Artikel Penelitian

The Role of Brixia Score as a Predictor of Coronavirus Disease-19 (COVID-19)-associated Hemostatic Abnormalities (CAHA) Based on D-dimer Levels

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Abstract

Introduction: *Coronavirus Disease-19 (COVID-19) is a systemic disease that causes complications in respiratory system and coagulopathy, which is called COVID-19-associated hemostatic abnormalities (CAHA). The Brixia chest X-ray scoring system may benefit in detecting CAHA. This study aims to investigate the role of the Brixia score as a predictor of CAHA based on D-dimer levels.*
Methods: *This was a cross-sectional study that used medical records from Radiology Installation, Sanglah General Hospital, Bali, during August 2020 until August 2021. Subjects were confirmed and hospitalized COVID-19 patients with mild to critical degree and aged 18-59 years old. Any other pulmonary diseases than COVID-19 in X-ray was excluded. Brixia score was determined independently and blindly determined by two radiologists. The incidence of CAHA was defined as an elevation of D-dimer in pulmonary COVID-19. We conducted interobserver Bland-Altman, followed by correlation test, receiver operating characteristic (ROC) analysis, and multiple logistic regression test to control for confounding factors.*
Result: *This study included 70 subjects selected through random sampling. We found a positive correlation between the Brixia score and D-dimer levels ($r=0.329$, $p<0.05$). The ROC analysis indicated that a Brixia score cut-off ≥10 is the best predictor of CAHA, with a positive predictive value of 95.8% and a negative predictive value of 40.9%. Subjects with a Brixia score ≥10 were found to have a higher risk of developing CAHA (aOR 14.78, $p<0.05$) after controlling for age, gender, nutritional status, and comorbidities.*
Conclusion: *There was a statistically significant association between Brixia score and CAHA in COVID-19 patients based on D-dimer levels. The Brixia score could be used as a predictor of CAHA with the cut-off value ≥10.*

Keywords*: COVID-19; Brixia score, chest X-ray, CAHA, D-dimer*

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Peran Skor Brixia sebagai Prediktor Kejadian Coronavirus Disease-19 (COVID-19)-associated Hemostatic Abnormalities (CAHA) Berdasarkan Kadar D-dimer

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Abstrak

Pendahuluan: *Coronavirus Disease-19 (COVID-19) merupakan penyakit sistemik yang dapat menyebabkan komplikasi pada sistem pernapasan dan koagulopati yang disebut COVID-19-associated hemostatic abnormalities (CAHA). Pemeriksaan Rontgen toraks dengan sistem skor Brixia dianggap memiliki manfaat dalam mendeteksi kejadian CAHA secara sederhana. Studi ini bertujuan untuk menilai peran skor Brixia sebagai prediktor kejadian CAHA yang dinilai berdasarkan kadar D-dimer.*

Metode: *Studi potong-lintang ini menggunakan data rekam medik dari Instalasi Radiologi RSU Sanglah, Bali, selama Agustus 2020 hingga Agustus 2021. Subjek merupakan pasien terkonfirmasi COVID-19 derajat ringan-kritis yang menjalani rawat inap dan berusia 18-59 tahun. Kelainan paru selain COVID-19 pada Rontgen toraks akan dieksklusi. Skor Brixia dinilai oleh dua ahli radiologi secara independen dan tersamar. Kejadian CAHA dinilai dengan peningkatan kadar D-dimer pada COVID-19 fase pulmoner. Studi ini melakukan uji keandalan inter-pengamat Bland-Altman, dilanjutkan dengan uji korelasi dan analisis receiver operating characteristic (ROC), serta uji regresi logistik multipel untuk menyingkirkan variabel perancu.*

Hasil: *Studi ini melibatkan 70 subjek yang diperoleh secara acak. Terdapat korelasi positif antara skor Brixia dengan kadar D-dimer ($r=0,329$, $p<0,05$). Berdasarkan analisis ROC, nilai titik potong skor Brixia sebagai prediktor CAHA adalah ≥10 dengan nilai prediktif positif 95,8% dan nilai prediktif negatif 40,9%. Subjek dengan skor Brixia ≥10 memiliki risiko yang lebih tinggi untuk mengalami CAHA dibandingkan skor <10 (aOR 14,78, $p<0,05$) setelah dikontrol dengan variabel usia, jenis kelamin, status nutrisi, dan komorbid.*

