), transferrin saturation—41% (20–35), ferritin—7 ng/mL (10–120). Sinus tachycardia on ECG with a normal chest roentgenogram. Well's score for PE was 3 (moderate risk). CT pulmonary angiography was suggestive of pulmonary thromboembolism involving segmental pulmonary arteries (Fig. 1). The final diagnosis of left lower limb proximal DVT with PE was made. The patient was initially given unfractionated heparin for 2 days at 18 mg/kg/hour infusion with monitoring of international normalized ratio (INR) and later low molecular weight (LMW) heparin was then started with tablet acenocoumarol (oral anticoagulant) to achieve the target INR of 2–3. The patient improved symptomatically and was discharged on tablet acitrom and oral iron supplements and advised to follow up regularly.

Case 2
A 45-year-old lady, with no comorbidities presented to the emergency unit with complaints of left lower limb swelling associated with pain for 1 month and swelling in right lower limb for 1 week. There was...
Iron Deficiency Anemia for Unprovoked DVT in Young Patients

no history of prolonged immobilization prior to the development of limb swelling. On examination the patient was conscious, oriented to time, place and person, pulse rate—98/min, BP—108/72 mm Hg, and mild pallor. Pitting edema was present involving the left and right lower limb up to the level of mid-thigh. The local temperature was raised in the left lower limb. There was mild tenderness present in the left thigh along with redness of the skin over the lower part of left shin. Respiratory, cardiovascular, and abdominal examinations revealed normal findings. Investigations were hemoglobin—8.2 g/dL, total leucocyte count—9600 (N70L23), platelet—5.8L, MCV—79.8, MCH—25.2, MCHC—31.5, normal liver and renal profile and D-dimer—1340ng/mL. The iron profile showed serum iron 29.0 µg/dL, TIBC—445 mg/dL, transferrin saturation—41%, ferritin—8 ng/mL (10–120). Bilateral lower limb venous Doppler showed echogenic content in left common femoral vein extending till the bifurcation with distal common femoral vein showing normal flow whereas proximal common femoral vein showing decreased flow and echogenic foci was also noted in the right common femoral vein, superficial femoral vein and deep femoral vein along with subcutaneous tissue edema and thickness in both the limbs suggestive of bilateral lower limb DVT with bilateral lower limb cellulitis. ECG was suggestive of sinus tachycardia with Q3T3 pattern (Fig. 2). Well’s score for PE—high risk. CT pulmonary angiogram was done revealing peripheral subpleural consolidation with pleural thickening in the posterior segment of the right upper lobe with hypoattenuation of right upper lobe segmental arteries suggestive of the pulmonary infarct. A thrombophilia profile was sent which showed a deficiency of protein C with a value of 38.67 (normal range 70–140). Serum homocysteine level was normal. Ultrasound whole abdomen and pelvis showed grade 2 fatty liver with rest normal findings. Contrast-enhanced computerized tomography abdomen and pelvis was normal. The patient was diagnosed with a case of B/L lower limb DVT with pulmonary infarction with iron deficiency anemia. The patient was started on an injection of low molecular weight heparin. The patient improved symptomatically and anticoagulation was stabilized the patient was discharged on Tablet warfarin (oral anticoagulant) and oral hematinic, with advice

Figs 1A and B: Coronal section (A) and axial section (B) of CT pulmonary angiography reveals a thrombus involving segmental branches of the right lower lobe and left interlobar artery with involvement of segmental branches of the left lower lobe

Fig. 2: ECG showing Sinus tachycardia and Q3T3 pattern
Iron Deficiency Anemia for Unprovoked DVT in Young Patients

