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Immunopathol Persa. 2025;11(2):e40595 Original

Immunopathologia Persa

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DOI:10.34172/ipp.2025.40595

Low platelet counts and monocytosis were associated with reduced risk of severe COVID-19 manifestation: a single-center study from Indonesia

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Received 29 Sep. 2023
Accepted 15 Nov. 2024
ePublished 11 Jan. 2025

Keywords: COVID-19, Monocyte, Monocytosis, Platelet, Thrombocytopenia, Indonesia

Abstract

Introduction: Severe morbidity and mortality in COVID-19 are linked to an inflammatory 'cytokine storm' driven by hyperactive macrophages and altered monocyte function. Identifying early immune predictors of severe COVID-19 outcomes is critical for optimizing patient care and resource allocation, especially under a resource-limited setting.

Objectives: This study aimed to investigate the relationship between monocyte and platelet levels and COVID-19 severity at a secondary hospital in East Java, Indonesia.

Patients and Methods: A single-center, cross-sectional study was conducted by utilizing electronic medical health records from 100 patients admitted to the Siti Khodijah Muhaammadiyah Sepanjang hospital May to September 2021. Initial complete blood counts were retrieved from adult patients who tested positive for COVID-19 by real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). A backward-stepwise multivariate regression model was incorporated to evaluate the association between platelet and monocyte levels with COVID-19 severity.

Results: Despite the non-association in the bivariate analysis, thrombocytopenia significantly reduced the risk of severe COVID-19 manifestation in the multivariate model (aPR 0.184; 95% CI: 0.047-0.722). Interestingly, patients with monocytosis had a lower risk of the severe disease compared to those with normal monocytes both in the bivariate and multivariate analyses (PR 0.364; 95% CI [0.157-0.841] and aPR 0.334; 95% CI [0.126-0.882], respectively). However, there was no significant increase in severity among those presenting with low monocyte or high platelet counts.

Conclusion: There is a unidirectional association between low platelets and high monocyte levels with severe manifestations of COVID-19 disease. Further research is warranted to validate these findings and explore their utility in risk stratification and clinical management of COVID-19 patients.

Citation: Subkhan M, Mulki TM, Ambar NS, Irfana L, Widyaningsih S, Permana PBD, Widodo ADW, Paramitasari A. Low platelet counts and monocytosis were associated with reduced risk of severe COVID-19 manifestation: a single-center study from Indonesia. Immunopathol Persa. 2025;11(2):e40595. DOI:10.34172/ipp.2025.40595.

Introduction

In December 2019, a novel coronavirus strain, SARS-CoV-2, emerged in Wuhan, Hubei, China, leading to widespread outbreaks and prompting the World Health Organization to declare it a global health pandemic, naming it COVID-19 (1). As of May 13, 2023, the Indonesian Ministry of Health reported increased COVID-19 active cases in Indonesia, with 1245 confirmed cases and 25 deaths (2). While the recovery rate for patients remains high, Indonesia's case-fatality rate for that month stands at a staggering 2.5%, which was double than the global percentage of 0.9% (1). A poorer clinical manifestations of this disease are commonly found on elderly patients, of male sex, with obesity, and had prior chronic diseases such as diabetes mellitus, cancer, cardiovascular diseases, and chronic lung diseases (3). The underlying mechanism of COVID-19 morbidity and mortality are attributed to an exaggerated

Key point
- Thrombocytopenia and monocytosis were associated with 81.6% and 66.6% reduction in the risk of severe COVID-19 manifestation, respectively.
- In contrast, both thrombocytosis and monocytopenia were not associated with any significant increase in the risk of COVID-19 manifestation.

