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# Brixia Chest X-ray Severity Scoring System is in Relation with C-reactive Protein and D-dimer Values in Patients with COVID-19

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## ABSTRACT

**Background:** The Brixia scoring system interpreted chest X-ray changes, serves as an indicator of the extent of changes in the lung parenchyma. **Objective:** To indicate the effect of D-dimer and C-reactive protein (CRP) on Brixia score in patients with positive polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). **Methods:** The research had prospective, descriptive and analytical character, and included patients (n=104) with Coronavirus disease 2019 (COVID-19) diagnosis. Chest X-ray, as well as calculation of Brixia score was done on admission, in the first week of hospitalization, on discharge, and 10 days after discharge (the patient was considered a post-COVID patient. Maximum CRP and D-dimer values were taken into account, along with data about dependence of mechanical ventilation and oxygen therapy. **Results:** Initial Brixia score was significantly associated with the values of CRP (r = .23, p <.05). Higher level of CRP affected the higher result on the Brixia score after the initial X-ray. High CRP and D-dimer were significantly associated with oxygen use in patients, while high D-dimer was also statistically significantly associated with comorbidity. The mean value of Brixia score (during four time points) was significantly related to the values of CRP, D-dimer, the use of mechanical ventilation and oxygen therapy, but also with the existence of comorbidities. The largest statistically significant positive correlaton of Brixia scora is with the values of D-dimer (r = .45, p <.000), but also with the values of CRP (r = .36, p <.000). **Conclusion:** Values of CRP have an impact on Brixia score. Investigation of clinical characteristics and outcomes of severe clinical presentation of COVID-19 along with CXR scoring system will contribute to early prediction, accurate diagnosis and treatment as well as to improve the prognosis of patients with severe illness.

**Keywords: COVID-19, lung, inflammation, X-Ray.**

## 1. BACKGROUND

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). It is believed that mild disease occurs in about 81%, severe disease (dyspnea, hypoxia, or> 50 percent lung involvement on imaging within 24 to 48 hours) in 14%, while critical disease (respiratory failure, shock, or multiorgan dysfunction) was reported in 5% (2). The clinical course depends on the variant of SARS-CoV-2 (3), and for the first time in the recent history of medicine, the treatment of the patient itself depended on daily learning and new data from the literature. The biggest fear of the health system was the fear of a potentially large number of patients who could burden the health system, which highlighted the need to stratify patients in relation to the risk of developing a severe clinical course. Vaccination also reduced the risk of severe clinical course, as well as mortality rate (4). Chest radiographs are part of the routine treatment of the patient in the initial stage of the disease. In the early stage or mild disease the findings may be normal, and most often they will go in the direction of consolidation or ground-glass opacities, bilateral or peripheral, or in the lower lung zones (5). The

Brixia scoring system interpreted chest X-ray changes, serves as an indicator of the extent of changes in the lung parenchyma (6). A higher score correlates with a more severe clinical course and higher morality (6). The question is whether it should be correlated with laboratory findings that are initially done, or whether it is correlated with dependence on oxygen therapy, and the use of mechanical ventilation.

## 2. OBJECTIVE

The aim of this study was to indicate the effect of D-dimer and C-reactive protein (CRP) on Brixia score in patients with positive polymerase chain reaction (PCR) test for SARS-CoV-2.

## 3. MATERIAL AND METHODS

**Patients and study design**

The research had prospective, descriptive and analytical character, and included patients (n=104) who were hospitalized in the General Hospital "Prim. dr. Abdulah Nakas" in Sarajevo, Bosnia and Herzegovina, in the period from 01 March 2021 to 01 April 2021.

**Methods**

From the hospital information system, laboratory parameters during hospitalization were verified, along with Chest X-ray during hospitalization and ten days after hospitalization. Inclusion criteria in the study were: patients who were real time polymerase chain reaction (PCR) tested positive for SARS-COV2 (verified COVID-19), who has peripheral saturation higher than 88%, older than 18 years, and patients who had documented values of C-reactive protein (CRP) and D dimer values during hospitalization. The exclusion criteria were met in case if the patient had incomplete documentation. Reference ranges for parameters were: CRP up to 5.0 mg/L, D-dimer up to 804 µg/L. Chest X-ray, as well as calculation of Brixia score was done on admission, in the first week of hospitalization, on discharge, and 10 days after discharge (the patient was considered a post-COVID patient.

