mutiara medika
Jurnal Kedokteran dan Kesehatan
Vol 23 No 1 Page 57-63, January 2023

Mutiara Medika: Jurnal Kedokteran dan Kesehatan
http://journal.umy.ac.id/index.php/mm

Correlation Between Platelets Count, Platelet Index and D-Dimer in Covid-19 Patients

Nelly Tolla[1,2]*, Rachmawaty[3], Andi Salsa Anggeraini[1], Darmmawaty R[4], Faidah Nur[1]

[1]Department of Biomedical Science, Faculty of Medicine and Health Science, Universitas Muhammadiyah Makassar, South Sulawesi, Indonesia

[2]Department of Clinical Pathology, Faculty of Medicine and Health Science, Universitas Muhammadiyah Makassar, South Sulawesi, Indonesia

[3]Department of Clinical Pathology, Faculty of Medicine and Health Science, Hasanuddin University, South Sulawesi, Indonesia

[3,4]Department of Clinical Pathology, Faculty of Medicine and Health Science, Bosowa University, South Sulawesi, Indonesia

DATE OF ARTICLE:
Received: 10 Sep 2022
Reviewed: 04 Oct 2022
Revised: 11 Feb 2023
Accepted: 28 Feb 2023

***CORRESPONDENCE:**
nellymashuri@med.unismuh.ac.id

DOI:
10.18196/mmjkk.v22i2.16121

TYPE OF ARTICLE:
Research

Abstract: Hypercoagulation in the alveoli of the lungs is one of the causes of death in SARS-CoV2 virus infection. Hypercoagulation is defined by an elevation in D-Dimer, which typically rises on the fifth day of therapy. This parameter is not available in all hospitals and is still relatively expensive in preventing premature death. Platelets count and indices are suggested to describe the thromboinflammatory condition in COVID-19 patients. This research is an observational analytic study with a cross-sectional study design in 59 COVID-19 patients treated at Hassanuddin University Hospital. The patients who are declared COVID-19 based on the results of radiological examinations and PCR swabs underwent routine blood tests and D-Dimer before undergoing therapy. Data were analyzed using the Spearmen test in SPSS version 26 to reveal the correlation between platelet count, platelet indices, and D Dimer in COVID-19 patients with severe and non-severe conditions. Platelet count, platelet indices, especially MPV, and D-Dimer values were found to correlate in both groups COVID-19 using the Spearman rho correlation test ($p < 0.000$) with strengths correlation between -44.6 and 60.5. There was a significant association between platelet count and MPV value with D-Dimer in COVID-19 patients.

Keywords: COVID-19; D-Dimer; platelets; platelet index

INTRODUCTION

The World Health Organization (WHO) declared COVID-19, a viral infectious disease that originated in Wuhan, China, and has since spread all over the world, as a new pandemic disease in March 2020.[1] Acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and even death are possible clinical symptoms of COVID-19, which spreads through respiratory droplets and has an incubation period of 1 to 14 days.[2,3] A higher risk is associated with advanced age, smoking, and comorbid conditions such as diabetes, hypertension, cardiovascular disease, chronic obstructive lung disease, and cancer. Patients with COVID-19 have a more severe condition and die more frequently than those without COVID-19 [3,4]

In COVID-19, ARDS and progressive respiratory failure are the main mortality. Endothelial damage, blood flow stasis, and hypercoagulation are the Virchow triad's three components that comprise the COVID-19 ARDS and respiratory failure mechanism. In COVID-19, endothelial injury can arise due to proinflammatory cytokines or direct SARS-CoV-2 invasion into endothelial cells, leading to cell damage. A thrombotic condition brought on by endothelial damage may end in hypercoagulation.[5,6,7]

Acute respiratory distress syndrome and respiratory failure can be carried on by pulmonary vascular micro thrombosis, which can be brought on by hypoxia, endothelial damage, and inflammatory response. Platelets are essential for the processes of coagulation, hemostasis, thrombosis, immunomodulation, and

inflammation.[8,9] Recent studies have shown that in pneumonia driven by SARS-CoV2, platelet aggregation, adhesion, infiltration, and inflammatory response contribute to pulmonary damage and microvascular thrombosis.[10] Significant prognostic markers that can anticipate disease severity and mortality at an early stage include platelet count and platelet indices.[11]

Thromboembolism is characterized by an increase in D-Dimer > 1.0 l/mL.[5,6,7] D-dimer is a byproduct of fibrinolysis, the process by which blood clots are degraded. Pneumothorax, arterial and venous thrombosis, DIC, pregnancy, inflammation, cancer, chronic liver disease, trauma, surgery, and vasculitis are all linked to high D-dimer levels.[12,13] Dimer D levels usually start increasing on the fifth day of therapy, which makes it more difficult for COVID-19 patients to undergo early treatment and protects them from death.[13,14] Hence, a parameter of the same precision as D-Dimer is required, cheap, and accessible in all hospitals to prevent premature death. The D-Dimer examination is typically not affordable in all facilities treating COVID-19 patients.

