Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 25; 10(B):2417-2422.
https://doi.org/10.3889/oamjms.2022.9037
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Intensive Care*

Correlation of Coagulation Parameters with Clinical Outcome of Critically Ill Patients with COVID-19 Admitted to an Intensive Care at Rsup Dr. M. Djamil in Indonesia

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Edited by: Ana Vucurevic
Citation: Kurnia D, Yerizel E, Ekaputra A, Elvira D. Correlation of Coagulation Parameters with Clinical Outcome of Critically Ill Patients with Covid-19 Admitted to an Intensive Care at Rsup Dr. M. Djamil in Indonesia. Open Access Maced J Med Sci. 2022 May 25; 10(B):2417-2422. https://doi.org/10.3889/oamjms.2022.9037
Keywords: COVID-19; Critically ill; Coagulation; INR; D-dimer; Platelet; Days 5
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E-mail: dedykurnia@med.unand.ac.id
Received: 18-Feb-2022
Revised: 21-Mar-2022
Accepted: 24-Mar-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: COVID-19 is a condition that is characterized by an abnormal coagulation state, which is a reason for severe thrombotic problems.

AIM: We aim to determine the correlation of coagulation parameters levels with clinical outcomes of critically ill patients with COVID-19 admitted to intensive care at a national referral hospital in Indonesia.

METHODS: This retrospective cohort study analyzed 227 patients with a primary diagnosis of COVID-19 on mechanical ventilation who were admitted to the COVID-19 intensive care unit, Dr. M. Djamil from 2020 to 2021 taken in the medical record. Numerical data were analyzed using an independent t-test, while the categorical data were analyzed using the Chi-square test.

RESULTS: One hundred and one patients were >65 years old. The mean ± SD of INR levels, D-dimer levels, and platelet count on the first and the 5th days were 1.22 ± 0.77 and 1.36 ± 1.16; 4.624 ± 3.533 μg/L and 4.334 ± 3.365 μg/L; and 160.162 ± 117.203/μl and 234.070 ± 126.816/μl. There was a significant correlation between age (p = 0.002), INR levels on the 5th day (p = 0.041), platelet count on the 5th day (0.012) with clinical outcomes of patients.

CONCLUSION: There is a significant increase in the average platelets and INR levels on day 5. There is a significant correlation between INR levels and platelet count on ***5th*** days with clinical outcomes of patients.

Introduction

The coronavirus disease 2019 (COVID-19) presents with a wide range of symptoms, from asymptomatic to severe respiratory distress, multiple organ dysfunction, and death. Although initially thought to be a respiratory disease, rapidly accumulating data suggests that COVID-19 generates a unique and profound prothrombotic environment that leads to both arterial and venous thrombosis. Consistently, elevated D-dimer levels have emerged as an independent risk factor for poor outcomes, including death. Several other laboratory markers and blood counts have also been associated with a poor prognosis, possibly because of their association with thrombosis [1].

At present, the pathophysiology underlying the hypercoagulable state is poorly understood. However, a growing body of data suggests that the initial event occurs in the lungs. The severe inflammatory response, originating in the alveoli, triggers a dysfunctional cascade of inflammatory thrombosis in the pulmonary vasculature, leading to a state of local coagulopathy. This is followed, in patients with more severe disease, by a generalized hypercoagulable state, resulting in macrovascular and microvascular thrombosis. Of concern, however, is the observation that anticoagulants may be inadequate in many circumstances, highlighting the need for alternatives or adjuncts. Several ongoing studies investigating the pathophysiology of COVID-19-associated coagulopathy may provide mechanistic insights that can guide appropriate intervention strategies [1].

COVID-19 infection increases the risk of thrombosis by different mechanisms. Although still debated, elevated D-dimer has been proposed as a first-line hemostasis test associated with thromboembolic risk and poor prognosis. The study was conducted on 127 hospitalized patients with confirmed COVID-19, 24 hospitalized patients with COVID-19 negative pneumonia, and 12 healthy subjects. Clinical characteristics, tissue factor-induced thrombin formation with and without soluble thrombomodulin, as well as by silica, as well as other biochemical parameters were assessed. Despite the frequent use of

heparin, COVID-19 patients had similar thrombin levels to healthy controls [2].

