

Brixia Score as Predictor of D-Dimer Levels of COVID-19 Patients in Intensive Care Unit

Yanuaresza Totti Adyanata¹⁾, Widiastuti Soewondo²⁾,
Arifin³⁾, Dhani Redhono³⁾

¹⁾Student of Medical Study Program, Faculty of Medicine, Universitas Sebelas Maret

²⁾Department of Radiology, Faculty of Medicine, Universitas Sebelas Maret

³⁾Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: COVID-19 is caused by a novel virus that can cause lung abnormalities which can be measured with new chest x-ray scoring system named Brixia score. In COVID-19 patients, coagulation disorders are often found that can be seen through D-Dimer levels. This study aimed to prove the Brixia Score as a predictor of D-Dimer levels.

Subjects and Method: This study was an observational analytic study with a cross-sectional approach. The subjects were 94 COVID-19 patients which taken from ICU Melati 1 Dr. Moewardi General Hospital, Surakarta from March 2021 to August 2021 who met the exclusion and inclusion criteria. The independent variable is Brixia score performed by radiologists and dependent variable is D-Dimer levels taken from laboratory results. Sampling was obtained by purposive sampling and the data were investigated using the receiver operating characteristic (ROC) curve.

Results: 94 samples were obtained for analysis. The average Brixia Score of patients with D-Dimer <2 µg/mL was Mean= 15.85; SD= 1.43 and D-Dimer ≥2 µg/mL was Mean= 17.29; SD= 0.96. There was a significant difference between the Brixia Score of patients with D-Dimer <2 µg/mL and D-Dimer ≥2 µg/mL ($p < 0.001$). Analysis with the ROC curve shows an area under the curve (AUC) of 0.793. The optimal cutoff value of the Brixia Score for predicting D-Dimer levels was 16.5 (sensitivity 77.9%, specificity 73.1%).

Conclusion: Brixia Score proved to be a predictor of D-Dimer levels of COVID-19 patients in ICU care.

Keywords: COVID-19, ICU, brixia score, predictor, D-Dimer.

Correspondence:

Widiastuti Soewondo, Radiology Department, Faculty of Medicine, Universitas Sebelas Maret. JL. Ir. Soetami No. 36A, Surakarta 57126, Indonesia. E-mail: widiastuti.sprad56@staff.uns.ac.id. Mobile: 082134368592

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BACKGROUND

Coronavirus disease 2019 (COVID-19) is caused by a novel virus, the disease also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Currently, COVID-19 is becoming a pandemic, many areas are exposed to this virus

(WHO, 2021). On October 20, 2021, a total of 241,411,380 people were exposed and 4,912,112 people died (WHO, 2022). The mortality rate in Indonesia until October 2021 based on data from the covid task force was 3.38% with the highest increase in June-July of 350% (Andrea, 2021). COVID-

19 symptoms can appear within a few days ranging from mild symptoms such as fever and dry cough to severe symptoms such as acute respiratory distress syndrome (ARDS) and septic shock. As many as 80% of patients experienced mild symptoms, 13.8% went into severe symptoms, and 6.1% had a critical condition. 60-90% of hospitalized patients have comorbidities where the most frequent comorbidities are hypertension and diabetes (Susilo et al., 2020; Wiersinga et al., 2020). COVID-19 can also potentially have long-term effects known as "Long COVID", with persistent effects such as shortness of breath, cognitive impairment, and chest pain (Soewondo et al., 2021). Human to human transmission became the main source of transmission. Transmission of SARS CoV-2 mainly through droplets released when talking, sneezing, or coughing (Susilo et al., 2020; Wiersinga et al., 2020).

Chest x-ray are often used to aid the diagnosis of COVID-19. Lung abnormalities often found in COVID-19 are diffuse ground glass opacity, air-bronchograms, focal consolidation, and pleural effusion (Susilo et al., 2020; Wiersinga et al., 2020). Chest x-ray is useful for monitoring the progressivity of pulmonary lesions, especially in patients who need ICU treatment. In its development, a new scoring system was created to measure the severity of pulmonary abnormalities of infected patients, named Brixia Score. This scoring system divides the lungs into six parts and each part will be scored with a score of 0-3. Total Brixia score to measure the severity of patient abnormalities ranging from 0-18 (Borghesi and Maroldi, 2020).

