

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

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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 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.

Aim and objectives

The aim of this research was to develop and validate a tool to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS. To achieve this aim, the following objectives were defined: identify existing methods of risk stratification of suspected COVID-19 patients worldwide; establish predictors of severe COVID-19 illness measurable in LRS; derive a risk stratification tool to assist facility-based healthcare providers in LRS in evaluating in-hospital mortality risk; and validate tool SST in the African setting using real-world data.

Methods

To achieve the aim of this dissertation, quantitative and review methodologies were employed across four studies. First, a scoping review was conducted to identify all studies describing screening, triage, and severity scoring of suspected COVID-19 patients worldwide. These tools were then compared to usability and feasibility standards for LRS emergency units, to determine viable tool options for such settings. Following this, a systematic review and meta-analysis were undertaken to evaluate existing literature for associations between COVID-19 illness severity, and historical characteristics, clinical presentations, and investigations measurable in LRS. Three online databases were searched to identify all studies assessing potential associations between clinical characteristics and investigations, and COVID-19 illness severity. Data for all variables that were statistically analysed in relation to COVID-19 disease severity were extracted and a meta-analysis was conducted to generate pooled odds ratios for individual variables' predictive abilities. In the third study, machine learning was used on data from a retrospective cohort of Sudanese COVID-19 patients to derive the AFEM COVID-19 Mortality Score (AFEM-CMS), a contextually appropriate mortality index for COVID-19. Following this, a fourth study was conducted with a more recent Sudanese dataset to validate the tool.

Results

The scoping review identified COVID-19 risk stratification 23 tools with potential feasibility for use in LRS. Of these, none had been validated in LRS. The systematic review then identified 79 eligible articles, including data from 27713 individual patients with laboratory-confirmed COVID-19. A total of 202

features were studied in relation to COVID-19 severity across these articles, of which 81 were deemed feasible for assessment in LRS. Meta-analysis of two demographic features, 21 comorbidities, and 21 presenting signs and symptoms with appropriate data available identified 19 significant predictors of severe COVID-19, including: past medical history of stroke (pOR: 3.08 (95% CI [1.95, 4.88])), shortness of breath (pOR: 2.78 (95% CI [2.24-3.46])), chronic kidney disease (pOR: 2.55 (95% CI [1.52-4.29])), and presence of any comorbidity (pOR: 2.41 (95% CI [2.01-2.89])). These significant predictors of severe COVID-19 were then considered for inclusion in the AFEM-CMS. Data from 467 COVID-19 patients in Sudan were used to derive two versions of the tool. Both include age, sex, number of comorbidities, Glasgow Coma Scale, respiratory rate, and systolic blood pressure; in settings *with* pulse oximetry, oxygen saturation is included and, in settings *without* access, heart rate is included. The AFEM-CMS showed good discrimination: The model including pulse oximetry had a C-statistic of 0.775 (95% CI: 0.737-0.813) and the model excluding it had a C-statistic of 0.719 (95% CI: 0.678-0.760). The tool was then validated against a second set of data from Sudan and found to once again 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 and relevance

This dissertation establishes what is, to our knowledge, the first COVID-19 mortality prediction tool intentionally designed for frontline providers in LRS and validated in such a setting. The derivation and validation of the AFEM-CMS highlight 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.

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ABBREVIATIONS

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-2019
CURB-65	CURB-65 Severity Score
DALYs	Disability-adjusted life years
DCP	Disease Control Priorities
EC	Emergency care
ECS	Emergency care system
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
NEWS2	National Early Warning Score 2
NHC	National Health Committee of the People's Republic of China
NOS	Newcastle-Ottawa Scale Quality Assessment Scale for Cohort Studies
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
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SST	Severity scoring tool

TRIPOD

Transparent Reporting of a Multivariable Prediction Model for Individual
Prediction or Diagnosis guidelines

WHO

World Health Organization

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Chapter 1: Introduction

1.1 General introduction

1.1.1 Emergency care

Emergency conditions contribute substantially to disability and premature death worldwide, and make up around half of the total global burden of disease.¹ This burden includes not only traumatic injuries, but also non-communicable diseases, obstetric conditions, and infectious diseases—conditions where patients could have averted permanent disability or death if they received more timely and appropriate care. Furthermore, the resulting death and disability from these emergency conditions also create a significant social and economic toll. For example, most of the victims of traumatic injuries tend to be young, working age individuals between the ages of 15 to 44 years old.²

However, despite advances in emergency care (EC) worldwide, the burden of emergency conditions disproportionately affects the lowest income countries, where over 90% of all injury-related deaths occur.³ In terms of disability-adjusted life years (DALYs), emergency conditions are nearly 60% worse in low-resource settings (LRS), which experience a burden of 25,186 DALYs per 100,000 population – nearly double the 15,691 DALYs seen per 100,000 in middle-income countries.^{4 5} Part of this trend is due to the rapid urbanisation and increasing access to motorised vehicles and weapons in LRS, and also the growth of non-communicable diseases such as hypertension, diabetes, and cardiac conditions that can lead to emergencies such as cardiac arrest and stroke—all of which are likely to increase in LRS in the coming decades. Despite the prevalence of emergency conditions and the consequential negative health and economic impact though, most LRS lack relevant EC policies and capacities.