Maximum CRP and D-dimer values were taken into account, along with data about dependence of mechanical ventilation and oxygen therapy. Presence of comorbidities was recorded. The period in which the study was conducted coincided with the presence of the delta variant of SARS-CoV-2 (Delta was a highly contagious variant of SARS-CoV-2) (7). Brixia score (Figure 1-4) divides the image into six zones on frontal chest projection (posteroanterior or anteroposterior projection): upper zones (A and D): above the inferior wall of the aortic arch, middle zones (B and E): below the inferior wall of the aortic arch and above the inferior wall of the right inferior pulmonary vein (the hilar structures), lower zones (C and F): below the inferior wall of the right inferior pulmonary vein (the lung bases) (6).

Each zone is scoring as: Score 0 no lung abnormalities, Score 1 interstitial infiltrates, Score 2 interstitial and alveolar infiltrates (interstitial predominance), Score 3 interstitial and alveolar infiltrates (alveolar predominance) (6). Ethical approval was obtained from the Ethical Committee of the General Hospital "Prim.dr. Abdulah Nakaš ", Sarajevo, Bosnia and Herzegovina.

| Model/ Variable | SD β | t | p | Model summary | |
|---|---|---|---|---|---|
| 1# | Gender | -.05 | -0.50 | .618 | R = .27<br>$R^2$ = .07<br>p = .052 |
| | Age | .32 | 2.83 | .006 | |
| | Comorbidity | -.14 | -1.23 | .223 | |
| 2# | Gender | -.02 | -0.160 | .873 | R = .346<br>$R^2$ = .119<br>ΔR = .045<br>p = .027 |
| | Age | .30 | 2.29 | .008 | |
| | Comorbidity | -1.75 | -1.56 | .122 | |
| | C-reactive protein | 1.64 | 1.64 | .105 | |
| | D-dimer | .10 | 1.00 | .319 | |

Table 1. Regression analysis of Brixia score

| | Brixia score | C-reactive protein | D-dimer | Mechanical ventilation | Oxygen therapy | Comm-orbidity |
|---|---|---|---|---|---|---|
| Brixia score | 1 | .23* | .12 | .09 | .17 | .05 |
| C-reactive protein | | 1 | .32** | .24.* | .23* | .13 |
| D-dimer | | | 1 | .12 | .32** | .35*** |
| Mechanical ventilation | | | | 1 | .06 | .09 |
| Oxygen | | | | | 1 | .27** |
| Commorbidity | | | | | | 1 |

Table 2. Correlation of initial Brixia score and monitored parameters. *<.05; **<.01; ***<.001

**Statistical analysis**

For statistical analysis of the obtained data, the software package SPSS Windows (version 21.0, SPSS Inc, Chicago, Illinois, USA) was used. For data processing, regression analysis, t-test for independent variables, and Spearman's correlation coefficient were used. All analysis results with $p<0.05$ or at a 95% confidence level were considered statistically significant.

## 4. RESULTS

The study included 104 patients, of which 62 men and 42 women, aged between 41 and 88 years, mean age 64.11 (sd =12). Out of a total number, only 3 (2.9%) patients were on a mechanical ventilation, and 91 (87.5%) patients were on oxygen therapy. 81 subjects (77.9%) had comorbidity.

Regression analysis of the initial Brixia score is shown in Table 1.

In the first block, we put sociodemographic variables (gender, age, and presence of comorbidity). In the second block, we add two parameters of blood (CRP, D-dimer). The obtained results of the regression analysis showed that the first block expanded 7% of the variance of the Brixia score. The final model explained 11.9% of the variance of the brixia score. Age of the patients was statistically significant predictor of the variance ($\beta = 0.300$; $t = 2.29$ $p < 0.01$).