inflammatory response to the SARS-CoV-2 virus infection, characterized by elevated circulating cytokine levels, leading to a phenomenon commonly known as 'cytokine storm'(4). This cytokine overproduction is hypothesized to result from the hyperactivation of macrophage, which are accompanied by the respective increase in monocyte levels, as macrophages are direct derivatives of monocytes (5,6). Monocytes and macrophages serve as sentinel cells that detect invasive infections and initiate inflammasome formation, which triggers caspase-1 and gasdermin D activation, ultimately leading to pyroptosis and release of potent inflammatory mediators such as tumour necrosis factor α (TNFα), interleukin (IL)-1β, and IL-6 (7,8). Alterations in monocytes structure and function largely contribute to immune dysregulation, with evidence reporting a decrease of non-classical (CD14-CD16+) and an increase of intermediate (CD14+CD16+) monocyte (9–11). Other notable abnormal laboratory findings in COVID-19 were primarily attributed to hematological changes, including lymphopenia, eosinopenia, neutrophilia, mild thrombocytopenia, and occasionally, thrombocytosis (12). Low platelet count during the cytokine storm is hypothesized to result from the coronavirus infection extending to the bone marrow, impending thrombocyte synthesis (13). A meta-analysis highlighted the significant association of thrombocytopenia with a threefold increase in intensive care unit admissions, progression to acute respiratory distress syndrome (ARDS), and mortality (14). Hence, these markers provide valuable insights for clinicians in predicting the severity of COVID-19 and its subsequent prognosis.

Objectives

This study aimed to evaluate the association between monocyte and platelet levels with COVID-19 severity at a secondary hospital located in East Java, Indonesia.

Patients and Methods

Study design, setting, and participants

This single-center, cross-sectional study was conducted in Siti Khodijah Muhammadiyah Sepanjang hospital, Sidoarjo, from August to December 2022. This hospital is classified as a secondary healthcare facility located in one of the major cities in East Java. Electronic medical health records were utilized to identify inpatient adults (age >17 years) who tested positive for COVID-19 based on the quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) results. Initial complete blood count (CBC) test was retrieved from each participant during their stay at the hospital for the analysis. Individuals with Dengue infections, idiopathic thrombocytopenic purpura (ITP), lymphoma, leukemia, acquired immunodeficiency syndrome (AIDS), autoimmune disorders, and incomplete medical records were excluded from the study. A simple random sampling frame was implemented and 100 samples were necessary to achieve a robust 95% confidence level with a 5% significance threshold based on the Lameshow's formula. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (15).

Operational definitions

COVID-19 severity was determined based on the Indonesian Ministry of Health and the Indonesian society of respirology criteria, which were as follows:

1. Asymptomatic COVID-19
   a. No clinical manifestation
   b. No clinical symptom
2. Mild COVID-19
   a. Mild disease without any complication
   b. Specific symptoms: fever, cough, fatigue, anorexia, dyspnea, myalgia
   c. Nonspecific symptoms: sore throat, nasal congestion, headache, nausea, vomiting, anosmia, ageusia prior to any respiratory symptoms
   d. Immunocompromised and elderly showing atypical symptoms e.g., fatigue, loss of consciousness, reduced ambulation, diarrhea, anorexia, delirium, and no fever
3. Moderate COVID-19
   a. Mild pneumonia
   b. Fever, cough, dyspnea, tachypnea, without any signs of severe pneumonia
   c. Respiratory rate (RR) 20-30 x/min
   d. Peripheral oxygen saturation (SpO2) >93% in room air
4. Severe COVID-19
   a. Severe pneumonia/upper respiratory tract infection
   b. Severe respiratory distress
   c. SpO2 <93% in room air
5. Critical COVID-19
   a. ARDS, sepsis, or septic shock
   b. Onset within 7 days
   c. Bilateral opacity, pleural effusion with no explainable reason, lung collapse, lobar collapse, or nodule in the chest imaging
   d. Presence of edema associated with respiratory failure, and not attributed to heart failure or volume overload.

Statistical analysis

All statistical analysis was conducted with IBM Statistical

Package for Social Sciences (SPSS) software version 26 for Mac. Data was extracted from the electronic medical records and presented as frequency (for categorical variables) or median/mean (for continuous variables). Comparison in COVID-19 severity with the clinical characteristics of the study participants were conducted using chi-square, Fisher's exact, independent t test, and Mann-Whitney U tests. To determine the association between variables with COVID-19 severity, a multivariate backward-stepwise binary logistic regression was employed, in which variables were included in the model if the score statistic was <0.05 and excluded if it was >0.2. Prevalence ratio (PR) and adjusted prevalence ratio (aPR) represents the measure of the association. Statistical significance was determined if p-value <0.05.

