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Correlation of serum D-dimer level and the event microvessel cardiac thrombosis observed on core biopsy in post mortem COVID-19 Patients in Dr. Soetomo Hospital Surabaya, Indonesia

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ABSTRACT

Background: Microvascular coronary thrombosis is an emerging risk factor that worsens the prognosis of COVID-19 patients. This study aims to show for the first time a descriptive of histopathologic findings from post-mortem COVID-19 patients and to analyze whether D-Dimer serum level, a marker of hyper-coagulopathy, correlates with coronary microvascular thrombosis from the cardiac core biopsy.

Method: This was an observational analytic study with a retrospective cohort design from July-December 2020. Cardiac core biopsy was taken from patients who died while treated at the isolation ICU at Dr. Soetomo due to severe COVID-19. The samples were taken in 1-hour post-mortem and then analyzed histopathologically with Hematoxylin-eosin staining under a light microscope to evaluate the presence of coronary microvascular thrombosis and other pathological findings from the cardiac biopsy. Clinical information and D-Dimer levels from medical records and analyzed for coronary microvascular thrombosis using Man-Whitney and C-statistic analysis using SPSS 22 software.

Result: There were 39 samples of post-mortem patients in this study. The majority were men (71.8%), with a mean age of 48.9 years old. Focal microvessel coronary thrombosis was found in 28%). The median D-Dimer level was increased from the average baseline (3460 mg/dl). However, there was no significant difference in D-dimer levels between focal microvessel coronary thrombosis incidents (p-value 0.827, C statistic AUC 0.523). The lack of focal necrosis in the surrounding tissue suggests that the thrombosis resulted from proximal embolization to distal capillary coronary, which already happened before, rather than the primary in-situ process in microvascular, hence may explain why D-Dimer was not correlated with the finding of coronary microvascular thrombosis in this study.

Conclusion: D-dimer serum levels were not associated with focal microvessel thrombi in post-mortem COVID-19 patients. This result supports previous studies that showed D-Dimer was not specific to detect thrombosis in microvascular.

Keywords: histopathologic, microvessel coronary thrombosis, post-mortem, COVID-19.
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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2), confirmed by a positive SARS-CoV-2 Nasopharyngeal Polymerase Chain Reaction (PCR) swab test.The disease has been declared by the World Health Organization (WHO) as a pandemic from 2020 to date.[1] COVID-19 has infected many people from more than 200 countries and territories. According to data dated April 7th 2020, there were around 1,400,000 cases worldwide reported by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University.[2]

One mechanism that worsens the prognosis of COVID-19 patients is the hypercoagulability state in relation to microvascular or macrovascular thrombi that affect multiple organ systems. Studies from China and the United States (US)

suggest markers such as D-dimer may be associated with increased mortality in patients hospitalized with COVID-19, with follow-up studies showing associated complications.[3]

Microthrombi is one of the significant variable cardiac factors in COVID-19 patients. Microthrombi is one of the risk factors that aggravate a patient's prognosis. SARS-CoV2, through the ACE2 receptor, binds to the surface of the virus spike protein (S), causing endothelial dysfunction, microvascular dysfunction, systemic inflammation, and cytokine storms. This triggers endothelial exocytosis, resulting in microvascular thrombosis and inflammatory processes.[3,4] In the pathological study by Pellegrini et al., an autopsy examination was carried out on 40 hearts of subjects who died due to COVID-19 infection, and the results of the study showed that 14 (35%) had evidence of myocyte necrosis 3, especially the left ventricle. In the study subjects, there was cardiac microthrombi in 11 of 14 (78.6%) cases with myocyte necrosis, with 2 of 14 (14.2%) having epicardial coronary artery microthrombi, while 9 of 14 (64.3%) had microthrombi in myocardial capillaries, arterioles, and arteries.[4]

This research is necessary because research on the relationship between serum D-Dimer levels and cardiac microvessel thrombosis in COVID-19 patients using the core biopsy technique has never been carried out in Indonesia or even the world. The autopsy technique was not chosen because it considered several aspects, including the social part.