Kesimpulan: *Terdapat hubungan yang bermakna secara statistik antara skor Brixia dengan kejadian CAHA yang dinilai berdasarkan kadar D-dimer. Skor Brixia dapat digunakan sebagai prediktor CAHA dengan nilai titik potong ≥10.*

Kata kunci*: COVID-19, skor Brixia, Rontgen toraks, CAHA, D-dimer*

Introduction

Since December 2019, Coronavirus Disease-19 (COVID-19) has caused substantial global morbidity and deaths, and also considerable strain on health system throughout the world.[1,2] As of May 2023, Indonesia has reported 766,895,075 cases of COVID-19 with 6,935,889 deaths. In Bali Province, one of the main tourism destination in Indonesia, there have been 173,617 cases of COVID-19 with 4,906 deaths.[3,4] COVID-19 continues to cause significant morbidity and mortality worldwide. Although the number of deaths has decreased due to vaccination and public health interventions, COVID-19 remains a major health issue until today.[5]

COVID-19-associated thrombosis and coagulopathy (CAHA) is one of the most feared complications of COVID-19, which can lead to thrombosis, multi-organ damage, and death. CAHA is defined as meeting two or more of the following four criteria: (1) decreased platelet count (<150x109/L), (2) increased D-dimer levels >1 µg/mL; (3) prolonged prothrombine time (PT) >1 second or

international normalized ratio (INR) >1.2; and (4) the presence of thrombosis. Among these criteria, D-dimer levels appear to be the best currently available laboratory diagnostic marker for CAHA.[6] D-dimer a rapid, simple, and inexpensive marker that can detect thrombosis in any part of the venous system. Recent studies have shown that D-dimer levels are elevated in 36-43% of COVID-19 patients, with a VTE (venous thromboembolism) incidence of 25-46% and a mortality rate of 24.1%.[7] The sensitivity of D-dimer levels for the incidence of pulmonary embolism in COVID-19 patients has been reported as 100% (95%CI 87.6-100%), but the specificity was 11.9% (95%CI 7.9-17.1%). Therefore, some studies suggest the D-dimer levels >1.0 µg/mL as a sensitive laboratory marker for CAHA.[8,9]

On the other hand, chest X-ray is a simple imaging method used to diagnose and monitor the progression of COVID-19.[10] Although it has a sensitivity of 69% for diagnosis, it is still valuable for monitoring the rapid progression of pulmonary COVID-19.[11,12] Several chest X-ray scoring systems have been developed to enhance the diagnostic value in COVID-19 One such system is the Brixia scoring system, which provides a useful method for ranking the stratification risk of pulmonary COVID-19 based on the severity. The Brixia score offers a detailed presentation and distribution of the lungs (divided into 6 regions) and sensitivity levels (categorized into 4 levels).[13,14] In comparison, another scoring system known as RALE (Radiographic Assessment of Lung Edema) is considered to lack detail as it only divides lung into 2 regions, making it less specific for smaller lesions and more complex when scoring chest X-rays to diagnose COVID-19 pneumonia.[14,15] Therefore, the aim of this study is to investigate the role of Brixia score as a predictor of CAHA based on D-dimer levels.

Methods

This study was a retrospective cross-sectional study conducted at the Radiology Installation of Sanglah General Hospital in Denpasar, Bali. This research protocol was approved by the local ethical committee with protocol number 2022.02.1.0118. The data used in this study were obtained from electronic medical record spanning from August 2020 to August 2021.

This study included hospitalized patients who were confirmed cases of COVID-19 and aged between 18 and 59 years old. The severity of the disease in the subjects ranged from mild to critical degree, as determined by the National Institute of Health United States guidelines.[16] Subjects with pulmonary disease other than COVID-19 based on chest X-ray (pleural effusion, cardiomegaly, pulmonary edema, lung cavities, pulmonary nodules, and lung metastases) were excluded from the study. Additionally, subjects with incomplete data were also excluded. The assessment of the Brixia score of chest X-rays and D-dimer examination were conducted at the same time during hospitalization upon initial admission. The subjects were selected using simple random sampling, using the Picture and Communication System (PACS) and a random number generator.

