Utility of the Brixia CXR score, C-Reactive Protein and Absolute Neutrophil Count in Predicting the Need for Invasive Mechanical Ventilation, Length of Hospital Stay, and Mortality in Moderate to Severe COVID-19 Patients

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Background: The Brixia Chest X-ray (CXR) score, C-reactive protein (CRP), and the absolute neutrophil count (ANC) have been useful to predict outcomes in Coronavirus disease 2019 (COVID-19 patients). We studied the utility of the Brixia CXR score, CRP, and ANC in predicting the outcomes in terms of the need for invasive mechanical ventilation, length of stay, and mortality in moderate-severe COVID-19 patients.

Materials and Methods: This was a single-centre, retrospective, study on 122 COVID -19 patients. Brixia CXR score, CRP, and ANC on admission to the hospital and the fifth day of hospital stay were noted along with the need for invasive mechanical ventilation (IMV), prolonged length of stay (LOS) ≥ 14 days, and mortality.

Results: 122 patients were included for analysis. The median and interquartile range (IQR) for baseline CRP was 81.50 (39 -151) mg/L and 11.0 (4-30) mg/L ($p < 0.001$) on the fifth day. The median and IQR for baseline Brixia score was 10.0 (7-13), and on the fifth day was 7 (4-11) ($p <0.001$). The receiver operating characteristic curve (ROC) showed that the baseline CRP ≥ 52.5mg/L predicted both the need for IMV, with an area under the curve (AUC) of 0.628, and prolonged LOS with an AUC of 0.608. The ROC curve depicted that the baseline ANC >8500/µL predicted IMV requirement with an AUC of 0.657. The fifth day CRP ≥ 32 mg/L, ANC ≥ 11,000/ µL and Brixia CXR score ≥ 7 predicted a higher mortality in hospitalized patients.

Conclusion: Baseline CRP (> 52.5mg/L) predicts the need for IMV and a prolonged LOS, but not mortality. Baseline ANC (> 8500/µL) predicted the need for IMV. CRP, Brixia CXR score, and ANC on the fifth day were not useful to predict LOS or mortality, though there was a significant reduction in CRP and Brixia CXR score on the fifth day compared to baseline after treatment. The fifth day CRP ≥ 32 mg/L, ANC ≥ 11,000/ µL and Brixia CXR score ≥ 7 predicted a higher mortality.

Keywords: Coronavirus disease 2019, Brixia chest X-ray score, C-reactive protein, invasive mechanical ventilation, length of hospital stay, mortality.

Introduction

The clinical spectrum of COVID-19 disease can be classified as mild, moderate or severe.[1,2] The moderate-severe category patients require hospitalization which is often prolonged, with patients requiring ≥14 days stay.[3]

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Among the laboratory parameters in COVID-19, the role of measuring C reactive protein (CRP) in the assessment of disease severity and disease progression is undebatable.[4] Existing evidence and meta-analysis have concluded its role as a reliable inflammatory marker in COVID-19 patients to predict adverse outcomes.[4,5]

COVID- 19 being an acute respiratory viral illness, affects the lungs in the majority of patients. Computerized Tomography (CT) scan

undoubtedly is the best choice to look for the extent of lung involvement and the presence of ground glass opacities which is the hallmark of this disease.[6,7,8,9] In resource-limited settings where the burden of the disease is high, the feasibility of doing CT scans along with follow-up scans for every patient admitted to the hospital is challenging.

Literature has emphasized sterilizing the CT machine each time a scan is done and there is difficulty in shifting patients when they are sick, requiring intensive monitoring or oxygen therapy.[10] Considering these factors, other modalities like chest radiography (CXR) and lung USG have been advised, even though it is not as sensitive as a CT scan in the early stages of the disease process.[10,11]

The Brixia CXR score has been validated for prognostication of COVID-19 patients.[12,13,14] CXR findings have also been useful prognostication tools in resource-limited settings to predict ICU admission and mortality.[15] Apart from CXR scoring and CRP being predictors of adverse outcomes, absolute neutrophil count (ANC) at admission, which is available in any setting has also been proven to predict an adverse outcome.[16,17] Thus we aimed to study the utility of Brixia CXR score, CRP, and ANC in predicting the outcomes of hospitalised moderate-severe COVID-19 patients.

