Association Between D-Dimer Level with Clinical Severity and Radiological Imaging of Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

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Abstract

Background: D-dimer could be used as a biomarker to distinguish the severity of COVID-19. High D-Dimer levels are associated with increased clinical severity and poor radiological imaging. This study aims to identify the correlation between D-dimer levels with clinical severity and radiological features of confirmed COVID-19 patients at RSUP dr. M. Djamil Padang.

Methods: This was a cross sectional study of 202 COVID-19 confirmed patients at RSUP dr. M. Djamil Padang using medical record data from 1 January to 31 March 2021. The data were collected using convenience sampling technique and analyzed by Kruskal Wallis Test to determine the association between D-dimer levels with clinical severity and radiological features.

Results: Majority of patients were in age groups of below 50 and 50-59 years, with equal proportion between men and women, and were in moderate clinical severity (58,4%). Most radiological imaging was in severe degree of 91 patients (45%). The association between D-dimer levels and clinical degree of COVID-19 patients as well as the association between D-dimer levels and severity of radiological imaging of COVID-19 patients were statistically significant (*P*=0.0001).

Conclusion: Elevated D-dimer level was a common feature at COVID-19 confirmed patients. High levels of D-dimer were associated with increased clinical severity and severe radiological features in COVID-19 patients.

Keywords: clinical severity of COVID-19, D-dimer, radiological imaging of COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 mainly due to the speed and scale of disease transmission.[1] On April 6, 2021 WHO recorded 131,309,792 confirmed cases of COVID-19, with a death rate of 2,854,276.[2]

Abnormal coagulation function is one of the factors thought to be associated with disease progression due to SARS-CoV-2 infection characterized by elevated levels of D-dimer based on laboratory blood tests. Xiaokang He et al conducted a study that pointed out a significant difference between D-dimer levels and the degree of disease. D-dimer levels were more likely to be high in patients with severe and critical cases than in patients with mild or moderate cases.[3]

This result was supported by a study conducted by Mert Ozen which stated that 63.3% of patients experienced an increase in D-dimer, and it tended to escalate as the patient's clinical condition worsened. Another study reported that clinically severe levels of D-dimer were significantly higher, and these levels increased significantly with disease severity. Based on these results, it is suspected that D-dimer levels can be a biomarker in determining disease severity and prognosis of COVID-19 patients due to the activation of diffuse inflammation and coagulopathy which are symptoms of severe disease.[4–6]

The severity of the disease could also be assessed from the radiological imaging of the patient. The main chest X-ray features observed in COVID-19 patients were bilateral, peripheral, predominantly lower lung opacity, described as hazy, ground glass opacity, and consolidation. A systematic review by Vidali et al obtained that most of the patients had consolidated chest radiographs (68%) and ground

glass opacity (48%) with bilateral pulmonary involvement and mostly distributed in the lower and peripheral lower lungs.[6]

Research conducted by Marco Francone et al. which used CT scores to assess the extent of lung involvement in patients with COVID-19 found that there was a statistically significant relationship between CT scores and D-dimer levels. The reliance on CT scans creates a huge burden on the radiology department and this makes chest X-rays (CXR) a substitute for CT scans, although CXR are considered less sensitive (the sensitivity of CXR is only 56%) for detecting pulmonary involvement in early-stage disease, but are useful for monitoring progression of early lung abnormalities in COVID-19, especially in critical patients who are treated in intensive care units because it is more practical and economical.[7,8]

METHODS

This was a cross-sectional study using secondary data that was conducted in COVID-19 isolation room of Dr. M. Djamil Hospital Padang from January to September 2021. The study population was all COVID-19 patients who were treated in the COVID-19 isolation room of Dr. M. Djamil Hospital Padang from January 1, 2021 to March 31, 2021.

Inclusion criteria were COVID-19 patients treated in the COVID-19 isolation room of Dr. M Djamil Padang from January 1 to March 31, 2021, had complete medical record data, age >18 years. Meanwhile, the exclusion criteria were pregnant patients with confirmed COVID-19 at the time of admission to isolation treatment and COVID-19 patients with comorbidities of malignancy and stroke at the time of admission to isolation treatment.

Radiological imaging was chest X-ray when the patient was first admitted (<48 hours), classified into severity score and validated by a radiologist. Scores were assessed based on pulmonary involvement. Score 0 if no pulmonary involvement, score 1 if pulmonary involvement ≤25%, score 2 with pulmonary involvement 25-50%, score 3 if pulmonary involvement 50-70%, and score 4 if pulmonary

involvement ≥70%. The measurement results were declared mild if the total severity was 0-2, moderate if 3-5, and severe if 6-8.