According to the obtained results, the initial Brixia score was significantly associated with the values of CRP ($r = .23$, $p < .05$). Higher level of CRP affected the higher result on the Brixia score after the initial X-ray (Table 2). High CRP

| | Brixia score | C-reactive protein | D-dimer | Mechanical ventilation | Oxygen therapy | Commorbidity |
|---|---|---|---|---|---|---|
| Brixia score | 1 | .36*** | .45*** | .28*** | .35*** | .22* |
| C-reactive protein | | 1 | .32** | .24.* | .23* | .13 |
| D-dimer | | | 1 | .12 | .32** | .35*** |
| Mechanical ventilation | | | | 1 | .06 | .09 |
| Oxygen | | | | | 1 | .27** |
| Commorbidity | | | | | | 1 |

Table 3. Correlation of mean Brixia score and monitored parameters. *<.05; **<.01; ***<.001

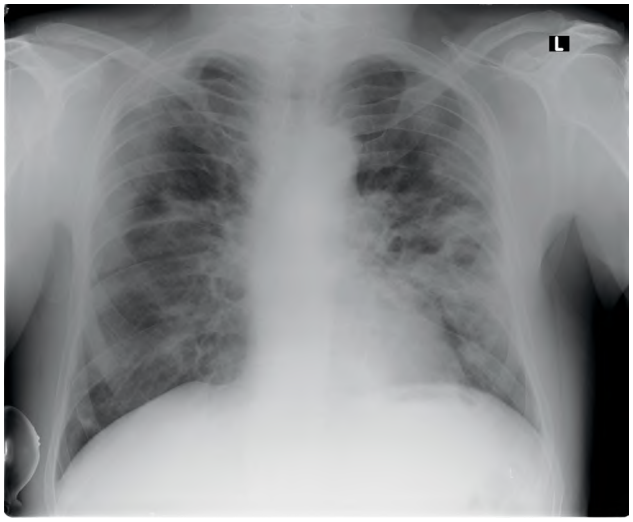


Figure 1. Brixia score 12-13

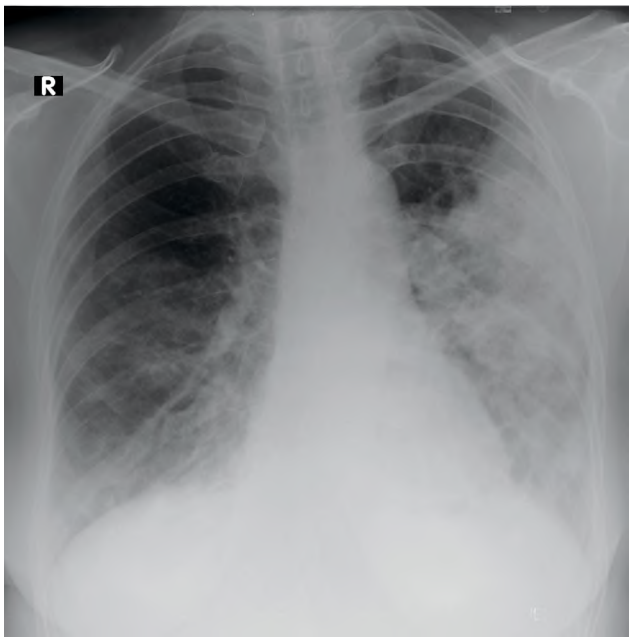


Figure 2. Brixia score 14-15

and D-dimer were significantly associated with oxygen use in patients, while high D-dimer was also statistically significantly associated with comorbidity.

