VALIDATION OF A SEVERITY SCORING TOOL FOR COVID-19 ILLNESS IN SUDAN

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DECLARATION

I, Yasein Omer, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABBREVIATIONS AND ACRONYMS

AFEM	African Federation for Emergency Medicine
AFEM-CMS	African Federation for Emergency Medicine COVID-19 Mortality Scale
AUROC	Area under the receiver operating curve
CFR	Case fatality ratio
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPR	Cardiopulmonary resuscitation
CURB-65	CURB-65 Severity Score
EC	Emergency care
ECS	Emergency care system
EM	Emergency medicine
EU	Emergency unit
GAM	Generalised additive model
GCS	Glasgow Coma Scale
HICs	High-income countries
ICU	Intensive care unit
IQR	Interquartile range
LASSO	Least absolute shrinkage and selection operator
LICs	Low-income countries
LMICs	Low- and middle-income countries
LRS	Low-resource setting
MICE	Multiple imputation by chained equations
MEWS	Modified Early Warning Score
NEWS	National Early Warning Score
NHC	National Health Committee of the People's Republic of China
NOS	Newcastle-Ottawa Scale Quality Assessment Scale for Cohort Studies
PaO2/FiO2	Arterial partial pressure of oxygen to fraction of inspired oxygen
PCR	Polymerase chain reaction

PPE	Personal protective equipment
pOR	Pooled odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
qSOFA	Quick Sequential Organ Failure Assessment
REMS	Rapid Emergency Medicine Score
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMOH	Sudanese Ministry of Health
SST	Severity scoring tool
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis guidelines
WHO	World Health Organization

ABSTRACT

Background

The COVID-19 pandemic has profoundly impacted some of the most vulnerable populations in low-resource settings (LRS) across the globe. These settings tend to have underdeveloped healthcare systems that are exceptionally vulnerable to the strain of an outbreak such as SARS-CoV-2. LRS-based clinicians are in need of effective and contextually appropriate triage and assessment tools that have been purpose-designed and validated to aid in evaluating the severity of potential COVID-19 patients. In the context of the COVID-19 crisis, a low-input severity scoring tool could be a cornerstone of ensuring timely access to appropriate care and justified use of critically limited resources. Machine learning was used on data from a retrospective cohort of Sudanese COVID-19 patients to derive a contextually appropriate mortality scale for COVID-19, the African Federation for Emergency Medicine COVID-19 Mortality Scale (AFEM-CMS) model.

This MSc aimed to validate the AFEM-CMS, to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS emergency units (EUs) in Sudan.

Methods

A retrospective quantitative analysis of data collected on adult patients aged 18 years and older screened as potentially positive for COVID-19 was undertaken to validate the AFEM-CMS in the same Sudanese setting from which it was derived. Data for this study were collected retrospectively by non-clinical personnel from four government referral hospitals in Sudan's Khartoum State from 01 September 2020 and 31 January 2021.

This study's primary outcome was in-hospital mortality due to SARS-CoV-2 infection. A set of predictor variables was collected for all patients based on the requisite inputs for the AFEM-CMS tool. The predictor variables comprise demographic and historical data (age and sex), the number of existing comorbidities a patient has on presentation, and a number of clinical inputs (GCS, systolic blood pressure, respiratory rate, heart rate, and pulse oximetry). The AFEM-CMS was validated using C-index measurements (area under the receiver operator curve (AUROC)) in the validation dataset. All analyses were performed in R (version 4.1.0, © The R Foundation) with the *dplyr*, *finalfit*, *glmnet*, *mice*, *pROC*, *rmda*, and *tidyverse* packages.

Missing datapoints were managed using multiple imputation by chained equations (MICE), which imputed values for predictor variables with less than 33% of data points missing.
Ethical approvals for this study were obtained from the University of Cape Town and the Sudanese Ministry of Health.

Results

In this study, the AFEM-CMS was validated against a 936-patient cohort, all of whom All of these included cases met the WHO definitions for suspected, probable, or confirmed SARS-CoV-2 infection. Similar to initial derivation outcomes, the tool was found to have reasonable discriminatory power in identifying those at greatest risk of death from COVID-19: The model including pulse oximetry had a C-statistic of 0.732 (95% CI: 0.687-0.777) and the model excluding pulse oximetry had a C-statistic of 0.696 (0.645-0.747).

Conclusions

This dissertation establishes what is, to our knowledge, the validation of the first COVID-19 mortality prediction tool intentionally designed for frontline providers in LRS. The validation of the AFEM-CMS highlights the feasibility and potential impact of real-time development of clinical tools to improve patient care, even in times of surge in LRS. This study is just one of hundreds of efforts across all resource levels suggesting that rapid use of machine learning methodologies holds promise in improving responses to pandemics and other emergencies. It is our hope that, in future health crises, LRS-based clinicians and researchers can refer to these techniques to inform contextually and situationally appropriate clinical tools and reduce morbidity and mortality.

1. INTRODUCTION

1.1 Background

Despite containment efforts, Coronavirus disease 2019 (COVID-19) reached pandemic status on March 11, 2020. Nearly two years later, the pandemic endures. As of February 2022, there are 380 million confirmed cases worldwide, with over 5.6 million deaths;[1] these numbers are only expected to grow as the pandemic continues into the coming months. Although data surrounding the novel coronavirus are rapidly evolving, estimates of early variants depicted a dire situation: between 15% and 20% of infections led to severe or critical disease.(2) (3) The Omicron variant, first identified in South Africa in November 2021, appears less likely to lead to severe disease, with only 4.3% of patients requiring intensive care unit (ICU) admission in a large South African hospital.(4) To date, nearly nine billion vaccine doses have been administered worldwide.(2) Unfortunately, the distribution of these doses has been very unequal: While high- and upper-middle-income countries have received more than 167 doses per 100 people, lower-middle-income countries (LMICs) have received 85 doses per 100 people and low-income countries (LICs) have received just 11 doses per 100 people.(5) The unvaccinated remain highly vulnerable to more severe forms of the illness, as do those populations compromised by malnutrition and comorbid diseases.(6) Mortality has varied across settings, but current data suggest a variable case fatality rate ranging from 0.5% to 4.5%.(4, 7-10)

As the COVID-19 pandemic continues, healthcare systems worldwide are under severe strain.(11, 12) High volumes of patients in need of critical care limit systems' abilities to provide such care; this is occurring even in the most highly-resourced settings.(11, 12) The countries with the most limited capacity to respond have been affected on a large scale.(13, 14) Early recognition, resuscitation, and referral have proven key to effective responses, yielding lower morbidity and mortality from COVID-19 disease.(15, 16) These processes are, however, significantly more challenging in low-resource settings (LRS). Many LMICs have scarce critical care resources – they are LRS – with limitations in the availability of oxygen and other basic resources as well as healthcare provider shortages.(17, 18) While ongoing acute and emergency care system strengthening efforts are underway and showing impact in many of these settings, these efforts will not be able to keep pace with emerging demand due to

COVID-19. Immediate targeted efforts are needed to assist these countries in managing and treating large numbers of acutely ill patients.

Frontline providers in emergency units (EUs) need to make challenging decisions surrounding rationing of resources, including oxygen and ventilators, upon initial assessment of COVID-19 patients. Clinical guidance for evaluating patients' respiratory needs and subsequent dispositions is essential, particularly in LRS. A range of scoring systems are available to guide care for severely ill patients. While these tools may have some utility in predicting COVID-19 patient severity, they are likely limited in this unique context. Some scores are designed for specific care settings, such as ICUs, which are a very scarce resource in LRS.(19) While selected COVID-19 patients can be treated in ICUs, most patients are less critical, requiring interventions more appropriate for general ward and emergency unit (EU) settings. Thus, a tool predicting outcomes based solely on those already admitted to ICU may have reduced utility across the range of illness severity seen in this disease. Other scoring systems were purpose-designed for patients presenting with specific conditions, such as pneumonia and sepsis.(19, 20) Condition-specific tools may be of some use in assessing COVID-19 patients but are likely limited in that these patients initially present with a range of symptoms, only some of which involve respiratory disease or septic shock.(21) High burdens of data entry seen in many tools can lead to increased time-to-decision making and frequent missing data points.(22-24) Some tools also involve additional investigations, including blood tests and imaging, that have very limited availability in LRS.(19, 25-27)

The global threat posed by COVID-19 and its likely impacts on LRS make it essential for tools with the potential to reduce mortality be made widely available. A severity scoring tool (SST) holds promise in aiding frontline providers in LRS in managing the pandemic SARS-COV-2 infection and COVID-19 disease by allowing them to assess potential resources that a patient will need throughout the duration of both EU and hospital stays.

The Republic of Sudan

The Republic of Sudan is Africa's third largest nation. The country of 41.8 million has many young citizens - half of the population is under the age of 18 and 80% are under 40 - and the average life expectancy is 64.1 years.[28] Road traffic injuries and cardiovascular conditions are

among the leading causes of death, co-existing with persistent challenges in maternal and child mortality.(29-32) The public healthcare system responsible for managing these issues in Sudan is decentralized across three levels - federal, state, and local – and there are two levels of facilities that provide formal emergency care – known as district and referral hospitals. District hospitals provide lower-level care and tend to be located in rural and peri-urban areas, while referral hospitals offer more advanced care in urban centres.

COVID-19 has severely impacted Sudan's economy, health status, and social programs.(33, 34) Unfortunately, these ramifications are expected to persist, as only a small proportion of Sudan's population – 3.3 %- has been fully vaccinated against COVID-19 to-date; this represents one of the lowest vaccination rates worldwide.(2) Plagued by a series of country emergencies in recent decades, including political strife and natural disasters, the Sudanese healthcare system entered the COVID-19 pandemic already in crisis.(29, 35-37) Since the COVID-19 pandemic reached Sudan, its already strained healthcare system has struggled to keep pace with the response. The emergency care system (ECS) has proven vital to the response, with frontline EUs becoming a catch-all for potential COVID-19 patients. Despite these challenges, recent pre-pandemic investments in emergency care meant that it had a somewhat robust system for collecting data at the frontlines, making it an ideal study setting for the derivation and validation of a COVID-19 SST for LRS.

