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Relationship of D-dimer Value to Mortality in Covid-19 Patients with Acute Coronary Syndrome at Haji Adam Malik Hospital Medan

Dian Primadia Putri[1*], Rahmad Isnanta Sembiring[2], Tambar Kembaren[2], Putri Eyanoer[3]

[1] *Study Program of Internal Medicine, Faculty of Medicine, University of Sumatera Utara*
[2] *Departement of Internal Care, Faculty of Medicine, University of Sumatera Utara*
[3] *Departement of Preventive and Community Medicine, Faculty of Medicine, University of Sumatera Utara*

***Corresponding Author**: Dian Primadia Putri, E-mail: drdianprimadiaputri@gmail.com

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ABSTRACT

Introduction: Coronaviruses (CoVs) are single-stranded positive-sense RNA viruses, which can trigger cardiovascular disease. Inflammation caused by SARS-CoV-2 can affect atherosclerotic plaques, induced prothrombotic changes in the blood and endothelium and caused their instability and myocardial infarction. Several prospective studies have demonstrated an association between increased baseline D-dimer levels and the risk of subsequent cardiovascular events. Several studied had showed the relationship of D-dimer value to mortality in COVID-19 patients with acute coronary syndrome at H. Adam Malik Hospital Medan.

Method: This study was a descriptive analytic study using medical record data from central installation patients at H. Adam Malik Hospital in the period August 2020 to August 2021. The sample was calculated using the Lemeshow formula. Then the distribution test was carried out using Shapiro Wilk test. Inferential statistical analysis was performed to assess the relationship of D-dimer to mortality in COVID-19 patients with acute coronary syndrome at H. Adam Malik Hospital Medan using chi-square test. If chi-square criteria were not met, the inferential statistical analysis used was Fisher's exact or other alternative tests. The results were statistically significant if the p value <0.05.

Results: 70 subjects participated in the study and the average age of the research subjects was 58.2 years, majority were male. Most subjects experienced severe COVID-19; ECG found ST elevation and comorbid factors were mostly hypertension followed by hypertension and diabetes type 2. There was a relationship between D-dimer value and mortality in COVID-19 patients with acute coronary syndrome, with p value = 0.005.

Conclusion: D-dimer values was associated with mortality in COVID-19 patients with acute coronary syndrome.

Keywords

D-dimer, mortality, acute coronary syndrome, COVID-19

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INTRODUCTION

Coronaviruses (CoVs) are single-stranded, positive-sense RNA viruses that causes acute respiratory infections, including influenza, respiratory syncytial virus (RSV), and bacterial pneumonia, which triggers cardiovascular disease (CVD). The underlying cause is usually associated with comorbidities, increasing the incidence and severity of these infectious diseases [1].

Several studies and case reports had explained the relationship between COVID-19 and acute coronary heart disease. An observational study of 115 STEMI patients showed that COVID-19 patients had increased D-dimer levels and a higher thrombotic events compared to non-COVID patients [2].

Inflammation caused by SARS-CoV-2 can affect atherosclerotic plaques, induce prothrombotic changes in the blood and endothelium and cause their instability, leading to myocardial infarction. Coagulation dysfunction in COVID-19 patients increased the development of severe disease and fatal outcome, and was characterized by increased D-dimer and thrombus in veins and arteries [3]. Measuring serum D-dimer levels can be appropriate as a marker with high sensitivity and relatively high specificity to differentiate MI from UA in patients with suspected ACS [4]. Some prospective studies showed an association between increased D-dimer levels and subsequent risk of cardiovascular events, whereas others did not [5].

Other studies had discussed the role of increased oxygen demand, pro-inflammatory state during infection in COVID-19 patients and the effects of other respiratory tract infections and the impact of their complications on the pathogenesis of ACS [3,6] . Therefore, it was important to evaluate the incidence of acute coronary syndrome in patients with COVID-9 and warned clinicians about early complications as to prevent the risk of mortality in COVID-19 patients. As well as research on COVID-19 which was new pandemic that had occurred in large countries, especially in Indonesia, there was limited data on this matter, therefore, based on the background, researchers were interested in evaluating the relationship between the D-dimer value and the mortality of COVID-19 patients with acute coronary syndrome at H. Adam Malik General Hospital Medan.