Data analysis was carried out descriptively and analytically. Bivariate analysis was used to find the correlation between the independent and dependent variables using Kruskal Wallis test.

RESULTS

The basic characteristics of the study subjects are presented in Table 1. Majority of the age groups were less than 50 years and 50-59 years, each of which was 59 patients (29.2%). The proportion of patients by gender was the same as that of men and women (101 patients or 50%, respectively). Based on clinical symptoms upon admission to the hospital, moderate clinical symptom was the most common observed in 118 patients (58.4%). Majority of the patients (45.0%) had severe radiological features. The D-dimer levels ranged from 163 to >10000 ng/mL with a median of 1690.5.

Table 1. Basic Characteristics of Confirmed COVID-19 Patients treated at Dr. M. Djamil Hospital Padang (N=227)

Patient Characteristics	Total	%
Ages		
<50 years	59	29.2
50-59years	59	29.2
60-69years	52	25.7
≥70 years	32	15.8
Gender		
Male	101	50.0
Female	101	50.0
Clinical Severity		
Moderate	118	58.4
Severe	12	5.9
Critical	72	35.6
Radiological imaging (chest X-ray)		
Mild	78	38.6
Moderate	33	16.3
Severe	91	45.0
D-Dimer Level		
Median (min-max)	1690.5 (163 - >10000)	

The level of D-dimer in confirmed COVID-19 patients with moderate clinical grade was the lowest with a median of 865.5 ng/ml and ranged from 163 to >10000 ng/ml, while the highest was found in the critical grade of 3389 ng/ml. and ranged from 587 to >10000 ng/ml as shown in Table 2.

Table 2. Correlation of D-Dimer Levels with Clinical Severity of Confirmed COVID-19 Patients at Dr. M. Djamil Hospital Padang

Variable	Clinical Severity			P
	Moderate (n = 118)	Severe (n = 12)	Critical (n = 72)	
D-dimer level, ng/ml	865.5	1964	3389	0.0001
[median (min-max)]	(163 to >10000)	(685 to >10000)	(587 to >10000)	

Table 3. Correlation of D-dimer Levels with Radiological Imaging (Thorax X-ray) of Confirmed COVID-19 Patients at Dr. M. Djamil Hospital Padang

Variable	Radiological Imaging			P
	Mild (n = 78)	Moderate (n = 33)	Severe (n = 91)	
D-dimer level, ng/ml	621.5	1458	2987	0.0001
[median (min-max)]	(163 to >10000)	(215 to >10000)	(591 to >10000)	

Based on the results of the normality test of data distribution and the homogeneity of the data variance according to the clinical degree, the results were not normal and not homogeneous ($P < 0.05$), so that the difference analysis was performed using Kruskal Wallis non-parametric test and obtained $P = 0.0001$. It was stated that the D-dimer level was correlated to the clinical degree of confirmed COVID-19 patients treated at Dr. M. Djamil Hospital Padang in the period of 1 January to 31 March 2021. The level of D-dimer tended to increase along with the severity of the clinical degree.

Table 3 shows that D-dimer levels in confirmed COVID-19 patients with mild radiological features ranged from 163 to >10000 ng/ml with a median of 621.5 ng/ml. In patients with moderate radiological features, it ranged from 215 to >10000 ng/ml with a median of 1458 ng/ml, and in severe radiological features, it ranged from 591 to >10000 ng/ml with a median value of 2987 ng/ml.

Based on the results of the normality test of data distribution and the homogeneity of data variance according to the radiological feature, the results were also not normal and not homogeneous ($P < 0.05$). Difference analysis was carried out with Kruskal Wallis non-parametric test and $P = 0.0001$ was obtained. D-dimer levels were associated with the radiological features of confirmed COVID-19 patients treated at Dr. M. Djamil Hospital Padang on 1 January to 31 March 2021. The D-dimer level also tended to increase along with the degree of severity observed from the radiological imaging.

DISCUSSION

This study pointed out that the prevalence of COVID-19 was observed equally highest in both the age group of less than 50 years with a mean age of 37.70 years and the age group of 50-59 years with mean age of 54.91 years (29.2%, respectively). Study conducted in Jakarta by Surendra also received the similar results with the median age of 46 years and the highest range being at the age of 32-57 year.[9] This was also in line with the study from Viradanti et al which showed that the highest age range was 40-59 years (57.3%).[10] Surendra stated that younger age at the time of admission was generally associated with a greater distribution of younger age in the general population on Jakarta.[9]

