DOI: 10.7860/NJLM/2025/78762.2920

Original Article

Pathology Section

Clinical and Aetiological Profile of Thrombocytopenia in Adults: A Cross-sectional Study

MD HUSSAIN D PAGE[1], PREETI GUPTA[2], TRUPTI PISAL[3]

ABSTRACT

Introduction: Thrombocytopenia, characterised by low platelet count, is a common haematological condition associated with various infectious diseases, including dengue and malaria. Understanding the relationship between the severity of thrombocytopenia and bleeding manifestations is crucial for effective patient management.

Aim: To determine the clinical and aetiological profile of patients with thrombocytopenia and assess the association between the severity of thrombocytopenia and bleeding manifestations across different conditions.

Materials and Methods: This cross-sectional study was carried out at a tertiary care hospital from July 2022 to January 2024 and a total of 197 patients with platelet counts below 150,000/µL were included. Patients were categorised based on their platelet counts and World Health Organisation (WHO, 1981) bleeding grades. Clinical data, including demographics, laboratory findings and bleeding manifestations, were collected and analysed. The need for platelet transfusion was assessed in relation to the severity of thrombocytopenia. Descriptive statistics were used and results presented in means and percentage.

Results: Dengue (n=97, 49.2%), malaria (n=47, 23.9%) and sepsis (n=19, 9.6%) were the most frequent aetiological causes of thrombocytopenia, with *P. vivax* malaria diagnosed in 31 (65.9%) of the malaria patients. Physical examination revealed skin manifestations (petechiae, purpura, bruises, ecchymosis and hyperpigmentation) in 14 (60.9%) patients, followed by bleeding gums in 8 (34.8%) patients. The prevalence of moderate thrombocytopenia (75,000-150,000/µL) was noted in 73 (37.1%) patients, while only 40 (20.3%) had severe thrombocytopenia with platelet counts <25,000/µL. Among the 23 patients with bleeding, 16 (69.6%) had WHO grade 1, with 15 (65.2%) requiring platelet transfusion.

Conclusion: The study highlighted the high prevalence of moderate thrombocytopenia in patients with dengue and malaria. Patients with moderate and severe thrombocytopenia presented with bleeding manifestations and required platelet transfusion.

Keywords: Aetiology, Bleeding manifestation, Dengue, Malaria, Platelet

INTRODUCTION

Thrombocytopenia, a frequently prevalent clinical condition, is characterised by a decrease in peripheral blood platelet counts below the normal threshold of 150,000/µL [1]. Based on the platelet counts, thrombocytopenia is categorised as mild (100,000 to 150,000/µL), moderate (50,000 to 100,000/µL) and severe (less than 50,000/µL) [2]. The severity of thrombocytopenia is closely correlated with the risk of bleeding, as evidenced in the literature. For instance, patients with platelet counts above 50,000/µL are often asymptomatic, while those with counts between 30,000 and 50,000/µL may present with purpura or experience bleeding only with trauma [3]. In contrast, counts below 30,000/µL significantly increase the risk of spontaneous bleeding, petechiae and bruising, particularly when counts drop below 10,000/µL, which is considered a haematological emergency [4].

In recent years, fever accompanied by thrombocytopenia has emerged as a common clinical presentation in tertiary care hospitals, often complicating the diagnostic and therapeutic landscape. Established infectious causes, particularly dengue fever, are well-documented for their association with thrombocytopenia, exhibiting a prevalence of 40-79% and posing a significant risk of mortality due to bleeding complications [2]. Additionally, malaria, endemic in many regions of India, is frequently linked to mild thrombocytopenia, with studies indicating an incidence range of 40.5-85% [5]. The clinical implications of thrombocytopenia extend beyond platelet counts, as factors such as coagulopathy and the underlying aetiology significantly influence bleeding risk. For instance, in primary Immune Thrombocytopenic Purpura (ITP), the severity of thrombocytopenia does not consistently predict bleeding outcomes, indicating that platelet function and other haemostatic factors are critical [6].

Given the complexity of thrombocytopenia and its associated risks, early identification and intervention are crucial to prevent fatal outcomes. While numerous studies have focused on specific aetiologies or symptoms like fever in adults with thrombocytopenia [7,8], there remains a notable gap in comprehensive research addressing the wide aetiological spectrum of thrombocytopenia in India [9,10]. Therefore, the present study aimed to elucidate the clinical and aetiological profiles of patients with thrombocytopenia without bicytopenia or pancytopenia, while examining the concordance between the severity of thrombocytopenia and bleeding manifestations.