The mean value of Brixia score (during four time points) was significantly related to the values of CRP, D-dimer, the use of mechanical ventilation and oxygen therapy, but also with the existence of comorbidities (Table 3). The largest statistically significant positive correlaton of Brixia scora is with the values of D-dimer (r = .45, p <.000), but also with

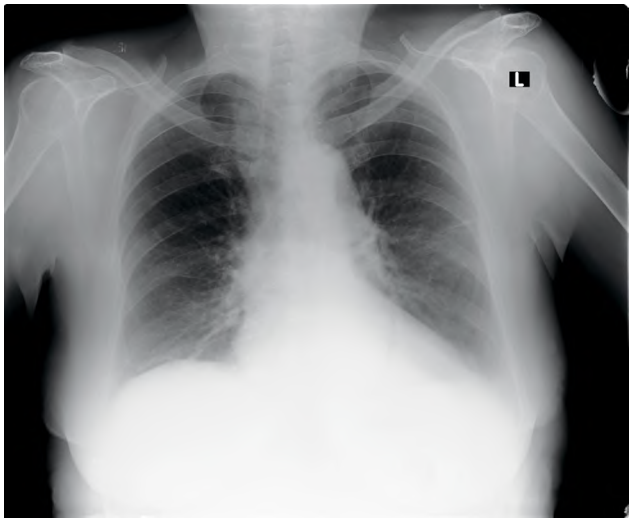


Figure 3. Brixia score 4

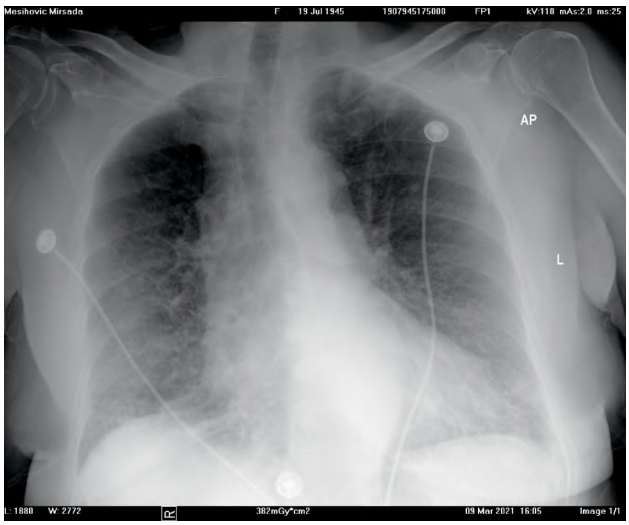


Figure 4. Brixia score 8-9

the values of CRP (r = .36, p <.000). Higher level of CRP is in relation with higher Brixia score during COVID-19. High CRP and D-dimer values were significantly associated with oxygen use in patients, while high D-dimer was also statistically significantly correlated with comorbidity existence.

Figure 5 presents the results of four Brixia scores in relation to the D-dimer level. According to the obtained results, Brixia score increases from measuring point I to measuring point II, where it reaches its maximum value in most patients during the first week of illness, then decreases from measuring point II through measuring point III to measuring point IV. On the Figure 1 we can see that there is no statistically significant difference during the initial

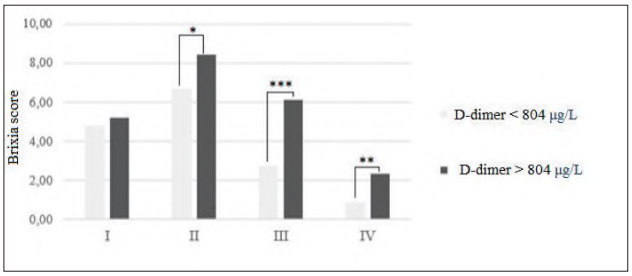


Figure 5. Difference of Brixia score during four measuring points in patients with elevated D-dimer compared to patients with low D-dimer (I – initial, II – in the first week, III – last week, IV – post-COVID)

measurement of Brixia score compared to patients who have medically significantly elevated D-dimer compared to patients who have a score in the reference values. The difference between patients who had a significantly elevated D-dimer compared to patients who had a result in the reference values was statistically significant in measurement point II, ie during the first week (t (102) = -2.21, p = .029), during the last week (t (102) = -4.44, p <.001), but also in the postCOVID time (t (102) = -2.74, p <.007).

