

# Risk stratification of hospital admissions for COVID-19 pneumonia by chest radiographic scoring in a Johannesburg tertiary hospital

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**Background.** Chest radiographic scoring systems for COVID-19 pneumonia have been developed. However, little is published on the utility of these scoring systems in low- and middle-income countries.

**Objectives.** To perform risk stratification of COVID-19 pneumonia in Johannesburg, South Africa (SA), by comparing the Brixia score with clinical parameters, disease course and clinical outcomes. To assess inter-rater reliability and developing predictive models of the clinical outcome using the Brixia score and clinical parameters.

**Methods.** Retrospective investigation was conducted of adult participants with established COVID-19 pneumonia admitted at a tertiary institution from 1 May to 30 June 2020. Two radiologists, blinded to clinical data, assigned Brixia scores. Brixia scores were compared with clinical parameters, length of stay and clinical outcomes (discharge/death). Inter-rater agreement was determined. Multivariable logistic regression extracted variables predictive of in-hospital demise.

**Results.** The cohort consisted of 263 patients, 51% male, with a median age of 47 years (interquartile range (IQR) = 20; 95% confidence interval (CI) 46.5 - 49.9). Hypertension (38.4%), diabetes (25.1%), obesity (19.4%) and HIV (15.6%) were the most common comorbidities. The median length of stay for 258 patients was 7.5 days (IQR = 7; 95% CI 8.2 - 9.7) and 6.5 days (IQR = 8; 95% CI 6.5 - 12.5) for intensive care unit stay. Fifty (19%) patients died, with a median age of 55 years (IQR = 23; 95% CI 50.5 - 58.7) compared with survivors, of median age 46 years (IQR = 20; 95% CI 45 - 48.6) ( $p=0.01$ ). The presence of one or more comorbidities resulted in a higher death rate (23% v. 9.2%;  $p=0.01$ ) than without comorbidities. The median Brixia score for the deceased was higher (14.5) than for the discharged patients (9.0) ( $p<0.001$ ). Inter-rater agreement for Brixia scores was good (intraclass correlation coefficient 0.77; 95% CI 0.6 - 0.85;  $p<0.001$ ). A model combining Brixia score, age, male gender and obesity (sensitivity 84%; specificity 63%) as well as a model with Brixia score and C-reactive protein (CRP) count (sensitivity 81%; specificity 63%) conferred the highest risk for in-hospital mortality.

**Conclusion.** We have demonstrated the utility of the Brixia scoring system in a middle-income country setting and developed the first SA risk stratification models incorporating comorbidities and a serological marker. When used in conjunction with age, male gender, obesity and CRP, the Brixia scoring system is a promising and reliable risk stratification tool. This may help inform the clinical decision pathway in resource-limited settings like ours during future waves of COVID-19.

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SARS-CoV-2 is the novel viral pathogen responsible for the potentially serious pulmonary infection known as COVID-19 pneumonia, now a global pandemic.<sup>[1,2]</sup> The clinical disease progression varies from asymptomatic to severe pneumonia with multiorgan dysfunction that may result in death.<sup>[2,3]</sup> The benchmark test for COVID-19 is a nucleic acid amplification test (NAAT) using reverse transcriptase polymerase chain reaction (RT-PCR) to detect SARS-CoV-2 in respiratory samples.<sup>[4,5]</sup> However, it has limitations, including false negative rates of up to 58%,<sup>[6]</sup> difficulties associated with large-scale testing in low- and middle-income countries and lengthy turnaround times during the height of the pandemic.<sup>[7,8]</sup> Thus various radiological imaging modalities have proven to be integral ancillary tools in the triage and management of COVID-19.<sup>[9,10]</sup>

The most sensitive imaging tool to detect COVID-19-related lung changes is computed tomography (CT), and quantification methods to help assess disease severity have been developed.<sup>[11,12]</sup> The sensitivity for typical COVID-19 features using CT is as high

as 98%,<sup>[13]</sup> but CT is not universally used as first-line imaging, particularly in resource-constrained environments, owing to various factors that include the unavailability of CT, logistics required to transport patients while limiting cross-infection and disinfection of the CT scanner in between patients. The sensitivity for detecting COVID-19-related lung changes using chest radiographs (CXR) is low compared with CT, with reported sensitivities ranging from 38% to 89%.<sup>[12,14,15]</sup> Despite CXR sensitivity being inferior to CT, it has been widely used as first-line imaging both internationally and locally owing to its availability, ability to be performed at the bedside, cost-effectiveness, lower radiation dose than CT, fast patient throughput and rapid disinfection.<sup>[16,17]</sup> Locally, CXR has been employed as the first-line imaging tool, with CT reserved for specific scenarios and problem-solving situations.

The CXR abnormalities during COVID-19 chest infection span a range of findings. The most commonly described abnormalities are ground-glass opacification and areas of lung consolidation<sup>[17,18]</sup>

usually with bilateral involvement, lower zone and peripheral predilection.<sup>[12,17]</sup> Pleural effusion, pneumothorax and cavitation have also been reported. However, these are not common.<sup>[17,18]</sup> A recent South African (SA) study corroborated ground-glass opacification and consolidation as the most frequent radiographic findings, the majority of which were bilateral.<sup>[19]</sup> This study reported the presence of pleural effusion in 29.1% of cases,<sup>[19]</sup> which is high compared with international publications, and was considered unusual.<sup>[12,18,19]</sup>

CXR scoring systems have been developed and implemented as triaging and risk stratification tools in multiple settings with promising results, helping to quantify disease severity, prognosticating disease course and outcome and ultimately aiding clinical decision-making.<sup>[16,20-26]</sup> These scoring systems are based on airspace opacities and interstitial findings.<sup>[16,20,22]</sup>