In COVID-19 patients, complications of thrombosis and coagulation disorders such as disseminated intravascular coagulopathy (DIC) caused by viruses or cytokine storms are often found (Wool and Miller,

2021). D-Dimer is a product of fibrin degradation that describes the function of coagulation. Examination of D-Dimer by immunoturbidimetric method requires expensive costs and trained personnel (Rustandi et al., 2010). Normal levels of D-Dimer are 0.5 µg/mL and may increase with age. Although not specific, elevated levels of D-Dimer are common in COVID-19 patients (Wierrsinga et al., 2020). This increase is in line with the poor prognosis (Conte et al., 2021; Poudel et al., 2021). Increased levels of >2 µg/mL increased patient's mortality risk (Zhang et al., 2020). This study aimed to prove the Brixia Score as a predictor of D-Dimer levels.

SUBJECTS AND METHOD

1. Study Design

This is an analytical study with a cross-sectional approach. Secondary data were collected from Dr. Moewardi General Hospital, Surakarta on May - June 2022. Medical records and chest X-rays were used for this study.

2. Population and Sample

The subjects of this study were COVID-19 patients in ICU Melati 1 from March-August 2021. The inclusion criteria are patients with complete chest x-ray and D-Dimer data from admission to discharge from the hospital, patients aged >18 years, and patients in the ICU care for ≥48 hours. Exclusion criteria are patients with pregnancy conditions, a history of disease or immune-suppressive treatment, and malignant conditions. The minimum sample for this study of 47 samples.

3. Study Variables

The Independent variable is Brixia Score and the dependent variable is D-Dimer levels.

4. Operational definition of variables

The Brixia Score is a chest X-ray scoring system for COVID-19 patients. The assess-

ment was carried out by dividing the lungs into 6 parts. Each part is given a value of 0-3. The value of 0, if there are no abnormalities; 1, if there are interstitial infiltrates; 2, if there are interstitial with alveolar infiltrates (interstitial predominant); 3, if there are interstitial with alveolar infiltrates (alveolar predominant).

D-Dimer levels are obtained from the patient's medical record. Then the data were grouped into D-Dimer $<2 \mu\text{g/mL}$ and D-Dimer $\geq 2 \mu\text{g/mL}$. Patients were categorized by D-Dimer levels to $<2 \mu\text{g/mL}$ and $\geq 2 \mu\text{g/mL}$. The category was chosen based on previously stating that the optimal cutoff of D-Dimer in COVID-19 patients is $\geq 2 \mu\text{g/mL}$.

5. Study Instruments

The Brixia Score was measured by radiologists (W & L with experience >10 years & >5 years). Data for D-Dimer levels were obtained from the medical records.

6. Data analysis

The data obtained will be analyzed using Statistical Product and Service Solution (SPSS) Version 26. An independent T-test is used if the data is normally distributed. If the data distribution is abnormal, Mann-Whitney u-test will be used. The normality test uses the Kolmogorov-Smirnov test. Data analysis is declared significant if the p-value <0.05 . The ROC curve is used to determine the predictive power and optimal cutoff of the Brixia Score against the D-Dimer level.

7. Research Ethics

Research ethical issues including informed consent, anonymity, and confidentiality, were addressed carefully during the study process. The research ethical clearance approval letter was obtained from the Research Ethics Committee at Dr. Moewardi Hospital, Surakarta, Indonesia, No. 464/-IV/HREC/2022, on April 8, 2022.

RESULTS

1. Sample Characteristics

In this study, 94 samples were obtained. A total of 26 samples had D-Dimer $<2 \mu\text{g/mL}$ and 68 samples with D-Dimer $\geq 2 \mu\text{g/mL}$. Characteristics of the subject of the study can be seen in table 1.