1.2 Motivation

LRS tend to have underdeveloped healthcare systems that are exceptionally vulnerable to the strain of an outbreak such as SARS-COV-2.(38) Clinicians in resource-limited contexts are in need of effective and contextually-appropriate triage and assessment tools that have been purpose-designed to aid in evaluating the severity of potential COVID-19 patients. In the context of the COVID-19 crisis, a low-input SST could be a cornerstone of ensuring timely access to appropriate care and justified use of critically limited resources.

Historically, the publication of data from time-sensitive incidents such as pandemics is slow, and it can be even slower in LRS, where data collection infrastructure are limited. The rapid publication of COVID-19 data, however, provides a unique opportunity to identify potential features of severe COVID-19 disease and develop a severity scoring system in real-time, while

the pandemic continues. Strong data collection mechanisms have been set up in Sudan that allowed for rapid validation of a severity scoring tool. Validation of a low-input SST in a LRS is a key step in providing reliable guidance for SST implementation in LRS globally. The health systems in Sudan are as strained as any in Africa and therefore a tool that is accurate, valid, and functional in Sudan should be translatable to many other African countries.

1.3 Aim and objectives

The MSc was conducted as a part of a larger PhD, which had the following objectives:

1. Identify features predictive of severe COVID-19 illness (study one).
2. Derive the SST using data from a LRS (study two).
3. Validate the SST in the African setting using real-world data (study three).

This MSc was part of the third study of the PhD, which sought to validate a contextually relevant SST to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS EUs in Sudan. **The objectives of this MSc are as follows**:

1. Evaluate SST performance characteristics based on multiple measures of patient outcome and disposition.
2. Assess mortality risks predicted by the SST.
3. Describe basic demographics and dispositions of potentially positive COVID-19 patients at hospitals in Sudan.

The proposal for this MSc is provided in Appendix 1.1.

2. LITERATURE REVIEW

2.1 COVID-19 severity classifications

Published literature on COVID-19 uses a number of definitions for severity of COVID-19 disease, the heterogeneity of which can make it challenging to compare outcomes of published studies and evaluate COVID-19 SSTs side-by-side.(39) Most organizations define COVID-19 infections as mild, moderate, or severe. The WHO defines mild patients as those who have upper respiratory tract disease, moderate patients as those who have pneumonia but do not require oxygen, and severe patients as those have pneumonia and require oxygen, and critical patients have acute respiratory distress syndrome or sepsis and often require ventilation.(40) The National Health Committee of the People's Republic of China (NHC) also describes three categories of COVID-19 severity: mild (few or no respiratory symptoms, no pneumonia manifestations on imaging), severe (respiratory distress, respiratory rate greater than 30 breaths per minute, resting SpO2 < 93% and ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ≤300mmHg), and critical (respiratory failure, shock, and combined failure of other organs requiring mechanical ventilation and ICU-level care).(41) The National Institutes of Health in United States takes a symptom-based approach with four categories: mild illness (any signs and/or symptoms of COVID-19 without shortness of breath, dyspnea, or abnormal chest imaging, moderate illness (individuals with signs of lower respiratory disease on assessment or imaging, with an oxygen saturation (SPO2) above 94% on room air), severe illness (SPO2 below 94% on room air, PaO2/FiO2 below 300 mm Hg, a respiratory rate greater than 30 breaths/min, or lung infiltrates greater than 50%), and critical illness (respiratory failure, multiple organ dysfunction, and/or septic shock).(42) Many research studies have also described COVID-19 severity using proxies such as inpatient mortality or likelihood of ICU admission, likely due to the ease of availability of such datapoints in comparison to granular information regarding symptoms, vital signs, and diagnoses.(43, 44)

2.2 Features associated with COVID-19 severity

The research surrounding factors associated with COVID-19 severity has grown steadily throughout the course of the pandemic, and there is now a robust evidence base surrounding which factors may be predictive of severe illness. COVID-19 severity has been linked to a

number of symptoms, vital signs, patient demographics and comorbidities, laboratory values, and imaging findings.

Symptoms such as haemoptysis have been associated with ICU admission and death.(45) Izquierdo *et al*. (2020) found associations between ICU admission and the presence of cough, fever, and dyspnoea.(43)

Low oxygen saturation and increased respiratory rate are commonly associated with poor outcomes in COVID-19.(46, 47) Heart rate and blood pressure may also be moderately predictive of COVID-19 severity.(47, 48)

Age may also be significant predictor of COVID-19 severity, with estimates that, for each year of increase in age, a patient has a 13% increased risk of mortality from COVID-19.(49) In addition, male patients are almost three times as likely to require ICU treatment compared to females.(50)

Emerging evidence suggests that patients with any comorbidity are more likely to suffer severe COVID-19 than patients who are otherwise healthy.(51, 52) However, studies have also targeted specific comorbidities as severity predictors. One study showed an apparently high mortality rate in patients presenting with hypertension and COVID-19: 48% versus 23% of survivors.(44) Type 2 diabetes has also been liked to poorer outcomes from COVID-19.(53) Multiple laboratory values have also been linked to COVID-19 severity. For example, lymphopenia, elevated lactate dehydrogenase, and elevated C-reactive protein have all been linked to worse outcomes.(54) In addition, chest CT and ultrasound findings may also be used to prognosticate COVID patients.(55, 56)

In a study conducted in eastern Sudan it was shown that increasing age and lower PaO2 values were linked to increased mortality (57) other studies in Africa also showed that Older people and individuals with chronic conditions such as HIV, tuberculosis and anaemia experience severe forms COVID-19 leading to hospitalisation and death. Also a high burden of chronic obstructive pulmonary disease, high prevalence of tobacco consumption were factors that contributed to increased risk of death from covid in Africa.(58)

2.3 COVID-19 in low-resource settings

COVID-19 has increased the need for PPE, oxygen, ventilators, and health care personnel and has resulted in health care strain worldwide.(59) LRS, which already experience shortages of health care providers and essential infrastructure such as critical care resources, have been disproportionately affected.(60)

Accurately measuring the COVID-19 disease burden in LRS has been difficult due to a lack of access to testing. Six in seven COVID-19 cases in Africa may go undetected.(61) Mortality is also underreported in LRS.(62) Mortality in COVID-19 patients admitted for critical care in Africa significantly exceeds the global average, with an excess mortality up to 23 deaths per 100 patients. This excess mortality is seen despite patients in LRS being healthier upon admission.(62) Patients in LRS are not only less likely to have access to critical care resources, they are less likely to receive evidence-based interventions, even if those interventions are present.(60) An increased prevalence of comorbidities such as diabetes and coronary artery disease in LRS also increases the vulnerability of these populations to COVID-19.(63)

2.4 Severity scoring tools used for COVID-19

Screening acts an initial sieve at the entrance to healthcare facilities, sorting patients according to their likelihood of being infected, and can be used to maximize limited resources.(64) Ideally, it is done to separate those at higher risk of being infected into a separate patient flow stream from those at lower risk. Following screening, patients should be triaged: a method of sorting patients by their acuity – their clinical status independent of their diagnosis or risk of having COVID-19 infection – and directing patients to the appropriate level of care.(65) Unlike screening and triage, severity scoring is a disease-state specific method of prognosticating patients, meaning that SSTs are typically purpose-designed for a singular disease state or illness. Such tools which may help further inform decision making on their management. Prognostication using SSTs may include outcomes such as likelihood of requiring ICU admission or likelihood of death.(63)

A large and ever-growing number of SSTs – at present, more than 100 – have been developed for COVID-19. These SSTs are heterogenous and use a wide range of inputs, including clinical signs and symptoms, vital signs, demographics, and comorbidities. SSTs using imaging

modalities, including lung ultrasound and chest CT, as predictive inputs have also been published. Even within input categories, tools do not consistently include similar inputs.(66) For example, a wide range of comorbidities are included: while some SSTs include chronic respiratory diseases as a key, predictive comorbidity, others focus on conditions like cardiovascular disease. Research shows that age and male sex have similar predictive values, but age – a more challenging datapoint to gather, particularly when a patient is incapacitated - is more commonly included in tools in comparison to male sex.(66)

Most tools have been purpose-designed for COVID-19 disease. In addition, several pre-existing tools have been repurposed to prognosticate COVID-19 patients. The CURB-65 severity score (CURB-65) is a severity scoring tool designed for pneumonia severity stratification that has been used for COVID-19.(67) Similarly, the Quick Sequential Organ Failure Assessment (qSOFA), previously used for sepsis patients, and has been demonstrated to be effective in prognostication of severe COVID-19 patients.(67) The Modified Early Warning Score (MEWS) and Rapid Emergency Medicine Score (REMS), two prognostication systems that are similar in input, with the exception that REMS includes SPO2, were also examined as options for severity scoring COVID-19 patients in China.(68)

A majority of tools have been developed for hospital admissions and ICUs, and only a small number to-date have been purpose-designed for emergency units.(66)

Validation is essential to ensuring that a tool is appropriate and accurate for the setting in which it is being used. The need for tools in real-time due to COVID-19 has led to rapid development and/or implementation of novel severity scoring tools. Given the challenge of conducting real-time research in clinical settings amidst a pandemic, prospective validation of COVID-19 SSTs is uncommon and most have only been retrospectively validated.(66)

2.5 COVID-19 severity scoring tools in low-resource settings

Prognostication systems have been demonstrated to improve patient outcomes across a range of disease and injury categories in LRS.(69) However, nearly all of the tools developed for COVID-19 have been developed and published in high-income countries (HICs). In a scoping review of severity scoring tools being utilised worldwide, less than six percent of tools

were implemented in low- and lower-middle income countries.(66) Furthermore, prior to this study, no COVID-19 SSTs had been validated in LRS.