Materials and Methods

It was a single-centre, retrospective study done on COVID-19 patients who were admitted the hospital between July 2020 and September 2020. After Institutional Ethical Committee Registry-India (CTRI) registration clearance (IEC 654-2020) and Clinical Trial (CTRI/2020/11/029266), 126 patients were included in the study. Since it was a retrospective study, informed consent was waived by the IEC.

All patients aged between 18-90 years who had tested positive for COVID-19 as per reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test and were admitted to the hospital with moderate-severe COVID-19 were included in the study.

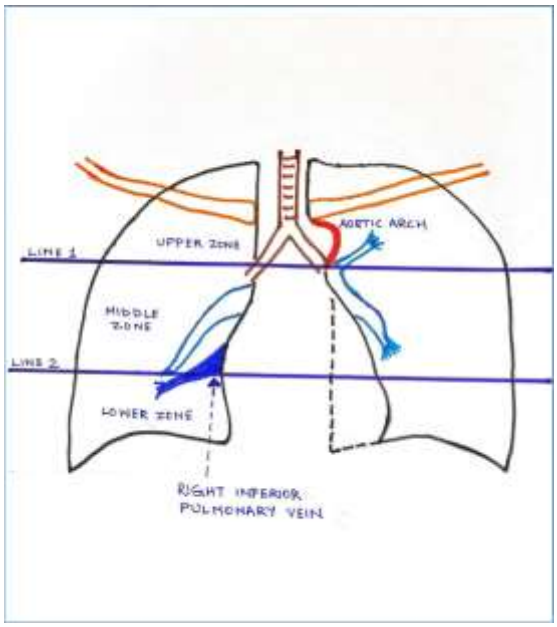
All patients had received treatment as defined by the institutional COVID-19 guidelines for moderate-severe disease, comprising Remdesivir for five days and corticosteroids as per physicians' discretion.

Patients excluded were those who were not administered Remdesivir for five days, patients discharged before five days of hospital stay, or any patients whose investigations of CRP, CXR, and neutrophil were not repeated on the fifth day after treatment.

Data of age, gender, and co-morbidities were collected from the hospital's electronic database. Baseline CRP level, Brixia CXR score, and ANC before starting treatment were noted, and CRP, Brixia CXR score, and ANC after five days of stay and treatment were noted.

Need for invasive mechanical ventilation (IMV), days of hospital stay, and in-hospital mortality were noted from the records. Patients with a prolonged hospital stay (≥14 days) were recorded separately. Patients with microbiological evidence of bacterial infection were excluded.

Image 1: *Depiction of the upper, middle and lower zones chest X- ray*



The CXR Brixia score analysis was done after extracting CXR images from the Picture Archives and Communication Systems (Insta RISPACS) of the hospital. Brixia CXR scoring involved two steps.[12] During the first stage, the lung regions were divided into six zones (three on each side), by two lines 1, 2 as shown in figure 1.[12]

Upper zones: above the inferior wall of the aortic arch.

Middle zones: below the inferior wall of the aortic arch and above the inferior wall of the right inferior pulmonary vein (i.e., the hilar structures).

Lower zones: below the inferior wall of the right inferior pulmonary vein. During the second stage, a score (from 0 to 3) was given to each zone depending on the pattern of lung abnormalities detected in the CXR.[12]

Score 0: No lung abnormalities.

Score 1: Interstitial infiltrates were present.

Score 2: Both interstitial and alveolar infiltrates were present, but however, there was interstitial predominance.

Score 3: Both interstitial and alveolar infiltrates were present, however, there was alveolar predominance.[12]

The total score of six lung zones (three zones on each side) was calculated from 0 to 18.[12]

The primary outcome was the utility of baseline and fifth-day CRP, CXR Brixia score, and ANC on the need for IMV, prolonged LOS, and in-hospital mortality. The secondary outcome was a change in CRP, Brixia CXR score, and ANC at baseline (on admission) and after five days of hospitalization and treatment.