In table 1, it is known that based on gender, patients with D-Dimer $<2 \mu\text{g/mL}$ and D-Dimer $\geq 2 \mu\text{g/mL}$ have almost the same proportion where mostly male patients are 61.5% and 64.7%.

From table 1 it is known that individuals who experience D-Dimer $<2 \mu\text{g/mL}$ are aged 30-40 years 5(19.2%) people, 41-50 years 4(15.4%) people, 61-70 years 11(42.3%) people, and age >70 years 6 (23.1%) people. Meanwhile, individuals who experienced D-Dimer $\geq 2 \mu\text{g/mL}$ aged 41-50 years 9(13.2%) people, aged 51-60 years 35(51.5%) people, aged 61-70 years 15 (22.1%) people, age >70 years 7(10.3%) people

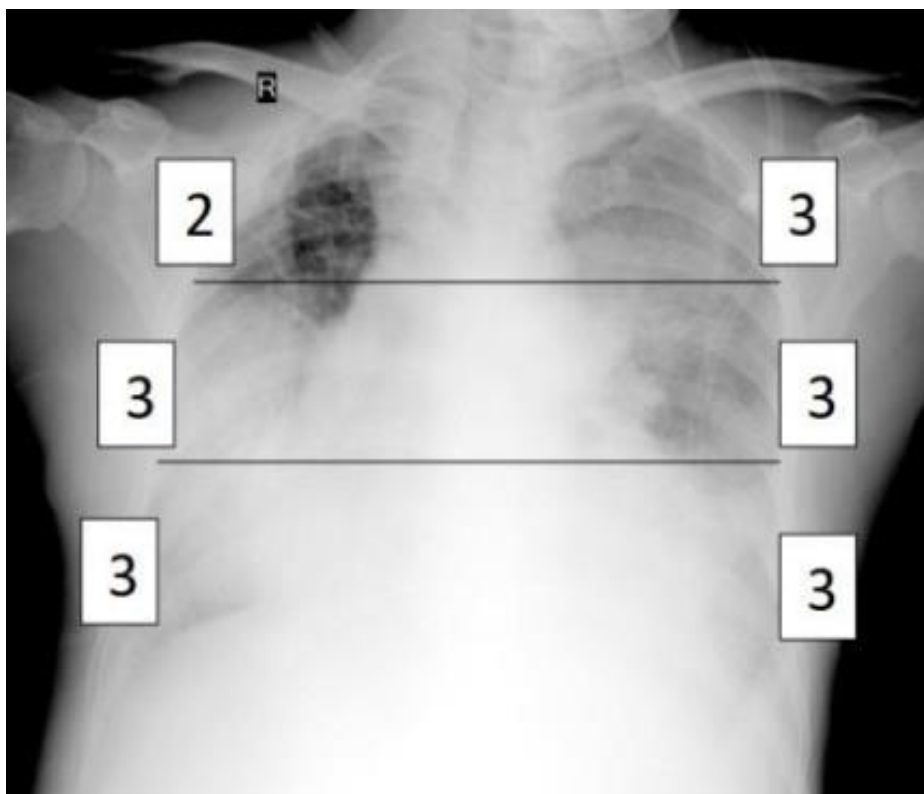
2. Bivariate Analysis

Based on table 2, it is known that the Brixia Score in patients with D-Dimer $<2 \mu\text{g/mL}$ Mean= 15.85; SD= 1.43 with a median of 16 and a range between 13-18. Brixia Score in patients with D-Dimer $\geq 2 \mu\text{g/mL}$ Mean= 17.29; SD= 0.96 with a median of 18 and a range between 14-18. The results of the statistical test obtained a value of $p<0.001$ ($p<0.05$) which means there is a significant difference in Brixia Score in patients with D-Dimer $<2 \mu\text{g/mL}$ and D-Dimer $\geq 2 \mu\text{g/mL}$, thus Brixia Score can be used as a predictor of D-Dimer levels.