The Brixia scoring tool, an 18-point scoring system that divides the lungs into six equal zones, incorporates the character of lung abnormalities and has defined a clear threshold score ( $\geq 8$  points) for severe disease.<sup>[22,23]</sup> Borghesi *et al.*<sup>[22]</sup> pioneered the Brixia scoring system and conducted a study that determined that the Brixia score, age and immunosuppression were factors that conferred the highest risk of death.<sup>[20]</sup> Their study did not include obesity or laboratory markers.<sup>[20]</sup> In addition, the Brixia scoring system consistently conferred good, and in certain instances, near-perfect inter-rater reliability in local and international studies.<sup>[16,19,27]</sup> To the authors' best knowledge, Brixia is the most widely investigated CXR scoring tool for COVID-19 pneumonia. When compared with various other scoring systems, Brixia demonstrated superior inter-rater reliability,<sup>[22,24]</sup> was quicker to use<sup>[27]</sup> and is the only chest radiographic scoring system designed specifically with COVID-19 in mind, with a clear threshold score for severe disease.<sup>[23]</sup> Table 1 compares these scoring systems.

The utility of the Brixia scoring system in a SA setting has only been evaluated once, and while that study found that higher Brixia scores were related to increased risk of demise, the study did not compare the scores with comorbid conditions or laboratory markers.<sup>[19]</sup> In addition to the authors' best knowledge, other international studies utilising the Brixia scoring tool have not found obesity, specific anthropometric parameters, diabetes mellitus and poor glycaemic control to have a powerful predictive power of final patient outcome.<sup>[16,20]</sup>

Locally and internationally, ethnicity and comorbid disease, such as obesity, diabetes mellitus and HIV, have been associated with increased COVID-19 mortality.<sup>[32-34]</sup> It has been shown that HIV-positive participants not receiving antiretroviral therapy are specifically at increased risk of death from COVID-19.<sup>[34]</sup> Obesity's role in the disease course and prognostication of hospitalised individuals with COVID-19 has been assessed, with multiple studies implicating it as a potential risk factor for progression to severe disease<sup>[35,36]</sup> and possibly higher risk of death.<sup>[37]</sup> A meta-analysis by Booth *et al.*<sup>[38]</sup> evaluating data from 76 studies found that severe obesity was a commonly reported comorbidity for adverse outcome. Early local epidemiological data indicated that around 5.5% of SA patients who died from COVID-19 suffered from obesity.<sup>[39]</sup> It has been demonstrated that diabetes mellitus and substandard glycaemic control may confer a worse prognosis in those hospitalised with COVID-19.<sup>[40,41]</sup>

The study focus was to evaluate the utility of the Brixia scoring system combined with participant demographics, comorbidities and laboratory parameters for predicting disease course and patient outcome (in-hospital demise v. discharge) in the SA context, where we have a high prevalence of HIV co-infection,<sup>[42]</sup> among other comorbidities.

## Methods

### Ethical considerations

Ethical clearance was secured from the Human Research Ethics committee of the University of the Witwatersrand (ref. no. M2011113).

### Population and sampling strategy

We identified hospitalised participants with RT-PCR confirmed COVID-19 pneumonia from a period spanning 1 May 2020 to 30 June 2020. Inclusion criteria comprised the following: (i) patient  $\geq 18$  years; (ii) a CXR, either mobile anteroposterior or erect posteroanterior, must have been performed while in the hospital receiving treatment for RT-PCR-confirmed COVID-19 pneumonia; and (iii) the clinical outcome, defined as either death or discharge from the hospital for each participant. A total of 263 participants were retrospectively enrolled in the study.

### Data collection

Participant demographic information, clinical parameters and laboratory data were collected. These data consisted of the participant sex, age, comorbidities (to meet the case definition of obesity a documented body mass index of  $\geq 30$  kg/m<sup>2</sup> must have been recorded), laboratory data, need for ventilatory support (both non-invasive and invasive techniques), length of stay, days spent in intensive care unit (ICU) and recovery or demise. The corresponding CXR for each participant was retrieved from the hospital picture archiving and communication system (PACS) (Philips Intellispace PACS Radiology version 4.4.532.1, SA).

### Image acquisition and scoring

All images were obtained using mobile computed radiographic and digital radiographic systems with tube voltages ranging from 60 to 70 kVp and exposure times of 3.2 mAs - 6.4 mAs. No grids were employed. All CXRs were obtained at the bedside as anterior-posterior projections to limit the risk of departmental contamination and cross-infection.

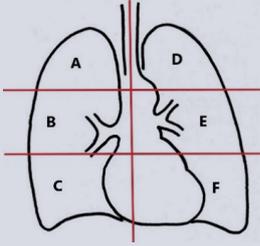
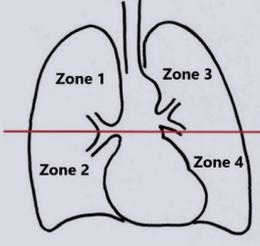
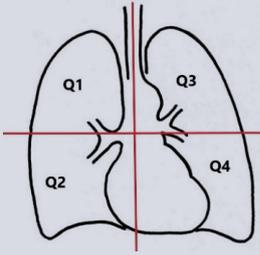
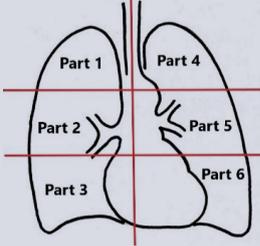
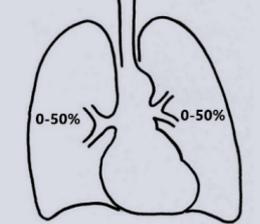
All participants had CXRs performed either on admission or based on clinical need as determined by the attending physician's local expertise – for example, if clinical deterioration was apparent. Where a participant had more than one radiograph, the radiograph with the most severe findings was chosen for the Brixia score calculation.

