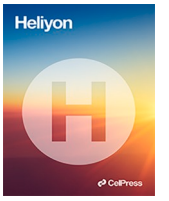
Heliyon 9 (2023) e21733

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



COVID-19: An evaluation of predictive scoring systems in South Africa

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A B S T R A C T

Background: | The Coronavirus Disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2, has resulted in more than 700 million cases worldwide. Sepsis and pneumonia severity scores assist in risk assessment of critical outcomes in patients with COVID-19. This allows healthcare workers to triage patients, by using clinical parameters and limited special investigations, thus offering the most appropriate level of care.
Methods: | A retrospective cohort study of 605 adult patients hospitalised with moderate to severe COVID-19, at a tertiary state hospital in South Africa. Evaluating the utility of the CURB65, NEWS2 and ISARIC-4C Mortality Score, in predicting critical outcomes, using clinical characteristics on admission. Outcomes included in-hospital mortality, invasive mechanical ventilation, and intensive care unit admission (ICU). Performance of severity scores and risk factors was assessed by area under the receiver operator characteristics (AUROC) analysis and logistic regression.
Findings |: A total of 605 records were used, 129 (21 %) non-survivors, 101 (17 %) ICU admissions and 77 (13 %) requiring invasive ventilation. Greater odds of mortality was associated with moderate and severe risk groups of the CURB65, ISARIC-4C and NEWS2 score. Mortality AUROC curve analysis for the CURB65 score was 0·76 (95 % CI: 0·71–0·8), 0·77 (95 % CI: 0·73–0·81) for the ISARIC-4C and 0·77 (95 % CI: 0·73–0·82) for the NEWS2 score. The CURB65 score had a sensitivity of 86 % with 12·8 % mortality, ISARIC-4C score a sensitivity of 87·6 % with 8 % mortality and NEWS2 score a sensitivity of 92·2 % with 8·6 % mortality.
Interpretation |: In 605 hospitalised patients with moderate to severe COVID-19, predominantly infected by the ancestral strain, good performance of the NEWS2 and ISARIC-4C score in predicting in-hospital mortality was noted. The CURB65 score had a high mortality rate in its low-risk group suggesting unexplained risk factors, not accounted for in the score, thus limiting its utility in the South African setting.

1. Introduction Research in context

1.1. Evidence before this study

Critical care service use increased exponentially during the COVID-19 pandemic with global reports of healthcare facilities being overwhelmed and ICU bed shortages. Due to the anticipated shortage of ICU beds and ventilators in low-middle-income countries (LMICs) with limited resources, there was a need to develop local triage standard operating procedures. These protocols aimed to ensure fair and equitable access to critical care services. Clinical severity tools and frailty scores were adopted as preliminary triage measures. We searched PubMed and Clinical Query using the terms “SARS-CoV-2”, “severity of illness index” and “community acquired infections” following which restricted searches involving the terms “CURB65”, “NEWS” and “ISARIC” were performed.

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https://doi.org/10.1016/j.heliyon.2023.e21733
Received 28 June 2023; Received in revised form 25 October 2023; Accepted 26 October 2023
Available online 4 November 2023

According to South African and global recommendations, low-risk groups in Non-SARS-CoV-2 community acquired pneumonia, as determined by CURB65 scores, have a predicted mortality of below 4 %, therefore outpatient management is advised. Recent studies on SARS-CoV-2 pneumonia abroad have shown higher mortality rates above 10 % in low-risk groups. There is a paucity of data on clinical prediction tools in Africa, notably the NEWS2 score and the ISARIC-4C Mortality score.

1.2. Added value of this study

We evaluated in-hospital mortality predictions of the CURB65 score alongside the recent NEWS2 and ISARIC-4C Mortality score in hospitalised patients with moderate to severe COVID-19. Severity grades ranged from low risk to very-high risk with our study showing a mortality rate of 12.8 % in the low-risk group of the CURB65 score whereas low risk groups of the NEWS2 and ISARIC-4C Mortality score had mortality rates of 2.3 % and 1.6 % respectively. Each score was assessed at literature defined thresholds for clinical intervention with the NEWS2 score being the most sensitive severity scoring system at 92.2 %.

1.3. Implications of all available evidence

In SARS-CoV-2 pneumonia, the CURB65 score shows a high mortality rate in low-risk stratified patients. However, there is conflicting data from South African studies regarding the use of the CURB65 score in Non-SARS-CoV-2 community acquired pneumonia. The paucity of clinical prediction tool data in South Africa and other African LMIC's for the NEWS2 score and ISARIC-4C mortality score underscore the need for further research in the region with our study showing improved sensitivity of the NEWS2 and ISARIC-4C score in predicting low and intermediate risk group mortality.