This research aims to determine the relationship between platelets, platelet indices, and D-Dimer in COVID-19 patients. A routine hematological profile test is considered to identify the severity and mortality of the condition before an increase in D-Dimer occurs.

MATERIAL AND METHOD

This observational analytic study used a cross-sectional design involving 59 patients diagnosed with Covid-19. This study used probability sampling in COVID-19 patients treated at Hassanuddin University Hospital from September 2022 to November 2022. At the time of chest X-ray evaluation, Covid-19 was identified by PCR test, either with or without pneumonia. Patients with hematologic and oncologic malignancies, immune thrombocytopenia, coagulopathy, bone marrow and other related pathologies (essential thrombocytosis, myelodysplastic syndrome, aplastic anemia, etc.), patients with other diseases of platelet number and function that are affected by drug use, patients with liver cirrhosis, splenomegaly, and renal disease were all excluded from this study. This study was evaluated and accepted by the Ethics Committee. (Approval number is 861/UN4.6.4.5.31/PP36/2021/13-19. Date: 31.12.2021).

Patients who visit the emergency department with symptoms including coughing, fever, and shortness of breath are typically given complete blood counts and biochemical testing. D-dimer levels will be evaluated in blood samples from patients who match the inclusion criteria. On an automated hematology system, a CBC with MPV, PDW, and PCT was done. The particle-enhanced immunoturbidimetric assay was used to measure D-dimer. The reference ranges for MPV, PDW, PCT, and Platelet were 150–450 (x103/L), 7.2–11.1 fL, 9–13%, and 0.15–0.40%. D-reference Dimer's range was 500 pg/L.

There are two groups of patients. All patients who required respiratory support with invasive or non-invasive ventilation or a high-flow oxygen device with a respiratory rate > 30 breaths/min or with an SPO2 of 93% on room air were classified as COVID-19 patients with severe disease. Patients with mild-moderate symptoms also need oxygen through a mask or nasal cannula and have an SPO2 greater than 93%.

The mean and standard deviation represented all continuous variables (SD). A Kruskall-Wallis test or an independent sample T-test was used to compare the characteristics of severe and non-severe COVID-19 patients. If the data was not normally distributed, the Spearman rho correlation analysis was used to examine the correlation between the variables. The findings of this regression analysis were presented as 95% adjusted odds ratios, and all variables with a p-value of less than 0.05 were included in the multivariate analysis.

RESULT

From September to November 2022, this research was conducted at Hassanuddin University Hospital. Patients who arrived at the hospital with COVID-19-like symptoms were admitted to a specific Emergency department. Before being moved into a specific isolation room for COVID-19 therapy, all patients who declared COVID-19 based on the PCR swab examination and chest X-ray results had routine blood testing, blood chemistry, and inflammatory indicators such D-Dimer. Fifty-nine patients met the eligibility requirements for inclusion. The patient's comorbid disease was tracked down using remnants of medical data based on Table 1.

Table 1. Characteristics of COVID-19 Patients as Participants

Parameter	Non-Severe N/(Mean±SD)	Severe N/(Mean±SD)	p-Value
Gender			
Male	11(18.64%)	16(27.11%)	
Female	19(32.20%)	13(22.03%)	
Age (Years)	38.8 ±16	53±15.4	0.156*
Hb (g/dl)	12.99±2.10	11.56±2.70	0.200*
WBC ($x10^3/\mu L$)	7.63±2.84	12.79±16.26	0.200*
PLT($x10^3/\mu L$)	298±117	224±157	0.200*
MPV (fL)	9.167±2.373	13.50±4.323	0.070*
PDW (%)	11.39±3.91	19.92±34.61	0.000
PCT (%)	0.273±0.153	0.230±0.058	0.120*
D-Dimer (pg/L)	148±227	942±883	0.000
Comorbid			
Without comorbid	17(28.8%)	1(1.69%)	
With Comorbid	13(22.03%)	28(47.45%)	
Hypertension (HT)	6(10.16%)	6(10.16%)	
DM	3(5.08%)	5(8.47%)	
COPD	1(1.69%)	13(22.03%)	
Cardiovascular disease	2(3.38%)	4(6.77%)	
RA	1(1.69%)	0	