**Discussion**

Patients who present with unprovoked DVTs require thorough investigation for underlying malignancy and thrombophilia disorders. Of note, screening tests for thrombophilia disorders can be impacted by anticoagulants and should be performed after discontinuing vitamin K antagonists for 2 weeks or direct oral anticoagulants for 2–3 days. About 20–40% of DVTs are associated with PE. Hence, DVT and PE require a rapid diagnosis and adequate treatment. Our patient presented with DVT lower extremity where no cause or risk factor could be found despite detailed investigations. However, both these cases had one common finding i.e. moderate anemia and one case also had thrombocytosis. Anemia can be a cause of unprovoked DVT in these two cases. There can be many explanations suggesting IDA is a cause for the thrombotic event. Firstly, iron is considered a regulator of thrombopoiesis, and normal iron levels are required to prevent thrombocytosis by inhibiting thrombopoiesis and its consequent hypercoagulable state. It has been postulated that iron by either direct or indirect mechanisms inhibits the rise in platelets above steady state by inhibitory mechanisms; and is also required for the production or synthesis of one or more essential platelet components. By this, it was postulated that when an iron deficiency occurs, at first it affects the inhibitory compartment, and stimulates thrombopoiesis leading to thrombocytosis; if the iron depletion is more severe, the essential component is affected leading to thrombocytopenia. However, the level of iron deficiency at which the switch occurs is yet to be established. Another mechanism by which iron deficiency may contribute to a hypercoagulable state is by affecting flow within the vessels. Microcytosis in ID/IDA by reducing cell deformability leads to hypercoagulation through increasing blood viscosity and disrupting the normal blood flow pattern.4

Akin et al. have suggested that the decrease in antioxidant defense in iron deficiency anemia may lead to oxidative stress which may result in a tendency favoring platelet aggregation. Abnormal platelet count and function observed in iron deficiency anemia could act synergistically to promote thrombus formation, especially in the setting of an underlying atherosclerotic disease. All these conditions lead to turbulence in blood flow, which may damage the endothelium and cause platelets to come more frequently in contact with the endothelial lining.5

To conclude, IDA is a prothrombotic factor and may be associated with DVT. From the above two cases, we suggest IDA can be a significant association and/or cause for unprovoked DVT, therefore basic signs like anemia and lower extremity edema should not be overlooked. It should be worked up, diagnosed, and treated adequately as PE induced by DVT can be fatal. More studies with a good number of patients will be helpful in establishing the association between DVT and IDA.

**References**

Atypical Multiple Myeloma Case: Atypical Clinical Presentation, in Female and at Young Age

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ABSTRACT

Background: Multiple myeloma (MM) is ranked as the 14th most prevalent cancer, making up 1.8% of all cancers and 10% of blood cancers, rarely seen below 35 years. MM presented aggressively in the young age group, including greater incidences of extramedullary plasmacytomas, plasma cell leukemia (11%), osteolytic lesions, kidney failure (25%), and Bence Jones proteinuria (81%). Though youngsters have an aggressive presentation, their response to treatment is as similar to older patients.

Case: We reported a case of a young female from the rural Konkan region of Maharashtra with complaints of right limb radicular pain and back pain diagnosed with MM with acute kidney injury and hypercalcemia. First-line treatment for her included conventional chemotherapy mixed with a proteasome inhibitor (bortezomib) and intravenous hydration for acute kidney injury and hypercalcemia with injection (inj) zoledronate.

Conclusion: The case study shows how MM must be ruled out before being considered as a possible diagnosis for a young child who has neurological problems and mass lesions.

INTRODUCTION

The word “multiple myeloma” is Greek (myelo—marrow and oma—mass). It is indeed a malignant B-cell disease that results in plasma cells that are actively proliferating and secreting monoclonal (M) immunoglobulins. It is ranked as the 14th most prevalent cancer, making up 1.8% of all cancers and 10% of blood cancers. When compared to Western nations, Asia and India have lower rates of MM.

As per the Indian Cancer registry from 2012–2014, about 1.9% of the total of all malignancies are MM, the male-to-female ratio is 1.4:1. About <2% of MM patients are under the age of 40, and the disease only rarely affects people under the age of 35 (0.5%). The average age of MM diagnosis is 69 years old. The typical symptoms of MM include anemia, bone pain, hypercalcemia, as well as an elevated erythrocyte sedimentation rate; however, patients might also occasionally appear without symptoms or with unusual clinical findings. Many investigations found that MM presented aggressively in the young age group, including greater incidences of extramedullary plasmacytomas, plasma cell leukemia (11%), osteolytic lesions, kidney failure (25%), and Bence Jones proteinuria (81%). The young age and atypical clinical presentation lead to a delay in diagnosis and may lead to an aggressive disease course.