2. Background

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in more than 700 million cases worldwide as of early 2023 [1]. Case severity ranges from asymptomatic viral infection to severe illness requiring hospitalisation and intensive care unit (ICU) admission. In addition to the development of novel scoring systems, the pandemic prompted the evaluation of existing sepsis and pneumonia severity scores to classify illness severity and predict mortality outcomes upon presentation to healthcare services [2–5]. Standardised scoring systems allow healthcare workers to triage patients with severe COVID-19 using clinical parameters and limited special investigations, available at the bedside, to offer the most appropriate level of care [6–8].

Commonly utilised scores include the National Early Warning System Score 2 (NEWS2), ISARIC WHO Clinical Characterization Protocol 4C Mortality score (ISARIC-4C) and the CURB-65 score. The NEWS2 score, adopted by the National Health Service (NHS) in the United Kingdom, incorporates physiologic parameters for assessment of illness severity, and is highly predictive of mortality in sepsis where an aggregate score of five is associated with a 23 % risk of mortality. Other predictive tools such as the ISARIC-4C score and CURB-65 pneumonia severity score include demographic and biochemical data [9,10]. The ISARIC-4C score categorised into risk groups infers a mortality risk of 1·2 % in the low risk group as compared to 61·5 % in the very high-risk group [10]. The CURB-65 score is a commonly used severity assessment model for adult patients with community acquired pneumonia classified into three treatment groups: non-severe low risk, non-severe moderate risk, and severe risk with a predicted 30 day all-cause mortality of 1·5 %, 9·2 % and 22 % for each grade respectively [6,11,12].

In one study these scores showed limited utility in predicting adverse outcomes among patients with COVID-19 as all scores were poorly predictive for ICU admission [13]. Preliminary data in a multi-hospital cohort using the NEWS2 score for COVID-19 was shown to have a greater negative predictive value for early mortality outcomes [13]. Whilst the above study described limited utility in predicting critical outcomes in COVID-19, a subsequent study comparing outcomes of the NEWS2 score and COVID-GRAM, showed that a NEWS2 score of four had a positive likelihood ratio of 2·9 for critical illness [14]. A retrospective analysis of the CURB-65 score prior to the pandemic at a South African institution, albeit a modest cohort, highlighted its use in reducing hospital admissions at point of emergency care in community acquired pneumonia [6]. Utility scores have shown benefit in treatment decisions involving high flow nasal cannula oxygenation where traditional practices involving early intubation may not be feasible due to limited availability of intensive care services [5]. Research validating these scoring systems is needed to reduce mortality and direct healthcare services effectively and equitably in a region with limited resources. To our knowledge, no studies in South Africa, have compared the effectiveness of these scoring systems in predicting outcomes in patients with moderate to severe COVID-19. Therefore, the aim of our study was to evaluate the utility of severity scoring systems for risk stratifying patients with COVID-19 in a low-middle-income country (LMIC) setting.

3. Methods

3.1. Study design and participants

The study was a retrospective single centre cohort study. It included 605 adults admitted with moderate to severe COVID-19, during the period of March 2020 to September 2020, at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary state hospital in South Africa. The cohort included all adult inpatients diagnosed with COVID-19 by laboratory confirmed positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR), using oropharyngeal and naso-pharyngeal swabs, with the

predominant variant of concern (VOC) being the ancestral variant, Asp614Gly mutation, according to published data by the National Institute of Communicable Diseases (NICD) [15]. Exclusions of analysis were age <18 years, pregnancy, and outpatient observation. Approval for the study was obtained from the University of the Witwatersrand Medical Human Research Ethics Committee [M220116].

3.2. Study data

All relevant clinical data was anonymously extracted from a password protected electronic database and transferred to a local secure data research application. Demographic and clinical data necessary for calculating the NEWS2, ISARIC-4C and CURB-65 scores were documented. Parameters of each score are available in Table 1. The NEWS2 score was calculated based on respiratory rate (breaths/min), peripheral oxygen saturation, systolic blood pressure (mmHg), pulse rate (beats/min), mental state, temperature (Celsius) and supplemental oxygen use [9]. The ISARIC-4C score was based on age (years), gender, number of comorbidities, respiratory rate (breaths/min), peripheral oxygen saturation, Glasgow coma scale, urea (mmol/L) and C-reactive protein (mg/L) [10]. Finally, the CURB-65 score which utilises age (years), mental state, urea (mmol/L), respiratory rate (breaths/min), systolic and diastolic blood pressure was calculated [11]. Demographic and clinical variables in the descriptive statistics were categorised based on scoring system factors. However, continuous variables with a low cell frequency were treated as continuous or re-categorised during inferential analysis. Based on the aggregate score, patients were classified into three risk groups: low, medium, and high risk, with an additional very-high risk category in the ISARIC-4C mortality score.

Table 1
NEWS2, ISARIC-4C and CURB65 scoring systems.