METHOD

Our study is an observational analytic study with a retrospective cohort design. The sample of this study was 47 patients who died while being treated at the Special Isolation Room of Dr Soetomo due to COVID-19 from July 2020 – December 2020. Samples were taken based on consecutive sampling. Those who met the inclusion and exclusion criteria were included in this study until the end of the sampling period. A core heart biopsy was taken 1 hour after the patient died. The biopsy was taken in three sites with the guidance of the patient's last chest radiological examination. An anatomical pathologist observed the finding of micro-vessel thrombosis in the heart through histopathological examination of the biopsy samples. Heart tissue samples were fixed with neutral buffered formalin 10%, followed by Haematoxylin – Eosin staining. The histopathological picture of micro-vessel thrombosis is characterized by cardiac micro-vessels filled with thrombus fibrin. Or defined as the finding of thrombus in small blood vessels (capillaries/arterioles) in the myocardium. Examining plasma D-dimer levels was carried out during patient care in the isolation room. Confirmed COVID-19 patients coming to Dr. Soetomo were given treatment and care per the standard hospital service procedures.

Statistical analysis

Univariate analysis was performed to describe the distribution of each variable, independent and dependent variables, and descriptions of the characteristics of research subjects. The association between independent and dependent variables was analyzed by comparing the mean or median D-Dimer values between samples with and without microvascular thrombosis, using the Independent T-Test for normal data distribution or the Mann-Whitney test for abnormal data distribution.

The sensitivity and specificity values of the D Dimer values were obtained from the receiver operating characteristic (ROC). Clinical and laboratory parameters were tested for Chi-square analysis to see the correlation with the outcome for nominal data. All tests were 2-sided, and a p-value < 0.05 was considered significant. Data were processed with the SPSS 22 software.

RESULT

Baseline Characteristics

Recruitment was done using consecutive sampling of 47 patients who met the inclusion and exclusion criteria. Eight patients were excluded due to incomplete data, so there were a total of 39 patients who were analyzed in this study. Our study cohort of 39 confirmed COVID-19 samples had a mean age of 48.9 ± 12.3, and 71.8% were male. The median C-Reactive Protein (CRP) level was 9.65 (0.2-40.7) mg/dL; the median D-dimer level was 3460 (450-35200) ng/mL. Of the three comorbidities, diabetes mellitus was the most prevalent at 74,5%. (Table 1)

On histopathological anatomy evaluation using hematoxylin-eosin staining, we found signs of coronary microvascular thrombosis (figure 1) in 11 subjects (28%).

Clinical and Laboratory Parameters and Microvascular Coronary Thrombosis

Correlations of clinical and laboratory parameters in nominal were evaluated using Chi-square analysis. There were no significant correlations between clinical parameters and the event of coronary microvascular thrombosis (Table 2).

According to their normality, numerical data were evaluated using t-test and mann-whitney analysis for its correlation to the event of coronary microvascular thrombosis. There were no significant correlations between clinical and laboratory parameters and the possibility of microvascular coronary thrombosis, both in data with normal and abnormal distribution (Tables 3 and 4).

D-dimer level and Microvascular Coronary Thrombosis

The correlation between D-dimer level and coronary microvascular thrombosis evaluated using Mann-Whitney analysis showed no significant correlation (Table 5). Further analysis of sensitivity and specificity of D-dimer to the event of microvascular thrombosis was assessed using ROC and showed no significant difference in D-dimer levels between focal microvessel coronary thrombosis incidents (p-value 0.827, C statistic AUC 0.523) (Figure 2).

