Original Article

Correlation Between Brixia Score Imaging and Clinical Laboratory Results in Severe-Critical Covid-19 Patients Receiving Standard Therapy Compared to Tocilizumab

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Abstract

Background : *Coronavirus infection disease 19* (COVID-19) is a global health issue. Brixia score and inflammatory markers can assess COVID-19 severity. Severe-critical phase becomes the main concern of clinicians in the management of COVID-19 to reduce mortality. Standard therapy for moderate to severe COVID-19 is convalescent plasma which functions as an antiviral and immunomodulator, while tocilizumab is an IL-6 antagonist which underlies the occurrence of cytokine storms in severe-critical COVID-19. This study was aimedto examine the correlation between the Brixia score and clinical laboratory results in patients with severe-critical degree of Covid-19 who received both standard therapy and tocilizumab

Methods : A retrospective cohort study of Brixia score, with clinical laboratory results of D-dimer, fibrinogen, ferritin, and CRP (C-reactive protein) COVID-19 patients with severe-critical phase who were administered standard therapy and tocilizumab who were treated at RSUP DR Kariadi Semarang, then a correlation was carried out between the Brixia score and clinical laboratory results using a correlation test Spearman.

Results : The research data consisted of 72 subjects divided into groups that were adiminstered tocilizumab therapy (36 subjects) and standard therapy (36 subjects). There was a significant correlation between the Brixia score and the D-dimer result with *p* = 0.024 (*p* <0.05), correlation coefficient = 0.377 in the standard pre-therapy and post therapy. A *p-value* of less than 0.05 indicates no significant correlation between the Brixia score and clinical laboratory results before or after tocilizumab therapy.

Conclusion : There is a significant correlation between the Brixia score results and the D-dimer results in COVID-19 patients who are adiministered standard therapy, but not significant correlation in tocilizumab.

**Keywords :** COVID-19, Brixia score, tocilizumab, convalescent plasma

INTRODUCTION

World Health Organization (WHO) declared coronavirus infection disease 19 (COVID-19) as a public health emergency of international concern (PHEIC) due to a significant increase in confirmed cases in various countries. In Indonesia, the first case of COVID-19 was reported on March 2, 2020, in a woman who had close contact with the 24th confirmed case in Malaysia, while the second case was the mother of the first case. Over time, the number of confirmed COVID-19 cases in Indonesia reached 4,208,013 by July 2020, with 141,467 deaths.[1]

The diagnosis of COVID-19 is established based on a combination of medical history with contact tracing, physical examination, hematological examination, antigen swab test, real-time reverse transcriptase polymerase chain reaction (RT-PCR), and imaging. However, the definitive diagnosis still relies on RT-PCR results. Radiological imaging plays an important role in the diagnosis of COVID-19, although knowledge about this pneumonia is still evolving. Radiological imaging is used to detect early signs of pneumonia, assisting clinicians in making a diagnosis. It also provides insights into the severity, disease progression, and post-infection control.[4] The main imaging modalities used to detect COVID-19 are chest X-rays and computed tomography (CT) scans. Chest X-rays are less sensitive compared to CT scans, as approximately 40% of cases do not show abnormalities on X-rays. However, the American College of Radiology (ACR) does not recommend using CT as the first-line screening tool for diagnosing COVID-19.[5] CT scans are limited to symptomatic patients with specific clinical indications due to the challenges in infection control and prevention of cross-contamination. In chest X-rays of patients with COVID-19 pneumonia, findings such as ground-glass opacity (GGO), infiltrates, peribronchial thickening, focal consolidation, and other findings can be observed. A study conducted by Zubo Wu *et al* in 2021 found a significant correlation between the degree of pneumonia and thoracic radiological findings in severe-critical COVID-19 patients.[5–7]

Based on the pathogenesis of COVID-19, most deaths occur in the severe-critical phase. This phase is of primary concern to clinicians in the management of COVID-19 as it determines prognosis. Therefore, treatment modalities for COVID-19 in the severe-critical phase are crucial in reducing patient mortality.[14] The most effective measures to reduce the incidence of COVID-19 are early detection, source isolation, and supportive care for confirmed cases. According to the COVID-19 Management Guidelines (3rd edition) issued by five professional medical organizations in Indonesia, the treatment for asymptomatic, mild, and moderate cases of COVID-19 is clear. However, in severe-critical cases, if there is no improvement with standard treatment, there are four treatment modalities still under operational research and have varying success rates among different studies: tocilizumab, convalescent plasma, IVIG, and stem cells. Therefore, this study aims to examine the correlation between Brixia Score imaging and clinical laboratory results in severe-critical COVID-19 patients receiving standard therapy compared to tocilizumab, to predict patient morbidity and mortality during treatment.[13]

