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## Original Article

# The Prognostic Effect of Thrombocytopenia on the Clinical Severity in COVID-19 Patients

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## Abstract

**Background:** Thrombocytopenia is associated with the severity and increased morbidity and mortality of COVID-19. Therefore, understanding this association can aid in diagnosing the disease, predicting outcomes, and reducing mortality and morbidity.

**Materials and Methods:** Patient data from the teaching hospital's archives were considered. The severity of the disease was classified into four categories: mild, moderate, severe, and very severe, based on the national protocol. A total of 82 patients were analyzed, including 41 with thrombocytopenia and 41 without, who were admitted to the teaching hospital from February 2021 to the end of March 2022. This allowed for a comparative analysis.

**Results:** Thrombocytopenia was significantly associated with longer hospital stays ( $p < 0.001$ ) of more than 5 days. Thrombocytopenic patients were more likely to be admitted to the ICU (90.2%) compared to non-thrombocytopenic patients (14.6%) ( $p < 0.0001$ ). Thrombocytopenic patients also had lower SpO<sub>2</sub>, with values below 90% in 90.2% of cases ( $p = 0.046$ ). Thrombocytopenia was linked to DIC and ARDS and had a substantial impact on disease outcome, with mortality rates of 75.6% and 7.3% in thrombocytopenic and non-thrombocytopenic patients, respectively. Severity and various laboratory variables (LDH, D-dimer, CRP, and CPK) also showed significant differences between the two groups. The association between thrombocytopenia and disease severity was significant, with 75.6% categorized as very severe and 22% as severe ( $p < 0.0001$ ).

**Conclusion:** The study found a clear correlation between hospital stay length and admission location for both patient groups. In the ICU, thrombocytopenic patients experience longer stays and lower SpO<sub>2</sub> levels. Thrombocytopenia significantly impacts disease outcome and is closely linked to DIC and ARDS, with an increased risk of mortality. Notable differences exist in LDH, D-dimer, CRP, and CPK levels between the two groups. Thrombocytopenia is associated with higher disease severity, particularly in thrombocytopenic patients. Age, gender, hospital stay length, and disease severity correlate meaningfully. Male patients and those with higher clinical severity tend to have longer stays. Additionally, SpO<sub>2</sub> levels, respiratory rate, DIC, disease outcome, CPK, and clinical severity are significantly related.

**Keywords:** Prognostic effect, Thrombocytopenia, Severity, COVID-19

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## Introduction

In December 2019, there was a significant increase in coronavirus-related pneumonia cases in Wuhan, Hubei Province, China. This virus spread rapidly to other provinces within China and then to other countries<sup>1</sup>. COVID-19 is a disease that affects the respiratory system and the whole body, with around 10-15% of patients developing severe pneumonia<sup>2</sup>. The most common symptoms observed in COVID-19 patients are fever, fatigue, and a dry cough, which can gradually lead to difficulty breathing<sup>3,4</sup>. Some patients may initially experience mild symptoms without an obvious fever. Unusual symptoms include abdominal pain, headache, palpitations, and chest pain. In severe cases, COVID-19 can cause critical illness, including complications such as acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), and can ultimately result in venous thromboembolism<sup>5</sup>.

In individuals affected by COVID-19, notable alterations in blood parameters frequently occur, characterized by reductions in lymphocyte and platelet counts, whereas white blood cell counts typically remain within the normal range. Furthermore, partial thromboplastin time (PTT) tends to be prolonged, and D-dimer levels are elevated in approximately 26% of cases, despite the majority of patients exhibiting normal prothrombin time (PT) levels<sup>6,7</sup>.

Multiple lines of evidence have shown that viral infections can lead to platelet activation, either directly or indirectly. This activation contributes to increased platelet consumption<sup>8</sup>. It has been reported that decreased platelet numbers can be a marker for poor prognosis in various infectious diseases, including rapidly evolving coronaviruses<sup>9</sup>. COVID-19 is not an exception to this rule. Considering this information and the results of multiple studies that have found a correlation between low platelet count and an increased risk of severe disease<sup>10</sup>, it is reasonable to assume that COVID-19 patients with thrombocytopenia will have a higher risk of adverse outcomes<sup>9</sup>.