MATERIALS AND METHODS

This cross-sectional hospital-based study was conducted over 19 months (July 2022 to January 2024) in the Department of Medicine at Jagjivan Ram Hospital, Mumbai, Maharashtra, India. The study was carried out in accordance with the Declaration of Helsinki and Indian Council of Medical Research (ICMR) and Good Clinical Practice (GCP) guidelines and written informed consent was obtained from the patients. The study was approved by the Scientific Reserach Committee of Jagjivan Ram Railway Hospital (No. E/MD/173//1/MS/Pt-III/DNB, Dated: 11 July 2022).

Inclusion criteria: Patients of both sexes aged over 18 years who attended the in-patient or out-patient departments with a platelet count below 150,000/µL, regardless of their symptoms were included in the study.

Exclusion criteria: Patients with bicytopenia (thrombocytopenia with either leukopenia or erythrocytopenia) or pancytopenia (thrombocytopenia combined with leukopenia and erythrocytopenia) were excluded from the study.

Sample size estimation: Sample size was estimated by prevalence and was calculated to be 197 patients using the following formula:

$$n=\frac{Z^2\,pq}{L^2}$$

Where z=standard normal variate at a 95% confidence interval (1.96), p=prevalence of thrombocytopenia in the general population (29.3%), q=100-p, 100-29.3=70.7, and L=allowable error at a 95% confidence interval and 5% level of significance [12].

Data collection: Data collection was conducted using a detailed case report form after obtaining written informed consent. A detailed clinical history was recorded, documenting symptoms such as bleeding manifestations (e.g., epistaxis, gum bleeding, haematemesis, melena, bleeding per rectum, menorrhagia and haematuria) and signs (e.g., petechiae, purpura, intracerebral haemorrhage). General examinations assessed physical parameters, including pallor, cyanosis, clubbing, pedal oedema and neck veins, along with an evaluation for splenomegaly and hepatomegaly.

Routine investigations, including Complete Blood Count (CBC), Random Blood Sugar (RBS), Renal Function Test (RFT), Liver Function Test (LFT), urine routine and microscopy (urine R/M), Human Immunodeficiency Virus (HIV), hepatitis B surface antigen (HBsAg), Electrocardiogram (ECG), chest X-ray, Bleeding Time (BT), Clotting Time (CT), peripheral smear and serial platelet counts, were performed for all patients. Special investigations, such as bone marrow examination, were conducted only when required for planning further management according to the departmental treatment protocol.

Haemorrhagic manifestations were classified based on the involvement of skin, subcutaneous tissue, mucous membranes, soft tissue and muscle. Data collection and analysis utilised the World Health Organisation (WHO, 1981) grading system for haemorrhagic manifestations. Platelet counts were categorised into grade 1 (75,000–150,000/µL), grade 2 (50,000–75,000/µL), grade 3 (25,000–50,000/µL) and grade 4 (<25,000/µL) for analysis [11].

All patients received supportive care, including platelets and blood transfusions when necessary, along with specific treatment tailored to their aetiology, following hospital protocols.

Study protocol: Baseline platelet counts were performed on the day of admission and repeated on alternate days until a normal or near-normal platelet count was achieved. In patients with bleeding manifestations or a platelet count below 50,000/µL, daily platelet counts were conducted until a rising trend was observed. All patients received supportive care and specific treatment following a definitive diagnosis. Patients with platelet counts below 20,000/µL or with bleeding manifestations were treated with platelet concentrate, as indicated. Patients were monitored throughout their hospital stay and diagnoses for each case were recorded. The proportion of patients receiving platelet transfusions due to bleeding manifestations and those requiring prophylactic platelet transfusions was determined.

The classification of platelet transfusion into either therapeutic (to treat bleeding) or prophylactic (to prevent bleeding) was based on the modified WHO bleeding score [13]. Recommendations for prophylactic transfusion relate to patients with bleeding scores of 0 or 1, while therapeutic transfusion is indicated for patients with bleeding scores of 2 or higher.

STATISTICAL ANALYSIS

Descriptive statistics were used. Categorical and continuous variables were represented as frequency (percentage) and mean±standard deviation, respectively.