Data was analyzed using EZR software, and the mean and SD of continuous variables were calculated. Median and interquartile range (IQR) was calculated for continuous variables having skewed distribution. Fischer exact test and Pearson Chi-square test were used to test statistical significance between categorical data. A p-value < 0.05 was considered significant. Paired sample t-test was the parametric test used to compare values of continuous variables measured at two different time points from the same patients. Wilcoxon signed rank test was the non-parametric test applied to compare values of continuous variables measured at two different time points from the same patients.

The reliability of CRP, ANC, and Brixia CXR score for predicting the need for IMV, prolonged LOS, and in-hospital mortality was analyzed by receiver operating curve (ROC) and area under the curve (AUC) along with cut-off values with sensitivity and specificity.

Results

A total of 122 patients were included for statistical analysis. For analysis of the utility of CRP for predicting outcomes, 120 patients were included. For analysis of the utility of Brixia CXR score for predicting outcomes, 121 patients were included and for analysis of the utility of ANC, 118 patients were included. The demographic and outcome variables are depicted in Table 1. The mean and SD of the age of the 122 patients was 59.02 ± 14.28 years. A majority of the patients were males (77.86%). The number of patients who required invasive mechanical ventilation was 39/122 (32%). The means and SD of the number of days of hospital stay were 14.79 ± 6.46. A total of 91/122 (74.6%) patients survived at the end of the hospital stay as shown in Table 1.

Table 1: *Depiction of the patients requiring invasive mechanical ventilation, length of stay, and outcome*

N =122	**Values**	
Age in years (Mean ± SD)	59.02 ± 14.28	
Gender	Males 77.86% (n = 95)	Females 22.13% (n = 27)
Invasive mechanical ventilation	Yes 32% (n=39)	No 68% (n=83)
Length of hospital stay in days (Mean ± SD)	14.79 ± 6.46	
The outcome of hospital stay	Survived 74.6% (n=91)	Expired 25.4% (n=31)

The CRP, Brixia CXR, and neutrophil values at baseline and fifth day are depicted in Table 2.

There was a significant reduction in the CRP level on the fifth day of the hospital stay 11.0 (4-30) mg/L as compared to the baseline 81.50 (39-151) mg/L, as depicted in Table 2.

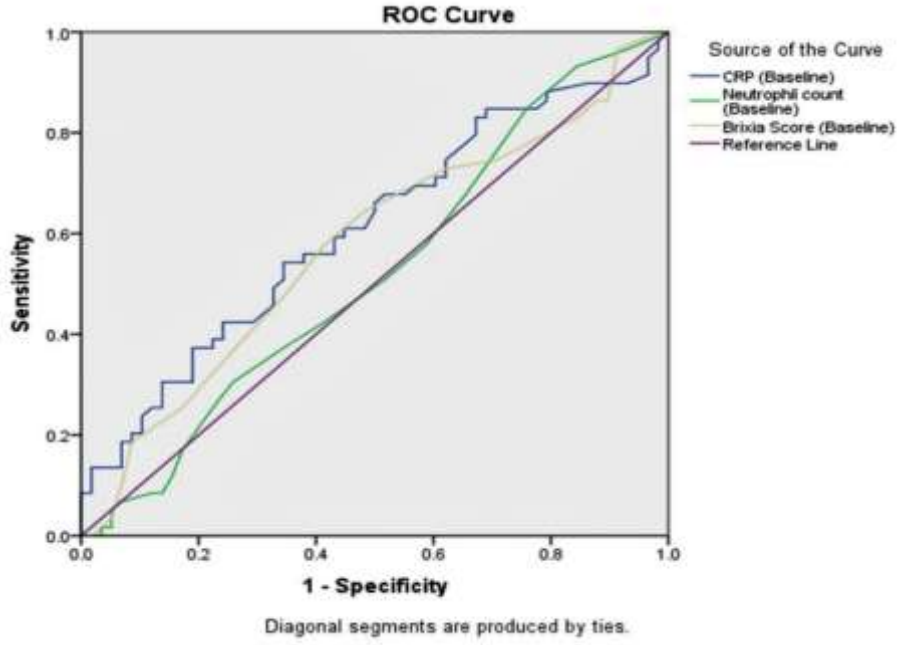
The Brixia CXR scores of the patients had also improved significantly on the fifth day 7 (4-11) as compared to the baseline 10 (7-13), as shown in Table 2. However, there was a significant rise in the ANC on the fifth day as compared to the baseline as shown in Table 2.

