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The effect of blood parameters on the frequency of thromboembolic events in COVID-19 patients

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Abstract:

BACKGROUND AND AIM: Coronavirus Disease 2019 (COVID-19) infection is associated with an increased incidence of thromboembolic events. This study aimed to evaluate the frequency of in-hospital thromboembolic events in patients with COVID-19 and investigate the impact of blood parameters, measured at the time of diagnosis, on the development of thromboembolic events.

METHODS: Demographic data, the frequency of thromboembolic events, and blood parameters at the time of diagnosis were recorded for all patients.

RESULTS: A total of 2,323 patients, including 1,136 women (48.9%) and 1,187 men (51.1%) were included in the study. Thromboembolic events occurred in 103 (4.4%) patients during hospitalization. Deep vein thrombosis (DVT) was observed in four patients (0.2%), pulmonary thromboembolism (PTE) in three patients (0.15%), peripheral arterial disease in four patients (0.2%), cerebrovascular events in 17 patients (0.7%), mesenteric ischemia in one patient (0.05%), and myocardial infarction (MI) in 74 patients (3.2%). The frequency of thromboembolic events was significantly higher in patients with hypertension (HT) (p=0.03), heart failure (p=0.023), chronic kidney disease (p=0.017), and chronic obstructive pulmonary disease (COPD) (p=0.035) compared to those without these conditions. Patients with thromboembolic events were significantly older than those without such events (p=0.003). Among laboratory parameters, hemoglobin levels were significantly lower (p=0.002), and mean platelet volume (MPV) was significantly higher (p=0.009) in patients with thromboembolic events. Multiple regression analysis identified age (odds ratio [OR]: 1.014, 95% confidence interval [CI]: 1.001–1.027; p=0.032), hemoglobin levels (OR: 0.906, 95% CI: 0.824–0.997; p=0.043), and MPV (OR: 1.197, 95% CI: 1.030–1.391; p=0.019) as risk factors for thromboembolic events.

CONCLUSIONS: Advanced age is a risk factor for thromboembolic events in patients with COVID-19. It is believed that hemoglobin levels and MPV at the time of hospital admission may also contribute to predicting thromboembolic events.

Keywords:

Coronavirus Disease 2019 (COVID-19), hemoglobin, mean platelet volume, thromboembolic events

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is an infectious agent that emerged in Wuhan, China, in December 2019. It can affect multiple organs and systems, including the cardiovascular, nervous, and gastrointestinal, and especially the respiratory system. To date, SARS-CoV-2 has spread rapidly worldwide, causing a pandemic in a short period. The pandemic is characterized by peaks in different countries, with many people still being infected and succumbing to the disease. Health systems in numerous countries have struggled to cope with the pandemic. Emerging variants, such as the Elis variant, have added complexity and challenges to the management of the pandemic. Despite the wealth of information obtained from studies conducted since the beginning of the pandemic, many issues remain unresolved regarding its pathogenesis, clinical manifestations, and complications.[1]

Although SARS-CoV-2 infection mostly causes asymptomatic cases or flu-like symptoms, it can also present with clinical variability, ranging from pneumonia and Acute Respiratory Distress Syndrome (ARDS) to multi-organ failure and death, sometimes accompanied by bacterial infections.[2] Various antiviral, anticytokine, and anti-inflammatory drugs are under investigation for the treatment of the disease. Despite treatments recommended by current national and international studies, severe complications such as macrophage activation syndrome (MAS) in adults and multisystem inflammatory syndrome in children (MIS-C) continue to be observed.[3,4] Multifactorial risks such as endothelial dysfunction, resulting directly from the cytopathic effects of the virus; immobility during the disease; stasis due to immobility; and hypercoagulability caused by a cytokine storm, characterized by the excessive release of cytokines observed in some patients, have contributed to frequent thromboembolic events, especially in patients with severe Coronavirus Disease 2019 (COVID-19). Excessive thrombosis in the microvascular system can lead to microcirculatory dysfunction and subsequent diffuse intravascular coagulation.[5,6] Zhou et al.[4] were the first to examine the relationship between COVID-19 and thromboembolic events, reporting a frequency of thromboembolic events of 2.9%.