Here, we reported a case of a young female from the rural Konkan region of Maharashtra with complaints of right limb radicular pain and back pain diagnosed with MM with acute kidney injury and hypercalcemia. Managed with intravenous hydration and first-line treatment for her included conventional chemotherapy mixed with a proteasome inhibitor (bortezomib), showed improvement symptomatically.

CASE DESCRIPTION

A 32-year-old female who was experiencing lower backache arrived at the orthopedics department and right lower limb radicular pain with difficulty in getting up from bed for 2 months, aggravated over the last 2 weeks. She had a significant weight loss of 8–10 kg in the last 1 year. She had no history of any comorbidities, including diabetes mellitus (DM), hyperthyroidism, tuberculosis (TB) or TB contact, any surgical interventions, or malabsorption. There was no significant family history. On admission to the hospital, she was clinically stable with no focal neuro deficit except deep tendon reflexes were brisk but normal sensory examination. Other systemic examinations were normal, with no evidence of papilledema.

Laboratory findings showed creatinine is 2.26 mg/dL, 10.4 g/dL of hemoglobin, 189 mg/dL of urea, serum calcium = 14 mg/dL, serum vitamin = 57.6 ng/mL, alkaline phosphatase = 162.9 IU/L, serum phosphorus = 5.38 mg/dL, serum thyroid-stimulating hormone = 0.51 uIU/mL, serum lactate dehydrogenase (LDH) = 430.5 U/L (225–445), tumor markers cancer antigen (CA) 125 = 23.3 U/mL (0–35), CA19.9 = 2 U/mL (0–37), carcinoembryonic antigen = 3.58 mg/mL (range 0–2.5).

A radiographic examination of the skeleton revealed numerous well-defined, rounded, and punched-out lesions in the side and skull (Fig. 1) and ribs (Fig. 2). Computerized tomography (CT) showed multiple lytic lesions involving the body, spinous processes, and transverse processes of all visualized vertebrae (Fig. 3), ribs (Figs 4 and 5) and sternum, along with wedging of the vertebral bodies of D3, D8, and D10 vertebrae, suggestive of MM.

Bone marrow aspiration examination was positive for atypical cells showing plasmacytoid morphology (Figs 6A and B), confirming the diagnosis of MM.

Baseline B2 microglobulin = 15183 ng/mL, immunofixation qualitative serum report showed a band in the A region. Serum protein electrophoresis (SPEP) (Fig. 7) showed albumin/globulin = 1.27, comprehensive MM panel by fluorescence in situ hybridization was negative for all chromosomes [11q
Atypical Multiple Myeloma Case

This is an atypical presentation of MM in a young female of only 32 years of age, complaining of radicular leg pain with aggressive disease. The normal median age of presentation of MM is 69 years, and it rarely occurs below 35 years (0.5%) only, with male preponderance was 1.27/1,000,00 compared to females with 0.95/1,00,00.

Fatigue, anemia, bone aches, and/or hypercalcemia plus renal insufficiency are common symptoms of MM, as are the calcium elevation; renal insufficiency; anemia; bone abnormalities (CRAB) characteristics (high serum calcium levels, impaired kidney function, anemia, and/or bone disease). Our patient reported having radicular leg pain, losing weight, having difficulty getting out of bed, and having hypercalcemia with renal failure. The neurological side effects, which typically include radiculopathy or peripheral neuropathies, are linked to compression of the spinal cord or neural compression resulting from bone deterioration, less frequently bone infections.