Table 2: *Parameters at baseline and on the fifth day of hospital stay. Wilcoxon signed-rank test*

Parameter	Baseline values of investigations	Fifth-day values of the investigations	P value
CRP (Median and IQR)	81.50 (39-151) mg/L	11.0 (4-30) mg/L	< 0.001
Brixia CXR score (Median and IQR)	10 (7-13)	7 (4-11)	< 0.001
ANC (Median and IQR)	8000 (5000-11,000) μL	10,000 (7000-12,000) μL	< 0.001

The receiver operating curve (ROC) of baseline CRP for predicting prolonged LOS (≥14 days) is depicted in Figure 1. The AUC of CRP for predicting prolonged length of stay was 0.608, $p < 0.05$, cut-off 52.5mg/L, sensitivity 70%, specificity 40%, 95% confidence interval (CI) was [0.505, 0.710]). However, the AUCs of the plotted ROCs of the Brixia CXR score and the neutrophil count to predict a prolonged LOS (≥ 14 days) was not significant.

Figure 2: *ROC curves of CRP, Brixia score and neutrophil count predicting prolonged LOS*



The AUC of baseline CRP for predicting prolonged length of stay was 0.608, $p < 0.05$, cut-off 52.5mg/L, sensitivity 70%, specificity 40%, 95% confidence interval (CI) was [0.505,0.710]) (Figure 2)

The AUC of baseline Brixia CXR for predicting long LOS was 0.577, p=0.153, cut-off 8.50, sensitivity 72.9%, specificity 38%. (Figure 2). The AUC of baseline neutrophil count for predicting LOS was not significant. (Figure 2)

Figure 3: *The AUC of baseline CRP and neutrophil count for predicting the need for IMV.*

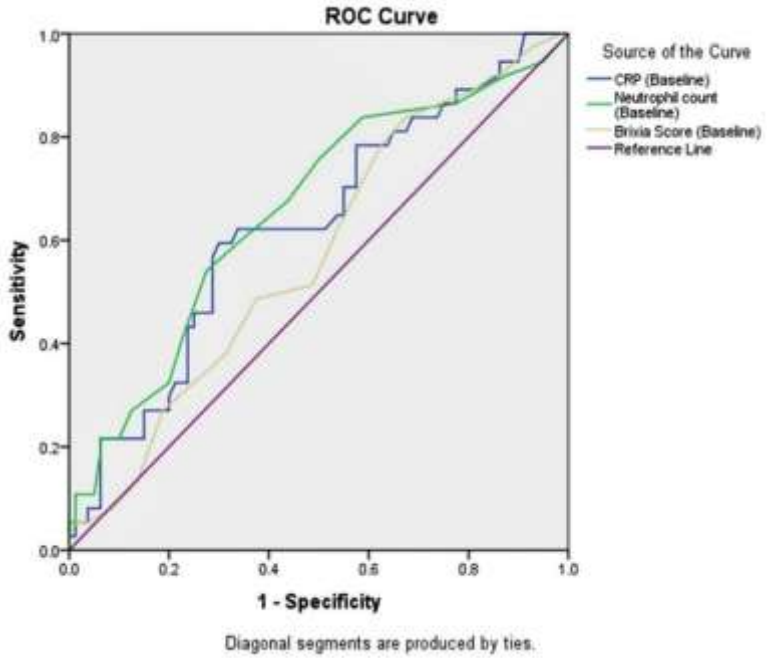
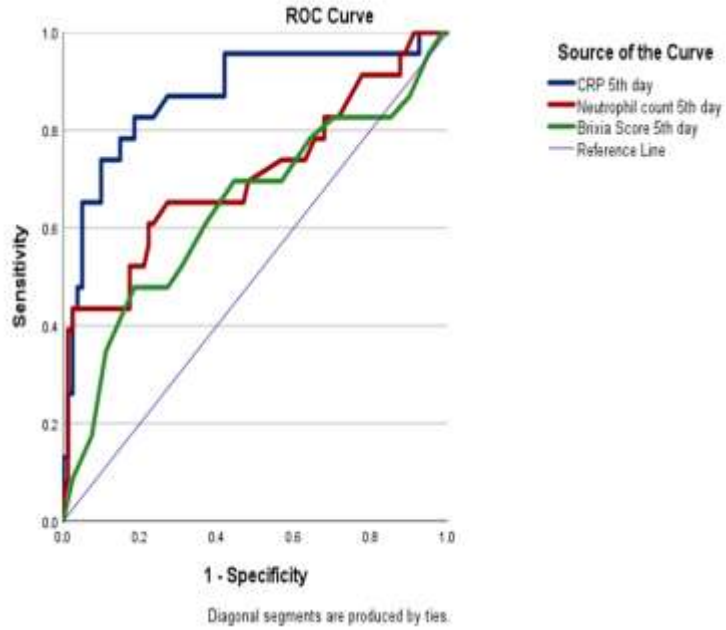