To prevent such events in hospitalized patients, thromboprophylaxis with anticoagulants and/or mechanical protective measures is implemented, considering various risk factors for bleeding. However, some patients experience thromboembolic events despite all preventive measures, and fatalities can occur due to these complications. This study aimed to investigate the development and frequency of thrombotic events using blood parameters during hospitalization in patients admitted to the general ward and intensive care unit of our hospital since the onset of the pandemic. Additionally, the study sought to determine the relationship between these complications and associated risk factors.

Materials and Methods

The records of 2,323 patients aged 18 years and older, who were hospitalized with a diagnosis of COVID-19 between March 2020 and May 2021, were retrospectively analyzed. All patients included in the study were informed about the research, and informed consent was obtained. Both definite COVID-19 cases (confirmed by a positive nasopharyngeal polymerase chain reaction (PCR) test) and highly probable COVID-19 cases (based on clinical and radiological findings consistent with COVID-19, with at least two PCR tests conducted 24–48 hours apart yielding negative results) were included in the study.

The treatment modality was determined based on guidelines published by the Ministry of Health of the Republic of Türkiye, national and international publications, and clinical experience. At the beginning of the pandemic, patients were treated with hydroxychloroquine and favipiravir, followed by molnupiravir. Based on emerging studies, steroid treatment was shown to be beneficial in patients in the hyperinflammatory phase, and 6 mg dexamethasone or an equivalent corticosteroid was added to the treatment, particularly for hypoxic patients. Additionally, mini-pulse steroid therapy and tocilizumab were initiated in patients diagnosed with MAS.

All hospitalized patients were assessed for bleeding risk, and those not at high risk of bleeding received thromboprophylaxis with low-molecular-weight heparin, standard heparin, or fondaparinux. In addition to COVID-19, patients with suspected bacterial infections, based on clinical, radiological, and laboratory findings, were started on empirical antibiotic treatment until culture results were obtained. Treatment was then adjusted based on the culture results.

Demographic data, the frequency of thromboembolic events, blood parameters at the time of hospitalization, comorbidities, signs of poor clinical outcomes, and length of hospital stay were recorded.

Artificial intelligence (AI) technology was not used in the preparation of this article. The study received ethical approval from the Kocaeli University Ethics Committee on June 17, 2021, with the decision number KÜ GOKAEK-2021/12.14, in compliance with the Declaration of Helsinki.

All statistical analyses were performed using IBM SPSS for Windows, version 20.0 (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. Continuous variables were expressed as mean±standard deviation or median (25^{th}–75^{th} percentiles), and categorical variables were expressed as counts (percentages). Comparisons of continuous variables between groups were performed using the Mann-Whitney test. Comparisons of categorical variables between groups were performed using the chi-square test. Correlations between variables were analyzed using Spearman correlation analysis. Logistic regression analysis was conducted to determine the risk factors associated with the development of thromboembolic events. A two-sided p value of <0.05 was considered statistically significant.

Results

A total of 2,323 patients, comprising 1,136 females (48.9%) and 1,187 males (51.1%), with a median age of 58 years (range: 18–101) were included in the study. The median length of hospital stay was 5 days (range: 1–80). At least one comorbidity was present in 1,538 patients (66.2%). The need for intensive care developed in 214 patients (9.2%) and 172 patients (7.4%) died. Thromboembolic events occurred in 103 patients (4.4%) during hospitalization (Table 1).

Deep vein thrombosis (DVT) was identified in four patients (0.2%), pulmonary thromboembolism (PTE) in three patients (0.15%), peripheral arterial disease in four patients (0.2%), cerebrovascular events in 17 patients (0.7%), mesenteric ischemia in one patient (0.05%), and myocardial infarction (MI) in 74 patients (3.2%). The frequency of thromboembolic events was similar between genders. Patients with hypertension (HT) (p=0.03), heart failure (p=0.023), chronic kidney disease (p=0.017), and chronic obstructive pulmonary disease (COPD) (p=0.035) demonstrated a higher frequency of thromboembolic events compared to those without these conditions. The frequency of thromboembolic events was also higher in patients requiring intensive care (p=0.003) (Table 2).

