The Relation Between D-dimer Level and Chest X-Ray (CXR) Scoring in COVID-19 Patients:

What We can Learn from?

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Abstract—Coronavirus disease is a kind of pneumonia cause by infection of SARS-CoV-2. In most cases, patients only get mild manifestation or even asymptomatic. Some patient can get severe disease, especially elderly people or someone with comorbid, leading to cytokines storm that triggers SIRS and induce coagulation dysregulation (marked by D-dimer elevation) so that increasing risk to get thrombosis. Recent pathology finding suggest that micro-thrombosis has contribution to ARDS due to lung's fibrosis. We use a CXR scoring system to assess lung parenchyma involvement in COVID-19 patients and D-dimer level to see coagulopathy then performing an analysis to investigate the relationship between both. Based on the Spearman test, we find that there is a significant relationship between D-dimer level and CXR scores of COVID-19 patients describe as a positive correlation ($p=0.023$; $r=0.358$).

Keywords—D-dimer, CRX SCORE, COVID-19

I. INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a kind of pneumonia caused by SARS-CoV-2 infection [1–3]. It is believed that this virus was transmitted from animal to human (zoonosis) through bat as the vector [2,4,5]. COVID-19, firstly found in Wuhan in mid-December 2020, now already spread through almost all countries in the world. Indonesia reports total 927,380 confirmed cases including 26,590 mortality (2.9 % case fatality rate/CFR). This CFR makes Indonesia gets second place as the country with the highest mortality case due to COVID-19 in Asia Pacific after North Mariana Islands [6]. COVID-19 already spread in all Indonesia's province with local transmission happens on some district [7].

Recent studies show that mostly COVID-19 patient has a mild disease or even asymptomatic. But some patients looked to have a severe infection on admission accompanied by a high mortality rate. It is important to differentiate patients with a higher risk of deterioration so that health care providers can use different therapy at early-stage disease to prevent mortality [8]. COVID-19 patients with severe manifestation can experience dyspnea and hypoxemia within 1 week since the onset of the

disease that developed progressively become Acute Respiratory Distress Syndrome (ARDS) or end-organ failure leading to death [9]. Besides typical ARDS, coagulopathy and thromboembolic events are suspected to contribute to mortality in COVID-19 due to thrombotic necrosis of pulmonary capillaries that is reported to be happening. In the lungs, pulmonary microvascular thrombosis may lead to dead-end effects such as ventilated area that is leading to severe hypoxemia just like ARDS [10]. Coagulopathy, marked by increasing of D-dimer level, occur in 3.75 – 68% of COVID-19 patients [11]. Abnormality of coagulation is more commonly found in deadly COVID-19 patients where mortality in-hospital death is connected with D-dimer level of more than 1 µg/ml [8,11]. Chest X-ray (CXR) is used especially in critical setting like intensive care to monitor progressivity of COVID-19 with severe illness. A scoring system, named CXR score, is developed to help non-radiologist understanding lung involvement in COVID-19 patients [12–14].

Mandal et al. [15] report that there is 9% with deteriorating CXR and 30% with persistent elevating D-dimer level in patients discharged from hospital following COVID-19. Whether the significance of persistent elevating D-dimer level has clinical implication is unknown but deteriorating of chest radiography appearance suggests developing of lung fibrosis. The relation between coagulopathy and lung involvement is still unclear. So that, this study's aim is to look for a correlation between D-dimer level that usually marks coagulation dysfunction and severity of lung involvement assessed by CXR score.

II. METHODS

It is a cross-sectional analytic design study using secondary data from medical records collected from two centers (Dustira Hospital and Kebon Jati Hospital) located in Cimahi City, West Java Province, Indonesia. The subject of this study is the COVID-19 patient confirmed by RT-PCR that hospitalized during March – December 2020. We include patients with complete data consist of identity, diagnosis, D-dimer level, and

CXR result. The sample is collected by the consecutive method. The minimal sample in this study is thirty patients and calculated based on the formula below:

$$n = \left[\frac{(Z_{\alpha} + Z_{\beta})}{0,5 \ln \left[\frac{(1+r)}{(1-r)} \right]} \right]^2 \quad (1)$$

n = size of sample

Z_{α} = alfa deviation (1,96)

Z_{β} = beta deviation (0,84)

r = correlation between two variable that is investigated (0,491)

For the CXR result, we asses it semi-quantitatively using a scoring system which divided each lung into 3 zones (see Fig. 1) that are upper (from the apex until the aortic arch), middle (between the aortic arch until the lower margin of left lung's hilus), and lower zone (from the lower margin of left lung's hilus until diaphragm). Every zone can be given score from the scale 0 until 3. Zero means there is no abnormality of lung's parenchyma, 1 means we can see infiltrate on this zone, score 2 is given when there is less than 50% opacity on lung's parenchyma, and score 3 is get when there is $\geq 50\%$ opacity on lung's parenchyma or alveolar predominance [14,16].