Figure 3 shows the ROC of baseline CRP, Brixia CXR score, and neutrophil count for predicting the need for IMV. (The AUC of baseline CRP for predicting the need for IMV was 0.628, cut-off 52.5mg/L sensitivity 78.4%, specificity 42.5%, p= 0.026, 95% CI [0.520, 0.737]. AUC for baseline neutrophil count to predict the need for IMV was 0.657, sensitivity 59.5%, specificity 66%, and cut-off 8500/uL, p=0.007, 95% CI [0.549, 0.765].

The AUC for baseline Brixia CXR score for predicting the need for IMV was lower at 0.573 and was not significant, p=0.208 (Figure 3).

Figure 4: *The AUC of fifth-day CRP, Brixia CXR, and neutrophil count to predict mortality*



The AUC of baseline CRP, Brixia CXR, and neutrophil count was not significant to predict mortality.

The AUC for the fifth day CRP to predict LOS was low, being 0.470, and was not significant (p=0.601). The AUC for the fifth day Brixia CXR scores and neutrophil count to predict LOS was also low (AUC 0.527 and 0.492 respectively), and was not significant as well (p = 0.641, p=0.888 respectively).

We found that the fifth day CRP ≥ 32 mg/L was significant to predict mortality (AUC 0.873, p <0.001, 95% CI [0.781-0.965], 74% sensitivity, and 88% specificity (Figure 4).

The fifth day ANC ≥ 11,000/µL was also significant to predict mortality (AUC 0.707, 95% CI [0.570- 0.843], 61% sensitivity, 77% specificity (Figure 4). The fifth-day Brixia CXR score ≥ 7 was also significant to predict mortality (AUC 0.639, 95% CI [0.498- 0.780], 70% sensitivity, and 63% specificity (Figure 4).

Thus, the values of the fifth day of hospitalization and treatment with a CRP of cut-off ≥ 32 mg/L, the ANC with a cut-off ≥ 11,000/µL and the Brixia CXR score with a cut-off ≥ 7 were predictors of mortality in hospitalized COVID-19 patients, with CRP having the highest AUC of 0.873, followed by the ANC (AUC 0.707) and then the Brixia CXR (AUC 0.639).

Discussion

With each wave of the COVID-19 pandemic causing immense strain on hospital resources, especially in developing countries, any baseline investigation which can help the treating physician to analyse which patient might

require ventilatory support or have a prolonged hospital stay will be immensely beneficial. The patient relatives may be counseled at the time of admission itself about the possible disease course.