METHOD

Study Design and Research Subjects

A total of 70 medical records of COVID-19 patients with acute coronary syndrome who were hospitalized at the H. Adam Malik Hospital Medan Installation from August 2020 to August 2021 were included in this analytic descriptive study using consecutive sampling technique based on inclusion criteria and exclusion criteria. Patients were collected during period February 2022.

Inclusion criteria in this study were age ≥ 18 years, treated at H. Adam Malik General Hospital Medan from August 2020 to August 2021, positive RT-PCR swab examination results for COVI D -19, COVID-19 patients of all severity degrees and comorbidities. Patients without results/waiting for the results of a rapid test, PCR or CT *scan* ; pulmonary TB, history of PCI and CABG, malignancy, and history of long bed rest were excluded from this study.

Research methodology

This study used medical record data to obtain personal information about the subject, such as gender, severity of COVID-19, ECG features, D-dimer level, and patient mortality. D-dimer levels were increased if >500 ng/mL and normal if 500 ng/mL.

Statistical Analysis

Statistical analysis was performed using *Statistical Product and Service Solution* (SPSS) software. Data were analyzed as descriptive and inferential statistical analysis. Descriptive statistical analysis was used to determine the frequency distribution of demographic data. Inferential statistical analysis was performed to assess the relationship between D-dimer values and mortality in COVID-19 patients with acute coronary syndrome at H. Adam Malik General Hospital Medan using the chi-square test. If the chi-square requirements are not met, the inferential statistical analysis was used with Fisher's exact or other alternative tests. The results were statistically significant if the p value <0.05.

RESULT

Characteristics of Research Subjects

There were 70 patients who were hospitalized at the H. Adam Malik General Hospital Medan Installation who met the inclusion and exclusion criteria. The average age of the research subjects was 58.2 years, with the youngest being 24 years old and the elderly being 88 years old. The majority of research subjects were men, as many as 58 people (82.9%). Based on the degree of severity of COVID-19, the majority of research subjects

experienced severe disease, around 31 people (44.3%). Based on the ECG description, majority had ST elevation, as many as 44 people (62.9%). Majority of patients had comorbid hypertension, as many as 37 people (52.9%). Majority of COVID-19 patients with acute coronary syndrome died, as many as 42 people (60%). Demographic and clinical characteristics of research subjects were presented in table 1.

Table 1. Demographic Characteristics of Research Subjects

Variable	Frequency
Age (years)	
Mean ± SD	58.2 ± 12.00
Median (minimum-maximum)	58 (24-88)
Gender, n (%)	
Man	58 (82.9)
Woman	12 (17.1)
Degree of severity of COVID-19, n (%)	
Moderate	27 (38.6)
Severe	31 (44.3)
Critical	12 (17.1)
ECG, n (%)	
ST Depression	26 (37.1)
ST Elevation	44 (62.9)
Comorbid, n (%)	
Type 2 DM	12 (17.1)
Hypertension	37 (52.9)
Hypertension and Type 2 DM	14 (20.0)
None	7 (10.0)
Mortality, n (%)	
Life	28 (40.0)
Die	42 (60.0)

Characteristics of Laboratory Examination Parameters

Table 2. showed the parameters of the laboratory examination. The average D-dimer was 1577.10 ± 1364.71 ng/mL, the CK-MB average was 85.13 ± 86.40 U/L, the Troponin I average was 19.93 ± 28.53 ng/mL, the characteristics of laboratory examination parameters were presented in table 2.

Table 2. Characteristics of Laboratory Examination Parameters

Parameter	*Means*	*Standard Deviations*	Median	Min value	Maximum value
D-dimer	1577,10	1364,71	805.50	232	>4000
CK-MB	85,13	86,40	58	15	550
Troponin-I	19.93	28.53	10.06	0.01	170

Table 3. Classification Characteristics of Laboratory Examination Parameters

Variable	Frequency
D-dimer	
Normal (<500 U/L)	14 (20.0%)
Increase	56 (80.0%)
CK-MB	
Normal (<24 U/L)	6 (8.6%)
Increase	64 (91.4%)
Troponin I	
Normal (<0.03U/L)	1 (1.4%)
Increase	69 (98.6%)

The majority of research subjects had increased levels of D-dimer, as many as 56 people (80%) and normal D-dimer, as many as 14 people (20%). The majority of study subjects also experienced an increased in CK-MB and troponin I, as many as 64 people (91.4%) and 69 people (98.6%), respectively (table 3).