Based on figure 2 and table 3, it is known that the Brixia Score gets an AUC value of 0.793. Brixia Score cutoff value of 16.5 with a sensitivity of 77.9% and a specificity of 73.1%. The positive predictive value (PPV) and negative predictive value (NPV) were 88.3% and 55.9%.

Table 1. Sample characteristics

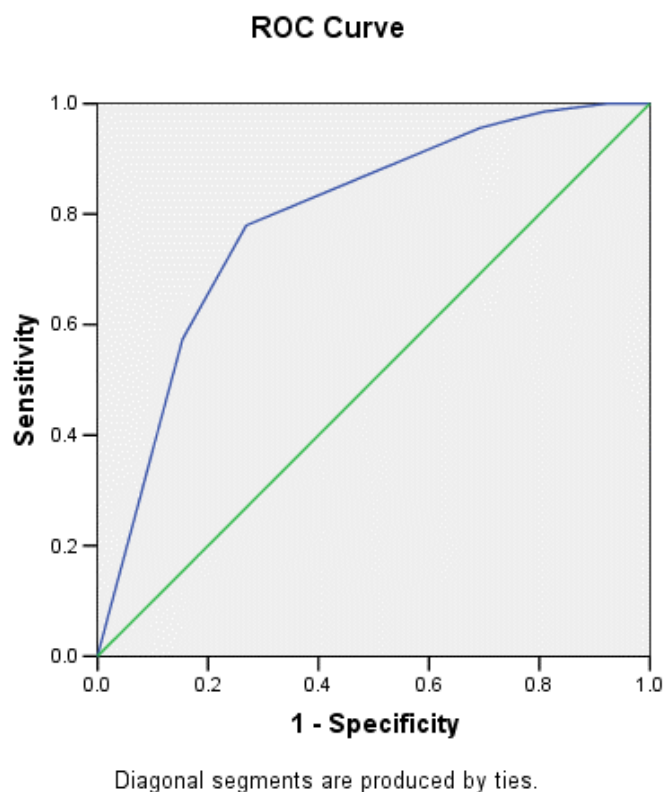
Characteristics	Total (n=94)	D-Dimer	
		<2 µg/mL (n=26)	≥2 µg/mL (n=68)
Sex			
Male	60 (63.8%)	16 (61.5%)	44 (64.7%)
Female	34 (36.2%)	10 (38.5%)	24 (35.3%)
Age			
<30 years	2 (2.1%)	0	2 (2.9%)
30-40 years	5 (5.3%)	5 (19.2%)	0
41-50 years	13 (13.8%)	4 (15.4%)	9 (13.2%)
51-60 years	35 (37.2%)	0	35 (51.5%)
61-70 years	26 (27.7%)	11 (42.3%)	15 (22.1%)
>70 years	13 (13.8%)	6 (23.1%)	7 (10.3%)

**Figure 1. Patient with Brixia Score 17****Table 2. Brixia score between patients with D-dimer <2µg/mL and D-dimer ≥2µg/mL**

Variable	D-Dimer					p
	Mean	SD	Median	Min	Max	
Brixia Score						
<2 µg/mL (n=26)	15.85	1.43	16	13	18	
≥2 µg/mL (n=68)	17.28	0.96	18	14	18	<0.001

Table 3. Brixia Cutoff Results as Predictor of D-Dimer

Variable	AUC	Brixia Score Cutoff Value	Sensitivity	Specificity	PPV	NP V	p
Brixia Score	0.793	16.5	0.779	0.731	0.883	0.55 9	<0.001

**Figure 2. Brixia Score ROC Curve as Predictor of D-Dimer Levels**

DISCUSSION

Of the 94 samples in this study, there were 60 (63.8%) male and 34 (36.2%) female. This study's results align with previous studies that COVID-19 cases are more common in men (Ng et al., 2020). This may be due to men's more outdoor activities as well as differences in biological characteristics in women where the estrogen hormone in women makes the immune system work better in dealing with infections compared to men (Mubarak et al., 2021). In this study, it was found that most of the samples that had D-Dimer levels $\geq 2 \mu\text{g/mL}$ were men with a total of 44 samples. The results of the statistical analysis of sex on D-Dimer levels ob-

tained a value of $p = 0.775$ which means there was no significant difference in sex characteristics between patients with D-Dimer $< 2 \mu\text{g/mL}$ and $\geq 2 \mu\text{g/mL}$. Men and women have similar baseline D-Dimer levels, but men are more at risk of getting high D-Dimer levels (Marik et al., 2021).