Many LRS lack access to laboratory testing and imaging, and SPO2 monitoring may also be limited in availability.(64, 70) Many tools developed in HICs settings rely on laboratory testing, imaging, and SPO2 for prognostication of COVID-19 patients. If not available, a final prognostication for a patient cannot be calculated using these tools. Given these constraints, few published tools from HIC settings are feasible for consistent use in LRS.(66)

Some repurposed SSTs, such as CURB-65 and qSOFA, are likely feasible for use in LRS, and they have been shown to predict in-hospital mortality for COVID-19 patients in higher-resource settings.(67) REMS and MEWS both effectively prognosticated COVID-19 patients in China, an upper-middle income country. REMS showed increased sensitivity, suggesting that monitoring SPO2 may increase the ability of an EU to stratify patients by COVID-19 severity, but MEWS, which does not require an SPO2 reading, may be more easily implemented in LRS.(68)

Tools that are feasible in LRS are not guaranteed to perform well. Validation data from non-COVID-19 studies showed that tools including the National Early Warning Score (NEWS) vary in accuracy between high- income and upper-middle-income settings, suggesting that there may be even more variability in accuracy when used in low-income settings.(66)

2.6 Sudan's disease burden

With a population of nearly 44 million, Sudan is one of Africa's most populous nations.(29) A drawn out war led to the split of the country and formation of South Sudan in 2011.(71) As a result of this and other long-standing conflicts with neighbouring countries, and general political instability, much of Sudan's health infrastructure has been damaged and health outcomes remain poor. Sudan is ranked 170 out of 189 on the UN Human Development Index, suggesting that its residents face limited access to healthcare and education, and a poor socioeconomic outlook.(72)

Sudan's healthcare system is severely strained by road traffic injuries, by communicable and noncommunicable diseases, and by persistent challenges in maternal and child mortality with maternal mortality rates as high as 295 deaths for every 100,000 live births.(29) The communicable disease burden is higher than that for noncommunicable diseases, at 53.8% and 33.9%, respectively.(29)

Communicable diseases remain the leading cause of deaths and disability in Sudan, and the top risk factor for death and disability due to infectious disease is primary malnutrition.(29) Adequate access to clean water also remains a driving factor in the country's high communicable disease burden.(71) Obesity and type 2 diabetes have also been increasing in prevalence in the country, leading to a growing double burden of communicable and non-communicable diseases.(71) Inadequate health facilities, an inadequate provider workforce, and lack of access to diagnostic testing are all significant barriers to care, as are the financial costs to seeking such care.(73)

Traumatic injuries also contribute to the burden of disease, accounting for 13.4% of Sudan's overall mortality.(73) As a result of both prolonged droughts in the east and west and war, more than two million displaced people have migrated to the capital, Khartoum, in the south-central area of the country.(73) This migration has been accompanied by a rise in the number of vehicles in the capital. Due in large part to unsafe vehicles and a lack of road safety regulation, Sudan is ranked thirteenth globally in terms of incidence of road traffic accidents. road traffic injuries are the fifth leading cause of death and disability combined in the country.(73)

2.7 The Sudanese healthcare system

Sudan's healthcare system is severely strained by the substantial burden of injury and illness experienced in the country.(29) The present health care system in Sudan serves a majority of the population, and according to the interim Constitution of Sudan, all citizens have access to free primary health care and emergency services.(74) The country's health system infrastructure is notably heterogenous, with health services being more accessible in wealthier and more urban areas,(29) and only 5.6 doctors per 10,000 population instead of the WHO standard of 10 per 10,000 population.(35) Sudan's capacity for nursing and

midwifery is also below standard, with 12.1 nursing and midwifery personnel per 10,000 population instead of the recommended 23 per 10,000.(35) The WHO Universal Health Coverage Service Coverage Index score, which tracks coverage for essential health services is about average for the region at 44.(75) Country crises have longitudinally burdened already-weakened health systems in Sudan, as shortfalls in health staff, medical supplies, medicines, and vaccines become increasingly common. Infrastructure concerns, such as lack of safe water, fuel, power, and safe access compromise health service provision. Emergency care is rapidly developing in Sudan, with the establishment of specialist physician and nurse training programmes in emergency medicine.

The public health system is decentralised across three levels - federal, state, and local – and there are two levels of hospitals, known as district and referral. District hospitals provide lower-level care and tend to be located in rural and peri-urban areas, while referral hospitals typically offer more advanced care in urban centres. It is important to note that, throughout the COVID-19 pandemic, these facilities have been providing similar levels of care, regardless of their designation as a district or referral hospital. Private hospitals also exist in Sudan, although they tend to be accessed only by wealthier populations with private insurance coverage and those in need of specialty care.

Many of these aspects of Sudan's healthcare system, including its heterogeneity, division of public and private sector healthcare services, and early investments in emergency care, lend it to being a prime case study for the COVID-19 pandemic's impacts in the African region and in LRS.

2.8 Emergency care in Sudan

Sudan's emergency care system remains nascent. The Interim constitution of Sudan mandates that emergency services be provided to Sudanese citizens for free; however, emergency services remain underdeveloped.(76) A state-run prehospital ambulance service was initiated in 2006.(73) This service has a centralised emergency response number that is free to access.(73) However, most citizens are not aware of how to access emergency care services and do not have the ability to pay care rendered.(73) Prehospital providers are

trained in cardiopulmonary resuscitation (CPR) and first aid but are not typically trained in basic or advanced life support.(73)

In 2001, in an attempt to reduce mortality, the Sudanese Ministry of Health (SMOH) implemented triage in the ECS, but, to-date, no formal triage system has been broadly implemented.(77) An emergency medicine (EM) residency program was started in Khartoum in 2011.(77) Despite this, staffing EU 24/7 with EM specialists remains difficult due to a lack of trained providers.(77)

3. METHODOLOGY

3.1 The AFEM-CMS model

The AFEM-CMS was derived in a previous 2021 study using a criterion-based method of model selection.(78) The AFEM-CMS is an SST that was developed using a dataset from Sudanese EUs. GAMs were used to determine the deviance explained by independent predictors, and variables explaining greater than one percent of the overall deviance were included in the final model. Coefficients of predictors were then estimated using LASSO logistic regression, with a 10-fold cross-validation to identify the optimal value of lambda. L1 penalised coefficients were proportionally scaled to create a usable scoring scale for the AFEM-CMS for two use cases – with and without pulse oximetry as a predictor - and scatter plots distributions comparing scores and CFRs were visually inspected to determine clinically-meaningful cut-off points for risk groups. The final AFEM-CMS tools are shown below in Tables 3.1a* and 3.1b*, and mortality risk predictions are shown in relation to AFEM-CMS scores in Table 3.2.

Table 3.1a: AFEM COVID-19 Mortality Scale (AFEM-CMS) for in-hospital mortality due to COVID-19 in low-resource settings *with* access to pulse oximetry.(78)

Variable	**Score**
Sex at birth	
Female	0
Male	1
Age (years)	
<65	0
≥65	1
No. of comorbidities*	
<2	0
≥2	1
Glasgow Coma Scale	
15	0
<15	2
Systolic blood pressure (mmHg)	
>100	0
≤100	1
Respiratory rate (breaths/min)	
<20	0
≥20	1
Peripheral oxygen saturation on room air (%)	
≥92	0
<92	2

Table 3.1b: AFEM COVID-19 Mortality Scale (AFEM-CMS) for in-hospital mortality due to COVID-19 in low-resource settings *without* access to pulse oximetry.(78)

Variable	Score
Sex at birth	
Female	0
Male	1
Age (years)	
<65	0
≥65	1
No. of comorbidities*	
<2	0
≥2	1
Glasgow Coma Scale score	
15	0
<15	2
Systolic blood pressure (mmHg)	
>100	0
≤100	2
Respiratory rate (breaths/min)	
<20	0
≥20	1
Heart rate (beats/min)	
≤90	0
>90	1

*Comorbidities are defined as follows: Alcohol use, cardiovascular disease (one or more of the following: atrial fibrillation, congestive heart failure, coronary artery disease, deep vein thrombosis, dilated cardiomyopathy, ischaemic heart disease, myocardial infarction, and small vessel disease), chronic respiratory disease (one or more of the following: asthma, chronic obstructive pulmonary disease, and tuberculosis), chronic neurological disease (one or more of the following: epilepsy, haemorrhagic or ischaemic stroke, and Parkinson's disease), cirrhosis, chronic kidney disease, current or former smoker status, diabetes (types 1 and 2), hypertension, hypothyroid, and malignancy.

Table 3.2: Mortality risk stratification based on AFEM COVID-19 Mortality Scale (AFEM-CMS) scores.(78)

Mortality risk	AFEM-CMS score
< 33%	0 to 2
33% to 66%	3 to 5
> 66%	6 to 9

3.2 Study design

Machine learning was used on data from a retrospective cohort of Sudanese COVID-19 patients to derive a contextually appropriate mortality scale for COVID-19, the AFEM-CMS model.

In this study, the AFEM-CMS was validated using C-index measurements (area under the receiver operator curve (AUROC)) in the validation dataset. All analyses were performed in R (version 4.1.0, © The R Foundation) with the *dplyr*, *finalfit*, *glmnet*, *mice*, *pROC*, *rmda*, and *tidyverse* packages. Validation and reporting processes adhered to the TRIPOD guidelines (Appendix 3.1).(79)

A retrospective quantitative analysis of data collected on adult patients greater than 18 years of age screened as potentially positive for COVID-19 was undertaken. SST accuracy in predicting patient status and disposition was assessed.

3.3 Study population

Patients included in this study were adults aged 18 years and over who presented to four government hospital EUs in Khartoum State between 01 September 2020 and 31 January 2021. All patients met WHO criteria for being a suspected, probable, or confirmed case of SARS-CoV-2 infection,(80) and had a recorded ultimate disposition of either death or discharge from hospital. This dataset is unique from the dataset that was used to derive the AFEM-CMS.

The target sample size required for SST performance characteristics analyses was based on a conservative estimated area under the receiver operating characteristic curve (AUROC) of 0.65 for the SST and a null AUC value of 0.5. Statistical significance was set at an alpha value of 0.05 with a power of 80%.(81) Based on a previous study of COVID-19 mortality,(3) we calculated an estimated ratio of survivors to non-survivors of 24:1, resulting in a required minimum sample size of 775 patients.

3.4 Data collection

Data for this study were collected retrospectively from four government referral hospitals in Sudan's Khartoum State. Data collection did not affect health system capacity during this crisis: All data required for this study were already being collected in Sudanese EUs and data collectors were paid, non-clinical personnel. On-site data collectors retrospectively logged deidentified historical and clinical information for patients presenting to four government hospital study sites from paper records into a secure electronic Microsoft Excel (© Microsoft, Redmond, WA, USA) database. Data collection took approximately 10 days at each site and was conducted in February 2021.

Data were stored locally and shared with study investigators via a secure, cloud-based sharing platform (© Dropbox, San Francisco, CA, USA).