Each radiograph was independently scored by two general radiologists (2 and 15 years' experience) who were blinded to all clinical data, except for RT-PCR-confirmed COVID-19 pneumonia. Readers were instructed to score radiographs utilising the Brixia scoring system.<sup>[16,20,22]</sup> Readers were also required to comment on the technical quality of each CXR image as either good or poor, and needed to note if a pleural effusion was present.

### Statistical analysis

IBM SPSS version 28 (IBM Corp., USA) was used for the statistical analysis. The Shapiro-Wilk test showed that the data deviated from a normal distribution, and continuous variables were therefore expressed as median with interquartile range (IQR), while categorical data variables were expressed in frequencies and percentages. Inter-rater agreement between the radiologists for the Brixia scores was determined through the intraclass correlation coefficient (ICC). To investigate the association between demographic and clinical factors and patient outcomes, the Pearson  $\chi^2$  and Mann-Whitney U tests were used for categorical and continuous variables, respectively. Factors found to be significantly associated with patient outcomes were then included in binary logistic regression modelling to determine

**Table 1. Summary of pertinent radiographic scoring systems used to determine disease severity in COVID-19**

Scoring system	Method	Utility of scoring system
<p>Brixia<sup>[16,20,22,27-30]</sup></p> 	<p>The scoring system divides the radiograph into three zones for each lung. Each zone (A - F) is scored 0 - 3 based on the type of opacification in each zone (0 - normal; 1 - interstitial pattern; 2 - interstitial and alveolar opacities with interstitial predominance; 3 - alveolar and interstitial opacities with an alveolar predominance). This would yield a minimum score of 0 and a maximum score of 18.</p>	<p>Developed during the COVID-19 pandemic by thoracic radiologists, specifically for COVID-19<sup>[22,23]</sup></p> <p>This scoring tool and its utility in determining disease severity has been widely cited and investigated with good to excellent inter-rater reliability<sup>[16,20-22]</sup></p> <p>Assigning a Brixia score is faster compared with assigning and tallying a RALE score<sup>[27]</sup></p>
<p>24-point composite<sup>[24]</sup></p> 	<p>Drawing a line to equally divide the hila, each lung is divided into two zones. Four zones are scored on a 3-point scale for extent (no zonal involvement - 0; &lt;one-third of the zone - 1; 1-two-thirds of zone - 2; &gt;two-thirds of a zone - 3) and severity (no airspace disease - 0; opacification not obscuring bronchovascular markings - 1; partial bronchovascular obscuration - 2; complete alveolar and interstitial opacification - 3) of disease, instead of the six zones used in Brixia. The score is tallied to a potential maximum of 24 points.</p>	<p>Successfully helped predict outcome in those hospitalised with COVID-19, however the study by Reeves <i>et al.</i><sup>[24]</sup> demonstrated a lower inter-rater reliability compared with the Brixia score</p>
<p>RALE<sup>[27,31]</sup></p> 	<p>Lungs are separated into four quadrants. Each quadrant is allocated a consolidation score (0 - none; 1 - &lt;25%; 2 - 25 - 50%; 3 - 50 - 75%; 4 - &gt;75%) and a density score (1 - hazy; 2 - moderate; 3 - dense). The consolidation and density scores are multiplied and tallied for a potential maximum of 48 points.</p>	<p>Developed in the pre-COVID-19 era with several scoring steps involved.<sup>[31]</sup> Au-Yong <i>et al.</i><sup>[27]</sup> found that applying the RALE score took almost half a minute longer per participant, compared with the Brixia scoring tool</p>
<p>Pennine<sup>[26]</sup></p> 	<p>The lung divisions are similar to Brixia (6 parts). Each part is scored 0 - 2 (0 - no opacity; 1 - ground glass opacity; 2 - consolidation) based on severity of involvement. A maximum score would tally to 12 points.</p>	<p>To the authors best knowledge, it has not been as widely cited and investigated as the Brixia scoring tool</p>
<p>Percentage lung involvement<sup>[16,27]</sup></p> 	<p>This score entails a visual estimate of lung opacification for each lung from 0 - 50%. If both lungs are maximally affected the percentage of involvement would tally to 100%.</p>	<p>Au-Yong <i>et al.</i><sup>[27]</sup> found that it was simple and fast to assign a percentage of lung involvement; however, in their study comparing the inter-rater reliability for this system, it was inferior to the Brixia scoring tool</p>

whether they were significant predictors of patient death. The logistic regression modelling consisted of initial univariate analyses to select the patient and clinical factors to include as covariates in the subsequent multivariate modelling. This selection was based on a less strict cut-off of  $p < 0.20$  to avoid excluding variables that could be associated with patient death. Confounding was assessed by backward elimination of non-significant predictors, and the Hosmer and Lemeshow test ascertained if the final model was a good fit.