RESULTS

The patients were predominantly male (n=126, 64%) and belonged to the age group of 18-30 years (n=85, 43.1%). The patients mainly presented with fever (n=162, 82.2%), generalised weakness (n=127, 64.5%) and headache (n=77, 39.1%), with the most common sign being conjunctival suffusion (n=69, 35%), followed by dehydration (n=66, 33.5%) and rashes (n=45, 22.8%). Dengue (n=97, 49.2%), followed by malaria (n=47, 23.9%) and sepsis (n=19, 9.6%), were the most frequent causes of thrombocytopenia. One patient had both malaria and enteric fever. Among patients with malaria, the majority were diagnosed with *P. vivax* malaria (n=31, 65.9%). Less than half of the patients had a non vegetarian diet (n=94, 47.7%) and around one third had a history of alcohol intake (n=63, 32%) [Table/Fig-1].

Characteristics	n (%)
Age group, years	
18-30	85 (43.1)
31-40	49 (24.9)
41-50	18 (9.1)
51-60	18 (9.1)
61-70	27 (13.7)
Gender	
Male	126 (64)
Female	71 (36)
Symptoms	
Fever	162 (82.2)
Generalised weakness	127 (64.5)
Headache	77 (39.1)
Chills and rigour	61 (31.0)
Abdominal pain	58 (29.4)
Vomiting	28 (14.2)
Loss of weight	10 (5.1)
Breathlessness	10 (5.1)
Cough	8 (4.1)
Bleeding gum	8 (4.1)
Haematuria	7 (3.6)
Diarrhoea	6 (3.0)
Constipation	6 (3.0)
Oliguria	5 (2.5)
Asymptomatic	2 (1.0)
Signs	
Conjunctival suffusion	69 (35.0)
Dehydration	66 (33.5)
Rashes	45 (22.8)
Gastrointestinal bleed	5 (2.5)
Altered sensorium	4 (2.0)
Diagnosis (n=198)	
Dengue	97 (49.2)
Malaria	47 (23.9)
Sepsis	19 (9.6)
Immune Thrombocytopenic Purpura (ITP)	15 (7.6)
Enteric fever	7 (3.5)
Chronic liver disease	6 (3.0)
Unknown	5 (2.5)
Pyrexia of unknown origin	1 (0.5)
Myelodysplastic syndrome	1 (0.5)
Type of malaria (n=47)	
Vivax malaria	31 (65.9)
Clinical malaria	9 (19.2)

Falciparum malaria	7 (14.9)
History (n = 197)	
Non vegetarian diet	94 (47.7)
Alcoholism	63 (32.0)
H/O Thrombocytopenia in past	27 (13.7)
H/O travel	18 (9.1)
H/O platelet transfusion	16 (8.1)
Any long-term medication	14 (7.1)
H/O recent vaccination	13 (6.6)
Family H/O thrombocytopenia/bleeding	9 (4.6)
H/O Liver disease	8 (4.1)

[Table/Fig-1]: Demographic and clinical characteristics.

Of the 15 (7.6%) patients with ITP, 9 (60%) were female. These patients primarily presented with rashes, conjunctival suffusion and generalised weakness (each n=5, 33.33%) and were mainly managed with Eltrombopag + Steroids (n=6, 40%), Eltrombopag + Vitamin B12 injections (n=4, 26.7%) and Eltrombopag + Rituximab (n=4, 26.7%) [Table/Fig-2].

Characteristics	n (%)
Gender	
Female	9 (60.0)
Male	6 (40.0)
Signs and symptoms	
Rashes	5 (33.3)
Conjunctival suffusion	5 (33.3)
Generalised weakness	5 (33.3)
Bleeding gum	3 (20.0)
Haematuria	3 (20.0)
Asymptomatic and no signs	2 (13.3)
Gastrointestinal bleed	1 (6.7)
Loss of weight	1 (6.7)
Dehydration	1 (6.7)
Treatment modality	
Eltrombopag + Steroids	6 (40.0)
Eltrombopag + Vitamin B12 injections	4 (26.7)
Eltrombopag + Rituximab	4 (26.7)
Platelet transfusion	3 (20.0)
Antibiotics	3 (20)
Withdrawal of offending drug	2 (13.3)
Eltrombopag only	1 (6.7)

[Table/Fig-2]: Characteristics of ITP cases.
ITP: Immune thrombocytopenic purpura

On physical examination, petechiae, purpura, bruises, or ecchymosis (n=24, 12.2%) were the most frequently observed, followed by pallor (n=8, 4.1%). Of the 197 patients, 23 (11.7%) had haemorrhagic manifestations, mainly skin manifestations (petechiae, purpura, bruises, ecchymosis and hyperpigmentation) (n=14, 60.9%), followed by bleeding gums (n=8, 34.8%) [Table/Fig-3].