Characteristics of patients by gender in this study were comparable between men and women. Yu et al obtained the same result of equal distribution between men and women (50%, respectively).[11] Study from Long et al had male as the majority of the subjects (57.4%).[12] Men are more susceptible to infection associated with increased reactivation of immunity to viral infections compared to women due to increased antibody production so that they are effectively resistant to infection.[13] Chen et al obtained more women as the study subjects because women in East Asia express higher ACE-2 receptors so they are more likely to be infected with SARS CoV-2.[14]

Most of the clinical severity were moderate (58.4%). The results obtained were due to confirmed cases of COVID-19 with moderate clinical severity had comorbidities so that further treatment was needed and could not be carried out in regional hospitals. Garcia-Alvarado et al in their study obtained similar results which stated that the most clinical severity was moderate (62.7%), followed by severe (21.5%), and critical (15.6%).[15] Long et al observed that the most clinical severity was severe (41.7%), followed by moderate (33.9%) and critical

clinical severity (24.3%).[12] A higher proportion of moderate symptoms in this study was also associated with exclusion criteria which excluded the comorbidities of stroke and malignancy, pregnancy, as well as younger age.

Chest X-ray (CXR) has a low sensitivity in diagnosing COVID-19 but has advantages over CT-scan which is more practical and easier to access.[16] The sensitivity of CXR is only 56%.[8] Based on the radiological imaging, almost half of the patients (45%) had severe degree, followed by mild degree (38.6) and moderate degree (16.3%). Study from Setiawati et al showed that severe degrees of CXR imaging were more visible in as many as 92 COVID-19 patients, followed by moderate degrees in as many as 90 patients and mild degrees in as many as 43 patients.[17]

On the other hand, study from Baratella in 140 patients stated that pulmonary involvement of 1–25% was found the most in as much as 41.4% patients, followed by the pulmonary involvement of 26–50% in 22.1% patients, pulmonary involvement of 51–75% in 18.6% patients, pulmonary involvement of 76–100% in around 12.9% patients and without pulmonary involvement in 5% patients.[18] Yasin observed that mild degree of CXR was the most common (65.7%), followed by moderate degree (23.4%) and severe degree (10.9%).[7]

D-dimer is an indirect marker of active coagulation and thrombin formation, which is released when plasmin, a fibrinolytic enzyme cleaves fibrin for reducing blood clotting and indicates an endovascular thrombotic process.[6] The levels of D-dimer in this study ranged from 163 to 10000 ng/mL with a median of 1690.5. Yu et al obtained that the median level of D-dimer was 700 (300-1600) ng/mL.[19]

Alterations in coagulation factors during SARS-CoV-2 infection, especially D-dimer, are associated with severe clinical symptoms and a positive relationship with the severity of lung damage (CURB-65).[6] Elevated D-dimer level indicates progressive severity of COVID-19 infection and is used as a predictor of the need for aggressive critical care.[20]

This study pointed out that D-dimer levels increased with clinical severity of the patients and a significant correlation was obtained ($P<0.0001$). Garcia-Alvarado et al in their study noticed that the median levels of D-dimer at moderate, severe, and critical levels were 208 (145-327) ng/mL, 262 (210-456) ng/mL, and 858.5 (386-932) ng/mL, respectively, with $P=0.001$.[15] Yao observed that the median D-dimer level increased about 7 times from moderate to critical clinical severity (4.76 [2.02-13.30] mg/L vs 0.6 [0.33-1.49] mg/L; $P=0.000$). Yao also reported that D-dimer level escalated significantly with the increasing clinical severity of COVID-19 ($P=0.000$).[21]

A meta-analysis conducted by Gungor et al in 34 studies stated that there was an association between high D-dimer levels and severe clinical conditions (weighted mean difference/ WMD=0.45 mg/L; 95% CI=0.34-0.56; $P<0.0001$). D-dimer levels were also analyzed as a binary variable using 12 studies and in 828 severe cases as well as 1757 non-severe cases; D-dimer levels that exceeded the upper limit (>500 ng/mL) were significantly associated with disease severity with an increased risk of 1.58 times. (RR=1.58; 95% CI=1.25-2.00; $P<0.0001$).[22]

The diagnostic sensitivity of D-dimer as a predictor of COVID-19 severity among 2014 patients in meta-analysis from Zhan et al ranged from 43–100% and specificity ranged from 57–89%. The sensitivity and specificity obtained in meta-analysis from Zhan et al were 77% (95% CI=58–89%) and 71% (95% CI=64–77%).[23] Elevated D-dimer level is a serious problem in COVID-19 and is associated with higher mortality. This is correlated with an 18-fold increased risk of death compared to patients with normal D-dimer levels.[24]

The pathogenesis of SARS-CoV-2 infection involves the binding of viral glycoproteins to ACE2 identified in the alveolar epithelium and endothelium along with continuous activation of the inflammatory response and coagulation pathways resulting in a pro-coagulation state. This predisposes to systemic microthrombotic changes leading to multiorgan failure and DIC.[6]