Platelet count, a readily measurable biomarker, has been demonstrated to have an independent association with disease severity and the risk of mortality in the intensive care unit (ICU)<sup>11</sup>. Notably, in patients afflicted with severe acute respiratory syndrome (SARS), thrombocytopenia, characterized by a low platelet count, was observed in 55% of cases, serving as a robust predictor of mortality<sup>12</sup>. In light of these significant insights, our central objective is to evaluate and comprehensively understand the correlation between thrombocytopenia and COVID-19 severity, with a specific emphasis on its implications for patient outcomes and its potential prognostic value in this context.

## Methods

This prospective study was conducted on patients hospitalized at Modarres Hospital from February 2021 to the end of March 2022. The study focused on patients with moderate and severe cases of COVID-19. Ethical approval was obtained from the faculty research committee, and patient information was collected from the hospital archive after reviewing similar studies. The inclusion criteria were patients aged 18 to 90 years who were hospitalized at Modarres Hospital with a diagnosis of COVID-19, as determined by CT scans and PCR tests. Exclusion criteria included thrombocytopenia caused by factors other than COVID-19, known systemic diseases, and previous conditions such as cirrhosis, MDS, leukemia, drug-induced, and chemotherapy-induced thrombocytopenia.

The severity of the disease was categorized as moderate, severe, and very severe according to the national protocol. Patients with moderate severity exhibited respiratory symptoms with or without fever, SpO<sub>2</sub> levels between 90% and 94%, and lung involvement of less than 50%. Patients with severe severity experienced rapid progression of respiratory symptoms: respiratory rate > 30, SpO<sub>2</sub> < 90 percent, and increased on CT scan. Patients with very severe/critical severity displayed symptoms of respiratory

failure despite non-invasive oxygen therapy, signs of septic shock, and multi-organ failure. The study involved 41 patients with thrombocytopenia and at least 41 patients without thrombocytopenia who presented with COVID-19 at Modarres Hospital during the study period. Various variables, including platelet count, ferritin, LDH, CRP, troponin, lymphocyte count, and D-dimer, were examined.

Data analysis was conducted using SPSS version 25. Quantitative data were presented as means and standard deviations, while qualitative data were presented as numbers and percentages. The relationship between the variables studied, thrombocytopenia, and the clinical severity of the disease was assessed using Fisher's test, Chi-Square test, and T-test. The significance level for all tests was set at  $P < 0.05$ .

The studies involving human participants were reviewed and approved by Shahid Beheshti University of Medical sciences (IR.SBMU.MSP.REC.1401.351). The patients/participants provided their written informed consent to participate in this study.

## Results

In this study, 82 patients were evaluated, divided into two groups: those with and those without

thrombocytopenia. The examination of demographic variables demonstrated a significant difference in gender ( $P < 0.0001$ ) between the two groups of patients with and without thrombocytopenia. The percentage of men (75.6%) with thrombocytopenia was significantly higher than that of women. There was no significant difference in patient age between the two groups with and without thrombocytopenia ( $P = 0.153$ ). A significant correlation was observed between hospitalization duration and a 5-day cutoff in both groups ( $P = 0.001$ ). 87.8% of patients with thrombocytopenia had a hospital stay of more than 5 days. A significant correlation was seen between DIC (Disseminated Intravascular Coagulation) and ARDS (acute respiratory distress syndrome) with thrombocytopenia ( $P > 0.0001$  in both cases). The relationship between the clinical and vital signs of patients with thrombocytopenia is shown in Table 1.

The findings demonstrate a significant impact of thrombocytopenia on disease outcome ( $P > 0.0001$ ). Specifically, 75.6% of patients with thrombocytopenia experienced mortality, compared to only 7.3% of patients without thrombocytopenia.

The relationship between laboratory findings and thrombocytopenia is shown in Table 2. The results showed that among the laboratory variables investigated, LDH ( $P = 0.018$ ), D-dimer ( $P = 0.043$ ), CRP

