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Contents

EDITORIAL
1. Prevention in Cardiology Myths or Reality .......................... Lekha Adik-Pathak .......................................................... 11

ORIGINAL ARTICLE
3. Rationalizing the Use of COVID-19 Questionable Efficacy Drugs in a Low Middle-income Country: A Hospital Tocilizumab Committee Experience Naveen Hegde, Ankit Kumar, Gurpreet K Batra, Mahesh Devnani, Rachna Rohilla, Pankaj Malhotra, Amol N Patil ............................................ 18
4. Pulmonary Manifestations in Patients of Rheumatoid Arthritis and its Correlation with Severity of Disease Liyakat A Gauri, Bharat Sharma, Ketan Bhatnagar, Nadeem Liyakat, Parvez Sameja, Kuldeep Saini, Ravi Dutt, Mohit S Khokhar, Vikas Kumar, Anjali Garg ................................................................. 25
6. Thrombocytopenia in Children: A Large Prospective Study on Clinical Manifestations, Seasonal Variation, Etiology, and Outcome Isha Bhatia, Avinash Sharma, Sandesh Guleria, Ajay Sharma, Ranbir S Jaswal, Ajay Vaid, Neha Rehalia, Amar Thakur ........................................... 37
7. Lipid Profile as an Indicator of Severity in Cirrhosis of Liver: Hospital based Cross-sectional Study Jeewanandham Yamuna, Anbazhakan Akila, Vellaichamy Uvaraj Muruganandam, Krishnamurthy Sivakumar, Kumar Natarajan, Arumugam Muruganathan .................................................. 42
8. Serum Levels of Activin-A: Predictor of Insulin Resistance and Atherosclerosis in Prediabetes Ajay Chauhan, Asmita Gupta, Parul Goyal, Tarun Kumar ................................ 46
9. Correlation of Anemia with Glycated Hemoglobin among Euglycemic Type 2 Diabetic Patients Meenaxi Sharda, Nikhil Gandhi, Dharmendra Bansal, Maneesh Gadhwal ......................................................... 56

REVIEW ARTICLE
12. Spectrum of Disorders associated with Tetany Gouranga Santra ......................................................................... 73

CASE REPORT
14. Hirayama Disease: A Rare Case Report and Review Heli Kapoor, Varuna Yadav, Shubha L Margekar, Debasish Chaudhury, Ashok Kumar, Ankur Verma ......................................................... 88
15. Diphtheritic Polynuropathy: A Case Report Harshavardhan L, M Anantha krishna .................................................... 92

MEDICAL PHILATELY
16. Apple Tree to Gliiflozins Jayant Pai-Dhungat ......................................................................................... 96

CORRESPONDENCE
17. Prevalence of Metabolic Syndrome and Risk Factors in a Rural Population of Rajasthan Arvind K Sharma, Vaseem N Baig, Jitendra Ahuja, Sudhanshu Kacker, Rajeev Gupta .................................................................................. 97
19. Cluster of Differentiation 68 Negative Eruptive Adult Xanthogranuloma Amritha Muralitharan, Reena Rai, Umamaheswari Gurusamy ............. 99

ANNOUNCEMENTS
20. Going Green .......................................................................................................................... 24
21. Update Mobile Number / Email Id .................................................................................. 34
22. API Announcement: Elections of API, ICP and PRF .................................................. 35
23. Fellowship of the Indian College of Physicians (FICP) at APICON 2023 at Ahmedabad ................................................................................. 36
24. I.C.P. Monographs ............................................................................................................. 41
25. Dr. Vithalrao Nadgouda Best All India Annual Thesis Award ..................................... 60
26. Short Certificate Update Course .................................................................................. 101
27. Eligibility Criteria for the Award of Fellowship of Indian College of Physicians .............................................................................. 102
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¹. AWACS MAT July ’22  ². Bailie GR. Arzneimittelforschung. 2010 Jun;60(06):386-98.
Coronary heart disease is the leading cause of mortality all over the world. It is high time that we should discuss prevention. It is said, “prevention is better than cure.” Preventive cardiology means to prevent first and subsequent heart attacks. There are plenty of misconceptions and outdated ideas about prevention. We need to know properly about the myth and reality of risk factors for the prevention of coronary heart disease.

The new wave of prevention in the present era came from the European Society of Preventive Cardiology on 17th April 2021, an online discussion about this hottest science. This provided a stimulus to think and rethink prevention. The author aims to discuss myths and realities related to coronary artery disease (CAD) in India.

Myth–I
It is known that CAD common in rich and developed countries is a myth. Rich in living, consuming food rich in cholesterol and fat, calories, alcohol, smoking, and a sedentary lifestyle is known.

Martin is responsible for the area of cardiovascular diseases at the World Health Organization (WHO) state—the issue of rich and poor people regarding CAD and also comments that it is a myth. CAD is equally common in underdeveloped countries and among poor people.

A study by Achutti World Health Organization clearly demonstrates the relationship between poverty and risk factors is awakening. He says the lower the education level, the higher exposure to risk factors. In India, CAD is equally common in poor people. Two-thirds of all death occur in developing countries in poor people. It appears that an increase in risk factors due to economic burden and an increase in life expectancy, and an unhealthy lifestyle may be responsible factors in developing countries.

Myth–II
Coronary artery disease (CAD) affects elderly males and is less common in females. CAD is common in elderly males is no more true. It is a matter of concern that CAD is more common in young adults and females. CAD in women is always understood, underdiagnosed and undertreated. It is actually the number one killer in causing one in three females death due to acute myocardial infarction (AMI). CAD rapidly involves women from the age of 25 years. There is more hypertension, diabetes, smoking and stress, and drugs in the young generation. This factor leads to plaque formation of about 40–50%, which can rupture during physical and mental stress, leading to clots in arteries and heart attack.

Martin (WHO) cites that one-third of heart attacks occur below 65 years. One must take seriously about chest pain in females and young adults. CAD in young is called malignant CAD and it is imposed that lipoprotein(a) is a missing factor.

Myth–III
Smoking is injuries is not a myth. Tobacco in any form is bad—chewing, smoking, and snuffing are a precursor to thrombosis. Tobacco causes increases in heart rate and blood pressure and enhances atherosclerosis.

Dr Nicolle Kraenkel from the European Society of Cardiology said that e-cigarettes make it easier to quit.

Myth–IV
Fats and cholesterol are bad for your heart is not a myth but a reality. Fats are an important part of our diet. Not all fats are bad. Tran’s fat is the worst of all fats and is generally found in baked processed food. It increases the low-density lipoprotein (LDL) cholesterol—called bad cholesterol. Tran’s fats are important and responsible for heart attack, stroke, and diabetes. Saturated fats are found in red meat, butter, coconut oil, etc. As we all know increases your cholesterol and LDL cholesterol and reduces high-density lipoprotein (HDL)—good cholesterol. The higher the HDL—the longer the lifespan; hence consumption of saturated fat in our diet is restricted. Polyunsaturated fats are better and reduce LDL cholesterol. Sunflower oil, flax seeds oil, and Salmon fish are a few examples. Monosaturated fats are also good for use found in olive oil, avocado, peanut oil, etc.

The ideal suggestion is to change the oil every 3 months to get the best of all oils.

Replacing saturated and trans fats with unsaturated and polyunsaturated oils helps in reducing LDL cholesterol. Actually, the ideal optimal diet is controversial.

Myth–V
Cholesterol-lowering drugs and eating habits—give a wrong sense of security; one can eat anything, and the drug will take care of it. Your diet should be planned as recommended by your doctor. It is necessary to check your lipid profile every 3 months. Elevated LDL non-HDL, triglycerides, and low HDL are a great risk and need correction from time to time. Lipid-lowering drugs should be taken as advice from the cardiologist. Newer lipid-lowering drugs are excellent in reducing LDL, non-HDL, cholesterol, and triglycerides. But HDL is a hard nut. Attempts were made to elevate HDL but were unsuccessful. The ideal way is to do exercise every day.

Myth–VI
Can you exercise if you have CAD?
Exercise is good. It improves circulation, lowers cholesterol level, increases HDL cholesterol, and strengthen your heart muscle.

You can exercise, but you must know when to stop it. The best exercise is to walk 4 km in 45 minutes every day.

So it is a reality to walk for your heart. “heart says if you walk for me, I will keep beating for you.”

Myth–VII
Coronary artery disease (CAD) that runs in families is a reality. If both parents have a heart attack—the child will get 100% prematurely and at a younger age, 50% chance that 1 of the parents having CAD and may escape also.

Myth–VIII
Blood pressure and diabetes are important risk factors for CAD is a reality.

Both are known as “silent killer” and untreated hypertension can lead to heart...
Dr Kraenkel said—to focus first on body weight, an effective way of reaching children is school—the best environment, digital technology plays a very important role in prevention.

Role of Public Press in Prevention? Is a Reality

Scientific information reaches the public via the lay press that rapidly spread medical terms and practices. The lay public is easily influenced by press and media. This is an ideal way to prevention.

The population will be more beneficial and better diffused by media. Recently we have more number of people doing exercise, the proliferation of fitness centers and change in habit.

We all feel that these measures discussed above will be useful in destroying deeply rooted myths. An important contribution to preventing CAD at individual or collective levels is effectiveness.

References
1. ESC Preventive cardiology 2021 – Myths and facts about Prevention of Heart Disease.
2. World Health Organization – 2016
3. American Heart Association – 2018

Myth-IX
What is Heart Failure?
Means heart attack or the heart will stop beating—(cardiac arrest); all three are different.

Heart failure is a heart muscle disease when one becomes weak due to various reasons. Heart attack is due to blockage of the coronary artery and cardiac arrest when the heart stops beating. Heart failure is a serious disease, and newer drugs in the treatment of Heart failure have reduced repeated admissions and prolonged life.

Myth-X
Can a Heart Attack Lead to Cardiac Arrest?
Reality
The reality in some cases where cardiac arrest is the first and last expression of coronary artery disease. In cardiac arrest—no pulse and no blood pressure. The patient was unconscious, cold and with clammy extremities, and no breath sounds.

Myth-XI
Coronary angioplasty is far safer than coronary artery bypass graft in truth and reality. It is a noninvasive procedure, with 90% radial intervention short stay in the hospital for 48 hours, except for patients with heart failure and cardiogenic shock. It’s a short and sweet treatment.

Myth-XII
Stress and strain of life lead to CAD, hypertension, and diabetes—lifestyle diseases is a reality. One must learn how to relax in life to avoid these diseases. One must practice yoga and meditation regularly.

During the pandemic—leading expert from Europe and UD Professor Anu Abreu—Congress Chairperson for Edmonton Social Planning Council said social isolation, home working, sedentary lifestyle with increased consumption of high-calorie food and drinks, anxiety, stress, uncertainty strategies to maintain physical and emotional balance and prevent diseases is a reality and all of us have experienced this.

Myth-XIII
To relax—one must take out 1 hour for yourself. You should do any activity which gives you relaxation, for example, reading, writing, watching TV, singing, talking to your friend, and ventilating yourself.

Childhood is the best time to adopt a healthy lifestyle is a reality.
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Validity and Test-retest Reliability of perceived Wellness Survey among Geriatric Population: A Community-based Study from North Eastern India

Prasanta K Bhattacharya¹, Kuldeep Deka², Bhupen Barman³, Md Jamil⁴
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ABSTRACT

Objectives: Chronic illness and functional decline threaten elderly well-being. “Perceived Wellness Survey (PWS),” which measures psychosocial, physical, and intellectual well-being, may be appropriate for assessing the wellness of the geriatric population. This work has been planned to find out the validity and test-retest reliability of a PWS as a wellness-measuring tool for community-based elderly people.

Materials and methods: This observational study was undertaken to assess PWS in 60 elderly individuals (≥65 years). The validity of PWS was tested using Pearson product-moment correlation test. For test-retest reliability, the internal consistency of PWS was tested by Cronbach’s alpha test.

Result: Around 60 individuals ≥65 years (mean 69.45 ± 4.27 years), 48 males were selected by convenient sampling. Pearson’s correlation showed psychological, emotional, and physical subscale scores had a very strong positive relationship (0.734, 0.703, and 0.722, respectively) with a composite score of PWS score. Spiritual, intellectual, and social subscales showed a strong positive relationship with the composite PWS score. Test-retest variability between observations for subscales was ≥0.8, which showed good reliability, except for the physical subscale, which showed unacceptable reliability.

Conclusion: Perceived Wellness Survey (PWS) is an effective, feasible, highly reliable, and valid measure as a clinical assessment tool for assessing wellness in the elderly population.

INTRODUCTION

In the elderly population, the quality of life (QoL) depends on the interplay between independence and social inclusion, covering both subjective and objective parameters.¹,² Well-being of any individual is the estimation of the overall QoL of the individual as an active and integral person in the community.³ Thus, assessing QoL in the elderly population needs a specific measure which can identify the different aspects of wellness. Although various structured instruments in the form of questionnaires have been used in assessing the health condition and QoL in the elderly, there is a lack of consensus on the use of these instruments in measuring the QoL in the elderly.⁴ One of the common assessing tools for measuring wellness is the “PWS,” being used commonly for the different normative populations.⁵ PWS has certain advantages over other tools as it focuses on the perception of various dimensions of wellness in the form of psychological, emotional, social, physical, spiritual, and intellectual wellness.

The elderly population in India has been gradually increasing over the years, and as a measure of improving their health and socioeconomic problems, it is pertinent to focus on strategies to improve the overall QoL of the elderly. India is a developing country with an increasing prevalence of the elderly population.⁶ Assessment of both objective functioning and subjective well-being provides valuable information about their overall health status, but it requires proper validation.⁷

To measure wellness among the elderly population, one needs a valid and reliable scale. However, such a reliable and valid scale to assess the perception of wellness has not been utilized for assessment in the elderly population of this region. Therefore this work has been undertaken to assess the validity and reliability of the PWS for the geriatric population in a community setting from the North Eastern Region of India.

MATERIALS AND METHODS

An observational study was carried out in the community to determine the validity and test-retest reliability of PWS in the geriatric population aged 65 years and above. Participants were selected by convenient sampling from two municipality wards of Guwahati, Assam, India, between June 2015 and January 2016. The two municipality wards were selected randomly from the official ward register of the city. All the participants who satisfied the selection criteria completed the PWS in the first set. The researchers repeated the assessment after a period of 1 week with the same participants. Sample size calculation was done from the equation—the 4PQ/L, where P is the prevalence (4% elderly population in Guwahati), Q = 1−P and L = permissible error (which is taken as 5%) based on which sample size was 59 which was approximated to 60.

Participants were included on satisfying the inclusion and exclusion criteria mentioned below:

- Inclusion criteria: Participants, both males and females aged 65 years and above, have adequate comprehension skills in English.
- Exclusion criteria: Participants with problems of vision, cognitive impairment, and acute illness hampering concentration.

Ethical clearance was obtained from Institutional Ethics Committee, Guwahati Medical College and Hospital, Guwahati, Assam, India. Participants were included in the study after obtaining their written informed consent.

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Perceived Wellness Survey in Geriatric Population

Measuring Instruments

The PWS is a tool that measures the perception of well-being by an individual in the six dimensions of psychological, emotional, social, physical, spiritual, and intellectual, each of which has six possible grades of scoring from 1 (i.e., very strongly disagree) to 6 (i.e., very strongly agree). In each of the six parameters, the participant can select one grade of the score (between 1 and 6). The total score of PWS is the sum total of the individual scores of each parameter (dimension). A description of the various dimensions of the PWS is shown in Table 1.

For the purpose of this study, the PWS was translated into Assamese, the official state language of the Indian state of Assam. This involved the process of translating the English version into Assamese, then translating this Assamese version back into English and comparing the two English versions for any inconsistencies, which, if found, were then resolved. PWS questionnaire was first adapted from Adams et al. 1997.

Table 1: Definition of segments of the "PWS"5

<table>
<thead>
<tr>
<th>Segment</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>A feeling by the person that he/she will experience positive outcomes from events and circumstances in life</td>
</tr>
<tr>
<td>Emotional</td>
<td>To possess a sense of secured self-identity and a positive sense of self-regard</td>
</tr>
<tr>
<td>Social</td>
<td>A feeling by the person of having support available from family or friends in times of need and of being a valuable provider of support to others</td>
</tr>
<tr>
<td>Physical</td>
<td>A positive feeling and expectation by the person about physical health</td>
</tr>
<tr>
<td>Spiritual</td>
<td>A belief in a unifying force between the mind and body or a positive perception of meaning and purpose in life</td>
</tr>
<tr>
<td>Intellectual</td>
<td>A feeling by the person of being internally energized by an optimal amount of &quot;intellectually stimulating activity&quot;</td>
</tr>
</tbody>
</table>

Adapted from Adams et al. 19975

explained to the participants about how to respond to each question in the Likert scale and where the necessary explanation was provided. All participants completed the PWS at their own locality twice, with 1 week gap between the two sessions. In both sessions, the sequence of the components attempted to remain the same. Complete data were collected and entered in a Microsoft Windows Excel sheet for analysis.

Statistical Analysis

Data analysis was done by Statistical Package for the Social Sciences for Windows, version 16.0, manufacturer—IBM, Chicago, Illinois, United States of America. Demographic data were expressed in mean and standard deviation (SD). “Pearson product-moment” correlation test was used for testing the validity of PWS. This correlation test was done by correlating each component of the subscale score with the composite score of PWS of baseline data. Item-item questionnaires that significantly correlated with composite scores indicated that the items were valid. For test-retest reliability, the internal consistency of PWS was tested by Cronbach’s alpha test.

RESULTS

A total of 60 elderly participants, comprising 12 females and 48 males (female: male ratio of 1:4) with a mean age of 69.45 ± 4.27 years, were assessed for perceived wellness. The demographic parameters are shown in Table 2.

Table 2: Demographic characteristics of the participants

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of participants (n)</th>
<th>Range</th>
<th>Age (years)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>12</td>
<td>65.00 – 78.00</td>
<td>69.58 ± 4.35</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>65.00 – 83.00</td>
<td>69.58 ± 4.27</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>65.00 – 83.00</td>
<td>69.58 ± 4.35</td>
<td></td>
</tr>
</tbody>
</table>

The test-retest variability between observations for all the items (subcales) of PWS was determined from the mean ± SD values (Table 4).

The intra-class coefficient (ICC) of the items (subcales) and total score of PWS were done with a confidence interval (CI) of 95%, and significance levels were noted (Table 5). Among subscale items, psychological, emotional, social, spiritual, intellectual, and composite PWS scores were ≥0.8, which showed good reliability, but the physical subscale showed unacceptable reliability with a score of 0.478.

DISCUSSION

Aging is a progressive biological process involving various physical, psychological, and hormonal changes, as well as changes in the social domain. There is a definite gap in knowledge and understanding between the sense of well-being experienced by the elderly and the healthcare professionals extending their support. In the evaluation of patient outcomes, the patient’s perspective is as important as the clinician’s assessment. Therefore, while planning management strategies for the elderly, evaluation of wellness profile, risk factors, and wellness promotion activities should be integral components of the care strategies. One important aspect of geriatric wellness measurement is the lack of adequate published data on the measurement of well-being in the geriatric population. PWS measures all dimensions of wellness—psychological, emotional, social, physical, spiritual, and intellectual, except the occupational dimension. As the elderly population is mostly retired from jobs and homebound, there is very little need for assessing occupational dimensions. Perhaps that is why PWS may be the appropriate wellness measure for the geriatric population. Perceived wellness, although measured in different normative populations, use in special groups like the elderly has been very limited, and there is a necessity to rate the self-perceived wellness (well-being) of the geriatric population. Our study primarily intended to determine the validity and test-retest reliability of this PWS in geriatric people in the North Eastern Region of India so that this scale can be used.
Table 3: Pearson product-moment correlation test of the PWS

<table>
<thead>
<tr>
<th>Test</th>
<th>Psy (total)</th>
<th>Emo (total)</th>
<th>Soc (total)</th>
<th>Phy (total)</th>
<th>Spi (total)</th>
<th>Int (total)</th>
<th>PWS (composite)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological (total)</td>
<td>Pearson correlation</td>
<td>1</td>
<td>0.356</td>
<td>0.482</td>
<td>0.595</td>
<td>0.348</td>
<td>0.369</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>0.005</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
</tr>
<tr>
<td>Emotional (total)</td>
<td>Pearson correlation</td>
<td>0.356</td>
<td>1</td>
<td>0.365</td>
<td>0.409</td>
<td>0.446</td>
<td>0.484</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>0.004</td>
<td>0.001</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
</tr>
<tr>
<td>Social (total)</td>
<td>Pearson correlation</td>
<td>0.482</td>
<td>0.365</td>
<td>1</td>
<td>0.546</td>
<td>0.161</td>
<td>0.118</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>0.004</td>
<td>0.001 60</td>
<td>&lt;0.001 60</td>
<td>0.219</td>
<td>0.369</td>
<td>&lt;0.001 60</td>
</tr>
<tr>
<td>Physical (total)</td>
<td>Pearson correlation</td>
<td>0.595</td>
<td>0.409</td>
<td>0.546</td>
<td>1</td>
<td>0.352</td>
<td>0.335</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>0.006</td>
<td>0.009</td>
<td>0.009</td>
<td>&lt;0.001 60</td>
</tr>
<tr>
<td>Spiritual (total)</td>
<td>Pearson correlation</td>
<td>0.348</td>
<td>0.486</td>
<td>0.161</td>
<td>0.352</td>
<td>1</td>
<td>0.477</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>&lt;0.001 60</td>
<td>0.219</td>
<td>0.352</td>
<td>1</td>
<td>0.477</td>
<td>&lt;0.001 60</td>
</tr>
<tr>
<td>Intellectual (total)</td>
<td>Pearson correlation</td>
<td>0.369</td>
<td>0.484</td>
<td>0.118</td>
<td>0.335</td>
<td>0.447</td>
<td>1</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>0.009</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
</tr>
<tr>
<td>PWS (composite)</td>
<td>Pearson correlation</td>
<td>0.734</td>
<td>0.703</td>
<td>0.548</td>
<td>0.722</td>
<td>0.638</td>
<td>0.571</td>
</tr>
<tr>
<td>Significance (two-tailed)</td>
<td>n = 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
<td>&lt;0.001 60</td>
</tr>
</tbody>
</table>

Emo, emotional; Int, intellectual; Phy, physical; Psy, psychological; PWS, perceived wellness survey; Soc, social; Spi, spiritual

Table 4: Intra-rater variability of the PWS in the participants

<table>
<thead>
<tr>
<th>Item</th>
<th>Number of participants</th>
<th>Test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological (total): Test 1</td>
<td>60</td>
<td>26.20</td>
</tr>
<tr>
<td>Psychological (total): Test 2</td>
<td>60</td>
<td>26.43</td>
</tr>
<tr>
<td>Emotional (total): Test 1</td>
<td>60</td>
<td>22.01</td>
</tr>
<tr>
<td>Emotional (total): Test 2</td>
<td>60</td>
<td>21.98</td>
</tr>
<tr>
<td>Social (total): Test 1</td>
<td>60</td>
<td>25.81</td>
</tr>
<tr>
<td>Social (total): Test 2</td>
<td>60</td>
<td>26.46</td>
</tr>
<tr>
<td>Physical (total): Test 1</td>
<td>60</td>
<td>19.08</td>
</tr>
<tr>
<td>Physical (total): Test 2</td>
<td>60</td>
<td>23.51</td>
</tr>
<tr>
<td>Spiritual (total): Test 1</td>
<td>60</td>
<td>23.20</td>
</tr>
<tr>
<td>Spiritual (total): Test 2</td>
<td>60</td>
<td>23.88</td>
</tr>
<tr>
<td>Intellectual (total): Test 1</td>
<td>60</td>
<td>23.43</td>
</tr>
<tr>
<td>Intellectual (total): Test 2</td>
<td>60</td>
<td>24.60</td>
</tr>
</tbody>
</table>

Test 1, first-time testing for intra-rater variability; Test 2, repeat testing for intra-rater variability

as a measuring tool of wellness for geriatrics in this region.

We have observed a positive correlation among each dimension of wellness of the PWS. The psychological dimension showed a perfect correlation with physical (0.595) and composite score (0.734), whereas the physical dimension correlated well with psychological (0.595), social (0.546), and composite score (0.722). This implies that with a greater degree of activity, the elderly, in their societal roles, have better physical and mental health, a concept which has its domains of implication in the definition of health according to the World Health Organization.12 Other dimensions like emotional, spiritual, and intellectual dimensions showed a strong perfect correlation only in the composite PWS score with values of 0.703, 0.638, and 0.571, thereby indicating their roles as another dimension of health. A strong positive correlation among every individual parameter with the composite PWS score indicates the construct validity of the PWS among the elderly population studied. However, the construct validity of all wellness measuring instruments is dependent on their definition of wellness.13

Validity requires that an instrument is reliable, but an instrument can be reliable without being valid.14 Stability of measures administered at different times of PWS showed a good internal consistency for the dimension of psychological, emotional, social, spiritual, and intellectual and for the composite score of PWS. But the physical dimensions (ICC = 0.478) of PWS showed poor reliability and the reason behind this implies that the physical dimension may have poor theoretical values, and may greatly depend on the expectation of one’s own better well-being on day-to-day variation. Another reason may be the reduction of physical activity and functional fitness in the elderly due to the aging process, which may have a negative impact on the perception of being
healthy for the elderly. The fundamental factors which successful aging include both subjective and objective perspectives and include having a self-perception about one’s own health, psychological support, adequate social resources, and coping mechanism to be able to adapt to life’s changes. Wellness is a subjective perception as to how much an individual is satisfied with one’s own life and the positive and negative emotions that are associated with the status of health of the individual.

In summary, it can be stated that the use of the PWS to assess the overall wellness in the geriatric population has been found to be effective, feasible, highly reliable, and a valid measure. It can therefore be used as a tool for the clinical assessment of wellness in the elderly. However, further studies should focus on measuring perceived wellness in a larger geographical region.

The subjects for the study were selected by convenient sampling from a limited geographical area of a city. This is the limitation of the study.

**Conclusion**

The aim of our study was to determine the validity and test-retest reliability of PWS in the elderly people population in an urban setting in order that this test can be used to measure the wellness of the geriatric community in India. The test-retest reliability of the PWS has been found to be good and valid and can be used to measure wellness in the elderly population of the community.

**References**

Rationalizing the Use of COVID-19 Questionable Efficacy Drugs in a Low Middle-income Country: A Hospital Tocilizumab Committee Experience

Naveen Hegde1, Ankit Kumar2, Gurpreet K Batra3, Mahesh Devnani4, Rachna Rohilla5, Pankaj Malhotra6, Amol N Patil7*

Accepted: 02 November 2022

ABSTRACT

Background: Only corticosteroids have confirmed mortality benefits in coronavirus disease of 2019 (COVID-19). Rational use of costlier drugs with questionable benefits poses a great concern to hospital pharmacies in low-middle-income countries.

Aim: The present study aimed to assess the rational utilization of hospital supply tocilizumab and understand its clinical benefits in hospitalized COVID-19 pneumonia patients.

Methods: The Hospital Tocilizumab Committee (HTC) decision support system framework was developed to make patients eligible or ineligible for tocilizumab procurement from the hospital pharmacy. A total of 33 consecutive patients receiving tocilizumab were analyzed retrospectively in the 3-month study period. The records of the inpatient stay of the patients were observed for pulse, blood pressure, respiratory rate (RR), oxygen saturation (SpO2), fraction of inspired oxygen (FiO2) laboratory work-up, hospital stay duration, and mortality benefit, if any. Patients were analyzed as “died,” “survived,” and “composite” subgroups.

Results: The study observed death as a final outcome in 48% of patients. The study observed a significant effect of tocilizumab on C-reactive protein (CRP) (p = 0.02) and ferritin (p = 0.018) levels on a 10-day follow-up when all patients were analyzed together. Rising and declining trends of RR and FiO2 were observed among the “died” (RR, p = 0.02; FiO2, p = 0.03) and survived (RR, p = 0.03; FiO2, p = 0.05) subgroups. The second dose of tocilizumab was received by 88% of survivors as against 50% of patients who died (p = 0.04).

Conclusion: Hospital Tocilizumab Committee (HTC) was successfully established to continue the assessment of the costlier drug with uncertain treatment benefits. A repeat dose of tocilizumab may provide a mortality benefit in Asian Indians.

ORIGINAL ARTICLE

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Conclusion: Hospital Tocilizumab Committee (HTC) was successfully established to continue the assessment of the costlier drug with uncertain treatment benefits. A repeat dose of tocilizumab may provide a mortality benefit in Asian Indians.

INTRODUCTION

The respiratory and cardiovascular systems are the prime targets of COVID-19. Patient hospitalization, triaging, and hospital indoor course require special attention to the SpO2 in patient blood, oxygen demand trend, and vitals, coupled with laboratory SpO2 in patient blood, oxygen demand course require special attention to the need for mechanical ventilation.

Background: Only corticosteroids have confirmed mortality benefits in coronavirus disease of 2019 (COVID-19). Rational use of costlier drugs with questionable benefits poses a great concern to hospital pharmacies in low-middle-income countries.

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Conclusion: Hospital Tocilizumab Committee (HTC) was successfully established to continue the assessment of the costlier drug with uncertain treatment benefits. A repeat dose of tocilizumab may provide a mortality benefit in Asian Indians.

Rationalizing the Use of COVID-19 Questionable Efficacy Drugs

Tocilizumab was hypothesized as having a potential role in the management of COVID-19 pneumonia, especially for critical cases. To rationalize the use of tocilizumab, an in-house requisition form was developed for rapid communication and quick approvals for fully eligible patients. A WhatsApp group was formulated by three HTC members for regular discussions in the morning and night at 9 o’clock for critical cases, besides routine quick approvals for fully eligible patients.

All three HTC members had to make a common decision of “eligible” or “not eligible” for indenting the tocilizumab from the hospital pharmacy. The due common decision was communicated to the treating clinicians looking after the COVID-19 pneumonia patient were requested to fill up the tocilizumab requisition forms and send them via WhatsApp. A WhatsApp group was formulated by three HTC members for regular discussions in the morning and night.

A WhatsApp number of a pharmacologist HTC member was mentioned on the requisition form for rapid communication. The treating clinicians looking after the COVID-19 pneumonia patient were requested to fill up the tocilizumab requisition forms and send them via WhatsApp. A WhatsApp group was formulated by three HTC members for regular discussions in the morning and night.

Table 1: Requisition form developed in-house for tocilizumab procurement

<table>
<thead>
<tr>
<th>To be submitted by WhatsApp to</th>
<th>Dr XYZ</th>
<th>Mobile number: 987654321</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of request</td>
<td>CR number/IPD number</td>
<td></td>
</tr>
<tr>
<td>Name of patient</td>
<td>Ward number and bed number</td>
<td></td>
</tr>
<tr>
<td>Age and gender</td>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Complete diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First RT-PCR positivity date for current illness</td>
<td>Patient contact number</td>
<td></td>
</tr>
<tr>
<td>Date of symptom onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of Hospital admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2 with AND without oxygen</td>
<td>with ( ) and without oxygen ( )</td>
<td></td>
</tr>
<tr>
<td>Oxygen support type</td>
<td>Continuous positive airway pressure /nasal cannula/high flow nasal cannula/non-rebreather face mask/incubator</td>
<td></td>
</tr>
<tr>
<td>Maximum NEWS2 score on request day</td>
<td>RR SBP pulse rate temp</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consciousness (on the range from 0 to 20, with higher scores indicating greater clinical risk)</td>
<td></td>
</tr>
<tr>
<td>Steroid name dose and date of start</td>
<td>Name</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Date of start</td>
<td></td>
</tr>
<tr>
<td>Steroid dose escalation details</td>
<td>Date of dose modification 1 dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Date of dose modification 2 dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td></td>
</tr>
<tr>
<td>Hepatic impairment [alanine transaminase (ALT) &gt; 1.5 upper limit of normal (ULN)] present?</td>
<td>Y/N</td>
<td></td>
</tr>
<tr>
<td>Adjunct treatment received/ongoing</td>
<td>Received dose date of start</td>
<td>Ongoing dose date of start</td>
</tr>
<tr>
<td>Past history of immunomodulator drug use</td>
<td>Y/N</td>
<td>History of tuberculosis–Y/N</td>
</tr>
<tr>
<td>Indication (if not mentioned below)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal work up (galactomannan level/ potassium hydroxide smear/any other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count (inclusive of neutrophil lymphocyte ratio)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-dimer level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture report</td>
<td>Blood bronchoalveolar lavage urine any other</td>
<td></td>
</tr>
<tr>
<td>Cycle threshold (CT) score if available/ chest X-ray findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All unused vials must be sent back to pharmacy within 24 hours of receipt.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remarks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab is available in limited supply. Kindly use judiciously.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of consultant</td>
<td>Signature</td>
<td>Mobile number</td>
</tr>
</tbody>
</table>

CR, case record; IPD, in patient department
Rationalizing the Use of COVID-19 Questionable Efficacy Drugs

Inclusion Criteria
Consecutive patients aged 18 years and above, diagnosed with oxygen-dependent COVID-19 pneumonia, diagnosis confirmed by reverse transcriptase polymerase chain reaction (RT-PCR), having COVID-19 disease symptoms onset within past 2 weeks, cytokine storm onset within 1 week, receiving tocilizumab from the hospital supply was included in the analysis.

Exclusion Criteria
Those patients who had mild to moderate COVID-19 infection confirmed by RT-PCR, SpO2 ≥ 93, CRP ≤ 75, showing appreciable response to corticosteroid therapy in terms of FiO2 and SpO2, receiving any other off-label drug, having any other fungal or bacterial or tubercular infection, absolute neutrophil count (ANC) <500, platelet count <50,000, liver enzyme elevation more than five times the upper limit of the normal range, and elevated risk of gastrointestinal (GI) perforation, were excluded.

The Institutional Ethics Committee (IEC) approved the study via communication dated INT /IEC/2021/SPE/102 dated 20.07.2021. A predesigned case record form was used for the collection of the data. Patient files were traced from the medical record office of the institution. The demographic details, including age, gender, height, weight, body mass index, COVID-19 history, RT-PCR reports, background medications, laboratory, and vitals assessments before and up to 10 days after tocilizumab use, were recorded. The data entry was cross-examined by the second investigator of the study. Any discrepancy noted in the data entry was resolved by confirmation from the third investigator.