Baseline characteristics

A total of 100 of COVID-19 positive subjects enrolled in the study May to September 2021. The majority of subjects were male (59%), with a median age of 53 years. Hypertension were the most prevalent comorbidities (20%), followed by diabetes mellitus (16%) and cardiovascular diseases (9%). Physical examination of respiratory function revealed a median respiratory rate (RR) at 22x/min and peripheral oxygen saturation (SpO_2) at 93.5%. A total of 43 subjects presented with severe COVID-19 disease manifestation. CBC following initial presentation revealed 26% subjects with abnormal platelets level and 62% with abnormal monocyte level. Among those with these abnormal values, the subjects were mostly had thrombocytopenia (18%) and monocytosis (60%) were the most prevalent presentation of these abnormalities (Table 1).

Table 1. Characteristics of the study participants (N = 100)

Characteristics	No. (%)
Gender	
Male	59 (59%)
Female	41 (41%)
Age (years), median (IQR)	53 (16)
Comorbidities	
Hypertension	20 (20%)
Diabetes Mellitus	16 (16%)
Cardiovascular Diseases	9 (9%)
Respiratory Function	
RR (x/min), median (IQR)	22 (3.5)
SpO2 (%), median (IQR)	93.5 (9)
COVID-19 severity	
Moderate	57 (57%)
Severe	43 (43%)
Platelets (×10³/µL), median (IQR)	228.5 (137.5)
Thrombocytopenia (<150 000/µL)	18 (18%)
Normal (150 000-400 000/µL)	74 (74%)
Thrombocytosis (>400 000/µL)	8 (8%)
Monocytes (%), median (IQR)	8.7 (5.4)
Monocytopenia (<2%)	2 (2%)
Normal (2-8%)	38 (38%)
Monocytosis (>8%)	60 (60%)

N: frequency; IQR: interquartile range; RR: respiratory rate; SpO2: peripheral oxygen saturation.

Comparison between clinical characteristics with COVID-19 severity

Significant differences were identified in the categorical platelets and monocytes level with COVID-19 severity ($P=0.045$ and $P=0.033$, respectively; Table 2). Nonparametric Mann-Whitney U tests also revealed significant differences in the continuous values of platelets and monocytes level ($P=0.002$ and $P=0.012$, respectively). No significant differences were identified in other clinical characteristics with disease severity.

Association and predictive values of platelet and monocyte levels with COVID-19 severity

Table 3 describes the association between the clinical characteristics of subjects, including alterations in platelet and monocyte levels, with a severe COVID-19 manifestation. Interestingly, patients with monocytosis (>8%) had a 71.6% lower risk of severe COVID-19 compared to those with normal monocyte (2-8%) both in the bivariate and multivariate analysis (PR 0.364; 95% CI [0.157-0.841]; $P=0.018$ and aPR 0.334; 95% CI [0.126-0.882]; $P=0.027$, respectively). Despite the non-association in the bivariate analysis, thrombocytopenia significantly reduces the risk of severe COVID-19 manifestation in the multivariate model (aPR 0.184; 95% CI [0.047-0.722]; $P=0.015$). However, no significant increase in COVID-19 severity was identified among those presenting with monocytopenia and thrombocytosis, both in the bivariate and multivariate analysis. Additionally, gender, age, hypertension, diabetes mellitus, and cardiovascular diseases were not associated with severe COVID-19 manifestations. The receiver operating characteristics (ROC) curves were generated to identify the predictive values of platelets and monocytes for severe COVID-19 (Figure 1A-B). Both monocyte and platelet levels demonstrate modest performance in predicting severe COVID-19, with an AUC value of only 0.647 (95% CI 0.533-0.760; $P=0.012$) and 0.682 (95% CI 0.575-0.789; $P=0.002$), respectively.