The updated International Myeloma Working Group consists of CRAB and myeloma-defining events (MDE). Regardless of the absence of a CRAB characteristic, at minimum, one MDE is necessary to diagnose MM. The following MDE parameters are:

- A bone marrow examination that shows 60% or more clonal plasma cells.
- A ratio of serum involved or uninvolved free light chain should be equal to or >100, and with the absolute amount of the associated light chain is at least 100 mg/L.
- Focal lesions on an MRI should be multiple with at least 5 mm in diameter or larger.

Multiple myeloma (MM) can be distinguished from other plasma cell proliferative illnesses, most notably gammopathy of undetermined significance, solitary plasmacytoma, and smoldering MM. This distinction is crucial.

A typical Multiple Myeloma Case

Fig. 2: Chest X-ray showing multiple well-defined rounded cystic lesions seen in ribs on both sides and on both scapulae

Fig. 3: Well-defined rounded lytic lesion in the right pedicle of L5

Fig. 4: Lytic lesions of 9th right rib (arrowhead) with multiple lytic lesions of vertebrae (arrow)

Fig. 5: CT scan abdomen: Lytic lesion of right 5th rib (arrowhead) with multiple lytic lesions of vertebrae (arrow)

Figs 6A and B: Plasmacytoid morphology on bone marrow (BM)
Atypical Multiple Myeloma Case

because each of these conditions will have a different course of treatment and prognosis upon progression to MM.11,12

In order to diagnose and assess this illness, a thorough history and physical examination are crucial. Additional MM tests include a simple blood test along with a microscopic examination, SPEPs, serum calcium, kidney function, immunoglobulin levels, and a 24-hour urine sample for proteinuria. The majority of the time, the radiographic studies such as CT scans and regular chest, skull, and spine radiographs are helpful in verifying the diagnosis. A total of 97% of MM cases have M protein generated and released mostly by malignant plasma cells. Immunoglobulin G is the most often generated heavy chain, occurring in 50% of cases, and the malignant plasma cells may produce—(1) either immunoglobulin heavy chains and light chains; (2) light chains alone; (3) or neither. When compared to λ, κ is typically the dominating light chain by a factor of 2 to 1. The immunofixation qualitative serum report for our patient revealed a band in the λ area, with a free κ/λ ratio of <0.01. The diagnosis of MM must be made using a bone marrow aspiration and biopsy after the completion of all the aforementioned studies. The bone marrow of most patients with MM will contain 10% or more plasmacytoid morphology. Our bone marrow and aspiration report shows atypical cells with plasmacytoid morphology. A high degree of clinical suspicion seems essential since MM may appear with several unusual symptoms or associated symptoms to the CRAB criteria, notably back pain, an infectious disease, or secondary to the pathological fracture.

The median survival rate in MM is approximately 5–7 years, and it depends on the staging of the tumor, host factors, cytogenetic abnormalities, and the patient’s response to the treatment.13 Both Durie Salmon Staging and International Staging Systems are used to calculate the burden of morbidity. Disease biology is employed as a prognostic index that aids in patient clinical care, such as the presence of significant cytogenetic abnormalities or higher LDH levels.14

The four stages of therapy are the most important.

Stages:

• Initial therapy stage.
• Stem cell transplantation (if necessary).
• Maintenance therapy stage.
• Recurrence management.

Patients who qualify for transplants often go through four cycles of initial therapy, collection of stem cells, and then ASCT. Delayed ASCT is an option for some patients with basic risk MM that respond well to induction. Using this technique, stem cells are collected after four cycles of initial treatment and then cryopreserved for later use. Patients who cannot receive a transplant typically receive care for 12–18 months. Consolidation/maintenance therapy should be considered after the initial therapy and/or ASCT. The existence or absence of more significant cytogenetic characteristics typically affects the decision of maintenance and length of therapy. In cycle one, our patient got bortezomib—0.9 mg (On days 1, 8, 15, and 22 at 1.3 mg/m²), dexamethasone—20 mg (On days 1, 8, and 8–11), and lenalidomide 10 mg as induction chemotherapy. Melphalan at a high dose (200 mg/m²), then two additional cycles of consolidation with bortezomib and dexamethasone.