This study found that the age ranged from 29-89 years old. The results of the statistical analysis of the age difference between D-Dimer levels $< 2 \mu\text{g/mL}$ and D-Dimer $\geq 2 \mu\text{g/mL}$ received a value of $p\text{-value} = 0.314$ which means there is no significant difference in age to D-Dimer levels. The results of this study are different from previous studies which stated that age affects

the disruption of the thrombosis process where old age is more at risk of having higher D-Dimer levels in COVID-19 patients (Kumar and Ghodke, 2020). This may occur due to the influence of comorbidities that each patient suffers from differently, such as diabetes melitus and hypertension that can predispose patients to thrombosis.

Our study shows a significant difference between the patient's Brixia Score with D-Dimer $<2 \mu\text{g/mL}$ and D Dimer $\geq 2 \mu\text{g/mL}$ with a $p < 0.001$ ($p < 0.05$) which means there is a relationship between Brixia Score and D-Dimer. This is in line with other studies that there is a significant relationship between Brixia Score with D-Dimer levels in patients, where a higher D-Dimer level is accompanied by a higher Brixia Score (Munirathnam et al., 2020; Viradanti and Kusmala, 2021; Garg et al., 2022). Some previous research reports that most COVID-19 patients have elevated D-Dimer levels due to excessive inflammatory response of lung parenchymal cells and endothelial cells in the lung blood vessels that causes dysregulation in the coagulation system. This state can lead to thrombosis and fibrin disposition on pulmonary blood vessels. This can cause a hypoxemia condition that will activate hypoxia induce factor which will activate more proinflammatory cytokines, tissue factor, and plasminogen activator inhibitor-1 (PAI-1) that can cause excessive thrombosis and elevated D-Dimer highly suggests an increase in vascular thrombosis (Yao et al., 2020; Zhou et al., 2020; Mahardika et al., 2021; Poudel et al., 2021; Viradanti and Kusmala, 2021).

The buildout of microthrombi in the lung capillaries can lead to acute respiratory distress syndrome (ARDS) which can be seen in chest X-rays (José et al., 2020; Viradanti and Kusmala, 2021). The patient's chest X-ray will show pulmonary abnormalities, such as diffuse ground glass opacity,

air-bronchograms, and focal consolidation (Wiersinga et al., 2020). These abnormalities can be calculated using Brixia score to see the severity (Borghesi and Maroldi, 2020). The higher Brixia score, the more severe the lung abnormalities. So therefore, Brixia Score as a chest X-ray scoring system can be used to measure the severity of COVID-19 patients besides D-Dimer value (Wang et al., 2020; Abo-Hedibah et al., 2021).

In this study, further analysis was carried out using the ROC curve to determine the ability of the Brixia Score in predicting D-Dimer levels and obtained results of the area under the curve (AUC) of 0.793. Where the value indicates moderate accuracy because it has an AUC value of >0.7 (Poudel et al., 2021). The optimal cutoff Brixia Score for predicting D-Dimer levels is 16.5 with a sensitivity of 77.9% and a specificity of 73.1%. Because there is no other research related to the Brixia Score as a predictor of D-Dimer levels, further research is needed. The limitation of this study is that it has not been associated with comorbid factors that are likely to aggravate the patient's condition, so it will affect the value of D-Dimer.

This study concluded that the Brixia Score proved to be a predictor of D-Dimer levels of COVID-19 patients in ICU care.

AUTHOR CONTRIBUTIONS

All authors had equal contribution in collecting the data for this research, radiological scoring, and wrote the manuscript.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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