Haemoglobin (Hb), *White Blood Cell* (WBC), *Platelet* (PLT), *Mean Platelet Volume* (MPV), *Diabetes Mellitus* (DM), Chronic obstructive pulmonary disease (COPD), *Rheumatoid Arthritis* (RA), *Platelet Distribution Width* (PDW), *Plateletcrit* (PCT), * Normal data distribution (P>0.05)

T-test and Kruskall-Wallis test showed significant differences in both groups on PLT, MPV and D-Dimer Values in COVID-19 patients. Platelet counts in COVID-19 patients with severe degrees were lower than mild-moderate degrees. However, the platelet count in both groups was still within normal limits. The MPV and PDW values were higher in patients with severe degrees compared to those with mild-moderate degrees (Table 2).

Table 2. Analysis of PLT, MPV, PDW, PCT and D-Dimer values differences in non-severe and severe COVID-19

Parameter	Non-Severe N/(Mean±SD)	Severe N/(Mean±SD)	p-Value
PLT ($x10^3/\mu L$)	298±117	224±157	0.043*
MPV (fL)	9.167±2.373	13.50±4.323	0.000**
PDW (%)	11.39±3.91	19.92±34.61	0.198
PCT (%)	0.273±0.153	0.230±0.058	0.164
D-Dimer (pg/L)	148±227	942±883	0.000**

*T-test, **Kruskall-Wallis Test

To assess the correlation between the four variables in the two groups, the Spearman rho test was used as an alternative. The study showed a correlation between PLT, MPV, and D-Dimer values in severe and non-severe COVID-19 patients with a correlation of p 0.000 (Table 3).

Table 3. Analysis of Correlation between PLT, Platelet index and D-Dimer in non-severe and severe COVID-19

Parameter	COVID-19	
	r	p
PLT ($x10^3/\mu L$)	-44.5	0.000*
MPV (fL)	60.5	0.000*
PDW (%)	16.9	0.201
PCT (%)	-70.6	0.568
D-Dimer (pg/L)	60.5	0.000*

***** *Spearman rho*

In addition, a correlation test was performed between platelet count and platelet index with D-Dimer using the Spearman-Rho test in this study. Spearman Rho test showed a correlation between PLT, MPV and D-Dimer values in COVID-19 patients with a correlation of p 0.000 (Table 4).

Table 4. Analysis of Corelation between PLT, Platelet index and D-Dimer in COVID-19

Parameter	D-Dimer	
	r	p
PLT ($x10^3/\mu L$)	-42.6	0.001*
MPV (fL)	56.1	0.000*
PDW (%)	29.5	0.025
PCT (%)	-15.0	0.909

***** *Spearman rho*

DISCUSSION

In this study, there were more than 32 (54.23%) female COVID-19 patients, 13 (22.03%) of whom were with severe disease. 11 (18.64%) patients had mild-moderate symptoms, and 27 (45.76%) patients were male. Patients suffering from the severe disease were 53 years old on average. It aligns with research by Yardimci *et al.,* which found that patients with severe symptoms were, on average, 57.21 years old.[15]

Patients are more likely to acquire COVID-19 infection with severe disease seriousness if they have a history of coexisting conditions. HT, chronic obstructive lung disease (COPD), diabetes mellitus (DM), and cardiovascular illnesses were the most frequent comorbidities. According to Zang's research, individuals older (>65 years) and with concomitant conditions such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and cancer are more likely to develop this illness. If they are infected with COVID-19, their condition will worsen and even increase fatalities. [3,4,5]

Four major proteins—spike (S), nucleocapsid (N), membrane (M), and envelope—make up the coronavirus genome (E). When protein S interacts with the ACE2 receptor, infection happens.[16] As SARS-CoV-2 builds up in the lungs, it disrupts alveolar epithelial and endothelial cells and infiltrates inflammatory cells, producing proinflammatory cytokines, including IL-1, IL-6, and TNF. This immune response may become excessive in people with severe COVID-19, leading to a cytokine storm that sets off the systemic inflammatory response syndrome (SIRS). [5,9] The enhanced activation of the coagulation cascade and excessive thrombin generation brought on by COVID-19's hyperinflammation. The prothrombotic state brought on by coagulation issues in COVID-19 raises the risk of thromboembolism and venous and arterial thrombosis.[16,17]