Data missingness

Missing datapoints were managed using multiple imputation by chained equations (MICE), which imputed values for predictor variables with less than 33% of data points missing. In no instances did a variable have greater than 33% missingness. Data were assumed to be missing completely at random. Ten iterations of MICE were conducted, using predictive mean matching for continuous variables and binary logistic regression for two-level variables. Distributions of missing and observed data were reviewed for each predictor. To combine results of individual iterations, Rubin's rules were employed to pool parameter estimates.(82)

3.5 Outcomes

Primary outcome

This study's primary outcome was in-hospital mortality due to SARS-CoV-2 infection.

Predictor variables

A set of predictor variables was collected for all patients based on the requisite inputs for the AFEM-CMS tool.(78) The predictor variables comprise demographic and historical data (age and sex), the number of existing comorbidities a patient has on presentation, and a number of clinical inputs (GCS, systolic blood pressure, respiratory rate, heart rate, and pulse oximetry).

3.6 Ethical considerations

Ethical approvals were obtained from two institutions: the University of Cape Town, and the Sudanese MOH (Appendix 3.2). Research did not commence until all approvals were obtained. Facilities in Sudan have been selected for this study because of interest from AFEM partners in this country and knowledge of strong COVID patient data collection mechanisms. Children (aged <18 years) were not included in this study. It is, however, acknowledged that the participants in this study were vulnerable in that they were seeking emergency healthcare. There was a risk for breach of privacy and confidentiality for participants included in this study, as their records were accessed for data extraction. To reduce this risk and prevent the potential stigmatisation that can come from a COVID-19 diagnosis, no identifying information was extracted from patient records. All electronic data was stored in encrypted, password-protected files. Only study personnel had access to these data. Analyses was conducted anonymously and at the aggregate level.

There were no risks that adversely affected patient care by collection of this data, as requisite data points were already being documented in EU and ward clinical notes were being scanned electronically. This study therefore placed no additional burden on frontline providers. All data were entered as usual in notes and was later extracted retrospectively by data collectors for the purposes of this study.

Data collectors had no contact with patients. Data collectors abstracted deidentified data from electronic EU and ward clinical notes which were routinely scanned by hospital clerks. They accessed records through a secure connection in the administrative suite of each hospital. The administrative suite is isolated from the clinical environment and therefore

posed a minimal risk of SARS-COV-2 contamination. Data collectors were trained in personal protective measures as appropriate. Data collectors were paid a fair, but not coercive, stipend in accordance with local advertised rates, and reimbursed for transport costs.

3.7 Methodological limitations

The primary limitation of this study's methodology is the use of EU disposition as a proxy for severity upon arrival. The gold standard in SST validation is the use of standardised case vignettes. There are factors outside of severity that may compound EU disposition, such as lack of bed availability (e.g., a patient who would otherwise go to ICU but ends up on the wards due to a lack of open ICU beds) and social factors (whereby patients are admitted due to their lacking a caregiver at home). However, by studying this early in the epidemic curve, it is less likely that these factors apply.

4. RESULTS

Characteristics of study population

In total, 936 patients that presented to the four included study sites between 01 September 2020 and 31 January 2021 met inclusion criteria (Table 4.1). All of these included cases met the WHO definitions for suspected, probable, or confirmed SARS-CoV-2 infection,(80) and nearly all patients (90.8%) had a positive PCR testing result (the remaining 9.2% of patients had missing or negative PCR test results). Of this cohort, 391 patients died during their admission, generating an overall CFR of 41.8%. More survivors were female (48.3%) than non-survivors (24.8%), and survivors tended to be younger than non-survivors: The median age of survivors was 62 (IQR: 18) years, while the median age of non-survivors was 68 (IQR: 13) years. Rates of diabetes (45.1% in non-survivors versus 37.5% in survivors) and hypertension (51.2% in non-survivors versus 37.7% in survivors) were notably higher in non-survivors (Table 4.1). Cardiovascular disease (12.4% in non-survivors versus 18.4% in survivors) and chronic respiratory diseases (8.3% in non-survivors versus 15.5% in survivors) were also seen in higher rates in non-survivors. Across both groups, four fifths (80.7%) of patients reported at least one comorbidity. The prevalence of two or more coexisting comorbidities was more common in non-survivors (53.0%) than survivors (31.9%). Median GCS scores, pulse oximetry readings, and systolic blood pressures were lower in the non-survivor cohort. Median GCS, peripheral oxygen saturations on room air, and systolic blood pressures were lower in the non-survivor cohort when compared to survivors, while heart and respiratory rates and temperatures were higher in this group.

Table 4.1: Characteristics of study population.

Characteristic	Overall cohort (N = 936)		Survivor cohort (N = 545)		Non-survivor cohort (N = 391)	
	n (%) or median (IQR)	Total no patients (%)	n (%) or median (IQR)	Total no patients (%)	n (%) or median (IQR)	Total no patients (%)
In-hospital mortality	391 (41.8)	936 (100.0)	0 (0.0)	545 (100.0)	391 (100.0)	391 (100.0)
Positive PCR testing result	773 (90.8)	851 (90.9)	444 (90.8)	489 (89.7)	329 (90.9)	362 (92.6)
DEMOGRAPHICS						
Age (years)	65 (16.0)	936 (100.0)	62 (18.0)	545 (100.0)	68 (13)	391 (100.0)
Male sex at birth	576 (61.5)	936 (100.0)	282 (51.7)	545 (100.0)	294 (75.2)	391 (100.0)
COMORBIDITIES*						
Alcohol use	18 (2.0)	898 (95.9)	9 (1.7)	517 (98.3)	9 (2.4)	381 (97.4)
Cardiovascular disease	134 (14.9)	-	64 (12.4)	-	70 (18.4)	-
Chronic respiratory disease	102 (11.4)	-	43 (8.3)	-	59 (15.5)	-
Rheumatic/connective tissue disease	12 (1.3)	-	11 (2.1)	-	1 (0.3)	-
Chronic neurological disease	64 (7.1)	-	29 (5.6)	-	35 (9.2)	-
Cirrhosis	14 (1.6)	-	8 (1.5)	-	6 (1.6)	-
Chronic kidney disease	82 (9.1)	-	55 (10.6)	-	27 (7.1)	-
Diabetes (type 1 and 2)	366 (40.8)	-	194 (37.5)	-	172 (45.1)	-
Hypertension	390 (43.4)	-	195 (37.7)	-	195 (51.2)	-
Hypothyroid	9 (1.0)	-	8 (1.5)	-	1 (0.3)	-
Malignancy	56 (6.2)	-	18 (3.5)	-	38 (10.0)	-
Current or former smoker	84 (9.4)	-	42 (8.1)	-	42 (11.0)	-
Total number of comorbidities						
0	173 (19.3)	898 (95.9)	123 (23.8)	517 (98.3)	50 (13.1)	381 (97.4)
1	358 (39.9)	-	229 (44.3)	-	129 (33.9)	-
≥2	367 (40.9)	-	165 (31.9)	-	202 (53.0)	-

VITAL SIGNS						
Glasgow Coma Scale	15 (1)	862 (92.1)	15 (0)	486 (89.2)	14 (4)	377 (96.4)
Heart rate (beats/min)	97 (22)	885 (94.6)	95 (20)	513 (94.1)	100 (25)	372 (95.1)
Peripheral oxygen saturation (%)**	93 (10)	846 (90.4)	95 (6)	515 (94.5)	87 (16)	331 (84.7)
Systolic blood pressure (mmHg)	130 (33)	882 (94.2)	131 (26)	526 (96.5)	121 (47)	356 (91.0)
Respiratory rate (breaths/min)	25 (10)	892 (95.3)	24 (8)	536 (98.3)	28 (14)	356 (91.0)

PCR: Polymerase chain reaction

*Some comorbidities have been collapsed into the following clinically meaningful categories:

Cardiovascular disease includes one or more of the following: atrial fibrillation, congestive heart failure, coronary artery disease, deep vein thrombosis, dilated cardiomyopathy, ischaemic heart disease, myocardial infarction, and small vessel disease.

Chronic respiratory disease includes one or more of the following: asthma, chronic obstructive pulmonary disease, and tuberculosis.

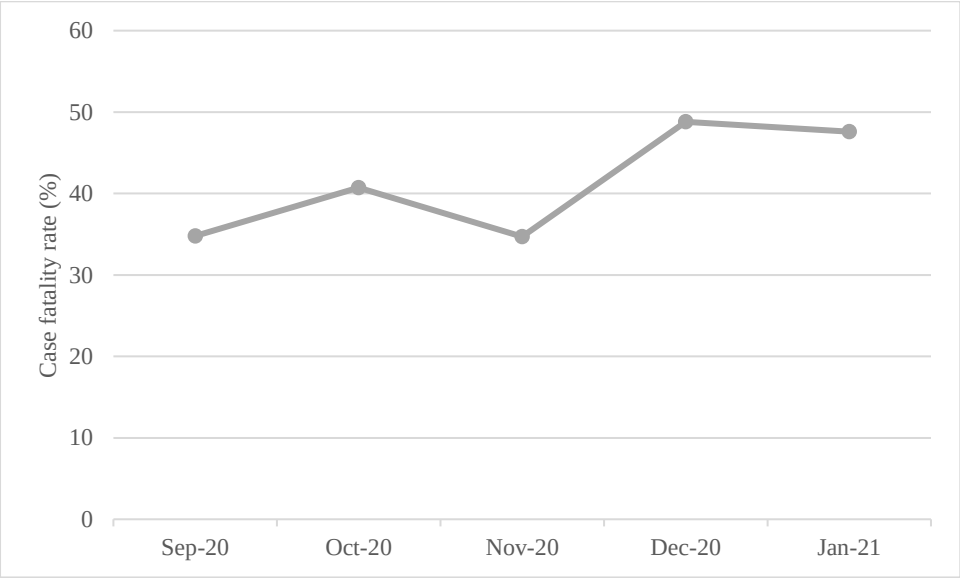
Rheumatic/connective tissue disease includes one or more of the following: gout, lupus, and rheumatoid arthritis.

Chronic neurological disease includes one or more of the following: epilepsy, haemorrhagic or ischaemic stroke, and Parkinson's disease.