In COVID-19 patients, the lag time for thrombin formation was positively correlated with markers of cell lysis (Lactate dehydrogenase [LDH]), inflammation (C-reactive protein, interleukin-6), and coagulation (D-dimer), whereas endogenous thrombin potential (ETP) was inversely correlated with D-dimer and LDH, and positively correlated with fibrinogen levels. Patients with longer lag times and decreased ETP had higher peak ISTH-DIC scores and had more severe diseases (vascular events and death) [2].

A study at a hospital in Addis Ababa, Ethiopia by analyzing the coagulation profile of COVID-19 patients found that a prolonged prothrombin time was found in 46.8% of patients with COVID-19 and a prolonged prothrombin time and an increase in INR in 53.3% of study subjects. with severe COVID-19 patients and 51% of critically ill patients. Thrombocytopenia was detected in 22.1% of COVID-19 patients. About 50.5% and 51.3% of COVID-19 patients aged over 55 years had thrombocytopenia and prolonged APTT, respectively. Abnormal coagulation parameters in COVID-19 patients are important prognostic factors of disease severity [3].

Methods

Study population

This retrospective cohort study analyzed 227 patients with a primary diagnosis of COVID-19 on mechanical ventilation who were admitted to the COVID-19 intensive care unit (ICU), Dr. M. Djamil from 2020 to 2021. Patients who were hospitalized for <48 h in the ICU and incomplete data were excluded from this study. Collecting data at Dr. RSUP. M. Djamil Padang is the national referral hospital for COVID-19 in West Sumatera.

We created two sets of models, the first employing patient characteristics and physiology on admission to the ICU, and the second using physiology, treatment, and complications during ICU admission. We captured each patient's most extreme physiological variables on days 1 and 5 of ICU admission.

This research involves humans as research subjects. The ethical implications of this research follow the provisions of the Declaration of Helsinki and have passed the ethical test from the ethics committee of RSUP Dr. M. Djamil Padang with number LB.02.02/5.7/507/2021. All medical matters relating to this research are confidential. Research subjects have the right to refuse to participate in the study if they do not agree. All research costs and other costs incurred as a result of this research are borne by the researcher.

Clinical data collection and outcome

We reviewed the electronic medical records system in the hospital and collected the clinical information of all participants, including demographic data such as age, sex, and results of laboratory findings included INR, D-dimer, platelet levels, and outcomes in the medical records of critically ill patients with COVID-19 were included in the study. INR, D-dimer, and platelet were obtained on initial evaluation.

The sampling method used was total sampling. The dependent variable of this study was the patient's outcome (died or improved) while the independent variable was the value of INR, D-dimer, and platelet based on the results of laboratory tests that were first performed when the patient was admitted and on the 5th day of therapy. We hypothesized that there is an association between INR, D-dimer, and platelet levels with clinical outcomes of critically ill patients.

Statistical analysis

All of the authors had unrestricted access to the raw data. Missing data were not imputed. Numerical data were summarized using the mean, standard deviation, minimum, and maximum with comparisons between groups using the independent t-test. Categorical data were presented as numbers and percentages with comparisons between groups using the Chi-square or Fisher's test with a significance level of 5%. Data processing used an application statistical package for the social science version 18 (SPSS Ver. 18).

Results

Two hundred and ninety-five critically ill patients with COVID-19 were screened on admission in intensive care at Indonesia's national referral hospital. We found that 219 of the 295 patients were patients who died with males (53.9%) and adults (64.8%) more than all critically ill COVID-19 patients. Adult males had worse outcomes. There was a significant correlation between age (p = 0.002) and gender (p = 0.003) of critical patients with clinical outcomes (Table 1).