## 5. DISCUSSION

Significant number of studies available through literature search evaluated correlation of laboratory findings and radiological data as prognostic factors for COVID 19 disease severity course. Patients critically ill with COVID-19 are caracterized with hyperinflammation, and the associated biomarkers may be beneficial for risk stratification (8). Our study identified age and comorbidities as statistically significant predictors of the variance. Assessment of available radiological, laboratory and clinical data of emergency room patients with COVID-19 evaluated by Gatti et al. identified significant independent predictors for in-hospital mortality as follows: age > 75 years, CRP>60 mg/L, PaO2/FiO2 ratio (P/F) < 250 and CXR "Brixia score" > 7 (9).

In the study of Gatti et al. based on evaluation of chest x ray findings sensitivity for the clinical course of COVID 19 infection identified CXR 61.1% (95%CI 55-67%) with a typical presence of bilateral (62.3%) infiltrates, predominantly with a lower zone (88.7%) and peripheral (43.4%) distribution. They also identified C-reactive protein (CRP) > 30 mg/L and interval between the onset of symptoms and the CXR apperance as major predictors for a positive CXR findings (9). Cozzi et al. also in their study identified CXR patchy or diffuse reticular-nodular opacities and consolidation, with basal, peripheral and bilateral predominance with baseline CXR sensitivity of 68.1% (10). Simililarly results of our study found the initial Brixia score significantly associated with the values of CRP (p <.05) with higher level of CRP affecting the higher result on the Brixia score after the initial X-ray.

Brixia score, age and cardiovascular disease served as independent predictors of death in the study of Balbi et al. They also identified CXR as a tool for assessing COVID-19 severity along with patient history, PaO2/FiO2 ratio and SpO2 values that could predict mortality and the need for ventilatory support (11). Study of Maroldi et al. identified the highest and lowest values of the Brixia score system registered along with scores on admission and end of hospitalization. The Brixia score was correlated with the outcome (death or discharge) (12).

Evaluating factors associated with hospital admission and critical illness among hospitalized patients the strongest risk for hospital admission was associated with age while other risks were heart failure, male sex, chronic kidney disease. The strongest risks for critical illness besides age were associated with heart failure, body mass index (BMI) >40 and male sex. Admission oxygen saturation of <88%, troponin level >1, CRP>200, and D-dimer level >2500 were strongly associated with critical illness than age or comorbidities (13). Prospective cohort study of Cummings et al. also identified higher concentrations of D dimer as one of factors leading to increased in-hospital mortality (14). A systematic review and meta-analysis investigating inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection identified the cutoff values as follows: 33.55 mg/L for CRP, 0.635 µ/L for D-dimer, and 263.5 U/L for LDH, each with high sensitivity and specificity for prediction of severe course of COVID 19 disease (15). Meta analysis of Huang et al. also identified an elevated D-dimer association with an increased poor outcome including mortality and severe COVID-19 (16). According to the results of our study high CRP and D-dimer were also significantly associated with higher oxygen use in patients, while high D-dimer was also statistically significantly associated with comorbidity.

Retrospective study of Ye et al. identified initial and peak value of D-Dimer in deceased patients statistically higher compared with survivors. There was also a more significant increasing value of D-Dimer during hospitalization in the deceased patients, while initial D-Dimer values lower than the peak tests (17). Our study identified peak D-dimer values in the first week of the disease along with peak values of Brixia scoring system.

COVID-19 positive patient's CXRs admitted to hospital over 3 months were reviewed and correlated with non-invasive ventilation, intubation and death in the study of Hanley et al. According to their results higher CXR severity scores were associated with intubation, need for non-invasive ventilation and death. A cut-off score of 6 had a sensitivity of 77% and specificity of 73% in predicting the need for intubation (18). Our study correlated with these results identifing the mean value of Brixia score as significantly related to the use of mechanical ventilation and oxygen therapy.

## 6. CONCLUSION

Values of CRP have an impact on Brixia score. Investigation of clinical characteristics and outcomes of severe clinical presentation of COVID-19 along with CXR scoring system will contribute to early prediction, accurate diagnosis and treatment as well as to improve the prognosis of patients with severe illness.

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- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms

- **Author's Contribution:** A.S., M.C., A.M., A.H.S., L.A.G., E.B. and M.B. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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