**Table 1.** The relationship between the clinical and vital signs of patients with thrombocytopenia (N=41).

Variables		Thrombocytopenia N (%)	No thrombocytopenia N (%)	P-value
Age	<45	5 (12.2)	10 (24.4)	0.153
	≥ 45	36 (87.8)	31 (75.6)	
Gender	Male	31 (75.6)	13 (31.7)	<0.0001
	Female	10 (24.4)	28 (68.3)	
Hospitalization period	> 5	5 (12.2)	19 (46.3)	0.001
	≤ 5	36 (87.8)	22 (53.7)	
Place of hospitalization	Section	4 (9.8)	35 (85.4)	<0.0001
	ICU	37 (90.2)	6 (14.6)	
SpO2	≤90	37 (90.2)	30 (73.2)	0.046
	> 90	4 (9.8)	11 (26.8)	
RR	≥30	3 (7.3)	34 (82.9)	<0.0001
	< 30	38 (92.7)	7 (17.1)	
DIC	No	23 (56.1)	40 (97.6)	<0.0001
	Yes	18 (43.9)	1 (2.4)	
ARDS	No	6 (14.6)	35 (85.4)	<0.0001
	Yes	35 (85.4)	6 (14.6)	
Disease outcome	Recovery	10 (24.4)	38 (92.7)	<0.0001
	Death	31 (75.6)	3 (7.3)	

**Table 2.** The relationship between laboratory findings and thrombocytopenia (N=41).

Variables		Thrombocytopenia N (%)	No thrombocytopenia N (%)	P-value
Plt.		31480.3 ± 104804.88	77160.40 ± 246853.7	<0.0001
Lymph	<1000	30 (73.2)	26 (63.4)	0.342
	≥1000	11 (26.8)	15 (36.6)	
Ferritin	120>	2 (4.9)	4 (9.8)	0.396
	120≤	39 (95.1)	37 (90.2)	
LDH	480>	8 (19.5)	18 (43.9)	0.018
	480≤	33 (80.5)	23 (56.1)	
D dimer	Normal	12 (29.3)	21 (51.2)	0.043
	Abnormal	29 (70.7)	20 (48.8)	
Trop	<0.06	33 (80.5)	38 (92.7)	0.105
	≥0.06	8 (19.5)	3 (7.3)	
CRP	Normal	0 (0)	4 (9.8)	0.040
	Abnormal	41 (100)	37 (90.2)	
CPK	170>	16 (40)	28 (68.3)	0.011
	170≤	24 (60)	13 (31.7)	

(P=0.040), and CPK (P=0.011) showed significant differences between patients with and without thrombocytopenia. Specifically, 80.5% of patients with thrombocytopenia had LDH levels above normal (NL), 70.7% had higher D-dimer levels, 60% had higher CPK levels, and 100% had higher CRP levels than NL. On the other hand, parameters such as Lymph (P=0.977), ferritin (P=0.396), and Trop (P=0.105) did not show significant differences between patients with and without thrombocytopenia. The relationship between thrombocytopenia and disease severity is depicted in Table 3, which shows a statistically significant association (p<0.0001). Among patients with thrombocytopenia, 75.6% presented with very severe disease, while 22% had severe disease. In contrast, among patients without thrombocytopenia, disease severity was moderate in 24.4% of cases, severe in 68.3%, and very severe in

**Table 3.** The relationship between thrombocytopenia and disease severity (N=41).

Variable	TP N (%)	No TP N (%)	P-value
Moderate	1 (2.4)	10 (24.4)	<0.0001
Severe	9 (22)	28 (68.3)	
Very severe	31 (75.6)	3 (7.3)	

7.3%.

## Discussion

The aim of this study was to comprehensively evaluate the impact of thrombocytopenia on COVID-19 severity among patients treated at a teaching hospital. A total of 82 patients were meticulously assessed and subsequently categorized into two distinct groups based on the presence or absence of thrombocytopenia. The findings uncovered a robust association between prolonged hospital stays exceeding 5 days in both patient groups. Additionally, a statistically significant correlation was discerned between the hospitalization location and the presence of thrombocytopenia. Notably, patients with thrombocytopenia exhibited a markedly higher rate of intensive care unit (ICU) admissions, at 90.2%, compared with 14.6% in those without thrombocytopenia. Furthermore, a conspicuous difference in oxygen saturation (SpO<sub>2</sub>) was observed between the two cohorts, with 90.2% of thrombocytopenic patients having SpO<sub>2</sub> below 90%. Moreover, thrombocytopenia demonstrated a significant association with disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). These compelling results strongly indicate that thrombocytopenia substantially impacts patient outcomes, ultimately resulting in a notably higher mortality rate of 75.6% in individuals with

thrombocytopenia, compared with 7.3% in those without this condition.