Conclusion

This shades not only how young patients might act aggressively but also potential care approaches for this. This case study illustrates that young patients could present more aggressively. The patient had MM at a young age and carried a significant disease burden. This case study shows how MM must be ruled out before being considered as a possible diagnosis for a young child who has neurological problems and mass lesions.

References


Fig. 7: Serum protein electrophoresis (SPEP)
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A 45-year-old female referred to the Endocrinology department with clinical features of a cervical hump, suspicious of Cushing’s syndrome. On clinical examination, excessive cervical pad of fat with grade II acanthosis (Fig. 1A) nigricans over the neck region. However, there were no other specific signs of Cushing’s syndrome such as striae, myopathy, ecchymoses, or bruises in the body. Her body mass index was 31 kg/m² and her waist circumference was 98 cm. On detailed history, she suffered from human immunodeficiency virus (HIV) infection and was on tenofovir, lamivudine, and efavirenz containing highly active antiretroviral therapy (HAART) for the past 3 years. Fasting lipid profile showed dyslipidemia with elevated total cholesterol 240 mg/dL, triglycerides 202 mg/dL, and low-density lipoprotein cholesterol 190 mg/dL with low high-density lipoprotein 34 mg/dL. Glycemic parameters including oral glucose tolerance test and hemoglobin A1c levels were within normal range. Hormonal evaluation was done to rule out exogenous and endogenous Cushing’s syndrome. Fasting 8 AM serum cortisol was 15.5 µg/dL (5–25 µg/dL), midnight serum cortisol was 3 µg/dL (normal <7.5 µg/dL), and overnight dexamethasone suppression test revealed suppressed serum cortisol levels 0.8 µg/dL (normal <2 µg/dL). Excessive fatty tissue over the cervical region was confirmed with computed tomography (CT) neck imaging (Fig. 1B). In view of isolated cervical hump and absence of other specific features of Cushing’s with no biochemical parameters suggestive of Cushing’s syndrome, the patient was diagnosed as pseudo-Cushing’s syndrome.

Pseudo-Cushing’s syndrome is defined as some or all clinical features of Cushing’s syndrome with or without biochemical evidence of hypercortisolism. The differential diagnosis of pseudo-Cushing’s syndrome are depression, chronic alcoholism, obesity, uncontrolled diabetes, and obstructive sleep apnea. After the advent of HAART for the treatment of HIV infection, there was a marked improvement in the quality of life as well as the life expectancy of persons living with HIV infection. Meanwhile with long term use of HAART therapy leading to various fat redistribution abnormalities and metabolic complications include diabetes mellitus.

HAART-associated lipodystrophy (LD) is characterized by selective damage of adipose tissue resulting from antiretroviral drugs and also HIV disease per se. LD syndrome encompasses fat redistribution, defined as fat wasting of extremities/face or buttocks, fat accumulation in abdomen or dorsocervical spine (buffalo hump), and metabolic complications like dyslipidemia and hyperglycemia. HAART-associated LD is more common in patients on protease inhibitors group of drugs, however, fat loss has been reported in patients taking nonprotease inhibitors antiretroviral drugs. LD associated with HAART is a difficult condition to manage; choices are either by switching of antiviral drugs and in some cases by reconstructive surgery.

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Basal Ganglia and Cerebellar Calcification: Rare Finding in Hypoparathyroidism