The evaluation of the Brixia score was conducted independently by two expert radiologists based on the chest X-rays (Figure 1). A score ranging from 0 to 3 was assigned accorrding to the lung abnormalities observed: no lung abnormalities (score 0), interstitial infiltrates (score 1), interstitial (dominant) and alveolar infiltrates (score 2), and interstitial and alveolar (dominant) infiltrates (score 3). The individual Brixia scores were then summed to obtain the cumulative score, which was interpreted as follows: mild disease (score ≤6,), moderate disease (score 7-12), and severe disease (score 13-18). In this research, CAHA was defined as pulmonary COVID-19 based on the chest X-rays, along with the additional hematologic marker of thrombosis, such as elevation of D-dimer levels. The severity of CAHA was graded according to the D-dimer levels as follows: no CAHA (<1 µg/mL), stage 1 (1-1.5 µg/mL), stage 2 (>1.5-3 µg/mL), and stage 4 (>3 µg/mL).

The data were analyzed using descriptive statistics to summarize data and normality test to assess the distribution of the variables. The Bland-Altman interobserver reliability test was performed to evaluate the consistency between the two examiners. Correlation tests were conducted to assess the relationships between variables. Additionally, receiver operating characteristic (ROC) analysis and sensitivity-specificity analysis were performed to determine the diagnostic accuracy of the Brixia score. To control for confounding variables such as age, gender, nutritional status, and comorbidities, multiple logistic regression analysis was conducted. The entire data analysis was carried out using the IBM Statistical Package for the Social Sciences (SPSS) version 25.0 software.

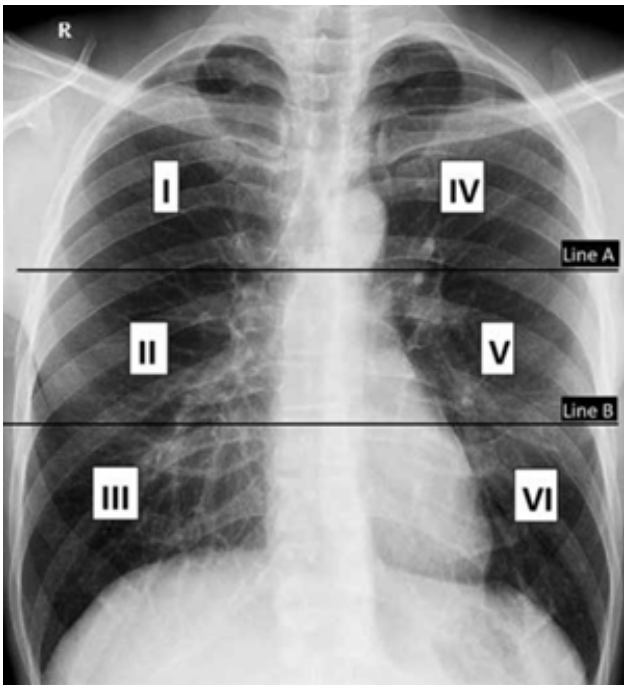

Figure 1. The Brixia Scoring System on the Chest X-ray.
The scoring system divides the chest X-ray into six zones based on the position of two lines: line a and line B. Line A is drawn at the level of the inferior wall of the aortic arch, while line B is drawn at the level of the inferior wall of the right inferior pulmonary vein. A and D are upper zones; B and E are middle zones; C and F are lower zones. Each zone may bs assigned with score of 0 to 3 based on the lung abnormalities found.

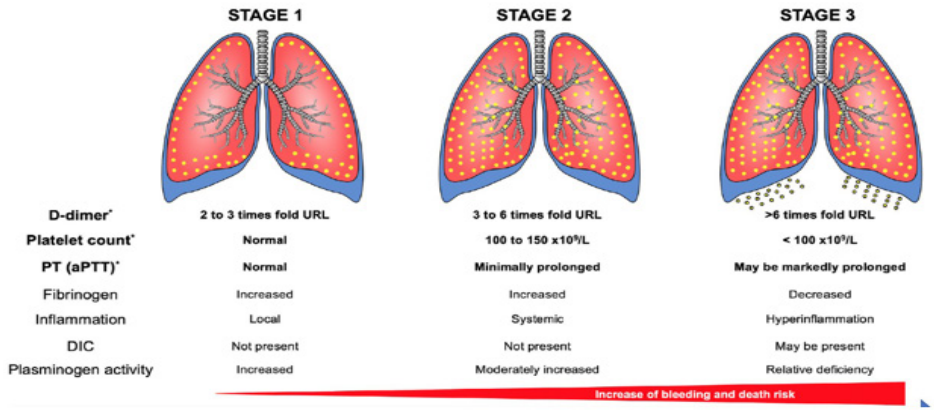

Figure 2. CAHA Staging[17]
Stage 1: mild symptoms with 2-3-fold increase in D-dimer above normal. Stage 2: more severe symptoms with 3-6-fold increase in D-dimer above normal. Stage 3: clinically severe condition with D-dimer increase >6-fold above normal.