Guidance for Tocilizumab use in COVID

- COVID positive patient
  - Time from symptoms onset - less than 2 weeks
  - Onset of cytokine storm - less than 1 week

  Oxygen dependence due to COVID pneumonia
  - No evidence of fungal, bacterial, tubercular infection
    (Procalcitonin < 0.15, preferably normal) AND No contraindications to use of Tocilizumab
  - Elevated Inflammatory markers
    (Any combination, within the past 48 hours)
    - CRP >75
    - IL-6 >30
    - LDH >280
    - D-dimer >600
    - Ferritin >500

  Received steroids?
  - No
    - Consider steroids as per clinical scenario
  - Yes
    - Status at 48–72 hours after steroids
      - Improvement in clinical status
        - Defer Tocilizumab
      - No improvement, Oxygen requirement increased in last 48 hours
        - Consider Tocilizumab;
          - Half dose if ALT > 1.5 times ULN

  Tocilizumab should be avoided if:
  - Absolute Neutrophil count <500
  - Platelet count < 50,000
  - ALT > 5 times the ULN
  - Elevated risk for GI perforation
  - Uncontrolled bacterial, fungal, tubercular infection

Fig. 1: Algorithm for rational use of hospital supply tocilizumab
### Table 2: Baseline characteristics of the two study subgroups

<table>
<thead>
<tr>
<th></th>
<th>Died (n = 16)</th>
<th>Survived (n = 17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58.12 ± 10.75</td>
<td>55.70 ± 1.82</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Gender ratio (M:F)</strong></td>
<td>10:6</td>
<td>10:7</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Place in hospital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward care received (n)</td>
<td>11</td>
<td>7</td>
<td>0.16</td>
</tr>
<tr>
<td>ICU care required (n)</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>5 (31%)</td>
<td>9 (53%)</td>
<td>0.308</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>9 (56%)</td>
<td>10 (59 %)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other comorbidity (n)</td>
<td>6 (37%)</td>
<td>5 (42%)</td>
<td>0.712</td>
</tr>
<tr>
<td>multiple comorbidities (n)</td>
<td>4 (25%)</td>
<td>4 (23%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Addiction history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic (n)</td>
<td>2/12</td>
<td>1/16</td>
<td>0.576</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>2/13</td>
<td>0/17</td>
<td>0.212</td>
</tr>
<tr>
<td><strong>COVID-19 symptom history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms onset before hospitalization</td>
<td>8.31 ± 5.57</td>
<td>6.16 ± 3.18</td>
<td>0.193</td>
</tr>
<tr>
<td>Symptoms onset before RT-PCR</td>
<td>5.69 ± 3.4</td>
<td>5.81 ± 1.97</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Oxygen consumption evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPO2 baseline ²⁶</td>
<td>88.87 ± 5.40</td>
<td>90.82 ± 4.69</td>
<td>0.276</td>
</tr>
<tr>
<td>SPO2 without O2 support (%)</td>
<td>78.56 ± 15.59</td>
<td>80.47 ± 9.17</td>
<td>0.669</td>
</tr>
<tr>
<td>SPO2 with O2 support (%)</td>
<td>90.50 ± 5.94</td>
<td>92.35 ± 3.18</td>
<td>0.269</td>
</tr>
<tr>
<td><strong>Supplemental oxygen type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>3</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>Noninvasive (nasal cannula/Non-rebreathing masks/Ventilation mode)</td>
<td>13</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>FiO2</td>
<td>0.6 ± 0.109</td>
<td>0.6 ± 0.18</td>
<td>0.87</td>
</tr>
<tr>
<td>Toci administration after x days of hospitalization</td>
<td>4.13 ± 2.58</td>
<td>2.94 ± 2.81</td>
<td>0.224</td>
</tr>
<tr>
<td><strong>COVID vaccination status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed two doses</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Fully unvaccinated</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Had received single dose of COVID vaccine</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline vitals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse (per minute)</td>
<td>88.62 ± 10.44</td>
<td>92.88 ± 18.50</td>
<td>0.42</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120.87 ± 20.75</td>
<td>135.70 ± 23.69</td>
<td>0.066</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>74.75 ± 11.69</td>
<td>79.94 ± 12.27</td>
<td>0.223</td>
</tr>
<tr>
<td>RR (per minute)</td>
<td>30.31 ± 5.08</td>
<td>28.05± 6.05</td>
<td>0.257</td>
</tr>
<tr>
<td><strong>Biochemistry based lab evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>124.91 ± 57.90</td>
<td>125.31 ± 46.36</td>
<td>0.982</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>3845.04 ± 5934.04</td>
<td>2892.81 ± 3566.09</td>
<td>0.578</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>1049.64 ± 479.69</td>
<td>1146.64 ± 342.25</td>
<td>0.007</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>636.12 ± 180.77</td>
<td>577.29 ± 60.86</td>
<td>0.232</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>3</td>
<td>3</td>
<td>0.319</td>
</tr>
<tr>
<td><strong>Radiological examination findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR/CT changes (n)</td>
<td>13</td>
<td>10</td>
<td>1.00</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3.5 ± 1</td>
<td>2 ± 2</td>
<td>0.182</td>
</tr>
<tr>
<td>Time lag in steroids administration after hospitalization (days)</td>
<td>2.93 ± 4.30</td>
<td>1.19 ± 5.63</td>
<td>0.34</td>
</tr>
<tr>
<td>Total stay of hospitalization (days)</td>
<td>10.33 ± 5.76</td>
<td>13.27 ± 6.0</td>
<td>0.183</td>
</tr>
<tr>
<td>Survival observed up to (days)</td>
<td>9.13 ± 5.5</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

$\text{None of the study participant patients having tuberculosis history or immunomodulatory drug use history; } *_{p < 0.05} \text{ were assumed significant}$
Table 3: Follow up progress of all the study participant patients during hospital stay

<table>
<thead>
<tr>
<th>Follow-up at</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse (per minute)</td>
<td>89.39 ± 13.44</td>
<td>93.42 ± 15.125</td>
<td>89.88 ± 15.463</td>
<td>90.12 ± 16.467</td>
<td>0.318</td>
</tr>
<tr>
<td>RR (per minute)</td>
<td>29.12 ± 5.69</td>
<td>28.88 ± 5.58</td>
<td>28.79 ± 5.53</td>
<td>29.21 ± 5.6</td>
<td>0.848</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>137.22 ± 22.46</td>
<td>132.38 ± 22.49</td>
<td>127.75 ± 31.11</td>
<td>130.31 ± 22.65</td>
<td>0.39</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>79.30 ± 8.17</td>
<td>78.48 ± 10.25</td>
<td>75.56 ± 10.72</td>
<td>74.58 ± 10.96</td>
<td>0.09</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>109.74 ± 72.29</td>
<td>84.94 ± 73.69</td>
<td>78.9 ± 78.87</td>
<td>82.87 ± 80.63</td>
<td>0.02**</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>3806.36 ± 5533.44</td>
<td>3691.87 ± 5576.87</td>
<td>3107.15 ± 4364.14</td>
<td>3044.75 ± 4368.8</td>
<td>0.246</td>
</tr>
<tr>
<td>Ferritin (mg/mL)</td>
<td>1043.07 ± 544.15</td>
<td>989.01 ± 603.57</td>
<td>895.03 ± 648.24</td>
<td>846.19 ± 553.6</td>
<td>0.018**</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>624.7 ± 239.9</td>
<td>597.09 ± 241.55</td>
<td>574.15 ± 203.59</td>
<td>572.7 ± 252.64</td>
<td>0.17</td>
</tr>
<tr>
<td>SPO2 (%)</td>
<td>3806.36 ± 5533.44</td>
<td>3691.87 ± 5576.87</td>
<td>3044.75 ± 4368.8</td>
<td>3107.15 ± 4364.14</td>
<td>0.246</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>91.08 ± 4.95</td>
<td>88.39 ± 10.62</td>
<td>89.06 ± 10.14</td>
<td>87.74 ± 11.89</td>
<td>0.13</td>
</tr>
<tr>
<td>FiO2</td>
<td>0.63 ± 0.18</td>
<td>0.62 ± 0.2</td>
<td>0.62 ± 0.2</td>
<td>0.63 ± 0.24</td>
<td>0.884</td>
</tr>
</tbody>
</table>

*p < 0.05 were assumed significant

Table 4: Follow up progress of “died subgroup” study participant patients during hospital stay

<table>
<thead>
<tr>
<th>Follow-up at</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse (per minute)</td>
<td>89.13 ± 13.366</td>
<td>97.19 ± 17.796</td>
<td>88.75 ± 18.996</td>
<td>90.63 ± 20.48</td>
<td>0.486</td>
</tr>
<tr>
<td>RR (per minute)</td>
<td>29.06 ± 6.07</td>
<td>28.81 ± 6.19</td>
<td>29.31 ± 5.98</td>
<td>31.88 ± 5.26</td>
<td>0.02**</td>
</tr>
<tr>
<td>SBP</td>
<td>139.13 ± 28.35</td>
<td>132.73 ± 30.66</td>
<td>131.6 ± 31.02</td>
<td>133.87 ± 30.84</td>
<td>0.625</td>
</tr>
<tr>
<td>DBP</td>
<td>78.12 ± 8.26</td>
<td>78.11 ± 11.38</td>
<td>73.56 ± 13.145</td>
<td>72.25 ± 13.79</td>
<td>0.267</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>121.88 ± 92.78</td>
<td>97.91 ± 84.16</td>
<td>93.28 ± 89.47</td>
<td>97.70 ± 93.52</td>
<td>0.261</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>4007.22 ± 5996.53</td>
<td>3913.16 ± 5996.0</td>
<td>3862.12 ± 5986.98</td>
<td>4231.26 ± 5977.17</td>
<td>0.521</td>
</tr>
<tr>
<td>Ferritin (mg/mL)</td>
<td>1078.15 ± 635.75</td>
<td>1079.05 ± 707.5</td>
<td>997.9 ± 751.17</td>
<td>931.15 ± 557.45</td>
<td>0.37</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>657.44 ± 276.92</td>
<td>645.62 ± 266.17</td>
<td>629.94 ± 267.33</td>
<td>623.56 ± 309.13</td>
<td>0.5</td>
</tr>
<tr>
<td>SPO2 (%)</td>
<td>89.68 ± 13.44</td>
<td>93.42 ± 15.125</td>
<td>89.88 ± 15.463</td>
<td>90.12 ± 16.467</td>
<td>0.318</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>91.08 ± 4.95</td>
<td>88.39 ± 10.62</td>
<td>89.06 ± 10.14</td>
<td>87.74 ± 11.89</td>
<td>0.13</td>
</tr>
<tr>
<td>FiO2</td>
<td>0.63 ± 0.18</td>
<td>0.62 ± 0.2</td>
<td>0.62 ± 0.2</td>
<td>0.63 ± 0.24</td>
<td>0.884</td>
</tr>
</tbody>
</table>

*p < 0.05 were assumed significant

Statistical Analysis

The follow-up data of all patients were analyzed using Statistical Package for the Social Sciences software version 26. A repeat measure analysis of variance test was used to assess the trend of vitals and laboratory data. An unpaired t-test was used for the comparison of two subgroups, “dead” and “survived.” Fischer’s exact test was used to analyze categorical variable data. The p-value <0.05 was assumed statistically significant.

Results

The study was conducted in 3 months, from Oct 2021 to Jan 2022. HTC received a total of 39 requisitions. A total of 33 (84%) requisitions were approved as per the HTC decision-making algorithm. The average time of approval or disapproval of the request from the receipt of the request was 3 hours, ranging from 40 minutes to 18 hours. The present study included 33 consecutive, moderate to severe COVID-19 patients receiving free tocilizumab from hospital supply in the final analysis.

The study observed death as a final outcome in 16 (48%) out of 33 patients. Study participant patients were stratified for the analysis as “dead” (n = 16) versus “survived” (n = 17) subgroups. All patients received parenteral remdesivir, heparin, dexamethasone, and supplemental oxygen support in the background. The requirement of ICU care, comorbidity status, addiction history, onset time of COVID-19 disease symptoms, and radiographic findings at the time of hospital admission did not bear any significant differences in both subgroups. Vitals such as pulse, RR, systolic blood pressure (SBP), diastolic blood pressure (DBP), SpO2, and oxygen demand FiO2, serum/blood levels of CRP, hepatic function status, D-dimer, ferritin, and lactate dehydrogenase (LDH) were also comparable in both the subgroups at the time of hospital admission (Table 2) (p > 0.05 for all parameters).

The average duration of hospital stay was 13.27 days in the “survived” subgroup. Vitals such as pulse, RR, systolic blood pressure (SBP), diastolic blood pressure (DBP), SpO2, and oxygen demand FiO2, serum/blood levels of CRP, hepatic function status, D-dimer, ferritin, and lactate dehydrogenase (LDH) were also comparable in both the subgroups at the time of hospital admission (Table 2) (p > 0.05 for all parameters).

On posttocilizumab follow-up assessment of all the patients together, the study showed a significant decline in CRP (p = 0.02) and ferritin (p = 0.018) levels, while there was no significant change in other parameters such as vitals, D-dimer, LDH, SpO2, and FiO2 (Table 3). The second dose of tocilizumab was received by 88% (15 out of 17) of survivors as against 50% (8 out of 16) of patients who died (p = 0.049).

When the two subgroups “dead” and “survived” were analyzed separately, two opposite direction trends were noted for the RR and FiO2 parameters. The study observed an increasing trend (RR, p = 0.02; FiO2, p = 0.03) in the “dead” subgroup (Table 4), while a decreasing trend of RR (p = 0.03) and FiO2 (p = 0.05) was noted in the “survived” subgroup (Table 5). In the latter subgroup, an additional depreciative effect of tocilizumab administration was observed on ferritin (p = 0.016).

In the comparative assessment of both the subgroups, the two parameters, namely RR (p = 0.009) and FiO2 (p < 0.001), showed statistically significant differences.

A decline in ferritin levels was observed in the patients who survived (p = 0.016) but not in the other subgroup.
Rationalizing the Use of COVID-19 Questionable Efficacy Drugs

Table 5: Follow-up progress of “survived subgroup” study participants during hospital stay

<table>
<thead>
<tr>
<th>Follow-up at</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 10</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse (per minute)</td>
<td>89.65 ± 13.92</td>
<td>89.88 ± 11.537</td>
<td>90.94 ± 11.723</td>
<td>89.65 ± 12.191</td>
<td>0.805</td>
</tr>
<tr>
<td>RR (per minute)</td>
<td>29.18 ± 5.5</td>
<td>28.94 ± 5.1</td>
<td>28.29 ± 5.21</td>
<td>26.71 ± 4.7</td>
<td>0.035**</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135.53 ± 16.371</td>
<td>132.06 ± 12.542</td>
<td>124.35 ± 31.735</td>
<td>127.18 ± 11.828</td>
<td>0.108</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>80.41 ± 8.186</td>
<td>78.94 ± 9.404</td>
<td>77.82 ± 7.650</td>
<td>76.76 ± 7.181</td>
<td>0.244</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>98.31 ± 45.79</td>
<td>72.74 ± 62.4</td>
<td>65.56 ± 67.43</td>
<td>68.91 ± 66.16</td>
<td>0.113</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>3621.55 ± 5281.62</td>
<td>3483.59 ± 5335.76</td>
<td>2275.46 ± 1866.66</td>
<td>2049.16 ± 1464.54</td>
<td>0.18</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>1010.06 ± 459.23</td>
<td>904.32 ± 496.52</td>
<td>798.22 ± 539.35</td>
<td>766.24 ± 544.63</td>
<td>0.016**</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>593.88 ± 203.03</td>
<td>551.41 ± 213.77</td>
<td>521.65 ± 99.31</td>
<td>524.82 ± 181.78</td>
<td>0.31</td>
</tr>
<tr>
<td>SPO2 (%)</td>
<td>92.39 ± 2.5</td>
<td>92.12 ± 2.9</td>
<td>93.35 ± 3.4</td>
<td>91.44 ± 10.41</td>
<td>0.492</td>
</tr>
<tr>
<td>FiO2</td>
<td>0.587 ± 0.17</td>
<td>0.518 ± 0.17</td>
<td>0.521 ± 0.21</td>
<td>0.498 ± 0.19</td>
<td>0.05**</td>
</tr>
</tbody>
</table>

*p < 0.05 were assumed significant

**Discussion**

The present naturalistic study was conducted to understand capacity building in the name of HTC to rationalize tocilizumab use in the hospital and simultaneously assess treatment benefits in the Asian Indian ethnicity patient population. Low income countries like India require locoregional evidence development to balance the cost burden on government hospitals vs maximizing the treatment benefits. Historical tocilizumab trials have had a few inherent limitations with unequivocal results. To name a few are—excluding patients receiving mechanical ventilation, baseline differences in COVID-19 severity, including only mild to moderate patients, inadequate representation of ethnic minorities and underserved populations, etc. The present study addressed all these issues by analyzing the records of 33 consecutive patients receiving tocilizumab.

The study observed two opposite trends of RR and FiO2. Patients in the “dead” subgroup showed a rising trend, while the other subgroup showed a declining trend. An increase found in both RR and oxygen demand indicates an inferior prognosis. This can be considered an important covariate for decision algorithm-making for second-dose eligibility in the same patient. The tocilizumab administration was 8 days, with a 75% patient survival rate in the study done by Surana et al. in a private hospital in Mumbai. The difference might be due to higher comorbidities observed in the tertiary care referral hospitals. The advantage of retrospective studies is that the natural course information is obtained in toto without controlling any covariate such as comorbidity.

The study observed two opposite trends of RR and FiO2. Patients in the “dead” subgroup showed a rising trend, while the other subgroup showed a declining trend. An increase found in both RR and oxygen demand indicates an inferior prognosis. This can be considered an important covariate for decision algorithm-making for second-dose eligibility in the same patient. The tocilizumab administration was 8 days, with a 75% patient survival rate in the study done by Surana et al. in a private hospital in Mumbai. The difference might be due to higher comorbidities observed in the tertiary care referral hospitals. The advantage of retrospective studies is that the natural course information is obtained in toto without controlling any covariate such as comorbidity.

**Limitations**

The study has a few limitations, such as the small sample size, the retrospective nature of the study, and the absence of a facility for IL-6-level lab investigation.

**Conclusion**

The present study confirms the successful establishment of HTC for controlled supply chain management of costly drugs with uncertain treatment benefits for the first time in India.

**References**


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Prof. Dr. Mangesh Tiwaskar
Editor-in-Chief, JAPI
Pulmonary Manifestations in Patients of Rheumatoid Arthritis and its Correlation with Severity of Disease

Liyakat A Gauri*, Bharat Sharma, Ketan Bhatnagar, Nadeem Liyakat, Parvez Sameja, Kuldeep Saini, Ravi Dutt, Mohit S Khokhar, Vikas Kumar, Anjali Garg

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by symmetric, peripheral polyarthritis. RA has a prevalence of 1–2% in the general adult population. The mortality rate in patients with RA increases during the course of the disease, with a tendency to accelerate after 15 years.

Aim: To study the pulmonary manifestations and their severity using [Disease Activity Score (DAS)—28 score] in patients of RA.

Materials and methods: Present study was conducted in the Department of Medicine, Sardar Patel Medical College and Associated Group of Hospitals Bikaner, Bikaner, Rajasthan, India, on 100 patients. This study was a cross-sectional, observational study conducted over 1 year. Consecutive cases of RA patients attending the outpatient department or admitted to the medicine wards were selected according to the inclusion and exclusion criteria.

Results: Pulmonary manifestation was present in a total of 38% of cases, while the remaining 62% of cases had no pulmonary manifestation. The presence of comorbidity and C-reactive protein (CRP) was significantly associated with pulmonary manifestation in RA patients. On high-resolution computed tomography (HRCT), the most common finding was interstitial lung disease (ILD) (60.5%), with usual interstitial pneumonia (UIP) as the most common pattern. On performing a pulmonary function test (PFT), 33 patients (86.84%) had an abnormal result, with restrictive as the most common pattern.

Conclusion: The patients of RA, especially those with advanced age, long duration of disease, male sex, and associated comorbidity, should be screened for pulmonary complications of RA using X-ray chest and PFT, supplemented by HRCT chest wherever required.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by symmetric, peripheral polyarthritis. RA has a prevalence of 1–2% in the general adult population. The greatest incidence occurs between 35 and 45 years of age with predominance in women of 3:1. It presents as a chronic, bilateral, and symmetrical erosive polyarthritis with diverse extra-articular manifestations that affect tissues and organs, such as peripheral nerves, blood vessels, the lung, eyes, heart, and spleen with the presence of rheumatoid nodules, anemia, and symptoms of systemic disease. Three types of clinical course are recognized in this disease—type I, a self-limited process; type II, a polycyclic variant; and type III, the most frequent, which is progressive and deforming. Since the 1980s, RA has been known to lower life expectancy, with a mortality rate similar to that observed in patients with Hodgkin disease, diabetes mellitus (DM), or cerebrovascular disease. Life expectancy can decrease by 4–7 years in men and by 3–10 years in women, but a decrease of up to 18 years has been reported. The mortality rate in patients with RA increases during the course of the disease, with a tendency to accelerate after 15 years. The main causes of death are cardiovascular, pulmonary diseases, cerebrovascular, neoplasm, and infections.

Pulmonary disease is a well-recognized and important extra-articular manifestation of RA. Although the focus has been on interstitial disease, there is increasing recognition of airway involvement. Such manifestations are usually recognized late in the course of the disease, possibly because respiratory involvement has a subclinical phase as the patient may well be limited by the articular disease. The aim of our study is to identify the pulmonary manifestations and its severity (using DAS-28 score) in patients with RA.

MATERIALS AND METHODS

The present study was conducted in the Department of Medicine, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Bikaner, Rajasthan, India. This study was a cross-sectional, observational study. Ethical approval was obtained from the institutional review board and written informed consent was taken from all patients.

- Study period: From March 2019 to February 2020 (1 Year).
- Sample size: A total of 100 cases were included in the study.

Consecutive cases of RA patients attending the outpatient department or admitted to the medicine wards of PBM Associated Group of Hospitals were selected according to the inclusion and exclusion criteria. Information regarding age, sex, smoking, family history, occupational history, and menstrual history were obtained using a predesigned pro forma. Patients were subjected to a thorough general and systemic examination.

Standard tests were used to analyze various parameters like the follows:

- Rheumatoid factor (RF) was measured by enzyme-linked immunosorbent assay (ELISA).
- C-reactive protein (CRP) test by latex agglutination.
- Erythrocyte sedimentation rate (ESR) by modified Westergren method.
- Anti-cyclic citrullinated peptide (CCP) antibody was measured by the second-generation ELISA test.
- Chest X-ray posterior-anterior view digital.

Pulmonary Manifestations in Patients of Rheumatoid Arthritis

The respiratory manifestation in RA include—

1. parenchymal diseases like ILD and rheumatoid nodules,
2. pleural diseases like pleurisy and pleural effusion,
3. vascular diseases like pulmonary artery hypertension and diffuse alveolar hemorrhage,
4. lower airway disease like bronchiectasis and bronchiolitis obliterans, and
5. upper airway disease like cricoarytenoid arthritis.

The respiratory manifestation in RA include—

- pulmonary function test (PFT) by spirometry.
- high-resolution computed tomography (HRCT) chest.

DAS Score

Disease Activity Score (DAS)—28 score was calculated by the following formula:

- Disease Activity Score (DAS)—28 = 0.56 × √(tender joints) + 0.28 × √(swollen joints) + 0.70 × Ln (ESR) + 0.014 × visual analogue score (VAS)

Swollen and tender joints score varies from 0 to 28 (right or left, shoulder, elbow, wrist, metacarpophalangeal joint 1–5, proximal interphalangeal joint 1–5, and knee). ESR (mm/hour), VAS from 0 to 100.

Inclusion Criteria

- All RA patients ≥16 years of age (the 2010 American College of Rheumatology/European league against rheumatism classification criteria for RA).

Exclusion Criteria

- Patients with a past and present history of smoking.
- Patients with preexisting pulmonary diseases like chronic obstructive pulmonary disease, asthma, tuberculosis, pneumonia, etc.
- Patients with any connective tissue disorder other than RA.
- Patients who are critically ill.
- Patients with chest and spine abnormalities like scoliosis and kyphosis.
- Patients on drugs affecting the pulmonary system, excluding the drugs used in RA.
- Pregnant or lactating females.
- Patients not willing to participate in the study.

Results

Demographic Characteristics

This study included 100 cases of RA, out of which 38 patients had pulmonary manifestations. The majority of the patients were female (77%), literate (59%), belonged to rural areas (74%), and were of lower socioeconomic status (70%). The mean age in the pulmonary manifestation absent group was 48.95 ± 11.74 years, while in the pulmonary manifestation present group, the mean age was 56.11 ± 11.41 years (p < 0.01).

Out of 38 pulmonary manifestation cases, 14 (36.8%) patients belonged to the age-group 61–70 years, while 11 (28.9%), 10 (26.3%), and three (7.9%) patients belonged to the age-group 51–60, 41–50, and 31–40 years age-groups, respectively, and no case was found in <30 years of age-group.

Clinical Characteristics

In the present study, pulmonary manifestation was present in a total of 38 patients (38%), while the remaining 62 patients (62%) had no pulmonary manifestation. The mean duration of disease in pulmonary manifestation absent cases was 7.47 ± 4.42 years, while in pulmonary manifestation present cases, the mean duration of disease was 9.97 ± 5.03 years (p < 0.05). Mean DAS in pulmonary manifestation absent cases was 4.67 ± 1.21, while in pulmonary manifestation positive cases, the mean DAS was 4.56 ± 1.20. The relationship was statistically insignificant (p > 0.05).

Of the total 38 patients who had pulmonary manifestation, 33 patients had symptoms, the most common being dry cough (n = 18), followed by productive cough (n = 11), chest pain (n = 10), dyspnea (n = 7), and fever (n = 8). The most common sign was crepitation (n = 22), followed by decreased air entry (n = 12), and wheeze (n = 9), while six patients had no signs (Table 1).

In the study group, 33 patients had comorbidity, and out of them, 20 had pulmonary manifestations; seven cases had DM, and out of them, five had pulmonary manifestation; seven cases had hypertension, and out of them, three had pulmonary manifestation; eight cases had both DM and hypertension, and out of them, six had pulmonary manifestation; 11 cases had hypothyroidism, and out of them, six cases had pulmonary manifestation. On applying a chi-squared test, the result was found to be statistically significant (p < 0.05) (Table 2).

Laboratory and Radiology Findings

In the present study, RF was positive in 15 (15%) patients and out of which six patients had pulmonary manifestations; anti-CCP was positive in 15 (15%) patients, and out of which eight patients had pulmonary manifestations; 42 (42%) patients were positive for both RA factor and anti-CCP, and out of them, 11 patients had pulmonary manifestations; while 28 patients were negative for both RA factor and anti-CCP, and out of them, 13 patients had pulmonary manifestations.

CRP was positive in 58 patients, out of which 19 cases had pulmonary manifestations and this was found to be statistically significant (p < 0.05) (Table 3).

Out of the total 38 patients who had pulmonary manifestations, 33 (86.84%) patients had their PFT abnormal, out of which the most common pattern was restrictive (n = 20), followed by mixed (n = 8), and obstructive (n = 5) (p < 0.001) (Table 4).

On HRCT, out of a total 38 pulmonary manifestation positive group, ILD was found in 23 patients (60.5%) and was the most common finding, followed by pleural effusion in 12 patients (31.5%), a pulmonary nodule in four patients (10.5%), and bronchiectasis in two patients (5.2%). The most common pattern of ILD observed in the study was UIP in 14 patients (60.86%), followed by nonspecific interstitial pneumonia in nine patients (39.13%).

Discussion

In the present study, pulmonary manifestations were there in 38 patients and the mean age in this group was 56.11 ± 11.41 years (p < 0.01). Among 33 patients who had comorbidity, pulmonary manifestations.

Table 1: Distribution of cases according to symptoms and signs

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>6</td>
<td>15.8</td>
</tr>
<tr>
<td>Dry cough + chest pain</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>Dry cough + dyspnea</td>
<td>7</td>
<td>18.4</td>
</tr>
<tr>
<td>Fever + chest pain</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Fever + productive cough</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Productive cough</td>
<td>6</td>
<td>15.8</td>
</tr>
<tr>
<td>Productive cough + chest pain</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>No complaint</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Distribution of signs according to symptoms

<table>
<thead>
<tr>
<th>Signs</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crepitation</td>
<td>31.6</td>
</tr>
<tr>
<td>Crepitation + decreased air entry</td>
<td>13.2</td>
</tr>
<tr>
<td>Wheeze</td>
<td>13.2</td>
</tr>
<tr>
<td>Decrease air entry</td>
<td>15.8</td>
</tr>
<tr>
<td>None</td>
<td>15.8</td>
</tr>
<tr>
<td>Wheeze</td>
<td>7.8</td>
</tr>
<tr>
<td>Wheeze + decrease air entry</td>
<td>2.6</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>
Pulmonary Manifestations in Patients of Rheumatoid Arthritis

20 had pulmonary manifestation and this was found to be statistically significant ($p = 0.015$). PFT was abnormal in 33 out of 38 patients, with the most common pattern being restrictive. Pulmonary manifestations were present in 19 out of 58 CRP-positive patients and this was statistically significant ($p < 0.05$). The most common finding on HRCT was ILD, with UIP as the most common pattern.

The mean age in the pulmonary manifestation present group was 56.11 ± 11.41 years, while in the pulmonary manifestation absent group mean age was 48.95 ± 11.74 years and this difference was found statistically significant ($p < 0.01$). The result was close to other studies done in the past.11-14 In the study by Alamoudi and Attar,14 the mean age in the pulmonary manifestation present group was 53.0 ± 15 years, while in the pulmonary manifestation absent group, the mean age was 43.2 ± 15.4 years. Banotra et al.11 demonstrated the mean age in the pulmonary manifestation group as 56.1 ± 9.77 years, and Assayag12 et al. reported a mean age of 55–69 years in RA-ILD patients. Similar results were also shown by Bilgici et al.13

In the present study, 33 patients had their PFT abnormal in which the most common pattern was restrictive ($n = 20; 52.6\%$), followed by mixed ($n = 8; 21.1\%$), and obstructive ($n = 5; 13.2\%) and this difference was found statistically significant ($p < 0.001$). A study conducted by Banotra et al.11 showed that PFT was abnormal in 16 (57.1\%) patients, with a predominant restrictive pattern in 14 (50\%) patients. In the study done by Fatima et al.17 27 patients (43\%) had abnormal PFT with restrictive pattern in 18 (29\%) and obstructive pattern in five (8\%) of the patients. In similar studies, the restrictive pattern was seen in 52.9\% and the obstructive pattern in 11.8\% of patients.18

Out of 58 CRP-positive patients, 19 patients had pulmonary manifestations and this was found to be statistically significant, but no significance was found with RA factor, anti-CCP Ab, and ESR. CRP is a marker of inflammation and is closely related to the articular as well as the extra-articular manifestation in RA. Alamoudi14 and Attar reported a significant association of pulmonary manifestations with CRP and RA factor, but no such significance was found with anti-CCP antibody.14 Similar result was also shown by Inui et al.19 and Korkmaz et al.20 However, Kelly et al.21 and Aubart et al.22 showed a strong association between anti-CCP level and pulmonary involvement.19-22

In the present study, HRCT was abnormal in 38\% of the patients. This value is lower than other studies done in the past. Alamoudi14 and

### Table 2: Distribution of cases according to comorbid illness in relation to pulmonary manifestation

<table>
<thead>
<tr>
<th>Comorbid Illness</th>
<th>Pulmonary manifestation</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>Absent</td>
<td>2</td>
<td>3.2</td>
<td>5</td>
<td>13.2</td>
<td>7</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>4</td>
<td>6.5</td>
<td>3</td>
<td>7.9</td>
<td>7</td>
<td>7.0</td>
</tr>
<tr>
<td>HTN</td>
<td>Absent</td>
<td>2</td>
<td>3.2</td>
<td>6</td>
<td>15.8</td>
<td>8</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>5</td>
<td>8.1</td>
<td>6</td>
<td>15.8</td>
<td>11</td>
<td>11.0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Absent</td>
<td>5</td>
<td>8.1</td>
<td>6</td>
<td>15.8</td>
<td>11</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>49</td>
<td>79.0</td>
<td>18</td>
<td>47.4</td>
<td>67</td>
<td>67.0</td>
</tr>
<tr>
<td>No complication</td>
<td>Absent</td>
<td>49</td>
<td>79.0</td>
<td>18</td>
<td>47.4</td>
<td>67</td>
<td>67.0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
<td>1.6</td>
<td>1</td>
<td>2.6</td>
<td>2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

χ² = 14.116


### Table 3: Distribution of cases according to serology in relation to pulmonary manifestation

<table>
<thead>
<tr>
<th>Anti-CCP</th>
<th>RA factor</th>
<th>Pulmonary manifestation</th>
<th>No. of cases</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>15</td>
<td>0.164</td>
<td>0.686</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>7</td>
<td>3.664</td>
<td>0.056</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ² = 80.361


### Table 4: Distribution of cases according to PFT in relation to the pulmonary manifestation

<table>
<thead>
<tr>
<th>PFT pattern</th>
<th>Pulmonary manifestation</th>
<th>Total</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Absent</td>
<td>62</td>
<td>100</td>
<td>5</td>
<td>13.2</td>
<td>67</td>
<td>67.0</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Absent</td>
<td>0</td>
<td>–</td>
<td>8</td>
<td>21.1</td>
<td>8</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Restrictive</td>
<td>Absent</td>
<td>0</td>
<td>–</td>
<td>20</td>
<td>52.6</td>
<td>20</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Obstructive</td>
<td>Absent</td>
<td>0</td>
<td>–</td>
<td>5</td>
<td>13.2</td>
<td>5</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Absent</td>
<td>62</td>
<td>38</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Attar demonstrated abnormal HRCT findings in around 67% of RA patients. The most common finding on HRCT was ILD (60.5%), followed by pleural effusion (31.5%). The most common ILD pattern was UIP, followed by NSIP. Wells et al., in their study also demonstrated UIP and NSIP patterns ranging for 40–60% and 11–30%, respectively. Banik et al. showed bronchiectasis and pleural effusion as 67.85 and 35.71%, respectively, in RA patients. In a study by Metafratzi et al. and another by Helmers et al., pleural effusion was observed at a frequency which is slightly lower than this study. The higher prevalence of effusion is explained by the fact that pleural effusion affects more middle-aged patients and occurs early in the disease, as demonstrated by Stanek and Mills. These patients had a small amount of fluid and was demonstrated only on imaging.

The presence of a cough was the most common symptom involving about half of the patients with pulmonary involvement. Similar results were also shown by Banotra et al. and Fatima et al. In the present study, the relation between the number of joints involved, number of tender joints, presence of deformities, and DAS score with pulmonary manifestation was not found to be statistically significant and the same was reported by Habib et al.

Several potential risk factors for pulmonary involvement in RA have been reported in the literature, including male gender, older age, high ESR, high serum RF, long-standing disease, genetic polymorphisms (e.g., human leukocyte antigen-DR4), smoking, therapeutic factors, and ExRA.

**Limitation**

The study was conducted in a single center and it included patients who were already on treatment. Drugs like methotrexate are known to have an impact on the respiratory system but our study did not differentiate whether the effect on the respiratory system was because of methotrexate or RA itself. To overcome this limitation, a randomized controlled trial is required.

**CONCLUSION**

Our study shows the significant prevalence of pulmonary manifestations in patients with RA. ILD was the most common manifestation, followed by pleural effusion. It is a systemic inflammatory disease and a major portion of morbidity and mortality are due to its extra-articular manifestations. Thus, patients of RA, especially the ones with advanced age, long duration of disease, male sex, and associated comorbidity, should be screened for pulmonary complications of RA using X-ray chest and PFT supplemented by HRCT chest wherever required.

**REFERENCES**

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Study of Characteristics of COVID-19 Patients with Fatal Outcome during Wave-2 from a Tertiary Care Center in Western India

Nisha Sadhwani1, Nupur Shah2*, Mahir Modi3, Nidhi Mehta4, Shams Kanuga5, Devarshi Patel6, Vipul Prajapati7, Asha N Shah8

Received: 30 April 2022; Accepted: 11 October 2022

ABSTRACT

Background: A large surge of intensive care unit (ICU) admissions leading to mortal outcome was observed in wave-2 of coronavirus disease 2019 (COVID-19) due to the higher virulence of the Delta variant of the COVID-19 virus, which led to the scarcity of resources in hospitals. This study was done to observe the clinical characteristics of COVID-19 patients with fatal outcome.

Materials and methods: We conducted a retrospective cross-sectional study in adults with COVID-19 pneumonia having fatal outcome during wave-2 of COVID-19, and their clinical characteristics were studied.

Results: Out of 136 patients included in the study, the most common risk factors leading to adverse outcome were in the male gender, age (middle and elderly), with hypertension and diabetes mellitus (DM) as predominant comorbidities, early onset dyspnea, high C-reactive protein (CRP), high neutrophil to lymphocyte ratio (NLR), high D-dimer, bilateral lower zone involvement of lungs in chest X-ray (CXR), and development of acute kidney injury (AKI).

Conclusion: The characteristics of the severely ill COVID-19 patients highlighted in the study could help clinicians in the early identification and management of high-risk patients. This study would help with resource planning and preparation for further COVID-19 waves and future pandemics.

INTRODUCTION

A new type of coronavirus was discovered to be the cause of unexplained pneumonia cases in Wuhan, China, in late December 2019.1,2 The virus belongs to the same genus as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome and was thus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses on 11th February 2020 (11/02/2020). The World Health Organization declared it as a pandemic on 11th March 2020.3 The first case of COVID-19 in India was reported on 30th January 2020.4 The time period between 1st September 2020 and 1st January 2021 was considered as the first wave.5 The second wave beginning in March 2021, with the predominant variant being B.1.617.2 (Delta), had severe consequences in the form of spiraling cases, reduced supplies of essential treatments, and increased deaths, particularly in the young population as compared to the first.