Relationship of demographic characteristics to mortality in COVID-19 patients with ACS

Based on table 4 below, gender was associated with mortality in COVID-19 patients with ACS (p=0.01) but the degree of severity of COVID-19, EKG features, patient comorbidities were not associated with mortality in COVID-19 patients (p>0.05).

Table 4 Analysis of the relationship between patient demographic characteristics and mortality in COVID-19 patients with acute coronary syndrome

Variable	*Outcomes*		p value
	Die	Life	
Gender			
Man	39	19	0.01*
Woman	3	9	
Degree of severity of COVID-19			
Moderate	13	14	
Severe	20	11	0.232***
Critical	9	3	
ECG			
ST depression	13	13	0.215**
ST elevation	29	15	
Comorbid			
Type 2 DM	7	5	
Hypertension	23	14	0.793***
Hypertension and type 2 DM	7	7	
None	5	5	

*Fisher's exact test; **chi square test; *** Kruskal Wallis test

Relationship of D-dimer to mortality in COVID-19 patients with Acute Coronary Syndrome

In this study, normal D-dimer levels were found in COVID-19 patients with acute coronary syndrome who died, as many as 13 people, and as many as 1 COVID-19 patient with acute coronary syndrome lived. There were 29 COVID-19 patients with acute coronary syndrome who died with increased D-dimer and 27 COVID-19 patients with increased D-dimer lived. Increased D-dimer was closely related to mortality in COVID-19 patients with acute coronary syndrome, with p=0.005, presented in table 5.

Table 5. Relationship of D-dimer to mortality in COVID-19 patients with acute coronary syndrome

D-Dimer	Mortality		p value
	Life	Die	
Normal	1	13	
Increase	27	29	0.005
Total	28	42	

*Chi square test

DISCUSSION

Acute coronary syndrome (ACS) was frequently reported in patients with coronavirus disease 2019 (COVID-19) and affected the clinical course and patient mortality. In this study, the average age of COVID-19 patients with acute coronary syndrome was 58.2 years. The majority of research subjects were men. This result was in line with research conducted by Perrin *et al.* (2020) [7] that of the 45 patients treated for ACS at the Geneva University Hospital during the COVID-19 period, 20% were women; with mean age of 63.8 ± 9.2 years.

Observational retrospective study by Kudo *et al.* (2021) [8] found that majority of ACS patients was 68.5 ± 12.0 years and was dominated by men. An increased incidence of myocardial implications in COVID-19 patients had been associated with cardiotoxicity, sepsis during hospitalization, inflammation, thrombosis due to plaque rupture, disequilibrium between demand and supply and electrolyte imbalance in myocardial supply [9].

Based on the ECG description of acute coronary syndrome patients with COVID-19, majority had ST elevation. Data from the ISACS-STEMI COVID-19 registry showed a significant reduction in the number of invasively treated ST-elevation MI (STEMI) patients from 2019 to 2020, with an 18.9% reduction for STEMI in the past year. The study conducted by Tam *et al*. (2022) [10] found patients with myocardial infarction with ST elevation (STEMI), myocardial infarction without ST elevation (Non-STEMI), and unstable angina (UAP) during pandemic reduced by 38.0%, 41.0%, and 63.3%., respectively. The delayed in ACS patients seeking emergency services primarily because of fear of contracting or spreading COVID-19 after admission to the hospital, as well as increasing the burden on the health care system. The study conducted by Ain *et al*. (2021) [11] in 50 COVID-19 patients, 10% global ischemia, 12% STEMI, 22% NSTEMI, 12% unstable angina, 8% ischemic heart disease, 12% inferior wall ischemia, 12% anterolateral wall myocardial infarction, 8% myocardial infarction, 4% acute heart failure.

The most common co-morbidities reported were hypertension, cardiovascular disease, and diabetes [12]. In this study, the majority of COVID-19 patients with acute coronary syndrome had comorbid hypertension. This was in line with research by Ain *et al*. (2021) [11] where 11.5% of COVID-19 patients with ACS suffered from diabetes, 96% were hypertensive, 4% had asthma and 2% were pregnant women. In a multicenter cohort study involving 191 patients hospitalized with COVID-19 in Wuhan, 48% of patients had co-morbidities (67% died), 30% of patients had hypertension (48% died), 19 % of those who died, patients had diabetes (31% died) and 8% had coronary heart disease (24% died) [13]. In a report involving 1,099 patients with COVID-19 from China, 24% of patients had co-morbidities (39% critical patients), 15% patients had hypertension (24% critical patients), 7% patients had diabetes (16% critical patients) and 3% of patients suffered from coronary heart disease (6% of critical patients) [14].