CURB65 Score [1]								
Parameter	Threshold				Points			
Mental status	Confusion				1			
Urea (mg/L)	≥7·0				1			
Respiratory rate (breaths/min)	≥30				1			
Blood pressure (mmHg)	Systolic ≤90 or Diastolic <60				1			
Age (years)	>65 years				1			
Aggregate Score	**Risk**				**Mortality (%)**			
0–1	Low risk				0–4			
2	Moderate risk				17			
≥3	Severe risk				26–33			
ISARIC-4C score [2]								
Parameter	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age (years)	<50		50–59		60–69		70–79	≥80
Sex at birth	Female	Male						
No. of comorbidities	0	1	≥2					
Respiratory rate (breaths/min)	<20	20–29	≥30					
SpO2 (%)	≥92		<92					
Glasgow coma scale	15		<15					
Urea (mmol/L)	<7	7–14		>14				
C-Reactive protein (mg/L)	<50	50–99	≥100					
Aggregate Score	**Risk**				**Mortality (%)**			
0–3	Low				1.2			
4–8	Intermediate				9.9			
9–14	High				31.4			
≥15	Very-high				61.5			
NEWS2 score [3]								
Parameter	**+ 3**	**+ 2**	**+ 1**	**0**	**+ 1**	**+ 2**	**+ 3**	
Respiratory rate (breaths/min)	≤8		9–11	12–20		21–24	≥25	
Sp02 Scale 1 (%)	≤91	92–93	94–95	≥96				
Sp02 Scale 2 (%)	≤83 (Air)	84-85 (Air)	86-87 (Air)	88-92 or ≥ 93 (Air)	93-94 (oxygen)	95-96 (oxygen)	≥97 (oxygen)	
Air or Oxygen		Oxygen		Air				
Systolic blood pressure (mmHg)	≤90	91–100	101–110	112–219			≥220	
Pulse (beats/min)	≤40		41–50	51–90	91–110	111–130	≥131	
Mental status				Alert			Confusion	
Temperature (°C)	≤35		35·1-36	36·1-38	38·1-39	>39		
Aggregate Score	**Risk**		**Response**		**Response team**			
0–4	Low		Ward-based response		General management			
5–6	Medium		Threshold for urgent response		Management of acutely ill patients			
≥7	High		Urgent or emergency response		Staff with critical care skills.			

Table 2
Risk severity grade according to CURB65, ISARIC-4C and NEWS2 score and association with in-hospital mortality, ICU admission and invasive ventilation.

	In hospital mortality				ICU admission				Invasive ventilation			
	Survivor N (%)	Non-Survivor N (%)	COR[a] (95 % CI)	P[b]	ICU N (%)	Ward N (%)	COR[a] (95 % CI)	P[b]	Yes N (%)	No N (%)	COR[a] (95 % CI)	P[b]
N	476 (78·6)	129 (21·3)			101 (16·7)	504 (83·3)			77 (12·7)	528 (87·3)		
Risk group by CURB65 score												
Low	407 (86)	60 (47)	Reference	**<0·001**	69 (68)	398 (79)	Reference	**0·065**	48 (62)	419 (79)	Reference	**0·004**
Moderate	55 (12)	47 (36)	5·8 (3·61-9·32)		24 (24)	78 (15)	1·8 (1·05-2·30)		22 (29)	80 (15)	2·4 (1·37-4·20)	
Severe	14 (2·9)	22 (17)	10·7 (5·17–21·96)		8 (7·9)	28 (5·6)	1·7 (0·72-3·77)		7 (9·1)	29 (5·5)	2·1 (0·88-5·07)	
Risk group by ISARIC-4C score												
Low	99 (21)	2 (1·6)	Reference	**<0·001**	6 (5·9)	95 (19)	Reference	**<0·001**	4 (5·2)	97 (18)	Reference	**0·004**
Intermediate	230 (48)	35 (27)	7·5 (1·77-31·92)		44 (44)	221 (44)	3·2 (1·30-7·65)		33 (43)	232 (44)	3·5 (1·19-10·0)	
High	136 (29)	83 (64)	30·2 (7·26–125·76)		50 (50)	169 (34)	4·7 (1·94-11·33)		39 (51)	180 (34)	5·3 (1·82-15·14)	
Very High	11 (2·3)	9 (7·0)	40·5 (7·74–211·72)		1 (1·0)	19 (3·8)	0·8 (0·09-7·32)		1 (1·3)	19 (3·6)	1·3 (0·14-12·06)	
Risk group by NEWS2 score												
Low	163 (34)	3 (2·3)	Reference	**<0·001**	9 (8·9)	157 (31)	Reference	**<0·001**	3 (3.9)	163 (31)	Reference	**<0·001**
Medium	91 (19)	21 (16)	12 (3·64-43·18)		12 (12)	100 (20)	2·1 (0·85-5·15)		12 (16)	100 (19)	6·5 (1·80-23.67)	
High	222 (47)	105 (81)	25·7 (8·01–82·41)		80 (79)	247 (49)	5·7 (2·76-11·58)		62 (81)	265 (50)	12·7 (3·92-41·16)	

[a] COR: Crude odds ratio.
[b] χ^2.