Much of this burden could be alleviated by effective and well-timed emergency care. For emergency conditions, delays or inappropriate care can mean the difference between life and death, and an organised emergency care system (ECS) provides critical access to immediate and urgent interventions for life- or limb-threatening diseases and injuries. In high-income countries (HICs) the implementation of state-wide trauma systems has resulted in reductions in risk-adjusted mortality, and up to a 15% reduction in overall mortality.⁶ Evidence also suggests that general organised systems of EC can lead to significant improvements in mortality outcomes,^{7 8} and an estimated 54% of annual deaths in LRS could be addressed with pre-hospital and facility-based EC.⁹ The effectiveness of EC is so significant that the Disease Control Priorities (DCP) project estimates that over half of deaths in low- and middle-income countries (LMICs) could be stemmed through the implementation of appropriate EC,¹⁰ and already data has shown that many of the most prominent and general causes of death and disability in LMICs such as diarrhoea, respiratory

infections, ischaemic heart disease, and road traffic injuries have been responsive to improvements in EC delivery.¹¹

1.1.2 Coronavirus-19 and the emergency care system

The global importance of effective ECS has become even more apparent during the worldwide Coronavirus-19 (COVID-19) pandemic. Despite containment efforts, in early 2020 the COVID-19 virus reached pandemic status, resulting internationally in many lockdowns, panic, and patients seeking care for a new disease. By June of 2021, there had been nearly 180 million confirmed cases and 3.9 million deaths due to COVID-19 worldwide,¹² and early studies witnessed 15-20% of cases leading to severe or critical disease.¹³ Highly vulnerable populations, compromised by malnutrition and comorbid diseases, have been at even higher risk of developing the more severe forms of the disease.¹⁴ However, as COVID-19 spread globally and healthcare systems worldwide were strained,^{15 16} early recognition, resuscitation, and referral proved to be effective responses that yielded lower mortality.¹⁷ Thus, the role of EC was critical in healthcare systems' response to COVID-19 patients. Furthermore, it was essential for ECS worldwide to continue maintaining their ongoing essential health services, as emergency conditions continue to occur through the pandemic. EC also became an especially essential function during the pandemic as other social and clinical services halted, creating an even greater dependency on ECS to support populations.

However, despite the importance of ECS for COVID-19 response, ECS are not evenly distributed around the world, and their organisation and function vary considerably across countries. Though LRS experience the highest burdens from emergency conditions, they are the most under-resourced to handle these loads, and this results in delays in initiating appropriate care, which results in many preventable deaths and disabilities, including from COVID-19. Studies have shown that as few as 19% of hospitals in sub-Saharan Africa have the capacity to deliver 24-hour EC.¹⁸ The treatment ability of these facilities also varies widely, and they have a scarcity of clinicians trained in EC and an often lack of oxygen and other basic resources.¹⁹ ²⁰ In a study of 192 facilities across 59 low-income countries (LICs), only 18% had physicians on staff with specialised emergency training, and only 4% surveyed had staff with these skills available fulltime.²¹ In locations where EC has not yet been established within a medical speciality, and which suffer from weak ECS, populations remain at risk of avoidable mortality and morbidity from diseases such as COVID-19. Where present, ECS in LRS struggle to meet demand, and even before the COVID-19 pandemic the volume of patients presenting at these facilities was nearly ten times those of HICs.¹¹ This is a reality further confirmed by the fact that individuals with life-threatening but treatable injuries are six times more likely to die in a LIC than in a HIC.³ With COVID-19 spreading in LRS, this adds even more strain to already struggling ECS.

1.2 Motivation

The COVID-19 pandemic continues to unfold in real time, with enduring impact on some of the most vulnerable LRS across the globe.²² COVID-19 will likely continue to heavily burden LMICs much longer than in HICs.²³ LMICs' swift implementation and strong enforcement of public health practices such as lockdowns were effective in stemming the early spread of COVID-19 and bought valuable time to build healthcare capacity in LMICs,²⁴ but these lockdowns had severe social, economic, and health-related costs that are not sustainable in the long term.²⁵ LMICs that were resource constrained to begin with have been pressured to further ease lockdowns, and as lockdowns are loosened, there have been rises COVID-19 cases.²⁶ This increase in spread, in addition to the forecast that only 20% of people in LMICs will be vaccinated against COVID-19 this calendar year,²⁷ suggests the pandemic may continue for the foreseeable future in LMICs.²⁸

LMIC settings tend to have underdeveloped healthcare systems that are exceptionally vulnerable to the strain of an outbreak such as SARS-COV-2. Prior to the pandemic, ECSs in LRS were already described as overwhelmed and underdeveloped, and systems development work was only in nascent stages in most of these regions.¹¹ Clinicians in LRS contexts were, and continue to be, strained by the additional demands that COVID-19 has placed on their systems. The increase of COVID-19 spread in LMICs, in addition to the already overburdened and under-resourced ECS of those countries, means that clinicians and health system planners must be able to prepare constrained ECS and allocate limited healthcare resources as COVID-19 cases inevitably rise. They need 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 risk stratification tool could be a cornerstone of ensuring timely access to appropriate care and justified use of critically limited resources, such as beds, medications, or providers. Such a tool could have significant positive impacts at many points in the patient care journey, including in emergency units (EUs), where many COVID-19 patients first access the healthcare system. Previous tools to do such things for other illnesses and injuries have been shown to improve patient outcome while also reducing resource utilisation.^{29 30} However, while some tools have been developed and applied to the COVID-19 response, none are specifically designed for and validated in LRS.^{19 31-33} The likely prolonged course of the COVID-19 pandemic on LMICs make it essential that LRS-specific tools be widely available to help reduce the sustained impact of COVID-19 in LMICs.