Platelet count, MPV, and D-Dimer values revealed a significant difference between severe and non-severe COVID-19 individuals based on a T-test, with a mean (298 vs. 224, 9.167 vs. 13.50, and 148 vs. 942, respectively). Although the platelet counts of COVID-19 patients in this study varied, 42 (71.1%) of them had normal platelet counts, and 18 (30.5%) had severe illness. Thirteen patients (22.03%) had thrombocytopenia, ten (16.94%) had serious illnesses, and one had thrombocytosis. In a similar vein, Yang *et al*. study's on 1476 COVID-19 patients, revealed that 306 individuals (20.7%) developed thrombocytopenia.[18]

It's different from the study by Fogarty *et al*. reporting that they did not find a significant decrease in platelets and fibrinogen. However, there was a significant increase in D-dimer. [19,20] According to Fan *et al*., all COVID-19 patients treated in the ICU and outside of the ICU had normal platelet counts, according to the platelet count results. According to Fan et al., most COVID-19 patients treated in the ICU had a normal platelet value since patients with COVID-19 infection do not have any platelet aggregation.[21,22]

In research from Wuhan, thrombocytopenia at admission in COVID-19 patients was linked to a 4.24-fold higher risk of inpatient mortality. In comparison to patients without thrombocytopenia (median 186 109/L), those with thrombocytopenia (median 105 109/L) were more likely to be older, male, have a higher APACHE II score, have lower absolute neutrophil and lymphocyte counts, have higher C-reactive protein (CRP) and have a lower PaO2/FiO2 ratio[23,24]. In COVID-19, thrombocytopenia can develop due to a few factors, along with a cytokine storm that kills bone marrow progenitor cells, a viral infection of the bone marrow that directly restricts hematopoiesis, an increase in autoantibodies and immune complexes that cause platelet destruction, and lung injury that causes platelet aggregation. Additionally, eating platelets decreased the number of circulating platelets.[25]

The average MPV value was greater than patients with less severe diseases (13.50 vs. 9.16 fL). The same outcomes were also discovered in a study by Geoffrey.[20] According to preliminary data, critically ill COVID-19 patients who were hospitalized and matched for platelet count had MPVs that were considerably larger than those who were not (11.6vs10.5 fL). Even among COVID-19 patients with normal platelet counts, this trend toward higher MPV is still significant.[26] Surprisingly, even at normal platelet counts, COVID-19 is linked to a rise in the proportion of immature platelets. It may be another factor contributing to the rise in clotting events in COVID-19 because immature platelets are known to be more functional.[27,28] Compared to healthy donors, non-COVID-19 patients, and mild-moderate COVID-19 patients, Zang *et al*. found that severe and critically severe COVID-19 patients had decreased PLT and PCT and increased MPV and PDW.[24] In contrary to COVID-19 patients with retained platelet counts, Liu *et al*. found that COVID-19 patients with thrombocytopenia had a statistically significantly higher mean platelet volume (MPV, median 10.3 fL) (median 9.9 fL).[22] The body's reaction to thrombocytopenia is an increased mean platelet volume, which, outside of congenital platelet abnormalities, means an increase in the number of circulating young platelets.[28]

Hottz *et al.* reported that individuals with severe COVID-19 who need ICU and IMV showed enhanced platelet activation and platelet-monocyte aggregation formation, but people with the mild disease would not. The distribution of distinct platelet sizes, a sign of platelet function and activation, is specified by PDW and MPV, respectively. In the acute phase of inflammation, PLT is elevated, and MPV is lowered because MPV and PLT have an inverse relationship.[10]