Discussion

This study offers intriguing insights into the role of conventional complete blood testing in assessing COVID-19 severity at a secondary hospital in East Java, Indonesia. Whilst both low platelet and high monocyte counts were significantly associated with reduced risk of severe COVID-19 manifestation, the associations were not bidirectional. Hence, patients presenting with increased platelet and decreased monocyte level may not necessarily

Table 2. Comparison between clinical characteristics and COVID-19 severity (N=100)

Characteristics	Moderate COVID-19	Severe COVID-19	*P* value
Gender			
Male	32 (54.2%)	27 (45.8%)	0.503
Female	25 (61.0%)	16 (39.0%)	
Age (y), mean±SD	49.40±13.4	54.19±11.71	0.065
Comorbidities			
Hypertension	11 (55.0%)	9 (45.0%)	0.840
Diabetes mellitus	8 (50.0%)	8 (50.0%)	0.537
CVD	6 (66.7%)	3 (33.3%)	0.728
Platelets (×10³/µL), median (IQR)	203 (126.5)	265 (87)	0.002*
Thrombocytopenia	14 (77.8%)	4 (22.2%)	
Normal	41 (55.4%)	33 (44.6%)	0.045*
Thrombocytosis	2 (25.0%)	6 (75.0%)	
Monocytes (%), median (IQR)	9.4 (4.1)	7.6 (6)	0.012*
Monocytopenia	1 (50.0%)	1 (50.0%)	
Normal	16 (42.1%)	22 (57.9%)	0.033*
Monocytosis	40 (66.7%)	20 (33.3%)	

*Significant association ($P < 0.05$).
N: Frequency; SD: Standard deviation; CVD; Cardiovascular diseases; IQR: Interquartile range.

Table 3. Bivariate and multivariate analysis of COVID-19 severity (N=100)

Characteristics	Severe, No. (%)	Bivariate Analysis		Multivariate analysis[a]	
		PR (95% CI)	*P* value	aPR (95% CI)	*P* value
Gender					
Male	27 (45.8%)	1.318 (0.586-2.963)	0.504	1.867 (0.735-4.477)	0.189
Female	16 (39.0%)	Ref.	Ref.	Ref.	Ref.
Age (y), mean±SD	54.19±11.71	1.031 (0.998-1.065)	0.069	-	-
Comorbidities				-	-
Hypertension	9 (45.0%)	1.107 (0.413-2.968)	0.840	-	-
Diabetes Mellitus	8 (50.0%)	1.400 (0.479-4.088)	0.538	-	-
CVD	3 (33.3%)	0.638 (0.150-2.708)	0.542	-	-
Platelets					
Thrombocytopenia	4 (22.2%)	0.355 (0.107-1.181)	0.091	0.184 (0.047-0.722)	0.015*
Normal	33 (44.6%)	Ref.	Ref.	Ref.	Ref.
Thrombocytosis	6 (75.0%)	3.727 (0.705-19.69)	0.121	6.120 (0.939-39.896)	0.058
Monocytes					
Monocytopenia	1 (50.0%)	0.727 (0.042-12.52)	0.826	0.740 (0.016-34.905)	0.878
Normal	22 (57.9%)	Ref.	Ref.	Ref.	Ref.
Monocytosis	20 (33.3%)	0.364 (0.157-0.841)	0.018*	0.334 (0.126-0.882)	0.027*

[a] Backward binary logistic regression (Step 5); *Significant association ($P<0.05$).
N: frequency; SD: standard deviation; PR: prevalence ratio; aPR: adjusted prevalence ratio; CI: confidence interval; CVD: cardiovascular diseases; Ref.: reference category.

yield worse disease severity.

Prior studies have also reported conflicting findings regarding these associations. A study conducted in Bali, Indonesia demonstrated a significantly lower platelet count in severe COVID-19 patients in comparison with both asymptomatic and mild-moderate disease (16). Additionally, evidence from Ethiopia revealed that patients with thrombocytopenia exhibited 4.57- and 6.10-fold higher risk of moderate and severe disease, respectively, in comparison with mild diseases (17). The association between thrombocytopenia in COVID-19 has been extensively studied, with several proposed mechanism being presented. SARS-CoV-2 are able to inhibits hematopoiesis in the bone marrow through CD13 receptors, resulting in the primary platelet depletion through a mechanism of which are similar to those happening in the HCoV-229E infection (18,19). Increased platelet destruction associated with circulating immune complexes containing anti-platelet membrane GPIIIa49-66 IgG and increased platelet consumption associated with the formation of microthrombi in damaged lung tissues have also been proposed as supporting mechanism that contributes to thrombocytopenic conditions (19). Despite this, a study from Basra, Iraq reported no significant