** Peripheral oxygen saturation obtained on room air.

CFRs were variable during the data collection period (Figure 4.1). Decreasing rates were seen in the later months of 2020, reaching a low of 34.2% in November 2020 before increasing to 49.3% in December 2021.

Figure 4.1: COVID-19 case fatality rates at four government referral hospitals in Sudan from September 2020 to January 2021



Model assessment

In both versions of the scale, most patients – 46.6% (n=437) in the tool with pulse oximetry, and 58.9% (n=552) in the one without - were estimated to have between 33% and 66% risk of death. Distributions of scores are shown in Table 4.2, and Figures 4.2a and 4.2b.

Table 4.2 Comparison of mortality risk rates by mortality risk group for 936 COVID-19 patients used to validate the AFEM-CMS

		AFEM-CMS without pulse oximetry score			AFEM-CMS with pulse oximetry score		
Mortality risk group	**Score**	**No. patients**	**No. fatalities**	**CFR (%)**	**No. patients**	**No. fatalities**	**CFR (%)**
< 33%	0 to 2	226	38	16.8	293	29	9.9
33% to 66%	3 to 5	552	216	39.1	437	173	39.6
> 66%	6 +	159	137	86.2	207	189	91.3

Figure 4.2a: Distribution of patients across AFEM COVID-19 Mortality Scale (AFEM-CMS) scores in validation cohort, for resource settings with access to pulse oximetry.

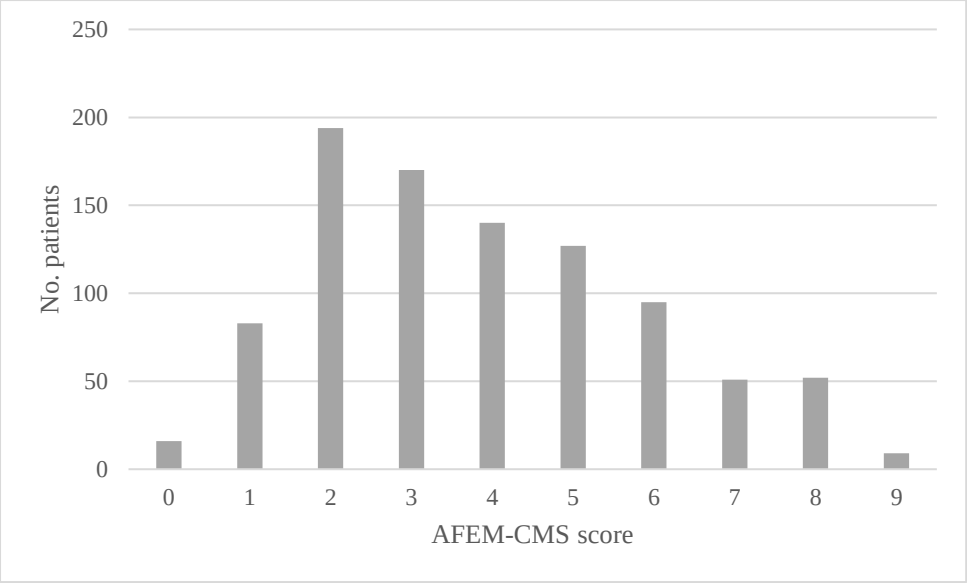
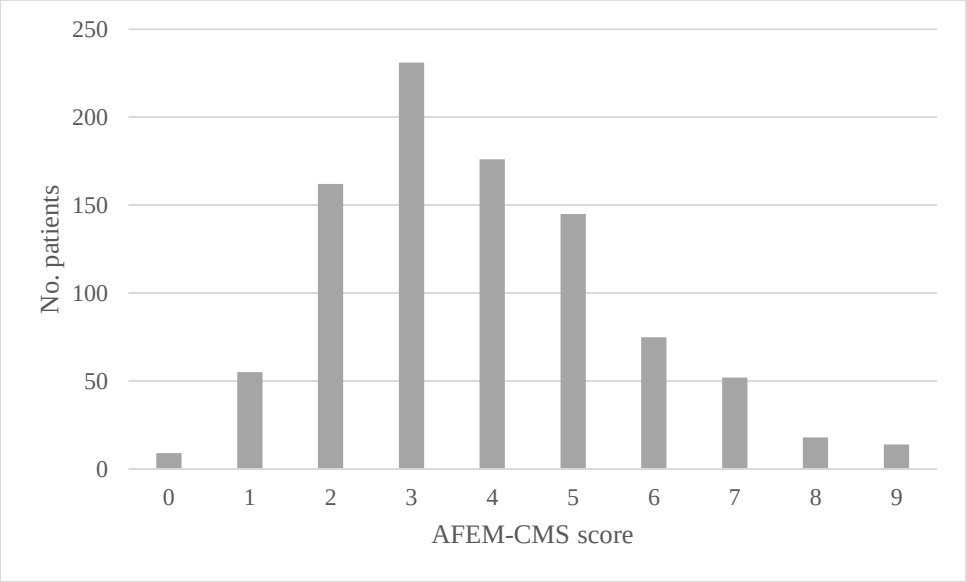


Figure 4.2b: Distribution of patients across AFEM-CMS scores in validation cohort, for resource settings without access to pulse oximetry.



Both versions of the mortality scale showed moderate discrimination in this validation study. The model including pulse oximetry had a C-statistic of 0.732 (95% CI: 0.687-0.777) and the model excluding pulse oximetry had a C-statistic of 0.696 (0.645-0.747).

5. DISCUSSION

This study provides the first validation of the AFEM-CMS. Its results suggest that, when applied to its intended setting – COVID-19 patients in Sudanese EUs – the tool has acceptable discrimination in identifying those at increased risk of death from COVID-19. This discriminatory power is similar, albeit slightly lower, than that originally described when the model was trained.(78) The dataset used for this study was more than twice the size of the derivation dataset, and came from both the two government referral hospitals included in the derivation dataset and two additional facilities. It is likely that this dataset provided a broader sampling of the population that is presenting to government hospitals with COVID-19 than its predecessor. It may also be more reliable: A greater percentage of the population was tested using PCR techniques and had laboratory-confirmed SARS-CoV-2 infection in the validation dataset, in comparison to the model on which the AFEM-CMS was trained. Additionally, the mortality rate associated with the validation data collection period was greater than ten percentage points lower than that of the derivation period, similar to that reported by Omar et al. in another region of Sudan.(57) Given that the burden of COVID-19 in Sudan increased in the later part of 2020, a decrease in mortality rate may suggest overall clinical and systems improvements in managing patients and preventing death from COVID-19.(83) This may have implications for the originally-defined risk categories that the tool is using, if these improvements have led to increased survival.

Results of this study are largely comparable to that of many other published COVID-19 mortality risk-stratification tools, most of which were developed with datasets many magnitudes larger than this. Validations of the 4C Mortality Score, COVID-GRAM, and Xie score found the tools to have C-indices of 0.77 (95% CI: 0.76-0.78), 0.71 (95% CI: 0.68-0.74), and 0.73 (95% CI: 0.70-0.75), respectively.(84-86) The key difference between the results of these other validation studies and our own lies within the CIs for C-indices: The CIs surrounding our results are wider, due in larger part to the relatively smaller size of our dataset.

The model including pulse oximetry had slightly higher discrimination than its counterpart excluding this input. However, C-statistic 95% CIs for the two versions of the tool overlap.

Based on this finding, it cannot be recommended that LRS prioritise the use of the tool including pulse oximetry, unless they have consistent access to a reliable pulse oximeter for all potentially positive COVID-19 patients. In settings where a pulse oximeter may not always be available, or where obtaining this measurement may cause a delay (e.g., an EU with only one pulse oximeter that needs to be retrieved from elsewhere in the unit), clinicians should focus on use of the tool that does not include this input. Heart rate, which is included as an input on in the tool without pulse oximetry, is likely serving as a proxy for decreased oxygenation, as it will typically increase to compensate for decreasing blood oxygen levels.

The derivation and validation of the AFEM-CMS highlight the feasibility of real-time development of clinical tools to improve patient care, even in times of surge in LRS. In LRS, where clinical information is typically recorded on paper and medical records are not linked electronically, it can often take multiple years to collect a dataset that is large enough to inform any single clinical tool, and the process must be repeated to validate it. By leveraging innovative machine learning techniques, smaller datasets can be used to derive and validate such tools in shorter periods of time. This study is just one of hundreds of efforts across all resource levels that suggests that being able to rapidly deploy machine learning methodologies holds promise in improving responses to pandemics and other emergencies. It is our hope that, in future health crises, LRS-based clinicians and researchers can refer to these techniques to inform situationally appropriate clinical tools and reduce morbidity and mortality.

Limitations

The AFEM-CMS's key limitation remains its generalisability: Only data from government referral hospitals located in Khartoum State, Sudan, were included in the tool's derivation and validation. As such, the AFEM-CMS's generalisability is likely limited outside of similar LRS settings similar to Sudan; this may include facilities in other nations included on the Development Assistance Committee's list of Least Developed Countries.(87) Until external validation has been conducted in other contexts and regions, broader use of the tool cannot be recommended.

The patients included in this cohort were, on average, older than Sudan's general population, with a greater proportion of males.(88) It is also likely that this dataset captured a sicker cohort than the general SARS-CoV-2-infected population in Sudan: A combination of barriers in access to care, public knowledge of limited resources at healthcare facilities, and stigma surrounding care-seeking for COVID-19 may have led to only extremely ill patients presenting to EUs and thus being recorded in this study. Furthermore, although it has been reported that all hospitals in Sudan have been providing similar levels of care during the COVID-19 pandemic, regardless of their designation as a district or referral hospital, more critical patients may still be self-selecting to present to the higher-level referral hospitals included in this study. The derivation and validation of this tool against a sicker cohort may limit its ability to prognosticate less severe COVID-19 patients.

This study's results may have been influenced by the inclusion of self-reported information in the AFEM-CMS, such as age and presence of comorbidities. When patients are extremely ill, such information may be provided to clinicians by a third party or not at all. While the MICE methodology used to impute missing data in this study was considered robust, it is not a perfect replacement for the information itself and may have skewed results. Data missingness was similar in the survivor and non-survivor cohorts, though, making it unlikely that imputation would have significantly impacted only one of these groups' datasets.