Table 1: Demographic characteristics of the study population (n=2.323)

	n	%
Gender		
Female	1,136	48.9
Male	1,187	51.1
COVID-19 diagnosis		
Definite	1,890	81.4
Highly probable	433	18.6
Smoking history		
Non-smoker	172	64.9
Current smoker	76	28.7
Former smoker	17	6.4
Comorbidity		
Present (+)	1,538	66.2
Hypertension	810	34.9
Diabetes mellitus	516	22.2
Coronary artery disease	179	7.7
Congestive heart failure	85	3.7
Chronic kidney disease	127	5.5
Chronic obstructive pulmonary disease (COPD)	105	4.5
Asthma	123	5.3
Malignancy	188	8.1
Interstitial lung disease	20	0.9
Collagen tissue disease	63	2.7
Clinical course of the disease		
Need for oxygen therapy	879	37.8
Need for intensive care unit (ICU)	214	9.2
Mortality	172	7.4
Thromboembolic complications		
Total	103	4.4
Myocardial infarction (MI)	74	3.2
Cerebrovascular events	17	0.7
Peripheral arterial disease	4	0.2
Deep vein thrombosis (DVT)	4	0.2
Pulmonary thromboembolism (PTE)	3	0.15
Mesenteric ischemia	1	0.05

The age of patients with thromboembolic events was significantly higher compared to those without thromboembolic events (62 years vs. 58 years, p=0.003) Among laboratory parameters, hemoglobin levels were significantly lower (p=0.002) and mean platelet volume (MPV) was significantly higher (p=0.009) in patients with thromboembolic events (Table 3).

Binary logistic regression was used for multivariate analysis.Variables were selected based on their significance in the univariate analysis. Serum lymphocyte, C-reactive

Table 2: Comparison of demographic characteristics based on the presence of thromboembolic events

	Thromboembolic complication				p
	(+)		(–)		
	n	%	n	%	
Gender					
Female	49	47.6	1,087	49	
Male	54	52.4	1,133	51	0.78
COVID-19 diagnosis					
Definite	86	83.5	1,804	81.3	
Highly probable	17	16.5	416	18.7	0.56
Comorbidity					
Present (+)	75	72.8	1,463	65.9	0.15
Hypertension	46	44.7	764	34.4	**0.033**
Diabetes mellitus	30	29.1	486	21.9	0.08
Coronary artery disease	10	9.7	169	7.6	0.44
Congestive heart failure	8	7.8	77	3.5	**0.023**
Chronic kidney disease	11	10.7	116	5.2	**0.017**
Chronic obstructive pulmonary disease (COPD)	9	8.7	96	4.3	**0.035**
Asthma	7	6.8	116	5.2	0.48
Malignancy	10	9.7	178	8	0.54
Interstitial lung disease	1	1	19	0.9	0.9
Collagen tissue disease	1	1	62	2.8	0.26
Clinical course of the disease					
Need for oxygen therapy	47	45.6	832	37.5	0.09
Need for intensive care unit (ICU)	18	17.5	196	8.8	**0.003**
Mortality	13	12.6	159	7.2	**0.039**

Table 3: Comparison of laboratory parameters at diagnosis based on the presence of thromboembolic events