A severity scoring tool (SST) can stratify patients with a diagnosis (e.g., confirmed or suspected COVID-19) based on risk of poor outcomes, such as mortality or admission to the intensive care unit, and aid providers in targeting scarce resources towards those in greatest need. These tools do, however, tend to be extremely intensive to develop: Substantial datasets are needed to derive and validate a truly predictive

scoring system, and these data can take many years to compile. In LRS, where data are often collected inconsistently and on paper, such datasets are rarely available.

Historically, the publication of data from time-sensitive incidents such as pandemics is slow. In this way, the COVID-19 pandemic has proven unusual: A combination of large-scale funding, existing international collaborations, and advances in technology have led to the prompt generation of datasets worldwide, including in some LRS. The rapid publication of COVID-19 data has provided 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.

Sudan serves as an example of a LRS that, prior to the pandemic, had begun initial investments in developing its ECS. As the pandemic ramped up, the government was able to leverage early improvements seen in data collection in EUs to begin robust collection of COVID-19-related data. These strong data collection mechanisms led to the identification of Sudan as an ideal setting for rapid development and validation of a SST for COVID-19 patients presenting to EUs. The health system in Sudan is as strained as any in Africa: if a tool works well in that setting, the findings should be directly extrapolatable to many other African settings.

1.3 Aim and objectives

1.3.1 Aim

The primary aim of this research was to develop and validate a severity scoring tool to assist frontline providers in rapidly predicting severe COVID-19 disease in low-resource settings.

1.3.2 Objectives

To achieve this aim, the following objectives were defined:

1. Identify existing methods of risk stratification of suspected COVID-19 patients upon initial presentation to healthcare systems worldwide.
2. Systematically identify predictors of severe COVID-19 illness measurable in low-resource settings.

3. Derive a pragmatic SST to assist facility-based healthcare providers in low-resource settings in evaluating in-hospital mortality risk, using only demographic and clinical inputs that are readily obtainable upon arrival in emergency units.
4. Validate the severity scoring tool in the African setting using real-world data.

1.4 Methodology

1.4.1 Methodological overview

To achieve the aim of this dissertation, a range of quantitative and review methodologies were leveraged.

First, a scoping review was conducted, with the goal of describing the landscape of existing risk stratification tools being used on COVID-19 patients in all resource settings. This review aimed to identify currently proposed and/or implemented methods of screening, triaging, and severity scoring suspected COVID-19 patients upon initial presentation to the healthcare system, and to evaluate the utility of these tools in LRS. A Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) scoping review design was used to identify all studies describing acute screening, triage, and severity scoring of suspected COVID-19 patients. Extracted information included clinical features, use of laboratory and imaging studies, and relevant tool validation data. These tools were then compared to predefined standards for feasibility in LRS EUs, to determine which, if any, may be viable options for implementation in such a setting.

Following this, a PROSPERO systematic review and meta-analysis were undertaken to evaluate existing literature for associations between COVID-19 illness severity, and historical characteristics, clinical presentations, and investigations measurable in LRS. Three online databases (PubMed, Scopus, and Web of Science) were searched using a combination of free-text phrases and medical subject headings to identify all studies assessing potential associations between clinical characteristics and investigations, and COVID-19 illness severity. Data for all variables that were statistically analysed in relation to COVID-19 disease severity were extracted. Meta-analysis was conducted to generate pooled estimates of odds ratios (pORs) for each individual variable to determine its potential predictive ability.

In the third study, a tool to assist LRS frontline providers in evaluating in-hospital mortality risk, using only easy-to-obtain demographic and clinical inputs, was developed. Machine learning was used on data from a retrospective cohort of Sudanese COVID-19 patients at two government referral hospitals to derive

contextually appropriate mortality indices for COVID-19, which were then assessed by C-indices. Following this, a fourth study was collected with a more recent dataset to validate the tool.

1.4.2 Ethics

Ethical approval for all work in this thesis was granted by the University of Cape Town (HREC REFS: 450/2020, 784/2020, and 814/2020). Full proposals and relevant approval letters are referenced within study chapters and included as appendices.

Additionally, for all derivation and validation research conducted in Sudan, local ethical approval was granted by the Sudanese Ministry of Health; these approvals are also referenced within the derivation and validation chapters (Chapters 4 and 5). Children aged less than 18 years were not included in these studies. To reduce risk of privacy and confidentiality breaches, and to prevent the potential stigmatisation that can come from a COVID-19 diagnosis, no identifying information was extracted from patient records. All electronic data were stored in encrypted, password-protected files. Only study personnel had access to these data and analyses were conducted anonymously and at the aggregate level.