Considering the severity and clinical complexity of severe-critical COVID-19, some studies have also analyzed the combination of multiple treatment modalities, such as convalescent plasma and tocilizumab. Mathew conducted a systematic review, and Khamis conducted a cohort study. In the systematic review by Mathew, which included seven retrospective studies
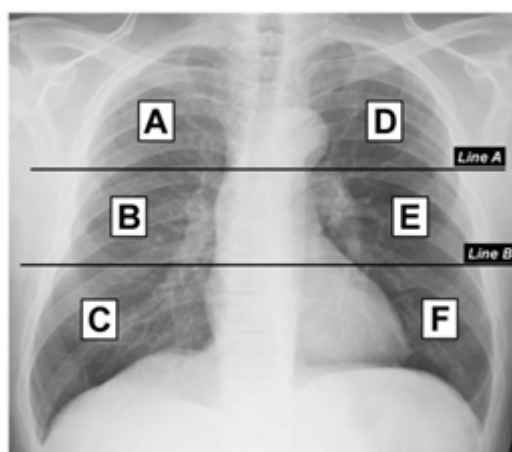
Figure 1. The 6 lung divisions on an anterior chest radiograph. A line is drawn from the inferior wall of the aortic arch. Line B is drawn from the inferior wall of the pulmonary vein. A and D are the upper zone, B and E are the middle zone, and C and F are the lower zone.[13]
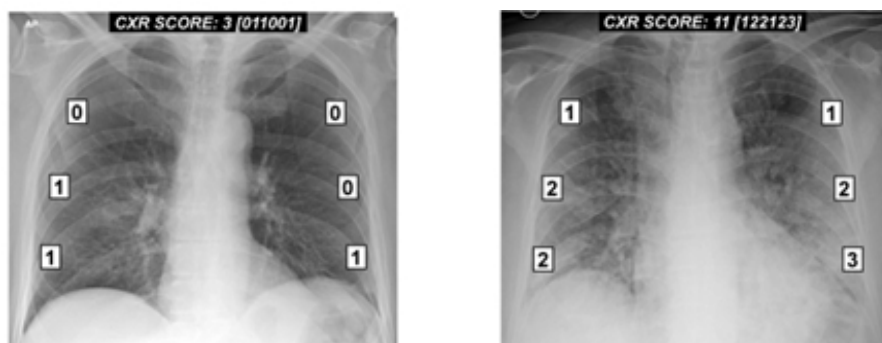
Figure 2. Example of assessing the degree of pneumonia score using the Brixia score, the top image
total score: 3, the bottom image: 11

involving 592 severe-critical adult COVID-19 patients, including 240 in the tocilizumab group, the mortality rate in the tocilizumab group was 16.3% (39/240), which was lower than the control group. Both studies concluded that the combination of convalescent plasma and tocilizumab treatment was associated with improvements in inflammatory conditions and disease progression.[7,8]

METHODS

This study was conducted to evaluate the correlation between Brixia Score findings and clinical laboratory results in critically ill COVID-19 patients receiving standard therapy compared to tocilizumab at Kariadi Hospital Semarang using an analytical retrospective cohort method, with the selection of research subjects based on patient data from January 2020 to December 2021, as recorded in the medical records and the Covid Team data of Kariadi Hospital Semarang. The research subjects were patients aged ≥18 years who were hospitalized at Kariadi Hospital Semarang and had been adjusted according to the inclusion and exclusion criteria. A total of 72 individuals were gathered as research subjects, and their Brixia Score values and clinical laboratory results were examined. The evaluation of clinical laboratory results was assessed on day 3 after therapy, while the evaluation of Brixia Score values was assessed on day 9 after therapy. The study took place at the Radiology Department of Kariadi Hospital Semarang, utilizing samples consisting of laboratory results (fibrinogen, CRP, ferritin, D-dimer) and chest X-rays from hospitalized patients diagnosed with severe COVID-19 who received either standard therapy or tocilizumab. The study was conducted from March to October 2022. This study was quantitative research with a retrospective cohort design, where the dependent variables were observed, and the independent variables were obtained from patients' medical records. The target population for this research included adult patients (both male and female) aged 18 years and above, who were hospitalized with a positive diagnosis of COVID-19 and received

tocilizumab or standard therapy at Kariadi Hospital Semarang. The research sample consisted of chest X-rays from patients who met the inclusion criteria (age ≥18 years, confirmed positive for COVID-19 through antigen or RT-PCR tests, hospitalized with chest X-ray findings showing opacities or pneumonia) and did not meet the exclusion criteria (no active tuberculosis lesions, no pleural effusion, lung mass, pulmonary vascular enlargement, or history of treatment with intravenous immunoglobulin or stem cell/secretome).[15]

The Brixia score values are divided into 4 groups: normal (0), mild pneumonia (1–6), moderate pneumonia (7–12), and severe pneumonia (13–18). In the tocilizumab therapy group, Brixia scores ranged from 0 to 16, while in the standard therapy group, Brixia scores ranged from 2 to 16. This study was aproved by Health Research Ethics Committee of RSUP Dr. Kariadi Semarang

RESULTS

The correlation between the Brixia score imaging and clinical laboratory results in critically ill COVID-19 patients receiving standard therapy
Based on the correlation test using the Spearman's rank correlation coefficient, a significant correlation was found between the Brixia score and D-dimer in convalescent plasma before therapy, with a *p-value* of 0.024 ($p < 0.05$) and a correlation coefficient of 0.377.