Results

We included a total of 913 patients who were hospitalized with COVID-19. After conducting randomization, we obtained 70 eligible subjects with complete medical records for further analysis. The characteristics of the subjects were shown in Table 1. The mean age of the subjects was 45.94 years old, male gender was predominant (60%), and 60% of them had one or more comorbidities. During the hospitalization period, a majority of the subjects experienced CAHA (84.2%). The median D-dimer levels among subjects with CAHA were 2.65 ng/dL, with a range from 1.05 to 21.05 ng/dL.

The median of Brixia score was 13 for Examiner 1 dan 14 for Examiner 2, but they yielded a very small mean difference (-0.6; 95%CI -0.84– -0.35) and suggested a high level of agreement ($r=0.938$, $p<0.001$). When categorizing the Brixia score from mild to severe disease, both examiners agreed on the classification of mild and severe cases. However, there was a discrepancy in the classification of moderate disease [Table 2]. Despite

Table 1. Subject Characteristics

Characteristics	N=70
Age (years, mean±SD)	45.94±9.8
Gender (n,%)	
Male	42 (60)
Female	28 (40)
Body Mass Index (n,%)	
Underweight	2 (4.3)
Normal	44 (62.9)
Overweight	11 (15.7)
Obese	12 (17.1)
Smoking (n,%)	
Yes	18 (25.7)
No	52 (74.3)
Comorbidities (n,%)*	
Yes	42 (60)
No	28 (40)
CAHA (n,%)	
No CAHA	11 (15.7)
CAHA stage 1	8 (11.4)
CAHA stage 2	27 (38.5)
CAHA stage 3	24 (34.2)
D-dimer levels (ng/dL, median[min-max])	2.15 (0.39-21.05)
No CAHA	0.79 (0.39-0.99)
CAHA stage 1-3	2.65 (1.05-21.05)
CAHA stage 1	1.23 (1.05-1.50)
CAHA stage 2	2.03 (1.51-2.88)
CAHA stage 3	9.29 (3.08-21.05)
Brixia Score (median[min-max])	
Examiner 1	13 (1.0-18.0)
Examiner 2	14 (1.0-18.0)

**Any of hypertension, diabetes mellitus, coronary artery disease, asthma, chronic kidney disease, or immunocompromise.*
CAHA, COVID-19-associated hemostatic abnormalities.

patients compared to a Brixia score <10. This suggests that a Brixia score ≥10 indicates a poor prognosis.[21] Supporting this finding, a

Table 3. The Brixia Score in CAHA and Non-CAHA Subjects

	Brixia score	
	Median (95%CI)	p*
Non-CAHA (n=11)	6 (3.5-9.9)	<0.05
CAHA (n=59)		
Mild (n=8)	11.5 (8.7-15.2)	
Moderate (n=27)	14.0 (10.2-14.2)	
Severe (n=24)	14.0 (11.6-14.7)	

**Kruskal-Wallis test for all stages of CAHA.*
CAHA, COVID-19-associated hemostatic abnormalities.

this discrepancy, the overall interobserver reliability remained good with kappa value of 0.756. In Table 3, it is observed that the median Brixia score in subjects with CAHA was higher compared to those without CAHA. Additionally, the Brixia score increased with the severity of the disease (p<0.05). This suggests a significant association between the Brixia score and the presence and severity of CAHA.

The Spearman correlation test revealed a positive correlation between the Brixia score and D-dimer levels (r=0.329, p<0.05). This suggests that as the Brixia score increases, there is a tendency for D-dimer levels to also increase. The sensitivity and specificity analysis showed that the Brixia score may be associated with the occurrence of CAHA, with an area under the curve (AUC) of 84.6% (95%CI 74.1-95%) [Figure 3]. The optimal cut-off point of the Brixia score for predicting CAHA based on D-dimer levels in this study was ≥10 ng/dL, with a sensitivity close to 0.80 and a specificity of 0.18 [Table 4].