Thrombocytopenia and viral infection can coexist for a range of reasons. Inflammatory signals and immune response are both significantly influenced by platelets. Viral infections have a procoagulant effect due to the interactions between endothelial cells, platelets, and leukocytes. In COVID-19, three hypotheses regarding platelet count and morphology are also proposed. First, as with other coronaviruses, thrombocytopenia is probably caused by an infection of the bone marrow. The immune system's elimination of platelets is the second. Third, platelet consumption is brought on by lung aggregation. Blood clots may be avoided by the fibrin degradation product known as D-dimer.[27,28] According to Zhou *et al.* study, the biggest predictor of mortality in COVID-19 patients was an increase in D-dimer >1.0 l/mL. [29] According to Cui *et al.* study, D-dimer >1.5 l/mL had a sensitivity of 85% and a specificity of 88.5% as a predictor of venous thromboembolism in COVID-19 patients. The D-dimer level varied between patients with severe and non-severe COVID-19, according to our study. D-dimer levels were greater in severe patients than in less severe patients (942883 vs. 148227).[28] D-dimers are much greater in COVID-19. The most likely causes are fibrinolysis and pulmonary vascular bed thrombosis. D-dimers show fibrin clot development, clot FXIIIa crosslinking, and fibrinolysis. The significant increase in D-dimers in COVID-19 is due to cytokine storm and viremia-induced coagulation activation, while superinfection and organ failure are also potential causes.[23,28]

The relationship between initial D-dimer levels and disease severity and outcome has been investigated in several studies. D-dimer has been found as a potential indication for COVID-19 patients' prognosis since the COVID-19 pandemic's outbreak. In numerous research, admission day D-dimer has demonstrated promise for predicting the illness severity.[12,13,14] D-dimer may be a valuable early marker for predicting in-hospital patient mortality, according to Zhang et al.'s study in China, which included 343 patients. They discovered that 2 g/ml was the ideal cut-off value for D-dimer. [23] Another study conducted in China discovered that a D-dimer value of more than 2 g/ml at admission was linked to a higher risk of mortality (odds ratio, 10.17 (95% CI, 1.10-94.38)).[12] The optimal cut-off value for admission of D-dimer to predict hospital mortality, according to an Indian study, was 1.44 g/ml. On the other hand, 2.01 g/ml was the ideal number for the highest D-dimer measurement taken while the patient was in the hospital to predict inpatient mortality.[29] Similar to our study, a statistically significant difference in MPV values was seen at admission for patients with PLT 100x103 L, patients with PLT between 100 and 150 x103 L, and those without thrombocytopenia (median 15.8 f L, (range: 9.3-19.5, median: 11.3 f L, range: 7.0-19.2, and median: 8.fL, range: 6.0-19.6, respectively).

However, few studies investigate the function of platelets and platelet index as early indicators of severe disease in COVID-19 patients by examining the connection between D-Dimer readings with platelet count and platelet index. With a D-Dimer value of 0.000 and a correlation between -44.5 and 60.5 in this study, there is a significant correlation between platelet count and MPV.

CONCLUSION

A significant correlation existed between platelet count and platelet index, especially MPV and D-Dimer, in COVID-19 patients. Platelet count and index could be used as alternative parameters to assess endothelial damage and the occurrence of early thrombosis in COVID-19 patients.

CONFLICT OF INTEREST

No conflict of interest.

REFERENCES

1. Hong ZS, Tan YY, Chen SD, Jin HJ, Guo YR, Cao Qing D, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res*. 2020;7(1):11. https://doi.org/10.1186/s40779-020-00240-0
2. Di Gennaro F, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N, *et al.* Coronavirus diseases (COVID-19) current status and future perspectives: A narrative review. *Int. J Environ Res Public Health*. 2020;17(8):E2690. https://doi.org/10.3390/ijerph17082690
3. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-e25. https://doi.org/10.1016/j.jinf.2020.04.021
4. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. *Eur Respir J*. 2020;55(5):2000547. https://doi.org/10.1183/13993003.00547-2020
5. Joly BS, Siguret V, Veyradier A. Understanding pathophysiology of haemostasis disorders in critically ill patients with COVID-19. *Intensive Care Med*. 2020;46(8):1603-1606. https://doi.org/10.1007/s00134-020-06088-1
6. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417- 1418. https://doi.org/10.1016/S0140-6736(20)30937-5
7. Ullah W, Saeed R, Sarwar U, Patel R, Fischman DL. COVID-19 Complicated by Acute Pulmonary Embolism and Right-Sided Heart Failure. *JACC Case Rep*. 2020;2(9):1379-1382. https://doi.org/10.1016/j.jaccas.2020.04.008
8. Li C, Li J, Ni H. Crosstalk Between Platelets and Microbial Pathogens. *Front Immunol* 2020; 11: 1962. https://doi.org/10.3389/fimmu.2020.01962
9. Assinger A. Platelets and infection an emerging role of platelets in viral infection. *Front Immunol* 2014; 5: 649. https://doi.org/10.3389/fimmu.2014.00649
10. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pão CRR, et al. Platelet activation and platelet-monocyte aggregates formation trigger tissue factor expression in severe COVID-19 patients. *Blood* 2020; 136: 1330-1341. https://doi.org/10.1182/blood.2020007252
11. Rapkiewicz AV, Mai X, Carsons SE, Pittaluga S, Kleiner DE, Berger JS, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *E Clinical Medicine* 2020: 100434. https://doi.org/10.1016/j.eclinm.2020.100434
12. Yao Y, Cao J, Wang Q, Liu K, Luo Z, Yu K, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. *Crit Care Emerg Med*. 2020;8:49. https://doi.org/10.1186/s40560-020-00466-z
13. Naymagon L, Zubizarreta N, Feld J, van Gerwen M, Alsen M, Thibaud S, et al. Admission D-dimer levels, D-dimer trends, and outcomes in COVID-19. *Thromb Res*. 2020; 196: 99–105. https://doi.org/10.1016/j.thromres.2020.08.032
14. Poudel A, Yashasa P, Anurag A, Barun B, Debika D, Tamanna B, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized

patients with COVID-19. Nepal : A retrospective study. *PLoS ONE* 16(8): e0256744. https://doi.org/10.1371/journal.pone.0256744

15. Yardimci AC, Yildiz S, Ergen E, Balli H, Ergene E, Balli H, et al. Association between platelet indices and the severity of the disease and mortality in patients with COVID-19. Retrospective Study. *European Review for Medical and Pharmacological Sciences*. 2021; 25: 6731-6740. https://doi.org/10.26355/eurrev_202111_27118
16. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multi-organ response. Curr Probl Cardiol. 2020:100618. https://doi.org/10.1016/j.cpcardiol.2020.100618
17. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol.* 2020;7(6):e438-e440. https://doi.org/10.1016/S2352-3026(20)30145-9
18. Henry BM, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and dearangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta*. 2020;507:167-173. https://doi.org/10.1016/j.cca.2020.04.027
19. Fogarty H, Townsend L, Cheallaigh CN, Bergin C, Martin-Loeches I, Browne P, *et al*. More on COVID-19 coagulopathy in Caucasian patients. *Br J Haematol*. 2020;186(6):1060-1061. https://doi.org/10.1111/bjh.16749
20. Geoffrey DW, Jonathan LM. The Impact of COVID-19 Disease on Platelets and Coagulation. *Chicago Pathobiology* 2021;88:15–27. https://doi.org/10.1159/000512007
21. Fan BE, Ng J, Chan SSW, Christopher D, Tso ACY, Ling LM, et al. COVID-19 associated coagulopathy in critically ill patients: A hypercoagulable state demonstrated by parameters of haemostasis and clot waveform analysis. *J Thromb Thrombolysis*. 2021; 51(3): 663–674. https://doi.org/10.1007/s11239-020-02318-x
22. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J Clin Virol.* 2020 Jun;127:104370. https://doi.org/10.1016/j.jcv.2020.104370
23. Hille L, Lenz M, Vlachos A, Grüning B, Hein L, Neumann FJ, *et al*. Ultrastructural, transcriptional, and functional differences between human reticulated and non-reticulated platelets. *J Thromb Haemost*. 2020 Aug;18(8): 2034–46. https://doi.org/10.1111/jth.14895
24. Zhang S, Liu Y, Wang X, Yang L, Li H, Wang Y. *et al.* SARS- CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. *J Hematol Oncol* 2020; 13: 120. https://doi.org/10.1186/s13045-020-00954-7
25. Liu Y, Sun W, Guo Y, Chen L, Zhang L, Zhao S, *et al*. Association between platelet parameters and mortality in coronavirus disease 2019: retrospective cohort study. *Platelets*. 2020 May;31(4):490–6. https://doi.org/10.1080/09537104.2020.1754383
26. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol*. 2020;99(6):1205-1208. https://doi.org/10.1007/s00277-020-04019-0
27. Helms J, Tacquard C, Severac F, Leonard-Lo- rant I, Ohana M, Delabranche X, et al. CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020 Jun;46(6):1089–98. https://doi.org/10.1007/s00134-020-06062-x
28. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(6):1421-1424. https://doi.org/10.1111/jth.14830
29. Zhou F, Ting Y, Ronghui D, Guohui F, Ying L, Zhibo L, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020 March-April: 395 (10229: 1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3