	Thromboembolic complication		
Median (25^{th}–75^{th} percentiles)	**(+)**	**(–)**	**p**
Age (years)	62 (50–76)	58 (44–69)	**0.003**
Length of stay (days)	5 (4–8)	5 (3–8)	0.18
Laboratory parameters at the time of diagnosis			
WBC, $\times 10^3$	6.2 (4.6–8.4)	6.0 (4.5–8.2)	0.55
Leukocyte count, $\times 10^3$	0.31 (0.22–0.39)	0.29 (0.22–0.39)	0.98
Leukocyte, %	68 (57.2–80.3)	68.5 (58.6–78.9)	0.84
Lymphocyte count, $\times 10^3$	1.09 (0.73–1.66)	1.15 (0.79–1.62)	0.46
Lymphocyte, %	20 (11.9–28.3)	19 (12–28.8)	0.81
NLR	3.37 (1.91–6.64)	3.43 (2.04–6.4)	0.95
Hemoglobin, (g/dL)	12 (11–13.5)	13 (11.5–14)	**0.002**
Platelet count, $\times 10^3$	192,500 (143,750–238,250)	192,600 (150,125–246,750)	0.41
MPV, (fL)	9.16 (8.5–10.02)	9 (8.1–10)	**0.009**
RDW, (fL)	13.9 (13–15.1)	13.6 (13–15)	0.23
D–dimer, (μg/mL)	0.76 (0.4–1.5)	0.6 (0.32–1.2)	0.06
Fibrinogen, (m/dL)	4.7 (4.01–6.2)	4.7 (3.8–5.8)	0.38
Procalcitonin, (ng/mL)	0.12 (0.1–0.3)	0.12 (0.1–0.19)	0.057
Ferritin, (μg/L)	248.9 (70.8–544.6)	164 (68–399)	0.087
CRP, (mg/L)	40.51 (9.8–134)	30 (9.3–93)	0.1
Albumin, (g/L)	36 (31–38.5)	36 (32.8–39.5)	0.07
LDH, (U/L)	310 (224–389.3)	286 (224–378.3)	0.28

WBC: White blood cell, NLR: Neutrophil–to–lymphocyte ratio, MPV: Mean platelet volume, RDW: Red cell distribution width, CRP: C–reactive protein, LDH: Lactate dehydrogenase

Table 4: Binary logistic regression analysis of risk factors associated with thromboembolic events

Variable	OR [95% CI]	p
Age (years)	1.014 [1.001–1.027]	**0.032**
Lymphocyte count (×10^3)	1.016 [0.909–1.136]	0.783
Hemoglobin, (g/dL)	0.906 [0.824–0.997]	**0.043**
MPV, (fL)	1.197 [1.030–1.391]	**0.019**
CRP, (mg/L)	1.001 [0.999–1.004]	0.326
LDH, (U/L)	1.001 [1.000–1.001]	0.287

OR: Odds ratio, CI: Confidence interval, MPV: Mean platelet volume, CRP: C-reactive protein, LDH: Lactate dehydrogenase

protein (CRP), and lactate dehydrogenase (LDH) levels are known to be important in monitoring COVID-19 progression. Therefore, these parameters were included in the multivariate analysis, even if they did not show significant differences in the univariate analysis. In the binary logistic regression analysis (Hosmer-Lemeshow Test: chi-square=3.106, p=0.928), the risk factors associated with thromboembolic events were age (odds ratio [OR]: 1.014, 95% confidence interval [CI]: 1.001–1.027; p=0.032), hemoglobin (OR: 0.906, 95% CI: 0.824–0.997; p=0.043), and MPV (OR: 1.197, 95% CI: 1.030–1.391; p=0.019) (Table 4).

Discussion

This study demonstrated that the frequency of thromboembolic events in hospitalized COVID-19 patients was 4.4%, with approximately three-quarters of these events being myocardial infarctions. It was found that age, hemoglobin level, and MPV values at the time of hospitalization may contribute to predicting thromboembolic events.

Although COVID-19 primarily affects the lungs, it can also impact other systems, including the hematological and cardiovascular systems, through various mechanisms.[7] One of the key underlying mechanisms is the increased inflammatory process and hypercoagulopathy, leading to various thrombotic events, including MI, in patients with COVID-19. While the overall mortality rate of COVID-19 is approximately 2–3%, this rate can increase to 45–50%, especially in cases associated with thrombotic complications.[8,9] Early prediction of thrombotic complications during hospitalization is therefore critical.