3.3. Statistical analysis

Relevant clinical data was analysed, using RStudio and R Statistical Software, and reporting measures done according to standard reporting guidelines [16–18]. The association between categorical variables and primary outcomes was studied using a Chi-squared and Fisher's exact test of association. Statistical significance was considered at a p-value ≤0·05. Correlation analysis was performed on all untransformed variables prior to multiple imputation by random forest for missing data. Outcome variables were not included in the imputation set. Univariate logistic regression was performed for variables associated with in-hospital mortality and labelled as risk factors. Multicollinearity was checked using variance inflation factor (VIF) and risk factors with a threshold p-value ≤0·25 in the univariate analysis were included in the final multivariable model. Backward stepwise regression was used to select significant risk factors with age, peripheral oxygen saturation and temperature amended to ensure reasonable odds calculation due to low cell frequency. The performance of the CURB65, ISARIC-4C and NEWS2 score in evaluating in-hospital mortality, ICU admission and invasive ventilation was assessed using Receiver Operator Characteristic Curve (ROC) analysis. The area under the curve (AUC), sensitivity, specificity, false positive rate (FPR) and true negative rate (TNR) were calculated on a univariate classifier, and 95 % confidence intervals computed by DeLong method. Event significance was assessed with equivalent Mann-Whitney-U statistic testing. Likelihood ratios, predictive values, and odds ratios (OR) were then calculated and tabulated for comparison of the primary outcomes. Risk groups were based on cut-offs from published literature [9–11]. Multivariable models based on amended regression parameters related to each score were assessed for goodness of fit using a Hosmer and Lemeshow test then compared by AUC.

3.4. Outcome measures

The primary outcome measures included in-hospital mortality, ICU admission and the need for invasive mechanical ventilation.