Fig. 1. Division of lungs into six zones on frontal chest radiograph [14].

The collecting data then be analyzed with SPSS version 25 for windows. We perform univariate analysis to see basic characteristic of population research. Bivariate analysis is also done using spearman test to see the correlation between D-dimer and CXR score in this study. *P-value* is considered significant if < 0.05 .

III. RESULTS

There is total forty patients confirmed by COVID-19 included on this study. Basic characteristic of this population research can be seen on Table 1. The majority of patients is female (57.5%) and aged between 40-59 years old (57.5%).

TABLE I. DISTRIBUTION OF POPULATION-BASED ON GENDER AND AGE

Patient		Total (n=40)
Gander	Male	17(42.5%)
	Female	23(57.5%)
Age (years)	20-39	7(17.5%)
	40-59	23(57.5%)
	≥ 60	10(25%)

We find that 82.5% patients on this study have elevated D-dimer level and only 17.5% have normal value (see Tab.2). The average value of D-dimer level is 1793.2 ng/mL as we can see on Table 3.

TABLE II. FREQUENCY OF ELEVATED D-DIMER LEVEL ON POPULATION STUDY

Category	Frequency	Percentage
Normal	7	17.5%
Increase	33	82.5%
Total	40	100%

TABLE III. DISTRIBUTION VALUE OF D-DIMER LEVEL

Variable	Mean	Median	SD	Min-Max
D-dimer	1793.2	861.58	2239.45	161.06-12235

TABLE IV. THE AVERAGE RESULT OF CXR SCORES

Variable	Mean	Median	SD	Min-Max
Skoring	6,860	6,150	3,5044	2-16.7

Table 4. shows the average score of CXR result is 6,860 with a median is 6,150, and the deviation standard is 3,5044. The maximal CXR score is 16,7 and the minimal value is 2.

We find abnormal distribution between D-dimer level and CXR scores ($p < 0.05$) so that we use the Spearman test to investigate the correlation. The result showed us a *p-value* that is less than 0.05 ($p = 0.023$) which means H_0 is rejected. The correlation between D-dimer level and CXR scores showing a positive value (see Tab.5) with medium strength ($r = +0.358$). Thus, the higher D-dimer level, the higher CXR scores as we can see on Fig. 2.

TABLE V. THE AVERAGE DISTRIBUTION D-DIMER LEVEL-BASED ON CXR SCORES

Variabel	R	R2	P-Value
Interpretasi Foto Thorax	0,358	0,128	0,023

Fig. 2. Scatter plot showing a positive correlation between D-dimer level and CXR scores.

IV. DISCUSSION

COVID-19 patients with severe disease can deteriorate rapidly into ARDS within days. The main pathogenesis is though due to diffuse alveolar damage (DAD) that severely impaired gas exchange function of the lungs. Beside this mechanism, recent pathological finding shows that one of distinguishing features of COVID-19 is an extensive vascular thrombosis accompanied by microvascular disease and also alveolar capillary occlusion. It's proposed that dramatic alveolar endothelial damage leading to a progressive endothelial pulmonary syndrome with microvascular thrombosis as an atypical factor leading to ARDS in COVID-19 patients [10]. The D-dimer level is a kind of measure used to detect thrombosis. It already reported increasing in COVID-19 patients and a 3 to 4-fold rise, especially at the early stage of the disease, is linked to a poor prognosis [17].

There is a correlation between CXR temporally change with severity of COVID-19. The CXR result evolves from typical ground glass opacity to predominantly consolidative at the same time as the progression of the disease. So that it describe how far lung parenchyma involvement at the disease [18].

Our study shows a positive correlation between D-dimer level and CXR scores in COVID-19 patients. It means that the higher D-dimer level, the higher CXR scores result. This demonstrates us how coagulopathy is related to the severity of lung parenchyma involvement on COVID-19 disease. This finding is similar with some previous research reporting the elevated of D-dimer level has a relation with the severity of pneumonia caused by coagulation dysregulation due to excessive inflammatory mediators induced by SARS-CoV-2 infection. Moreover, pro-inflammatory cytokine maybe involves in endothelial injury then activates coagulation cascade and inhibits fibrinolysis so that D-dimer is commonly used as a biomarker to see the deterioration of COVID-19 patients besides CXR [11,19].

V. CONCLUSION

The relation between D-dimer level and CXR scores shows us that severity of the coagulopathy can be used to predict how far lung parenchyma is involve in COVID-19 disease.

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