Characteristics	n (%)
Examination findings (n = 197)	
Petechia, purpura, bruises or ecchymosis	24 (12.2)
Pallor	8 (4.1)
Signs of liver failure, stigmata of alcoholism	6 (3.0)
Splenomegaly	6 (3.0)
Sternal tenderness	3 (1.5)
Hepatomegaly	2 (1.0)
Tenderness of any long bone or joints	1 (0.5)
Haemorrhagic manifestation (n = 23)	
Skin manifestation (petechiae, purpura, bruises, ecchymosis, hyperpigmentation)	14 (60.9)
Bleeding gums	8 (34.8)
Haematuria	7 (30.4)
Gastrointestinal bleed	5 (21.7)

[Table/Fig-3]: Examination findings in isolated thrombocytopenia and haemorrhagic manifestations.

Overall, the most common blood group was O positive (n=92, 46.7%), followed by B positive (n=45, 22.8%) and A positive (n=25, 12.7%), in decreasing order. In patients with dengue, malaria and ITP, the most common blood group was O positive (n=49, 50.5%; n=24, 51.1%; and n=6, 40%, respectively). In corresponding cases, the second most common blood group was B positive (n=23, 23.7%), while A and B positive (each n=8, 17%) and A positive (n=5, 33.3%) were also noted [Table/Fig-4].

Blood group	Total (n=197)	Dengue (n=97)	Malaria (n=47)	ITP (n=15)
O positive	93 (47.2)	49 (50.5)	24 (51.1)	6 (40.0)
B positive	45 (22.8)	23 (23.7)	8 (17.0)	2 (13.3)
A positive	25 (12.7)	12 (12.4)	8 (17.0)	5 (33.3)
O negative	11 (5.6)	4 (4.1)	3 (6.4)	0
AB positive	9 (4.6)	5 (5.2)	3 (6.4)	2 (13.3)
B negative	6 (3.0)	0	0	0
A negative	5 (2.5)	4 (4.1)	1 (2.1)	0
AB negative	3 (1.5)	0	0	0

[Table/Fig-4]: Blood groups of patients with dengue, malaria and ITP.

The majority of the patients had a platelet count in the range of 75,000-150,000 /cumm (n=73, 37.1%). Only 40 (20.3%) patients had a platelet count of <25,000 /cumm and 15 (37.5%) of these patients required platelet transfusion. Thus, platelet transfusion was required in only 15 (8%) patients of the study population [Table/Fig-5].

Platelet count (/cumm) range	No. of cases	Patients that required platelet transfusion		
		Cases	% of subgroup	% of total
<25000	40 (20.3)	15 (37.5%)	37.5%	8.0%
25000 - 50000	42 (21.3)	0	0	0
50000 - 75000	42 (21.3)	0	0	0
75000 - 150000	73 (37.1)	0	0	0

[Table/Fig-5]: Platelet counts of the study population.

Of the 23 (11.68%) patients with bleeding, the majority had WHO grade 1 (n=16, 69.6%), followed by grade 2 (n=5, 21.7%) and grade 3 (n=2, 8.7%). Among these patients with bleeding, 15 (65.2%) required platelet transfusion, with 46.7% (n=7) and 53.3% (n=8) being therapeutic and prophylactic in nature, respectively. Based on WHO grades, 8 (50%), 5 (100%) and 2 (100%) patients with grades 1, 2 and 3 bleeding, respectively, required platelet transfusion [Table/Fig-6].

WHO grade	No. of cases	No. of patients who required platelet transfusion
Grade 1	16 (69.6%)	8 (50%)
Grade 2	5 (21.7%)	5 (100%)
Grade 3	2 (8.7%)	2 (100%)
Total	23 (100%)	15 (65.2%)

[Table/Fig-6]: Comparison between the grade of bleeding and platelet transfusion.