The COVID-19 pandemic has affected over 12 million people worldwide and resulted in over 500,000 deaths<sup>13</sup>. While most patients have mild or no symptoms, older individuals with pre-existing conditions are at a higher risk of developing severe illness and experiencing poor outcomes, including ICU admission, ARDS, and death<sup>14,15</sup>. Thrombocytopenia, which is commonly seen in viral infections, is a marker of disease progression and worsened sepsis<sup>16</sup>. Previous studies have shown a correlation between low platelet counts and increased mortality and severity of COVID-19<sup>17</sup>.

The identification of markers for disease severity can significantly aid healthcare professionals in making timely and appropriate treatment decisions, potentially leading to improved patient outcomes. Further comprehensive research is imperative to gain a thorough understanding of the pivotal role of platelet count in predicting outcomes among COVID-19 patients. Previous studies have underscored that thrombocytopenia stands as a significant risk factor for severe infection and heightened mortality<sup>18</sup>. Moreover, additional investigations have highlighted that patients exhibiting a substantial increase in platelet count (over  $300 \times 10^9/L$ ) during treatment tended to experience prolonged hospital stays<sup>19</sup>. Thrombocytopenia, a prevalent symptom in COVID-19 patients, arises from a multitude of pathophysiological processes. These encompass direct coronavirus assault on stem cells, resulting in lung impairment due to the generation of anti-platelet antibodies. Furthermore, diminished TPO production, escalated platelet clearance, platelet consumption, lung impairment, and the administration of antiviral medications collectively contribute to the onset of thrombocytopenia in COVID-19 patients. These intricate mechanisms are intricately linked with disseminated intravascular coagulation (DIC) and multiorgan dysfunction syndrome, ultimately culminating in heightened mortality rates among severely ill patients<sup>3</sup>.

Most patients with mild to moderate disease have positive outcomes during treatment, while severe or very severe cases have a high mortality rate. Early diagnosis and treatment of severe COVID-19 patients

can significantly reduce mortality. However, no laboratory marker is available to predict disease progression or prognosis. In addition to the mechanisms mentioned, a gradual decrease in platelet count may predict cytokine storm and platelet destruction due to an uncontrolled immune response in COVID-19 patients. Therefore, monitoring platelet count may be a simple and effective indicator for disease progression. Further studies with larger sample sizes are needed to validate this hypothesis. The mechanisms discussed have the following implications: first, targeted treatment can be designed based on the severity of thrombocytopenia. Glycyrrhizic acid and stem cells have immune-regulatory and anti-inflammatory effects, which can help reduce the likelihood of cytokine storm<sup>20,21</sup>. Additionally, glycyrrhizic acid has antiviral effects, and stem cells promote tissue repair and maintain balance in the bone marrow microenvironment<sup>22,23</sup>. Second, damage to stem cells can be treated using polysaccharide astragalus to improve hematopoietic function. The combination of astragalus polysaccharides with rhTPO or TPORA may be a promising approach for treating hematopoietic cell damage and reducing TPO production<sup>23</sup>.

A study has shown that low platelet count is associated with increased mortality and disease severity in COVID-19 patients, indicating that it should be used as a clinical indicator during hospitalization. Another study compared clinical characteristics between patients with and without thrombocytopenia<sup>17</sup>. It demonstrated that thrombocytopenia at admission was associated with nearly triple the mortality rate compared to patients without thrombocytopenia, and platelet count was an independent risk factor for COVID-19 mortality<sup>24</sup>.

Various clinical studies support the activation of increased platelets, leading to platelet deposition in damaged lung blood vessels. This is a prominent feature of severe acute respiratory syndrome (SARS). Thrombocytopenia, occurring in over 50% of SARS patients, is an important predictive factor<sup>25,26</sup>. A meta-analysis of 1,779 COVID-19 patients revealed that thrombocytopenia is associated with a threefold increased risk of severe COVID-19, and that lower platelet counts were observed in cases resulting in mortality<sup>17</sup>. Similarly, our current study confirms an association between thrombocytopenia at admission

and mortality in COVID-19 patients. In SARS patients, platelet counts show a negative correlation with sVCAM-1 levels. sVCAM-1 is involved in adhesion and chemotaxis, contributing to initial vascular injury and the suppression of T-cell function<sup>27</sup>. Using Cox regression for multivariable analysis, we found that platelets and PCT are independent risk factors for mortality<sup>28,29</sup>. In summary, platelet count is an important predictor of outcomes in COVID-19 patients, and dynamic platelet levels closely correlate with mortality during treatment<sup>30</sup>.