Table 2. Interobserver Reliability Test on Categorical Scale of the Brixia Score

Brixia Score Examiner 1 (n,%)	Brixia Score Examiner 2 (n,%)			
	Mild	Moderate	Severe	Total
Mild	12 (17.1%)	0	0	12
Moderate	2 (2.9%)	12 (17.1%)	7 (10%)	21
Severe	0 (0)	1 (1.4%)	36 (51.4%)	37
Total	14 (20%)	13 (18.6%)	43 (61.4%)	70 (100%)

(r=0.405, p<0.001). Based on the findings of this study, the Brixia score can be utilized as a predictor of CAHA.

In this study, a Brixia score cut-off value of ≥10 is associated with a higher likelihood of developing CAHA in COVID-19

Subjects with a Brixia score ≥10 (n=48) had a higher incidence of CAHA compared to those with a Brixia score <10 (n=22) (95.8% vs. 59.1%, crude odds ratio (OR)=15.92). The cut-off point of Brixia score ≥10 provided a positive predictive value (PPV) of 95.8% and

a negative predictive value (NPV) of 40.9%. The validity test yielded a sensitivity of 78% (95%CI 65.27-87.71%), a specificity of 81.8% (95%CI 48.22-97.72%), and an accuracy of 78.6% (95%CI 67.1-87.5%).

After conducting a multiple logistic regression analysis, controlling for age, gender, nutritional status, and comorbidities, the adjusted odds ratio (OR) for a Brixia score ≥10 with CAHA incidence was 14.78 (p=0.002). This indicates that subjects with a Brixia score ≥10 have a significantly higher risk of developing CAHA compared to those with a Brixia score <10. Subjects with a Brixia score ≥10 also had higher D-dimer levels compared to subjects with a Brixia score <10 (Median[95%CI]: 2.6[4.1-7.9] vs. 1.3[1.2-4] ng/dL, p<0.001).

Table 4. The Brixia Score Cut-off

Brixia Score	Sensitivity	Specificity
≥ 1	1.00	0.82
≥ 2	0.98	0.73
≥ 3	0.93	0.63
≥ 4	0.89	0.63
≥ 5	0.88	0.63
≥ 6	0.88	0.54
≥ 7	0.83	0.45
≥ 8	0.81	0.36
≥ 9	0.78	0.27
≥ 10	0.78	0.18
≥ 11	0.74	0.18
≥ 12	0.69	0.18
≥ 13	0.56	0.91
≥ 14	0.30	0.00
≥ 15	0.22	0.00
≥ 16	0.11	0.00
≥ 17	0.03	0.00
18	0.00	0.00

Discussion

The characteristics of the subjects in this study provide insight into the demographic and clinical profile of COVID-19 patients treated in referral hospitals. The mean age of 45 years suggests that the study included adult patients, and the predominantly male composition aligns with previous findings that indicate a higher incidence of COVID-19 in males compared to females. Additionally, the presence of comorbidities among the subjects is consistent with the understanding that COVID-19 patients with chronic diseases are more susceptible to developing severe symptom.[18,19] The observation that a normal BMI was predominant among the subjects aligns with studies conducted in Bangladesh, which reported a higher susceptibility to COVID-19 in individuals with normal BMI. However, it is important to note that the distribution of BMI may vary across populations.[18]

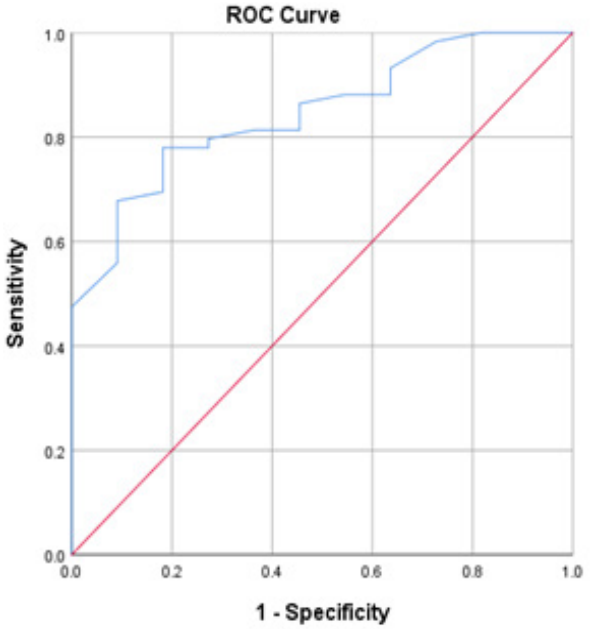

Figure 3. Receiver Operating Characteristic Curve.
The area under the curve was 84.6% (95%CI 74.1-95%).