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CASE DESCRIPTION

A 45-year-old female presented with complaints of muscle cramps and generalized body aches. She had a doubtful history of one episode of seizure at home a few days back lasting for seconds to minutes, resolved spontaneously. On examination, her vitals were normal, the trousseau sign was positive but there was no evidence of any tremors or choreiform movements, and systemic examination was unremarkable. The patient had a history of cataract surgery in both eyes at the age of 40 years. Investigations revealed hypocalcemia with serum calcium levels of 5.3 mg/dL with high phosphate levels of 7.6 mg/dL. Her ionized calcium was also low, 0.5 mmol/l (normal range 1.13–1.32 mmol/l) and she had low intact parathyroid hormone (PTH) levels of 5.4 pg/mL. CT Head was done which showed bilateral symmetrical basal ganglia and cerebellar calcifications (Figs 1 and 2). The patient was diagnosed with hypoparathyroidism and was evaluated for the etiology of the same. She had no previous history of goiter or neck surgery. There was no history of jaundice, arthralgia, any coexistent autoimmune disorder, skin or dental abnormalities, tremors, or hyperpigmentation. Biochemical workup did not reveal any etiology and hence, a diagnosis of idiopathic hypoparathyroidism was made. She was started on calcium and calcitriol therapy with urinary calcium monitoring. The patient improved symptomatically within a duration of 2 weeks with no more evident tetany or muscle cramps.

DISCUSSION

Parathyroid hormone (PTH) plays a vital role in the maintenance of calcium homeostasis. Primary Hypoparathyroidism is defined by an abnormally low level of PTH, leading to hypocalcemia and hyperphosphatemia. Basal ganglia calcification (BGC) is a nonspecific finding, reported in 1% of computed tomography (CT) head scans done due to any cause.¹ It can be physiological or pathological. Physiological BGC is usually an incidental asymptomatic finding in elderly patients while pathological calcifications may lead to tremors, extrapyramidal symptoms, or cognitive decline in affected patients.¹ Two most common causes of pathological BGC include Primary hypoparathyroidism and pseudo-hypoparathyroidism.² Other reported causes are—sarcoidosis, malignancies, certain infections including HIV, tuberculosis, birth asphyxia, carbon monoxide toxicity, lead exposure, radiation therapy, and certain inherited neurodegenerative disorders. The mechanism of intracranial calcification in Primary hypoparathyroidism is not completely understood. Altered calcium phosphate products could be one of the causes, however, has failed to explain all manifestations. Intracranial calcification is found to be related more to the duration of hypocalcemia and hyperphosphatemia rather than the level of PTH. Basal ganglia is the most commonly affected area, however, certain other areas in the brain are involved too including cerebellum, grey-white junctions, thalamus, and dentate nuclei.³,⁴ These calcifications have been reported in 0.3–1.5% of patients with hypoparathyroidism, and are often detected incidentally,³,⁴ but are significantly associated with cognitive decline, cerebellar dysfunction, and parkinsonism in affected patients. An adequate treatment maintaining the calcium and phosphate homeostasis to near normal levels may slow the progression of intracranial calcification and lead to remarkable improvement in neurological manifestations.

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First Woman Doctor of Medicine

Ajay K Jha

Elizabeth Blackwell (1821–1910) became the first woman to receive an MD degree from an American medical school. She was born in Bristol in 1821. Her father, Samuel, died in 1838 leaving her wife and nine children in the lurch. After his death, Elizabeth and her sisters began teaching and set up a school to provide the family with financial stability. She had graduated from Geneva Medical College in New York and became the first woman to receive an MD degree. Elizabeth worked in the clinics in Paris and London for 2 years, where unfortunately she lost sight in one eye because of a purulent infection. She returned to America in 1851 and established a medical practice in New York. In 1853 she opened her own dispensary. Her sister Emily, who had also qualified as a doctor, joined her and together with Dr Marie Zakrzewska, they opened the New York Infirmary for Women and Children in 1857. She decided to move back to Britain in 1869 where she founded the National Health Society in 1871 which aimed to educate people about the benefits of hygiene and healthy lifestyles. Their motto “Prevention is better than Cure” is a phrase that still exists true and the world nowadays is following the same during the pandemic of COVID-19.