## Results

Within the study period, 303 patients tested RT-PCR positive, and 265 had CXRs. Those without CXRs were excluded. Two further participants were excluded, the first owing to age (<18 years), while the second participant's final clinical outcome (in-hospital demise v. discharge) could not be traced. Ultimately 263 participants were enrolled for the study. The demographic, clinical and laboratory details are summarised in Tables 2 and 3. The study population was almost evenly split by sex, with 134 males (51%) and 129 females (49%). The median age was 47 years (IQR = 20; 95% CI 46.5 - 59.9). Most participants were black (221; 84%). There were 7 (5.4%) pregnant participants. The most common comorbid condition was hypertension (101; 38.4%), followed by diabetes (66; 25.1%), obesity (51; 19.4%) and HIV (41; 15.6%). Only 6 (2.3%) participants were noted to have active pulmonary tuberculosis.

The clinical course is summarised in Table 4, while the final clinical outcome (in-hospital demise v. discharge) is summarised in Tables 5A and 5B. The length of stay in hospital was recorded for 258 of the individuals, with the median length of stay found to be 7.5 days (IQR = 7; 95% CI 8.2 - 9.7). A total of 54.1% of patients required

some level of respiratory support, most frequently via a rebreather mask (95; 36.7%).

Some 15.9% of participants were in the ICU, and the median length of stay in ICU was 6.5 days (IQR = 8; 95% CI 6.5 - 12.5). Twenty-two of the 30 intubated participants died (73.3%;  $p < 0.001$ ), v. 28 participants from the 233 non-intubated group (12%;  $p < 0.001$ ).

In total, 50 (19%) patients died in hospital, and these patients were older than those who survived, with a median age of 55 years (IQR = 23; 95% CI 50.5 - 58.7) for those who died v. 46 years (IQR = 20; 95% CI 45 - 48.6) for those who lived ( $p = 0.01$ ). There was a higher mortality among males (24%) than females (14%) ( $p = 0.04$ ), and among patients with one or more comorbid conditions compared with those without (23% v. 9.2%;  $p = 0.01$ ). In addition, a higher proportion of patients with obesity, chronic kidney disease and underlying chronic cardiovascular disease died compared with those without these conditions ( $p < 0.05$ ). However, neither HIV co-infection nor diabetes mellitus were linked to increased mortality. Deceased patients had significantly higher C-reactive protein (CRP) counts, lactate dehydrogenase (LDH) levels, and neutrophil counts ( $p < 0.001$ ). Lymphopenia was a common finding, and the lymphocyte count was lower for the participants who died ( $p = 0.05$ ). HbA1c value for diabetic participants who died was higher (11.3% v. 9.5%,  $p = 0.07$ ) but this difference was not statistically significant.

Brixia scores assigned by the readers ranged from 0 to 18 (Fig. 1A-B). The averaged median Brixia scores for patients who died were significantly higher than for those who survived: median score 14.5 (IQR = 7.5; 95% CI 11.6 - 14.4) v. 9.0 (IQR = 8.8; 95% CI 8.4 - 9.8), respectively ( $p = 0.001$ ). The inter-rater agreement for Brixia score calculation between readers was good (ICC 0.77; 95% CI 0.6 - 0.85;  $p < 0.001$ ) (Tables 6 and 7). Notably, even when readers indicated that the radiograph was of a technically poor quality, this did not significantly alter agreement (ICC 0.78; 95% CI 0.62 - 0.88;  $p < 0.001$ ) (Table 7). Only 10 patients were assessed to have a pleural effusion. The ICC for this small cohort was 0.86 (Table 7).

The multivariable logistic regression analysis is summarised in Table 8. Brixia score, age, male gender and obesity were found to be significant independent predictors of patient death. CRP was the only laboratory marker found to have significant predictive power for in-hospital death. Receiver operating curve (ROC) analysis was conducted for the predictive variables (Figs 2A-C). The models with the best predictive power for in-hospital demise incorporated Brixia score, age, male gender and obesity (area under curve (AUC) = 0.78; 95% CI 0.70 - 0.85;  $p < 0.001$ ; sensitivity 84%; specificity 63%) as well

**Table 2. Descriptive statistics of categorical variables (N=263)**

Variable	n (%)
Gender	
Male	134 (51)
Female	129 (49)
Race	
Black	221 (84)
Indian/Asian	27 (10.3)
White	10 (3.8)
Mixed ethnicity	5 (1.9)
Comorbidities	
Comorbid condition (overall)	187 (71.1)
Hypertension	101 (38.4)
DM2	65 (24.7)
DM1	1 (0.4)
Obesity	51 (19.4)
HIV	41 (15.6)
Chronic kidney disease	16 (6.1)
IHD	8 (3.1)
Other chronic CVD	8 (3.1)
Active tuberculosis	6 (2.3)
COPD	7 (2.7)
Chronic lung disease other than COPD	3 (1.1)
Liver cirrhosis	4 (1.5)
CVA	1 (0.4)
Previous organ transplant	1 (0.4)
Pregnant	7/129 (5.4)

DM2 = type 2 diabetes mellitus; DM1 = type 1 diabetes mellitus; IHD = ischaemic heart disease; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident.