Regarding significant markers for determining the outcome in COVID-19 patients which will be widely available, we considered one radiological parameter (Brixia CXR score), one inflammatory parameter (CRP), and one hematological parameter (ANC). We did the retrospective study and analysed the utility of baseline CRP, Brixia CXR score, and ANC to predict IMV, a prolonged LOS, and survival. We also determined the utility of fifth-day CRP, Brixia CXR score, and ANC to determine a prolonged LOS and survival.

Regarding the Brixia CXR score, the literature concluded that it strongly correlates with disease severity and prognosis; it may assist in decision-making, particularly in patients with moderate-to-severe signs and symptoms.[14] The authors had concluded that the Brixia score should be incorporated in a prognostic model, which would be desirable, particularly in resource-constraint scenarios.[14]

It has been observed that a total Brixia CXR score of >9 or if the score doesn't fall <7 after treatment, then poor outcomes can be expected.[14] In our study a reduction in Brixia score was seen on the fifth day of hospitalization. We also found that the fifth day Brixia CXR score was useful to predict mortality. If despite treatment, the fifth day Brixia CXR score was ≥ 7, then it predicted a higher mortality with 70% sensitivity and 63% specificity.

The results in our study are similar from those of Borghesi A where the investigators observed that the risk factor strongly associated with in-hospital mortality is a higher age group, high Brixia score > 8, and immunosuppressive conditions.[13] The ROC analysis in their study showed the cut-off for the Brixia score ≥ 8 and for age, it is 71, for predicting worse outcomes and hospital mortality.[13] In our study we could not conclude that baseline CXR Brixia score may be useful to predict the need for IMV, length of stay, or mortality. However, we could find that the fifth-day Brixia CXR score was significant to predict mortality.

Literature has shown that CRP > 10mg/L in COVID-19 indicated poor prognosis.[4] In a meta-analysis that included 13 trials, an increase in CRP was related to increased chances of ICU admission, but not mortality.[4]

The findings were similar to that of our study. We found baseline CRP >52.5mg/L was associated with a prolonged hospital stay and need for IMV, but not mortality.

We also found that even post-treatment, the fifth day CRP is ≥ 32 mg/L, it predicted mortality. This higher value of CRP which we found, compared to the previous one may be due to the enrolment of only moderate-severe COVID-19 cases in our study. The results of our study corroborate with the results of the study done by Asghar M, where CRP was elevated in the patients who required ICU admission.[16] CRP is a marker of disease severity as well correlated with lung lesions.[17]

Hyperinflammation is related to the severity of COVID-19 and also leads to pulmonary inflammation and neutrophil activation.[18] The formation of neutrophil extracellular traps, neutrophil activation, and a high neutrophil-lymphocyte ratio, all indicate pulmonary inflammation and damage.[18] This may explain the findings in our study, that ANC was predictive of the need for IMV, with a count > 8500/μL predicting its need. This was also similar to the results in a previous study where a neutrophil percentage >75% was associated with a higher need for ICU admission.

However, we could also conclude that fifth day ANC ≥ 11,000/ μL was a predictor of mortality, as was proven in a previous study where the investigators found that the neutrophils >75% predicted mortality.[16,17]

Conclusion

Baseline CRP (>52.5g/dL) in moderate-severe COVID-19 hospitalized patients predict the need for IMV and prolonged hospital LOS (≥14 days). Baseline ANC (>8500/μL) predicts the need for IMV, but not prolonged LOS. Baseline Brixia CXR score can neither predict the need for IMV nor prolonged LOS. Baseline CRP, ANC, and Brixia CXR did not predict mortality. There was a significant reduction in CRP and Brixia CXR scores after five-day treatments with Remdesivir and corticosteroids in moderate-severe COVID-19 patients. If even post treatment with Remdesivir and corticosteroids, the fifth-day values of CRP was ≥ 32 mg/L, Brixia CXR score was ≥ 7 and ANC was ≥11,000/μL, it predicted a higher mortality in hospitalized COVID-19 patients.

Conflict of interest

The authors declare no conflict of interest.

Sources of funding

None

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