Based on the correlation test using the Spearman's rank correlation coefficient, a significant correlation was found between the Brixia score and D-dimer in convalescent plasma after therapy, with a *p-value* of 0.314 ($p < 0.05$) and a correlation coefficient of 0.359.

Based on the correlation test using the Spearman's rank correlation coefficient, a significant correlation was found between the Brixia score and clinical laboratory results in critically ill COVID-19 patients receiving tocilizumab therapy
Based on the correlation test using the Spearman's rank correlation coefficient, a *p-value* of less than 0.05 was not

TABLE 1
Comorbidities among patients receiving standard and tocilizumab therapies

Comorbidities	Tocilizumab group	Tocilizumab group
Hypertension	3 patients (8.3%)	3 patients (7.9%)
Type 2 diabetes mellitus	4 patients (11.1%)	7 (18.4%) patients
Benign prostatic hyperplasia	1 patient (2.8%)	–
Heart failure	2 patients (5.6%)	1 patient (2.6%)
Ischemic heart disease	–	1 patient (2.6%)
Pulmonary embolism	1 patient (2.8%)	–
Hepatitis B	1 patient (2.8%)	–
Obesity	2 patients (5.6%)	–
No comorbidity	22 patients (57.9%)	29 patients (68.5 %)

obtained, indicating that there is no significant correlation between the Brixia score and clinical laboratory results before or after tocilizumab therapy.

DISCUSSION

Hyperinflammation phase in the pathogenesis of Covid-19 infection occurs during the severe and critical phases. In the severe phase, there is a cytokine storm characterized by increased levels of CRP, D-dimer, and procalcitonin. In the critical phase, systemic inflammation occurs with elevated levels of procalcitonin, ferritin, and C-reactive protein. IL-6 and other inflammatory cytokines are also increased, leading to the failure of various organ functions. Additionally, blood coagulation disorders may occur, as indicated by elevated D-dimer and prothrombin time.[6–8]

Patients with severe-critical Covid-19 infection who were treated at Kariadi Hospital Semarang and became subjects of the study experienced an increase in Brixia Score values (Brixia Score values in this study ranged from 2 to 16). This is consistent with a previous study conducted by Zubo Wu *et al*. in 2021, which found a significant correlation between the degree of pneumonia and chest X-ray findings in critically ill Covid-19 patients. The study results showed that in patients with moderate-severe Covid-19, both in the tocilizumab therapy group and the standard therapy group, there was an increase in clinical laboratory values of inflammatory markers such as C-reactive protein, fibrinogen, ferritin, and coagulation marker D-dimer. This is in line with a study conducted by Ana Karla *et al*. in 2021, which stated that interleukin 6, ferritin, and C-reactive protein are biomarkers that increase and play an important role in the cytokine storm associated with poor prognosis in Covid-19 infections.[9,10]

Spearman rho analysis revealed a significant correlation between Brixia score and D-dimer values, both before and after therapy, in the standard therapy group. The obtained *p-value* was 0.024 ($p < 0.05$) with a correlation coefficient of 0.377 before therapy, and a *p-value* of 0.314 ($p < 0.05$) with a correlation coefficient of 0.359 after therapy. These findings are consistent with a previous study conducted by Amela Sofic, which found a significant correlation between Brixia score and D-dimer and CRP levels.[7] However, in this study, CRP levels did not show a significant correlation with Brixia score.[8] In the previous study, the inclusion criteria included patients hospitalized with a maximum CRP level of 5.0 mg/L, while in this study, the CRP levels ranged from 6–19 mg/L. In the previous study, Pairwise comparison using Shapiro-Wilk test revealed significant differences in Brixia score and D-dimer values for both tocilizumab and standard therapy ($p > 0.05$). This indicates that both therapies significantly affect the Brixia score and D-dimer values. These findings are consistent with a study conducted by Ahn *et al*. in 2021, which showed improvement in chest X-rays of Covid patients after six to ten days of convalescent plasma therapy.[4] Additionally, 12 patients demonstrated significant improvement in lung lesions on chest CT scans after five days post-transfusion of convalescent plasma. A study by Xiang Xu *et al*. also reported significant improvement in chest CT scans for severely ill Covid-19 patients treated with tocilizumab on day 14 of therapy.[4]

CONCLUSION

In this study, it is concluded that there is a significant correlation between Brixia score and D-dimer values in critically ill Covid-19 patients receiving standard therapy. This indicates a relationship between the

severity of the disease and the level of inflammation. Furthermore, both tocilizumab therapy and standard therapy showed significant differences in their effects on Brixia score and D-dimer values. These findings suggest that both therapies have distinct effects on managing inflammation and coagulation in critically ill Covid-19 patients.

For future research, it is recommended to consider the use of Brixia score in relation to more specific clinical laboratory parameters, such as interleukin-6 (IL-6), which is a key cytokine in the occurrence of cytokine storms in Covid-19 infections.[17] Additionally, further studies can broaden the scope by exploring the correlation between Brixia score and clinical severity using more diverse data in terms of age, evaluation days, and comorbidity factors. By doing so, the research outcomes will be more relevant and provide a deeper understanding of the impact of Brixia score on the clinical condition and management of severe Covid-19 patients.[19,20]

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