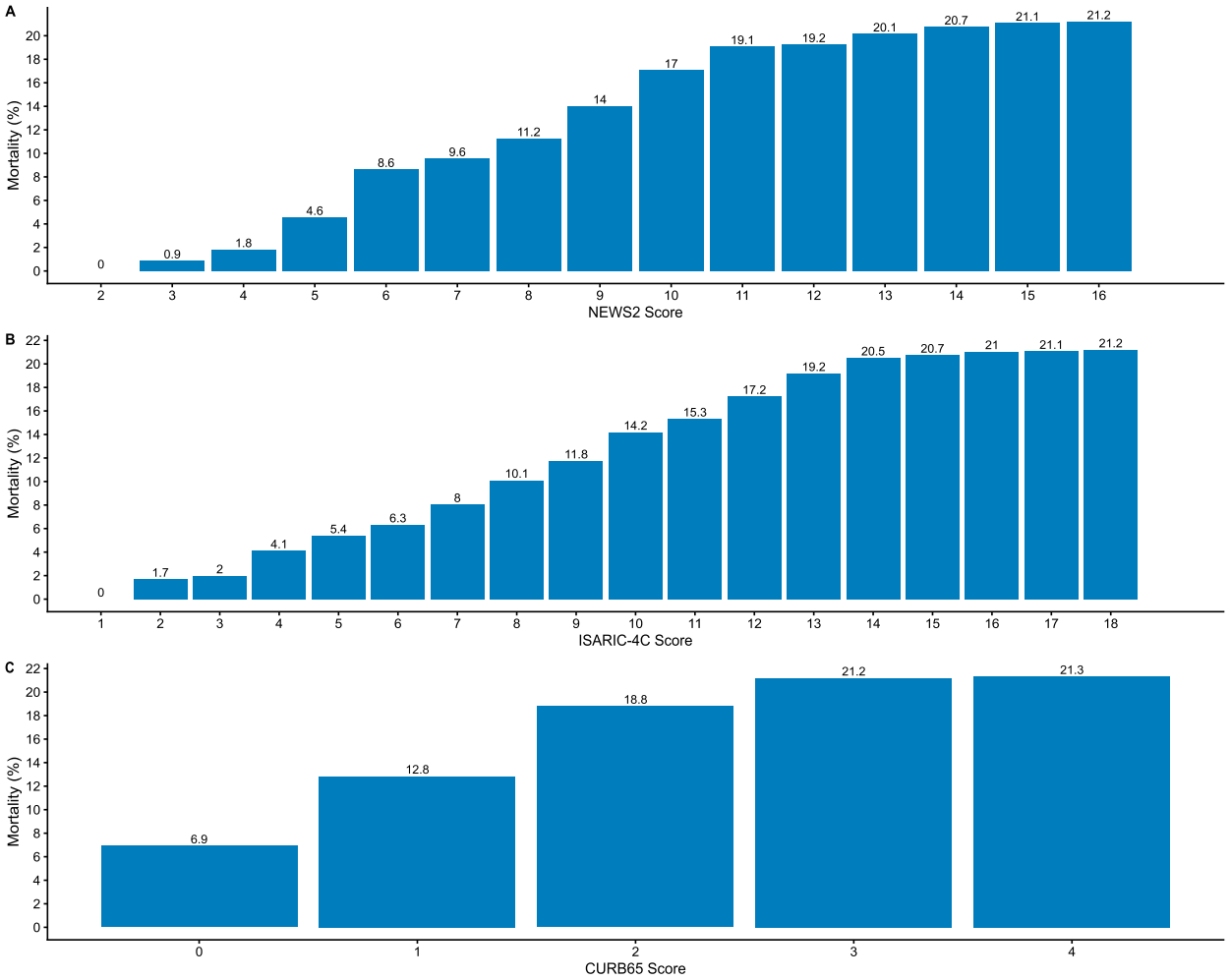

Fig. 1. Mortality for various threshold values of (A) NEWS2 score, (B) ISARIC-4C score, (C) CURB65 score.

4. Findings

4.1. Baseline characteristics of CURB65, NEWS2 and ISARIC-4C score risk groups

A total of 605 records were included in the study, of which 129 (21 %) were non-survivors, 101 (17 %) admitted to ICU and 77 (13 %) required invasive ventilation (Table 2). Greater odds of in-hospital mortality was associated with moderate and severe risk groups of the CURB65, ISARIC-4C and NEWS2 score. The low-risk group (n = 467) of the CURB65 score accounted for 77 % of the total cohort. This low-risk group included 47 % (n = 60) of non-survivors, 68 % (n = 69) of ICU admissions and 62 % (n = 48) of ventilated patients. The severe risk group of the CURB65 score accounted for 17 % (n = 22) of non-survivors with a ten-fold increase in the odds of in-hospital mortality (COR:10·7; 95 % CI: 5·17–21·6, p < 0·001) and a two-fold increase in the odds of invasive ventilation (COR: 2·1, 0·88–5·07, p = 0·004) whereas ICU admission was not associated with CURB-65 risk group (Table 1).

The low risk group (n = 101) of the ISARIC-4C score had a mortality rate of 1·6 % (n = 2) whereas the proportion of non-survivors in the high risk group was 64 % (n = 83) (Table 2) with a 30-fold increase in the odds of in-hospital mortality (COR: 30·2; 7·26–125·76, p < 0·001) (Table 2). The high-risk group of the ISARIC-4C score constituted 50 % (n = 50) of ICU admissions and 51 % (n = 39) of ventilated patients with a four-fold and five-fold increase in odds of ICU admission (COR: 4·7; 1·94–11·33, p < 0·001) and invasive ventilation (COR: 5·3; 1·82–15·14, p = 0·004), respectively.

The NEWS2 score had a mortality rate of 81 % (n = 105) and a 25-fold increase in the odds of in-hospital mortality (COR: 25·7; 8·01–82·41, p < 0·001) in the high-risk group wherein 79 % (n = 80) required ICU admission and 81 % (n = 62) invasive ventilation. The CURB65 score had a mortality rate of 6·9 % at a threshold of zero, whereas the NEWS2 and ISARIC-4C score both had 0 % mortality at their lowest thresholds (Fig. 1(A–C)).

4.2. Logistic regression analysis

Multivariable logistic regression identified respiratory rate, mental status, urea, and age to be significant risk factors for in-hospital mortality of the CURB65 score whereas blood pressure was not associated with mortality (Table 2). Controlling for covariate effects a respiratory rate ≥30 breaths/min (AOR: 4·57; 95 % CI: 1·37–3·57; p < 0·001) was shown to have a four-fold increase in the odds of mortality while altered mental status (AOR: 3·29; 1·89–5·72; p < 0·001) and urea ≥7 mmol/L (AOR: 3·05; 1·97–4·75; p < 0·001) were associated with a three-fold increase in odds (Table 3). Age ≥65 years was shown to have a two-fold increase in the odds of mortality (AOR: 2·26; 1·37–3·7, p < 0·001).

Variable selection by univariate regression excluded the number of comorbidities as a potential risk factor for in-hospital mortality

Table 3
Multivariable logistic regression for in-hospital mortality using factors related to the CURB65, ISARIC-4C and NEWS2 score.