DISCUSSION

Thrombocytopenia, characterised by a platelet count below 150,000/µL, is a prevalent clinical condition with varying severity and bleeding risks. Mild cases are often asymptomatic, while severe

thrombocytopenia (<30,000/µL) increases the risk of spontaneous bleeding. Infectious diseases like dengue and malaria are major causes, with reported incidences of 40–85%. Platelet count alone may not predict bleeding severity, as coagulation factors also play a role. Despite several studies on specific causes, comprehensive research on the diverse aetiologies of thrombocytopenia in India is limited. This study evaluated the clinical and aetiological profiles of thrombocytopenia and its concordance with bleeding manifestations.

The principal findings of the study reveal that dengue was the most common aetiology, followed by malaria and sepsis. Most patients had grade 1 thrombocytopenia and a few had bleeding manifestations (11.68%), primarily skin-related. Additionally, the majority of patients with bleeding manifestations were classified as WHO grade 1, while all patients with grades 2 and 3 required platelet transfusions.

The most common aetiology of newly diagnosed thrombocytopenia in adults was dengue (49.2%). Dengue viruses have been isolated from polymorphonuclear leukocytes, monocytes/macrophages, dendritic cells and megakaryocyte progenitors, as well as being detected in megakaryocyte progenitors and circulating platelets [7]. Impaired thrombopoiesis and peripheral platelet destruction are proposed mechanisms for dengue-induced thrombocytopenia, which aligns with studies identifying dengue as the leading cause [14]. Malaria (23.9%) was the second most common cause, with thrombocytopenia observed in both *P. falciparum* and *P. vivax* malaria. In the present study, 65.9% of malaria patients had *P. vivax,* consistent with the findings of Krishna P and Chalamalasetty MK, who reported fever in 42% of patients with thrombocytopenia due to *P. vivax* [15]. The reported frequency of thrombocytopenia in malaria ranges from 24-94% [5]. It is postulated that malaria-induced thrombocytopenia results from malarial antigens binding to platelet surfaces, promoting the attachment of antimalarial antibodies, which leads to the in situ formation of immune complexes [15].

In the present study, 15 patients were diagnosed with ITP, of whom 60% were female, indicating a potential gender predisposition. This aligns with prior studies reporting a higher prevalence of ITP in women, particularly during their reproductive years, possibly due to hormonal and autoimmune factors [16]. Patients primarily presented with clinical symptoms that were consistent with the disease pathophysiology, where low platelet counts lead to bleeding and microvascular haemorrhages. Treatment predominantly included Eltrombopag combined with steroids, Vitamin B12 injections and Rituximab. Eltrombopag, a thrombopoietin receptor agonist, stimulates platelet production, especially in refractory patients. Steroids reduce immune-mediated platelet destruction, while Vitamin B12 addresses potential deficiencies that may exacerbate thrombocytopenia. Rituximab, an anti-CD20 monoclonal antibody, targets B cells producing platelet-specific antibodies in refractory ITP [17].

In the present study, 11.7% of patients exhibited bleeding symptoms, with the most common being petechiae, purpura, bruises, or ecchymosis and hyperpigmentation, observed in 60.9% of patients, followed by bleeding gums (34.8%). Choudhary MK et al., reported that 60% of patients had bleeding manifestations, with petechiae, purpura and ecchymosis noted in 30%, followed by gum bleeding in 16.6% [18]. In contrast, Moluguri S et al., reported that bleeding manifestations were observed in 12% of severe thrombocytopenia cases (platelet count <20,000/mm^3) during the defervescence phase, with melena being the most common, followed by epistaxis, gum bleeding and cutaneous bleeding [19]. The difference could be attributed to the exclusion of patients with anaemia, leucopenia and pancytopenia in the present study.

The present study observed moderate thrombocytopenia among the study population, highlighting that patients, particularly those with viral infections like dengue and malaria, often exhibit moderate reductions in platelet counts rather than severe thrombocytopenia. The relatively low incidence of severe thrombocytopenia suggests that while thrombocytopenia is common, critically low platelet counts are less frequent in this cohort. The prevalence of moderate thrombocytopenia is attributed to the pathophysiological mechanisms of dengue and malaria. In dengue, thrombocytopenia occurs primarily due to impaired thrombopoiesis, platelet sequestration in the spleen and immune-mediated destruction of platelets [2]. Similarly, in malaria, thrombocytopenia is caused by splenic sequestration and immune-mediated destruction, particularly in patients with *P. falciparum* and *P. vivax* infections [5]. The moderate platelet counts observed may reflect the compensatory mechanisms of the body, maintaining platelet levels above critical thresholds despite increased platelet destruction. These findings align with Gebreweld A et al., who reported that 67% of patients had moderate thrombocytopenia, with malaria due to *P. vivax* being the most common aetiology in 75.34% of patients [20]. However, studies have reported a correlation between moderate to severe thrombocytopenia and bleeding outcomes in dengue and malaria, indicating that platelet count alone is a poor predictor of bleeding in dengue patients, where platelet dysfunction may also contribute to bleeding [21].