DISCUSSION

Microvascular coronary thrombosis, also known as intramyocardial microthrombus, is a blockage in an arteriole or capillary by a blood clot. Blood clotting disorders, inflammatory regulation, and endothelial injury influence it. The risk of thrombosis increases with an inflammatory reaction and an imbalance in the interaction of platelets and endothelium in COVID-19. Magro et al. and Zuo et al. demonstrated the involvement of complement factors and neutrophils in microvascular thrombosis

in patients with COVID-19 infection.[5,6] The formation of microthrombi in COVID-19 is initiated through several pathways, including a direct viral infection of endothelial and myocardial cells, neutrophil extracellular traps, hypoxic injury, pro-inflammatory cytokines, as well as a cascade of complement factors.[7,8]

All patients were examined for D-dimer levels, and found no significant relationship between D-dimer levels at admission and the incidence of microvascular coronary thrombosis. This finding is similar to the study by Brener et al., who performed autopsies on the hearts of 69 COVID-19 patients and found no association between D-dimer and hs-cTnT levels and the incidence of intra-myocardial microthrombi, although this pathology is one of the most common cardiac injury phenotype findings in COVID-19 patients.[8]

One possibility that causes the D-dimer level to be unrelated to the incidence of intra-myocardial micro thrombosis in COVID-19 is the difference in the mechanism of underlying thrombosis pathogenesis, in which the immune system plays a more important role and other components of thrombosis such as fibroblasts have different phenotypes and characters. Pellegrini et al. found differences in 53 microthrombus constituents of patients with and without COVID-19 infection, where infected patients had microthrombi that were richer in the complement system and fibrin.[4] The results of the immune histopathological examination and genetic markers of fibroblast activation showed signaling of cardiac fibroblasts specific for thrombosis, anti-fibrinolysis, and immune activation that may promote microthrombus formation.[8] Study by Nicolai et al. also supports the role of dysregulation of immunothrombosis in the formation of intramyocardial thrombosis, in which immunofluorescence examination shows neutrophils and platelets trapped in fibrin clots.[9,10] The finding of inflammatory cells within the intracapillary thrombus on histopathological examination of study subjects supports this possibility.

D-dimer is a molecule formed due to the degradation of cross-linked fibrin molecules during fibrinolysis. In particular, the formation of D-dimer requires the activity of three enzymes, namely thrombin, factor XIIIa, and plasmin. The process of forming D-dimers begins early in the coagulation process, starting with thrombin converting fibrinogen into fibrin monomers. Then the fibrin monomers experience cross-linking in the fibrin D domain.[11] In the final step, plasmin causes the degradation of fibrin accompanied by the formation of a D-dimer molecule. In the process, the presence of D-dimer describes the process of coagulation and, at the same time, fibrinolysis.[12,13] D-dimer has a half-life of about 6 - 8 hours, so it takes several days (even weeks) to return to "normal" values when it has increased to a certain level.[13] D-dimer concentrations can increase in physiological conditions (such as pregnancy physical activity) or pathological conditions (such as infection, systemic inflammation, malignancy, and others). D-dimer values can also be normal in patients who have clinically significant episodes of thrombosis either

Table 1. Baseline Characteristics

No	Characteristics	(mean ± SD)	Median (min-max)	(n, (%))
1	Gender, Male			28 (71.8)
2	Age (years)	48.9 ± 12.3		
3	Diabetes Mellitus			29 (74.4)
4	Hypertension			22 (56.4)
5	Chronic Kidney Disease			5 (12.8)
6	C Reactive Protein (mg/dL)		9.65 (0.2-40.7)	
7	D-dimer (ng/mL)		3460 (450-35200)	