The results of this study indicate that the interobserver reliability of the Brixia score, both in scores and categories format, is high. The Brixia score may allow for the easy and rapid determination of the risk stratification and severity index of lung abnormalities in COVID-19 patients.[14,15] According to Signorino, et al.[13], the Brixia score system is a reliable scoring method that offers a detailed image and distribution of the lungs, as well as high sensitivity.

This study demonstrates a correlation between the Brixia score and D-dimer levels. As the Brixia score increases, there is a corresponding increase in D-dimer levels. This can be explained by the hypothesis of the Brixia score, which indicates the degree of COVID-19 progression based on the severity of lung damage, while D-dimer serves as a measure of coagulation dysfunction.[17] In cases of severe COVID-19 infection, the extent of lung abnormalities visible on a chest X-ray, as determined by the Brixia score, aligns with elevated D-dimer levels indicating the pathogenesis of severe COVID-19.[20] Aydoğan Eroğlu, et al.[20] discovered a positive correlation between the Brixia score and D-dimer

study by Boari, et al.[21] demonstrated that a Brixia score of 8 is predictive of the prognosis of COVID-19 patients, with a significant decline in survival observed at hospital admission or during follow-up.

The advantage of the Brixia score is its high PPV of 95.8%. However, if a Brixia score <10 is obtained, it should be confirmed with D-Dimer levels due to its relatively low NPV of 40.9%. Based on the findings of this study, the Brixia score can be used for early diagnosis of CAHA and as a recommendation for more comprehensive management. Additionally, according to the study by Boari et al.,[21] the Brixia score demonstrates excellent predictive power and has recently been recognized as a useful risk stratification tool in WHO documents.

The study findings indicate that the Brixia score is independently associated with the occurrence of CAHA in COVID-19 patients. Patients with a Brixia score ≥10 have approximately 15 times higher chances of developing CAHA compared to those with a Brixia score <10, even after considering confounding variables. This association aligns with the understanding that elevated D-dimer levels reflect the severity of pneumonia caused by dysregulated coagulation due to excessive inflammatory mediators triggered by SARS-CoV-2 infection. Inflammatory cytokines may contribute to endothelial damage, leading to activation of the coagulation cascade and inhibition of fibrinolysis. Therefore, D-dimer is frequently used as a biomarker alongside chest X-rays to identify worsening COVID-19 patients.[22]

The clinical significance of this study lies in the identification of the Brixia score as a potential alternative predictor of CAHA in COVID-19. By utilizing a cut-off value ≥10, clinicians can assess the likelihood of CAHA in hospitalized COVID-19 patients who have not undergone D-dimer testing. If the Brixia score is ≥10, it indicates a high probability of CAHA, and appropriate therapy can be initiated accordingly. On the other hand, if the Brixia score is <10, further evaluation of D-dimer levels is recommended to ensure the absence of CAHA. This approach provides a practical and accessible method for risk assessment in COVID-19 patients using chest X-ray findings and can aid in timely decision-making and appropriate management strategies.

This study does have certain limitations that should be acknowledged. Firstly, the data relied on medical records, which introduces the possibility of variations in data quality and accuracy. Additionally, the study only included adult patients, so the findings may not be applicable to pediatric or elderly populations who may have different clinical characteristics. Another limitation is the possibility of false-positive D-dimer results, as elevated D-dimer levels can be observed in various medical conditions other than coagulation dysfunction. Furthermore, the use of anticoagulant medications in patients with comorbidities may influence D-dimer levels and complicate the interpretation of results. These limitations should be taken into consideration when interpreting the findings of this study and further research is warranted to address these limitations and validate the results in diverse patient populations.

Conclusion

There is a correlation between the Brixia score and the incidence of CAHA in adult COVID-19 patients, as indicated by the correlation by the correlation with D-dimer levels. As the Brixia score increases, there is a corresponding increase in the staging of CAHA in COVID-19 patients.

The cut-off value of ≥10 for the Brixia score appears to be a useful predictor of CAHA. Patients with a Brixia score ≥10 should be closely monitored and considered for early intervention to prevent coagulopathy and its associated complications.

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