AIM

To describe the clinical characteristics of fatal cases of COVID-19 during wave-2 in the hope that in the future, this will help clinicians to identify patients with poor prognosis at an early stage.

MATERIALS AND METHODS

A retrospective cross-sectional observational study was carried out in the Department of Medicine, GCS Medical College, Hospital, and Research Centre, Ahmedabad, Gujarat, India, a tertiary care center in Western India. A study was done on 136 reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen proven COVID-19 patients with fatal outcome during wave-2 of COVID-19. Approval was obtained from the Scientific Review Committee and Ethics Committee. All the patients included in the study were evaluated in detail and managed by the medicine department in the COVID-19 ICU or high dependency unit (HDU). We accessed the case files with due permission from the concerned authorities from the Medical Records and Statistics Department. The data regarding the demographic profile of the patients, history, examination, vital parameters, investigations, and treatment were recorded from the case files. The guidelines issued by the Ministry of Health and Family Welfare (MoHFW) were followed for the diagnosis and treatment of COVID-19.

Inclusion Criteria

• Hospitalized confirmed cases of COVID-19 via a rapid test or RT-PCR in ICU or HDU with fatal outcome during the second wave.
• Age ≥18 years.

Fig. 1: Age group involvement

Exclusion Criteria

• Age <18 years.
• Coronavirus disease 2019 (COVID-19) recovered patients.

Statistical Analysis

Categorical data were presented as frequency and proportions, while continuous data were summarized as mean or median, as appropriate.

OBSERVATION AND DISCUSSION

Age-group Involvement

The above chart (Fig. 1) represents the number of individuals in particular age-groups infected with COVID-19, who had mortal outcome. Here, about 52.2% of people belonged to the elderly age-groups (60 or above), while 47.8% of people belonged to the younger age-group.

The median age in our study was 61 years. According to Carbonell et al., the median age was 63 years, whereas, in Ismail et al., the age was 63 years.

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median age was 53 years, which is consistent with our study.

**Sex**

Our study shows there is a male preponderance, as 67.6% (N = 92) were men, while only 32.4% (N = 44) were females (Fig. 2).

Two important studies, with the target population being critically ill patients with COVID-19, that is, Carbonell et al. and Ismail et al., also showed 71.6% and 84.6% of the population being male, respectively. These findings are consistent with our study.

The predilection of COVID-19 in the male gender might be due to increased expression of angiotensin-converting enzyme 2 (ACE2) receptor in males > females and due to sex-based immunological differences based on sex hormones and the X chromosome.8,9

**Symptomatology**

The common presenting complaints were cough with or without expectoration (63.9%), fever (63.9%) and dyspnea (63.9%), weakness (32%), cold (20%), sore throat (10%), and body ache (7.35%) (Fig. 3). Nearly 10% of patients presented with less common symptoms, such as diarrhea, vomiting, headache, anosmia, and chest pain. Early onset of shortness of breath may be indicative of poor prognosis.

**Oxygen Saturation (SpO2) on Admission**

Out of the 136 covid patients, 67.6% (N = 92) of patients came to the hospital with SpO2 of <90. While 19.1% (N = 26) of patients had SpO2 of <94, and 13.2% (N = 18) of patients presented with SpO2 of 94 or more on admission (Fig. 4). SpO2 levels classification was taken according to Clinical Management Protocol, MoHFW.

This implies that the majority of the patients presented with severe conditions.

Out of 136 patients on admission, 86.7% (N = 118) had hypoxia, that is, SpO2 of <94, but only 63.9% (N = 87) had clinically significant dyspnea. So, 22.7% (N = 31) had hypoxia but paradoxically did not complain of breathlessness. This might be attributed to the phenomenon of happy hypoxia in COVID-19. The underlying mechanism is complex and less understood, but desensitization of chemoreceptors and a leftward shift of the oxygen dissociation curve might be the underlying cause.10

**Acute Respiratory Distress Syndrome (ARDS)**

Out of 136 patients, 47.1% (N = 64) of patients developed ARDS (Fig. 5). Out of which, 18.4% (N = 12) of patients developed mild, 27.9% (N = 18) of patients developed moderate, and 53.7% (N = 34) of patients developed severe ARDS (Fig. 6). This is classified according to Berlin’s score for ARDS.

According to Carbonell et al., out of 136 patients, 96.4% developed ARDS, out of which 12.6% of patients developed mild, 42.4% developed moderate, and 28.4% of patients developed severe ARDS.

This signifies that ARDS may be the most likely cause of death in patients with fatal outcome.

**Comorbidities**

Out of 136 patients, 47.05% (N = 64) had hypertension and 33.82% (N = 46) had DM, 8.08% (N = 11) and 2.2% (N = 3) had cardiovascular disease (CVD) and cerebrovascular disease, respectively, while 33.82% (N = 46) people did not have any comorbidities but had fatal outcome (Fig. 7 and Table 1). This suggests that patients without any comorbidities had lethal outcome, which may be due to the virulent nature of the strain in wave-2. According to Zhou et al., the findings showed that, among patients with severe or fatal COVID-19, the most prevalent comorbidities were hypertension (40%), followed by diabetes (17%), CVD (13%), respiratory disease (8%), cerebrovascular disease (6%), malignancy (4%), chronic kidney disease (3%), and liver disease (2%) (Table 1). In our study, hypertension followed by diabetes were the most common comorbidities. Knowledge of these factors could help clinicians better identify those populations at a higher risk of COVID-19 and provide more specific approaches to prevent severe or fatal outcome.

According to Carbonell et al., 49.4% of the critically ill patients were hypertensive, 26.7% were diabetic, followed by CVD, that is, 10.7% (Table 1).

Among the 46 patients with no comorbidities, about 52.17% (N = 24) of patients belonged to the age-group <60 years and 47.83% (N = 22) of patients were ≥60 years, who had fatal outcome. Among them, 67.39% (N = 31) of patients presented with SpO2 of <90, 19.56% (N = 9) of patients presented with SpO2 of >90–<94, and 13.04% (N = 6) of patients presented with SpO2 of >94. The risk factors, that is, age-group and SpO2 levels remain the same for patients with or without any comorbidities. This is suggestive of virus
virulence, which maybe the reason that has led to fatal outcome even in patients without any comorbidity.

Out of the 61 cases of DM, 75.4% patients already had diabetes, 13.1% of patients were newly diagnosed with DM-2 at the time of admission, and 11.5% of patients were pre diabetic (Fig. 8). The diagnosis was done according to hemoglobin A1c. The patients may have presented with impaired glycemic control, probably due to steroids taken before admission. This emphasizes the importance of early screening for DM as these patients had more risk of acquiring severe disease.

**Acute Kidney Injury (AKI) Stages**

Out of 136 patients who were admitted to the ICU, about 42.4% (N = 58) of patients had AKI (Fig. 9). Out of those with AKI, about 64.3% (N = 37) of patients were in stage I, 12.5% (N = 7) were in stage II, and 23.2% (N = 14) had stage III AKI (Fig. 10). This was done according to the standard Kidney Disease: Improving Global Outcomes classification.

According to Chan et al., out of 976 patients admitted to the ICU, 76% of patients developed AKI, about 28% of patients had stage I AKI, 14% developed stage II, and 58% of patients developed stage III AKI. The discrepancy between the prevalence of AKI in the two studies is probably due to the small sample size in our study. In Chan et al.’s study, it was seen that AKI was associated with poor outcomes, and this finding is consistent with our study. COVID-19 virus affects renal cells directly via ACE2 receptors or causes renal microvascular dysfunction, probably due to endothelial damage and cytokine storm. The high mortality in patients with AKI can be attributed to the overwhelmed dialysis facility due to the huge burden of severely ill patients, leading to a long waiting period.

**X-ray Changes**

All 136 patients (100%) had pulmonary involvement observed on CXR, 71.1% (N = 97) of patients had bilateral lung zone involvement, while 28.9% (N = 39) with unilateral involvement (Fig. 11).

Among these 28.9% (N = 39) of patients, 51.2% (N = 20) of patients had right side involvement and 48.8% (N = 19) with left side involvement.

Out of the 20 patients of the right side, 86.4% (N = 16) of patients presented with lower, 11.4% (N = 2) with middle, and 2.3% (N = 1) with upper zone involvement (Fig. 12).

**Table 1:** Comparison of prevalence of Comorbidities in different studies with critically ill patients

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Our study</th>
<th>Racquel Carbonell</th>
<th>Yue Zhou</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>N = 136</td>
<td>N = 1316</td>
<td>N = 1243</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (47.05%)</td>
<td>650 (49.4%)</td>
<td>497 (40%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>46 (33.82%)</td>
<td>351 (26.7%)</td>
<td>211 (17%)</td>
</tr>
<tr>
<td>CVD</td>
<td>11 (8.08%)</td>
<td>141 (10.7%)</td>
<td>162 (13%)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>3 (2.2%)</td>
<td>–</td>
<td>74 (6%)</td>
</tr>
</tbody>
</table>

Fig. 7: Comorbidities

Fig. 8: Diabetes mellitus type 2

Fig. 9: Acute kidney injury (AKI) on admission

Fig. 10: Count of KDIGO criteria for AKI

Fig. 11: X-ray changes according to sides involvement

Fig. 12: Involvement on the right side
According to Goyal et al., the most commonly observed CXR findings in COVID-19 pneumonia were bilateral multifocal air space opacities (consolidation), predominantly involving lower zones and peripheral lung. This is consistent with our study, where most patients have involvement of the bilateral lower zone of the lungs. This implies that SARS-CoV-2 affects bilateral lower zones in most patients.

Neutrophil to Lymphocyte Ratio (NLR)
In our study, where the median NLR was 7.85, 90.40% (N = 123) of patients had NLR of >3 (normal value = 1–3), and 25% (N = 34) of patients had NLR of >11.75. According to the research from the Wiley Journal of Medical Virology, after adjusting for confounding factors, NLR of >11.75 was significantly correlated with all-cause in-hospital mortality.

According to Stringer et al., among those who died, the median CRP level was 86 mg/L (48–173.5 mg/L) compared with 53 mg/L (16–109 mg/L) among those who survived. Here, for patients with CRP of ≥40 mg/L, mortality was 31.9% compared with 15.0% for patients with CRP of <40 mg/L.

This suggests that the association of higher CRP with worse outcomes may be due to the severity of the disease consistent with the “cytokine storm” theory of COVID-19, where the innate immune system is activated, releasing tumor necrosis factor α, interleukin (IL)—6, and IL-1.

Using a threshold of 40 offered a high sensitivity and negative predictive value but a low positive predictive value. A simple threshold of 40 mg/L can be used within the clinical practice to guide disease severity and likely disease progression.

D-dimer on Admission
The median D-dimer in our study is 800 ng/dL. In our study, 66.17% (N = 90) of patients had D-dimer >500 ng/dL (0.5 mg/dL).

According to Yao et al., D-dimer elevation ≥0.5 mg/L was seen in 74.6% (185/248) of the patients with in-hospital mortality. This is consistent with our study and suggests significantly higher levels are found in those with thrombosis, critical illness, and death. Thromboinflammation is central to the pathophysiology of COVID-19 associated coagulopathy (CAC). Three major underlying mechanisms of CAC are—(1) direct damage to the endothelium through ACE2 receptor, (2) viral replication triggers a cytokine storm with the release of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α, which upregulates coaguloaualts like tissue factor, fibrinogen, factor VIII, and (3) vWF. Complement activation and deposition leading to microthrombosis.

However, patients were not assessed for venous thromboembolism/pulmonary embolism using imaging techniques owing to the high cost and huge patient load.

Days of Illness
Out of 136 patients, 81.6% (N = 111) of patients presented before 7 days of illness, while 18.4% (N = 25) of patients presented after 7 days of illness (Fig. 14).

This suggests that the Delta variant in wave-2 of COVID-19 seemed more virulent, which may have led to the early worsening of the clinical condition.

Out of 91 patients with SpO2 of <90% on admission, 70.3% (N = 64) of patients presented within 7 days of illness and 29.7% (N = 27) presented after 7 days of illness (Fig. 15).

This suggests that the virus led to early involvement of the lungs leading to the early onset of ARDS or pneumonia, leading to death.

Average Hospital Stay
Among 136 patients who had fatal outcome, the median hospital stay was 6 days.
Among the 136 patients, 56.7% (N = 77) of patients died before 7 days of hospital stay and 43.3% (N = 59) of patients died after 7 days of hospital stay (Fig. 16).

Out of 91 patients who presented with SpO2 of <90%, 57.1% (N = 52) of patients with low SpO2 had fatal outcome earlier than 7 days of hospitalization (Fig. 17).

(N = 39) of patients had fatal outcome after died before 7 days of hospital stay and 42.9% of hospital stay (Fig. 16).

and 43.3% (N = 59) of patients died after 7 days of patients died before 7 days of hospital stay.

For these characteristics to be considered as prognostic markers, we need a larger cohort prospective multicenter study with a control group of favorable outcome vs those with fatal outcome.

**REFERENCES**

**API Announcement**

**Elections of API, ICP and PRF**

(Full details circular No. 1 & 2/2023)

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

**Governing Body of API:**
- President-Elect: One; Vice President: One; Elected Members: Six

**Faculty Council of ICP:**
- Dean-Elect: One; Vice Dean: One and Elected Members: 4 posts

**Board of PRF:**
- Director Elect: One; Board members: Two

Separate nominations must be submitted for each post.

**Requirements for eligibility contest of election to the Governing Body of API**

1. **President Elect:** To contest for the post of President Elect the candidate should be a life member of API for at least 10 years and have completed at least two full terms of 3 years each in any elected position in the Governing Body.
2. **Vice President:** To contest for the post of Vice President the candidate should be a life member of API for at least 5 years and should have completed at least one continuous full term of 3 years in any elected position in the Governing Body.
3. **Governing Body Member:** To contest for the post of Member of the Governing Body, continuous membership of the Association of at least 3 years is mandatory.

**Requirements for eligibility contest of election to Board of PRF**

- **Director Elect:** A member of API for at least 10 years with research experience and having 10 research publications in peer reviewed indexed journals.
  - The members contesting for the PRF election must attach copies of the Research Papers as mentioned above is mandatory.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for API/PRF posts shall be proposed by one valid member and seconded by another valid member of API and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Governing Body if elected.

**Requirements for eligibility for the contests of election to ICP**

- **Dean Elect:**
  - i. A member of API for at least 15 years and
  - ii. A Founder Fellow or a Fellow of the College of 7 year standing and
  - iii. Any person who has held the position of President/Secretary of API or served as Vice Dean for one full term or elected member of the Faculty Council for one term.

- **Vice – Dean:**
  - i. A member of API for at least 12 years and
  - ii. A Founder Fellow or a Fellow of the College of 5 year standing and
  - iii. Any person who has held the position of Secretary of API or has been a Jt Secretary from HQ for one full term or a member of the Faculty Council.

- **Elected Members:** A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.

Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP posts shall be proposed by one valid Founder Fellow/Fellow and seconded by another valid Founder Fellow/Fellow of ICP and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.

A member shall not contest simultaneously for more than one post (i.e., President-Elect, Vice-President, Member of the Governing Body (Dean-Elect; Vice Dean and Elected Members of Faculty Council) and also (Board members of PRF) Post means not only an office-bearer but also member of the Governing Body of API or Faculty Council of ICP or Board of PRF.

Every member is supplied with a nomination form. The nomination form completed in all respects should reach the API Office not later than 31st May 2023. For every post on the Governing Body/Faculty Council/Board of PRF, the nomination must be accompanied by a sum of Rs. 7500/- + 1350/- (GST) (Rupees eight thousand eight hundred fifty only) nonrefundable in the form of Demand Draft payable at Mumbai. The nomination paper NOT accompanied by the Bank Draft of Rs. 8850/- will be deemed invalid.

**Important**

Canvassing in any form should not be done by the candidate for the election. Instead, they are requested to send a short bio-data NOT MORE THAN 200 words along with the nomination paper which will be printed and circulated along with the ballot paper. Excess of bio-data beyond the first two hundred words shall be deleted. Canvassing in any form or in favor of the candidate shall not be permitted. THE CANDIDATE WILL HAVE TO CERTIFY AND SIGN THAT THE INFORMATION PROVIDED IN HIS/HER BIODATA IS CORRECT. The results will be declared at the end of counting of votes and announced in the subsequent issue of JAPI. The report will be placed before the Governing Body for intimation.

**DEAD LINES OF ELECTION PROCEDURE**

- Last date to receive the nomination at API Office: 31st May 2023
- Last date for withdrawal: 20th June 2023
- Last date to receive ballot papers at API Office: 31st August 2023

Dr. Agam Vora  
Hon. General Secretary
The following members were awarded the Fellowship of the ICP at Ahmedabad APICON 2023:

1. Dr. Apu Adhikary – Siliguri
2. Dr. Ajay Aggarwal – New Delhi
3. Dr. Deeptes G. Aggarwal – Mumbai
4. Dr. Pawan Kumar Agarwal – Howrah
5. Dr. Ram Gopal Agrawal – Bharatpur
6. Dr. V. N. Alagavenkatesan – Madurai
7. Dr. Praveen Arora – Jodhpur
8. Dr. Gita Arora – Bharatpur
9. Dr. Kuldeep Kumar Ashta – Lucknow
10. Dr. Gian Badlani – Ahmedabad
11. Dr. Bapilal Bala – Cochin
12. Dr. Sanjay Bansal – Gwalior
13. Dr. Kartik Kumar Baruah – Jorhat
14. Dr. Ashok Kumar Behera – Cuttack
15. Dr. Vivek Bhardwaj – Patna
16. Dr. Ramesh Bhargava – Bhopal
17. Dr. Sanjay Bhattacharya – Rajkot
18. Dr. Abhijit Bhattacharya – Kolkata
19. Dr. Koushik Bhattacharya – Nadia
20. Dr. Paramita Bhattacharya – Nadia
21. Dr. Pradip Bhattacharya – Agartala
22. Dr. Pradeep Kumar Chakrabarty – Kolkata
23. Dr. Amit Kumar Chakrabarty – Kolkata
24. Dr. Debmalya Bhuyan – Shillong, Meghalaya
25. Dr. Soumendu Biswas – Kolkata
26. Dr. Uttam Biswas – Kolkata
27. Dr. Pritom Kumar Borthakur – Guwahati
28. Dr. Amitava Chakrabarty – Kolkata
29. Dr. Pratim Kumar Chakrabarty – Darjeeling
30. Dr. Supratik Chakrabarty – Murshidabad
31. Dr. Kumar Pratull Chandra – Lucknow
32. Dr. Sumit Chatterjee – Nadia
33. Dr. Asim Kumar Chaudhuri – Kolkata
34. Dr. Jugal Kishore Chhaparwal – Udaipur
35. Dr. Debashish Danda – Vellore
36. Dr. Sant Kanta Datta – Durgapur
37. Dr. Supriya Datta – Kolkata
38. Dr. Piyush H. Desai – Surat
39. Dr. Anupam Dey – Bhurbaneswar
40. Dr. C. Dharmaraj – Madurai
41. Dr. L. C. Dhoka – Jaipur
42. Dr. Samanta Dibakar – Medinipur
43. Dr. Shallesh Dixit – Jaipur
44. Dr. Dinesh Kumar Gautam – Jaipur
45. Dr. Swapnil Gautam – Mumbai
46. Dr. Manoj Kumar Gogoi – Tinsukia
47. Dr. Sunil Kumar Gothwal – Jaipur
48. Dr. Mahendra Kumar Goyal – Kolkata
49. Dr. Alok Gupta – Jodhpur
50. Dr. Deepak Gupta – Jaipur
51. Dr. Mukulesh Gupta – Lucknow
52. Dr. Tapan Haldar – Malda
53. Dr. Suman Hansraj – Baran
54. Dr. Anish Jain – Chittorgarh
55. Dr. Sampat Jain – Kolkata
56. Dr. N. G. Javal – Raichur
57. Dr. Pradeep Joshi – Bhavnagar
58. Dr. Anchin Kalia – Jaipur
59. Dr. Amit Kumar Kalwar – Silchar
60. Dr. Arun Kumar Kedia – Raipur
61. Dr. Manoj Khanna – New Delhi
62. Dr. David Pradeep Kumar – Madurai
63. Dr. Kailash Kumar – Jhunjhunu
64. Dr. Mrittunjay Kumar – Gaya
65. Dr. Prabir Kumar Kundu – Kolkata
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67. Dr. Suresh Kumar Kushwaha – Agra
68. Dr. Harshvardhan Leeneshwar – Jaipur
69. Dr. Sunil Kumar Mahavir – Kota
70. Dr. Sujay Majumdar – Kolkata
71. Dr. Anupam Mandal – Malda
72. Dr. Pijush Kanti Mandal – Malda
73. Dr. Prakash G. Mantur – Vijayapura
74. Dr. Chandra Bhan Meena – Jaipur
75. Dr. Chandra Prakash Meena – Kota
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77. Dr. Amar Kumar Misra – Kolkata
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82. Dr. Alok Kumar Mukhuti – Howrah
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84. Dr. Bhaskar Kanti Nath – Cachar
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87. Dr. Sujit Kumar Pal – Medinipur
88. Dr. Sujay Panchadhyayee – Kolkata
89. Dr. Dhiren C. Patel – Surat
90. Dr. Arvind B. Patil – Raichur
91. Dr. K. Prabhakar – Kolar (Karnataka)
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93. Dr. Apurba Bikash Pramanik – Kolkata
94. Dr. Vivian Rahim – Raipur
95. Dr. Mehebub Rahman – Kolkata
96. Dr. Alok Rai – Raipur
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102. Dr. Dhiman Sen – Kolkata
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104. Dr. Upal Sengupta – Kolkata
105. Dr. A. Senthilmarai – Madurai
106. Dr. Balam Sharma – Jaipur
107. Dr. Dinesh Kumar Sharma – Bhilwara
108. Dr. Rajendra Prasad Sharma – Nadiadwara
109. Dr. Ankit Shivastav – Ranchi
110. Dr. Sanjay Shivastav – Chandwa
111. Dr. Ajay Kumar Singh – Bhaupalgar
112. Dr. Akash Kumar N. Singh – Vadodara
113. Dr. Jitendra Singh – Varanasi
114. Dr. Sarat Chandrak Singh – Cuttack
115. Dr. Neeraj Singla – Chandigarh
116. Dr. Arijit Sinha – Kolkata
117. Dr. Rashmi Sinha – Ranchi
118. Dr. Shivendra Sinha – Ayodhya
119. Dr. Amit Sreen – New Delhi
120. Dr. Achal Kumar Srivastava – New Delhi
121. Dr. Ashish Srivastava – Sultanpur
122. Dr. N. Subramanian – Tirunelveli
123. Dr. Shamima Sultan – Guwahati
124. Dr. Bharat Vanani – Surat
125. Dr. Harsh Vardhan – Patna
126. Dr. Umesh Varma – New Delhi
127. Dr. P. Velammal – Coimbatore
128. Dr. A. Vijaykumar – Bidar
129. Dr. Roopak Wadhwa – Delhi

Hon. Fellowship of ICP
Dr. Roman Jaeschke – Canada
Dr. Arun Maskey – Kathmandu
Dr. Roman Jaeschke – Canada
Dr. Arun Maskey – Kathmandu
Dr. Roman Jaeschke – Canada
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Thrombocytopenia in Children: A Large Prospective Study on Clinical Manifestations, Seasonal Variation, Etiology, and Outcome

Isha Bhatia1, Avinash Sharma2, Sandesh Guleria3, Ajay Sharma4*, Ranbir S Jaswal5, Ajay Vaid6, Neha Rehalia7, Amar Thakur8

Received: 17 July 2022; Accepted: 16 November 2022

A B S T R A C T

Aim: To study the clinico-etiological profile of children with thrombocytopenia.

Methods: This prospective hospital-based study included all children (<18 years) with thrombocytopenia at the time of hospitalization and/or thrombocytopenia during the course of their hospital stay. A detailed history was recorded and appropriate laboratory investigations were carried out.

Results: The study group comprised 246 children (mean age, 9.29 years; median age, 10 years) with male to female ratio of 1.5:1. Nearly 45% of children were above 10 years of age. Trends of admissions showed that the majority of children with thrombocytopenia (n = 115) got hospitalized during the rainy season, followed by summer (n = 84). Fever (72.8%), pallor (52.8%), bleeding manifestations (22%), lymphadenopathy (20.3%), and splenomegaly (20.3%) were common clinical features. Petechiae was the most common bleeding manifestation (63%). Septicemia (24%) was the most common etiology, followed by megaloblastic anemia (14.6%), undiagnosed fever (10.2%), local infection (9.3%), hepatitis (6.5%), and scrub typhus (6.1%). About nine children died. All those who died had septicemia and multi-organ dysfunction (MOD). On logistic regression analysis, age >10 years, presence of bleeding, arthralgia, rash, pallor, gastrointestinal (GI) symptoms, hematological disorders, and malignancy were associated with severe thrombocytopenia.

Conclusion: Thrombocytopenia is a common hematological observation. This study revealed seasonal variation in the occurrence of thrombocytopenia in children, with the maximum number of cases in the rainy season. Septicemia is the commonest etiology. The majority of children with thrombocytopenia have no bleeding manifestations. Age >10 years, presence of bleeding, arthralgia, rash, pallor, GI symptoms, hematological disorders, and malignancy are associated with severe thrombocytopenia.

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INTRODUCTION

Platelets are small, anuclear, biconvex, and discoid cells, 7–9 fl in volume, derived from hematopoietic lineage through megakaryocytes.1 The main function of platelets is primary hemostasis. The universal definition of thrombocytopenia is a platelet count <150 × 10^3/µL, whereas a platelet count >450 × 10^3/µL is thrombocytosis.2,3 Thrombocytopenia is sometimes the only presentation of systemic conditions and may or may not be associated with the involvement of another cell lineage.

The common causes of thrombocytopenia in children are infections, acute lymphoblastic leukemia and other malignancies, nutritional deficiencies, immune thrombocytopenic purpura (ITP), autoimmune disorders like systemic lupus erythematosus (SLE), disseminated intravascular coagulation (DIC), hypersplenism, and drugs.4-5 In a tropical country like India, infectious causes predominate and are usually associated with fever. Thrombocytopenia may give a clue to the presence of infections like malaria, dengue, leptospirosis, and viral infections. Seasonal variations in the incidence of thrombocytopenia may also point toward etiology, as tropical infections leading to thrombocytopenia are more common during the rainy season in India.6-9

A systematic approach should be followed to evaluate a child with thrombocytopenia, as it may provide an important clue to different diseases. The involvement of other cell lines, which is seen on the peripheral blood smear, also provides clues.6-8 The principal management goal in all patients who have thrombocytopenia is to maintain a safe platelet count to prevent significant bleeding.6-11

In developing countries, as a result of decreased awareness and insufficient healthcare institutions, diagnoses of these disorders are often made late, resulting in increased mortality and morbidity. These cases are to be picked up at the earliest and subjected to judicious investigative procedures for early diagnosis. In India, data are lacking and details on the epidemiological profile of children with thrombocytopenia are not available from this region. The present study was designed to know the clinico-etiological profile of thrombocytopenia in a tertiary care institute in the Northwestern Himalayan region in a rural setting.

METHODOLOGY

This prospective hospital-based study was conducted in the Department of Pediatrics of Dr. Rajendra Prasad Government Medical College Kangra at Tanda, Kangra, Himachal Pradesh, India, over a period of 1 year, from April 2019 to March 2020. It included all children (<18 years) with thrombocytopenia (≤150 × 10^3 cells/µL) at the time of hospitalization and/or thrombocytopenia during the course of the hospital stay.

Detailed history, baseline characteristics like age, sex, residence, time of presentation, date of admission and discharge, socioeconomic status, signs and symptoms, investigations, management, and outcome, including mortality and morbidity, were recorded. Laboratory parameters, such as complete blood counts, including platelet count with manual recheck, coagulation profile, bone marrow examination, dengue serology, and other evaluation as necessary, were carried out.

Statistical Analysis

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

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Thrombocytopenia in Children

### Results

The study group comprised 246 children (<18 years) with a mean age of 9.29 years and a median age of 10 years (range, 1–18 months).

### Discussion

Thrombocytopenia can reflect numerous underlying conditions in children. Multiple etiologies, such as infections, autoimmune conditions, drugs, connective tissue disorders, hematological, and reticuloendothelial malignancies, may manifest in the form of thrombocytopenia only.4,5,12

In our study, the largest group of children with thrombocytopenia according to age was that of >10 years (45.1%), followed by school-going children aged between 5 and 10 years (24%), and males outnumbered females. This is in concordance with studies by other workers.6,8,13–15 The higher incidence of thrombocytopenia in older children and males may be attributed to the prolonged outdoor activities by grown-up male children as compared to infants and girls, and hence

### Table 1: Age distribution of the study participants

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male children</td>
<td>147</td>
<td>59.8</td>
</tr>
<tr>
<td>Female children</td>
<td>99</td>
<td>40.2</td>
</tr>
</tbody>
</table>

### Table 2: Clinical features in children with thrombocytopenia on presentation

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>179 (72.8)</td>
</tr>
<tr>
<td>Pallor</td>
<td>130 (52.8)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>54 (22.0)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>50 (20.3)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>50 (20.3)</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>49 (19.9)</td>
</tr>
<tr>
<td>Facial puffiness</td>
<td>48 (19.5)</td>
</tr>
<tr>
<td>Arthralgia/headache</td>
<td>44 (17.9)</td>
</tr>
<tr>
<td>and myalgia</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>43 (17.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>37 (15.04)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>35 (14.2)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>34 (13.8)</td>
</tr>
<tr>
<td>Petechial spots</td>
<td>34 (13.8)</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>14 (5.7)</td>
</tr>
<tr>
<td>Vesicular rash</td>
<td>13 (5.3)</td>
</tr>
<tr>
<td>Seizure</td>
<td>12 (4.9)</td>
</tr>
</tbody>
</table>

### Table 3: Bleeding manifestations in children with thrombocytopenia

<table>
<thead>
<tr>
<th>Bleeding manifestations</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>34 (63.0)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5 (9.2)</td>
</tr>
<tr>
<td>Subconjunctival hemorrhage</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (1.85)</td>
</tr>
</tbody>
</table>

Categorical variables were expressed as frequency and percentages and compared using the chi-squared test. Odds ratios (OR) were calculated using logistic regression analysis. The p-value of <0.05 was considered significant.
increased exposure to mosquito and other vectors for tropical infections.

As far as the seasonal distribution of cases was concerned, most of the cases were admitted during the months of July, August, and September (Fig. 1), during which the northwest monsoon is active in this region, though sporadic cases were also seen during other months of the year. There are limited data on seasonal variation of thrombocytopenia. Studies conducted have reported a temporal increase in ITP incidence during the spring and early summer. Our findings are also in concordance with a study by Nair et al. and Lakshmikumar et al., who in studies on thrombocytopenia with special reference to complications and seasonal variations reported a majority of cases of thrombocytopenia in the monsoon season. This could be a universal phenomenon where certain infective conditions like dengue and scrub typhus are known to have seasonal presentations.

In our study, the common symptoms on presentation were fever (72.8%), bleeding manifestations (22%), GI symptoms (19.9%), arthralgia/headache, and myalgia (17.9%). While the common examination findings were fever (73.6%), pallor (52.8%), lymphadenopathy (20.3%), and splenomegaly (20.3%). Fever, headache/myalgia, and GI symptoms were seen in less number of patients in our study than in studies by Nair et al., Subramanian et al., Raveendran, and Aggarwal et al. This can be due to the fact that these studies were conducted in Southern India and Delhi where tropical infections and viral illnesses are more common in comparison to our region, and increased exposure to mosquito and other vectors for tropical infections.

<table>
<thead>
<tr>
<th>Table 4: Etiology with the severity of thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology                                      Moderate (n = 105)</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Septicemia (n = 59)                                   18</td>
</tr>
<tr>
<td>Megaloblastic anemia (n = 36)                         9</td>
</tr>
<tr>
<td>Undiagnosed fever (n = 25)                            10</td>
</tr>
<tr>
<td>Local infection (n = 23)                              0</td>
</tr>
<tr>
<td>Hepatitis (n = 16)                                    2</td>
</tr>
<tr>
<td>Scrub typhus (n = 15)                                  3</td>
</tr>
<tr>
<td>Enteric (n = 10)                                      4</td>
</tr>
<tr>
<td>Leukemia (n = 10)                                     0</td>
</tr>
<tr>
<td>Autoimmune diseases (n = 9)                           3</td>
</tr>
<tr>
<td>ITP (n = 8)                                           0</td>
</tr>
<tr>
<td>Tuberculosis (n = 7)                                  3</td>
</tr>
<tr>
<td>Drug-induced (n = 4)                                  3</td>
</tr>
<tr>
<td>Dengue (n = 2)                                        0</td>
</tr>
<tr>
<td>Human immunodeficiency virus (n = 1)                   1</td>
</tr>
<tr>
<td>Others (n = 21)                                       17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5: Bivariate logistic regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate thrombocytopenia</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Age &lt;=10 years</td>
</tr>
<tr>
<td>&gt;10 years</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Pallor</td>
</tr>
<tr>
<td>GI symptoms</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Hematological disorders</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
</tbody>
</table>
these symptoms are frequently seen in viral illness. These studies also included subjects having thrombocytopenia with tropical infections only; thus, some symptoms like fever are bound to be seen in nearly all patients.

Among 246 children, 27.6% had severe thrombocytopenia, 42.7% had moderate thrombocytopenia, and 29.6% had mild thrombocytopenia. On logistic regression analysis, it was found that age >10 years had 1.82 (1.03–3.20) higher odds of severe thrombocytopenia in comparison to the children aged ≤10 years. Age >10 years, presence of bleeding, arthralgia, rash, pallor, GI symptoms, hematological disorders, and malignancy were associated with severe thrombocytopenia (Table 5). These findings are comparable to the studies by Ayub et al.21 and Palange et al.,22 although these studies have looked into specific subjects, unlike our study, where we have included all the children with thrombocytopenia.

A total of 54 (21.95%) children with thrombocytopenia presented with bleeding manifestations and petechiae (63%) as the most common bleeding manifestation, followed by GI bleeding in 11.1%, and gum bleeding in 11.1%. Bleeding manifestations were more common in children with severe thrombocytopenia. Other studies have also shown that the majority of patients with thrombocytopenia have no bleeding manifestations, followed by petechiae, ecchymosis, and mucosal bleeding, occurring in patients with severe thrombocytopenia.6,8,23

In the pediatric population, thrombocytopenia may be asymptomatic, and bleeding doesn’t occur until platelet count falls below 100 × 10^9/L, but this also depends on the cause of thrombocytopenia, for example, surgical bleeding due to decreased platelet count usually occurs if the count is <50000/µL, and spontaneous bleeds often don’t occur at platelet count >20000/µL. The decrease in the number of platelets is either due to decreased production at the level of bone marrow or increased destruction. We observed isolated thrombocytopenia in 163 (66%) children, bicytopenia in 25 (10%) children, and pancytopenia in 58 (23%) children (Table 4).

In our study, septicemia (23%) was the most common underlying cause of thrombocytopenia, followed by megaloblastic anemia (14%), undiagnosed fever (10%), and local infection (9%) (Table 4). The etiology of thrombocytopenia in sepsis is multifactorial. It is commonly associated with DIC and is caused by splenic destruction of immune complex coated platelets, platelet adhesion to the damaged vascular surface, and by direct platelet toxicity caused by a microorganism. Megaloblastic anemia due to vitamin B₁₂ and folic acid deficiency was found in 14% of patients in whom thrombocytopenia was believed to be due to impaired deoxyribose nucleic acid synthesis resulting in ineffective thrombopoiesis. Nair et al.6 in Delhi reported septicemia (26.6%) as the major cause of febrile thrombocytopenia. Subramaniam et al.8 described infections (86%) as the most common cause of thrombocytopenia, followed by malignancy (6%), megaloblastic anemia (3%), drug-induced (1%), and connective tissue disorders (0.7%). In a study by Patil et al.,23 the two most common causes of thrombocytopenia were malaria (54%) and dengue (15%).