**Fig. 1. The Brixia scoring system: each lung is divided into three equal zones (A - F). 1A: For a good-quality radiograph the upper line is drawn along the lower wall of the aortic arch. The lower line is drawn at the inferior margin of the right pulmonary vein. 1A totals a score of 0. 1B: If one is unable to clearly discern the anatomical landmarks on the radiograph, the lungs are divided into three zones of equal size for scoring on each side. 1B was assigned a score of 15 by both readers. Brixia scoring system source: developed by Borghesi et al.<sup>[22]</sup>**

**Table 3. Descriptive demographic, clinical and laboratory statistics for continuous variables (N=263)**

Variable	n (%)	Normal range	Median	IQR	95% CI
Age (years)	263/263 (100)	-	47	20	46.5 - 49.9
HIV CD4 count (cells/μL)	34/41 (83)	332 - 1642	404	503.2	306.5 - 558.5
HIV viral load (copies/mL)	33/41 (80)	<20	0	30	-31 140.3 - 98 439.3
Diabetes: HbA1c (%)	55/66 (83)	*	9.8	4	9.4 - 11.1
WCC (× 10 <sup>9</sup> /L)	260/263 (99)	3.92 - 10.40	8	4.8	8.3 - 9.5
Hb (g/dL)	260/263 (99)	13.4 - 17.5	13.7	2.8	13.1 - 16.6
Platelets (× 10 <sup>9</sup> /L)	260/263 (99)	171 - 388	249.5	150.7	255.5 - 283.6
Neutrophils (× 10 <sup>9</sup> /L)	203/263 (71)	1.60 - 6.98	5.8	4.2	6.2 - 7.5
Lymphocytes (× 10 <sup>9</sup> /L)	209/263 (79)	1.40 - 4.20	1.2	1	0 - 6
CRP (mg/L)	257/263 (98)	≤10	96	165	109.3 - 134.6
PCT (μg/L)	187/263 (71)	†	0.2	0.7	1.5 - 5
Beta-D-glucan (pg/mL)	104/263 (40)	≤80	39	48.2	53 - 83.3
Sodium (mmol/L)	259/263 (98)	136 - 145	138	6	137.3 - 138.9
Potassium (mmol/L)	260/263 (99)	3.5 - 5.1	4.45	1.1	4.4 - 5.4
Urea (mmol/L)	260/263 (99)	2.1 - 7.1	5.6	4.9	7.1 - 9.5
Creatinine (μmol/L)	260/263 (99)	64 - 104	93.5	55.7	104.4 - 152
D-dimer (mg/L)	221/263 (84)	0 - 0.25	0.6	1.5	2 - 4.5
Ferritin (ng/mL)	191/263 (73)	13 - 150	782.5	1065	699.7 - 1 291
hs-troponin-T (ng/L)	164/263 (62)	14 - 100	9	17	16.8 - 35.6
LDH (U/L)	167/263 (63)	100 - 190	452	316	487.3 - 579.8
Total protein (g/L)	239/263 (91)	60 - 78	71	11	70.2 - 72.6
Albumin (g/L)	244/263 (93)	35 - 52	37	8	36.4 - 37.9
Total bilirubin (μmol/L)	246/263 (94)	5 - 21	8	7	8.9 - 13.9
Conjugated bilirubin (μmol/L)	246/263 (94)	0 - 3	3	3	3.8 - 6.5
ALT (U/L)	247/263 (94)	10 - 40	27	22	26.3 - 79.1
AST (U/L)	247/263 (94)	15 - 40	41	28	34.1 - 118.2
ALP (U/L)	244/263 (93)	53 - 128	92.3	47.5	90.6 - 101.8
GGT (U/L)	244/263 (93)	<68	58	72.7	87.6 - 122.5
IL-6 (pg/mL)	6/263 (2)	≤7.0	91.8	483.2	-350.2 - 1061.4

IQR = interquartile range; CI = confidence interval; HbA1C = glycated haemoglobin; WCC = white cell count; Hb = haemoglobin; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; IL-6 = interleukin-6.  
 \*Target of <7.0 for optimal control.  
 †PCT ranges: <0.1μg/L = no signs of any bacterial infection; 0.1 - 0.25μg/L = localised bacterial infection unlikely; 0.25 - 0.5μg/L = localised bacterial infection possible; >0.5 μg/L = suggestive of a lower respiratory tract bacterial infection; 0.5 - 2 μg/L = systemic infection is possible; 2 - 10 μg/L = suggestive of systemic infection; >10 μg/L = severe systemic infection/septic shock.

**Table 4. Clinical disease course**

Variable	n (%)	Median, days	IQR, days	95% CI
Respiratory support				
None	119/259 (46)	-	-	-
Rebreather mask	95/259 (36.7)	-	-	-
HFNC	13/259 (5)	-	-	-
Non-invasive ventilation	2/259 (0.8)	-	-	-
Invasive mechanical ventilation	30/259 (11.6)	-	-	-
Hospital/ICU stay				
Length of in-hospital stay (days)	258/263 (98)	7.5	7	8.2 - 9.7
Number of patients in ICU care	42/263 (16)	-	-	-
Time spent in ICU (days)	42/263 (16)	6.5	8	6.5 - 12.5

IQR = interquartile range; CI = confidence interval; HFNC = high-flow nasal cannula; ICU = intensive care unit.

as a curve combining Brixia score and CRP (AUC = 0.78; 95% CI 0.71 - 0.85;  $p < 0.001$ ; sensitivity 81%; specificity 63%). The optimum cut-off values for Brixia score and age along the curve were 8 points and 43 years, respectively.

The same analysis was performed to extract variables that may be predictive of admission to the ICU. The predictive variables were the Brixia score (odds ratio (OR) = 1.1; 95% CI 1.0 - 1.3;  $p = 0.03$ ) and CRP (OR 1.0; 95% CI 1.0 - 1.0;  $p = 0.03$ ). However, the

predictive power of these factors was not particularly strong. When ROC-curve analysis was performed (not shown) for ICU admission as the end point, the AUCs for Brixia score and CRP were 0.69 and 0.62, respectively.

## Discussion

Our local study population was much younger than in most similar studies performed in the European setting.<sup>[16,20,21,43]</sup> In addition,

whereas these international studies were performed with mostly (sometimes exclusively) white participants,<sup>[20-22]</sup> most patients in our study were black.