Table 1: Characteristic patients and correlation with clinical outcomes of critically ill patients with COVID-19

Variable	Recovery		Death		Total		p-value*
	f (n = 76)	%	f (n = 219)	%	f (n = 295)	%	
Age							
Adult	61	20.7	133	45.1	194	64.8	0.002*
Elder	15	5.1	86	29.2	101	34.2	
Gender							
Men	30	10.2	129	43.7	159	53.9	0.003*
Women	46	15.6	90	30.5	136	46.1	

The number of adult patients was 61 people improved and 133 people died, while in old age there were 86 patients improved and 15 patients died, with

p = 0.002 which means statistically significant or related (Table 1).

There was a significant increase in the number of INR levels and platelets on day 1 and day 5, while the number of D-dimer on day 1 and day 5 decreased but was not significant. In patients who died, there was an increase in INR on day 1 and day 5 and a decrease in D-dimer and platelets on day 1 and day 5. In recovered patients, there was an increase in INR and platelets on day 1 and day 5, while D-dimer on day 1 and day 5 decreased. The mean ± SD serum of INR levels on the first and 5th days were 1.22 ± 0.77 and 1.36 ± 1.16; mean ± SD serum of D-dimer on the first and 5th days were 4.624 ± 3.533 µg/L and 4.334 ± 3.365 µg/L; and mean ± SD serum of platelet count on the first and 5th days were 160.162 ± 117.203/µl and 234.070 ± 126.816/µl (Figure 1). Complete data can be seen in Supplementary 1.

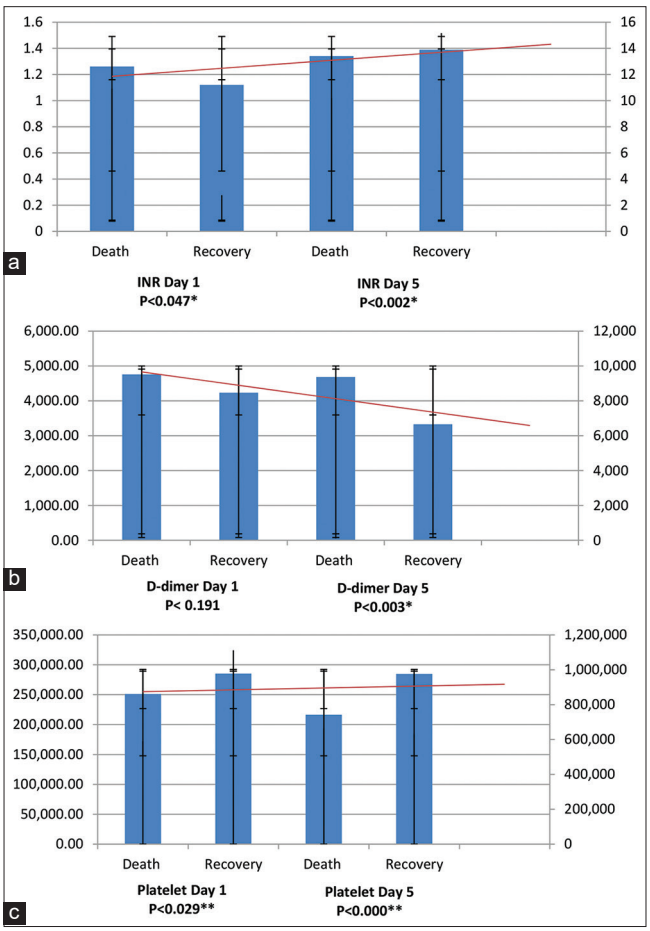

*Figure 1: Mean of INR, D-Dimer, and platelets count of critically Ill patients with COVID-19. (a) INR levels; (b) D-dimer levels; and (c) Platelet count. Redline: linieritas, p-value; *with independent t-test, **with Mann–Whitney because the data are not normally distributed*

INR dan D-dimer levels increased more in patients who died on day 5 (Figure 2 - complete data can be seen in supplementary 2)

There was a significant correlation between age (p = 0.002), INR levels on the 5th day (p = 0.041), platelet count on the 5th day (0,012) with clinical outcomes of patients. There was no significant relationship between INR, D-dimer, and platelet count on the 1st day and D-dimer on day 5 with clinical outcomes of patients (Table 2).