The literature suggests a link between the severity of thrombocytopenia and bleeding risk, as lower platelet counts increase the likelihood of bleeding. In the present study, 37.5% of patients with platelet counts <25,000/µL required platelet transfusion, suggesting that severe bleeding is more common in cases of critically low platelet counts. This was consistent with findings from Gamit M and Rathod G, who reported that 19.75% of patients needed transfusions, with 8.75% of these patients having counts below 25,000/µL and 44% with counts above 10,000/µL [10]. In contrast, patients with moderate thrombocytopenia typically experience milder bleeding, such as petechiae or bruising and are less likely to need transfusions. However, studies suggest that bleeding can occur even with moderate thrombocytopenia, indicating that factors like coagulopathy or underlying health conditions also influence bleeding risk [22].

In the present study, the majority of patients with bleeding were classified as WHO grade 1 (69.6%), followed by grade 2 (21.7%) and grade 3 (8.7%), indicating that mild bleeding events predominated in this cohort. This pattern is likely due to the underlying conditions causing thrombocytopenia, such as dengue, malaria and ITP, which typically result in moderate platelet reductions rather than severe thrombocytopenia [23]. The higher incidence of grade 1 bleeding can be attributed to relatively stable platelet counts in many patients, leading to mild symptoms like petechiae or minor bruising, instead of severe haemorrhagic events [24]. Among patients with bleeding, 65.2% required platelet transfusion, with 50% of grade 1 patients needing transfusions, suggesting that even mild bleeding may require intervention, especially in the context of underlying infections. All (100%) patients with grade 2 and 3 bleeding required transfusions, emphasising the higher risk of severe bleeding as thrombocytopenia worsens. Vigneron C et al., found a strong correlation between bleeding severity and transfusion requirements in haematologic malignancies, which aligns with these findings [25]. Conversely, Balitsky AK et al., suggested that grade 1 bleeding may not always necessitate transfusion, as many patients can be managed with supportive care alone [26].

Limitation(s)

The present study examined thrombocytopenia in patients with dengue, malaria and ITP, offering insights into their clinical and haematological profiles. However, the findings may be limited by the relatively small sample size of 197 patients, which affects generalisability. Larger studies could provide more robust data on the relationship between bleeding severity and thrombocytopenia. Additionally, the cross-sectional design may introduce biases related to data collection and patient selection.

CONCLUSION(S)

The aetiological findings of the study demonstrated that dengue, malaria and sepsis are significant contributors to thrombocytopenia, with dengue being the most prevalent. The majority of patients exhibited moderate thrombocytopenia and a notable proportion experienced bleeding manifestations, primarily classified as WHO grade 1, with bleeding symptoms being predominantly skin-related. This indicates the need for vigilant monitoring of patients. Furthermore, the requirement for platelet transfusions, particularly among those with WHO grades 2 and 3, emphasises the importance of timely intervention in managing thrombocytopenia-related complications.

Acknowledgement

Authors would like to thank Dr. Vikas S. Sharma (MD), CEO, Maverick Medicorum® (India), for statistical analysis and medical writing assistance in the preparation of this article.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Medicine, Jagjivan Ram Hospital, Mumbai, Maharashtra , India.
2. Senior Divisional Medical Officer, Department of Medicine, Jagjivan Ram Hospital, Mumbai, Maharashtra, India.
3. Senior Divisional Medical Officer, Department of Medicine, Jagjivan Ram Hospital, Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Preeti Gupta,
Senior Divisional Medical Officer, Department of Medicine, Jagjivan Ram Hospital, Mumbai-400008, Maharashtra, India.
E-mail: preetigupta401@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 24, 2025
- Manual Googling: Apr 03, 2025
- iThenticate Software: Apr 26, 2025 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 23, 2025**
Date of Peer Review: **Mar 08, 2025**
Date of Acceptance: **Apr 29, 2025**
Date of Publishing: **Jul 01, 2025**