The most commonly encountered comorbidities listed are similar to what has been described in other local studies.<sup>[34]</sup> However, we noted a larger proportion of obese patients, which could be explained by 'missing' obesity data in the cohort described by Jassat *et al.*<sup>[34]</sup> The in-hospital death rate of our sample is comparable with national figures.<sup>[34]</sup>

Borghesi *et al.*<sup>[20]</sup> did not include obesity or CRP in their final predictive models for the Brixia score. Similar to other data, however, we identified both obesity and CRP as predictors of in-hospital mortality,<sup>[37,38,40,44]</sup> and CRP was successfully introduced into a risk stratification model with the Brixia score. Comparable with local and international publications,<sup>[40,43]</sup> LDH was also statistically significantly higher for participants who died, but could not be introduced into a multivariate prediction model for participant demise. In accord with Venturas *et al.*<sup>[45]</sup> we also concluded that being HIV-positive did not confer a higher risk of in-hospital fatality. However, subsequent work has suggested a higher fatality rate for HIV-positive patients, in particular those not on antiretroviral therapy (ART).<sup>[34]</sup> Although we could not accurately identify patients who were on ART, the median viral load for HIV-positive individuals in our sample was 0 (recorded for 80.5% of the HIV-positive participants), which suggests that most participants in our sample were likely receiving ART. However, the number of HIV-positive participants in our sample was small (41; 15.6%), and this may explain the differences in outcomes between our data and those described by Jassat *et al.*<sup>[34]</sup>

International publications using ICC to assess Brixia score inter-rater agreement have yielded excellent results.<sup>[16]</sup> Similarly, in our setting the inter-rater reliability between the two general radiologists was good (ICC 0.77) despite differing levels of experience and no prior exposure to the Brixia scoring system. Another local publication also concluded good inter-rater agreement (Kappa = 0.64) for Brixia scoring between a registrar with 2 years of experience and a radiologist with 10 years' experience and subspecialty training in thoracic imaging.<sup>[19]</sup>

The optimal Brixia cut-off value along the ROC curve of 8 points in our study population affirms the findings by Borghesi *et al.*,<sup>[20]</sup> whereas the optimal age cut-off was much younger in our study (43 years v. 71 years). This is accounted for by a much younger study population in our sample.

This study is the first local effort to develop risk stratification models to predict clinical outcomes for patients hospitalised with COVID-19 pneumonia, showing that a higher Brixia score, increasing age, male gender, obesity and CRP were risk factors conferring the highest risk of in-hospital mortality. After multiple models were considered, the two best models combined Brixia score, increasing age, male gender and obesity as the first model, and Brixia score combined with CRP as the second model. International papers evaluating the utility of the Brixia score have yielded similar results. The models from this pilot study require follow-up studies with validation in larger clinical data sets. Thereafter, a potential use of these models may be to consolidate the models into existing medical records of patients upon hospital admission with computational risk stratification of death. This may help direct therapeutic decisions such as early consideration for more aggressive care in a high care/ICU setting (which is a limited resource in our local setting) and early consideration for immunomodulatory agents such as higher-dose dexamethasone, baricitin and tocilizumab. We recommend validation studies of these models in the pre-vaccination era and follow-up study during the era of vaccination.

**Table 5A. Final clinical outcome (in-hospital death) categorical variables**

Variable	Deceased, n (%)	p-value
Gender		
Male	32/134 (24)	0.04
Female	18/129 (14)	
Race		
Black	39/221 (17.6)	0.59
Indian/Asian	7/27 (25.9)	
White	3/10 (30)	
Mixed ethnicity	1/5 (20)	
Comorbid condition		
Comorbid condition (overall)	43/187 (23)	0.01
No comorbidity	7/76 (9.2)	
Hypertension	22/101 (21.8)	0.42
No hypertension	28/162 (17.3)	
DM	17/66 (25.8)	0.11
No DM	33/197 (16.8)	
Obesity	19/51 (37.3)	<0.001
No obesity	31/212 (14.6)	
HIV	5/41 (12.2)	0.282
No HIV	45/222 (20.3)	
Chronic kidney disease	6/16 (37.5)	0.05
No chronic kidney disease	44/247 (17.8)	
IHD	2/8 (25)	0.65
No IHD	48/255 (18.8)	
Other chronic CVD	4/8 (50)	0.02
No other CVD	46/254 (18.2)	
Active TB	0/6 (0)	0.23
No active TB	50/257 (19.5)	
COPD	3/7 (43)	0.103
No COPD	47/256 (18.4)	
Chronic lung disease other than COPD	1/3 (33.3)	0.47
No other chronic lung disease	49/260 (18.8)	
Liver cirrhosis	2/4 (50)	0.111
No liver cirrhosis	48/259 (18.5)	
CVA	0/1 (0)	0.627
No CVA	50/262 (19.1)	
Previous organ transplant	1/1 (100)	0.04
No previous organ transplant	49/262 (18.7)	
Pregnancy	2/7 (28.6)	0.246
No pregnancy	16/123 (13)	

DM = diabetes mellitus; IHD = ischaemic heart disease; CVD = cardiovascular disease; TB = tuberculosis; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident.

### Study limitations

This was a single-centre retrospective study. No comparison was made with patients with other causes for radiographic lung changes such as non-COVID-19 pneumonia or heart failure. Two general radiologists with differing levels of experience allocated Brixia scores. The gold standard would have been to involve subspecialised thoracic radiologists; however, these are not widely available (if at all) in SA. It must, however, be argued that for the scoring system to have local applicability, the agreement between general radiologists, as the available resource, must be good, as was the case in our study. The study cohort is from early in the pandemic prior to the vaccination era.