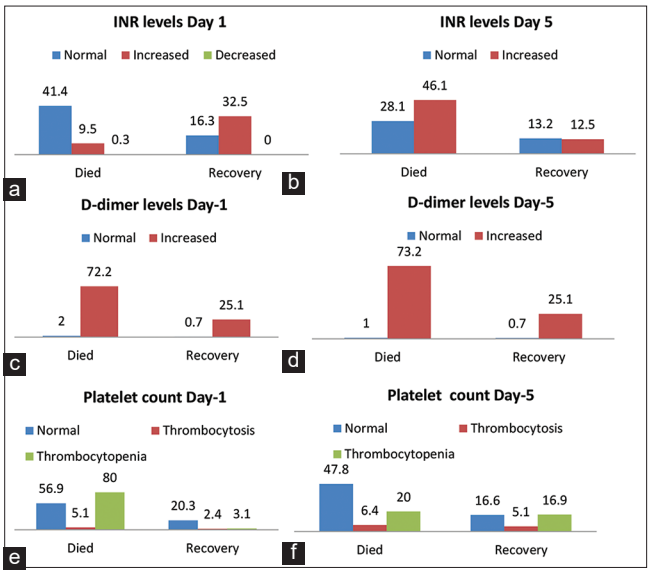

Figure 2: Percentage (%) INR, D-Dimer, Platelets count, and outcome of critically ill patients with COVID-19. INR levels at admission (a), day 5 after corticosteroid administration (b), D-dimer levels at admission (c), day 5 after corticosteroid administration (d), platelet count at admission (e), day 5 after corticosteroid administration (f) in the peripheral blood of patients. Normal count (blue), increased count (red), and decreased count (green) in serum IL-6 and ferritin

Discussion

The results of this study are shown in Table 1, 101 patients aged >65 years. Worse prognosis in men, older age, than women, younger. Several factors may contribute to these differences, including the type of healthcare systems, patient characteristics, or prevalence of diagnostic testing. Patient comorbidities such as hypertension, diabetes, and obesity are associated with higher COVID-19 mortality. Since the number of comorbid conditions steadily increases with age, this could be another logical explanation of the observed increased mortality in older patients.

Table 2: Correlation of serum IL-6 and ferritin levels with clinical outcomes of critically ill patients with COVID-19

Variable	p-value
INR levels Day-1	0.461
INR levels Day-5	0.041*
D-dimer levels Day-1	0.96
D-dimer levels Day-5	0.463
Platelets count Day-1	0.538
Platelets count Day-5	0.012*

*p < 0.050 with Chi-square test.

This study is in line with a study at a hospital in Addis Ababa, Ethiopia by analyzing the coagulation profile of COVID-19 patients, it was found that a prolonged prothrombin time was found in 46.8% of patients with COVID-19 and a prolonged prothrombin

time and increased INR in 53 3% of study subjects with severe COVID-19 patients and 51% of critically ill patients. Thrombocytopenia was detected in 22.1% of COVID-19 patients. About 50.5% and 51.3% of COVID-19 patients aged over 55 years had thrombocytopenia and prolonged APTT, respectively [3].

Data from China has shown that older adults, especially those with serious health conditions, are at higher risk for severe COVID-19-related illness and death than younger people. Although most of the reported cases of COVID-19 in China are mild (81%), about 80% of deaths occur among adults aged 60 years; only one (0.1%) death occurred in a person aged 19 years [4].

In this report, cases of COVID-19 in the United States occurring from February 12 to March 16, 2020, and severity of illness (hospitalization, ICU admission, and death) were analyzed by age group. A total of 4226 cases of COVID-19 in the United States have been reported to the CDC, with many cases reported among older adults living in long-term care facilities. Overall, 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of COVID-19-related deaths occurred among adults aged 65 years with the highest percentage of severe outcomes among people aged 85 years. In contrast, no ICU admissions or deaths were reported among persons aged 19 years. Similar to reports from other countries, these findings suggest that the risk of serious illness and death from COVID-19 is higher in older age groups [5].