In a tropical country like India, infectious causes predominate and are usually associated with fever. Thrombocytopenia may be a pointer to the presence of infections like malaria, dengue, leptospirosis, and other viral infections. Most of the studies in different areas of India were conducted to know the etiology of febrile thrombocytopenia and excluded those who presented without fever, and thus the majority of children with thrombocytopenia presenting during monsoons can be explained. However, in our region, dengue and malaria are not so frequent, and we have enrolled patients with thrombocytopenia regardless of fever.

In this study, we also investigated the patients for rheumatological disorders and primary immunodeficiency disorders and found that autoimmune diseases like SLE and juvenile idiopathic arthritis (JIA) were present in 3.7% of patients with thrombocytopenia. In SLE and JIA, thrombocytopenia is because of immune-mediated reaction. No cases of primary immune deficiency were detected, though common variable immunodeficiency, autoimmune lymphoproliferative syndrome, and Wiskott–Aldrich syndrome are reported causes of thrombocytopenia.24

Nearly nine (3.6%) children in our study died and all had septicemia with MOD. The majority of patients (91%) recovered. A study by Modi et al.9 also reported 5% mortality in their cohort, and more than half of these patients had septicemia with MOD. In another study by Patil et al.23 on the clinical evaluation of a patient with thrombocytopenia, recovery was reported in 95% of patients and mortality in 5% of patients. In this study, the major cause of death was septicemia in 60% of patients, followed by malaria and viral fever. So, these studies show that mortality may not be related to the severity of thrombocytopenia but to the underlying etiology leading to MOD syndrome (MODS).

To conclude, thrombocytopenia may be the only presentation of different local and systemic conditions. It is also a common hematological observation in the evaluation of the sick child. In this study, the seasonal analysis revealed the maximum number of cases in the rainy season, followed by summer and winter. Septicemia was the commonest etiology, followed by megaloblastic anemia and undiagnosed fever. Majority of children with thrombocytopenia have no bleeding manifestations, and there was a significant association between severe thrombocytopenia and bleeding manifestations. On logistic regression analysis, age >10 years, presence of bleeding, arthralgia, rash, pallor, GI symptoms, hematological disorders, and malignancy were found to be associated with severe thrombocytopenia. Even though the study group came across platelet count as low as 1000 cells/µL, mortality was only 3.6%, which was associated with septicemia and MODS.

Compliance with Ethical Standards

Contributors

Isha Bhatia: IB; Avinash Sharma: AS; Sandesh Guleria: SG; Ajay Sharma: AJ; Ranbir Singh Jaswal: RJ; Ajay Vaid: AV; Neha Rehalia: NR; Amar Thakur: AT.


Ethical Approval

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

References

Lipid Profile as an Indicator of Severity in Cirrhosis of Liver: Hospital based Cross-sectional Study

Jeevanandham Yamuna1, Anbazhakan Akila2, Vellaichamy Uvaraj Muruganandam3*, Krishnamurthy Sivakumar4, Kumar Natarajan5, Arumugam Muruganathan6

Received: 16 March 2022; Accepted: 24 November 2022

ABSTRACT

Background: Various scoring systems are available to assess the severity of cirrhosis, that is, the Child-Pugh score and Model for End-Stage Liver Disease (MELD) score. Since the liver is the major site for converting excess carbohydrates into various lipids, the deranged lipid profile can act as a prognostic biomarker of cirrhosis. We assessed the lipid profile abnormalities among patients with cirrhosis of the liver and correlated them with the severity of cirrhosis.

Materials and methods: This is an analytical cross-sectional study on lipid profile as an indicator of severity in cirrhosis of the liver among patients admitted to the medical ward of a tertiary care teaching hospital in Tamil Nadu. Following detailed investigation and confirmation of cirrhosis, a fasting serum lipid profile was measured in all eligible patients with cirrhosis. Total serum cholesterol, triglyceride (TGL), and high-density lipoprotein (HDL) were measured by direct method and serum low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were calculated by using the Friedwald formula.

Results: A total of 120 patients were studied. Of them, 76 (63%) were male. Of them, alcohol (84, 75.0%), hepatitis B (8, 7.1%), and nonalcoholic steatohepatitis (NASH) (6, 5.4%) were the most common cause of cirrhosis. A clear dose-response relationship (decreasing trend) is seen in the levels of lipids for increasing severity based on the Child-Pugh score and MELD score (except for a score of ≤10). Further, the cholesterol, LDL, and HDL were significantly lower among patients with ascites or with spontaneous bacterial peritonitis compared to their respective groups. However, none of the lipid profiles significantly differed based on the presence of upper gastrointestinal (UGI) bleeding.

Conclusion: This study observed that there is a significant reduction in levels of lipid profile parameters like serum total cholesterol, LDL, VLDL, TGL, and HDL in patients with cirrhosis as the severity increases. Further formulation of the scoring system in association with a preexisting scoring system may provide a better assessment of patients’ prognosis in view of morbidity and mortality. We recommend it is necessary to assess the fasting lipid profile in all patients with cirrhosis and prognosticate their disease progression.

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INTRODUCTION

Liver cirrhosis represents the advanced stage of hepatocellular injury caused by various etiologies, which may gradually end in hepatic failure and hepatocellular carcinoma. The global prevalence of cirrhosis ranges from 4.5–9.6%, that is, >50 million. In the United States of America, it is the second leading cause of death. The global prevalence and mortality have increased in recent years in the United States of America.

Various scoring systems are available to assess the severity of cirrhosis, that is, Child-Pugh score and MELD score. The liver plays an essential role in lipid metabolism, as it is the major site of converting excess carbohydrates into TGLs and fatty acids. The liver synthesizes large quantities of cholesterol and phospholipids. Synthesis and metabolism of cholesterol are impaired in CLD. This eventually results in a decrease in plasma levels. HDL cholesterol and its major apolipoproteins have been shown to be reduced in cirrhosis because of the severe metabolic derangement as also the serum levels of LDL cholesterol. With this background, we assessed the lipid profile abnormalities among patients with cirrhosis of the liver and its correlation with the severity of cirrhosis.

MATERIALS AND METHODS

Study Design

It is an analytical cross-sectional study.

Study Setting

The study was conducted in a tertiary care teaching hospital situated in the Western part of Tamil Nadu, India. The hospital has 1,000 beds, including all medical and surgical specialties. Outpatient and inpatient services related to hepatology services are provided by the Department of Internal Medicine of the hospital. All clinically diagnosed patients with cirrhosis are admitted as inpatients and investigated in detail for further management.

Study Population and Period

We included patients with cirrhosis admitted to the medical wards of the study hospital between July 2017 and June 2018. The inclusion and exclusion criteria are given below.

Inclusion Criteria

• Patients of age ≥18 years with cirrhosis.
• Admitted to the medical wards.

Exclusion Criteria

• Diabetes mellitus/hypertension.
• Cerebrovascular disease.
• Patients on lipid-lowering drugs.
• Pancreatitis.
• Chronic kidney disease.
• Hypo/hyperthyroidism.

Sample Size and Sampling

Based on results reported by Suman et al., we calculated the sample size considering the

© The Author(s), 2023. Open Access. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/). Please refer to the link for more details.
Lipid Profile as an Indicator of Severity in Cirrhosis of Liver

The mean ± standard deviation (SD) difference of VLDL between the patients with MELD score 19–24 (16.8 ± 2.7) and >24 (15.0 ± 2.0), at 95% confidence interval and 80% power using Open Epi software. The calculated (minimum) sample size was 58.

**Study Procedure**

All clinically diagnosed cirrhosis patients were prescribed a complete hemogram, renal function test, liver function test including serum proteins, ultrasonogram of the abdomen, coagulation profile, and upper gastrointestinal endoscopy as part of the routine care. Further, disease severity is categorized using Child-Turcotte-Pugh (CTP) score. CTP score is calculated using the following parameters, namely grading of ascites, serum albumin, serum bilirubin, prothrombin time, and severity of encephalopathy. CTP scoring has three grades; score 5–6 is class A, score 7–9 is class B, and score 10–15 is class C. After informed consent, the fasting serum lipid profile is measured among patients with cirrhosis. Total serum cholesterol, TGL, and high-density lipoprotein (HDL) were measured by the direct method, and serum LDL and VLDL were calculated using Fried Wald formula (LDL cholesterol = Total cholesterol − [HDL cholesterol − TGL/5]) and VLDL = Sr. TGLs/5).

Model for End-Stage Liver Disease (MELD) score is used for preassessment for liver transplantation. It includes serum sodium, creatinine, bilirubin, INR, and the need for renal replacement therapy.

**Statistical Analysis**

The primary data was collected, and it was analyzed using Statistical Package for the Social Sciences 16.0 version software. Multiple variables between variable groups of a single population are done by using the chi-squared test. Quantitative data between two or more groups were analyzed using the analysis of variance (ANOVA) test. A p-value of <0.05 was considered statistically significant.

**Ethics**

Ethical approval was obtained from the Institute Ethics Committee of the study hospital. Written informed consent was obtained from all participants.

**Results**

A total of 150 patients with cirrhosis were admitted during the study period. Of them, 30 were excluded from the study based on the exclusion criteria, and finally, 120 patients were included in the study. Of them, 76 (63%) were males, and 44 (37%) were females. Alcohol (84, 75.0%), hepatitis B (8, 7.1%), and NASH (6, 5.4%) were the most common cause respectively. Similarly, based on the MELD score, 4 (3.3%), 16 (13.4%), 37 (30.8%), and 63 (52.5%) were classified under the scores ≤10, 11–18, 19–24, and >24, respectively.

The mean and SD of each lipid level for each category based on the Child-Pugh score is given in Table 1. A clear dose-response relationship (decreasing trend) is seen in the levels of lipids for increasing severity based on the Child-Pugh score.

Similarly, the distribution of each lipid level for each category based on the MELD score is given in Table 2. Except for the patients with a MELD score of ≤10, a clear dose-response relationship (decreasing trend) is seen with all other levels of lipids for increasing severity based on the MELD score.

The distribution and association of lipid profile with the presence of ascites, spontaneous bacterial peritonitis, and UGI bleeding are given in Tables 3 to 5, respectively. The cholesterol, LDL, and HDL were significantly lower among patients with ascites and among patients with spontaneous bacterial peritonitis compared to their respective groups. However, none of the lipid profiles significantly differed based on the presence of UGI bleeding.

**Discussion**

In this tertiary care hospital-based study, we found significantly low levels of lipids among patients with severe cirrhosis (based on the Child-Pugh score or MELD

**Table 1**: Lipid profile according to Child-Pugh score classification among patients with cirrhosis

<table>
<thead>
<tr>
<th>Lipid profile characteristics</th>
<th>A (n—44)</th>
<th>B (n—50)</th>
<th>C (n—26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>176.9 (12.0)</td>
<td>148.6 (11.8)</td>
<td>121.4 (9.5)</td>
</tr>
<tr>
<td>Range</td>
<td>152–210</td>
<td>130–178</td>
<td>102–134</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>173.2–180.5</td>
<td>145.3–152.0</td>
<td>117.6–125.3</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TGL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>152.1 (9.0)</td>
<td>130.1 (8.6)</td>
<td>92.7 (9.9)</td>
</tr>
<tr>
<td>Range</td>
<td>125–174</td>
<td>110–145</td>
<td>74–112</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>149.3–154.8</td>
<td>127.7–132.6</td>
<td>88.7–96.7</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>101.5 (12.4)</td>
<td>86.6 (10.9)</td>
<td>74.3 (10.3)</td>
</tr>
<tr>
<td>Range</td>
<td>77–140.6</td>
<td>69.6–116</td>
<td>57.6–94.4</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>97.7–105.3</td>
<td>83.5–89.7</td>
<td>70.1–78.5</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VLDL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>30.4 (1.8)</td>
<td>26.0 (1.7)</td>
<td>18.5 (2.0)</td>
</tr>
<tr>
<td>Range</td>
<td>25–34.8</td>
<td>22–29</td>
<td>14.8–22.4</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>29.9–31.0</td>
<td>25.5–26.5</td>
<td>17.7–19.3</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>45.0 (5.2)</td>
<td>36.0 (4.7)</td>
<td>28.6 (4.3)</td>
</tr>
<tr>
<td>Range</td>
<td>34–55</td>
<td>28–45</td>
<td>22–37</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>43.4–46.5</td>
<td>34.7–37.3</td>
<td>26.8–30.3</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lipid Profile as an Indicator of Severity in Cirrhosis of Liver

Results were consistent with previous studies. In our study, we found that parameters like serum total cholesterol, LDL, VLDL, HDL, and TGLs were significantly lower as the stage of severity of cirrhosis advanced. Fazl et al. conducted a similar study in which they concluded that serum cholesterol, LDL, and HDL were significantly reduced in patients with cirrhosis in comparison with control, where TGL levels were statistically not significant. Serum cholesterol and other parameters are significantly reduced as the

Table 2: Lipid profile according to MELD score classification among patients with cirrhosis

<table>
<thead>
<tr>
<th>Lipid profile characteristics</th>
<th>MELD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤10 (n—4)</td>
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<tr>
<td>Cholesterol</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Range</td>
<td>143–188</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>135.2–194.8</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TGL</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>116.6–169.9</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Range</td>
<td>85.4–107.4</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>79.6–110.1</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Range</td>
<td>24.6–31.6</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>23.3–34.0</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Range</td>
<td>33–49</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>31.0–52.0</td>
</tr>
<tr>
<td>p-value (ANOVA)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Presence of ascites and distribution of lipid profile characteristics

<table>
<thead>
<tr>
<th>Lipid profile characteristics</th>
<th>Ascites</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n—98)</td>
<td>No (n—22)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Mean ± SD</td>
<td>150.3 (22.6)</td>
</tr>
<tr>
<td>TGL</td>
<td>Mean ± SD</td>
<td>129.1 (24.0)</td>
</tr>
<tr>
<td>LDL</td>
<td>Mean ± SD</td>
<td>87.5 (14.9)</td>
</tr>
<tr>
<td>VLDL</td>
<td>Mean ± SD</td>
<td>25.8 (4.8)</td>
</tr>
<tr>
<td>HDL</td>
<td>Mean ± SD</td>
<td>36.9 (7.6)</td>
</tr>
</tbody>
</table>

*Independent t-test

Table 4: Presence of spontaneous bacterial peritonitis and distribution of lipid profile characteristics

<table>
<thead>
<tr>
<th>Lipid profile characteristics</th>
<th>Spontaneous bacterial peritonitis</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n—23)</td>
<td>No (n—97)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Mean ± SD</td>
<td>142.5 (21.0)</td>
</tr>
<tr>
<td>TGL</td>
<td>Mean ± SD</td>
<td>124.0 (25.3)</td>
</tr>
<tr>
<td>LDL</td>
<td>Mean ± SD</td>
<td>83.0 (11.7)</td>
</tr>
<tr>
<td>VLDL</td>
<td>Mean ± SD</td>
<td>24.8 (5.1)</td>
</tr>
<tr>
<td>HDL</td>
<td>Mean ± SD</td>
<td>34.7 (8.4)</td>
</tr>
</tbody>
</table>

*Independent t-test

score). Lipid profile abnormalities have a well-documented negative correlation with the severity of cirrhosis. This study ensures that lipid profile abnormalities in cirrhosis as the synthetic function is impaired in those patients.
Lipid Profile as an Indicator of Severity in Cirrhosis of Liver

The association of lipid profile with the short admission period during the study period. However, we have included all eligible patients correlated with the severity of cirrhosis. In addition, we have reported viral disease as the most common cause of cirrhosis, and in our case, it is alcohol.10

The decreased levels of LDL and HDL might be attributed to the reduced of apolipoproteins A and B. Since apo B is involved in the synthesis of VLDL, the reduced level of TGs is explained in cirrhosis. This can be due to insulin resistance found in liver cirrhosis. The insulin signaling mechanism in cirrhosis is found to be critical for lipogenesis regulated by phosphoinositide 3-kinase and AKT serine/threonine kinase 2 signaling pathways. Among the various transcription factors, sterol regulatory element binding protein-1c has a stimulatory effect on the genes involved in lipogenesis.

Unlike other studies, in our study, all the parameters of lipid profile, namely, serum total cholesterol, serum HDL, TGs (measured by direct method), serum VLDL, and LDL (calculated by formula), have been negatively correlated with the severity of cirrhosis. In addition, we have included all eligible patients admitted during the study period. However, the association of lipid profile with the short and long-term clinical outcomes in parallel or integrated with the Child-Pugh score or MELD score was not done.

Considering lipid profile abnormalities in CLD is of paramount importance to assess the severity since the changes are correlating statistically significant with previously existing severity assessment scores like the CTP score and with the MELD score.

CONCLUSION
Lipid profile changes are common findings in patients with cirrhosis. In this study, it was found that there is a significant reduction in levels of lipid profile parameters like serum total cholesterol, LDL, VLDL, TGL, and HDL in patients with cirrhosis as the severity increases. The presence of low lipid levels in cirrhosis patients presenting with altered sensorium and renal failure can aid in the diagnosis of hepatic encephalopathy and hepatorenal syndrome, respectively. Further formulation of the scoring system in association with a preexisting scoring system may provide a better assessment of patients’ prognoses in view of morbidity and mortality. It is also a cost-effective method. We recommend it is necessary to assess the fasting lipid profile in all patients with cirrhosis and prognosticate their disease progression.

REFERENCES

Table 5: Presence of upper gastrointestinal bleeding and distribution of lipid profile characteristics

<table>
<thead>
<tr>
<th>Lipid profile characteristics</th>
<th>Upper gastrointestinal bleeding</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n—29)</td>
<td>No (n—91)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Mean ± SD 154.7 (26.3)</td>
<td>152.5 (23.0)</td>
</tr>
<tr>
<td>TGL</td>
<td>Mean ± SD 130.9 (24.3)</td>
<td>129.8 (23.7)</td>
</tr>
<tr>
<td>LDL</td>
<td>Mean ± SD 89.8 (15.4)</td>
<td>89.3 (15.4)</td>
</tr>
<tr>
<td>VLDL</td>
<td>Mean ± SD 26.2 (4.8)</td>
<td>25.9 (4.7)</td>
</tr>
<tr>
<td>HDL</td>
<td>Mean ± SD 38.7 (7.8)</td>
<td>37.4 (7.9)</td>
</tr>
</tbody>
</table>

*Independent t-test
**ORIGINAL ARTICLE**

Serum Levels of Activin A: Predictor of Insulin Resistance and Atherosclerosis in Prediabetics

Ajay Chauhan**, Asmita Gupta, Parul Goyal, Tarun Kumar

Received: 21 February 2022; Revised: 06 November 2022; Accepted: 22 November 2022

**Abstract**

Background: Pathological effects of dysglycemia and insulin resistance on atherosclerosis and cardiac remodeling starts as early as in the prediabetic state before the onset of overt diabetes. Activin A is a molecule with multiple functions, including an important part in glucose homeostatic mechanisms as well as inflammatory processes and is therefore being researched as a useful novel biomarker for prompt recognition of the risk of cardiovascular disease (CVD) in prediabetic individuals, thereby helping in disease prognostication and early institution of therapeutic measures.

Objective: The study aimed to measure serum levels of activin A in prediabetic patients and evaluate them in comparison to normoglycemic controls. The association of activin A with carotid intima thickness (CIMT), left ventricular diastolic dysfunction (LVDD), and homeostatic assessment of insulin resistance (HOMA-IR) was also studied.

Materials and methods: A total of 60 prediabetic cases and 60 normoglycemic control subjects (matched as per age, gender, and body mass index (BMI)) were recruited. Measurement of serum glucose levels (fasting and postprandial) and fasting insulin levels and glycated hemoglobin (HbA1c) levels were done in all the subjects. The values of HOMA-IR were computed using established formulae. Enzyme-linked immunosorbent assay (ELISA) kits were used for the evaluation of serum levels of activin A in both groups. Parameters for the two groups were compared. In the cases, CIMT (using B-mode ultrasound) and LVDD (using two-dimensional (2D) echocardiography) were measured and correlated with activin A levels.

Results: Serum fasting insulin (miU/L) was considerably higher in cases than in the controls (p < 0.001). HOMA-IR median [interquartile range (IQR)] was 4 (3.25–4.93) in some cases, and that in the control group was 1.2 (0.88–1.5) (p < 0.001). Serum activin A levels in the cases group had a median (IQR) of 263.55 (227.1–279.5) ng/mL, which was substantially greater as compared to the control group 159.9 (130.7–178.7) ng/mL (p < 0.001). A significant positive association of serum activin A levels with HOMA-IR (p = 0.75, p < 0.001) and CIMT (p = 0.50, p < 0.001) was found. In LVDD grade I and II groups, the serum levels of activin A were 257.86 (219.3–271.2) ng/mL and 269 (244.19–291.5) ng/mL, respectively (p = 0.12).

Conclusion: A substantial proportion of morbidity and mortality related to dysglycemic states can be attributed to cardiovascular complications. Elevated levels of activin A in prediabetes can act as an indicator of subclinical CVD leading to early diagnosis and intervention.

**Introduction**

Diabetes mellitus is a metabolic disease characterised by hyperglycemia, secondary to defective insulin secretion or resistance to insulin action. Prediabetes, regarded as a precursor of diabetes, encompasses states of impaired fasting glucose (IFG) (fasting blood glucose 100–125 mg/dL), impaired glucose tolerance (IGT) (2 hour-post prandial blood glucose 140–199 mg/dL), or HbA1c 5.5–6.4%. Indians have been found to have one of the highest incidence rates of diabetes and a faster rate of progression from prediabetes compared to other ethnic groups.

Prediabetic state is linked to insulin resistance, defects in pancreatic β cell function, changes in incretin response, hepatic glucose output, and inflammatory cytokines. Insulin resistance is evident in individuals with IGT or IFG and precedes the evolution to overt diabetes. The correlation between prediabetic dysglycemia and major cardiovascular events such as myocardial infarction and stroke has also been established. A meta-analysis found that patients with prediabetes had an elevated CVD risk [relative risk (RR) 1.30 and 1.13, respectively, for IGT and IFG, coronary heart disease (1.20 and 1.10, respectively), and mortality (1.32 and 1.13, respectively). B-mode ultrasound imaging is a high-resolution, noninvasive, and inexpensive technique that can be used for the assessment of atherosclerosis by measuring CIMT. Increased CIMT can be used to estimate the risk of clinical cardiovascular events. Furthermore, echocardiographic abnormalities in the form of diastolic dysfunction have been demonstrated in diabetic adults, representing the earliest preclinical manifestation of diabetic cardiomyopathy. This association of dysglycemic states with diastolic dysfunction is mediated by glucose metabolism and insulin resistance mechanisms, which cause disruption in glucose oxidation, mitochondrial function and oxidative stress.

The knowledge and evidence regarding the fact that the pathogenetic mechanisms responsible for these complications are setup early in the disease course make it imperative to devise methods and markers for early prediction and assessment of risk.

Activin A is a multifunctional cytokine belonging to the transforming growth factor-β superfamily, shown to have roles in glucose regulation and inflammatory processes. Activin A has been studied to be an important marker in heart failure as well as in association with the severity of coronary atherosclerotic burden.

The study aimed to measure serum levels of activin A in prediabetes, evaluate them in comparison to normoglycemic controls and find the correlation with CIMT, reflecting the risk of atherosclerotic complications and left ventricular dysfunction.

**Materials and Methods**

This study was conducted in the Department of General Medicine, Biochemistry, Radiology, and Cardiology, Atal Bihari Vajpayee Institute of Medical Sciences & Dr Ram Manohar Lohia Hospital, Delhi, India.

Study Design

Cross-sectional observational study.

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Serum Levels of Activin A

Sample Size
A total of 60 prediabetic cases and 60 normoglycemic control subjects (matched as per age, gender and BMI) were recruited for the study from Medicine outpatient department (OPD), emergency and in-patient wards at Atal Bihari Vajpayee Institute of Medical Sciences & Dr Ram Manohar Lohia Hospital, Delhi, India.

Calculation

**Primary Objective**
To compare the serum levels of activin A in prediabetic cases and normoglycemic controls.

The study done by Kuo et al. in 2018 was used as a reference for the calculation of sample size.

The mean value of serum activin A in normal subjects and in pre-diabetics was 491.2 ± 165.3 and 559 ± 178.5, respectively. Taking the power of the study (β) as 80%, the level of significance (α) as 5%, the required sample size with these values was calculated to be 101 patients in both cases and control groups.

For comparing the mean of the two groups,

\[
N \geq 2 \left( \frac{(SD)^2}{\text{mean difference}^2} \right) \left( Z_{\alpha} + Z_{\beta} \right)^2
\]

where \(Z_{\alpha} = Z\) at two-sided α-error 5%; \(Z_{\beta} = Z\) at a power of 80%; and

\[
SD = \sqrt{\frac{(S_1)^2 + (S_2)^2}{2}}
\]

where \(S_1\) and \(S_2\) are standard deviation (SD) of group 1 (cases) and group 2 (controls), respectively;

\[
N \geq 2 \left( \frac{172.026^2}{67.8^2} \right) (1.96 + 0.84)^2
\]

\(N = 101\) (approx)

The sample size was later reduced to 60 prediabetic cases and 60 control subjects due to the coronavirus disease of 2019 pandemic and decreased footfall in Medicine OPD.

**Inclusion Criteria**

- A total of 60 prediabetics (cases) of age 18–65 years, as defined by:
  - Fasting blood glucose 100–125 mg/dL or
  - A 2-hour oral glucose tolerance test (OGTT)/2-hour postprandial glucose 140–199 mg/dL or
  - HbA1c 5.7–6.4%.
- A total of 60 normoglycemic controls (matched as per age, gender, and BMI), with:
  - Fasting blood glucose <100mg/dL.
  - A 2-hour postprandial glucose/2-hour OGTT < 140mg/dL.
  - HbA1c < 5.7%.

**Exclusion Criteria**

- Systemic hypertension
- Substance abuse
- Past history of cardiovascular events such as myocardial infarction, stroke, or peripheral arterial disease
- Cardiomyopathy
- Ulcerative colitis/Crohn’s disease
- Inflammatory arthritis
- Use of statins, other lipid-lowering drugs or antiplatelet drugs.
- Pregnancy.

**Methods**

**Clinical Examination**
The study participants were required to fill out a proforma consisting of questions about gender, age, and past ailments.

**Anthropometric parameters** were measured, and BMI was calculated as per the universal formula. Two readings of resting blood pressure were measured, and the mean value was recorded.

**Investigations**

- Fasting blood glucose.
- A 2-hour postprandial glucose.
- HbA1c levels.
- Fasting plasma insulin levels.
- Lipid profile.
- Serum activin A levels: Samples were collected and centrifuged for 10 minutes at 3000 rpm. Separated serum was then stored in aliquot tubes at −20°C for analysis by ELISA.
- Calculation of HOMA-IR was done using the universal formula:

\[
\text{HOMA-IR} = \frac{\text{FPG} \times \text{FPI}}{405}
\]

Where, FPI—fasting plasma insulin (mIU/L)

FPG—fasting plasma glucose (mg/dL)

**Serum Activin A**
The kit used a sandwich ELISA for the measurement of activin A levels in plasma, serum or other biological fluids. The range of values specified with the kit was 7.8 ng/mL–300 ng/mL.

**Procedure**

1. The procedure was carried out after bringing all the samples to room temperature.

2. Dilution of the standard with standard diluent was done using the multiple proportion dilution method.

3. Standard wells, blank wells and sample wells were prepared as below:
   - Standard wells: 50 µL standard was added.
   - Sample wells: 10 µL sample and 40 µL special diluent were added (this resulted in a five times sample dilution, and therefore, during the final calculation result was multiplied by five).
   - Except for the blank well, 50 µL horseradish peroxidase was added to every well. This was followed by incubation for an hour at 37°C.

4. After discarding the extra liquid and drying, the wells were filled with washing liquid, followed by mixing and gentle shaking. The washing liquid was then discarded, and absorbent papers were used to dry the plate. The above procedure was repeated five times.

5. A 50 µL chromogen solution A followed by chromogen solution B was added to all wells. This was followed by gentle shaking and incubation at 37°C for 10 minutes.

6. A 50 µL of stop solution was added to each well to halt the ongoing reaction (blue colour converted to yellow instantly).

7. For the final measurement, the blank well was set as zero, and optical density (OD) at 450 nm wavelength was measured using an ELISA reader within 15 minutes of adding the stop solution.

8. Calculation of the standard curve linear regression equation was done in accordance with standard's concentration and corresponding OD values. The concentration of the samples was then calculated by applying corresponding OD values on the standard regression equation.

9. The final concentration of serum activin A for each sample was calculated by multiplying the obtained values (ng/mL) by 5.

**B Mode Ultrasonographic Examination**

(only done for cases)
B-mode ultrasound was done for all cases for measurement of CIMT. The distance between echogenic lines representing carotid intima and media was recorded from common carotid arteries bilaterally, and mean CIMT was calculated. A single operator, blinded to clinical data related to participants, performed all scans and measurements.

**Two-dimensional (2D) Echocardiography**

(only done for cases)
All cases underwent echocardiographic examination for the assessment of ejection fraction.
Serum Levels of Activin A

Moreover, 96.7% of cases had a HOMA-IR value greater than 2 in contrast to 6.7% of controls. Serum activin A median (IQR) was 263.55 (227.1–279.5) (ng/mL) in cases and 159.9 (150.7–178.7) ng/mL in controls (p < 0.001) (Fig. 2 and Tables 2 and 3). The mean (SD) of mean CIMT (mm) was 0.69 (0.10), ranging from 0.5–0.9 among the study cases. (Table 4 and Fig. 3)

A positive correlation was found between mean CIMT (mm) and serum activin A (ng/mL), which was statistically significant (ρ = 0.5, p <0.001) (Table 5 and Fig. 4). For every 0.1 increase in mean CIMT (mm), serum activin A (ng/mL) was found to increase by 23.1 units.

A strong positive correlation between serum activin A and HOMA-IR was also found (ρ = 0.75, p < 0.001) (Table 5 and Fig. 5).

Serum activin A (ng/mL) in the LVDD grades I and II group was 257.86 (219.3–271.2) and correlate with CIMT and left ventricular dysfunction. It was an observational case-control study wherein 60 prediabetic cases, and 60 normoglycemic controls were recruited. Matching with respect to gender, age and BMI was ensured amongst the two groups. The following data was recorded. (Tables 1 and 2)

Table 1: Demographic characteristics and anthropometric measures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (SD)]</td>
<td>45.80 (10.06)</td>
<td>43.68 (9.66)</td>
<td>0.242</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (40.0%)</td>
<td>27 (45.0%)</td>
<td>0.580</td>
</tr>
<tr>
<td>Female</td>
<td>36 (60.0%)</td>
<td>33 (55.0%)</td>
<td></td>
</tr>
<tr>
<td>BMI [mean (SD)]</td>
<td>24.83 (3.02)</td>
<td>24.82 (2.58)</td>
<td>0.976</td>
</tr>
<tr>
<td>Waist circumference (cm) [mean (SD)]</td>
<td>87.9 (6.16)</td>
<td>87.17 (7.24)</td>
<td>0.542</td>
</tr>
<tr>
<td>Systolic blood pressure (BP) (mm Hg) [mean (SD)]</td>
<td>117.20 (6.35)</td>
<td>118.13 (8.64)</td>
<td>0.265</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg) [mean (SD)]</td>
<td>75.77 (4.70)</td>
<td>74.30 (4.77)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Table 2: Biochemical parameters

<table>
<thead>
<tr>
<th>Parameter (IQR)</th>
<th>Cases</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dL)</td>
<td>107 (101.25–118)</td>
<td>84 (78–90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPBG (mg/dL)</td>
<td>169 (155.5–182.25)</td>
<td>126 (114–132.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.95 (5.8–6.21)</td>
<td>5.1 (4.8–5.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum fasting insulin (mIU/L)</td>
<td>15.3 (12.2–18.62)</td>
<td>6 (4.2–7.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4 (3.25–4.93)</td>
<td>1.2 (0.88–1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum activin A (ng/mL)</td>
<td>263.55 (227.18–279.56)</td>
<td>159.9 (150.73–178.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Serum activin A (ng/mL) levels

<table>
<thead>
<tr>
<th>Serum activin A (ng/mL)</th>
<th>Group</th>
<th>Wilcoxon-Mann-Whitney U Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>254.09 (46.24)</td>
<td>164.84 (25.84)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>263.55 (227.18–279.56)</td>
<td>159.9 (150.73–178.75)</td>
</tr>
<tr>
<td>Range</td>
<td>132.02–355.8</td>
<td>100.6–239.26</td>
</tr>
</tbody>
</table>

Table 4: Distribution of the prediabetics in terms of mean CIMT (mm)

<table>
<thead>
<tr>
<th>Mean CIMT (mm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>0.69 (0.10)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.7 (0.6–0.75)</td>
</tr>
<tr>
<td>Range</td>
<td>0.5–0.9</td>
</tr>
</tbody>
</table>
Serum Levels of Activin A

**Table 5:** Correlation of serum activin A with CIMT and HOMA-IR

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Spearman correlation coefficient</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>HOMA-IR vs serum activin A (ng/mL)</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CIMT (mm) vs serum activin A (ng/mL)</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 6:** Correlation between LVDD grade and serum activin A

<table>
<thead>
<tr>
<th>Serum activin A (ng/mL)</th>
<th>LVDD grade</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>246.90 (49.97)</td>
<td>269.63 (35.66)</td>
<td>201.07 (16.31)</td>
<td>7.658 (0.022)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>257.86 (219.3–271.2)</td>
<td>269 (244.1–291.5)</td>
<td>201.07 (195.3–206.83)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>132.02–355.8</td>
<td>209–352.5</td>
<td>189.54–212.6</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 4:** Correlation between serum activin A (ng/mL) and mean CIMT (mm)

**Fig. 5:** Correlation between serum activin A (ng/mL) and HOMA-IR

269 (244.19–291.5) respectively (p = 0.12) (Table 6 and Fig. 6).

**Discussion**

The study showed increased activin A levels in prediabetic patients in comparison to controls. In addition, a strong positive association of serum activin A with HOMA-IR as well as CIMT was found.

In a study by Wu et al., a positive correlation of serum activin A levels with fasting plasma glucose (p < 0.001), HbA1c (p = 0.003), and HOMA-IR (p < 0.01) was found, which persisted after adjustment for confounding variables. Harada et al. also found that activin A levels were elevated in diabetics in comparison to controls.

However, a specific normal range of activin A has not been established in the existing studies. The currently published literature only implies a comparison of levels of activin A in specific study subjects and controls.

The only antecedent study done assessing the correlation between activin A and CIMT in individuals with prediabetes was conducted by Kuo et al. They showed that prediabetics had significantly raised activin A levels (pg/mL) (559 ± 178.5) than the normal glycemic group (491 ± 165.3) (p < 0.001). They also found a significant correlation of activin A with CIMT in normoglycemic (r = 0.236, p = 0.001) as well as prediabetic individuals (r = 0.264, p = 0.001).

There are a few other studies conducted previously evaluating the association of activin A with CIMT in different study groups. A study conducted by Peng et al. in community-dwelling adults aged >53 years found that CIMT was significantly higher in the tertile with high activin A values (0.75 ± 0.17 mm), as compared to medium (0.73 ± 0.16 mm) and low (0.67 ± 0.15) activin A tertiles (p < 0.001). In a recent study conducted in 2019, Yonata et al. observed a significant correlation between activin A and CIMT (r = 0.449; p = 0.001) in chronic kidney disease patients and suggested an important part of activin A in atherosclerotic process and vascular calcification.

In this study, the activin A levels in groups with different grades of LVDD have also compared a correlation of activin A with a grade of LV diastolic dysfunction was found, however statistically insignificant. Activin A was higher in the LVDD grade II than in the LVDD grade I group, but lower activin A values were seen in the group with LVDD grade III. However, the appropriate conclusion cannot be drawn from this observation because there were only two subjects (3.3%) with grade III LVDD.

The association between activin A and left ventricular function has been seen in diabetic individuals in an earlier study by Chen et al. They found a positive correlation of activin A with the left ventricle mass/volume.
Serum Levels of Activin A


(Atherosclerotic and cardiovascular risk (alone or with the help of other markers like CIMT) in prediabetic patients, thereby helping in earlier recognition of CVD and employment of lifestyle modifications and targeted medical therapy. Further studies are also warranted to definitively establish the correlation.