Validation accuracy may also be affected by the inclusion of all patients that presented to study sites meeting the WHO definitions of suspected, probable, or confirmed COVID-19 infection.(80) In comparison to the derivation dataset, there was a substantial increase in the number of patients that were then laboratory-confirmed to have COVID-19. Ninety-one percent of patients in the validation dataset received PCR testing, a significant increase over the one-third of patients in the derivation dataset that were PCR-tested. Furthermore, nearly all of those tested were confirmed COVID-19 positive. But approximately twenty percent of the cohort received a negative PCR result for COVID-19 or was not tested at all. Without definitive laboratory testing, it cannot be known that all of these patients were truly infected with SARS-CoV-2. However, the significant increase in laboratory-confirmed infections over the previous derivation set does generate confidence in the validity of these findings in the study setting.

6. CONCLUSION AND RECOMMENDATIONS

The findings of this dissertation, to our knowledge, are the first which validate a COVID-19 mortality scale developed in a LMIC. These results demonstrate the potential of what LRS clinicians and researchers can develop from tools needed for a given patient population with a specific disease burden while rationing scarce healthcare resources in the COVID pandemic and beyond.

Overall, the AFEM-CMS was shown to be useful when applied in the low resource clinical setting and will be of great benefit in providing limited resource clinicians guidance in determining the allocation of resources to COVID-19 patients needing treatment.

6.1 Recommendations

The following recommendations are made to the Sudanese ministry of health and international health agencies:

- LRS-based clinicians and researchers use machine learning techniques to create situationally appropriate clinical tools that may reduce morbidity and mortality during health crises.
- After further validation in other countries, international protocols should incorporate this tool in LMIC protocols.
- The AFEM-CMS should be incorporated into the Sudanese national case management guidelines as a tool to aid clinicians in allocating the critical care resources and beds.
- The AFEM-CMS should be used in the referral offices for COVID 19 to allow the referral teams to prioritise the disposition of patients according to the bed availability and their score on the tool.
- Healthcare providers should be trained to use the tool to prioritise the allocation of resources in hospitals specially at times of patient overload.

6.2 Directions for future research:

This research shows that the tool is valid for use in LRS like Sudan but cannot yet be generalised to other settings.

- More research is needed to validate the tool in other settings to allow for its general application in determining severity of COVID patients.

- Considering the emerging COVID 19 strains that can potentially behave and manifest differently than previous strains, more research is needed with the new variants.
- As this tool was developed for adults, research is needed to develop a version of this tool for risk stratification for adolescents and children.

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8. APPENDICES

Appendix 1.1: MSc proposal.

VALIDATION OF A SEVERITY SCORING TOOL FOR COVID-19 ILLNESS IN LOW-RESOURCE SETTINGS

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DECLARATION

I, Yasein Omer, hereby declare that the work on which this proposal is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 06/11/2020

SUMMARY

The COVID-19 pandemic is unfolding in real time, quickly reaching some of the most vulnerable LRS across the globe. These settings tend to have underdeveloped healthcare systems that are exceptionally vulnerable to the strain of an outbreak such as SARS-COV-2. Clinicians in resource-limited contexts are in need of effective and contextually-appropriate triage and assessment tools that have been purpose-designed to aid in evaluating the severity of potential COVID-19 patients. In the context of the COVID-19 crisis, a low-input SST could be a cornerstone of ensuring timely access to appropriate care and justified use of critically limited resources.

Historically, the publication of data from time-sensitive incidents such as pandemics is slow. The rapid publication of COVID-19 data, however, provides a unique opportunity to identify potential features of severe COVID-19 disease and develop a severity scoring system in real-time, while the pandemic continues on. Strong data collection mechanisms have been set up in Sudan that will allow for rapid validation of the potential tool. The health systems in these two countries are as strained as any in Africa: if these tools work well in that setting, the findings should be directly extrapolatable to many other African settings.

This MSc aims to validate a severity scoring tool (SST) to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS.

A series of three studies are proposed to develop and validate such a SST. Study one will use a systematic review and meta-analysis to evaluate existing COVID-19 literature for relationships between historical characteristics, clinical presentations, and diagnostic investigations, and illness severity. In study two, analytic statistics will first be used to identify the features most predictive of severe COVID-19 disease in a Sudanese COVID-19 dataset. Then, a series of machine learning prediction algorithms will be employed to identify a singular algorithm that is most predictive of severe COVID-19 disease to become the SST. SST generated in study two will then be validated against retrospective data from study three.

Should validation findings prove promising, the study team intends to disseminate the SST and an associated training package across Africa via the African Federation for Emergency Medicine, and share it with WHO. Alternatively, should results show poor accuracy, the SST development process will be revisited for further tool refinement.

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1. INTRODUCTION

1.1 Background

Despite containment efforts, COVID-19 has reached pandemic status. As of 30 June 2020, there are 10.6 million confirmed cases worldwide, with over 520,000 deaths1 2; these numbers are only expected to grow as the pandemic continues into the coming months. Although data surrounding the novel coronavirus are rapidly evolving, current estimates depict a dire situation: Between 15% and 20% of infections lead to severe or critical disease.2 3 Highly vulnerable populations, compromised by malnutrition and comorbid diseases, are at higher risk for developing more severe forms of the illness.6 Mortality has varied across settings, but current data suggest a variable case fatality rate ranging from 0.5% to 4.5%.7-10

As COVID-19 spreads, healthcare systems worldwide are being strained.11 12 Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.15 High volumes of patients in need of critical care limit systems' abilities to provide such care; this is occurring even in the most highly-resourced settings.11 12 It is increasingly likely that the countries with the most limited capacity to respond will be affected on a large scale.13 Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.15 These processes are, however, significantly more challenging in low-resource settings (LRS). Many low- and middle-income countries (LMICs) have scarce critical care resources – they are LRS – with limitations in the availability of oxygen and other basic resources as well as healthcare provider shortages.17 18 While ongoing acute and emergency care system strengthening efforts are underway and showing impact in many of these settings, these efforts will not be able to keep pace with emerging demand. Immediate targeted efforts are needed to assist these countries in managing and treating large numbers of acutely ill patients.

Frontline providers in emergency units (EUs) need to make challenging decisions surrounding rationing of resources, including oxygen and ventilators, upon initial assessment of COVID-19 patients. Clinical guidance for evaluating patients' respiratory needs and subsequent dispositions is essential, particularly in LRS. A range of scoring systems are available to guide

care for severely ill patients. While these tools may have some utility in predicting COVID-19 patient severity, they are likely limited in this unique context. Some scores are designed for specific care settings, such as intensive care units (ICUs), a very scarce resource in LRS.19 While selected COVID-19 patients can be treated in ICUs, most patients are less critical, requiring interventions more appropriate for general ward and EU settings. Thus, a tool predicting outcomes based solely on those already admitted to ICU may have reduced utility across the range of illness severity seen in this disease. Other scoring systems were purpose-designed for patients presenting with specific conditions, such as pneumonia and sepsis.19 20 Condition-specific tools may be of some use in assessing COVID-19 patients but are likely limited in that these patients initially present with a range of symptoms, only some of which involve respiratory disease or septic shock.21 High burdens of data entry seen in many tools can lead to increased time-to-decision making and frequent missing data points.22-24 Some tools also involve additional investigations, including blood tests and imaging, that have very limited availability in LRS.19 25-27

The global threat posed by COVID-19 and its likely impacts on LRS make it essential for tools with the potential to reduce mortality be made widely available. A severity scoring tool (SST) holds promise in aiding frontline providers in LRS in managing the pandemic SARS-COV-2 infection and COVID-19 disease by allowing them to assess potential resources that a patient will need throughout the duration of both EU and hospital stays.

1.2 Motivation

The COVID-19 pandemic is unfolding in real time, quickly reaching some of the most vulnerable LRS across the globe. These settings tend to have underdeveloped healthcare systems that are exceptionally vulnerable to the strain of an outbreak such as SARS-COV-2.38 Clinicians in resource-limited contexts are in need of effective and contextually-appropriate triage and assessment tools that have been purpose-designed to aid in evaluating the severity of potential COVID-19 patients. In the context of the COVID-19 crisis, a low-input SST could be a cornerstone of ensuring timely access to appropriate care and justified use of critically limited resources.

Historically, the publication of data from time-sensitive incidents such as pandemics is slow. The rapid publication of COVID-19 data, however, provides a unique opportunity to identify potential features of severe COVID-19 disease and develop a severity scoring system in real-time, while the pandemic continues on. Strong data collection mechanisms have been set up in Sudan that will allow for rapid validation of the potential tool. The health systems in these two countries are as strained as any in Africa: if these tools work well in that setting, the findings should be directly extrapolatable to many other African settings.

1.3 Aim and objectives

This MSc aims to develop and validate a SST to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS.

To achieve this aim, the MSc has the following objectives:

1. Identify features predictive of severe COVID-19 illness (study one).
2. Validate the SST in the African setting using real-world data (study two).

2 METHODS

2.1 Study one: Clinical and historical features associated with severe COVID-19 infection: a systematic review and meta-analysis.

2.1.1 Aim and objectives

This study aims to systematically evaluate existing COVID-19 literature for relationships between historical characteristics, clinical presentations, and diagnostic investigations, and illness severity.

To achieve this aim, this study has the following objectives:

1. Describe existing literature surrounding historical characteristics, clinical presentations, and diagnostic investigations that have been evaluated as potential predictors of severe COVID-19 disease.
2. Synthesise all available evidence on these features in relation to severe COVID-19 disease.
3. Identify features that can feasibly be evaluated in LRS.

4. Obtain summary estimates of the effects of these LRS-appropriate features on illness severity.

2.1.2 Study design

A systematic review and meta-analysis will be conducted to identify papers that studied potential associations between demographics, comorbidities, clinical presentations and investigational studies, and COVID-19 illness severity. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines will be adhered to throughout this process.[55]

2.1.3 Search strategy

Three online databases (PubMed, Scopus, and Web of Science) will be searched using a combination of free-text phrases and medical subject headings. Results will be restricted to those in the English, Spanish, and Mandarin languages, published from 01 December 2019 to-date (TBC). Search terms related to COVID-19 infection ("NCoV", "Coronavirus", "severe acute respiratory syndrome coronavirus 2", "COVID", "COVID-19", "Coronavirus infections") and illness severity ("Severity of Illness Index", "severity", "critical", "critical illness", "critical care", "patient admission", "length of stay", "outcome", "morbidity", "mortality", "death", "respiratory insufficiency", "respiratory distress syndrome, adult", and "respiration, artificial") will be used in combination with those for demographics ("demographic", "demographic", "age", "sex", and "gender"), historical features ("comorbidity", "co-morbidity"), "pre-existing", and "condition"), clinical presentation ("signs and symptoms", "symptom", "characteristic", "clinical" and, "presentation"), and diagnostic investigations ("investigation", "laboratory", "blood test", "imaging", "X-ray" and, "CT"). Refer to Appendix 1A for full search strategy.