**Table 5B. Final clinical outcome (in-hospital demise) continuous variables**

Variable	Normal range	Median (n; %)	IQR	95% CI	p-value
Age in years (died)	-	55 (50; 19)	23	50.5 - 58.7	<0.001
Age in years (discharged)		46 (213; 81)	20	45.0 - 48.6	
HbA1c (died)	*	11.3 (15; 27.2)	5.1	9.65 - 12.89	0.07
HbA1c (discharged)		9.5 (40; 72.8)	3.73	8.95 - 10.85	
WCC (× 10 <sup>9</sup> /L) (died)	3.92 - 10.40	9.7 (49; 18.8)	6.51	9.4 - 12.47	<0.001
WCC (× 10 <sup>9</sup> /L) (discharged)		7.54 (211; 81.2)	4.57	7.81 - 9.17	
Hb (g/dL) (died)	13.4 - 17.5	13.6 (49; 18.8)	2.7	12.72 - 13.88	0.4
Hb (g/dL) (discharged)		13.8 (211; 81.2)	2.9	13.13 - 17.36	
Platelets (× 10 <sup>9</sup> /L) (died)	171 - 388	280 (49; 18.8)	159.5	239.18 - 307.27	0.7
Platelets (× 10 <sup>9</sup> /L) (discharged)		248 (211; 81.2)	148	253.21 - 284.30	
Neutrophils (× 10 <sup>9</sup> /L) (died)	1.60 - 6.98	7.45 (38; 18.7)	5.12	6.99 - 10.46	<0.001
Neutrophils (× 10 <sup>9</sup> /L) (discharged)		5.7 (165; 81.3)	3.97	5.81 - 7.22	
Lymphocytes (× 10 <sup>9</sup> /L) (died)	1.40 - 4.20	1.11 (39; 18.7)	0.96	-7.18 - 25.92	0.05
Lymphocytes (× 10 <sup>9</sup> /L) (discharged)		1.3 (170; 81.3)	1.03	1.36 - 1.73	
CRP (mg/L) (died)	≤10	203 (48; 18.7)	196.5	166.16 - 230.38	<0.001
CRP (mg/L) (discharged)		79 (209; 81.3)	127	91.83 - 117.09	
PCT (µg/L) (died)	†	0.99 (40; 21.4)	5.18	2.13 - 9.18	<0.001
PCT (µg/L) (discharged)		0.16 (147; 78.6)	0.45	0.63 - 4.63	
Beta-D-glucan (pg/mL) (died)	≤80	49 (25; 24)	62.5	43.68 - 128.96	0.17
Beta-D-glucan (pg/mL) (discharged)		37 (79; 76)	44	47.66 - 77.61	
Sodium (mmol/L) (died)	136 - 145	138 (50; 19.3)	9	136.80 - 141.44	0.8
Sodium (mmol/L) (discharged)		138 (209; 80.7)	6	137.07 - 138.70	
Potassium (mmol/L) (died)	3.5 - 5.1	4.5 (50; 19.2)	1.3	4.36 - 4.84	0.79
Potassium (mmol/L) (discharged)		4.4 (210; 80.8)	1.03	4.38 - 5.68	
Urea (mmol/L) (died)	2.1 - 7.1	7.55 (50; 19.2)	7.83	7.88 - 13.52	<0.001
Urea (mmol/L) (discharged)		5.3 (210; 80.8)	4.33	6.50 - 9.07	
Creatinine (µmol/L) (died)	64 - 104	110 (50; 19.2)	68.75	111.48 - 192.36	0.01
Creatinine (µmol/L) (discharged)		92 (210; 80.8)	51	94.71 - 150.56	
D-dimer (mg/L) (died)	0 - 0.25	0.85 (40; 18)	1.58	-0.38 - 8.85	0.27
D-dimer (mg/L) (discharged)		0.67 (181; 81.9)	1.58	1.87 - 4.30	
Ferritin (ng/mL) (died)	13 - 150	633 (36; 18.8)	865.75	599.22 - 1 304.56	0.43
Ferritin (ng/mL) (discharged)		531 (155; 81.2)	1111	649.04 - 1 361.99	
hs-Troponin-T (ng/L) (died)	14 - 100	23 (32; 19.5)	42	17.74 - 89.95	<0.001
hs-Troponin-T (ng/L) (discharged)		7 (132; 80.5)	12	11.75 - 27.34	
LDH (U/L) (died)	100 - 190	594.5 (32; 19.2)	307.75	538.11 - 716.14	<0.001
LDH (U/L) (discharge)		427 (135; 80.8)	303	458.44 - 564.42	
Total protein (g/L) (died)	60 - 78	70 (47; 19.7)	8	67.03 - 71.65	0.05
Total protein (g/L) (discharged)		72 (192; 80.3)	12	70.64 - 73.32	
Albumin (g/L) (died)	35 - 52	35 (48; 19.7)	6.75	32.73 - 36.44	<0.001
Albumin (g/L) (discharged)		38 (196; 80.3)	7	37.05 - 38.66	
Total bilirubin (µmol/L) (died)	5 - 21	10 (47; 19.1)	8	4.12 - 27.84	0.17
Total bilirubin (µmol/L) (discharged)		8 (199; 80.9)	7	9.01 - 11.76	
Conjugated bilirubin (µmol/L) (died)	0 - 3	4 (47; 19.1)	5	1.5 - 15.01	0.01
Conjugated bilirubin (µmol/L) (discharged)		3 (199; 80.9)	3	3.78 - 5.14	
ALT (U/L) (died)	10 - 40	28 (47; 19)	22	22.08 - 59.88	0.98
ALT (U/L) (discharged)		27 (200; 81)	23.5	23.19 - 87.88	
AST (U/L) (died)	15 - 40	43 (47; 19)	33	44.23 - 105.85	0.05
AST (U/L) (discharged)		40 (200; 81)	25	24.94 - 128.01	
ALP (U/L) (died)	53 - 128	87 (47; 19.3)	47	82.03 - 101.80	0.91
ALP (U/L) (discharged)		85 (197; 80.7)	49	90.66 - 103.82	
GGT (U/L) (died)	<68	55 (47; 19.3)	70	48.83 - 156.62	0.14
GGT (U/L) (discharged)		59 (197; 80.7)	72.5	87.95 - 123.36	
IL-6 (pg/mL) (died)	≤7	130.2 (3; 50)	-	-6.14 - 216.34	0.51
IL-6 (pg/mL) (discharged)		48 (3; 50)	-	-1 803.39 - 3 015.45	