Based on Figure 1, There was a significant increase in the number of INR and platelets on day 1 and day 5, while the number of D-dimer levels on day 1 and day 5 decreased but was not significant. In patients who died there was an increase in INR levels on day 1 and day 5 and a decrease in D-dimer levels and platelets on day 1 and day 5. In recovered patients, there was an increase in INR levels and platelets on day 1 and day 5, while D-dimer on day 1 and day 5 decreased. The mean ± SD serum of INR levels on the 1st and 5th day was 1.22 ± 0.77 and 1.36 ± 1.16; mean ± SD serum of D-dimer on the 1st and 5th day was 4.624 ± 3.533 μg/L and 4.334 ± 3.365 μg/L; and mean ± SD serum platelet count on the 1st and 5th day was 160.162 ± 117.203/μl and 234.070 ± 126.816/μl.

Based on Figure 2 and Table 2, INR dan D-dimer levels were most elevated in patients who died on day 5. There was a significant correlation between age (p = 0.002), INR levels on the 5th day (p = 0.041), platelet count on the 5th day (0.012) with clinical outcomes of patients. There was no significant relationship between INR, D-dimer, and platelet count on the 1st day and D-dimer levels on day 5 with clinical outcomes of patients.

An increase in INR and platelets due to Platelet-leukocyte aggregates and platelet-endothelial interactions appear to play a role in the pathogenesis of acute lung injury due to physical/chemical damage and influenza infection, respectively. The interactions between endothelial cells, platelets, and leukocytes play a critical role in the procoagulant effect of viral infections. Platelets also appear to play a role in recruiting and activating circulating leukocytes to the endothelial surface, leading to leukocyte diapedesis. By combining thrombotic and immune recruitment functions, platelets may help focus hemostasis and immune responses against potential infectious agents to prevent microbial invasion. Platelets and their released products have been variably reported suppressing viral infection and supporting virus persistence, depending on the particular infection. While platelets contribute to the basal barrier integrity of the alveolar capillaries, they may also contribute to lung injury in a variety of pulmonary disorders and syndromes.

Coagulation disorders occur in the early stages of COVID-19 infection, with 50 (43.5%) patients elevated D-Dimer levels and 74 (64.3%) patients increased Fibrinogen. D-Dimer and Fibrinogen levels correlate with clinical classification. Of the 23 patients who died, 18 had elevated D-dimer in the first lab test, 22 had elevated D-dimer in the second and third lab tests, and 18 had prolonged PT in the third. The results of the ROC analysis for the risk of death showed that the AUC of D-Dimer was 0.742, 0.818, and 0.851 in three tests, respectively; PT is 0.643, 0.824, and 0.937. In addition, with disease progression, CT imaging changes were closely associated with elevated D-dimer levels ($p < 0.01$) [6]. Coagulation dysfunction is more likely in severely ill and critically ill patients. D-dimer and PT can be used as significant indicators in predicting COVID-19 mortality.

In our hospital, increasing D-dimer levels were given anticoagulant therapy (Unfractionated heparin [UFH] or enoxaparin). UFH is the drug of choice for the first line. In our hospital with a high risk of hypercoagulopathy, we give heparin, UFH, or enoxaparin. UFH is given in the absence of thrombocytopenia. UFH is given at a dose of 1 × 6 mg IV for 5 days and can be extended depending on the patient's condition according to the assessment of the medical doctor in charge. We noted that 12% of cases developed thrombocytopenia in patients given IV UFH.

The study has several limitations. First, the data collection in this study was from medical records so that the INR, D-dimer, and platelets were taken according to the clinical condition of the patient. Second, this was a single-center study that was performed at an Indonesian national referral hospital in Padang. Therefore, the patients may have had more complex conditions or comorbidities than in the general population. Furthermore, additional studies are needed in a wider population. We suggest in future studies to collect data from other national referral hospitals in Indonesia.

Conclusion

There is a significant increase in the average platelet count on day 1 and day 5. There is a significant relationship between INR levels with platelet counts on the 5th day with clinical outcomes of patients.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Acknowledgments

We thank the Directors of Dr. M. Djamill General Hospital who has supported and assisted in providing data and information for the purpose of this research. We thank Arif Gusman, MD, Wiwi Monika Sari, MD, and all nurses ICU COVID for collecting data and Regi Alfajrin Putra, MD for processing the data and creating the figure.