Based on the degree of severity of COVID-19, the majority of research subjects experienced severe disease. Disease severity and case fatality rates tended to be higher in COVID-19 patients with cardiovascular comorbidities [15]. Patients with cardiovascular disease had a higher risk of developing acute coronary syndrome in acute infection. Although the underlying pathogenesis remained unclear, several potential mechanisms had been hypothesized. SARS-CoV-2, by binding to the ACE2 receptor expressed on the surface of host cells, could infect pneumocytes, macrophages and endothelial cells. Patients with severe disease often showed decreased platelet counts, higher levels of D-dimer, ultra-large multimer von Willebrand factor, tissue factor, and prolonged prothrombin time, reflecting a prothrombotic state. Endothelial dysfunction had been described as a consequence of direct viral effects and a hyperinflammatory environment. Expression of tissue factor, von Willebrand factor, thromboxane, and *plasminogen activator inhibitor* -1 enhances prothrombotic status. In addition, endothelial cells produce superoxide anion, with increased local oxidative stress, and endothelin-1, which affects the vasodilator/vasoconstrictor balance and platelet aggregation. Cardiovascular comorbidities are common in COVID-19 patients who require immediate treatment to reduce morbidity and mortality [12,16].

Majority of COVID-19 patients with acute coronary syndrome died. Most studies found similar in-hospital mortality for STEMI during the pandemic compared to controls (1.7% vs 1.8%, p=0.67 from the British National Institute of Cardiovascular Outcomes Research database) [17]. The presence of myocardial injury was associated with worse prognosis significantly. In an initial report of 41 patients with COVID-19 in Wuhan, 5 patients had myocardial injury with elevated high-sensitivity cardiac troponin I levels (>28 pg/ml), and 4 of these 5 patients were admitted to the ICU. In a multicenter cohort study of 191 patients with COVID-19, 33 patients (17%) experienced acute cardiac injury, 32 died [13]. In a subsequent study of 416 patients hospitalized with COVID-19, 82 patients (20%) had evidence of cardiac injury, which was associated with a

5-fold increased for invasive mechanical ventilation and an 11-fold increased in mortality. Cardiac injury was an independent risk factor for in-hospital death [18].

The D-dimer average was 1577.10 ± 1364.71 ng/mL, the CK-MB average was 85.13 ± 86.40 U/L , the Troponin I average was 19.93 ± 28.53 ng/mL. Study by Han *et al*. (2020) of 94 COVID-19 patients, 40 healthy controls, among the infected group, during hospitalization, D-dimer levels average ± SD were found to be higher than the control group (10.36 ± 25.31 mgL^{-1} versus 0.26±0.18 mgL^{-1}; $p<0.001$). D-dimer levels increased with disease severity: those with normal (mild) disease had D-dimer level of 2.14±2.88 mgL^{-1} ($p<0.001$ compared to controls), those with severe disease had D-dimer level of 19.1±35.48 mgL^{-1} ($p<0.01$ compared to controls), and those with critical illness had 20.04±32.39 mgL^{-1}. The difference between normal and severe disease was significant ($p<0.05$). The majority of research subjects had increased levels of D-dimer, as many as 56 people (80%) and normal D-dimer, as many as 14 people (20%). The study conducted by Towsend *et al.* (2021) [19] found that increased D-dimer levels (> 500 ng/ml) were still found in 25.3% of patients up to 4 months after SARS-CoV-2 infection. An increased in D-dimer indicated that COVID-19 patients were in a hypercoagulable state, but the true pathophysiology remained unclear. SARS-CoV-2 was closely related to SARS-CoV, and they shared the same receptor, ACE2, but until now, there had been no relevant studies exploring the role of ACE-2 in COVID-19 patients with high concentrations of D-dimer. The overactive immune response in SARS-CoV-2 infection and the systemic inflammation associated with the cytokine storm could lead to blood hypercoagulation. In addition, stress (such as shock, acute respiratory distress syndrome, septicemia) or drug toxicity was associated with hypoxic reoxygenation, oxidative stress, acid-base imbalance and thus contributed to very high concentrations of D-dimer [20].