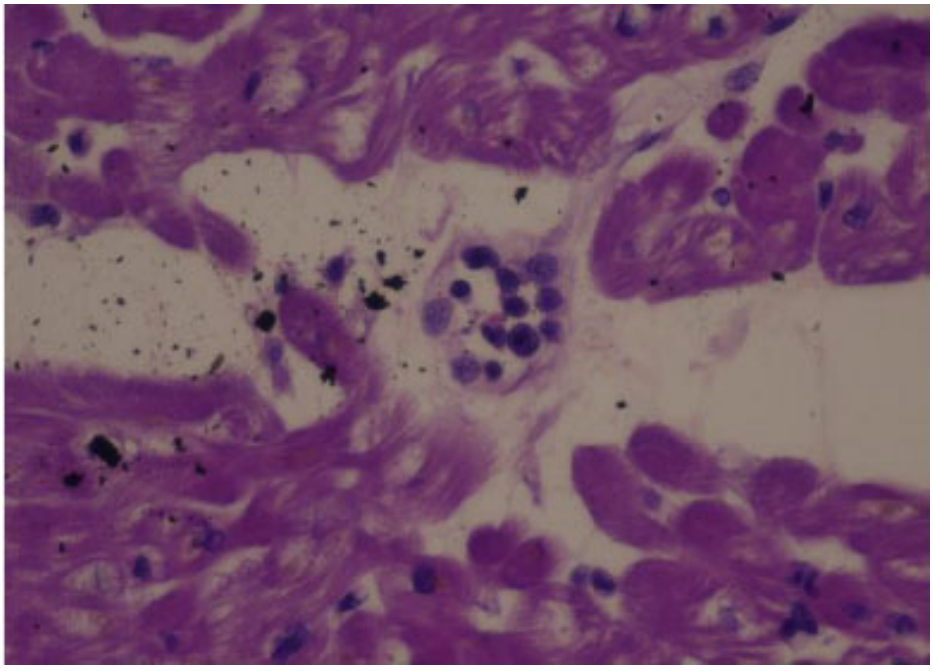

Figure 1. Microvascular Coronary Thrombosis on hematoxylin-eosin staining showing intravascular inflammatory cells.

Table 2. Correlation between clinical characteristics and the event of microvascular coronary thrombosis

Baseline Characteristics	Microthrombosis (%)	No Microthrombosis (%)	Total (n=39) (%)	p-value*
Diabetes Melitus	8 (27.6)	21 (72.4)	29 (74.4)	0.884
Chronic Kidney Disease (CKD)	3 (60)	2 (40)	5 (12.8)	0.091
Hypertension	6 (27.3)	16 (72.7)	22 (56.4)	0.883
Gender (Male)	8 (28.6)	20 (71.4)	28 (71.8)	0.935

Table 3. Correlation between clinical and laboratory parameters and the event of microvascular coronary thrombosis on t-test analysis

Clinical and Laboratory Parameters	Group	Mean	p-value
Age	MCT	53	0.200
	No MCT	47	
Heart rate	MCT	105	0.781
	No MCT	103	
Respiratory Rate	MCT	26	0.922
	No MCT	26	
Fibrinogen	MCT	503	0.296
	No MCT	571	
Platelet	MCT	265090	0.975
	No MCT	227535	

Table 4. Correlation Between Clinical and Laboratory Parameters and The Event of Microvascular Coronary Thrombosis on Mann-Whitney Analysis

Clinical and Laboratory Parameters	Group	Mean Rank	p-value
C-Reactive Protein	MCT	20.00	1.000
	No MCT	20.00	
White Blood Cell	MCT	18.89	0.333
	No MCT	22.82	
Neutrophil Lymphocyte Ratio	MCT	16.76	0.135
	No MCT	22.45	
Systolic Blood Pressure	MCT	19.14	0.897
	No MCT	19.65	
Diastolic Blood Pressure	MCT	19.54	0.974
	No MCT	19.41	

Table 5. Uji Mann-Whitney D-Dimer dan *coronary microvascular thrombosis* (MCT)

	Group	Mean Rank	p-value
D-dimer	With MCT	19.75	0.827
	Without MCT	20.64	

due to the formation of small clots (so that the amount of D-dimer produced is also minimal), old age (no longer able to be lysed by fibrinolytic enzymes) or as an effect of antithrombotic drugs currently in use.[13] D-dimer is a marker for a sensitive thrombotic process but not specific to the cause and location of a thrombosis.[14,15]

In general, COVID-19 patients have a higher incidence of thrombotic processes. Thrombosis that occurs in covid patients can be reviewed from Virchow's triad. Endothelial injury, hypercoagulation, and stasis conditions in critically ill patients due to immobilization support thrombotic conditions.[16] D-dimer as a coagulation marker parameter tends to increase in COVID-19 patients. D-dimer values and several other coagulation parameters are closely related to the severity and mortality of COVID-19 patients.[17,18] In this study, patients generally had an increased average D-dimer value in those with and without microvascular thrombosis. The characteristics of D-dimer in COVID-19 tend to increase on the third day of hospitalization. In one study, the D-dimer kinetics peaked earlier in severe cases and could decrease after the eighth day.[19] This shows that the examination period for disease onset and early hospitalization can affect the D-dimer values obtained.