Risk factors		AOR[a]	95 % CI	P[b]
CURB65 score				
Age	≥65	2·26	1·37-3·7	**<0·001**
Respiratory rate (breaths/min)	≥30	4·57	2·65-7·88	**<0·001**
Mental status	Altered	3·29	1·89-5·72	**<0·001**
Urea (mmol/L)	≥7	3·05	1·97- 4·75	**<0·001**
ISARIC-4C score				
Gender	Male	1·52	0·96-2·43	0·076
Age (years)	65–74	1·97	1·06-3·63	**0·03**
	≥75	3·02	1·15-7·86	**0·023**
Respiratory rate (breaths/min)	20–29	2·52	1·36-4·91	**0·005**
	≥30	7·50	3·52-16·61	**<0·001**
Urea (mmol/L)	7–14	2·36	1·38-4·01	**0·001**
	>14	4·05	2·20-7·48	**<0·001**
Glasgow coma scale	<15	3·37	1·85-6·15	**<0·001**
C-reactive protein (mg/L)	50–99	2·12	1·01–4·53	**0·046**
	>99	3·06	1·65-5·94	**<0·001**
SpO2 (%)	<92	2·02	1·18-3·56	**0·012**
NEWS2 score				
Supplemental oxygen	Oxygen	4·08	2·26-7·79	**<0·001**
Mental status	Altered	3·55	1·98-6·40	**<0·001**
Respiratory rate (breaths/min)	21–24	2·00	1·09-3·66	**0·023**
	≤8 or ≥25	2·79	1·57-5·00	**<0·001**
Pulse rate (beats/min)	41-50 or 91-110	1·52	0·85-2·79	0·16
	111–130	2·05	1·09-3·93	**0·026**
	<40 or ≥ 131	2·26	0·93-5·44	0·067
SpO2 (%)		0·97	0·96-0·99	**0·012**[c]
Temperature (Celsius)	35·1–36·0 or 38·1-39	0·48	0·26-0·88	**0·027**
	≤35 or >39	1·65	0·60-4·43	0·32

[a] AOD: adjusted odds ratio.
[b] χ [2].
[c] Continuous variable.

of the ISARIC-4C score (COR: 1·55, 0·95–2·54, p = 0·2) (Supplementary Table 2). Multivariable regression identified age, respiratory rate, urea, Glasgow coma scale, CRP and peripheral oxygen saturation as significant risk factors for in-hospital mortality using the ISARIC-4C score, whereas gender was not associated with mortality (Table 3). Controlling for covariate effects urea >14 mmol/L was associated with a four-fold increase in odds of mortality (AOR: 4·05; 2·2–7·48; p < 0·001), while CRP >99 mg/L (AOR: 3·06; 1·65–5·94, p < 0·001) and peripheral oxygen saturation <92 % (AOR: 2·02; 1·18–3·56, p = 0·012) were associated with three-fold and two-fold increases in odds, respectively (Table 3). Age group categorisation was amended for the multivariable analysis of the ISARIC-4C score model to ensure accurate calculation of odds ratios, where age ≥75 years showed a three-fold increase in the odds of in-hospital mortality (AOR: 3·02; 1·15–7·86, p = 0·023) (Supplementary Table 2).

Systolic blood pressure (mmHg) was excluded as a risk factor for in-hospital mortality, in the NEWS2 score, by univariate regression (COR: 1·85; 0·73–4·71, p = 0·4) (Supplementary Table 3). Supplemental oxygen, mental status, respiratory rate, pulse rate, peripheral oxygen saturation, and temperature were identified as significant risk factors for in-hospital mortality (Table 3). Controlling for covariate effects supplemental oxygen use was shown to have a four-fold increase in the odds of in-hospital mortality (AOR: 2·–267·79, p < 0·001) and pulse rate 111–130 beats/min a two-fold increase in odds (AOR: 2·05; 1·09–3·93, p = 0·026) whilst temperature ≤35·0 or > 39·0 Celsius was not associated with mortality. Peripheral oxygen saturation was modelled as a continuous variable and high-risk temperature categories were combined for accuracy of odds calculation for the NEWS2 score model (Table 3).

4.3. Area under receiver operator characteristics (AUROC) curve analysis

Performance in predicting in-hospital mortality for the CURB65, NEWS2 and ISARIC-4C score in Fig. 2 shows an AUROC of 0·76 (0·71–0·80, p < 0·001) for the CURB65 score, 0·77 (0·73–0·82, p < 0·001) for the NEWS2 score and 0·77 (0·73–0·81, p < 0·001) for the ISARIC-4C score based on a univariate classifier. The CURB65 score showed a sensitivity of 86 % with a 12·8 % mortality rate at a threshold of one whereas the NEWS2 score had a sensitivity of 92·2 % with an 8·6 % mortality rate at a threshold of six and the ISARIC-4C score a sensitivity of 87·6 % with an 8 % mortality rate at a threshold of seven (Table 4). In comparison multivariable models with the aforementioned amended regression parameters demonstrated AUROC values greater than 80 % for the NEWS2 score (AUROC: 0·81) and ISARIC-4C score (AUROC: 0·83) whereas the CURB65 score achieved an AUROC of 0·77. All multivariable models had an accuracy of greater than 80 % with Hosmer and Lemeshow goodness of fit p-value statistics of 0.681, 0.207 and 0.945 for the NEWS2, ISARIC-4C and CURB65 score, respectively. This indicates that the amended regression parameter models all fit the data well.