IQR = interquartile range; CI = confidence interval; HbA1c = glycated haemoglobin; WCC = white cell count; Hb = haemoglobin; CRP = C-reactive protein; PCT = procalcitonin; LDH = lactate dehydrogenase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase. \*Target of <7.0 for optimal control. †PCT ranges for lower respiratory tract infection: < 0.1 µg/L = no signs of any bacterial infection; 0.1 - 0.25 µg/L = localised bacterial infection unlikely; 0.25 - 0.5 µg/L = localised bacterial infection possible; >0.5 = suggestive of a lower respiratory tract bacterial infection; 0.5 - 2 µg/L = systemic infection is possible; 2 - 10 µg/L = suggestive of systemic infection; >10 µg/L = severe systemic infection/septic shock.

**Table 6. Brixia score radiograph analysis\***

Variable	Deceased			Alive			p-value
	Median	IQR	95% CI	Median	IQR	95% CI	
Brixia score reader 1	15.5	5	12.4 - 14.9	10	7.5	9.5 - 10.7	<0.001
Brixia score reader 2	14	12	10.7 - 14.1	7	10.5	7.2 - 8.9	<0.001
Average Brixia score	14.5	7.5	11.6 - 14.4	9	8.8	8.4 - 9.8	<0.001

IQR = interquartile range; CI = confidence interval.  
 \*Scores were obtained by two independent general radiologists blinded to all clinical data including patient outcome.

**Table 7. Inter-rater agreement for Brixia score analysis (N=263)**

Variable	n (%)	ICC	p-value
Brixia score, all cases	263 (100)	0.77	<0.001
Brixia score, poor-quality films	40 (15.2)	0.78	<0.001
Brixia score, participants with pleural effusion	10 (4)	0.86	<0.001

ICC = intraclass correlation coefficient (for ICC calculation an absolute agreement definition was used).

**Table 8. Multivariable logistic regression analysis of statistically significant variables**

Variable	OR (95% CI)	p-value
Brixia score	1.20 (1.10 - 1.20)	<0.001
Age	1.04 (1.04 - 1.10)	<0.001
Male	1.90 (0.99 - 3.97)	0.04
Obesity	2.30 (1.10 - 5.00)	<0.001
CRP	1.01 (1.004 - 1.01)	<0.001

OR = odds ratio; CI = confidence interval.

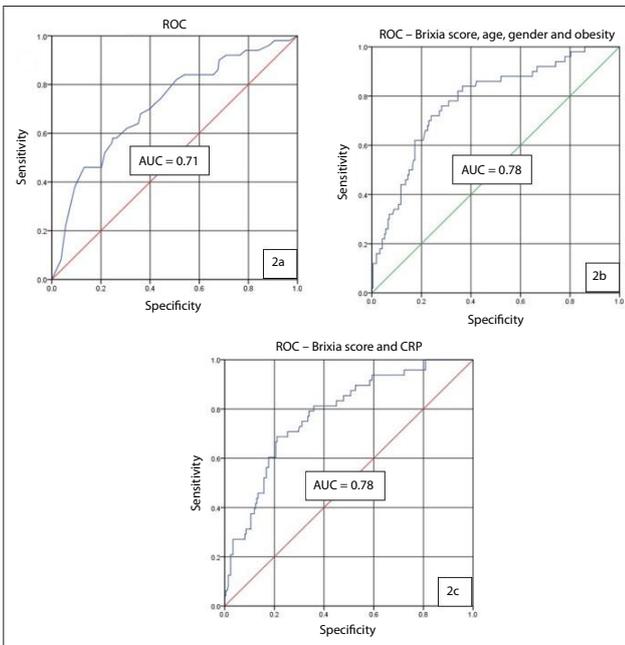


Fig. 2A. Receiver operating curve (ROC) for Brixia score alone (area under curve (AUC) = 0.71).

Fig. 2B. Receiver operating curve (ROC) combining Brixia score, age, male gender and obesity (area under curve (AUC) = 0.78).

Fig. 2C. Receiver operating curve (ROC) combining Brixia score with C-reactive protein (CRP) count (area under curve (AUC) = 0.78).

**Conclusion**

These are the first predictive models using a CXR scoring system that incorporate comorbidities and laboratory markers, and which was developed in a SA setting. The Brixia scoring system has been validated as a reliable tool internationally. This study shows that when used in conjunction with age, male gender, obesity and CRP, it is also a promising risk stratification tool locally. This may help inform the clinical decision pathway in resource-limited settings like ours during future waves of COVID-19.

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