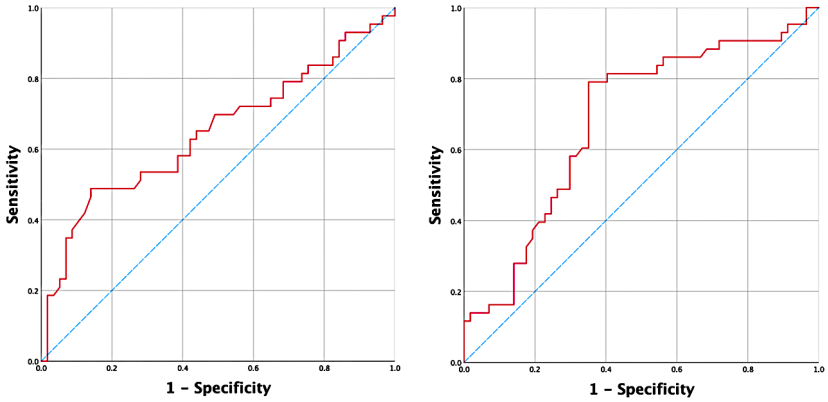

Figure 1. A) ROC Curve of Monocyte Levels (AUC 0.647, 95% CI [0.533-0.760], *P*=0.012); B) ROC Curve of Platelet Levels (AUC 0.682, 95% CI [0.575-0.789], *P*=0.002).

differences in platelets parameters were identified on different COVID-19 degree of severity, with all severe patients even exhibiting normal platelet level (20). Alterations in coagulation markers (PT, aPTT, fibrinogen, D-dimer), including platelets, were also found to not differ with COVID-19 manifestations in the Peruvian populations (21). Conversely, a tertiary hospital in Jakarta, Indonesia presented the first recorded case of extreme thrombocytosis in a patient with severe COVID-19, which platelets were normal on admission but subsequently progressed exceeding 1000×10^9 following the worsening in clinical condition (22). It was hypothesized that reactive thrombocytosis following severe inflammations were the underlying mechanism that induce this condition. Increased expressions of pro-inflammatory cytokines (e.g. IL-3, IL-6, IL-9, IL-11) during cytokine storm triggers the bone marrow production of megakaryocytes, which subsequently increased platelet formation (23,24). Nevertheless, both increase or decrease in platelets are able to characterize different inflammatory processes during COVID-19 progression. This dynamics were emphasized with an evidence indicating a significant decline in platelet levels following disease progression (25). A temporal analysis suggested that platelets' counts were lower in survivors than in non-survivors at beginning of the diseases, while the opposite was evident at the end of the follow-up (26). Therefore, the association between a low platelet count and a seemingly reduced risk of severe COVID-19 may be attributed to the acute nature of the disease progression, suggesting that continued monitoring could potentially reverse these associations, as evidenced in prior studies. Given platelets' critical role in hemostasis, inflammation, and immune response, closely monitoring platelet count changes can furnish valuable insights into the clinical progression of the disease (27).

The dysregulation of monocytes in the pathophysiology of COVID-19 remains a subject of extensive investigation, introducing a layer of complexity to our understanding of this intricate interplay. Previous research has firmly established that monocytopenia conditions are not only associated with the severity of COVID-19 but also serve as robust predictors of poorer clinical outcomes among patients (28). A meta-analysis of 35 studies reported significantly lower monocytes in severe patients compared to non-severe patients (1.08-fold) (29). Case-control evidence from Iraq showed that monocyte levels were associated with deaths in critically-ill patients with COVID-19, with mortality being identified from 90.9% of those with monocytopenia (30). However, it is important to note that monocyte level dynamics to predict disease progression cannot be necessarily interpreted in one measurement. This was emphasized with a study by Pehlivan et al (2021) which demonstrated that despite there were no difference in baseline monocytes among severe and non-severe cases, significantly higher proportion of severe COVID-19 patients had developing and persistent monocytopenia (31). Additionally, those with developing and persistent monocytopenia had shorter survival times among patients who died (31). Immune dysregulation in severe COVID-19 cases exhibit similar properties of those with cytokine storm syndrome, primarily attributed to macrophage activation followed by an excessive pro-inflammatory cytokine production, particularly TNF-α and interferon-gamma (IFN-ɣ) (32). It is elucidated that these excess cytokines leads to a decreased monocyte count due to hemophagocytosis in the bone marrow (33). An RNA-sequencing analysis of bronchoalveolar lavage fluids from COVID-19 patients revealed notable upregulation of monocyte chemoattractant CCL2 and CCL7, whereby mononuclear phagocytes (MNP) accounted for 80% of the cells in severe cases (40-60% in mild cases) (34,35). This marked increase in MNP reflects the presence of alveolar macrophage being recruited during disease manifestations, which are not only contribute acute inflammation but also responsible for the fibrotic complications among patients being treated with ventilators (36). A study by Park et al reveled higher levels of circulating monocytes—particularly the activated phenotype (CD169+) associated