D-dimer is increased under physiological conditions (severe physical activity, pregnancy), and its increase can occur in several pathological conditions that do not involve thrombotic processes (cancer, inflammation, infection, hypertension, etc.). In addition, D dimer levels can be found to be normal in patients with a clinically thrombotic process. This can be caused by a blockage that is too small so that the fibrinolysis that occurs does not increase significantly, a thrombotic process that has been going on for a long time and leaves an old blockage so that it can no longer be fibrinolized, the possibility that the patient's D-dimer examination is too fast or too slow relative to the course of the disease, there is an increase in additional fibrin such as in severe infections and cancer.[13,20] The small size of the micro thrombus occlusion and the presence of COVID-19 infection can lead to the masking of increased D-dimer levels, where groups of patients who experience thrombosis and those who do not experience both increases in D-dimer. In conditions with many confounding factors, the positive predictive value of D-dimer on thrombotic events, especially arterial thrombosis, is low.

Microembolism in the coronary microcirculation vessels can occur in COVID-19 patients. Microembolism can occur even in the absence of previous coronary atherosclerotic lesions.[21] At the autopsy of COVID-19 patients, 10-20% found thrombus rich in fibrin, platelets, and leukocytes in the microcirculation.[22,23] Intracoronary microthrombi were also seen in pathological analysis in 35% of patients who died from COVID-19 and with evidence of myocardial necrosis regardless of prior coronary artery disease. 4 Activated leukocytes and inflammatory mediators such as IL-6 are systemically responsible for the thrombogenic state of COVID-19 patients.[21,24]

The limitation of this study was that the D-dimer sampling process was carried out at different points of the disease course between samples. Although all patients were sampled on the first day of treatment, each patient's previous study of illness was not the same, and the days of illness for each patient and history of prior treatment were unknown. This can affect the measured D dimer level. In addition, histopathological samples were taken using the core biopsy method at three points, and there is a possibility that the samples taken were in a thrombosis-free area. Thus the number of patients with intramyocardial micro thrombosis is likely higher than measured.