1.4.3 Overview of study setting

The long-term impacts of the COVID-19 pandemic is particularly evident in LRS African nations, such as Sudan. As Africa's third largest nation, with a population of 41.8 million,³⁴ Sudan's healthcare system was strained even prior to the pandemic.^{34,35} Sudan has historically faced a disproportionate incidence of country crises such as political conflict and natural disasters, all of which has negatively impacted the healthcare system.^{36,37} When the COVID-19 pandemic reached Sudan, its already fragile healthcare system had to use its ECS to play a vital role in the pandemic response. Frontline EUs became a catch-all for a large portion of potentially positive COVID-19 patients and held responsibility for transferring patients between facilities. Additionally, there was a steep learning curve in coordinating ECS response with other services such as non-profit organizations, private healthcare services, and telecommunications,³⁸ and also with handling public service disruptions and securing funding sources including from foreign aid.³⁹ However, Sudan's recent investments in EC 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.

Geographic, demographic, and socioeconomic information

The Republic of the Sudan is a LIC situated in the northeast corner of the African continent.⁴⁰ Its capital city, Khartoum, is located centrally, and most of the country is composed of vast plains.⁴⁰ It is one of Africa's largest nations, comprising more than eight percent of the continent's land mass.⁴⁰ Although

temperatures are consistently high throughout the country, its climate varies: Weather is more arid in the north and more tropical in the south.⁴⁰

Although it is currently considered an LIC, its economy was growing rapidly prior to the COVID-19 pandemic: Sudan saw economic growth of more than 5% in 2015, supported in large part by improved economic policies and large-scale agricultural farming.⁴¹ Unfortunately, the pandemic has generated a downturn in growth, shrinking by 8.4% in 2020.⁴² The nation's economy is projected to remain in a recession through 2022, after which economic growth may return.⁴² Unfortunately, the growth seen earlier in the last decade did not translate into equivalent improvements in human development and reductions in poverty, and the outlook for these indicators remains poor.⁴³ Only two-thirds of households have access to clean drinking water, and just over one-quarter have access to modern sanitation facilities.⁴³ Access to primary school education is among the lowest in North Africa, with only three-quarters of children attending any primary school and 28 percent attending secondary school.⁴⁴

The population has more than doubled in the last 30 years, reaching 42.8 million in 2019,⁴⁵ with two-thirds of the nation's citizens living in rural areas.⁴⁶ Rapid population growth and a staggering 46.5% of the population living below the poverty line contribute to Sudan's poor overall health profile.⁴⁶ The country's population is young, with 80% of citizens under the age of 40. Life expectancy at birth is just 66.5 years,⁴⁶ and, while it has improved substantially in recent years, the infant mortality rate is 41.8 per 1,000 live births.⁴⁶

It is also important to contextualise Sudan as historically facing a disproportionate incidence of country crises (also called country emergencies), due mainly to political conflict. Natural (geological, hydrometeorological), biological (infectious disease outbreaks, such as the COVID-19 pandemic) and technological hazards all contribute to the burden of crises. The country is also listed as a Fragility, Conflict and Violence country by the World Bank, with notably high institutional and social instability.^{36 37} The World Health Organization (WHO) grades country emergencies into levels one, two, three or protracted, depending on the extent, complexity and duration of organisational and /or external support required. As of June 2021, Sudan was considered to be in a protracted emergency.^{36 37} These drawn-out crises have had profound impacts on the Sudanese population, with massive internal displacement and notable reductions in social sector performance.⁴⁷

The Sudanese healthcare system

Sudan's healthcare system is severely strained by road traffic injuries, with traumatic injuries making up 13.4% of overall mortality, 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.³⁴ The communicable disease burden is higher than that for noncommunicable diseases, at 53.8% and 33.9%, respectively.³⁴

The present health care system in Sudan serves a wide range of population, and according to the interim Constitution of Sudan, all citizens have access to free primary health care and emergency services.⁴⁸ The country's health system infrastructure is notably heterogeneous, with health services being more accessible in wealthier and more urban areas,³⁴ 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.³⁵ The WHO Universal Health Coverage Service Coverage Index score, which tracks coverage for essential health services is about average for the region at 44.⁴⁹ 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 and formal certification pathways for out-of-hospital providers.

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.

1.5 Structure of the dissertation

To achieve the above-stated objectives, this dissertation is composed of four empirical studies and related discussion presented across six chapters. Of these chapters, four (Chapters 2, 3, 4, and 5) are published or submitted works being reproduced here. In those chapters, manuscript text has been included verbatim, with additional text to introduce and discuss the studies. Citations, and table, figure, and appendix numbers have been changed to align with the formatting of this dissertation. Table, figure, and appendix numbers

are formatted by first listing the chapter number, followed by a period and then the sequence of presentation within the chapter. For example, Table 2 of Chapter 4 is denoted as “Table 4.2”.

The dissertation adheres to the following structure:

Chapter 1 provides a broad introduction to the dissertation, incorporating information on emergency care and the COVID-19 pandemic, motivation for this research, and the dissertation’s aim and objectives. It also includes information about the setting of tool derivation and validation, Sudan.

In Chapter 2, a scoping review is presented to describe all currently proposed or implemented tools for risk stratification of COVID-19 patients. The feasibility of these tools is then considered in the context of LRS, where resource constraints make many clinical inputs challenging to capture.

Following this, in Chapter 3, systematic review and meta-analysis methodologies are used to identify all potentially predictive features of COVID-19 that can be feasibly collected in LRS.