with reduced lung function (DLCOc%) and pro-inflammatory cytokines—in the COVID-19 convalescents regardless of residual symptoms, highlighting the role of monocytes and macrophages in the development of post-acute sequelae of COVID-19 (37). Iwabuchi et al (2022) revealed an interesting insight into the immune dysregulation inside the lung microenvironments by conducting an immune cell profiling in different sites of COVID-19 affected lobes. A higher proportion of CD68+ macrophage and CD14+ monocytes were found in the upper-to-middle lung lobes with mild-to-moderate inflammation, while CD8+ and CD3+ T cells tended to increase in middle-to-lower lobes with moderate-to severe inflammations (38). An immune prediction model identified classical monocytes as the primary contributors to the hyper-inflammatory, hypercytokinemia phenotype associated with severe COVID-19 manifestations. These monocytes significantly upregulated the expression of key cytokines involved in COVID-19, such as CCL2, CCR2, CXCL8, and TNF-α (39).

Conclusion

Baseline thrombocytopenia and monocytosis is associated with a reduced risk of severe COVID-19 manifestations at a secondary general hospital in Indonesia. However, this association were not bidirectional, in which that thrombocytosis and monocytopenia is not associated with severe COVID-19. In light of these findings, routine monitoring of platelets and monocytes should be considered an essential aspect of the clinical management in severe COVID-19. Further research is warranted to elucidate the temporal dynamics and potential interventions aimed at ameliorating the impact of immune dysregulation on COVID-19 outcomes.

Limitations of the study

It is important to note that this study had significant limitations. First, the single-center a nature of our study had limited applicability in the broader population. Furthermore, the cross-sectional design resulted in the inability to interpret causality and long-term relationships between changes in blood laboratory results with COVID-19 severity. However, despite the potential to not provide any applicable implications in the clinical setting following the end of the COVID-19 pandemic, this study highlighted that blood laboratory markers serves as an important information in the consideration of severe COVID-19 treatment.

Authors' contribution

Conceptualization: Mohammad Subkhan, Thariq Malikul Mulki, Nabil Salim Ambar, Laily Irfana, Sri Widyaningsih.
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Formal analysis: Mohammad Subkhan, Thariq Malikul Mulki, Laily Irfana, Sri Widyaningsih, Putu Bagus Dharma Permana.
Funding acquisition: Mohammad Subkhan.
Investigation: Mohammad Subkhan, Thariq Malikul Mulki, Nabil Salim Ambar, Laily Irfana, Sri Widyaningsih.
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Software: Mohammad Subkhan, Thariq Malikul Mulki, Putu Bagus Dharma Permana.
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Writing–review & editing: Putu Bagus Dharma Permana, Agung Dwi Wahyu Widodo, Aprilia Paramitasari.

Conflicts of interest

The authors declare that they have no competing interests

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Health Research Ethics Committee of Siti Khodijah Muhammadiyah Sepanjang Hospital with a reference number of No. 054/KET-KEPK/10-2. This study only utilized electronic medical records and did not acquire subjects' consent. However, all identifying data were anonymized. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

Funding/Support

The authors affirm that they have not received any financial backing or support, whether direct or indirect, from any external entity or party in connection with the conduct and funding of this study.

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