Author Contributions

Dedy Kurnia and Andani Eka Putra designed the study. Dedy Kurnia, and Dwitya Elvira acquired the data. Dedy Kurnia and Eti Yerizel were involved in statistical analysis and interpreted the data. Andani Eka Putra and Dwitya Elvira drafted the study. Andani Eka Putra, Dwitya Elvira, and Eti Yerizel revised the study. Dedy Kurnia supervised the study. All authors read and approved the final study.

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Supplementary Tables

Supplementary 1: Overview of INR, D-Dimer, platelets, and their relationship to clinical outcomes of critically COVID-19 patients on admission to the ICU of RSUP Dr. M. Djamil, Padang

Variable	Outcome	n	Mean	SD	Min	Max	p-value
Age	Death	219	61.14	12.08	21	89	0.002*
	Recovery	76	53.03	14.27	24	85	
	Total	295	59.05	13.14	21	89	
INR on admission	Death	219	1.26	0.87	0.78	10.9	0.047*
	Recovery	76	1.12	0.33	0.82	2.77	
	Total	295	1.22	0.77	0.78	10.9	
INR Day 5	Death	219	1.34	0.91	0.89	10.2	0.002*
	Recovery	76	1.39	1.69	0.84	15,15	
	Total	295	1.36	1.16	0.84	15,15	
D-Dimer on admission	Death	219	4.759.33	3,501.6	299	10,000	0.191
	Recovery	76	4.235.51	3,618.03	301	10,000	
	Total	295	4.624.38	3,533.21	299	10,000	
D-Dimer day 5	Death	219	4.682.89	3,427,67	115	10,000	0.003*
	Recovery	76	3.329.5	2,940.36	365	10,000	
	Total	295	4.334.22	3,365.9	115	10,000	
Platelets on admission	Death	219	251.386.15	105,949,47	259	590,000	0.029**
	Recovery	76	285.452.55	142,642.39	394	1,111,000	
	Total	295	160.162.58	117,203.88	259	1,111,000	
Platelet day 5	Death	219	216.501.41	116,215.14	164	665,000	0.000**
	Recovery	76	284.695.72	142.431.23	156	631,000	
	Total	295	234070.11	126,816.07	156	665,000	

n: Number of cases, SD: Standard deviation, Min: Minimum, Max: Maximum, * *P*<0.050 with independent t-test.

Supplementary 2: Overview of the frequency and number of INR, D-dimer, platelets and their relationship to clinical outcome of critical COVID-19 patients when admitted to the ICU Dr. M. Djamil, Padang

Variable	Recovery		Death		Total		p-value
	f (n = 76)	%	f (n = 219)	%	f (n = 295)	%	
Age							
Adult	61	20.7	133	45.1	194	65.8	0.002*
Old	86	29.2	15	5.1	101	34.2	
INR on admission							
Decreased	0	0	1	0.3	1	0.3	0.461
Normal	48	16.3	122	41.4	170	57.6	
Increased	28	32.5	28	9.5	124	42.4	
INR Day 5							0.041*
Decreased	0	0	0	0	0	0	
Normal	39	13.2	83	28.1	122	41.4	
Increased	37	12.5	136	46.1	173	58.6	
D-Dimer on admission							
Normal	2	0.7	6	2	8	2.7	0.96
Increased	74	25.1	213	72.2	287	97.3	
D-Dimer day 5							
Normal	2	0.7	3	1	5	1.7	0.463
Increased	74	25.1	216	73.2	290	98.3	
Platelets on admission							0.538
Thrombocytopenia	9	3.1	36	80	45	15.3	
Normal	60	20.3	168	56.9	228	77.3	
Thrombocytosis	7	2.4	15	5.1	22	7.5	
Platelets day 5							
Thrombocytopenia	12	16.9	59	20	71	24.1	0.012*
Normal	49	16.6	141	47.8	190	64.4	
Thrombocytosis	15	5.1	19	6.4	34	11.1	

%: Percentage, *p < 0.050 with Chi-square test.