Based on this, D-dimer levels are related to the clinical severity of confirmed COVID-19 patients. It was found that D-dimer levels elevated significantly

with the increasing clinical severity of COVID-19. The relatively high level of D-dimer early in infection identified the administration of anticoagulants. Bleeding risk was assessed using the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) score. It is not recommended to give anticoagulants if the IMPROVE score is >7, due to the risk of bleeding.[24]

This study also obtained that the higher the D-dimer level, the higher the severity of the radiological imaging ($P<0.0001$). The D-dimer levels in the study of Eroglu et al which differentiated CXR score of less than 5 and more than 5, were 500 (300-800) mg/L and 900 (0.6-1.3) mg/L, respectively with $P<0.001$.[16] Viradanti et al observed a significant relationship between D-dimer levels and radiological imaging scores assessed from CXR; the higher the D-dimer level, the higher the CXR score.[10]

A typical COVID-19 radiological feature in CXR is in the form of ground-glass opacity to predominance of consolidation along with disease progression. Although CXR is considered less sensitive for detecting early-stage lung involvement, they are useful in monitoring disease progression in COVID-19, especially in critically ill patients who are hospitalized intensively.[7] The existence of a relationship between D-dimer levels with CXR scores explained that coagulopathy associated with the severity of pulmonary parenchymal involvement in COVID-19 caused by dysregulation of coagulation due to excessive inflammatory mediators induced by SARS-CoV-2 infection.[10]

Recent studies have found micro- and macrothrombotic changes in the pulmonary microvasculature.[6] Clot formation in COVID-19 patients is rapid and difficult to degrade. Activation of the coagulation cascade is supported by endothelial tumefaction, pulmonary megakaryocytes in the capillaries and endothelium. This is due to the lung is the first target organ of SARS-CoV-2 infection, and the degradation of intra and extravascular fibrin in the alveolar and interstitial sacs results in diffuse alveolar damage.[25]

Binding of SARS-CoV-2 spike protein to the ACE2 receptor on respiratory epithelial cells will decrease the protective ACE2/Ang1-7/Mas axis, which will intensify PAI-1 expression.[25] The SARS-CoV-2 spike protein has a higher affinity for CD147 and extracellular matrix metalloproteinases which can induce the expression of various hematopoietic cells associated with thrombotic and inflammatory mechanisms in arteries and veins.[24]

Respiratory and pulmonary epithelium releases pro-inflammatory cytokines. The infiltrated immune cells are activated and attack normal lung tissue by releasing excessive cytokines. This cytokine will promote the expression of positive acute-phase proteins, TF, trypsin, and inhibit negative proteins (such as albumin). Trypsin activated matrix metalloproteinases will damage the basolateral membrane and the interstitial extracellular matrix. Endotheliopathy occurs in the infected capillaries to initiate a local hypercoagulable state. Quinine-bradykinin is activated by IL6 to stimulate the expression of tPA (tissue plasminogen activator) in endothelial cells. Fibrin deposition activates endothelial cells to express more IL8 which will suppress clot lysis time.[25]

Complementary C5b-9 in the vasculature of COVID-19 patients and neutrophil extracellular traps (NETs) may be associated with a prothrombotic mechanism.[73] NETs contribute to organ damage and promote thrombosis and fibrinolysis through lymphocyte/macrophage-like elastase.[25]

Based on this, there is a relationship between D-dimer levels with radiological features with coagulation dysregulation due to excessive inflammatory mediators induced by SARS-CoV-2 infection which then cause pulmonary parenchymal involvement in COVID-19. In Indonesia, the recommended prophylactic anticoagulant is Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) at a dose of 40 mg subcutaneous LMWH once daily, or 5000 units of subcutaneous UFH twice daily. Prophylactic anticoagulation is given while the patient is hospitalized, with monitoring for anticoagulant side effects such as bleeding or other complications. In critically ill patients, 40 mg of enoxaparin subcutaneously twice daily or 7500 units

of subcutaneous UFH three times daily is administered as a prophylactic anticoagulant.[24]

LIMITATION

This study had limitations with the samples and did not control for other factors in D-dimer levels which affected the clinical severity and radiological features of COVID-19 confirmed patients in Dr. M. Djamil Hospital Padang, so the potential for bias could occur in this study.

CONCLUSION

Characteristics of confirmed COVID-19 patients were comparable between men and women with the most age group of under 60 years, moderate clinical degree, and severe radiological feature. There was a correlation between D-dimer levels with clinical severity and radiological imaging of confirmed COVID-19 patients treated at Dr. M Djamil Hospital Padang.

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