Based on our findings in concert with the existing data, we suggest that increased activin A levels act as a potential early indicator of coronary atherosclerosis and cardiovascular risk in dysglycemic states. However, further studies in a wider population are needed to definitively validate the findings while bringing geographic and ethnic diversity into account.

**Conclusion**

Significant morbidity and mortality due to diabetes and dysglycemic states can be ascribed to cardiovascular complications. The exceeding burden of this disease in the current scenario makes it imperative to have a high suspicion and devise markers for earlier diagnosis of subclinical atherosclerosis and heart disease. Based on the results of the present study, it is proposed that serum activin A levels can be helpful in assessing atherosclerotic and cardiovascular risk (alone or with the help of other markers like CIMT) in prediabetic patients, thereby helping in earlier recognition of CVD and employment of lifestyle modifications and targeted medical therapy. Further studies are also warranted to definitively establish the correlation.

**References**

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 discomfort, and headache.

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

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

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

Additional information is available on request.

Last updated: January 03, 2023
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IN21DI00078
Correlation of Anemia with Glycated Hemoglobin among Euglycemic Type 2 Diabetic Patients

Meenaxi Sharda1, Nikhil Gandhi2*, Dharmendra Bansal3, Maneesh Gadhwal4

Received: 05 November 2022; Accepted: 22 November 2022

ABSTRACT

Background: Diabetes mellitus (DM) and anemia are both prevalent in India. Glycated hemoglobin (HbA1c) is the gold standard test for the diagnosis of DM and monitoring of glycemic status. Hemoglobin (Hb) being the integral component of HbA1c, there is a possibility that anemia can also affect the level of HbA1c apart from the various other factors.

Objectives: To study the prevalence, type of anemia, and correlation between HbA1c and anemia, including red blood cell (RBC) indices in euglycemic type 2 DM patients. The study was conducted with the objective of studying the correlation between HbA1c and anemia in euglycemic diabetic patients having controlled blood glucose over a period of 3 months.

Methodology: This cross-sectional study was conducted between May 2020 and May 2021 at the Department of General Medicine, Government Medical College, Kota, Rajasthan, India. All euglycemic diabetic patients with controlled blood glucose over a period of 3 months attending the outpatient department and fulfilling inclusion and exclusion criteria were enrolled in the study.

Inclusion criteria: All euglycemic type 2 DM patients with controlled blood glucose having three consecutive normal blood glucose levels (fasting blood sugar (FBS)—80–130 mg/dL and postprandial blood sugar (PP2BS) test—<180 mg/dL) over a period of 3 months from the outpatient department.

Exclusion criteria: Type 1 DM and latent autoimmune diabetes of adults, patients with hemolytic anemia, pregnancy, chronic alcoholism, chronic kidney disease, chronic liver disease, combined deficiency anemia, patients with increased FBS and PP2BS, acute and chronic inflammatory state, malignancy, anemia of chronic disease, and vitamin B12 deficiency were excluded from our study.

Detailed investigations of diabetes and anemia were conducted. The effect of anemia on HbA1c was assessed, and the correlation of anemia with mean HbA1c was analyzed statistically.

Results: The prevalence of anemia in diabetic patients is 56.8%. Normocytic normochromic anemia is the most common, which was observed among 48.86% of diabetic patients. The median HbA1c of anemic patients is higher than nonanemic patients (p < 0.01). There is a negative correlation between Hb and HbA1c (p < 0.01). The correlation of RBC indices, that is, mean corpuscular Hb (MCH), mean corpuscular volume (MCV), and MCH with HbA1c, is also negative (p < 0.01). There is a negative correlation between HbA1c and serum ferritin level, as indicated by the Pearson correlation test (p-value of <0.01).

Conclusion: Anemia is prevalent in type 2 DM patients without renal involvement, and also normocytic normochromic type is the most common, followed by iron deficiency anemia (IDA). HbA1c levels are significantly affected by the presence of moderate anemia in spite of controlled glycemia.

INTRODUCTION

Diabetes is one of the largest global health emergencies of the 21st century. About 415 million adults are estimated to have diabetes worldwide currently.1 India has an estimated 77 million people with diabetes, which makes it the second most affected in the world, after China.2 In addition, approximately 52% of adults with diabetes remain undiagnosed in India. One in six people (17%) in the world with diabetes is from India.3

Glycated Hb (HbA1c) is the most frequently occurring fraction of HbA1. American Diabetes Association guidelines have not only considered it as the primary target for glycemic control but also included it as a diagnostic criterion. Initially, it was believed that HbA1c was only altered by glucose levels;4,5 however, certain studies have noted its elevation in conditions other than diabetes, such as hemoglobinopathies, chronic kidney disease, pregnancy, and nutritional anemia.6,7

Diabetes prevalence estimates using HbA1c may be affected by iron deficiency; hence population-based research in areas with a high prevalence of anemia is needed before confirmation of the diagnosis of DM in such population. The mechanism through which iron deficiency and anemia influence HbA1c has yet to be fully elucidated; however, most epidemiologic studies suggest that IDA can result in spuriously high HbA1c values, though some suggest there is lower HbA1c among individuals with IDA or anemia. Mild anemia has little impact on the HbA1c level, whereas moderate to severe anemia can increase the level of HbA1c.

Glycated Hb (HbA1c) levels are expected to be in the control range if the three consecutive blood sugar fasting and postprandial levels measured over a period of 3 months duration are in acceptable control range; any deviation in range would suggest an alteration in the level of HbA1c due to some other factors in which presence of anemia is one such important and common factor. This postulation formed the basis of this study to assess the utility of HbA1c as a marker of glycemic control in anemic diabetics.

OBJECTIVES

- To study the prevalence and type of anemia in euglycemic type 2 DM patients with normal renal function.
- Further study the correlation between HbA1c and anemia, including RBC indices and serum ferritin in these euglycemic diabetic patients, having three consecutive controlled blood glucose
Results
The majority of the patients in our study were from the 51–60 years age group. The mean age is 58.43 years, and the standard deviation is 8.79. The gender-wise distribution shows that 55.5% of patients are females and 44.5% are males (Table 1). Out of 155 cases, a total of 88 patients, 54 females and 34 males, have anemia, so the prevalence of anemia in diabetic patients is 56.8% (Fig. 1). Out of the total of 88 anemic patients, 36 had mild anemia, and 52 had moderate anemia. The median HbA1c of moderately anemic patients is statistically significantly higher than mild-grade anemic patients ($p < 0.01$) (Table 2).

Methocytosis.

Methocytosis.

METEHOLOD.

- Study center: Department of General Medicine, Government Medical College, Kota, Rajasthan, India
- Study design: Cross-sectional study
- Study Period: May 2020–May 2021

After the selection of patient with the application of inclusion and exclusion criteria, informed written consent was taken. Detailed medical, past history and general, systemic physical examination and fasting, 2-hour postprandial blood glucose of last 3 months duration was recorded on a predesigned proforma. All the participants were further subjected to the following investigations complete blood count, peripheral blood smear, HbA1c, liver and renal function tests, human immunodeficiency virus, and hepatitis B surface antigen. According to World Health Organization (WHO) cutoff value of Hb for anemia patients was divided into two groups, euglycemic diabetic with anemia and without anemia. The euglycemic diabetic patients with anemia were further investigated with anemia profile to identify the type and cause of anemia. The anemia profile included serum ferritin, vitamin B12, lactate dehydrogenase, and reticulocyte count accordingly. Other investigations like serum iron, total iron-binding capacity, serum folic acid, Hb electrophoresis, and bone marrow were noted if done in any case. The effect of anemia on HbA1c level and correlation with mean HbA1c was analyzed statistically.

Operational definition of anemia as per WHO criteria Hb < 12 g/dL for females and Hb < 13 g/dL for males.

Statistical Analysis
Data were entered in Microsoft Excel 2017 and analyzed using excel and IBM Statistical Package for the Social Sciences statistics version 21. Mann–Whitney U and Pearson correlation tests were applied. A $p$-value of <0.05 was considered significant.

<table>
<thead>
<tr>
<th>Grades of anemia</th>
<th>No. of patients</th>
<th>Hb (g/dL)</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>36</td>
<td>11.5</td>
<td>6.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>52</td>
<td>10</td>
<td>7.15</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Mann–Whitney U test $p < 0.01$ $p < 0.01$

<table>
<thead>
<tr>
<th>Hemogram</th>
<th>Male Median</th>
<th>Male IQR</th>
<th>Female Median</th>
<th>Female IQR</th>
<th>Mann–Whitney U test Z value $p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>10.2</td>
<td>1.9</td>
<td>9.8</td>
<td>0.9</td>
<td>3.8</td>
</tr>
<tr>
<td>RBC (106/uL)</td>
<td>4.2</td>
<td>1.05</td>
<td>4.1</td>
<td>1.28</td>
<td>1.94</td>
</tr>
<tr>
<td>MCV</td>
<td>71.2</td>
<td>8.4</td>
<td>68.8</td>
<td>10.3</td>
<td>2.37</td>
</tr>
<tr>
<td>MCH</td>
<td>22.7</td>
<td>5.8</td>
<td>22.05</td>
<td>2.8</td>
<td>2.61</td>
</tr>
<tr>
<td>MCHC</td>
<td>28.85</td>
<td>2</td>
<td>28.1</td>
<td>2.1</td>
<td>2.33</td>
</tr>
</tbody>
</table>
Correlation of Anemia with HbA1c

There is a negative correlation between Hb and HbA1c as indicated by Pearson correlation test (p-value of <0.01) (Pearson correlation coefficient r = −0.71). It means with the decrease in Hb value, there is an increase in the Hb1Ac level (Fig. 4). Correlation of RBC indices, that is, MCH, MCV, and MCHC with HbA1c are also negative as indicated by Pearson correlation test (p-value < 0.01) (r = −0.56, −0.61, and −0.69, respectively). It means there is an increase in Hb1Ac value with a decrease in all RBC indices. (Table 5 and Figs 5 to 7) There is a negative correlation between HbA1C and serum ferritin level, as indicated by the Pearson correlation test (p-value of <0.01) (r = −0.48). It means an increase in HbA1c level is seen with a decrease in serum ferritin (Fig. 8).

**DISCUSSION**

The prevalence of anemia in diabetes is variable in various studies. All studies reveal that anemia is more common in females than males (62.79 vs 49.27% in our study). Similarly, the type of anemia also is variable, and the most common variety is the normocytic

<table>
<thead>
<tr>
<th>Category of patients</th>
<th>HbA1c</th>
<th>Test statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemic patients</td>
<td>6.8</td>
<td>0.9 Mann–Whitney U test</td>
</tr>
<tr>
<td>Nonanemic patients</td>
<td>6.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Table 5:** Correlation of HbA1c with RBC indices (N = 155)

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td>≤6.5</td>
<td>84.3</td>
<td>7.1</td>
<td>28.5</td>
</tr>
<tr>
<td>6.6–7.5</td>
<td>80.7</td>
<td>15.8</td>
<td>27</td>
</tr>
<tr>
<td>7.6–8.5</td>
<td>67.7</td>
<td>8.4</td>
<td>22.1</td>
</tr>
</tbody>
</table>

**Table 4:** Comparison of HbA1c between anemic and nonanemic euglycemic patients (N = 155)

Fig. 1: Prevalence of anemia in euglycemic patients (N = 155)

Fig. 2: Distribution of patients according to type of anemia (N = 88)

Fig. 3: Comparison of HbA1c between anemic and nonanemic euglycemic patients (N = 155)

Fig. 4: Correlation of HbA1c with hemoglobin (N = 155)

Fig. 5: Correlation of HbA1c with MCV (N = 155)

Fig. 6: Correlation of HbA1c with MCH (N = 155)
Correlation of Anemia with HbA1c

Fig. 7: Correlation of HbA1c with MCHC (N = 155)

Fig. 8: Correlation of HbA1c with serum ferritin (N = 44)

Anemia is prevalent in type 2 DM patients who are 56.8%. Normocytic normochromic anemia is the most common which was observed among 48.86% of diabetic patients. Median Hb1Ac of moderately anemic patients is statistically significantly higher than mild grade anemic patients. Serum Hb1Ac increases with a decrease in MCV, MCH, MCHC, and serum ferritin.

Our study shows that the median Hb1Ac of anemic patients is higher than nonanemic patients. In iron deficiency, red cell production decreases; consequently, an increased average age of circulating red cells ultimately leads to elevated Hb1Ac levels. As Hb glycation is an irreversible process, Hb subunit α1 (HbA1) levels in erythrocytes will increase with cell age.

Out of the total of 88 anemic patients, 36 had mild anemia and 52 had moderate anemia. The median Hb1Ac of moderately anemic patients is 7.15, which is statistically significantly higher than the median Hb1Ac of mild anemic patients, which is 6.6. Control-case study for the effect of IDA on Hb1Ac levels in nondiabetic individuals by Silva et al. showed higher Hb1Ac in patients with moderate and severe anemia compared to mild anemia and thus concluded that IDA affects Hb1Ac results, and the effect is dependent on anemia degree.11

In our study, there is a negative correlation of RBC indices MCV, MCH, and MCHC with Hb1Ac, as indicated by the Pearson correlation test (p-value of <0.01). Christy et al. in their study of the correlation between red cell indices and Hb1Ac in anemic subjects found no significant correlation between Hb1Ac and MCV (r = −0.23, p = 0.06), and a borderline significant association was found between Hb1Ac and MCH (r = −0.58, p = 0.05). Although the association of elevated A1c with the severity of IDA remains unexplained, its borderline association with red cell indices proves the role of erythrocyte morphology and lifespan in elevating A1c.12 Koga et al. studied the relationship between erythrocyte indices and Hb1Ac in premenopausal women. They found that MCV and MCH were negatively associated with Hb1Ac.13

In our study, there is a negative correlation between Hb1Ac and serum ferritin level, as indicated by the Pearson correlation test (p-value of <0.01). Ferritin is a storage form of iron, and it reflects the true iron status. In IDA, ferritin is decreased with an increase in the red cell life span, and an increased red cell life span is associated with increased Hb1Ac. Sharifi and Kazemzadeh14 did not find any significant correlation between Hb1Ac and ferritin in the diabetic population.

Hardikar et al., in their study in Indians, analyzed the effect of glycation and other nonglycemic parameters such as Hb, MCV, MCH, MCHC, age, sex, serum creatinine, alanine aminotransferase, white blood cell, Vitamin B12, and folate over Hb1Ac levels. They postulated that if Hb1Ac is used to diagnose prediabetes and diabetes in IDA patients, it will result in a false high prevalence.15 There are various confounding factors that can affect Hb1Ac and not the blood sugar level alone, especially iron deficiency, which is the most common deficiency disease worldwide. It is hence prudent to rule out IDA before making a therapeutic decision based on the Hb1Ac levels.

Our study shows that the median Hb1Ac of anemic patients is higher than nonanemic patients. In iron deficiency, red cell production decreases; consequently, an increased average age of circulating red cells ultimately leads to elevated Hb1Ac levels. Different studies have been carried out in both diabetic and nondiabetic groups; however, its distribution in well-controlled diabetics who are on regular therapy is inadequately studied. Although diabetes itself can elevate A1c levels, it has been proven that controlled plasma glucose levels for 3 months correlate very well with controlled Hb1Ac. Hence, patients with controlled plasma glucose levels are expected to have A1c below 6.5%.16

Limitation

- Anemic nondiabetic comparison group was not included in our study.
- Further study needs to be conducted to evaluate the effect of treatment of IDA in euglycemic DM patients on Hb1Ac values.

Bias

- Berkson’s bias as it is a hospital-based study.

Conclusion

Anemia is prevalent in type 2 DM patients and can lead to false elevation of Hb1Ac with an erroneous diagnosis of uncontrolled state when utilizing this only as a measure of optimal control leading to intensification of treatment protocol posing the patient at risk of hypoglycemia, especially in older people. The presence of anemia and iron status of the patient should be considered while utilizing Hb1Ac levels as a parameter of diabetes diagnosis and control of glycemla.

Recommendation

Anemia is prevalent in type 2 DM patients and can lead to false elevation of Hb1Ac with an erroneous diagnosis of uncontrolled state when utilizing this only as a measure of optimal control leading to intensification of treatment protocol posing the patient at risk of hypoglycemia, especially in older people. The presence of anemia and iron status of the patient should be considered while utilizing Hb1Ac levels as a parameter of diabetes diagnosis and control of glycemla.

References

Correlation of Anemia with HbA1c


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Jt. Secretary
Influence of N95 Mask-related Hypoxemia on Headache, Stress, Anxiety, and Quality of Sleep during COVID-19 Patient Care among Frontline Health Care Professionals

Arul Varman1, Devi R Nithiya2, Chetty Meghna3, Arun Tipandjan4, Srinivasan Thiagarajan5, Nirmala Saravanan6, Geethalakshmi Sivakumar7

Received: 18 April 2022; Revised: 12 October 2022; Accepted: 08 October 2022

Abstract

Background: Prolonged use of N95 masks by health care workers might affect physical health due to mask-related hypoxia in addition to the psychological effects of N95 masks. We tried to explore the association of N95 mask-related hypoxia and headache with stress, quality of sleep, and anxiety in the current study.

Materials and methods: The sample (N = 78) consisted of 41 doctors and 37 nurses involved in COVID-19 patient care and using N95 masks with or without PPE for at least 4 hours. Perceived stress scale (PSS), Coronavirus anxiety scale (CAS), and Pittsburgh sleep quality index (PSQI) were administered, and physical parameters like heart rate and oxygen saturation (SpO2) were measured.

Results: Around 42% of the study participants experienced headaches after wearing an N95 mask and had a higher increase in heart rate (mean percent: 10.5% vs 6.3%) and decline in SpO2 (mean percent: 2.6% vs 1.5%) compared to those who didn’t develop a headache after N95 mask use. Independent samples t-test showed a mean difference for PSS and CAS between those who experienced headaches and those who didn’t. The mean PSQI scores among the study participants were 8.91 ± 5.78; the score among those participants with and without headache was 10.57 ± 3.11 and 7.68 ± 2.53, respectively.

Conclusion: Perceived corona anxiety, poor sleep quality, and corona anxiety are associated with N95-related headaches and SpO2 drop among health professionals who wear N95 masks for at least 4 hours.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic posed several challenges to patients as well as health care providers. The COVID-19 virus spreads primarily through salivary and nasal droplets; hence wearing a face mask is important for the prevention of the aerial spread of COVID-19. Among various types of masks, N95 mask provides the most effective barrier, especially during aerosol-generating procedures like intubation. N95 mask is 95% efficient in filtering particles with a median diameter of 0.3 microns, the letter N denotes that the mask is not resistant to oil. Though the use of N95 face masks in the primary prevention of COVID-19 is undeniable, its prolonged use is accompanied by adverse health effects including reduced SpO2 and increased pulse rate. Breathing through the mask leads to insufficient oxygen intake thereby stimulating the sympathetic nervous system and resulting in tachycardia. Rapid breathing and higher incidence of chest discomfort develop as a result of hypoxemia due to usage of an N95 face mask for a continuous 4 hours duration. Humidity and temperature are altered significantly on the facial region exposed to the mask.

Health care workers involved in COVID-19 patient care experience compromised psychological well-being evident by increasing levels of anxiety and depression. The stress documented among COVID-19 health care providers was found to have a significant association with the work environment, long working hours, irregular work schedules, and challenging duties at the intensive care unit (ICU). Fear of being ostracized by society further adds to coronavirus-related anxiety. It is well known that stress and anxiety induce sympathetic overactivity resulting in tachycardia, headache, and sleeplessness. Several studies reported headaches and impaired sleep among healthcare providers who were otherwise healthy. Though the exact mechanism of the development of insomnia, headache, and anxiety in health care workers is unclear; it can be attributed to hypoxia which either directly or indirectly stimulates the sympathetic outflow. In this context, we intended to delineate the physiological and psychological factors by measuring the SpO2 and to study the influence of N95 mask-induced hypoxia on stress, anxiety, quality of sleep, and headache during COVID-19 patient care among frontline workers.

MATERIALS AND METHODS

Participants

This cross-sectional study was carried out for a period of three months at a “COVID-19 designated hospital” from 1st August 2020 to 31st October 2020. An informed, written consent was obtained from each participant prior to their recruitment in the study. A convenient sampling method was adopted due to the then-prevailing pandemic situation and hence we spatially defined our target population. Doctors and nursing officers using N95 face masks with or without PPE for at least four hours and who were directly involved in COVID-19 patients’ care were included in this study. Those who wore an N95 face mask for less than 4 hours were excluded from the study since changes in heart rate and SpO2 were insignificant as per available literature. Considering 72.4% prevalence of headaches after the use of masks among health care workers according to a study conducted by Lim et al.,1 and assuming a error as 5%, and error of margin as 10%, the calculated sample size was 90. However, the

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pandemic and busy duties in the COVID wards enabled us to collect completed questionnaires from only 78 out of the total 100 participants recruited. This study was approved by the Institute Research and Ethics Committee.

Procedure
Participants who consented to participate in the study were administered a questionnaire to be filled out through Google forms. The questionnaire aimed at collecting the background information of the participants with regard to age, gender, education, current employment status, current health status, past history of headache, insomnia, stress, and anxiety. Sleep quality was assessed using PSQI questionnaire prevalidated in an Indian setting, with Cronbach’s α of 0.73.12 A final global score ranging from 0 to 21 was obtained as a sum of seven components, each indicating a particular aspect of sleep.

Physiological Parameters
The participants were instructed to measure their heart rate and SpO2 before wearing and at the time of removing the N95 mask using Pulse rate Omron Pulse-Oximeter Md 300, Model: om-36 (Indore, India, 2018), and they were asked to complete the questionnaires on the same day.

Stress Assessment
Stress was measured using PSS, the participants were asked to rate the frequency of their feelings and thoughts about life events and situations using a 5-point Likert scale ranging from (0) Never to (4) Very Often (total score range 0 to 40).13

CAS
A 5-item CAS, developed by Lee was administered to assess anxiety specific to the coronavirus. Scoring was done using 0–4 points Likert scale and the total score ranged from 0 to 20, with 9 as the cut-off. Cronbach’s α for the scale is 0.74.14,15

Analytic Approach
Data entry was done in MS Excel 2010 and statistical analysis was accomplished by SPSS version 24 using both descriptive and inferential statistics. Chi-square, t-test/Mann–Whitney, correlation, and regression were used, and a p-value of <0.05 was considered significant. Subjects were categorized into two groups based on the presence or absence of headaches after N95 mask usage.

Results
The total number of participants who took part in the study was 78 (38 male and 40 female), with a mean age of 27.85 (SD ± 6.54). Out of 57 doctors and 21 nursing officers, 41 (52.6%) wore N95 along with PPE while 37 (47.4%) wore only N95 masks. A total of 42.3% (7 males and 26 females) of the participants experienced headaches after N95 mask usage, which included 16 doctors and 17 nursing officers. Among them, 22 wore N95 masks with PPE, and 11 wore N95 masks alone. Pulsatile headache was reported in 36.4% of the participants. Participants also reported uncomfortable levels of facial sweating (88%), congestion of the nose (63.6%), and congestion of the eyes (27.3%). Associated symptoms like nausea, vomiting, and photophobia were reported in 21%, 6%, and 24.2% of the subjects with a headache. The observed frequency of specific headache subtypes was tension headache (9%), cluster headache (30.3%) unspecified headache (33.3%), and migraine type (27.2%).

Comparison of changes in heart rate and SpO2 with the usage of an N95 mask; stress scores, corona anxiety scores, and sleep scores among individuals with and without headache are represented in Table 1.

Heart rate did not change significantly before and after N95 masks use. The heart rate changes between the N95-induced headache and no headache group showed no statistical difference with t = 1.442; p = 0.153. Similarly, the comparison of percentage increase in HR before and after N95 mask use, between N95-induced headache and no headache group showed no statistical difference with t = 1.54, p = 0.127. On the other hand, the reduction of SpO2 between the N95-induced headache and no headache group showed a significant statistical difference with t = 2.672; p = 0.009 (Table 2). Headache was observed more in those wearing N95 with PPE than without PPE.

Comparison of study parameters between N95-induced headache and no headache group showed a significant statistical difference, mean perceived stress with t = 3.616; p = 0.001, mean corona anxiety with t = 3.620; p = 0.001, quality of sleep with t = 4.514; p < 0.000. All the parameters showed a higher mean value for the N95-induced headache group (Table 1).

The correlation between the study parameters among no headache group showed that there was a statistically significant relationship observed between stress and corona anxiety (r = 0.400, p = 0.006), stress and sleep quality (r = 0.583, p = 0.042), stress and reduction in heart rate (r = 0.304, p < 0.001) and corona anxiety and sleep quality (r = 0.488, p = 0.001). On the other hand, the N95-induced headache group showed that there was a positive relationship between age and sleep quality (r = 0.510, p = 0.002), age and reduction of heart rate (r = 0.405, p = 0.019), stress and corona anxiety (r = 0.478, p = 0.005), stress and sleep quality (r = 0.582, p < 0.001), stress and reduction in heart rate (r = 0.398, p = 0.022), corona anxiety and sleep quality (r = 0.441, p = 0.010), sleep quality and reduction in heart rate (r = 0.349, p = 0.046), reduction in heart rate and reduction in SpO2 (r = 0.437, p = 0.011).

Discussion
The sociodemographic profile of participants in our study is similar to other studies.16 Health care workers providing services pertaining to counseling and home isolation allocation used N95 face masks without PPE and those working in a screening area, casualty, wards, and ICU used N95 with PPE.

Stress, Anxiety, and N95 Mask use
Different scales are in use to assess COVID-19-related stress, anxiety, and depression both in the general population and in health care professionals.17-21 PSS adopted by Shokri et al. and Haque et al. in the general population of Iran and India, respectively showed higher

| Table 1: Comparison of questionnaire scores among participants who used N95 mask with and without PPE |
|-----------------------------------|-------------------------------|---------|-----------------|----------------|-----------------|-----------------|
| Scales used                      | Group included               | N     | Mean             | SD           | SE mean         | p-value         |
| Pittsburgh Sleep Quality Index (PSQI) | Without PPE                 | 37    | 7.81             | 2.69         | 0.443           | <0.2            |
|                                   | With PPE                     | 41    | 9.90             | 3.17         | 0.496           |                 |
| Perceived stress scale (PSS)     | Without PPE                 | 37    | 16.91            | 5.84         | 0.961           | <0.08           |
|                                   | With PPE                     | 41    | 20.56            | 5.16         | 0.806           |                 |
| Coronavirus anxiety scale (CAS)  | Without PPE                 | 37    | 3.16             | 3.42         | 0.563           | <0.2            |
|                                   | With PPE                     | 41    | 5.2927           | 6.19372      | 0.96730         |                 |
Hypoxemia-related Health Problems Associated with N95 Mask usage

**Table 2: Comparison of study parameters between groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>t-value</th>
<th>p-value</th>
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<tr>
<td>Change in heart rate</td>
<td>N95-induced headache</td>
<td>33</td>
<td>8.21</td>
<td>11.32</td>
<td>1.442</td>
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<tr>
<td></td>
<td>No headache</td>
<td>44</td>
<td>5.06</td>
<td>7.94</td>
<td></td>
<td></td>
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<tr>
<td>Percentage change in heart rate</td>
<td>N95-induced headache</td>
<td>33</td>
<td>10.50</td>
<td>13.36</td>
<td>1.544</td>
<td>0.127</td>
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<td></td>
<td>No headache</td>
<td>44</td>
<td>6.39</td>
<td>10.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of SpO2</td>
<td>N95-induced headache</td>
<td>33</td>
<td>2.57</td>
<td>2.41</td>
<td>2.672</td>
<td>0.009*</td>
</tr>
<tr>
<td></td>
<td>No headache</td>
<td>44</td>
<td>1.46</td>
<td>1.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage reduction of SpO2</td>
<td>N95-induced headache</td>
<td>33</td>
<td>2.60</td>
<td>2.43</td>
<td>2.629</td>
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<tr>
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<td>No headache</td>
<td>44</td>
<td>1.49</td>
<td>1.23</td>
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<td></td>
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<tr>
<td>Perceived stress</td>
<td>N95-induced headache</td>
<td>33</td>
<td>21.39</td>
<td>5.82</td>
<td>3.616</td>
<td>0.001*</td>
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<td>44</td>
<td>16.95</td>
<td>4.98</td>
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<tr>
<td>Corona anxiety</td>
<td>N95-induced headache</td>
<td>33</td>
<td>6.57</td>
<td>5.78</td>
<td>3.620</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>No headache</td>
<td>44</td>
<td>2.60</td>
<td>3.91</td>
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<td>Sleep quality</td>
<td>N95-induced headache</td>
<td>33</td>
<td>10.57</td>
<td>3.11</td>
<td>4.514</td>
<td>0.000**</td>
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<tr>
<td></td>
<td>No headache</td>
<td>44</td>
<td>7.69</td>
<td>2.53</td>
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</tr>
</tbody>
</table>

**p<0.001, *p<0.05**

stress scores in Iran than in India.22,23 Anil Kumar et al. reported a slightly lesser mean PSS score.24 However, we did not come across studies focusing on N95 mask use and stress. The mean PSS score in our study was on par with these two studies from India. A higher level of PSS score was noted in subjects who wore N95 with PPE than without PPE, pointing to the unpleasant and physically challenging vestments. The data analysis also revealed good reliability of the PSS with Cronbach’s α of 0.90.

Studies from different parts of the world suggest the prevalence of anxiety related to coronavirus ranges between 11.3% and 50%.22,23 We observed a mean Corona anxiety score (CAS) of 6.7 in subjects wearing N95 with PPE, which was much lesser than the cut-off of 9 observed by Lee et al.34 Low CAS among N95 mask users26 with these two studies from India. A higher proportion of participants with a history of preexisting headache was in line with both the studies. Regarding subtyping of headache, in comparison with a similar study,11 we observed a very less proportion of tension-type headache (9% vs 54%), but a higher level of cluster headache (30.3% vs nil) unspecified pain (33.3% vs 13.9%) and an equal number of migraine type (27.2% vs 31%). Chow suggested headache as a confluent symptom due to altered physical and psychological health.17 Physical factors like hypoxia, hypercapnia, and physical compression and psychological factors like stress and sleep disturbances contribute to the development of headaches among N95 mask users.

### Changes in Heart Rate and SpO2 with N95 use

We observed an increase in heart rate after N95 mask use which was in concordance with the available literature.6,26,27 To our knowledge, no study compared the use of N95 masks and their effects on heart rate in a clinical setting and ours would be the first of its kind in India. Though Kim et al. observed an increase in heart rate and respiratory rate but didn’t find a significant reduction in SpO2 after the use of N95 masks.26 We used a noninvasive method of surface detection of SpO2 and our results were in line with the seminal work done by Kao et al. who used invasive techniques. They demonstrated a fall in partial pressure of oxygen in the arterial blood (PaO2) after N95 mask use.28 Tong et al. in their study on pregnant health care workers found reduced expired oxygen concentration by 3.2% and it had been proposed that increased resistance during breathing through N95 mask can cause fall in arterial partial pressure of oxygen and thereby reduce SpO2.29 Decreased SpO2 stimulates the regulatory mechanisms that cause a reflex increase in respiratory rate and heart rate.

### Headache and N95 use

In the current study, 42.3% experienced headaches after COVID-19 duty and 29.5% of them attributed it to N95 use, similar to Lim et al.11 Higher proportion (81%) of headaches was reported by Ong et al., where 53% attributed headache to N95/PPE use30 The proportion of participants with a history of preexisting headache was in line with both the studies. Regarding subtyping of headache, in comparison with a similar study,11 we observed a very less proportion of tension-type headache (9% vs 54%), but a higher level of cluster headache (30.3% vs nil) unspecified pain (33.3% vs 13.9%) and an equal number of migraine type (27.2% vs 31%). Chow suggested headache as a confluent symptom due to altered physical and psychological health.17 Physical factors like hypoxia, hypercapnia, and physical compression and psychological factors like stress and sleep disturbances contribute to the development of headaches among N95 mask users.

### Sleep Quality and N95 Mask

High anxiety, depression, stress, and insomnia were observed among health care workers involved in COVID-19 patient care. The current study demonstrates a compromised sleep quality with the usage of an N95 mask that is comparable to the available literature.10,32

In our study, those who experienced headaches fared worse (mean PQSI = 10.57 ± 3.11), suggesting the impact of headaches on sleep quality. Considering the multitude of factors contributing to poor sleep quality, compromised psychological health in the form of anxiety, and physiological derangements due to hypoxia-induced sympathetic drive, we arrive at the positive association of prolonged usage of N95 masks with headache in our study participants.

### Conclusion

From the discussion, it would be prudent to conclude that apart from anxiety due to coronavirus, prolonged N95 mask usage could affect the health care workers by virtue of physiological alterations due to hypoxia.

### Study Limitations

The sample size was small hence it could not represent the entire picture of the country. The bias and limitations associated with the snowball sampling technique exist in the study.

### Recommendations

Significant discomfort due to N95 mask use is observed in those who wear it for long hours continuously. Headache, change in heart rate and SpO2 developed due to prolonged mask usage can be prevented by restricting its use to less than four hours duration at a stretch. Adequate hydration could also help in minimizing headaches. A well-fitting N95 face mask would be recommended to avoid local skin changes due to friction.33,34
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REFERENCES


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1. J. Am Coll Cardiol 2021 Mar; 77 (10) 1300-1301 CV: Cardiovascular
COVID-19: Clinical Course and Outcome of hospitalized Hemodialysis Patients: Single-center Experience

Maulin Shah1*, Mital Parikh2, Samir Patel3, Vivek Kute4, Punam Bhende5, Jaishree Ganjiwale6, Krushan Yajnik7, Utkarsh Shah8, Jyoti Mannani9, Bhalendu Vaishnav10

Received: 05 December 2022; Accepted: 17 November 2022

ABSTRACT

Background: There is a paucity of data regarding the consequences of coronavirus disease 2019 (COVID-19) infection in patients with maintenance hemodialysis (MHD). Our objective was to identify the clinical manifestations and prognostic factors and to assess the impact of treatment schemes on the outcome.

Materials and methods: Here we present retrospectively collected data from medical records of patients on MHD hospitalized with COVID-19 infection from 1st June to 30th November 2020.

Result: Around 69 patients were admitted with a median age of 51 years. About 81% had hypertension, 41% had diabetes, and 24% had body mass index (BMI) ≥ 23 kg/m². Of all who died, 73.33% had dialysis vintage of <12 months (p = 0.06). Common presenting symptoms were fatigue (67%), fever (58%), cough (42%), and dyspnea (35%). Milder, severe, and critical disease was found in 35, 45, and 20% of patients, respectively. About 54 patients were living 4 weeks after discharge. Around 15 patients died, that includes all who received invasive ventilatory support. Nonsurvivors were older and had lower oxygen saturation on admission, lower hemoglobin (Hb), and worst lactate dehydrogenase (LDH), interleukin (IL)—6, and D-dimer values than survivors, which were statistically significant. Use of remdesivir and anticoagulant improves chances of survival (p-value 0.035 and 0.034, respectively)

Conclusion: About one-third of patients had mild disease. Those with critical disease displayed high mortality. Older age, male gender, short dialysis vintage, lower oxygen saturation on admission, anemia, lymphopenia, higher inflammatory markers (except C-reactive protein (CRP)), bilateral lung opacity, and requirement of the mechanical ventilator are poor prognostic factors. CRP, ferritin, and lymphopenia are not good prognostic markers unlike in the general population. These findings need to be verified in larger cohorts.