Chapter 4 leverages the information gained in Chapter 3 on predictive features of COVID-19 patients to derive a SST for LRS, using machine learning techniques on a Sudanese dataset.

Finally, in Chapter 5, the SST derived in Chapter 4 is validated with a second Sudanese dataset, to provide additional insight into its potential utility.

Chapter 6 finishes with a discussion of the dissertation’s research, highlighting contributions to the literature, limitations of the findings, and key next steps to continue this critical work.

Chapter 2: Potential solutions for screening, triage, and severity scoring of suspected positive COVID-19 patients in low-resource settings: A scoping review

2.1 Declaration by candidate

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	50

The following co-authors contributed to the work. Co-authors who are students at the University of Cape Town must also indicate the extent of their contribution in percentage terms. Co-author declaration forms for this study are provided in Appendix 2.1.

Name	Nature of contribution	Extent of contribution (%) (for student co-authors only)
Sarah Hirner	Contributed to concept and study design. Performed literature searches. Screened article titles, abstracts, and full texts for inclusion, and extracted data. Cross-checked all data extractions. Drafted manuscript and provided critical review of final article.	
Vanessa Naidoo	Screened articles titles, abstracts, and full texts for inclusion. Screened article titles, abstracts, and full texts for inclusion, and extracted data. Drafted manuscript and provided critical review of final article.	
Emilie Calvello Hynes	Led study conceptualization and design and oversaw research process. Provided critical review and contributed to the final article.	
Yasein Omer	Provided critical review and contributed to the final article.	5
Lee Wallis	Provided critical review and contributed to the final article.	
Corey Bills	Led study conceptualization and design and oversaw research process. Provided critical review and contributed to the final article.	

Candidate's signature



2.2 Study overview

Purposefully designed and validated screening, triage, and severity scoring tools are needed to reduce mortality of COVID-19 in LRS. However, many of the early tools designed for COVID-19 risk stratification were generated in HICs, where more developed scientific infrastructure lent to more rapid collection and analysis of large COVID-19 datasets. It is likely that many of these tools, while potentially effective in high-resource settings, are not feasible for use in LRS. For example, many tools rely on laboratory and imaging investigations, which are not feasible for routine use on all COVID-19 patients in LRS. Prior to developing a tool specific for LRS, it was essential to first describe the landscape of existing tools being used to risk-stratify COVID-19 patients across all settings. Following identification of potential tools, the inputs of these tools were analysed to understand their potential usability when applied to LRS.

This study has been submitted for publication. Initial searches were conducted prior to the systematic review and meta-analysis conducted in Chapter 3 and have been updated in recent months for forthcoming publication. Some statistics, such as global case and fatality rates related to COVID-19, may now be out-of-date. A verbatim copy of the manuscript, with citations, and table and figure numbers changed to align with the formatting of this dissertation, follows over the next 10 pages. Please note that this manuscript has been accepted for publication in *BMJ Open*.

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2.3 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global public health emergency on January 30, 2020.⁵⁰ In the time since, more than 153 million people have been infected and over 3.2 million have died.⁵¹ While many LMICs were relatively spared from high mortality rates, public health measures to contain the virus have put enormous strains on health systems and the ability of countries to care for existing disease burdens.⁵²⁻⁵⁴ The influx of Coronavirus Disease 2019 (COVID-19) patients stressed healthcare systems worldwide by increasing demand for personal protective equipment (PPE), diagnostics, oxygen, and mechanical ventilators.⁵⁵ LRS have limited access to these resources and remain disproportionately challenged during the COVID-19 pandemic.^{19 20} Even in regions where viral

transmission remains low, suspected COVID-19 patients require precautions, and confirmed cases require costly treatment and care. As the pandemic endures, continued resource demands have the potential to overwhelm LRS healthcare systems.⁵²

Early recognition and treatment of acute conditions are integral to reducing general mortality in LRS.²⁹ Previous evidence suggests three specific processes - screening, triage, and severity scoring of patients - improve patient outcomes in LRS.³⁰⁻⁵⁶ These practises reduce resource utilisation across a variety of settings and inform ongoing patient management,⁵⁷ but, appropriate implementation during public health emergencies can be challenging. The need for screening, triage, and severity scoring tools in real-time may lead to the use of both unvalidated and potentially ineffective protocols.

Although emergency care has developed rapidly in LMICs over the past two decades, it remains undeveloped in many regions, particularly outside of urban areas.⁵⁸ Many healthcare systems lack formal EUs, and those with dedicated spaces for emergency and acute care may not routinely screen or triage patients. Implementing these tools can be challenging in LRS, where equipment, staff, and systems are lacking.¹⁹ Despite the limitations, the exceptional risks of COVID-19 have placed screening and triage procedures at the forefront: Practical screening and triage protocols maximise use of limited available resources and keep patients and providers safe.