This study has limitations that should be acknowledged. Firstly, it should be noted that this is an observational study, which means it may be difficult to control for all potential factors that could affect the results, maintain data accuracy, and ensure consistency. As a result, the impact of certain variables on predicting prognosis may be underestimated. Secondly, our study found a significant association between Thrombocytopenia and disease outcome, as well as a close association with DIC and ARDS, both of which increase the risk of mortality. However, it is challenging to establish a cause-and-effect relationship based solely on these findings. Further investigations, such as basic research, animal experiments, or prospective trials, are needed to confirm this association. Lastly, we did not measure platelet counts and coagulation functions in survivors during the follow-up period.

The study by Ostrowski<sup>31</sup> shows that CRP levels increase significantly in COVID-19 due to alveolar damage caused by the virus. This type of alveolar damage was also observed during the SARS epidemic in 2002. Identifying biological markers that predict disease severity and prognosis is crucial for treating and managing COVID-19 patients. In elderly patients (over 60 years old), systemic symptoms, lymphopenia, thrombocytopenia, and increased CRP are more common.

According to the study by Kılıçaslan and colleagues<sup>32</sup>, LDH levels are relatively high at the time of diagnosis in patients with thrombocytopenia, but show slight improvement after treatment. The study by Arda Kiani<sup>33</sup> found that COVID-19 patients with high CPK levels upon admission are at risk of severe lung involvement, worsening oxygenation, and respiratory

failure. Therefore, early specialized care strategies for these patients are crucial.

The association of CPK with lung infection has been studied even before the COVID-19 pandemic. For example, Zhao et al.<sup>34</sup> reported that patients with community-acquired pneumonia have higher serum CPK levels compared to those without radiological evidence of pneumonia. Previous assessments have also shown that CPK levels are significantly higher in individuals who died from the influenza virus's intrinsic pneumonia subgroups, although CPK was not found to be an independent risk factor for mortality in multiple regression models.

A study conducted by Nikolaos Papageorgiou<sup>35</sup>, suggested that troponins can be used to predict cardiac and non-cardiac vascular events and outcomes in COVID-19 patients. The study also indicated that the use of troponins may affect patient management. Another study by Sarah<sup>36</sup> found a relationship between high levels of CK and severe cases of COVID-19, particularly in the initial CK levels. This suggests that measuring CK may not be particularly important. Interestingly, when CRP was used as an inflammatory marker, the only factor statistically associated with CK levels was disease severity. This could be because severe illness involves additional secondary disease factors. Furthermore, studies reporting an association between CK levels and disease severity assumed that CK values increase with other inflammatory markers, a relationship confirmed by a study conducted in Austria. Our research encountered certain limitations. Given the timing of this study during the COVID-19 pandemic, the involvement of the individuals under investigation was constrained. As a result, conducting studies with a larger sample size has the potential to yield more valuable and robust data for the assessment and comparison of diverse therapeutic approaches.

Future studies should prioritize validating our current findings and integrating data to identify additional biomarkers indicative of severe disease progression or unfavorable outcomes in individuals with COVID-19. Moreover, it is imperative to strategize further investigations to elucidate the precise underlying mechanisms responsible for the decline in platelet count observed in patients with severe COVID-19, delving into the potential hyper- or hypoactivation of platelets in this context.

## Conclusion

The results indicate a clear correlation between hospital stay length and place of admission in both groups of patients. In the ICU, thrombocytopenic patients generally have longer hospitalizations and lower SpO<sub>2</sub> levels. Thrombocytopenia plays a significant role in disease outcome and is closely linked to DIC and ARDS. This condition may also increase the risk of mortality. There are notable differences in LDH, D-dimer, CRP, and CPK levels between the two patient groups. Thrombocytopenia is associated with greater disease severity, particularly in thrombocytopenic patients. The patients' age, gender, length of hospital stays, and disease severity also exhibit a meaningful correlation. Male patients and those with higher clinical severity tend to have longer hospital stays. Furthermore, there is a significant relationship between SpO<sub>2</sub> levels, respiratory rate, DIC, disease outcome, CPK, and clinical severity.

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## Conflict of Interest

The authors declare no conflicts of interest related to this study.

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