In 1859 she became the first woman to have her name entered in the British General Medical Council’s medical register. In 1874, Elizabeth Blackwell British physicians Sophia Jex-Blake and Elizabeth Garret Anderson established the London School of Medicine for Women, primarily preparing women for the licensing exam of Apothecaries Hall. In 1875, Elizabeth was appointed professor of Gynaecology. Elizabeth published many books and was involved in a number of reform movements including moral reform, hygiene, medical education, preventative medicine, sanitation, and family planning. She had battled all her life and her successes had been monumental. In 1881, only 25 female doctors were registered in England and Wales but by 1911 there were 495 registered. Elizabeth Blackwell died in Hastings, England, on 31 May 1910. “U.S. Postal Service has honored Blackwell’s achievements and contributions to history with a commemorative stamp in 1974.”

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A Case of Contact Dermatitis to Venomous Snake

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Sir,

Allergic reactions to snake venom and antivenom are well known, along with the local and systemic features of snake envenomation. But, venomous snakes by way of their physical contact leading to skin lesions are not often reported. This is a short, at the same time curious report of one such incidence of dermatitis due to contact with a venomous snake along with a short review of literature.

A 35-year-old lady presented with skin lesions on the face and neck. She woke up suddenly at midnight when she felt some reptile crawling onto her face and the horrified lady just brushed aside the creature involuntarily. The relatives found a hump-nosed pit viper; a common venomous snake cited often in the neighborhood, hiding under the cot but it was killed, unfortunately. She did not have any symptoms except being very frightened by the whole incident and she then slept off. In the morning, when she got up, she found itching and burning all over the face and neck where the snake had crawled. She noticed erythematous skin lesions in the said area and there was no bite mark. She did not have any signs or symptoms of local or systemic snake envenomation (Fig. 1).

A detailed dermatological examination revealed erythematous, edematous plaque suggestive of urticaria on the forehead, eyelids, cheeks, chin, and neck. There were no erosions, vesicles, or bite marks on the skin. Her percentage of eosinophil in the blood was within normal limits. The patient was treated with antihistaminic, corticosteroid, and a skin emollient for application. She made a gradual recovery in 6 days and had no further problems. Elaborative counseling was done to downplay her fossilized myth that the skin which came into contact with the viper would ulcerate and never heal (Fig. 2).

Discussion

Snakes do not have any hair or epidermal dander and hence are less likely to produce allergies. But, allergies to snakes can occur though rarely as seen in our patient. Most

CORRESPONDENCE

A Case of Contact Dermatitis to Venomous Snake

Sadananda Naik B1, C S Jyothi2, Sangram Biradar3

1Senior Physician, Department of Internal Medicine, Alva’s Health Centre, Moodabidri, Karnataka; 2Dermatologist, Skin Care Clinic, Moodabidri, Karnataka; 3Professor, Department of Medicine, Mahadevapura Rampure Medical College, Kalaburagi, Karnataka, India

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Climate Medicine should be a Priority in Medical Curriculum

Gouranga Santra
Professor, Department of General Medicine, Deben Mahata Government Medical College & Hospital, Purulia, West Bengal, India

Sir,

Different greenhouse gases (GHG) are causing global warming (carbon dioxide > methane > nitrous oxide > fluorinated gases). Among them, the major contributing factor is carbon dioxide emission from fossil fuel combustion in transport, industry, electricity, residential and commercial places, and from nonfossil fuel combustion. Climate change due to global warming is causing both communicable and non-communicable diseases. But medical students are not being properly trained regarding climate-related health disorders. It is now of utmost importance to bring climate medicine into the medical curriculum considering its present and future impact on the healthcare system.

Climate change affects human health directly by extreme weather, e.g., heat waves, droughts, wildfires, extreme precipitations, floods, storms, etc., or indirectly by changing ecosystem causing water and vector-borne diseases, air pollution, etc. It also has an impact on occupation, nutrition, and mental health. Climate change can worsen many existing health disorders. Climate-related events can also affect healthcare infrastructure and delivery systems. Climate change affects mainly the susceptible population comprising of children, elderly people, persons with underlying health disorders, poor, and persons living in vulnerable geographic areas (e.g., sea shores, islands) and extreme weather.