Screening refers to the process of identifying and isolating patients with COVID-19 risk factors on initial presentation to the healthcare system, such as to outpatient clinics and EUs. It is a rapid process to evaluate potential risk of infection, typically using basic clinical and historical information. To be successful, it must be based on easily understood case definitions, as it is frequently performed by non-healthcare personnel (such as security guards). With screening, high sensitivity is typically prioritised over specificity, so that all cases are identified. This process is fundamentally different from diagnostic testing, which is also referred to as screening in some literature. *Triage* – a systematic method of sorting patients into priority groups based on the severity of their clinical syndrome, and matching these groups with available resources – is usually conducted following screening.⁵⁹ Triage is seen as a fundamental component of effective emergency care⁶⁰: In order for triage to improve patient outcomes, the triage protocol must effectively prioritise the sickest patients for emergency interventions and direct patients to the appropriate levels of care.⁶¹ *Severity scoring* stratifies patients with a diagnosis (e.g. confirmed or suspected COVID-19) based on risk of poor outcomes, such as mortality or admission to the intensive care unit, and can complement the triage process and further inform resource allocation.

To date, there have been no published reviews detailing available tools for identification and triage of COVID-19 patients. This review aimed to identify currently proposed and/or implemented methods of screening, triaging, and early severity scoring of suspected COVID-19 patients upon initial presentation to the healthcare system, and to evaluate the utility of these tools in LRS.

2.4 Methods

Search strategy

A systematic search was conducted to identify literature describing screening, triage, and severity scoring practices that have been implemented or proposed for use with suspected COVID-19 patients upon first presentation to emergency or acute care settings.

Five electronic databases (Embase, Ovid/Medline, PubMed, and Web of Science) were searched using keywords, with adaptations made based on controlled vocabulary standards for each database. Initial search terms included “COVID,” “COVID-19,” and “SARS-CoV-2”, coupled with “screening,” “triage,” “severity,” “risk,” and “stratification,” “prediction,” “tool,” “index,” “score,” (Appendix 2.2). A secondary search was completed after reviewer comments with the inclusion of emergency specific search terms to help refine the search given the overwhelming growth in the published literature on Covid-19 related topics. Targeted searches were conducted to identify grey literature through Google Scholar and Open Grey. Websites of key regional and international health organisations were also searched, including the European Centre for Disease Prevention and Control, Infection Control Africa Network, International Committee of the Red Cross, Medecins Sans Frontières. UNICEF, United States Agency for International Development, United States Centers for Disease Control and Prevention, and World Health Organization.

Inclusion and exclusion criteria

All studies published in English between 01 December 2019 and 01 April 2020 were eligible for inclusion. Multiple forms of literature, including published and preprint manuscripts, correspondence, reports, and published guidelines, were considered. Studies were required to describe screening, triage, and/or severity scoring of suspected-positive or confirmed COVID-19 patients performed by general practitioners or emergency care providers in the prehospital, hospital, or clinic setting. Both previously existing tools applied to COVID-19 patients and novel tools developed specifically for the COVID-19 response were eligible for inclusion. A description of the tool, including inputs (e.g., hypoxia) and any relevant parameters (e.g., value of input, such as oxygen saturation < 93%), was required. As this review aims to describe all tools that may be in use, outcomes data from implementation and/or validation studies were not requisite. Tools could be either proposed or in use, with or without validation. There were no restrictions on the populations that tools may be used in.

Studies in languages other than English or published prior to December 01, 2019 were excluded. Studies describing screening, triage, and/or severity scoring only by specialist physicians and those lacking a complete description of the tool were not included. Community- and population-based screening efforts,

performed by healthcare providers or otherwise, were excluded, as were at-home self-triage tools. Descriptions of physical screening or triage infrastructure (e.g., a walk-up or drive-through facility) and methods of administering screening (e.g., telehealth) were not included.

Data extraction and analysis

Multiple reviewers (SH, JLP, CBB, AVN) independently assessed studies for eligibility at the title, abstract, and full-text levels. Any discrepancies were resolved via discussion and a third independent reviewer (AVN, EJCH, CBB) where necessary. Relevant data was extracted from eligible texts, including, year of publication, country and setting in which the tool was proposed or implemented, status of the tool as proposed or implemented, and any tool inputs (e.g., comorbidities, clinical symptoms and findings, and diagnostic and laboratory results). A second researcher reviewed all data extractions to ensure accuracy. Descriptive analyses were performed, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Extension for Scoping Reviews checklist was used to guide analysis and reporting of these results.⁶² Feasibility of inputs for use in LRS was determined based on investigation of key literature, including The World Bank's Disease Control Priorities, Third Edition, and the African Federation for Emergency Medicine's 2013 consensus statement describing facility level specific, expected capacities for emergency care delivery on the continent.^{9 63} As with any other setting, LRS have hospitals of varying capacities. In this review, feasibility was targeted towards district level hospitals, as it is these facilities that the majority of LRS populations are likely to initially present to. Additionally, as fully resourced health facilities have struggled with COVID-19 surge, these feasibility inputs may also apply when excess patient volume consumes critical resources or makes imaging difficult.