In the study by Lalor et al.,[10] the rate of thromboembolic events was also reported to be 4.4%, consistent with our findings. In the study by Degrave et al.,[11] arterial or venous thrombosis was detected in 38 (10%) of 388 patients admitted to the ward requiring oxygen therapy. A meta-analysis by Malas et al.,[12] which included 8,271 patients across 42 studies, reported a venous thromboembolism rate of 31%, deep vein thrombosis at 28%, pulmonary embolism at 19%, arterial thromboembolism at 5%, and noted that thromboembolism significantly increased the likelihood of mortality in intensive care unit (ICU) patients (OR: 1.74; 95% CI: 1.01–2.98; p=0.04). The statistically higher rates of intensive care unit admission and mortality in patients with thromboembolic events observed in this study are consistent with findings reported in the literature.

Tashkandi's study demonstrated that hypertension and ischemic heart disease significantly increase the risk of thromboembolism.[13] In the study by Jurin et al.,[14] coronary artery disease, peripheral artery disease, and a history of cerebrovascular disease were independently associated with arterial thrombosis, while metastatic malignancies were linked to venous thromboembolism. In our study, thromboembolic complications were associated with HT, congestive heart failure, chronic kidney disease, and COPD.

Several studies have shown that laboratory parameters can aid clinicians in predicting and assessing the severity of disease and the risk of mortality in patients with COVID-19.[13,15–17] Studies have also demonstrated that maintaining hemostasis and platelet mass inversely correlates with platelet count, while a high MPV predicts venous thromboembolism (VTE).[18,19] In the study by Duan et al.,[20] an increase in MPV was observed in patients with VTE and COVID-19. Similarly, a meta-analysis by Zein et al.[21] found that the mean MPV was higher in patients with poor outcomes compared to those without poor outcomes. In the study by Gozukucuk et al.,[22] MPV was found to be elevated in deceased patients. Consistent with these findings, our study revealed that MPV at the time of hospitalization was higher in patients who experienced thromboembolic events.

Previous studies have identified MPV as a marker of platelet function and demonstrated its positive association with platelet activity, adhesion, and reactivity.[23,24] Increased MPV is known to result in more reactive platelets. Conditions such as hypoxemia, ventricular dysfunction, and impaired cardiac output are strong stimuli for platelet activation and promote the release of vasoactive mediators in bursts. In such scenarios, platelet activation serves as a potential risk factor for thromboembolic events.[25]

Low hemoglobin levels were associated with mortality and the need for intensive care in the study by Martinot et al.[26] Low hemoglobin levels were also correlated with thromboembolic events in the study by Sadegni et al.[27] Similarly, in our study, patients with thromboembolic events had lower hemoglobin levels, consistent with the literature.

Several mechanisms have been proposed to explain the thrombotic risk associated with low hemoglobin levels. These include reduced coronary and cerebral blood flow in anemia and increased exposure of platelets and coagulation factors to the vascular endothelium, leading to enhanced platelet-vessel wall adhesion.[28,29] Additionally, tissue hypoxia caused by reduced hemoglobin levels stimulates the synthesis of various vasoreactive substances, which predispose patients to thromboembolic events.[30,31]

There are several limitations to this study. First, the parameters were evaluated only at the time of initial hospital admission, and no comparison was made with post-treatment values. Second, the study included only inpatients, excluding outpatients. Third, it was a retrospective and single-center observational study. Nevertheless, despite these limitations, the inclusion of a larger number of patients distinguishes this study from others.

Conclusion

In conclusion, advanced age is a risk factor for thromboembolic events in COVID-19 patients. Hemoglobin levels and MPV at admission are thought to contribute to the prediction of thromboembolic events.

Ethics Committee Approval

The study was approved by the Kocaeli University Ethics Committee (No: KÜ GOKAEK-2021/12.14, Date: 17/06/2021.

Authorship Contributions

Concept – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Design – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Supervision – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Funding – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Materials – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Data collection &/or processing – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Analysis and/or interpretation – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Literature search – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Writing – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.; Critical review – Ö.B., H.K., S.A.B., S.A., S.F.A.S., R.G., İ.B., H.B., B.M.

Conflicts of Interest

There are no conflicts of interest.

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