Climate hazards cause changes in the incidence, prevalence, and geographical

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distribution of food and water-borne diseases e.g., salmonella, diarrhoeal diseases, etc. Increased rainfall and floods lead to the expansion of mosquitoes, fleas, ticks, mites, rodents, etc., and cause outbreaks of malaria, scrub typhus, dengue, chikungunya, leptospiral disease, plague, etc. Flood waters contaminate surface water and increase diarrhoeal disorders. Because of the decrease in salinity of sea water from excessive rainfall infections of vibrio vulnificus and cholerae are increasing. Animal movements and interactions (e.g., bats, rodents, primates) over larger areas foraging for limited food resources caused by drought or wildfires increase the jumping of viruses between species. Emerging infectious diseases with animal-to-human transmission (e.g., the COVID-19 pandemic) is due to animal movements and deforestation. Deforestation has an impact on climate change itself. Heavy precipitation and drought cause the movement of livestock to suitable areas and more human exposure leads to disease outbreaks like anthrax, hemorrhagic fever, etc. Mora C et al. in a study found that 58% of infectious diseases confronted by humanity worldwide have been aggravated by climatic hazards at some point, but 16% of infectious diseases were at times diminished also.2

Non-communicable diseases like snake bites due to floods and lightning injuries from thunderstorms are increased. Risks of body injuries and premature deaths are increased in extreme weather. Air pollution increases chronic obstructive pulmonary disorders, asthma, and lung cancer. Heat exposure and dehydration are important contributing factors of chronic kidney disease of unknown etiology which is being designated as heat-stress nephropathy. Climate change has an impact on cardiovascular disorders also. Increased incidences of heat stroke are occurring due to heat waves and humidity. Plant and fungal allergens aggravated by warming, flood, or storm cause allergic skin disorders and asthma. Surface water shortage is causing more use of shallow groundwater (shallow tube wells extracting arsenic-rich water from shallow aquifers, however, deeper aquifers are free of arsenic) endangering the risk of arsenicosis. Loss of crop fields and residential areas due to elevation of seawater as a result of warmth and melting of polar snow, and engulfment of lands by rivers lead to poverty, malnutrition, and homelessness. Anxiety, stress, and depression are common in climate refugees. Flash floods (“Harka-ban” in the local language) directly or indirectly cause losses of human life and damage to human health both physical and mental. Large debris and floodwaters cause structural damage to bridges and roadways causing breakage of the supply of food, medicine, and ambulance services. Ocean climate change due to acidification from excessive carbon dioxide and poor oxygen levels from heating reduces the biodiversity of the sea and reduces the seafood supply which can lead to poor nutrition of dependent persons. Training climate medicine in the medical curriculum will help our preparedness to combat climate-related health disorders. Ongoing research on the effects of climate change on health is also essential. Our targets are the promotion of a healthy lifestyle suitable for a changing climate, and the prevention and control of health consequences of climate change. Training regarding rehabilitation methods for mental and physical dysfunctions from climate hazards is also important. Strategic planning is essential to improve the resilience of the healthcare system in extreme weather and training in climate medicine is an integral part of it. But the health hazards from climate change are too numerous for comprehensive societal adaptation, so the root cause of the problem should be targeted. Medical students should know the principles of reducing GHG emissions in general and from the healthcare sector.3 Environmental stewardship is an urgent need both at the individual and community level. Awareness can be propagated by trained doctors regarding the benefits of renewable energy (e.g., solar, wind, and hydroelectric) rather than fossil fuels causing GHG emissions and also the benefits of the plantation of trees. Doctors can create echo consciousness in a community in a better way and with better acceptance and can influence world leaders whose action is insufficient in this regard. So, the doctor’s role is multidimensional from making awareness in the community, managing health hazards of climate change, and researching for a better future. Students should be aware of the ‘one health approach’ where environmental, animal, and human health are interconnected.

REFERENCES

In Hypertension and Hypertension associated with Diabetes

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Clinic BP

<table>
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<th>Achievement for target BP (%)</th>
<th>Telmisartan 40 mg</th>
<th>Olmesartan 40 mg</th>
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<td>77%</td>
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Home BP

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<td>61.2%</td>
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