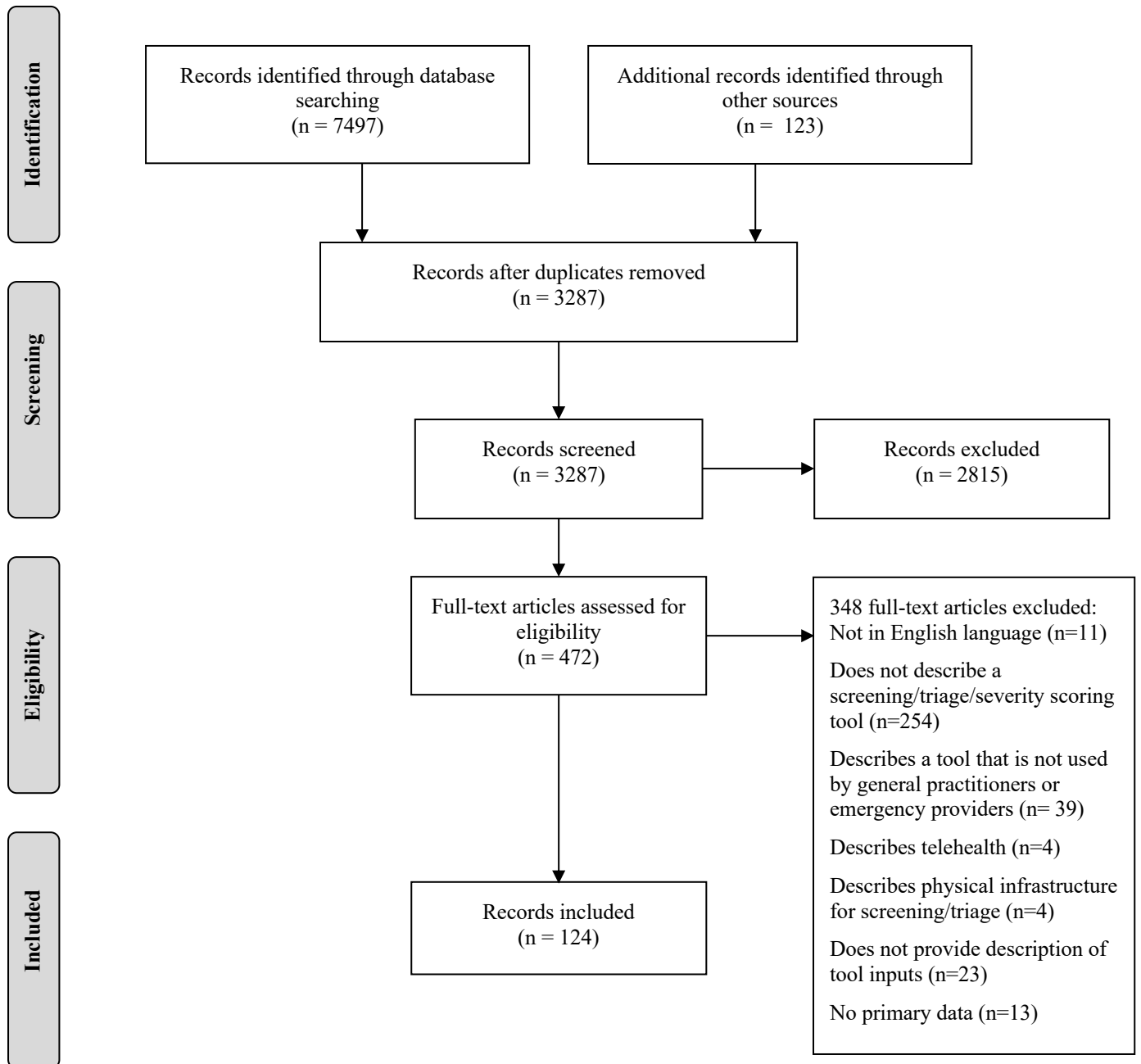
Patient and public involvement

Given the nature of this review, it was not appropriate to involve patients or the public in this study's design or execution.

2.5 Results

The search strategy yielded a total of 15232 articles (Figure 2.1). After duplicates were removed, 11091 unique titles were assessed for inclusion. Following title and abstract screening, 472 articles remained. Full-text review resulted in 124 articles for full inclusion and data extraction (Appendix 2.3, Tables 1-3).

Figure 2.1: PRISMA flow diagram.



Most articles were peer-reviewed (n=99, 79.8%) or preprint manuscripts (n=9, 7.3%). Three articles from the grey literature were also included in the review, reporting on three tools. Tools were similar in their lack of feasibility in LRS. Articles originated from 27 countries; with the majority published or conducted in China (n=41, 33.1%), followed by the United States (n=23, 18.5%) and Italy (n=10, 8.1%). International recommendations were described in three articles (2.4%).

More than half of the available literature described screening tools (n=48, 37.1%). Severity scoring tools were described in 54 articles (43.5%) and triage in 12 (9.7%). Some studies described more than one triage or severity scoring tool. In 10 studies, both screening and triage were described. In total, 57 screening, 23 triage, and 54 severity scoring tools were described (Table 2.1).

Table 2.1: Overview of tools used to screen, triage, and evaluate the severity of COVID-19 patients.