INTRODUCTION

In the 21st century, the world has faced outbreaks caused by three coronaviruses—severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, the Middle East respiratory syndrome coronavirus in 2012, and SARS-CoV-2 in 2019. SARS-CoV-2 has surpassed the previous two viruses in terms of incidence and global impact.1 It has led to >516 million infections and over 6 million deaths worldwide till now. India has the second highest number of COVID-19 confirmed cases just after the United States (US) (43 million COVID-19 confirmed cases) with nearly 5,24,000 deaths.2

End-stage renal disease (ESRD) patients are more susceptible to COVID-19 infection and its complications. This is due to coexisting multiple comorbid conditions like diabetes, hypertension, obesity, cardiovascular disease, stroke, and many more, which are themselves risk factors for COVID-19, independently along with chronic kidney disease (CKD) status.3,4 Uremic patients also have impaired immune function as well as malnutrition which increases their vulnerability to this deadly virus. Still, early reports from Wuhan, China, showed that the incidence of COVID-19 was lesser than expected, with potentially a milder course and good outcome in MHD patients.5 Data from Spain suggested high mortality in hospitalized dialysis patients.6 Only a few studies have been published recently regarding the impact of COVID-19 on MHD patients in India.7-9 Indian CKD patients are younger than those of the developed world and are comprised of males predominantly.10 Still, mortality in this group is high with COVID-19 infection. Home hemodialysis and peritoneal dialysis are not practiced much in India. Most of the patients prefer in-center hemodialysis. They usually utilize public transportation to reach the dialysis center. Moreover, dialysis centers are overcrowded. So, it’s difficult to maintain social distancing. These factors attribute to higher infection rates too.

OBJECTIVES

• To describe the clinic-demographic profile of ESRD patients with COVID-19 infection.
• To analyze clinical presentation, disease course, and outcome of COVID-19 infection in this patient population.
• To find out the association between epidemiological, clinical, laboratory, and radiological findings.
• To identify prognostic factors, and to assess the impact of treatment schemes on the outcome.

MATERIALS AND METHODS

It was a retrospective, observational, analytical single-center study carried out in COVID-19 designated center located in Central Gujarat, India.

Inclusion Criteria

All patients with ESRD on regular hemodialysis treatment admitted with COVID-19 infection from 1st June to 30th November 2020 were included in our study.

Exclusion Criteria

Those patients whose complete data is not available in hospital records are excluded from the study.

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Case Definition
Diagnosis of COVID-19 was made based on clinical history (presence of fever, cough, shortness of breath or presence of anosmia, ageusia/dysgeusia—any one symptom), radiological findings compatible with COVID-19, and laboratory confirmation of positive rapid antigen test or positive SARS-CoV-2 nucleic acid by polymerase chain reaction (PCR) testing on a clinical specimen (nasopharyngeal and oropharyngeal swabs and bronchoalveolar lavage) as per Indian council of medical research advisory on testing.

Explanation
Every patient admitted with clinical suspicion of COVID-19 infection was subjected to a rapid antigen test and reverse transcription (RT)—PCR (if the former was negative) of the nasopharyngeal and oropharyngeal swab. RT-PCR test was repeated if the first test was negative. In the instances, when rapid antigen and two RT-PCR swabs were negative, but clinical and radiological suspicion was high, they were considered positive cases and treated accordingly. All patients were subjected to laboratory tests like complete blood count, renal function test, electrolytes, liver function test, inflammatory markers (ferritin, LDH, D-dimer, CRP, IL-6), and radiological tests like chest radiogram. Lab parameters including inflammatory markers were repeated every 48–72 hours. Anticoagulant (conventional unfractionated heparin) was given to all admitted patients either prophylactic or therapeutic dose as per recommendation by the European Society of Cardiology for the general population with COVID-19 infection.11 Methylprednisolone was administered (40 mg bis in die) to all who require oxygen supplementation.12,13 Remdesivir injection (powder form—standard 5-day course) was offered to those who have persistent high spiking fever for >72 hours, hypoxia requiring oxygen supplementation, and/or severe radiological findings after taking informed written consent from patient’s kin where consent was negative.14–16

All were supplemented with oxygen whenever saturation drops below 92% by nasal prongs, venturi mask, non-rebreather mask, high flow nasal cannula, bilevel positive airway pressure (BiPAP), and invasive ventilation in that order to maintain adequate oxygenation. All were subjected to intermittent hemodialysis every alternate day to avoid any adverse impact of hyperkalemia volume overload or uremia on the overall outcome. Those who had hemodynamic instability were offered prolonged intermittent renal replacement therapy/sustained low-efficiency dialysis (PIRRT/SLED). Those who were afebrile for 72 hours and those who were maintaining adequate oxygen saturation for more than 24 hours and declining inflammatory markers were deemed fit for discharge. They were advised to do intermittent hemodialysis in an isolation day care dialysis facility till their swab become negative. Their RT-PCR swabs were taken at the end of the 2nd, 3rd, and 4th week till they become negative.

Data Source
Demographic data, clinical data, details of their hospital course, outcome, and follow-up till 4 weeks were obtained from the medical record. All methods were carried out in accordance with relevant guidelines and regulations. We used the Strengthening the Reporting of Observational Studies in Epidemiology checklist while writing our report.17

Ethical Approval
This study was approved by the Institutional Ethical Committee-2, H M Patel Center for Medical Care and Education, Karamsad, Gujarat, India, and also registered under the Clinical Trial Registry of India. As the study involved the collection of data retrospectively from electronic medical records of the hospital with the maintenance of privacy and confidentiality, waiver of informed consent was granted by the abovementioned ethical committee.

Statistical Analysis
Statistical analysis was done with IBM Statistical Package for the Social Sciences statistics for Windows, version XX. Quantitative variables are described with their mean ± standard deviation or median and interquartile range. Qualitative variables are summarized with their frequency distribution. Baseline characteristics of patients who died vs those who are still living were compared using the chi-squared test. Lab parameters/quantitative variables were compared with an independent t-test. We also used descriptive statistics to present the characteristics of those who received mechanical ventilation, those who received BiPAP, and those who died with a “do not intubate” consent.

RESULTS
We found 69 such patients fulfilling the inclusion criteria for our study. The median age of patients was 51 years. The lowest age was 19 years and the highest was 81 years. The deceased was older than the survivors (60 years [32–68] vs 51 years [19–81] p-value 0.024]. Males constitute 69.56% of all subjects and 73% of nonsurvivors. Out of 69 patients, 56 patients (81%) had hypertension, 28 patients (41%) had diabetes, and 17 patients (24%) had BMI ≥ 23 kg/m2 (as per Indian obesity classification, BMI ≥ 23 is considered overweight).18 Eight had ischemic heart disease (12%), three had underlying chronic lung disease (4.3%), one (1.44%) had the liver parenchymal disease, and one (1.44%) had metastatic malignancy. Four patients had failed renal allograft. A total of five patients were on some kind of immunosuppressive medications that include low-dose steroid and mycophenolate mofetil (MMF) in one patient with anti-neutrophil cytoplasmic antibodies vasculitis.

Table 1 shows detailed demographic, clinical, and radiological characteristics of all subjects.

A total of 28 out of 69 patients (40.58%) had dialysis vintage <12 months while 11 out of 15 patients (73.33%) who succumbed had dialysis vintage of <12 months (p = 0.06). Among all, 41 subjects had arteriovenous (AV) fistula as vascular access, 23 had temporary uncuffed double-lumen catheters and five patients had tunnel cuffed catheters as vascular access.

Overall common presenting symptoms were fatigue (67%), fever (58%), cough (42%), dyspnea on exertion or rest (35%), and other symptoms (9%). It was notable that 10 patients (14%) had fatigue/malaise alone as a presenting feature while three patients had fever and cough alone as presenting symptoms. A total of 62 patients were confirmed COVID-19 positive while seven patients had high clinical and radiological suspicion of COVID-19 (both rapid antigen and two successive RT-PCR negative reports; hence treated as COVID-19 positive). A total of 23 patients had bilateral radiological opacity, 21 had unilateral opacity, 21 had normal chest radiogram and four patients had other radiological abnormalities (that includes pulmonary edema and pleural effusion). The mean oxygen saturation on admission was 92 ± 7%. Around 24 patients did not require oxygen support at all at any time after COVID-19 diagnosis. Milder disease (no or mild pneumonia) was found in 35% of patients. Severe disease (eg, with dyspnea, hypoxia, or >50% lung involvement on imaging within 24–48 hours) was in 45% of patients while critical disease (eg, with respiratory failure, shock, or multiorgan dysfunction) was observed in 20% of patients.19,20 Among 45 patients who require oxygen support during a hospital stay, four had oxygen saturation >95% at the time of admission and later they require a variable amount of
COVID-19: Clinical Course and Outcome

A total of 56 patients were discharged with a median time from admission to discharge being 10 days (1–38). Out of those who were discharged, 54 patients were living for 28 days. Two patients died at home after discharge possibly due to coronary or thromboembolic events and not due to respiratory failure, despite prescribing oral anticoagulant therapy to them. A total of 10 subjects who received mechanical ventilator support and two subjects on BiPAP and one on a non-rebreather mask succumbed due to acute respiratory distress syndrome. Unfortunately, it was not possible

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n)</th>
<th>Survivors (at 28 days) (n)</th>
<th>Nonsurvivors (death in hospital or after discharge within 4 weeks) (n)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>69</td>
<td>54 (78.26%)</td>
<td>15 (21.73%)</td>
<td></td>
</tr>
<tr>
<td>Age (In years)</td>
<td>51.89 ± 14.35</td>
<td>50.22 ± 15.16</td>
<td>57.26 ± 10.08</td>
<td>0.024</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.987</td>
</tr>
<tr>
<td>Male</td>
<td>48 (69.56%)</td>
<td>37(68.51%)</td>
<td>11(73.33%)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>4 (2–8)</td>
<td>4 (2–8)</td>
<td>4 (2–6)</td>
<td>0.120</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56</td>
<td>47</td>
<td>9</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28</td>
<td>19</td>
<td>9</td>
<td>0.136</td>
</tr>
<tr>
<td>BMI ≥ 23 kg/m²</td>
<td>17</td>
<td>16</td>
<td>1</td>
<td>0.093</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0.186</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0.117</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Postrenal transplant</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0.570</td>
</tr>
<tr>
<td>On immunosuppressant medication (steroid/MMF)</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>Dialysis vintage</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>41(59.42%)</td>
<td>34(68.51%)</td>
<td>7(26.67%)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>28</td>
<td>17(31.49%)</td>
<td>11(73.33%)</td>
<td></td>
</tr>
<tr>
<td>Clinical presentation on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>40 (58%)</td>
<td>30</td>
<td>10</td>
<td>0.559</td>
</tr>
<tr>
<td>Cough</td>
<td>29 (42%)</td>
<td>19</td>
<td>10</td>
<td>0.04</td>
</tr>
<tr>
<td>Dyspnoea (on exertion/rest)</td>
<td>29 (42%)</td>
<td>20</td>
<td>9</td>
<td>0.144</td>
</tr>
<tr>
<td>Malaise/fatigue</td>
<td>46 (69%)</td>
<td>39</td>
<td>7</td>
<td>0.119</td>
</tr>
<tr>
<td>Other (gastrointestinal symptoms/altered mentation/other system involvement)</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1.000</td>
</tr>
<tr>
<td>Fever alone</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0.527</td>
</tr>
<tr>
<td>cough alone</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0.527</td>
</tr>
<tr>
<td>Fatigue alone</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0.103</td>
</tr>
<tr>
<td>Oxygen saturation on admission (%)</td>
<td>92.33 ± 7.52</td>
<td>93.59 ± 5.4</td>
<td>87.8 ± 11.58</td>
<td>0.078</td>
</tr>
<tr>
<td>Dialysis access</td>
<td></td>
<td></td>
<td></td>
<td>0.384</td>
</tr>
<tr>
<td>AV fistulae</td>
<td>41</td>
<td>34</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Temporary uncuffed catheter</td>
<td>23</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Tunnelled cuffed catheter</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dialysis session during admission</td>
<td>6 (1-14)</td>
<td>7 (1-14)</td>
<td>4 (1-7)</td>
<td></td>
</tr>
<tr>
<td>Radiological findings on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral opacity</td>
<td>21</td>
<td>18</td>
<td>3</td>
<td>0.527</td>
</tr>
<tr>
<td>Multifocal/bilateral opacities</td>
<td>23</td>
<td>11</td>
<td>12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other finding</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No acute findings</td>
<td>21</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Days of hospitalization</td>
<td>9 (1–38)</td>
<td>10 (1–38)</td>
<td>7 (3–12)</td>
<td>0.126</td>
</tr>
</tbody>
</table>

Bold values are statistically significant values.
to extubate any of the intubated patients. Median time from admission to in-hospital death was 6.5 days (3–14). Median time to become RT-PCR negative among survivors was 21 days (14–33). Table 3 reveals relevant laboratory data of all patients, survivors, and nonsurvivors. Total of 28 patients received remdesivir, out of which 18 survived. Around 14 out of 55 patients who received corticosteroids could not make up eventually. A total of 42 patients received a therapeutic dose of anticoagulation with unfractionated heparin out of which 29 survived (Table 4).

**Discussion**

Patients with ESRD due to their immunocompromised status and underlying chronic inflammatory status are the most vulnerable group. Studies from European countries and the US show high mortality. On the contrary study from China reveals milder nature of the illness. We report our experience of COVID-19 illness in 69 end-stage kidney failure patients. In our study median age of all COVID-19-positive ESRD patients was 51 years which is similar as the general population.\(^2\), \(^2\) Two studies from California noted a more atypical presentation of COVID-19 in dialysis patients while a study from New York described typical symptoms of COVID-19 in dialysis patients the same as the general population.\(^2\), \(^2\)

We found malaise/fatigue (66%) as a predominant presenting symptom in this group followed by fever (58%), cough (42%), and shortness of breath (42%). This is somewhat different than the general population but consistent with findings reported by findings by Wang et al., Yiqiong et al., and Goicoechea et al. that could be expected by possible immune dysfunction in end-stage renal failure patients.\(^2\),\(^2\)\(^5\),\(^2\)\(^4\) Our study shows 41% of patients with dialysis vintage <1 year. Among nonsurvivors, 73.3% of patients having dialysis vintage <1 year while 31.5% of patients were having dialysis vintage <1 year among survivors (p-value 0.006). Goicoechea et al. reported a median dialysis vintage of 29 months which is contradictory to our findings.\(^2\)\(^1\) Many of our patients were initiated on MHD within the few preceding months and thus have temporary uncuffed dialysis catheters as vascular access. This can be a possible reason for higher mortality in this group. Our study revealed nonsurvivors were sicker with lesser oxygen saturation on presentation (87.8 ± 11.58) as compared to survivors (93.59 ± 5.4) (p-value 0.078). About 11 out of 54 patients who are living and 12 out of 15 who died had multilocal/bilateral radiological opacity on chest radiogram done at the time of admission (p = <0.001). Deceased group had lower Hb and higher total leucocyte count as compared to survivors (p-value 0.013 and 0.036, respectively). Those who died had lower lymphocyte count as compared to those who are still living (p-value 0.183). Nonsurvivors had the worst peak values of several inflammatory markers including LDH, IL-6, and D-dimer than survivors (p-values 0.008, 0.019, and 0.038, respectively). This is similar to the study from Valeri et al., Jin et al., and other studies from the general population which is consistent with our pathophysiologic understanding of COVID-19.\(^2\),\(^2\),\(^2\)\(^5\) On the contrary, we could not find a similar association for serum ferritin between two groups. This is contrasting to studies in the general population where raised ferritin is a bad prognostic factor and associated with critical

**Table 2:** Mode of ventilation

| Requirement of O₂ support | 45 (65.28%) | No requirement of O₂ support | 24 (34.78%) | Invasive ventilatory support | 10 | Noninvasive ventilatory support | 4 | NP/FM/NRBM/HFNO | 31 |

FM, face mask; HFNO, high flow nasal oxygen; NP, nasal prong; NRBM, non-rebreather mask

**Table 3:** Lab parameters of patients with dialysis-dependent ESRD and COVID-19 admitted to a single centre in Shree Krishna Hospital, Karamsad, Gujarat, India

<table>
<thead>
<tr>
<th>Lab findings</th>
<th>All</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dL)</td>
<td>9.7 ± 2.49</td>
<td>10.08 ± 2.48</td>
<td>8.36 ± 2.13</td>
<td>0.013</td>
</tr>
<tr>
<td>Total Leucocyte count (/mm³) x 10⁶</td>
<td>12.22 ± 6.65</td>
<td>11.36 ± 5.41</td>
<td>15.4 ± 9.51</td>
<td>0.036</td>
</tr>
<tr>
<td>Lymphocyte count (/mm³)</td>
<td>2146.32 ± 1633</td>
<td>2271.64 ± 1774.14</td>
<td>1567.4 ± 748.09</td>
<td>0.183</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>119.33 ± 96.82</td>
<td>105.52 ± 99</td>
<td>171.98 ± 105</td>
<td>0.183</td>
</tr>
<tr>
<td>LDH (international unit/L)</td>
<td>405 ± 203.06</td>
<td>371.37 ± 192.08</td>
<td>527.53 ± 203.29</td>
<td>0.008</td>
</tr>
<tr>
<td>D-dimer (L/mL)</td>
<td>405 ± 203.06</td>
<td>371.37 ± 192.08</td>
<td>527.53 ± 203.29</td>
<td>0.008</td>
</tr>
<tr>
<td>Ferritin (µg/mL)</td>
<td>1282.71 ± 540.63</td>
<td>1338.78 ± 494.62</td>
<td>1080.82 ± 661.55</td>
<td>0.177</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>58.09 ± 94.87</td>
<td>44.06 ± 64.12</td>
<td>108.8 ± 156.98</td>
<td>0.019</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.80 ± 0.55</td>
<td>2.87 ± 0.55</td>
<td>2.54 ± 0.46</td>
<td>0.040</td>
</tr>
</tbody>
</table>

Bold values are statistically significant values

**Table 4:** Drugs received by patients with dialysis-dependent ESRD and COVID-19 admitted to a single-center in Shree Krishna Hospital, Karamsad, Gujarat, India

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All</th>
<th>Survivors (54)</th>
<th>Nonsurvivors (15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>28 (40.58%)</td>
<td>18 (33.33%)</td>
<td>10 (66.66%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>55 (79.71)</td>
<td>41 (75.92)</td>
<td>14 (93.33%)</td>
<td>0.274</td>
</tr>
<tr>
<td>Anticoagulation (conventional heparin) therapeutic dose</td>
<td>42 (60.86%)</td>
<td>29 (53.70%)</td>
<td>13 (86.66%)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

\(\text{CRP} = \text{C-reactive protein} \)
COVID-19: Clinical Course and Outcome

References


Spectrum of Disorders associated with Tetany

Gouranga Santra*

Received: 16 June 2022; Revised: 17 August 2022; Accepted: 23 September 2022

ABSTRACT

Introduction: Awareness regarding the etiological spectrum of tetany is poor among physicians. Because of poor awareness, tetany is underdiagnosed and undertreated.

Materials and methods: Databases like PubMed, PubMed Central, Scopus, and Google Scholar are searched to identify peer-reviewed articles on tetany. Case reports, case series, and original articles are analyzed to identify different causes of tetany prevalent in the community. Different causes found are analyzed and tabulated, and finally, a flowchart is made on the approach for diagnosing different underlying pathologies of tetany.

Results: Both metabolic and respiratory alkalosis are important causes of tetany because of reduced ionized calcium levels. Gitelman syndrome (GS) is associated with metabolic alkalosis, hypokalemia, hypomagnesemia and hypocalciuria, and frequently causes normocalcemic tetany. Recurrent vomiting and primary hyperaldosteronism also cause tetany due to metabolic alkalosis. Hyperventilation syndrome (HVS) leads to respiratory alkalosis and is a frequent cause of tetany. Hyperventilation-induced tetany is also seen after spinal anesthesia and in respiratory disorders like asthma. Vitamin D deficiency (VDD), primary hypoparathyroidism, and pseudohypoparathyroidism (PHP) (1a, 1b, and 2) cause hypocalcemic tetany. Hypomagnesemia causes hypocalcemia and tetany due to peripheral parathyroid hormone resistance and impaired parathyroid hormone secretion. Drugs causing tetany include bisphosphonates, denosumab, cisplatin, antiepileptics, aminoglycosides, diuretics, etc. Tetany is also seen in acute pancreatitis, dengue, falciparum malaria, hyperemesis gravidarum, tumor lysis syndrome (TLS), massive blood transfusion, etc.

Conclusion: The spectrum of disorders associated with tetany is diverse. Awareness of different causes will help early and proper diagnosis of tetany.

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INTRODUCTION

Tetany is a common clinical presentation in the general medical ward and in the emergency department. But awareness of the etiological spectrum of tetany is poor among clinicians despite its high frequency. Because of poor awareness, tetany is underdiagnosed, underinvestigated, and undertreated. Original research articles showing the prevalence and incidence of different causes of tetany in a comprehensive way are rare. Anecdotal case reports of tetany due to different causes are found in literature. Without proper idea and awareness of the spectrum of disorders associated with tetany in a community, diagnosis of tetany is likely to be missed.

PURPOSE OF REVIEW

This review article will mention and analyze different causes of tetany, which are usually prevalent in the community. The intention of writing this article is to make clinicians aware of the different causes of tetany. A flowchart is created on the approach for diagnosing different underlying pathologies of tetany, which will help clinicians to manage tetany cases properly.

MATERIALS AND METHODS

Databases like PubMed, PubMed Central, Scopus, and Google Scholar are searched to identify peer-reviewed articles on tetany. Case reports, case series, and original articles are included. Keywords searched are tetany, hypocalcemia, hypomagnesemia, hypokalemia, GS, Bartter syndrome (BS), alkalosis, vomiting, hyperventilation, hypoparathyroidism, etc. Searching was done with combinations of two keywords like tetany and metabolic alkalosis, tetany and GS, tetany and hyperventilation, tetany and VDD, tetany and hypokalemia, tetany and hypomagnesemia, tetany and hypoparathyroidism, etc. Different causes of tetany found are analyzed and tabulated, and finally, a flowchart is made on the approach for diagnosing tetany cases.

Epidemiology

Tetany is seen throughout the world and involves all ages, sexes, and races. As tetany is a symptom or sign, its prevalence and incidence depend on the vast number of underlying disorders. Geographic location influences occurrences of tetany as per underlying disorders. A higher incidence of tetany due to GS is seen in Japan, China, and possibly in some regions of India because of the higher prevalence of GS in Asia. Tropical climate, especially in summer, favors acute gastroenteritis and recurrent vomiting, occasionally leading to tetany. Young females throughout the world have a high incidence of tetany due to HVS. VDD is prevalent throughout the world, even in sunny countries, despite supplementation. But tetany due to severe VDD is rare now. It is usually seen in infants exclusively breastfed or infants born to mothers with VDD, or in adults with malabsorption disorders. Morbidity and mortality depend on the severity of the disorders associated with tetany. Tetany is also seen in animals. A form of tetany called grass tetany is prevalent in ruminants in the US, Europe, Australia, and New Zealand because of seasonal magnesium deficiency in the grass.

Tetany Presentation

Tetany is due to neuromuscular irritability from metabolic derangements. It is characterized by circulatory numbness, muscle twitching, cramps, paraesthesia of hands and feet, and carpopedal spasm. In severe cases, tetany patients may have laryngeal stridor, generalized muscle cramps, rhabdomyolysis, myocardial dysfunction, seizure, and coma. Tetany may be transient or chronic. It may be latent or overt. Latent tetany (spasmophilia) is more common than overt tetany. Trousseau sign and Chvostek sign unmask latent tetany. Trousseau’s sign is elicited as a carpopedal spasm induced by ischemia secondary to inflation of the sphygmomanometer cuff over the brachial artery 20 mm Hg above systolic blood pressure for 3 minutes (Figs 1 and 2). Chvostek sign is characterized by twitching of circulatory muscles with tapping on the facial nerve below the zygomatic process 2 cm anterior to the
Spectrum of Disorders associated with Tetany
due to low ionized calcium levels even in the
levels. Thus, tetany may occur in alkalosis
to albumin and decreases ionized calcium
on plasma pH. Acidosis decreases calcium
binding to albumin and thus increases ionized
on groups of albumin are responsible for this

Pathophysiology, Electrolytes, and Acid-base Balance
Serum calcium level is expressed as total serum calcium, corrected serum calcium, and ionized calcium. Total calcium concentration in plasma is 8.7–10.2 mg/dL (2.2–2.6 mmol/L). Any reduction below this range is called hypocalcemia. However, a reduction in total serum calcium can result from a decrease in albumin secondary to liver disease, nephrotic syndrome, or malnutrition, and it is corrected as per serum albumin level [corrected serum calcium = measured total Ca (mg/dL) + 0.8* (4.0 – serum albumin (g/dL))]. About 50% of plasma calcium is ionized, 40% is bound to proteins (90% of which is bound to albumin), and the remaining 10% of total serum calcium is bound to anions (e.g., phosphate, carbonate, citrate, lactate, and sulphate). Normal ionized calcium level is 1.12–1.32 mmol/L (4.5–5.3 mg/dL). A decrease in ionized calcium is specifically important for the causation of tetany, as it is the biologically active component.

Each gram of albumin binds 0.8 mg/dL of calcium at a plasma pH of 7.4. The carboxyl groups of albumin are responsible for this binding, and this binding is highly dependent on plasma pH. Acidosis decreases calcium binding to albumin and thus increases ionized calcium. It is protective of tetany. In contrary to this, alkalosis increases calcium binding to albumin and decreases ionized calcium levels. Thus, tetany may occur in alkalosis due to low ionized calcium levels even in the presence of normal total serum calcium. In patients of renal failure with hypocalcemia, rapid correction of acidosis or development of alkalosis may also trigger tetany. Both metabolic or respiratory alkalosis precipitate tetany by reducing ionized calcium levels. Apart from hypocalcemia, hypomagnesemia, and hypokalemia also increase neuromuscular irritability.

Different Etiologies
Original articles, case series, and case reports reveal different disorders which can present with tetany. Table 1 shows different causes of tetany found in literature.

The spectrum of disorders associated with tetany is diverse. Metabolic and respiratory alkalosis are responsible for a majority of cases of tetany. Among metabolic alkalosis, GS is found as an important cause with tetany. It is associated with metabolic alkalosis, hypokalemia, hypomagnesemia, and hypocalcemia. Total serum calcium is usually normal. However, hypocalcemic tetany is also reported in GS. In a study by Fujimura et al., 32.6% of cases with genetically proven GS had tetany. Among them, three were infants. They had decreased levels of serum calcium and increased levels of alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH). Their serum levels of 25-hydroxy (OH) cholecalciferol were markedly reduced (below 8 ng/mL). In an anecdotal case report, malabsorption disorders like celiac disease presented with tetany due to hypocalcemia and VDD. Malabsorption disorders, malnutrition, decreased sunlight exposure, and urbanization cause VDD. Indians are especially prone to VDD. VDD causes hypocalcemia and tetany if it is severe enough.

Hypoparathyroidism is associated with hypocalcemia, hyperphosphatemia, and low or inappropriately normal iPTH, and it causes neuromuscular irritability, myalgias, muscle spasms, and in extreme cases, tetany. Primary hypoparathyroidism may be iatrogenic (neck surgery and radiation therapy), autoimmune and congenital, or idiopathic. Tetany is commonly seen in iatrogenic hypoparathyroidism after

Fig. 1: Trousseau’s sign elicited in a patient with latent tetany due to recurrent vomiting

Fig. 2: Trousseau’s sign elicited in a patient with latent tetany due to recurrent vomiting

Oke et al. reported a case of a 4-year-old boy presenting with a history of carpopedal spasms following excessive vomiting. He had electrolyte derangement with metabolic alkalosis, hypokalemia, and decreased ionized calcium. In a case series by Richardson et al., tetany was caused by surreptitious vomiting leading to metabolic alkalosis, and BS was excluded by low urinary chloride level. Primary hyperaldosteronism, a rarer cause of metabolic alkalosis, causes tetany in the presence of hypertension and hypokalemia.
Spectrum of Disorders associated with Tetany

<table>
<thead>
<tr>
<th>S/N</th>
<th>Etiologies of tetany</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metabolic alkalosis—GS, BS, recurrent vomiting, hyperemesis gravidarum, and primary hyperaldosteronism</td>
</tr>
<tr>
<td>2</td>
<td>Respiratory alkalosis—HVS and spinal anesthesia, asthma</td>
</tr>
<tr>
<td>3</td>
<td>Hypoparathyroidism—iatrogenic (e.g., thyroid surgery), autoimmune, idiopathic, DGS, parathyroid apoplexy, hungry bone syndrome, maternal primary hyperparathyroidism (late neonatal tetany due to transient hypoparathyroidism), APS-1, and APS-2</td>
</tr>
<tr>
<td>4</td>
<td>Pseudohypoparathyroidism—PHP 1a (with AHO), PHP 1b, and PHP 2</td>
</tr>
<tr>
<td>5</td>
<td>VDD—malnutrition, malabsorption disorders (e.g., celiac disease), decreased sunlight exposure</td>
</tr>
<tr>
<td>6</td>
<td>Hypomagnesemia (e.g., chronic alcoholism, malabsorption disorders, intestinal lymphangiectasia, KCNA1 gene mutation, renal magnesium wasting (like GS/BS), drugs etc.)</td>
</tr>
<tr>
<td>7</td>
<td>Drug induced—anti-epileptics, bisphosphonates, denosumab, cisplatin, aminoglycosides, capreomycin, bevacizumab, PPIs, diuretics, etc.</td>
</tr>
<tr>
<td>8</td>
<td>Miscellaneous—acute pancreatitis, dengue, falciparum malaria, phosphate enema, massive blood transfusion, TLS (chemotherapy-induced or spontaneous), osteoblastic metastasis, short bowel syndrome, Crohn’s disease, Camurati-Engelmann disease, Sjogren’s syndrome, etc.</td>
</tr>
</tbody>
</table>

Abbreviations—GS, Gitelman syndrome; BS, Bartter syndrome; VDD, vitamin D deficiency; TLS, tumor lysis syndrome; PPI, proton pump inhibitor; APS, autoimmune polyglandular syndrome; PHP, pseudohypoparathyroidism for the prediction of postoperative tetany. 

<table>
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</tbody>
</table>

Abbreviations—GS, Gitelman syndrome; BS, Bartter syndrome; VDD, vitamin D deficiency; TLS, tumor lysis syndrome; PPI, proton pump inhibitor; APS, autoimmune polyglandular syndrome; PHP, pseudohypoparathyroidism

thyroid surgery, and it is either transient or permanent. 

Autoimmune and idiopathic hypoparathyroidism are well-known but rare causes of hypocalcemic tetany. Thyroid surgery is a major cause of iatrogenic hypoparathyroidism despite major surgical advances. Transient hypocalcemia is common after thyroidectomy (range 19–38%). Thyroid surgery occurs in 0–6% of cases after total thyroidectomy. 

Hypoparathyroidism is due to unintentional removal or damage of parathyroid glands or their blood supply during thyroidectomy or neck surgery. It has been noted that patients with Grave’s disease with VDD and high ALP levels are a high-risk group for postoperative tetany, and 25 (OH) vitamin D and ALP levels should be monitored before thyroidectomy. Intraoperative parathyroid hormone assay is helpful in Grave’s disease for the prediction of postoperative tetany. 

Hungry bone syndrome can cause tetany after parathyroidectomy in primary or secondary hyperparathyroidism. 

Tetany is very rarely reported with parathyroid apoplexy. 

Autoimmune hypoparathyroidism occurs in isolation or as a part of a polyglanulard endocrinopathy, usually autoimmune polyglanulard syndrome (APS-1). Hypocalcemia and tetany are also seen in APS-2, but this hypocalcemia is more likely due to malabsorption from celiac disease than hypoparathyroidism. 

DiGeorge syndrome (DGS) is a rare cause of hypocalcemic tetany due to congenital hypoparathyroidism. It results from abnormal development of third and fourth pharyngeal pouches and is characterized by varying combinations of hypoparathyroidism, cellular immunodeficiency secondary to thymic hypoplasia, congenital heart disease, and dysmorphic facial features like cleft palate. DGS, or velocardiofacial syndrome, is associated with a microdeletion on the long arm of chromosome 22 (22q11.2 deletion syndrome). Tetany is common in infancy in DGS but may occur in adults also. 

Tetany is also seen in PHP—PHP 1a, PHP 1b, and PHP 2, which are associated with hypocalcemia and elevated PTH levels because of resistance to PTH. 

Maternal primary hyperparathyroidism causing hypercalcemia during pregnancy can suppress fetal and neonatal parathyroid hormone secretion. Resultant transient hypoparathyroidism causes late neonatal hypocalcemic tetany. 

Oikonomou et al. reported a case of steroid-induced hypocalcemia with tetany in a patient with parathyroidism, who responded to intravenous calcium gluconate infusions and discontinuation of glucocorticoids. In hypoparathyroidism, impaired parathyroid hormone response to steroid-induced negative calcium balance results in severe symptomatic hypocalcemia and tetany. 

Camurati–Engelmann disease (CED), also known as progressive diaphyseal dysplasia, is a rare autosomal dominant disorder that commonly presents with skeletal pain, waddling gait, and muscular weakness. Xie et al. reported a case of CED in a 27-year-old Chinese man who presented with intermittent hypocalcemic tetany. CED was diagnosed from a genetic study and bone scintigraphy which showed abnormally increased uptake of the tracer in long bones of the upper and lower extremities as well as in the skull. Patient had thickened upper and lower extremities since childhood with similar family history. The patient had hypocalcemia and elevated ALP, but normal serum phosphate and PTH levels and tetany responded to IV calcium gluconate. 

Hypomagnesemia is due to poor dietary intake and renal or gastrointestinal loss of magnesium. Disorders associated with hypomagnesemia include chronic alcoholism, starvation, critical illnesses, malabsorption disorders, acute pancreatitis, inherited renal tubular disorders like GS and BS, and drugs like loop diuretics, proton-pump inhibitors (PPIs), aminoglycosides, amphotericin B, digitalis, cisplatin, cyclosporine, etc. 

Hypomagnesemia is an important cause of tetany. Chronic alcoholism causes tetany because of underlying hypomagnesemia. 

Intraparathyroid hypomagnesemia can cause tetany, which needs urgent intervention. 

A de novo mutation (p.Leu328Val mutation) in the potassium voltage-gated channel subfamily A member 1 (KCNA1) gene encoding the voltage-gated potassium (K+) channel Kv1.1 has been reported to cause hypomagnesemia and tetany. 

Tetany from hypomagnesemia due to intestinal lymphangiectasia has also been reported. Hypomagnesemia causes hypocalcemia by peripheral parathyroid hormone resistance. Impairment of parathyroid hormone secretion is also seen at very low serum magnesium levels (<1 mg/dL). Hypomagnesemia also causes kaliuresis leading to hypokalemia which can aggravate symptoms of tetany. 

Hypokalemia (normocalcemic) tetany is an entity in which the patient develops tetany despite normal serum-ionized calcium and magnesium levels. Selvagnesh et al. reported a case of Sjogren’s syndrome, who developed carpopedal spasm and acute quadriplegia in the presence of hypocalcemia and hyperchloremic metabolic acidosis. 

Her vitamin D, PTH, and magnesium levels were normal. The patient improved with the correction of hypokalemia and acidosis. Hypokalemia causes flaccid paralysis, so neuromuscular irritability is paradoxical. It is possible that the intra and extracellular K ratio and its transmembrane conductance determine neuromuscular irritability and tetany. Also, there may be differential effects on muscles (paralysis) and peripheral nerves (irritability). A few cases of isolated hypokalemia (normal pH, calcium, and magnesium in serum) causing tetany in the absence of alkalosis have also been reported in the literature. 