5. Discussion

This retrospective study analysed application of the CURB65, NEWS2 and ISARIC-4C score, in predicting critical outcomes in hospitalised patients with moderate to severe COVID-19. The predominant variant of concern being the ancestral variant, Asp614Gly mutation, in South Africa at the time [15]. Internationally validated clinical prediction models for communicable respiratory illnesses were used with comparable indices to previous studies observing in-hospital mortality [19–25]. The use of existing models that healthcare workers are familiar with is a pragmatic choice and evaluating their performance, in a LMIC setting, provides evidence for their relevance in our clinical setting.

All clinical prediction models in our study demonstrated an association between risk severity grade and in-hospital mortality, with a ten to 40-fold increase in odds among high-risk groups and an overall mortality rate of 21 %. This is consistent with mortality data in a national surveillance study, by Jassat et al., examining trends between SARS-CoV-2 variants of concern in South Africa [15]. The high-risk groups identified by the NEWS2 and ISARIC-4C scores had an approximate five-fold increase in the odds of ICU admission, which was also observed for invasive ventilation. In contrast, a paradoxical association between ICU admission and risk group was observed for the CURB65 score and a reduced odds of ICU admission for the very-high risk group of the ISARIC-4C score. This reduced odds may be attributed to sparse event data in the very-high risk group, however, it is possible that the ISARIC-4C score is an overall

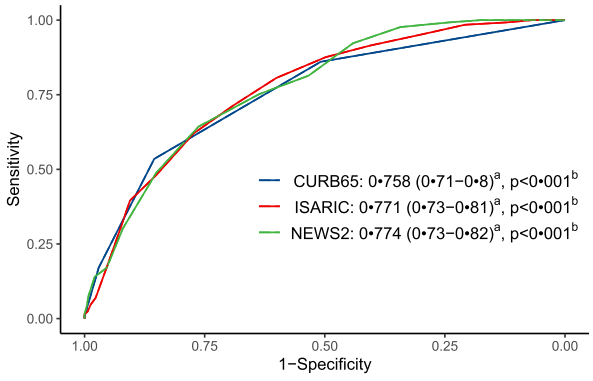

Fig. 2. ROC curve showing efficacy of risk scores to predict in-hospital mortality. [a] DeLong method (95 % CI); [b] Mann-Whitney-U statistic equivalent.

Table 4
AUROC of CURB65, ISARIC-4C and NEWS2 scores to predict in-hospital mortality.

	Threshold	Mortality (%)	Sensitivity (%)	Specificity (%)	PPV	NPV	LR+	LR-	AUC (95 % CI)
CURB65	1	12·8 %	86 (0·8-0·92)	50·8 (0·47-0·55)	32·2 (0·3-0·35)	93·1 (0·91-0·96)	1·8	0·3	0·76 (0·71-0·8)
ISARIC-4C	7	8·0 %	87·6 (0·81-0·92)	49·8 (0·46-0·55)	32·1 (0·29-0·34)	93·7 (0·91-0·96)	1·7	0·2	0·77 (0·73-0·81)
NEWS2	6	8·6 %	92·2 (0·87-0·97)	44·1 (0·39-0·48)	30·9 (0·29-0·33)	95·5 (0·93-0·98)	1·65	0.2	0·77 (0·73-0·82)

AUC: Area Under Curve; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive Likelihood. LR-: Negative Likelihood.

poor predictor of ICU admission, as demonstrated by Martin et al. where an AUROC of 0·62 was observed [26].