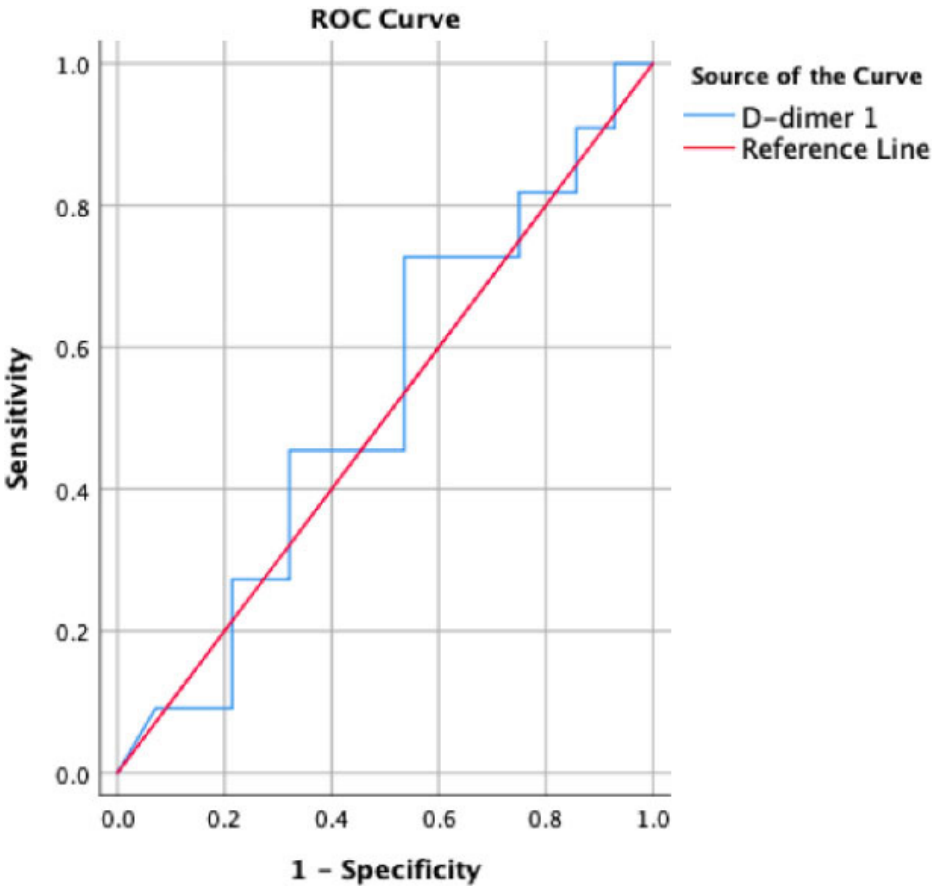

Figure 2. Receiver Operating Characteristic (ROC) of D-dimer level and coronary microvascular thrombosis.

CONCLUSION

This study showed no significant relationship between D dimer and intramyocardial micro thrombosis or coronary microvascular thrombosis in COVID-19 patients. Many factors may influence the D-dimer value. The D-dimer, although a marker of a thrombotic event, this marker was not specific for the cause of thrombosis. The elevation of D-dimer also depends on the onset of the disease and timing of measurement, size of the thrombotic, and many other factors. The interpretation of D-dimer needs to be individualized, especially in microvascular thrombosis.

DISCLOSURES

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Conflict of Interest

All authors have no conflict of interest to declare.

Ethical consideration

This study has been approbed by Ethical Committee Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo Hospital Surabaya with ethical clearance reference number 031/komitlitkes/2022.

Author Contribution

1. Galih Pratama Rinjani: Conceived and designed the study, collected and analyzed data, and contributed to the writing and revision of the manuscript.
2. Achmad Lefi: contributed to the concept, study design, and data analysis and critically reviewed the manuscript.
3. Muhammad Yusuf Alsagaff: involved in concepting the study, assisted in data analysis, contributed to manuscript preparation, and critically reviewed the manuscript.
4. R. Mohammad Budiarto: actively participated in concepting the study, contributed to designing the study, and revising the manuscript.
5. Priangga Adi Wiratama: Concepts, participated in data collection, analysis, and manuscript preparation.
6. Etty Hary Kusumastuti: Contributed to the study design and data analysis and critically reviewed the manuscript.
7. Isnin Anang Marhana: Participated in concepting the study, data analysis, and manuscript revision.
8. Alfian Nur Rosyid: Involved in study concept and design, data analysis, and manuscript writing.
9. Dwi Wahyu: Contributed to the study design, data collection, and manuscript revision.
10. Bambang Pujo Semedi: Provided guidance and expertise during the study, contributed to the study design, and critically reviewed the manuscript.
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12. Ryan Ernast Intan: Assisted in data collection, analysis, and manuscript revision.
13. Muhammad Ramadhan: Assisted in data collection and manuscript revision.
14. Ika Caesarina: Assisted in data analysis and manuscript writing.
15. Asiyah Nurul Fadila: Assisted in data collection and analysis and contributed to manuscript writing.
16. Muhammad Surya Tiyantara: Contributed to the study design and data analysis and critically reviewed the manuscript.
17. Gilang Muhammad Setyo Nugroho: Participated in data collection, analysis, and manuscript revision.
18. Ummi Maimunah: Concepts, assisted in data collection and analysis, and manuscript preparation.
19. Edi Suyanto: Contributed to the study design, data collection, and manuscript revision.
20. Adhitri Anggoro: Participated in data collection, data analysis, and manuscript writing.

21. I Komang Rusgi Yandi: Contributed to the study design and data analysis and critically reviewed the manuscript.
22. Jilieanastasia Godrace Lilihata: Assisted in data collection and analysis and contributed to manuscript writing.

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