Different acute emergencies, sepsis, and miscellaneous disorders cause hypocalcemia, hypomagnesemia and acid-base disorders and, consequently, cause tetany. Acute pancreatitis is an important cause of tetany. In a study by Chhabra et al., out of 105 patients with acute pancreatitis, 37 had hypocalcemia, 

75
Spectrum of Disorders associated with Tetany

Tetany has a bad prognostic significance in acute pancreatitis. Acute pancreatitis causes tetany due to the saponification of calcium by free fatty acids, which is precipitated in areas of fat necrosis and is also dissolved or suspended in ascitic fluid. Glucagon-stimulated calcitonin release, decreased PTH secretion, and hypomagnesemia also plays role in the causation of hypocalcemia in acute pancreatitis. TCS causes the rapid development of dyselectrolytemia, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Hyperphosphatemia due to acute kidney injury in TCS causes metastatic deposition of calcium phosphate leading to hypocalcemia, and that can cause tetany. Phosphate enema causes tetany due to hyperphosphatemia and subsequent development of hypocalcemia from metastatic calcium phosphate deposits. Anecdotal case reports of tetany are seen with hyperemesis gravidarum, short bowel syndrome, Crohn’s disease, and falciparum malaria. Dengue fever may aggravate hypocalcemia of primary hypoparathyroidism and can present with tetany. Osteoblastic metastasis, for example, prostate cancer, is reported to cause hypocalcemia and tetany. Massive blood transfusion can cause tetany from an acute decrease in ionized calcium due to calcium binding with citrate, which is used as an anticoagulant in stored blood. Drugs can cause hypocalcemia, hypomagnesemia, and acid-base disorders and subsequently can lead to tetany. Different drugs causing tetany include bisphosphonates, denosumab, cisplatin, antiepileptics (e.g., phenytoin and phenobarbital), aminoglycosides, diuretics, and PPIs. Kanamycin is reported to cause Gitelman-like syndrome along with tetany. Puri et al. reported tetany in an extensively drug-resistant tuberculosis patient due to capreomycin use which was associated with hypocalcemia, hypomagnesemia, and hypocalcemia. Correction of hypomagnesemia helped to normalize calcium and K levels in the patient. Salbutamol has also been reported to cause tetany, though the mechanism is not clear. Bisphosphonate therapy causes hypocalcemia and tetany, especially in individuals with VDD. Cisplatin causes hypomagnesemia, hypokalemia, and hypocalcemia due to high urinary losses from proximal renal tubular dysfunction. High ceiling diuretic like furosemide also causes hypocalcemia, hypomagnesemia, hypokalemia, and metabolic alkalosis. Tetany has been reported in patients with surreptitious furosemide use. If such patients continue to have muscle spasms on correction of calcium and K, they should have magnesium supplementation. PP1s and H2 receptor blockers reduce gastric acid secretion and thus slow fat breakdown, which is necessary to complex calcium for absorption from the gut. Prolonged therapy with anticonvulsants causes disordered vitamin D metabolism and hypocalcemia. Phenytoin induces cytochrome P450 enzymes and enhances vitamin D catabolism. Carbamazepine-induced hypocalcemic tetany has been reported in a case of trigeminal neuralgia in the early postoperative period. Here, hypocalcemia is linked to the long-standing effect of carbamazepine on vitamin D catabolism and inhibition of cellular response to PTH. Stress-related to surgery and anesthetics aggravated the symptom. Bevacizumab, a humanized anti-angiogenic monoclonal antibody used for the treatment of colorectal cancer, can cause tetany-related symptoms by interfering with calcium metabolism. Other mechanisms may be associated with hypomagnesemia and hypokaemla.

The severity and rapidity of the development of hypocalcemia are responsible for latent and overt features of tetany. In GS, BS, and VDD, latent tetany is common. As the process of developing VDD is prolonged, serum calcium level decreases slowly. Neuromuscular irritability is less in VDD because of slow changes in serum calcium level. In HVS, overt tetany is frequently seen, as rapid changes in ionized calcium in acute HVS cause increased neuromuscular irritability.

Approach to Tetany

Flowchart 1 is created as an approach for diagnosing major causes of tetany. For establishing the etiology of tetany, detailed history of patients is essential. History should include present and past history of (h/o) recurrent vomiting (metabolic alkalosis), HVS (respiratory alkalosis), weakness of limbs (hypokalemia in GS), thyroid and neck surgeries and radiation therapy (iatrogenic hypoparathyroidism), presence of polyuria and polydipsia (hypokalemia in GS causing nephrogenic diabetes insipidus), abdominal pain (acute pancreatitis), chemotherapy for malignant disorders (TLS), family h/o similar disorders (genetic), h/o drug intake, addiction to alcohol (hypomagnesemia), malabsorption disorders, decreased sun exposure (VDD), bone pain (VDD), etc. Detailed physical examination is done to find out clinical features such as hypertension (HTN), hyperventilation, dehydrosis, loss of muscle power, scar mark of thyroideidectomy (accidental parathyroidectomy), dysomorphic facial features including cleft palate, skeletal abnormalities (for Albright’s hereditary osteodystrophy (AHO), CED) etc. Features of any other autoimmune disorders (like vitiligo) should be searched for their association with autoimmune hypoparathyroidism, APS-1, and APS-2.

After history taking and physical examination, laboratory investigations are done to reach the diagnosis. Initial investigations include arterial blood gas (ABG) analysis, serum calcium, albumin, sodium, and K levels. Both ionized and total serum calcium levels are assessed and corrected according to serum albumin levels. Depending on the initial investigation reports, further tests are done, such as serum phosphate, ALP, iPTH, and serum magnesium levels, and urinary K, calcium, and chloride levels. Serum magnesium is assessed, especially when possibilities of GS/BS, chronic alcoholism, and drug-induced renal tubular dysfunction are considered. In the presence of HTN, plasma renin activity (PRA) and serum aldosterone levels are assessed.

Vitamin D deficiency (VDD) is diagnosed in the presence of decreased serum calcium and phosphate and increased ALP level and confirmed after assessment of 25 (OH)—cholecalciferol level. Primary hypoparathyroidism (iatrogenic/ autoimmune/congenital) is diagnosed in the presence of decreased serum calcium, increased phosphatide, and decreased/inappropriately normal iPTH. PHP is diagnosed in the presence of hypocalcemia and elevated PTH level, and classified into PHP 1a, PHP 1b, and PHP 2 as per the response of cyclic adenosine monophosphate to PTH, G,a subunit deficiency of adenylate cyclase enzyme, and AHO morphology. Hyperventilation-induced tetany shows respiratory alkalosis in ABG. Tetany due to recurrent vomiting is associated with metabolic alkalosis with decreased urinary chloride levels. GS is diagnosed if metabolic alkalosis is associated with hypokalemia, hypomagnesemia, decreased urinary calcium, and increased urinary K and chloride levels. BS is diagnosed in the presence of metabolic alkalosis associated with hypokalemia with or without hypomagnesemia and increased urinary calcium, K, and chloride levels. Genetic confirmation is required in GS, BS, CED, KCNA1 gene mutation, DGS, etc.
Spectrum of Disorders associated with Tetany

Flowchart 1: Approach for diagnosis of tetany. Abbreviations: ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; HTN, hypertension; GS, Gitelman syndrome; BS, Barter syndrome; PRA, plasma renin activity; VDD, vitamin D deficiency; TLS, tumor lysis syndrome; CKD, chronic kidney disease; ABG, arterial blood gas; PHP, pseudohypoparathyroidism; HVS, hyperventilation syndrome

Hypokalemic tetany is diagnosed in the presence of normal levels of ionized calcium and magnesium with normal or acidic pH, for example, in Sjogren’s syndrome.

Miscellaneous other disorders are diagnosed from obvious history, physical examination and directed laboratory tests like acute pancreatitis, dengue, falciparum malaria, massive blood transfusion, drug-induced tetany etc.

Management

Treatment of tetany depends on underlying disorders. Corrections of acid-base disorders and fluid and electrolyte imbalances are essential. Vitamin D, calcium, K, and magnesium supplementations are given. Intravenous calcium gluconate helps in acute hypocalcemic tetany. Normal saline and ringer lactate correct metabolic alkalosis and associated tetany developed from recurrent vomiting. HVS is managed with rebreathing technique and psychiatric counselling. Withdrawal of offending drugs causing tetany improves associated metabolic and acid-base disorders and causes the disappearance of tetany. Recurrence of tetany is infrequent with ongoing treatment of GS with K and magnesium supplementations and K-sparing diuretics like spironolactone, eplerenone, and amiloride. 1,25-dihydroxycholecalciferol (calcitriol) is required for hypoparathyroidism. Despite calcium and calcitriol supplementations, symptoms may persist in hypoparathyroidism. Nephrolithiasis may be a cause of morbidity due to prolonged high doses of calcium supplementation. Concomitant thiazide diuretics reduce nephrolithiasis. When specific treatments cure or stabilize miscellaneous disorders, associated tetany usually disappears.

Prognosis

The prognosis of tetany depends on the acute and chronic nature of underlying disorders and the associated severity, graveness and curability of the diseases.

Key Messages

- Ionized calcium is more important for the causation of tetany than total serum calcium.
- Alkalosis is associated with reduced ionized calcium, which precipitates tetany.
- Acidosis increases ionized calcium and is protective against tetany.
- Gitelman syndrome is associated with metabolic alkalosis, hypokalemia, hypomagnesemia, and hypocalciuria; and frequently causes tetany and/or hypokalemic paralysis.
- Tetany is commonly seen with HVS (respiratory alkalosis) and recurrent vomiting (metabolic alkalosis).
- Vitamin D deficiency (VDD) (in infants), hypomagnesemia, hypoparathyroidism, PHP, and miscellaneous other disorders can cause tetany.
- Hypokalemic tetany has normal calcium and magnesium levels with acidic pH (e.g., Sjogren’s syndrome) or normal pH.

Author Contribution

Dr Gouranga Santra—Concept, design, literature search, analysis, and manuscript writing.

References

Spectrum of Disorders associated with Tetany

35. Johnson MM, Patel S, Williams J.D. Don't take it 'Lytely': a case of acute tetany. Cureus 2019;11(10):e5845.
Spectrum of Disorders associated with Tetany


Role of Iron Therapy in Heart Failure: A Consensus Statement from India


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ABSTRACT

Iron deficiency (ID) with or without anemia is frequently observed in patients with heart failure (HF). Uncorrected ID is associated with higher hospitalization and mortality in patients with acute HF (AHF) and chronic HF (CHF). Hence, in addition to chronic renal insufficiency, anemia, and diabetes, ID appears as a novel comorbidity and a treatment target of CHF. Intravenous (IV) ferric carboxymaltose (FCM) reduces the hospitalization risk due to HF worsening and improves functional capacity and quality of life (QOL) in HF patients. The current consensus document provides criteria, an expert opinion on the diagnosis of ID in HF, patient profiles for IV FCM, and correct administration and monitoring of such patients.

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Introduction

Heart failure (HF) is a clinical syndrome that is progressive in nature. In India, patients with AHF have a 5-year mortality rate of 59% and a median survival of 3.1 years, as seen in the Trivandrum Heart Failure Registry. Furthermore, the majority of the patients had HF with reduced ejection fraction (HFrEF) (62%).

Impact of ID on HF Patients

Heart failure (HF) has frequently been linked to ID with or without anemia. Patients with AHF and CHF are known to have ID, which is acknowledged as an essential comorbidity and independent predictor of prognosis. Regardless of the prevalence of anemia, ID is a common comorbidity in HF patients (about 50%), and it is linked to a poor prognosis, diminished physical well-being, exercise intolerance, repeated hospitalizations, and an increase in death.

Prevalence of ID: Global and India

In a single-center observational study (n = 150) conducted in Rajasthan, ID was present in 76% of patients, while 48.7% of patients had absolute ID (serum ferritin <100 μg/L) and 27.3% of patients had functional ID (normal serum ferritin 100–299 μg/L) with low transferrin saturation (TSAT) <20%. An Indian-based study showed that 53.8% of hospitalized patients with CHF had ID.4

Impact of HF Hospitalization on Mortality

Recurrent HF hospitalizations (HFH) are frequent in patients with HF. There is a strong association between recurrent HFH and cardiovascular (CV) and all-cause mortality, with the risk increasing progressively with each recurrent HFH. This increases the burden on the patient and the healthcare system.

Pathophysiology and Clinical Implications of ID in HF

Data suggests that around half of HF patients with or without anemia have low iron levels. The causal relationship between ID and reduced aerobic capacity, endurance capacity, physical performance, and work efficiency has been clinically established. As a result, myocardial ID in HF patients may further enhance glucose utilization rather than fatty acid utilization and, when combined with reduced reactive oxygen species protection, may lead to myocardial dysfunction and unfavorable remodeling.

Diagnosis of ID in HF

Whom to Screen?

Each HF patient should receive periodic assessments for ID (including anemia), as per the 2021 European Society of Cardiology (ESC) HF guidelines. Additionally, it is advised that patients with AHF have their iron status (as measured by TSAT and ferritin) determined before discharge.8

According to the severity of the iron deficit and stage of HF, it is advised that clinicians check ID and anemia in all patients with HF periodically as an integral part of the clinical evaluation (about 1–2/year). Additionally, patients with suspected CHF, ambulatory patients or outpatients with progressing HF, and those who have undergone hospitalization for AHF should be evaluated for ID.9

Which Tests to use?

Transferrin saturation (TSAT) and ferritin should be assessed as part of the routine blood tests for comorbidities advised for individuals with suspected CHF (recommendation class I, evidence level C). To ensure a correct diagnosis of ID, ferritin, and TSAT should be measured at the same time.8

Diagnosis of ID

As per recent HF guidelines, ID is defined as ferritin below 100 μg/L or ferritin levels of 100–299 μg/L along with TSAT of <20%. Functional ID is commonly observed in the earlier stages of HF, with absolute ID developing as the disease progresses.11

Screening for Anemia

It is crucial to screen for anemia while assessing iron status, and anemia should be identified using the hemoglobin (Hb) thresholds (<12 g/dL in females and <13 g/dL in males).9

Correction of ID in HF

In patients with HFrEF and ID with or without anemia, IV iron replacement is reasonable to improve functional status and QOL (class 2), and erythropoietin-stimulating agents should not be used in patients with HF and anemia to reduce morbidity and mortality (class 3, harm); according to 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) guidelines regarding the management of anemia or ID.12 Table 1 mentions the suitable patient profiles for the correction of ID.

Management of ID in HF

Although both oral (HR 0.36) and IV (HR 0.58) iron supplementation reduced hospitalization for HF, IV iron supplements improved the 6-minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, while oral iron supplements did not influence these parameters.12 As seen by the iron-HF and iron-repletion effects on oxygen uptake in HF trials, oral supplementation has not been beneficial in correcting ID.13,14 IV FCM has emerged as a promising therapeutic agent in HF patients due to its clinical advantages in terms of reduced hospitalization functional status, exercise capacity and QOL. Oral iron consumption has been contraindicated mostly due to unpleasant gastrointestinal side effects.3 Darbepoetin alfa treatment did not significantly improve clinical outcomes in patients with systolic HF and mild-to-moderate anemia.15

Position, Clinical Efficacy, and Safety of IV FCM

Position of IV FCM in Guidelines

The AHA/ACC/HFSA, and ESC have made certain recommendations about using IV iron for the management of HF (Table 2).8,16

Efficacy of IV FCM

Benefits of Iron Correction by IV FCM

Iron supplementations increase the QOL and improve survival in patients with ID and HF. In the short term, correction of ID by IV FCM increases functional capacity (measured by New York Heart Association (NYHA) functional score). Secondly, IV FCM improves patients’ self-reported perception of well-being (measured by global patient assessment) after 4 weeks of therapy, and the effect was sustained for the duration of the 24-week study. The long-term benefits of IV FCM include reduced risk of hospitalization because of worsening HF, improvement in the 6MWT, fatigue score, and QOL. Important clinical studies evaluating benefits of IV FCM are mentioned in Table 3.

Impact of IV FCM on Hospitalization and Mortality

IV FCM reduces the rates of overall and HF hospitalization, time to first hospitalization, and mortality (maximally for the duration of the 24-week study).16

Table 1: Patient profiles for correction of ID as per ESC 2021 guidelines8

<table>
<thead>
<tr>
<th>Patient population</th>
<th>The benefit of IV FCM</th>
<th>COR, LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic patients who have a left ventricular ejection fraction (LVEF) &lt;45%</td>
<td>Alleviation of symptoms, improvement of exercise capacity and QOL</td>
<td>Ila, A</td>
</tr>
<tr>
<td>Pre- and post-discharge follow-up of patients hospitalized for AHF</td>
<td>Improvement of symptoms and reduced rehospitalization</td>
<td>Ila, B</td>
</tr>
<tr>
<td>Symptomatic patients recently hospitalized for HF with LVEF &lt;50%</td>
<td>Reduced risk of HF hospitalization</td>
<td>Ila, B</td>
</tr>
</tbody>
</table>
A meta-analysis concluded that IV iron supplementation significantly reduces the overall (OR: 0.52 and \( p = 0.004 \)) and HF (OR: 0.42 and \( p = 0.009 \)) hospitalization rate, compared to oral iron supplementation. Additionally, treatment with IV FCM significantly reduced the time to first HF hospitalization or CV mortality [rate ratio (RR) = 0.70 and \( p = 0.048 \)], though it did not significantly reduce the time to first CV death (RR = 0.94 and \( p = 0.655 \)).

Another meta-analysis concluded that IV FCM significantly lowers the hospitalization rate for worsening HF (RR = 0.34 and \( p = 0.0001 \)) and CV hospitalizations (RR = 0.49 and \( p < 0.0001 \)).

In a third meta-analysis, data indicated that patients on IV FCM had lower rates of recurrent CV hospitalizations and CV mortality (RR = 0.59 and \( p < 0.01 \)), reduced recurrent HFH and CV mortality (RR = 0.53 and \( p < 0.05 \)), recurrent CV hospitalizations, and all-cause mortality (RR = 0.60 and \( p < 0.01 \)).

Finally, the fourth meta-analysis mentioned iron therapy to be associated with a significant reduction in HF hospitalization (RR = 0.69 and \( p = 0.043 \)) compared to the standard of care.

Efficacy in Indian Patients

IV FCM significantly improved NYHA status and 6MWT in patients with symptomatic HF and ID. In another small prospective trial, 12 weeks of IV FCM compared with the standard of care (without iron), improved peak rate of oxygen (VO₂), NYHA functional classification, 6MWT, and reduced Minnesota Living with HF Questionnaire (MLHFQ) score.

**Safety and Tolerability of IV FCM**

Ferric carboxymaltose (FCM) is well tolerated by HF patients. Transient hypophosphatemia has been linked to the IV administration of FCM to iron-deficient individuals with HFrEF. Following a single dosage of IV FCM, biochemically significant hypophosphatemia is typical. As per existing clinical data, hypophosphatemia did not lead to serious clinical outcomes for most patients.

**Monitoring**

The patient must be observed for at least 30 minutes after administration of the IV iron injection. Reassessment of iron status:

- Reassess iron status after 3 months and check if further iron repletion is required.
- ID and anemia should be evaluated in HF patients as a routine clinical evaluation in such patients (once or twice a year based on the severity of ID and HF stage).
- IV iron should then be administered as needed.

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**Table 2:** Guideline recommendations for IV FCM

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
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</thead>
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<tr>
<td>2022 AHA/ACC/HFSA</td>
<td>In patients with HFrEF and ID with or without anemia, IV iron replacement is reasonable to improve functional status and QOL</td>
<td>II a</td>
<td>B-R</td>
<td>16</td>
</tr>
<tr>
<td>2021 ESC</td>
<td>IV FCM should be considered for the treatment of ID in symptomatic patients who have a LVEF &lt;45% to alleviate symptoms, improve exercise capacity and QOL</td>
<td>II a</td>
<td>A</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>IV FCM should be considered for the treatment of ID in pre- and post-discharge follow-up of patients hospitalized for AHF to improve symptoms and reduce rehospitalization</td>
<td>II a</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV FCM should be considered for the treatment of ID in symptomatic patients recently hospitalized for HF with LVEF &lt;50% to lessen the risk of HF hospitalization</td>
<td>II a</td>
<td>B</td>
<td></td>
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</tbody>
</table>

AHA/ACC/HFSA: American College of Cardiology/American Heart Association/Heart Failure Society of America; AHF: acute heart failure; COR: Class of recommendation; FCM: ferric carboxymaltose; HFrEF: heart failure with reduced ejection fraction; IV: intravenous; LOE: level of evidence; LVEF: left ventricular ejection fraction; QOL: quality of life
Data from the latest IRONMAN study showed that IV ferric derisomaltose, compared to usual care, reduced the number of recurrent hospital admissions due to HF and CV death by 28%, though not statistically significant (RR = 0.82; p = 0.070). The study reemphasizes the timely correction of ID in HF patients resulting in a reduction in HFH and CV death. In the COVID-19 analysis, the rate of the primary endpoint was lower in those assigned to IV iron and nominally statistically significant (RR = 0.76; p = 0.047). Furthermore, fewer patients had serious cardiac adverse events (36 vs 43%; p = 0.016). Thus, in patients with HF and ID, IV iron therapy appears to provide a general benefit that may be independent of the type of iron complex utilized, according to the consistency of the results from IRONMAN and AFFIRM-AHF (FCM).17,30

Need for Consensus

Despite IV FCM being recommended in American and European guidelines for HF management, without Indian-based guidelines, ID is underdiagnosed in India, and IV FCM is underutilized. There is an urgent need to have a national consensus on the diagnosis of ID and the role of IV FCM in HF patients. The current consensus paper gives criteria and an expert opinion on the diagnosis of ID in HF, patient profiles for IV FCM, and correct administration and monitoring of such patients.

Materials and Methods

The Indian consensus group included 50 experts, mainly comprising cardiologists, nephrologists, and endocrinologists from India, who convened for a national consensus meeting on 18th September 2022 to discuss the role of IV FCM in the management of HF. Objectives and topics related to parenteral iron therapy in HF, EF, HFpEF, and HFimpEF were discussed, and each expert shared their views which led to a group discussion. Experts framed statements based on available scientific evidence, experience, and collective clinical judgment from practical experience with IV FCM. This consensus meeting was moderated by a leading cardiologist of the country, who introduced few consensus statements. The final consensus statements were framed after >80% of the experts agreed on the statement. The consensus was formed if the agreement to the statement was >80% within the expert group.

Expert Opinion

Burden of ID in HF Patients in India

All the experts agreed that there is a high burden of ID in HF patients. ID causes a significant increase in mortality risk and a reduction in QOL. About 60–70% of patients with HF have ID and the prevalence of ID in India is about 65–75%. The pathophysiology of ID in HF patients was discussed. In ID, the mitochondrial adenosine diphosphate (ADP) becomes dysfunctional. Thus, achieving remodeling is not possible. ID in HF leads to reduced QOL, resulting in increased hospitalization for worsening HF and mortality.

Diagnosis

All the experts agreed that TSAT and ferritin levels must be used for the diagnosis of ID in patients with chronic HF. Most experts agree that measuring ferritin and TSAT levels 2–3 days before discharge is beneficial. Since ferritin may be falsely elevated in AHF, diagnosis of ID is difficult in such cases. There is a need to identify another biomarker for ID diagnosis. It was suggested that HF patients on sodium-glucose cotransporter-2 (SGLT2) inhibitors must be screened for ID. Other deficiencies in HF patients—vitamin B12 and vitamin D should be checked while diagnosing ID.

ID Correction

There are various studies and meta-analyses that prove that parenteral iron has more efficacy than oral iron. Both oral and IV iron reduced hospitalization for HF, IV iron improves 6MWT and KCCQ scores while patient on oral iron supplements did not have these benefits.

Parenteral iron therapy overshoots the limitations of oral iron (bypassing the pathway). Oral iron therapy should be recommended in patients with low hepcidin levels. Patients with high hepcidin should receive IV iron. However, hepcidin is not routinely measured in clinical practice, and therefore, it is difficult to identify patients with low/high hepcidin. HF and chronic kidney disease (CKD) have common risk factors. As per renal guidelines, correction of iron levels is followed by erythropoietin. The target Hb is 10–11 g/dL in such patients.

Management with IV FCM

All the experts agreed that IV FCM is the ideal choice for the management of ID in HF (Fig. 2). IV FCM reduces the time to first hospitalization, rates of overall and HF hospitalization, recurrent CV hospitalizations and CV mortality. All the experts agreed that if ferritin is low and TSAT is <20%, IV iron should be given irrespective of EF (or stage of HF). There is no data on FCM role in HFpEF.

Impact of ID Correction with IV FCM in HF Patients

Based on the available clinical evidence, the experts agreed that IV FCM helps in the reduction of hospitalization for HF, improvement in 6MWT, and improvement in functional NYHA class, and thus leads to the overall improvement in patient’s QOL. The resulting delay in the progression of HF remodeling could lead to the overall improvement of the patient’s condition. In a study, cardiac resynchronization therapy (CRT) nonresponders became responders after iron correction.

Safety of IV FCM

The safety and perception of parenteral iron, especially IV FCM, were discussed. IV iron does not increase the infection rate. IV FCM administration is not recommended in the presence of active infection or sepsis.

The most common dose of IV FCM administered in clinical practice is 1000 mg in 250 mL of normal saline over 15–20 minutes (Figs 3A and B).

Follow-up is recommended after 2–3 months. If the levels are still low, then the dose may be repeated. Precautions for administering IV iron at home should be emphasized. Hypoalbuminemia in ID and HF is common, and such patients must be administered protein supplementation if needed.

The experts drafted a clinical algorithm based on clinical practice, existing guidelines, and available scientific evidence of IV FCM. The algorithm includes diagnosis of ID in HF, dose calculation and administration of IV FCM, follow-up, and monitoring of such patients (Fig. 4).

Patient profiles for ferric carboxymaltose IV injection

1. Patients with stable CHF and NYHA class II/III who had a LVEF ≤ 45%.
2. Patients with iron deficiency who had an LVEF < 50% and had stabilized following an episode of AHF
3. Treatment benefit with IV iron has not been determined in patients with HFpEF since these patients were excluded from previous trials.

Fig. 2: List of patient profiles suitable for treatment with IV FCM
### Table 3: Clinical study details of IV FCM

<table>
<thead>
<tr>
<th>Study name, year</th>
<th>Major HF cardiac inclusion criteria</th>
<th>N</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Primary end points</th>
<th>Secondary end points</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM—AHF, 2020</td>
<td>AHF with concomitant ID, and LV EF &lt; 50%</td>
<td>1,110</td>
<td>IV FCM vs placebo For 24 weeks</td>
<td>52 weeks</td>
<td>Total hospitalizations for HF and CV death: FCM = 293 Placebo = 372 (RR 0.79, p = 0.059) Total CV hospitalizations and CV deaths: FCM = 370 Placebo = 451 (RR 0.80, p = 0.050)</td>
<td>Total HFH: FCM = 217 Placebo = 294 (RR 0.74, p = 0.013) Composite of first heart failure hospitalization or CV death: FCM = 181 (32%) Placebo = 209 (38%) (HR 0.80, p = 0.030) Days lost due to HFH and CV death (days per 100 patient-years): FCM = 369 Placebo = 548 (RR 0.67, p = 0.035) SAE: FCM = 250 (45%) Placebo = 282 (51%)</td>
<td>17</td>
</tr>
<tr>
<td>Myocardial-IRON Trial, 2020</td>
<td>HFrEF and ID anemia</td>
<td>53</td>
<td>IV FCM 20 mL (1000 mg of iron) administered over at least 15 minutes Vs Placebo</td>
<td>7 days</td>
<td>• T2* (observed T2) and T1 mapping were significantly lower (p = 0.025; and p = 0.001) (7 days) • T2* mapping were significantly lower in 30 days (p = 0.003) • T1 mapping were not significantly changed in 30 days (p = 0.577)</td>
<td>Significant improvement in KCCQ (p &lt; 0.001) and NYHA functional class (p &lt; 0.001) No significant change in NT-proBNP level, 6MWT and LVEF</td>
<td>18</td>
</tr>
<tr>
<td>PRACTICE-ASIA-HF, 2018</td>
<td>ADHF and ID anemia</td>
<td>50</td>
<td>IV FCM 1000 mg before discharge Vs Placebo For 12 weeks</td>
<td>No significant change in 6MWT distance (p = 0.956)</td>
<td>No significant change in KCCQ (p = 0.670) and VAS (p = 0.386)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>EFFECT-HF, 2017</td>
<td>HFrEF and ID</td>
<td>172</td>
<td>IV FCM Vs Placebo For 24 weeks</td>
<td>24 weeks</td>
<td>No significant change in peak VO₂ (p = 0.23)</td>
<td>• Improved NYHA functional class, Hb, ferritin, TSAT and patient global assessment (p &lt; 0.05) • NT-proBNP was not affected (p = 0.13)</td>
<td>20</td>
</tr>
<tr>
<td>CONFIRM-HF, 2015</td>
<td>HF, LVEF ≤45%, increased natriuretic peptides, and ID</td>
<td>304</td>
<td>IV FCM 200 mg weekly Vs Placebo For 52 weeks</td>
<td>52 weeks</td>
<td>• 6MWT distance improved significantly at week 24 (p = 0.002) in FCM group • Treatment effect of FCM was sustained to week 52 (p &lt; 0.002)</td>
<td>• Improved NYHA class (p = 0.004), PGA (p = 0.047) and fatigue score (p = 0.002) from week 24 onwards • Reduced risk of hospitalizations for worsening HF (HR = 0.39, p &lt; 0.01)</td>
<td>21</td>
</tr>
<tr>
<td>FAIR-HF, 2009</td>
<td>Chronic HF (NYHA II or III) and LVEF ≤45%, ID and Hb: 95–135 g/L</td>
<td>459</td>
<td>IV FCM 200 mg Vs placebo</td>
<td>24 weeks</td>
<td>More patients in FCM group showed improvement by one NYHA functional class (OR 2.40)</td>
<td>FCM significantly improved 6MWT and QOL</td>
<td>22</td>
</tr>
</tbody>
</table>

ADP, adenosine diphosphate; ADHF, acute decompensated heart failure; BMI, body mass index; BNP, brain natriuretic peptide; Hb, hemoglobin; HF, heart failure; HFrEF, heart failure reduced ejection fraction; KCCQ, kansas city cardiomyopathy questionnaire; LVDd, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; LVSd, left ventricular systolic dysfunction; NT-proBNP, N terminal- pro brain natriuretic peptide; NYHA, New York Heart Association; PE, primary endpoint; PGA, Patient Global Assessment; QOL, quality of life; RR, respiratory rate; SE, secondary endpoint; TSAT, transferrin saturation; VAS, Visual Analog Scale; VO₂, rate of oxygen; 6MWT, 6 minute walk test
Role of Iron Therapy in Heart Failure

Fig. 4: Algorithm for the diagnosis and management of ID in HF

Ganzoni formula-To calculate the patient’s total body iron deficit

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Body weight and dose of ferric carboxymaltose</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/dL</td>
<td>mmol/L</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>&lt;6.2</td>
</tr>
<tr>
<td>10–14</td>
<td>6.2–8.7</td>
</tr>
<tr>
<td>&gt; 14</td>
<td>&gt; 8.7</td>
</tr>
</tbody>
</table>

For patients above 35 kg, iron stores are at least 500 mg, the lower limit of normal for small women. Some guidelines use 10 mg to 15 mg iron/kg body weight while others use 1,000 mg iron for stores.

Ferric carboxymaltose 500–1000 mg single dose to correct iron deficiency

Fig. 3A and B: (A) Dose and administration of IV FCM; (B) Ganzoni formula
Final Consensus Statements

1. Iron deficiency (ID) is characterized by reduced ferritin (<15 µg/L). However, a higher cutoff for ferritin is recommended in chronic inflammatory conditions.

2. In chronic HF, absolute ID is defined as ferritin <100 µg/L, and functional ID is defined as ferritin between 100 and 299 µg/L when TSAT is <20%.

3. In the absence of any iron treatment, about 50% of patients with HF have low levels of available iron (absolute plus functional ID).

4. Iron deficiency (ID) should be more focused than IDA. The prevalence of ID is higher than IDA. It is in 60–70% of patients of HF.

5. Iron deficiency (ID) is a stronger prognostic factor than anemia in HF.

6. Mortality and morbidity increase when ID is present. Early detection of ID with timely treatment with parenteral iron therapy improves QOL and exercise tolerance along with reduction in risk of hospitalization for HF. It also leads to long-term healthy outcome.

7. As per ESC HF 2021 guidelines, serum Ferritin and TSAT are the key indicators of ID. Serum ferritin and TSAT should be done, preferably in all patients, as soon as they are diagnosed with HF.

8. Iron deficiency (ID) in HF patients is an independent predictor of mortality and prognosis.

9. Iron deficiency (ID) correction in HF patients by parenteral iron therapy has morbidity benefits including functional improvement in QOL, HRQOL, 6MWT as evident by clinical data (FAIR-HF, CONFIRM-HF, EFFECT-HF, PRACTICE ASIA-HF, Myocardial Iron, AFFIRM-AHF trials).

10. The functional benefits can be seen as early as first week after parenteral iron therapy.

11. Timely correction of ID enhances long-term mortality and morbidity benefits.

12. Intravenous (IV) FCM is superior to IV iron sucrose and iron dextran because of (a) no antigenicity, (b) no test dose requirement, (c) high dose can be administered, (d) low parenteral dose time, (e) it bypasses hepcidin block, (f) better bioavailability, (g) the safety of FCM has been well ascertained even in Indian pregnant patients as well.

13. Iron deficiency (ID) impairs reversal cardiac remodeling.

14. Intravenous (IV) FCM in ID with HF may enhance reversal of cardiac remodeling at the mitochondrial level.

15. Algorithm positioning of IV FCM in the therapy of HF as the fifth pillar has to be considered in Indian context due to high prevalence of significant ID. While sequencing the four pillars of HF therapy, early monitoring of ID and timely intervention with parenteral IV FCM as an emerging pillar will enhance better outcomes.

16. Intravenous (IV) FCM enhances CRT response in CRT nonresponder by correcting ID as documented by RIDE CRT study.

CONCLUSION

Iron deficiency (ID) is a very common public health problem in the Indian population with HF. ID correction with IV FCM has enormous clinical benefits in patients with ID with HF. It is therefore proposed to consider the position of FCM as the cornerstone in HF management with ID in the Indian context.

AUTHORS CONTRIBUTION

All the authors contributed to the concept and design of this consensus document. The manuscript draft was developed and critically reviewed by all the authors. All authors have approved the final draft of the manuscript.

CONFLICTS OF INTEREST

The expert group discussion was organized in association with Emcure Pharmaceuticals Ltd. Pune, India. Dr. Onkar C Swami is full-time employee of Emcure Pharmaceuticals Ltd. which actively markets Ferric carboxymaltose.

FUNDING DETAILS

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REFERENCES


17. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind,
Hirayama Disease: A Rare Case Report and Review

Heli Kapoor1, Varuna Yadav2, Shubha L Margekar3*, Debasish Chaudhury4, Ashok Kumar5, Ankur Verma6
Received: 04 August 2022; Accepted: 01 November 2022

ABSTRACT

Hirayama disease, or brachial monomelic amyotrophy, is not a common neurological disease characterized by unilateral or asymmetric bilateral lower motor weakness of distal upper limbs. The basic pathophysiology is compression of the dural sac and spinal cord during flexion of the neck. A case of a 21-year-old male presented with chief complaints of tremors in both hands (right more than left) with gradually progressive weakness of the right hand and forearm. Electromyography (EMG), nerve conduction velocity (NCV), and magnetic resonance imaging (MRI) neck in flexion showed focal atrophy of lower cervical myotomes and confirmed the diagnosis of monomelic amyotrophy.

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INTRODUCTION

Hirayama disease is an uncommon sporadic, self-limiting lower motor neurons disease; clinically restricted to the distal part of upper limbs, characterized by unilateral or bilateral (asymmetrical) weakness, and wasting of muscles (focal involvement) supplied by lower cervical cord predominantly C7, C8, and T1. It was first described in 1959 by Hirayama. The disease usually begins in the late teens and early 20s (15 and 25 years) with male preponderance (male: female ratio of 20:1).1

Diagnosis is based on clinical history, examination, neuroimaging (flexion MRI), and electrophysiological studies. Management mainly includes the administration of a cervical collar, muscle-strengthening exercises, and assistive devices like splinting and braces.1 We report a case of a 21-years male patient who presented with tremors in his right hand and bilateral asymmetrical (right > left) weakness and wasting of the upper limb. Electrophysiological studies and radiological investigations confirmed the diagnosis.

CASE DESCRIPTION

A 21-year-old, right-handed gentleman with no prior comorbidities presented with complaints of tremors in both hands (in the right hand for 3 years and in the left hand for 2 years), right more than left, and gradually progressive distal weakness in the right hand for 2 years. The tremors were coarse, aggravated during finger extension, and were associated with transient worsening during winters. The hand weakness resulted in difficulty in carrying out day-to-day activities like fine movements at hand, including holding a pen, buttoning, unbuttoning, and tying shoelaces. Consequently, he had to discontinue his studies because of difficulty in writing. There was no history of any weakness in the lower limbs. Also, he had no history of pain, sensory loss, dysphagia, dysarthria, ptosis, diplopia, headache, cramps, fasciculations, or bowel or bladder dysfunction. History of any fever, trauma, poliovirus infection history and any occupational exposure to any heavy metals or toxins was ruled out. He has no history of similar neurological disorders in any other family member.