All publications in the World Health Organization's (WHO) Database of Publications on Coronavirus Disease (COVID-19) will also be included.[56] Reference lists of all eligible full texts will be reviewed to identify additional relevant literature.

Duplicates will be manually removed. All articles will be screened for inclusion by two independent reviewers, after which a third reviewer will retrieve each eligible full-text and consider it for inclusion. Discrepancies in agreement at all stages will be resolved through discussion.

2.1.4 Selection criteria

This study will include all peer-reviewed, published full-text manuscripts that provide data on associations between the outcome of interest - disease severity - and demographics, comorbidities, symptoms, vital signs, and/or investigational studies of confirmed COVID-19 patients admitted to hospitals. Those not directly evaluating primary data, including literature reviews and meta-analyses, will be excluded. Pre-print articles, research-based correspondence pieces, opinion and editorial pieces, case reports, and clinical management guidelines will also be excluded. A range of definitions and parameters of disease severity will be considered acceptable as comparator outcomes, including disease severity itself (as defined by the article's authors), as well as proxy measures for disease severity, such as inpatient mortality and ICU admission.[57] Manuscripts that do not include statistical analyses evaluating significance will be excluded, as will those not reporting aggregate data across severity classifications. Those including statistical analyses will be include, regardless of significance testing results. To avoid selection bias, no quality restrictions will be placed on studies for inclusion.

There will be no restrictions to study design. For studies evaluating exclusively children or pregnant populations, or populations with a specific comorbidity, only comparisons between the population itself and a comparator group in the general population will be included. For example, a comparison between diabetics and non-diabetics, evaluating the direct effect of diabetes on illness severity, would be included. Predictors of illness only within these specific populations will not be included.

2.1.5 Data extraction and evaluation

Data extracted from each article will include author(s); title; countries involved; study population demographics; measure and definition of disease severity; and each presenting symptom, comorbidity, initial vital sign, and investigational study that was statistically assessed against disease severity, along with notation of whether each variable was found to be significantly associated with severity. Variables reported with a p-value <0.05 will be considered significantly associated with illness severity. One reviewer will extract data, and second reviewer will cross-check all extractions. All extracted variables will be documented categorically as 'significant', 'not significant' or 'not reported'.

The eight-question Newcastle-Ottawa Scale Quality Assessment Scale for Cohort Studies (NOS) (Appendix 1B) will be used to evaluate quality of included studies; studies will be assigned as "good", "fair" or "poor" quality based on ratings in each of the tool's three domains (selection, comparability, and outcome).[58] Two reviewers will score each study, reaching consensus via discussion when necessary.

2.1.6 Data synthesis and analysis

A descriptive analysis of the number of papers that reported each variable as significantly associated with illness severity will be conducted.

The results of this study's meta-analysis will be used to inform a LRS SST for use on patients immediately upon arrival to EUs (study two). Given this objective, this study will use meta-analysis to evaluate the effects on severity of only those features feasible to rapidly evaluate in LRS EUs. Available literature suggests that demographics, comorbidities, signs and symptoms, and some vital signs are considered feasible; other vital signs, and all laboratory and imaging investigations, are generally not.[17] As such, all feasible features relating to demographics, history and clinical presentation will be included in this portion of the analysis.

Data for each of these feature swill be aggregated across all studies. Individual patient data meta-analyses are less prone to bias than aggregate data meta-analyses; however, it is not feasible to obtain data at the patient-level when the number of included studies is expected to be high and raw data do not appear to be readily available online.[59] All data will be in the form of binary categorical variables. Pooled odds ratios and associated 95% confidence intervals and p-values will be calculated. Variables with a p-value <0.05 will be considered significant. The number of patients with each outcome (severe or not severe) and the prevalence of each feature across the two outcome groups will also be calculated.

Between-study heterogeneity will be assessed using the I^2 test.[60] A random-effects model (DerSimonian-Laird) will be used when significant heterogeneity is identified across studies, indicated by an I^2 value >50% (moderate or high heterogeneity).[61] Where this variance is not significant, a fixed model (Mantel-Haenszel) will be used. Funnel plots will be evaluated for symmetry to identify possible publication bias.[61 62] Forest plots will be used to display point estimates of individual studies and a summary estimate for each feature studied. [61]

2.1.7 Limitations

Due to the emergent COVID-19 pandemic and need for data to inform responses, rapid efforts are being made to publish any available information. To improve quality of included data, our review will include only publications that have undergone peer-review. All studies will be evaluated using the NOS to give readers additional context on the quality of included studies. There may also be heterogeneity in outcomes across studies, as well as potential publication bias. The I^2 test and funnel plots will be used to evaluate these risks and provide additional context around results.[61 62]

Findings of this study may also be limited in that numerous definitions for, and proxy measures of, illness severity are presented in the primary literature included in this review. While this variance may influence results, it cannot be avoided given the urgency of the COVID-19 pandemic and lack of existing evidence.

2.1.8 Ethical considerations

This study does not involve human participants and therefore poses no risk or harm. However, given that this study comprises part of a MSc, a waiver will be obtained from UCT HREC.

This review has been prospectively registered with PROSPERO, registration number CRD42020178098.

2.1.9 Reporting and implementation of results

Outcomes of study one will be used as evidence to inform the development of the SST in study two. Study results will be collated into a report for presentation to interested groups. Results will also be written into a manuscript and submitted for publication.

2.2 Study two: A retrospective evaluation of performance characteristics the Severity Scoring Tool for potentially positive COVID-19 patients in Sudan.

2.2.1 Aim and objectives

The aim of this study is to assess SST accuracy and utility in predicting disposition in patients that have screened potentially positive for COVID-19 infection upon entrance to LRS EUs in Sudan.

To achieve this aim, this study has the following objectives in Sudanese EUs:

1. Evaluate SST performance characteristics based on multiple measures of patient outcome.
2. Assess mortality risks predicted by the SST.
3. Describe basic demographics and dispositions of potentially-positive COVID-19 patients at hospitals in Sudan.

2.2.2 Study design

Once developed, there will be a critical need for preliminary data on the SST in LRS, to inform refinements and support wider rollout. While case vignettes serve as an ideal proxy for a gold standard against which to assess triage tool accuracy, these methods are conducted outside of clinical practice and take substantial time.[57 63] In the context of a global pandemic, it is neither realistic nor feasible to remove clinicians from their practice setting to test accuracy of a tool (never mind the lengthy process of developing a valid set of vignettes specific to COVID-19). An alternate mechanism for testing prognostic tool accuracy is to use proxy indicators of severity.[57] The more severely ill a patient, the more likely he/she is to die or to be admitted to intensive care and remain there. The less ill a patient, the more likely he/she is to be discharged. While not ideal, EU and hospital dispositions are often used as proxy measures.[57] The time-dependant need for such a tool in this current pandemic does not lend to more extensive evaluation processes such as case vignettes: only pragmatic, practice-based measures should be considered. Given this, the most logical method of assessing SST accuracy is to evaluate their performance in predicting patient status and dispositions.

A retrospective quantitative analysis of data collected on adult patients screened as potentially positive for COVID-19 will be undertaken.

2.2.3 Study setting

Twenty-one EUs in Sudan will be included in this study. These EUs are all urban, located in a mix of district and regional level facilities.

2.2.4 Study population

Data on all patients presenting to included facilities over an eight-week period; this will be the eight-week period directly following the cut-off of data collection for those patient records used in derivation of the SST.

The target sample size required for SST performance characteristics analyses are based on a conservative estimated area under the receiver operating characteristic curve (AUROC) of 0.65 for the SST and a null AUC value of 0.5. Statistical significance was set at an alpha value of 0.05 with a power of 80%.[46] Based on a previous study of COVID-19 mortality,[3] we calculated an estimated ratio of survivors to non-survivors of 24:1, resulting in a required minimum sample size of 775.

It is expected that a high volume of patients will present to EUs, all of whom will be screened for COVID-19 outside of the EU. Most patients are likely to screen negative for COVID-19, thus not entering the COVID-19 triage pathway. Based on current data, the Sudanese Ministry of Healthy (MOH) estimates that facilities will have screened a minimum of five patients as potentially positive each day, totalling a minimum of 2940 patients during the study period.

2.2.5 Data collection and management

Patient data will be collected retrospectively for all those presenting during the study period. Data collection will not affect health system capacity during this crisis: All data required for this study are already being collected in Sudanese EUs by non-clinical administrative personnel into an electronic platform and transferred to a national COVID-19 registry.

The following standardised data points will be obtained for the first 1000 adult patients logged in the Khartoum State MOH COVID-19 database:

- age,
- sex,
- comorbidities,
- initial vital signs,
- EU length of stay,
- EU disposition,

- date of admission (if admitted)
- respiratory status at 24-hours (ventilation and oxygen needs) (if admitted),
- hospital length of stay (if admitted), and
- 7-day disposition (if admitted).

All data used in this process will be deidentified prior to receipt. Extracted data will be accessible only by the study investigators listed in this application, stored locally on password-protected files in research offices. This dataset will only be used once: To avoid bias, these data will not be the same as those included in study two's validation process.

2.2.6 Data analysis

In an effort to thoroughly assess the tool's accuracy, the three SST severity levels will be compared to three measures of patient status: EU disposition, 24-hour respiratory status, and 7-day disposition. [57 63] As previously mentioned, while clinical vignettes are often considered a better standard for triage tool validation [57 63], the urgent need for data supporting these tools does not afford time to conduct such a study.

Multiple analyses will be conducted to evaluate SST accuracy. Performance characteristics, comparing severity scores to expected outcomes (described below in Table 2), along with AUROC scores, will be used to assess accuracy for severity categorisations. Utility will be assessed by evaluating mortality risks across severity categories. These metrics, along with associated 95% confidence intervals, will be calculated across all sites and across all facility levels where appropriate. Comparative statistics will be used to describe differences amongst sites and countries. Simple descriptive statistics will also be calculated. All statistics will be generated using R statistical software (© RStudio, Boston, MA, USA).