The majority of study subjects also experienced an increase in CK-MB and troponin I, as many as 64 people (91.4%) and 69 people (98.6%), respectively. Recent reports from the European Association of Cardiovascular Imaging (EACVI) and the American College of Cardiology (ACC) stated that in the case of COVID-19, elevated cardiac enzymes may be secondary to non-specific elevations during COVID-19 infection or other acute pathological complications (eg., sepsis, acute kidney injury, stroke). In addition, because the troponin elevation in patients with COVID-19 infection appeared to be lower than in most cases of ACS or acute myocarditis, the EAPCI recommends considering a marked increase (eg, >5 times the upper normal limit) in non-critically ill patients with suspected ACS with COVID-19 [21]. The overall incidence of acute cardiac injury has varied but approximately 8-12% of positive cases were known to develop a significantly elevated cTnI. Patients who were admitted to the ICU or suffered from severe/fatal illness were several times more likely to experience elevated troponins. The increased in troponin was very low (only 1-2%) in patients with mild disease who did not require ICU treatment [22].

In this study, increased D-dimer was closely related to mortality in COVID-19 patients with acute coronary syndrome, with p value =0.005. Studies from Italy demonstrated a substantial increase in STEMI mortality rates [*risk ratio* (RR) = 3.3, 1.7–6.6; $p < 0.001$] and complications (RR = 1.8; 1.1–2.8; $p = 0.009$) during pandemic compared to 2019 [21]. D-dimer level was one indicator used in patients to detect thrombosis. Increased D-dimer and fibrinogen concentrations in the early stages of COVID-19 disease, 3- to 4-fold increased in D-dimer levels was associated with a poor prognosis [23,24]. Plasma D-dimer levels were shown to be highly correlated with unfavorable outcomes. D-dimer greater than 2.0 g/mL on admission effectively predicted death in hospitalized COVID-19 patients, with a sensitivity of 92.3% and a specificity of 83.3. Retrospective study by Chen *et al.* (2020) found that the concentration of D-dimer in the deceased (4.6 g/mL) was significantly higher than in recovered patients (0.6 g/mL) [25].

In this study, gender was associated with mortality in COVID-19 patients with ACS (p=0.01). However, ECG features, patient comorbidities were not significantly associated with mortality in COVID-19 patients ($p>0.05$). The degree of severity of COVID-19 was related to mortality in COVID-19 patients with ACS but not so significant ($p = 0.232$). This results were in line with research conducted by Andrade *et al.* (2021) where hypertension and comorbidities were not risk factors for death. Study by Yendrapalli *et al.* (2022) [26] showed that patients presenting to the catheterization lab with ACS during the COVID-19 pandemic had a lower

number of overall risk factors (eg, hypertension, diabetes) compared to 2019. Research conducted by Dessie et *al*. (2021) found that chronic comorbidities, complications, and demographic factors including acute kidney injury, COPD, diabetes, hypertension, cardiovascular disease, cancer, increased D-dimer, male, older age, current smokers, and obesity were clinical risk factors for mortality in COVID-19 patients [27]. Albitar *et al.* (2020) using open access data worldwide found that male, advanced age, comorbidities (eg, hypertension and diabetes mellitus), and patient location in America were independent risk factors for death [28]. Many international studies have demonstrated the delay in women with ACS and also that they were typically older with a greater burden of comorbidities and less likely than men to receive therapy. Coronary plaques showed different pathophysiological features between sexes with women having a higher prevalence of plaque erosion and men having more frequent plaque ruptures, female patients having fewer STEMIs and more MINOCA. This low MINOCA number may be related to the further decrease in medical acceptance of such patients, who usually had atypical symptoms [29].

CONCLUSION

This study showed the profile of acute coronary syndrome patients with COVID-19 who were treated at H. Adam Malik General Hospital Medan from August 2020 to August 2021. The average age of the study subjects was 58.2 years, gender was male, ECG showed ST elevation. Based on the degree of severity of COVID-19, the majority of research subjects experienced severe disease. The majority of patients had comorbid hypertension and died. Based on laboratory tests, the majority of study subjects had increased levels of D-dimer, increased CK-MB and troponin I. The degree of severity of COVID-19 was associated with mortality in COVID-19 patients with ACS but not so significant. Increased D-dimer was closely related to mortality in COVID-19 patients with acute coronary syndrome, with a p=0.005.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and H. Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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