On examination, vitals were stable, and Mini-mental State Examination of 28/30. Central nervous system examination shows the bulk of the flexor aspect of the right forearm was reduced along with wasting of the thenar and hypothenar eminences. The tone was normal in all the limbs. The power was decreased (3/5) in the thenar, hypothenar, flexors, and extensors of the right forearm. Right brachioradialis was spared. Power in the left hand, forearm, shoulder, and right arm and shoulder, as well as in the bilateral lower limb, was normal. Tremors (minipolymyoclonus-like movement) were present in both hands (right > left). Fasciculations were seen around the right elbow. Deep tendon reflexes (DTR) were normal in all four limbs, and coordination was normal. No evidence suggestive of the sensory, autonomic system, cranial nerve, posterior column, and cerebellum involvement was present. The gait and stance were normal.

On investigations—complete blood count, kidney function tests, and liver function tests were normal. Thyroid-stimulating hormone was 1.55 µIU/mL, vitamin B12; 770 pg/mL, vitamin D; 30 ng/mL, and folate; 10.8 nmol/L. The extended autoimmune profile (antinuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-histone, anti-Ro, anti-La, and anti-scleroderma) was negative. Erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, creatine kinase, and creatine kinase-myoglobin binding were normal. Tridot tests, including hepatitis B, hepatitis C, and human immunodeficiency virus, were nonreactive.

Nerve conduction studies showed normal distal latency with decreased amplitude, and conduction velocities were normal in the right ulnar nerve. The right median left ulnar, left radial, and left median nerve showed normal amplitude, normal conduction velocities, and normal latency. F-wave was normal in all the nerves tested. Sensory nerve conduction study was normal.

Electromyography (EMG) revealed preganglionic neurogenic involvement of the C5-T1 segments on the right side with evidence of denervation and chronic reinnervation changes. A plain MRI brain and cervical spine revealed no abnormality. During flexion of the neck, MRI cervical spine revealed anterior displacement of the posterior theca such that it compresses the cord between it and the spinal column anteriorly from C4-C6 with a prominence of epidural venous dural space dorsal to dura with mild cord thinning from C4-C6. The posterior dural sac crescent appeared in T2/short-tau inversion recovery (T2/STIR) as a hyperintense entity and enhanced uniformly postcontrast (Figs 1A and B).

On the basis of clinical examination, electrophysiological, and radiological studies, the patient was diagnosed with monomelic amyotrophy, and he was prescribed a cervical collar so that further spinal cord injury due to repeated flexion of the neck could be prevented. Muscle-strengthening exercises were also advised. The patient’s complaints have been stable for the past 6 months with no new symptoms.

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Hirayama Disease: A Rare Case Report and Review

Discussion

Hirayama disease, also called monomelic amyotrophy, is not a common neurological entity affecting young males more than females in their late teens and early 20s. The condition is usually self-limiting, and characteristically involvement is limited to a few myotomes in the extremity, which is affected. This results in unilateral involvement and atrophy of muscles innervated by C7, C8, and T1, which travels obliquely along the volar and dorsal aspect of the forearm to the hands and forearms muscles with brachioradialis muscle being spared (“oblique amyotrophy” pattern). Disorder has also been termed benign focal amyotrophy, juvenile asymmetric segmental spinal muscular atrophy, and juvenile muscular atrophy of the distal upper extremity in the literature. It usually manifests as gradual onset muscle weakness and atrophy that can be unilateral or bilateral. Bilateral muscle weakness and atrophy (symmetrically or asymmetrically) are seen only in 10% of cases and were present in this case also.1,2

In neurological examination, there are absent or hypoactive muscle stretch reflexes or DTR in the muscles supplied by the spinal cord segment, which is involved with no upper motor neuron signs. The cranial nerves, pyramidal tracts, and autonomic nervous system are normal. Autonomic involvement, for example, cold skin, cold paresis (i.e., increase in weakness on exposure to cold environment), excessive sweating, bilateral minipolymyoclonus, and hair loss over the dorsum of the hands has been reported in 36% of cases. The progression of disease in terms of trophic changes is steady for the first 2–3 years; after that, most of the patients within 5 years stabilized. In about 20% of cases, the spread may be observed in the contralateral limb also.1

Proposed diagnostic criteria by Tashiro et al. for the Hirayama disease include (1) distal weakness and muscular atrophy in the forearm and hand; (2) unilateral upper extremity; (3) onset at the age between 10 and 20; (4) insidious onset with gradual progression for the first few years, followed by stabilization; (5) no involvement of the lower limbs; (6) No sensory disturbance and tendon reflex abnormalities; (7) exclusion of other diseases (motor neuron disease, multifocal motor neuropathy, spinal cord tumors, syringomyelia, abnormalities of cervical vertebral, anterior interosseous, or deep ulnar neuropathy).2 The above criteria were fulfilled in this reported case.

The neurological examination revealed lower motor neuron type of weakness of the hand and forearm muscles of the right hand with sparing of brachioradialis muscle without any sensory dysfunction. Neuroimaging and EMG studies confirmed the clinical diagnosis of Hirayama disease (diagnosis of amyotrophic lateral sclerosis (ALS) was ruled out due to segmental cervical atrophy instead of diffuse atrophy as seen in ALS).1

Electromyography (EMG) shows evidence of chronic denervation of affected muscles, with or without acute denervation potentials (in the form of positive sharp waves, fasciculations, and fibrillation potentials). EMG findings may be abnormal in seemingly healthy muscles.2 EMG, in this case, also showed almost the same findings.

Findings of MRI cervical spine (during neck flexion) are one of the essential pieces of evidence for the diagnosis of Hirayama disease according to expert lead guidelines using a modified Delphi technique.3 MRI cervical spine (during neck flexion) revealed anterior displacement of the posterior theca such that it compresses the cord between it and the spinal column anteriorly from C4-C6 with the prominence of epidural venous dural space dorsal to dura with mild cord thinning from C4-C6.2 The posterior dural sac crescent appeared in T2/STIR as a hypertensive entity and enhanced uniformly postcontrast.

A study by Jase et al. proposed a rare form of mechanically induced chronic ischemic focal cervical myelopathy, in which local anterior compression of the dura and spinal cord against the back of the vertebral bodies occurs. It is caused by repeated neck flexion resulting in ischemia of anterior horn cells because of compression of the anterior spinal artery. The difference in balance between the growth of the vertebrae and the dura mater leads to a “tight dural canal” and “overstretched cord,” which is unable to compensate during neck flexion for the increased length of the posterior wall. Negative pressure is also generated in the posterior venous plexus of the marrow.2 The affected part of the spinal cord is flattened anteroposteriorly, the anterior horn is largely gliotic and atrophied, and both large and small motor neurons are reduced in number, as shown in studies.4

Differential diagnosis of “Hirayama disease” includes—ALS (most common), spinal muscle atrophy, multifocal motor neuropathy with conduction block, syringomyelia, compressive myelopathy, C8-T1 radiculopathy, cervical spondylotic myelopathy, multifocal motor neuropathy, toxic neuropathy, and postpolio syndrome.2,5

The mainstay of treatment includes prevention of flexion of the neck by using a cervical collar (for a period of about 3–4 years) that may arrest the progression of the disease. Muscle-strengthening exercises and assistive devices like splinting and braces can also be used along with a cervical collar.1,6

Conclusion

“Hirayama disease” is not a commonly encountered condition in clinical practice. A
If a young male patient presents with lower motor weakness of hands and forearms, unilateral or bilateral (asymmetrical), flexion MRI, NCV, and EMG should be performed to establish the diagnosis at the earliest. Early diagnosis and timely administration of cervical collars can prevent further atrophy and may be helpful in halting the disease process.

**References**

Acid looks good in Bottle not in STOMACH

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The GR8 Reliever

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GR8-O D

Capsules

(Pantoprazole 40 mg + Domperidone 30 mg)

One for the Day!
Diphtheritic Polyneuropathy: A Case Report
Harshavardhan L1, M Ananthakrishna2*
Received: 03 July 2022; Revised: 15 September 2022; Accepted: 29 September 2022

Abstract
Diphtheria is showing a resurgence in recent years. A fall in the immunity of adults to diphtheria due to multiple reasons is showing a rise in diphtheria cases in the adult population. Diphtheritic polyneuropathy shows a prevalence of 20–27% of infections. It affects the axial muscle and the palatine muscle fast.
Here we report a case of diphtheritic polyneuropathy in a 27-year-old COVID-19-infected man.

Introduction
Diphtheritic polyneuropathy can occur 2–50 days after the local diphtheria infection. This is due to exotoxin-mediated inhibition of protein synthesis.
Cases with diphtheritic polyneuropathy show a descending type of muscle paralysis. It shows around 20% of cases with ventilator dependence. It usually shows a slower recovery in comparison to GBS.

Case Description
A 27-year-old male was admitted to KR hospital on 6th May 2021 with moderate COVID-19 infection. The patient had no history of childhood immunization. The patient started treatment according to COVID-19 protocol and was provided with dexona 6 mg OD, Inj remdesivir, and oxygen supplementation. The patient’s oxygen requirement gradually reduced from 8 L/min to 2 L/min over the time of hospital stay. At around 2 weeks of the hospital, stay patient developed difficulty in swallowing both liquid and solid followed by which the patient’s sensorium also started deteriorating, for which the patient was shifted to ICU. Where on examination patient was found to be in a stuporous state with flaccid paralysis of all four limbs with upper limb predominance and the patient was having paradoxical breathing and other signs of diaphragmatic weakness.

CNS Examination
• HMF: Not elicited as the patient was in a stuporous state.
• Cranial nerves: Normal (EOM: Normal) (Pupils: BERL)
• Bulb: Equal
• Tone:
  • Absent
• Reflex: Deep
• Sensory examination: Not done
• B/I plantar: Mute

The patient was ruled out of any neuro infections from the MRI brain with contrast and CSF analysis being normal. The patient’s ABG was suggestive of type 2 respiratory failure in CO2 narcosis (PCO2–111 mm Hg). For the same, the patient was intubated to put on mechanical ventilator support, during the process of intubation a greyish-yellow membrane was noted in the patient’s tonsillar, para-tonsillar, and parapharyngeal area. This membrane was removed with great difficulty without bleeding manifestation from the site and was sent for microscopic examination (Fig. 1). Which suggested clumps of C. diphtheria with Albert staining showing bipolar metachromatic

Fig. 1: Microscopy of the membrane, Albert stain showing k.l.b

Fig. 2: Patient showing improvement in weakness after antitoxin injection

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granules. The patient was started on procaine penicillin G 6 lakh unit BD and also with 1 lakh unit of diphtheria antitoxin IV stat after consultation with WHO personnel.

After intubation and CO₂ washout patient regained sensorium. And then after the antitoxin dose patient drastically showed improvement in his weakness to the extent patient was able to lift all four limbs (Fig. 2).

A detailed CNS examination was reviewed: he had gained consciousness and revealed quadripareisis with UL power 3/5 and LL power 4/5, with no sensory involvement. Pure motor quadripareisis.

But still, the patient’s diaphragmatic weakness persisted for which the patient required around 2 months of ventilator support and diaphragmatic exercise.

The patient was further evaluated with NCS of Both upper limbs and lower limbs with phrenic nerve NCS, which concluded the patient was having demyelinating polyneuropathy suggestive of diphtheritic polyneuropathy (Figs 3 and 4).

Patient was discharged after the patient was no longer ventilator dependent and had no residual weakness (Fig. 5). On follow-up patients’ diphtheria IgM titers were evaluated which showed an increasing trend in a gap of 2 months. A repeat NCS was not done due to financial constraints (Fig. 6).

Discussion

Acute flaccid paralysis is a common neurological abnormality that occurs in a wide variety of situations like infections and immunological neuronal damage.¹

One of the most common causes of flaccid paralysis in adults is GBS.²

Fig. 3: NCS of patient showing demyelinating polyneuropathy

Fig. 4: Phrenic nerve NCS showing demyelinating with axonopathy

Fig. 5: Patient showing improvement in diaphragmatic weakness, patient off the ventilator
Diphtheritic Polyneuropathy

But studies show that diseases like diphtheritic polyneuropathy must be considered above GBS in clinical circumstances suggestive of diphtheria exposure.1,2

The exotoxins of diphtheria bind to the HB-EGF receptor found predominantly on Schwann cells and myocardium. This exotoxin causes inhibition of protein synthesis.3,4

The first symptom occurred 2–50 days after the onset of local diphtheria infection. The neurological deterioration continued for a median of 49 days and improvement started 73 days after onset. Bulbar dysfunction occurred in 98% of patients with diphtheritic polyneuropathy. Patients were ventilator dependent for longer duration in diphtheritic polyneuropathy with a comparison with GBS.3–5

Antitoxin has been tried in diphtheritic polyneuropathy and shows the most effective within 2–3 days of disease onset.1,3,4

References

4. Diphtheritic polyneuropathy in wake of resurgence of diphtheria by Manikyamba, A. Satyavani.
5. Resurgence of diphtheria in areas of north Karnataka – Mahantesh V Parande.

Fig. 6: Patient with no residual deficit on follow-up after 2 months
The Big picture of diabetes management across a broad patient population

Presenting

Oxra-S
Dapagliflozin 5mg + Sultamic Acid 150mg Tablets

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Dapagliflozin 510mg tablets

Oxramet
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Oxramet XR
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Avior
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French chemists isolated a substance, phlorizin, from the bark of apple trees in 1835; bitter compound was referred to as apple glycoside. It was discovered that phlorizin caused significant glycosuria, polyuria, and weight loss in dogs as in diabetes. In the early 20th century, phlorizin-induced diabetes was used in canine models for research in diabetes as well as for evaluating renal physiology.

Few would have foreseen that a day might come when phlorizin-like analogs will be used in the treatment of diabetes itself by a potential novel mechanism for reducing hyperglycemia.

By the early 1970s, research with phlorizin revealed the active transport system responsible for glucose reabsorption via specific carriers such as sodium-glucose transporting system (SGLTs), in proximal renal tubules. Phlorizin had a much higher affinity for these transporters in tubular brush borders than glucose. Here, potential novel mechanism for reducing hyperglycemia was realized. Interest in phlorizin returned in the late 1980s to early 1990s concurrent with the characterization of SGLTs. Animal studies performed in 90% of pancreatectomized diabetic rats demonstrated that phlorizin-induced glucosuria normalized blood glucose levels and reversed insulin resistance.

Historically, the kidney has not been thought of as one of the major organs responsible for glucose homeostasis. However, we now understand that the kidney plays a major role in glucose homeostasis in two ways—(1) gluconeogenesis and (2) glomerular filtration and reabsorption of glucose in the proximal convoluted tubules. A greater understanding of this is being explored.

Phlorizin could not be pursued as a medication for the treatment of diabetes due to its poor gastrointestinal (GI) tract absorption and its inhibition of SGLT1 primarily found in the GI tract along with SGLT2. Analogs of phlorizin have been developed that circumvent these two problems; pursuing SGLT2 inhibitors from O-glucoside to C-glucoside-based structures was first employed in the successful production of dapagliflozin. Currently, several of these analogs like canagliflozin, appear to be pharmacologically viable.

Dapagliflozin was well tolerated in human clinical trials. Moreover, the clinical safety profile enabled combination with other antidiabetic agents in a single formulation. After the safety and efficacy of dapagliflozin was confirmed in multiple clinical trials, Food and Drug Administration approved the use of dapagliflozin as monotherapy or add-on therapy with other antidiabetic agents including insulin. Moreover, their associations with decreased renal and cardiovascular adverse events are being evaluated.

What was a medical curiosity over 150 years ago is now being utilized to provide a novel insulin-independent agent to treat type 2 diabetes.
Prevalence of Metabolic Syndrome and Risk Factors in a Rural Population of Rajasthan

Arvind K Sharma1, Vaseem N Baig2, Jitendra Ahuja3, Sudhanshu Kacker4, Rajeev Gupta5

1Associate Professor; 2Professor, Department of Preventive and Social Medicine; 3Assistant Professor, Department of Biochemistry; 4Professor, Department of Physiology, RUHS College of Medical Sciences; 5Chairman, Academic Research Development Unit, Rajasthan University of Health Sciences (RUHS), Jaipur, Rajasthan, India.

Worldwide prevalence of metabolic syndrome varies from 10 to 84%, depending upon region, the composition of the population, and the diagnostic criteria used.1 In India, most of the studies have been performed in urban locations and data regarding its prevalence in rural areas are limited.2 Rural areas in India are rapidly evolving and there is evidence of an urban–rural convergence in many cardiovascular risk factors due to changing lifestyles consequent to economic growth, urbanization, and modernization.3

We performed a population-based survey in a cluster of villages in Rajasthan to identify the prevalence of metabolic syndrome. The study is registered at www.ctri.nic.in (Clinical Trials Registry-India/2017/09/009710) and was performed at the primary health center affiliated with our college. A total of 10 villages were selected (n = 13,457, ≥20y = 7,648, stratified target n = 1,200). Details of medical history, lifestyle, and anthropometric variables were obtained using a health worker administered questionnaire and physical examination. A fasting blood sample was obtained for the estimation of glucose and lipid profiles. Metabolic syndrome was diagnosed using International Diabetes Federation harmonized criteria,1 and reported prevalence varying from 20 to 30% in older studies to 40–50% in more recent studies.2 In the

<table>
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<th>Age-group</th>
<th>Number</th>
<th>Metabolic Syndrome</th>
<th>Waist size ≥90cm, women &gt;80 cm</th>
<th>Raised BP ≥130/≥85</th>
<th>Glucose (F) ≥100 mg/dL or diabetes</th>
<th>Triglycerides ≥150 mg/dL</th>
<th>HDL cholesterol men &lt;40 mg/dL, women &lt;50 mg/dL</th>
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<td>20–29</td>
<td>95</td>
<td>14 (14.7)</td>
<td>56 (58.9)</td>
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<td>5 (5.3)</td>
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<td>158</td>
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<td>77 (48.7)</td>
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<tr>
<td>60 +</td>
<td>96</td>
<td>46 (47.9)</td>
<td>41 (42.7)</td>
<td>65 (67.7)</td>
<td>26 (27.1)</td>
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<td>544</td>
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<td>285 (52.4)</td>
<td>256 (47.0)</td>
<td>86 (15.8)</td>
<td>122 (22.4)</td>
<td>361 (66.4)</td>
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</table>

| Men       |        |                   |                                |                   |                                  |                        |                                      |
| 20–29     | 109    | 15 (13.8)         | 21 (19.3)                      | 42 (38.5)         | 19 (17.4)                        | 15 (13.8)              | 55 (50.4)                        |
| 30–39     | 116    | 23 (19.8)         | 12 (10.3)                      | 65 (56.0)         | 24 (20.7)                        | 26 (22.4)              | 65 (56.0)                        |
| 40–49     | 91     | 21 (23.1)         | 3 (3.3)                        | 50 (54.9)         | 23 (25.3)                        | 33 (36.3)              | 46 (50.5)                        |
| 50–59     | 50     | 16 (32.0)         | 4 (8.0)                        | 31 (62.0)         | 12 (24.0)                        | 18 (36.0)              | 27 (54.0)                        |
| 60 +      | 102    | 34 (33.3)         | 13 (12.7)                      | 47 (46.1)         | 33 (32.3)                        | 36 (35.3)              | 59 (57.8)                        |
| Total     | 468    | 109 (23.3)        | 53 (11.3)                      | 235 (50.2)        | 111 (23.7)                       | 128 (27.3)             | 252 (53.8)                       |

| Overall   |        |                   |                                |                   |                                  |                        |                                      |
| 20–29     | 204    | 29 (14.2)         | 77 (37.7)                      | 69 (33.8)         | 24 (11.8)                        | 26 (12.7)              | 112 (54.9)                       |
| 30–39     | 274    | 66 (24.1)         | 89 (32.5)                      | 125 (45.6)        | 42 (15.3)                        | 61 (22.3)              | 171 (62.4)                       |
| 40–49     | 211    | 58 (27.5)         | 69 (32.7)                      | 112 (53.1)        | 47 (22.3)                        | 58 (27.5)              | 125 (59.2)                       |
| 50–59     | 125    | 49 (39.2)         | 49 (39.2)                      | 73 (58.4)         | 25 (20.0)                        | 38 (30.4)              | 80 (64.0)                        |
| 60 +      | 198    | 80 (40.4)         | 54 (27.3)                      | 112 (56.6)        | 59 (29.8)                        | 67 (33.8)              | 125 (63.1)                       |
| Total     | 1012   | 282 (27.9)        | 338 (33.4)                     | 491 (48.5)        | 197 (19.5)                       | 250 (24.7)             | 613 (60.6)                       |

F, fasting; HDL, high-density lipoprotein; numbers in parentheses are percent
present study, we observed a prevalence of 28% (CI 25—31%), which is lower than the recent studies in better developed states of Tamil Nadu, Goa, Uttarakhand, Kerala, Puducherry, and Karnataka and similar to states whose developmental status is similar to Rajasthan. Similar observations have been reported for the prevalence of hypertension, diabetes, and hypercholesterolemia in India. It is likely that the rapid pace of globalization associated with decreased physical activity and rapid nutrition transition is the reason for rapidly increasing cardiometabolic abnormalities in India. 

**REFERENCES**


**Spontaneous Pneumomediastinum in COVID-19 Pneumonia: A Report on Two Cases**

Ritwik Dey¹, Ramadoss Ramu², Ramanathan Venkateswaran³, Senthilnathan Muthapillai⁴

¹Postgraduate; ²Assistant Professor; ³Additional Professor, Department of Medicine; ⁴Associate Professor, Department of Anaesthesiology and critical care, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, Tamil Nadu, India. Correspondence

Dear editor

Coronavirus disease 2019 (COVID-19) is a new evolving disease and we are yet to characterize its protean clinical manifestations fully. Spontaneous pneumomediastinum (SPM) and spontaneous pneumothorax (PTX), not related to any form of positive pressure ventilation, are uncommon complications of COVID-19 infection. Diffuse alveolar damage in severe COVID-19 disease causes alveolar rupture leading to these complications, which may manifest as worsening respiratory failure. Such complications hamper gas exchange in the lungs and alter the patient’s prognosis. This correspondence discusses the clinical presentation of two patients with severe COVID-19 disease who developed spontaneous pneumomediastinum.

**CASE DESCRIPTION**

**Case 1**

A 45-year-old male with chronic kidney disease had a fever, myalgia, and mild cough for 2 days. COVID-19 was confirmed by a rapid antigen test. He had no complaints of breathlessness, chest pain, or vomiting. Following the fever, he developed worsening hypoxia and respiratory distress in the 2nd week of illness, for which he required oxygen through a nonrebreather mask. He was started on corticosteroids, heparin, and antibiotics. High-resolution computed tomography (HRCT) of the thorax showed severe COVID-19 pneumonia and normal mediastinum. He never received positive pressure ventilation, and he was transferred out of the COVID-19 care facility on day 31. On reception in the medical intensive care unit, his respiratory rate was 32 breaths/minute and oxygen saturation (SpO₂) was 96% on a nonrebreather mask at 12 L/minute of oxygen. Hammer’s crunch was absent. Normal vesicular breath sounds were heard bilaterally. Hemogram showed leucocytosis with a total count of 22,800 cells/µL—neutrophils 86% and lymphocytes 9%. His serum urea was 167 mg/dL and serum creatinine—2.98 mg/dL. His arterial oxygen pressure/fraction of inspired oxygen ratio was 79, suggesting severe acute respiratory distress syndrome (ARDS). HRCT of the thorax (on day 31) showed pneumomediastinum extending from the thoracic inlet to the diaphragm (Fig. 1A). We managed him conservatively for isolated pneumomediastinum. Repeat HRCT of the thorax on day 36 showed near-total resolution of pneumomediastinum (Fig. 1B). His oxygen requirement was gradually tapered and he was discharged on room air after 42 days of hospitalization.

**Case 2**

A 34-year-old male without comorbidities presented with fever, headache, cough, and breathlessness for 5 days. Reverse transcription polymerase chain reaction assay for COVID-19 was positive. At presentation, his SpO₂ was 95% at 10 L/minute of oxygen and respiratory rate at 28 breaths/minute. Systemic examination was normal. He was started on enoxaparin, corticosteroids, remdesivir, and antibiotics. His hemoglobin was 13.3 mg/dL, and total leucocyte count at 16,040 cells/µL—neutrophils 94% and lymphocytes 4%. C-reactive protein was 5.4 mg/dL and serum ferritin was at 1226.3 ng/mL. On day 10 of symptoms patient developed sudden onset of swelling over the right side of the neck extending to the right side of the chest and right upper limb. Examination revealed palpable crepitus below the skin, suggestive of subcutaneous emphysema (SCE). He also had worsening hypoxia, tachypnea, and increasing oxygen requirements. HRCT of the thorax revealed moderate pneumomediastinum, gross SCE and minimal PTX in the right apical area (Fig. 2). Noninvasive ventilation was initiated. Since the size of the PTX was increasing, we placed an intercostal tube. Subsequently, he required intubation and mechanical ventilation. He later expired on day 22 of illness.

This report highlights two unusual complications of COVID-19 pneumonia— SPM and spontaneous PTX. Mechanisms of
Correspondence

Xanthogranuloma is a benign, asymptomatic, self-resolving disease of non-Langerhans cell histiocytosis (LCH).1,2 Herein, we report a case of multiple cutaneous eruptive xanthogranulomas with hypertriglyceridemia and central nervous system (CNS) manifestation in a young adult. A 28-year-old male presented with multiple, asymptomatic, skin-colored, and reddish–brown raised lesions over the face, neck, axillae, and forearms for 2 years. Cutaneous examination revealed multiple skin-colored, reddish–brown papules, nodules of varying sizes, few grouped, present all over the face, predominantly involving eyelids, periorbital area, nose, perioral area (Fig. 1A), neck, bilateral axillae (Fig. 1B), and bilateral cubital fossae which were not tender and soft. Few ulcerated nodules were seen in the axillae (Fig. 1B). The oral cavity, palms, and soles were normal. A differential diagnosis of eruptive xanthoma and xanthoma disseminatum was made. Routine blood investigations were within normal limits and lipid profile showed high triglyceride (300 mg/dL), borderline high total (208 mg/dL), and low-density lipoprotein (159 mg/dL) cholesterol levels. The ophthalmologic examination was normal. Histopathology revealed a dense diffuse infiltrate of cells comprising foamy macrophages, histiocytes, lymphocytes, plasma cells, neutrophils, and eosinophils in the dermis (Fig. 2A). Spindle cell proliferation with focal storiform pattern (Fig. 2B) and a few Touton type giant cells were observed (Fig. 2C). The foamy cells were negative for a cluster of differentiation 68 (CD68), melan-A, cytokeratin, and S-100 immunostains. Later, the patient developed weakness in the right upper and lower limbs and difficulty in speaking, for which contrast-enhanced magnetic resonance (MR) imaging with MR angiography of the Circle of Willis and neck was done, which revealed multiple focal lacunar infarcts at the midbrain and cerebellum on the left side. He was diagnosed with right hemiplegia with aphasia and posterior circulation stroke, possibly because of hypertriglyceridemia, and treated accordingly. Xanthogranuloma presents as red, yellow, or brown papules, nodules predominantly affecting infants, children, and rarely adults. The majority of the cases are solitary and multiple lesions occurring in an eruptive manner are rare.1 Xanthogranuloma is usually non-lipidemic, non-LCH, but it has also been associated with hypertriglyceridemia, as seen in our case.2 Extra cutaneous involvement can also occur in the eye, CNS, lung, liver, and kidney mostly in the juvenile variant.1 A newly revised classification of “histiocytosis”

To conclude, pneumomediastinum, PTX, and SCE can be spontaneous complications seen in COVID-19 patients. COVID-19 causes severe diffuse alveolar damage, leading to alveolar rupture, thereby causing air leak syndrome. It is a harbinger of worsening respiratory failure and heralds a poorer prognosis for the patients. As a potential indicator of worsening disease, COVID-19 patients with SPM needs close monitoring.

REFERENCES

Cluster of Differentiation 68 Negative Eruptive Adult Xanthogranuloma

Amrithaa Muralitharan1, Reena Rai2, Umamaheswari Gurusamy3

1Postgraduate; 2Professor and HOD, Department of Dermatology; 3Professor, Department of Pathology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.

Fig. 2: HRCT-thorax showing moderate pneumomediastinum (black arrow), gross SCE involving the lower neck, shoulders, and chest wall (white asterisk), and minimal PTX in the right apical area (white arrow). Bilateral lung parenchyma had peripheral and central ground-glass opacities with a CT severity score of 23/25.
Correspondence

Journal of the Association of Physicians of India, Volume 71 Issue 3 (March 2023)

100

...limbs, buttocks, and mucosal surfaces and are usually associated with diabetes mellitus and hyperchylomicronemia. In xanthoma, disseminatum papules, plaques, and nodules occur with oral mucosa involvement and diabetes insipidus.2,4 Our case is unique because of the CD68 negativity, eruptive manner of presentation, hypertriglyceridemia, and CNS manifestation.

Figs 1A to B: (A) Multiple skin-colored, reddish–brown papules and nodules over the face; (B) axillae shows multiple skin-colored, reddish–brown papules and few ulcerated nodules.

Figs 2A to C: (A) Upper and mid dermis is expanded by a dense diffuse infiltrate of cells comprising of foamy macrophages (red arrows), histiocytes, lymphocytes, plasma cells, neutrophils, and eosinophils (H and E, 40x); (B) spindle cell proliferation with focal storiform pattern (H and E, 10x); (C) a Touton type giant cell (black arrow) is seen (H and E, 40x).

was devised, dividing them into five groups, consisting of L, C, M, R, and H groups. Adult xanthogranuloma is included in the C-group comprising non-LCH of the skin and mucosa. The non-LCH group is defined by the accumulation of macrophages/dendritic cells that do not meet the ultrastructural and phenotypic criteria for the diagnosis of Langerhans cells. The non-LCH histiocytes are positive for CD-68 and factor XIIIa and negative for CD-1a, and S-100.5 CD68 is an organelle-specific marker for lysosomes rather than a lineage-specific marker. The negative CD68 expression in our case might be attributable to scant lysosomes in the mononuclear cells.7 Eruptive xanthoma and xanthoma disseminatum were considered differential diagnoses. In eruptive xanthoma, yellowish papules occur on the extensor aspect of limbs, buttocks, and mucosal surfaces and are usually associated with diabetes mellitus and hyperchylomicronemia. In xanthoma, disseminatum papules, plaques, and nodules occur with oral mucosa involvement and diabetes insipidus.2,4 Our case is unique because of the CD68 negativity, eruptive manner of presentation, hypertriglyceridemia, and CNS manifestation.
REFERENCES


SHORT CERTIFICATE UPDATE COURSE

The Short Certificate Update Courses (online) carried out under the aegis of ICP/API in 2022 had become very popular and generated a lot of interest. The courses were free of cost and participants were given certificates by ICP at the end of the course. Faculty wishing to conduct such courses in the year 2023 may apply with the following information:

- Name of the Course
- Name of the Course Director
- Short CV of the Course Director
- Course module—number of classes, topics, number of hours

Please apply at icpdean2023@gmail.com/api.hdo@gmail.com

Dr Jyotirmoy Pal
Dean, ICP

Journal of the Association of Physicians of India, Volume 71 Issue 3 (March 2023)
Indian College of Physicians

Eligibility Criteria for the Award of Fellowship of Indian College of Physicians

5.2.1.1 Minimum experience of 10 years after Post Graduation.
5.2.1.2 Continuous membership of the Association of Physicians of India for not less than 7 yrs.
5.2.1.3 Should have made a significant contribution to research/teaching/development in the field of medicine.
5.2.1.4 Should have contributed to API by way of scientific or Organizational works.

To make the selection objective, a point system has been followed in assessing the suitability of the applications.

The Criteria used by the Credentials Committee for the award of fellowship are:

1. Qualification
2. Experience in Medical Profession
3. Publications
4. Honors/Awards
5. Research work
6. Contribution to API
7. CME & Conference (API/ICP)
8. Social welfare/ community service

The Fellowship form should be proposed and seconded by Founder Fellow/Fellow of ICP only.
- The Proposer/Seconder should not propose/second more than 3 nominees for award of ICP in a particular year.
- It is responsibility of the Nominee/applicant to get the proposal completed by the proposer and seconder along with the citation.
- API Membership No. of the proposer/seconder should be entered by the proposer/seconder themselves.
- The proposer should satisfy the requirements for proposal as under:
  - The Nominee is a life member of API
  - The Nominee has completed 10 years after post-graduation
- The Nominee should read the Form carefully before filling the columns, to project their achievements appropriately.
- The Nominee should list their achievements in appropriate columns.
- Proof of qualifications, publications, honors, awards, must be submitted as supporting data. The supporting data should be numbered parawise (e.g. 1., 2., 3., etc.). For more than one supporting documents, the numbering should be in alphabets (e.g. 1 (a), (b), (c), etc.).
- No hand written applications will be accepted.
- One original and seven Xerox copies to be submitted

Dr. Agam Vora
Hon. General Secretary

Dr. A. M. Bhagwati
Jt. Secretary

Available on API and JAPI Websites: www.apiindia.org & www.japi.org
Format for Submission of Bio-Data of The Nominee for Consideration for Award of Fellowship of Indian College of Physicians.

1. **Name in Full (Surname First)**
   (in Block Letters)

2. **A. P. I. Membership No. and date of joining**

3. **Date of Birth**

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   *Certificates Attached*

6. **Experience in Medical Profession after Postgraduation in Medicine**

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7. **Publications: List below.** (If number of publications in Journals exceeds 8, publications which can qualify as research papers may be listed under Research section 9.)

   a) **Number of Publications in Indexed National/International Journals.**

   Attach title page/Abstract as Appendix

   b) **Number of Chapter in Books/monograms**

   c) **Editorship of National level or State level: Book /Monogram/Update Series**

8. **Honors and Awards** (list below with photocopy of proof)

   a) **Oration in National/State Association Meeting**

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### Award National/International/or State level

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<th>Year</th>
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### Research work (list below)

- (a) Research sanctioned & funded by Research Agency
  - Attach Letter of sanction.

- (b) Departmental Research. (To qualify, the findings should be published in National/International Journal) Do not include papers already listed under Publications
  - Attach title page/Abstract

### Contribution to API (list below and attach proof)

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### Participation in CME or Scientific Sessions of API or ICP as Faculty

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### Social welfare/Community service.

- (a) Emergency services during National calamities (Quakes/Floods/Cyclones, etc.)
- (b) Public education Program (Radio), TV talk/writing in newspapers.
- (c) Service in Rural Areas

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<th>Evidence</th>
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**N.B:** No handwritten application will be accepted. *To be typed on separate page*

*One original and seven Xerox copies of sets to be submitted*

Address: Turf Estate, No. 006 & 007, Dr. E. Moses Road, Opp. Shakti Mill Compound, Mahalaxmi (West), Mumbai – 400 011.
Indian College of Physicians

Citation

The Fellows proposing and seconding the nomination for Fellowship of Indian College of Physicians should highlight the professional/scientific achievements of the candidate and the contribution to A. P. I. from personal knowledge in 200 words, in the format given below:

| Name ________________________________ | Name ________________________________ |
| Membership No. ___________________________ | Membership No. ___________________________ |
| Signature Proposer ________________________ | Signature Seconder ________________________ |

Note: The Fellowship form should be proposed and seconded by Founder Fellow/Fellow of ICP only. In case there are more than 3 nominations by any proposer/seconder, the first three nominations in order of receipt in API Office and complete in all respects will be considered for award of Fellowship of ICP and the others rejected for consideration.
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<td>77%</td>
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\( p<0.01 \)

OLIVUS Study: Lowers rate of coronary Atheroma progression

OLIVUS Study: Lowers rate of coronary Atheroma progression


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Imeglimin Tablets

*Fundamentally Different & Effective*

Multi-targeted actions are rendered through mitochondrial bioenergetics in the pancreatic beta-cells, liver & the muscles