Table 1: Description of planned analyses for each country included in this study.

Analysis	Calculations
SST performance characteristics by proxy of: 1. EU disposition 2. 7-day disposition 3. Respiratory status at 24 hours	• Sensitivity and specificity; PPV and NPV; and over- and under-triage [64] • AUROC for overall prognostic accuracy [65]
Comparison of SST performance characteristics across sites and countries	• Pearson's X^2 (comparison of performance characteristics) • Pairwise comparison of ROCs using Mann-Whitney U test
EU and 7-day mortality risks, and 24-hour risk of needing respiratory interventions, according to SST category	• Adjusted ORs determined using multiple logistic regression
Comparison of EU and 7-day mortality risks, and 24-hour risk of needing respiratory interventions, according to SST category, across sites and/or countries	• Simple comparison of adjusted ORs • Use of Wald *z* statistics in multiple regression with additional adjustment for sites

Table 2 outlines expected patient outcomes based on the categories that will be defined by the SST. For example, those categorised with a severity of "critical" can be assumed to have the poorest prognosis across all measures including death, admission to and a prolonged stay in ICU, and a need for ventilatory support. "Severe" patients are expected to be admitted with severe but not critical prognoses, and "mild/moderate" patients are expected to need little treatment and be discharged, likely directly from the EU. These outcomes will be used to determine accurate and inaccurate severity designations.

Table 2: Expected patient outcomes based on IIT and SST categorisations.

SST	Expected EU disposition	Expected 7-day disposition	Respiratory status at 24hr
Mild/Moderate	Discharge	Discharged from EU	No oxygen needed
Severe	Admission to general ward	Discharged or remains on general ward	Some oxygenation required
Critical	Admission to ICU	Dead or remains in ICU	Mechanical ventilation required

Specific measures used to report on accuracy are defined below (Tables 3 and 4). Note that measures apply to all three severity category assignments and Table 4 uses the SST "severe" categorisations and expected general ward admission as an example to elaborate.

Table 3: Hypothetical contingency table illustrating numbers of severity scoring assignments by EU providers in comparison to severity scoring assignments by proxy of EU disposition.

		Severity level as determined by EU disposition*			
		Critical	Severe	Mild/Moderate	All
SST category assignment	Critical	a	b	C	U
	Severe	d	e	F	V
	Mild/Moderate	g	h	I	W
	All	X	Y	Z	

*EU disposition of death or ICU admission = critical; EU disposition of general ward admission = severe; and EU disposition of discharge = mild/moderate.

Table 4: Example definitions for accuracy performance characteristics for the acuity "severe" (general ward admission) [64].

Measure	**Equation**	**Description**
Sensitivity (%)	$\frac{e}{Y}$	Proportion of general ward admissions classified as severe by EU providers
Specificity (%)	$\frac{(U-b)+(W-h)}{X+Z}$	Proportion of deaths and ICU admissions (critical), and discharges (mild/moderate), classified as severe by EU providers
Under-Triage (%)	$\frac{h}{Y}$	Proportion of general ward admissions classified as mild/moderate by EU providers
Over-Triage (%)	$\frac{b}{Y}$	Proportion of general ward admissions classified as critical by EU providers
Positive Predictive Value	$\frac{e}{V}$	Proportion of patients classified as severe by EU providers that were general ward admissions
Negative Predictive Value	$\frac{(X-d)+(Z-f)}{U+W}$	Proportion of patients classified as critical or mild/moderate by EU providers that were deaths and ICU admissions, or discharges

2.2.7 Ethical considerations

Study three will not commence until ethical approval has been received from two institutions: the University of Cape Town and the Khartoum State MOH. The Khartoum State MOH has provided ethical approval for this work (Appendix A). Research will not commence until all approvals have been obtained. Facilities in Sudan have been selected for this study because

of interest from AFEM partners in these countries and knowledge of strong COVID patient data collection mechanisms.

Children (aged <18 years) will not be included in this study. We do, however, acknowledge the vulnerability of participants in this study in that they are seeking emergency healthcare. There is a risk for breach of privacy and confidentiality for participants included in this study, as their records are being accessed for data extraction. To reduce this risk and prevent the potential stigmatisation that can come from a COVID-19 diagnosis, no identifying information will be extracted from patient records. All electronic data will be stored in encrypted, password-protected files. Only study personnel will have access to these data. Analyses will be conducted anonymously and at the aggregate level.

In There are no risks that will adversely affect patient care by collection of this data, as requisite data points are already being documented in EU and ward clinical notes, and transferred to the national COVID-19 registry. This study therefore places no additional burden on frontline providers. All data will be entered as usual in notes and will later be extracted retrospectively by data collectors for the purposes of this study.

This study will benefit both study populations, as well as similar populations in other LRS, by providing much needed evidence to guide the potential rollout of the SST in Sudan and many other LRS countries which are likely to suffer COVID-19 outbreaks shortly and whose emergency care systems are severely constrained. The appropriate allocation of limited ICU beds and ventilatory support will aid frontline providers in the management of these patients. The potential benefits of this research to the population under study significantly outweigh the associated minimal risks to individual participants.

2.2.8 Limitations

The primary limitation of this study is the use of EU disposition as a proxy for severity upon arrival. As previously mentioned, the gold standard in triage tool validation is the use of standardised case vignettes. There are factors outside of severity that may compound EU disposition, such as lack of bed availability (a patient who would otherwise go to ICU but ends up on the wards) and social factors (whereby patients are admitted as they have no carer at home). However, by studying this early in the epidemic curve, it is less likely that these factors apply.

A secondary concern is the study's sample size: Patient screening rates are simply estimates provided by local authorities and there is potential for the sample size to ultimately be smaller than predicted. A smaller study population could limit confidence in results. But, given the breadth of this study and discussions with in-country partners, it is unlikely that a substantial sample size will not be reached during the study period.

2.2.9 Reporting and implementation of results

Study results will be collated into a report for presentation to interested groups. Results will also be written into a manuscript and submitted for publication. Should validation findings prove promising, AFEM intends to disseminate the SST, an associated training package, and relevant study findings across Africa, and share it with WHO. Should study three results show poor SST accuracy, the SST development process will be revisited for further tool refinement.

3. RESOURCES

There are no costs associated with these studies.

4. TIMELINE

YEAR	2020		2021				2022	
QUARTER	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**1**
Ethical approvals								
Proposal development	X							
EMDRC	X							
HREC	X							
In-country ethics approval (MNH and SMOH)	X	X						
Study one	X							
Study two								
Preparation		X						
Ethics approvals		X	X					
Data collection			X	X				
Tool derivation			X	X				
Manuscript preparation				X	X	X		
Results								
Dissemination of results					X	X		
Dissertation preparation						X	X	
Dissertation submission								X

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6. Appendices

Appendix 1.1: Ethical approval for use of Sudanese data from the Khartoum State MOH.

MINISTRY OF HEALTH

DEPARTMENT OF CURATIVE MEDICINE

ISOLATION COMMAND CENTER

KHARTOUM, SUDAN

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10 October 2020

Professor Marc Blockman
Human Research Ethics Committee
Faculty of Health Sciences
University of Cape Town

Dear Professor Blockman:

RE: DEVELOPMENT AND VALIDATION OF A SEVERITY SCORING TOOL FOR COVID-19 IN SUDAN (HREC Ref No. 450/2020).

I write to you today to confirm approval of the above-mentioned project by the Khartoum State Ministry of Health. Dr Yasein Omer and his co-investigators in the Division of Emergency Medicine at the University of Cape Town – Prof Lee Wallis and Mrs Jennifer Pigoga – have full permission to use de-identified data from the Khartoum State Ministry of Health COVID-19 database in their work to generate a severity scoring tool using machine learning. Additionally, the research team has permission to use the database for validation purposes.

All determinations regarding this project have been made based on the information submitted by the investigator. Any substantive modifications to the research must be submitted for review prior to initiation of the change.

This approval is granted for a one-year period, until 05 October 2021. Should this research continue past that date, the study protocol must be resubmitted and reviewed.

Should you have any questions regarding this matter, I can be contacted at shibonh@who.int

Yours sincerely,

Hala A. shibon
Steering Committee of ICC
Isolation Command Center KSMOH

Appendix 3.1: Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) guidelines for "*Validation of a contextually appropriate COVID-19 mortality scale for low-resource settings.*"

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	Describe eligibility criteria for participants.	4
	5c	Give details of treatments received, if relevant.	5
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	Explain how the study size was arrived at.	6
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	6
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	6
Risk groups	11	Provide details on how risk groups were created, if done.	6
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	7
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
Model development	14a	Specify the number of participants and outcome events in each analysis.	9
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	N/A
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9
	15b	Explain how to the use the prediction model.	6, 9
Model performance	16	Report performance measures (with CIs) for the prediction model.	9
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	9-11
Implications	20	Discuss the potential clinical use of the model and implications for future research.	9-11
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	22	Give the source of funding and the role of the funders for the present study.	11

Appendix 3.2: Ethical approvals.

University of Cape Town Human Research Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 December 2020

HREC REF: 784/2020

Prof L Wallis
Division of Emergency Medicine
F-51, OMB
Email: - lee.wallis@uct.ac.za
Student: yaziosman0@gmail.com

Dear Prof Wallis

PROJECT TITLE: VALIDATION OF A SEVERITY SCORING TOOL FOR COVID-19 ILLNESS IN LOW-RESOURCE SETTINGS. (SUB-STUDY LINKED TO 450/2020) (MSC CANDIDATE: DR Y OMER)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 December 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Yasein Omer will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC/REF:784/2020sa

Sudanese Ministry of Health Approval

MINISTRY OF HEALTH

DEPARTMENT OF CURATIVE MEDICINE

ISOLATION COMMAND CENTER

KHARTOUM, SUDAN

---

10 October 2020

Professor Marc Blockman
Human Research Ethics Committee
Faculty of Health Sciences
University of Cape Town

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Should you have any questions regarding this matter, I can be contacted at shibonh@who.int

Yours sincerely,

Hala A. shibor
Steering Committee of ICC
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