Multivariable regression models for in-hospital mortality of the NEWS2 and ISARIC-4C score demonstrated AUC values above 80 % compared to the CURB65 score at 0·77, however, this necessitated amending factors such as age group and peripheral oxygen saturation for the ISARIC-4C score and NEWS2 score, respectively. Indicating that the classification of these factors may not be predictive for our study whereas continuous variable retention was shown to have a significant association. The amended variables in the regression models were derived from their respective scoring system wherein these scoring systems had classified them into at least four factors resulting in sparse categories in our data set. Though sparse category data was encountered, these risk factors were still in line with preceding studies reporting an association between age and peripheral oxygen saturation for in-hospital mortality [19–22]. Significant risk factors for in-hospital mortality in our study included increased respiratory rate, use of supplemental oxygen, altered mental status, urea, CRP, and male sex. Scully et al. noted male sex to have a significant association for in-hospital mortality with the strongest association in the 18–49 year group adjusted for inflammatory markers proposing an inflammatory mediated sex differentiation, requiring further biologic exploration [21]. The ISARIC-4C Mortality score has since been superseded by the ISARIC-4C Deterioration model which includes revised parameters that have greater potential for clinical utility and generalisability in predicting clinical deterioration. These parameter improvements included continuous variable retention and the addition of supplemental oxygen use, radiographic infiltrates, nosocomial infection, and lymphocyte count as predictors. Gupta et al. reported an improvement in prediction of critical outcomes, within the London region, for the ISARIC-4C Deterioration model with an AUC of 0·77 compared to the ISARIC-4C Mortality score of 0.68 [27]. Though, pooled C–statistic values comparing the ISARIC-4C Mortality and Deterioration scores across England, Wales and Scotland were similar in a prospective validation study suggesting that model performance may differ across regions [28].

In-hospital mortality predictions of the CURB65, ISARIC-4C and NEWS2 score by ROC observed comparable performance using AUC for aggregate scores. The NEWS2 score was the most sensitive predictor, at publication thresholds of five for urgent response, followed by the ISARIC-4C score. Mortality rates of the NEWS2 and ISARIC-4C score were approximately 8 %, whereas the CURB65 score at a low-risk threshold was 12·8 %. Recommendations for community acquired pneumonia, in literature prior to the pandemic, advised clinicians to consider home based care in low-risk groups of the CURB65 score. These recommendations were based on observed mortality rates below 4 %, however, a higher mortality rate in the low risk group in our study limits concession to such recommendations [6,11,12]. A number of studies have reported an increase in mortality risk in the low risk group of the CURB65 score with Bradley et al. hypothesising endothelialitis, microthrombi and other SARS-CoV-2 cytokine mediated events as translatable measures by comparing models incorporating D-dimer and procalcitonin levels to the CURB-65 score and Pneumonia Severity Index (PSI) [29]. Unfortunately, these markers were not associated with an improvement in critical outcome predictions and consistently observed a higher mortality among SARS-CoV-2 pneumonia patients. Richards et al., in a placebo arm study of the PROWESS trial prior to COVID-19, observed a similar mortality risk in non-SARS-CoV-2 pneumonia for the CURB65 score [30]. Thus far, no clinical prediction tools are present in the literature that translate biologic cytokine events to measurable prognostic mortality tools.

The limitations we identified in our study included a small sample size resulting in low cell frequency requiring the amendment of factors inherent to both the ISARIC-4C and NEWS2 score, especially in older age groups. The study was also conducted at a single centre in a LMIC, which may limit generalisability of findings with different resources. Predictions of end-point outcomes using first assessment data compared to dynamic changes during hospital stay is considered an inherent limitation of point estimation. In view of the heterogeneity of disease presentation associated with variations in COVID-19 mutations, data may not be generalisable with each wave. Consistency of mortality data in our study with national health surveillance data suggests that our findings may be representative of our broader population thus strengthening recommendations in the LMIC setting. Our study was conducted on an infecting lineage prior to vaccination administration and no studies that we are aware of have reported an association between vaccination status and in-hospital point of care clinical characteristics. While vaccination and prior infection have been shown to be associated with a reduced risk of mortality and disease severity, we believe it is unlikely to affect current predictive severity scoring systems. Future research involving vaccinated cohorts in our region may provide further insight.

5.1. Interpretation

This retrospective study of 605 hospitalised patients with moderate to severe COVID-19, with the predominant variant of concern during the study period being the ancestral strain, noted good performance of the NEWS2 score and the ISARIC-4C score in predicting in-hospital mortality in our South African cohort. The CURB65 score was observed to have a high mortality rate in its low-risk group suggesting unexplained risk factors that are not accounted for in the score. A high mortality rate in SARS-CoV-2 and non-SARS-CoV-2 pneumonia, in our study and preceding literature for the CURB65 score, limit its utility in low-risk classification recommendations in

our South African setting. Our recommendations are based on the interpretation of available data and is intended to aid clinicians. However, therapeutic decisions in clinical practice should ultimately be guided by clinical judgement of healthcare providers.

Further research and collaboration are recommended to explore these factors, improve regional data access as well as improve model development for decision recommendations in LMIC settings.

Funding

All funding was self-provided by contributors of the research paper and no conflicts of interest were identified as declared by the authors.

Ethical approval

Approval for the study was obtained from the University of the Witwatersrand Medical Human Research Ethics Committee [M220116].

Data availability

The data that has been used for this research is not available in a publicly available repository as it is confidential.

CRediT authorship contribution statement

Prim Bta: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Kalla Is:** Writing – review & editing, Visualization, Supervision. **Zamparini J:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Mohamed F:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21733.

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