	Screening tools (n=57)		Triage tools (n=23)		Severity scoring tools (n=54)		All tools* (N=134)	
	n	%	n	%	n	%	n	%
SETTING								
Hospital	16	28.1%	5	21.7%	30	55.6%	51	38.1%
Hospital-based emergency care	12	21.1%	4	17.4%	3	5.6%	19	14.2%
Outpatient / general practitioner	8	14.0%	2	8.7%	0	0.0%	10	7.5%
Prehospital emergency care	2	3.5%	0	0.0%	0	0.0%	2	1.5%
Not specified	19	33.3%	12	52.2%	21	38.9%	52	38.8%
COUNTRY INCOME LEVEL								
High-income country	29	50.9%	14	60.9%	29	53.7%	72	53.7%
Upper-middle-income country	23	40.1%	5	21.7%	22	40.7%	50	37.3%
Lower-middle-income country	3	5.3%	3	13.0%	3	5.6%	9	6.7%
Low-income country	1	1.8%	0	0.0%	0	0.0%	1	0.7%
Not applicable	1	1.8%	1	4.3%	0	0.0%	2	1.5%
AGE GROUP								
Adults	1	1.8%	3	13.0%	4	7.4%	8	6.0%
Paediatrics	5	8.8%	2	8.7%	0	0.0%	7	5.2%
All ages	3	5.3%	1	4.3%	0	0.0%	4	3.0%
Not specified	48	84.2%	17	73.9%	50	92.6%	115	85.8%
IMPLEMENTATION								
Proposed	22	38.6%	15	65.2%	54	100.00%	91	67.9%
Implemented	35	61.4%	8	34.8%	0	0.00%	43	32.1%
VALIDATION SETTING								
High-income country	2	3.5%	1	4.3%	15	27.8%	18	13.4%
Upper-middle-income country	1	1.8%	1	4.3%	17	31.5%	19	14.2%
Lower-middle-income country	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Low-income country	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Not validated	54	94.7%	21	91.3%	22	40.7%	97	72.4%
FEASIBILITY IN LOW-RESOURCE SETTINGS								
Likely	31	54.4%	5	26.1%	15	27.8%	51	38.8%
Unlikely	26	45.6%	18	82.6%	39	72.2%	83	62.7%

*The total number of tools (N=134) does not equal the total number of papers (N=124), as some papers reported on more than one tool

Many tools were designed for hospital-wide (n=51, 38.1%) or EU (n=19, 14.2%) use. More than one-third (n=52, 38.8%) did not have a specified setting and were designed for broad use throughout the healthcare system. Seven tools (6.4%) – five for screening and two for triage – were specific to paediatric settings; nearly all others (n=115, 85.8%) lacked age specifications.

More than one quarter of tools (n=37, 27.6%) provided validation data supporting their use (Appendix 2.4), with four (3.0%) validated prospectively. Most tools were validated against the following outcomes: diagnosis of severe COVID-19 disease (n=8, 23.4%), confirmation of COVID-19 via reverse transcription polymerase chain reaction (RT-PCR) (n=5, 14.7%), or 30-day mortality (n=4, 11.8%). Only four screening tools (7.0%) and two triage tools (8.7%) had associated validation data, while 29 severity scoring tools (53.7%) did. All of these tools were validated in high-income (n=18, 48.6%) or upper-middle-income (n=19, 51.4%) country settings. Of those validated in upper-middle-income countries, 16 were validated in China (84.2%), two in Turkey (10.5%), and one in Mexico (5.3%).

A total of 204 unique inputs were included in the screening, triage, and severity scoring algorithms (Table 2.2 and Appendix 2.5).

Table 2.2: Overview of inputs in tools used to screen, triage, and evaluate the severity of COVID-19 patients.

	Screening tools (n=57)		Triage tools (n=23)		Severity scoring tools* (n=54)	
	No. unique inputs	%	No. unique inputs	%	No. unique inputs	%
Total combined inputs**	76	100.0%	108	100.0%	116	100.0%
Clinical interventions received	0	0.0%	5	4.6%	1	0.9%
Comorbid conditions	6	7.9%	15	13.9%	24	20.7%
Concurrent acute conditions	2	2.6%	14	13.0%	9	7.8%
Demographics	2	2.6%	4	3.7%	7	6.0%
Imaging investigations	3	3.9%	3	2.8%	3	2.6%
Laboratory investigations	22	28.9%	32	29.6%	42	36.2%
Other characteristics	3	3.9%	4	3.7%	2	1.7%
Signs and symptoms	28	36.8%	16	14.8%	11	9.5%
Vital signs	10	13.2%	15	13.9%	17	14.7%

*The total number of tools (N=134) does not equal the total number of papers (N=124), as some papers reported on more than one tool.

**Percents are out of the total combine inputs, not the number of tools.

Screening tools had a median of four (IQR: 3-7) inputs. Most (n=36, 63.2%) included epidemiologic risk factors. Fever was commonly included as a reported symptom (n=31, 54.4%) or a measured vital sign (n=17, 29.8%). Triage tools had a median of eight (IQR: 2.5-13.5) inputs. Oxygen saturation was the vital sign most used (n=22, 16.4%), followed by tachypnoea (n=20, 14.9%). Concurrently diagnosed acute conditions were present in multiple triage tools (n=6, 26.1%). Severity scoring tools had a median of five inputs (IQR: 1-8.5). The most frequently used inputs in these tools were age (n=22, 40.1%), lactate dehydrogenase (n=11, 20.4%), respiratory rate (n=7, 37.0%), and temperature (n=5, 9.3%).

Several studies used pre-existing severity tools to stratify suspected-positive COVID-19 patients: 11 for triage and 19 for severity scoring (Appendix 2.6). The most common tools for severity scoring, the Quick Sequential Organ Failure Assessment (qSOFA) and CURB-65 Severity Score (CURB-65), were used in five and four studies, respectively.

Tool inputs that rely on imaging and nearly all laboratory testing are largely impractical for routine use in many frontline EUs in LRS.^{19 20} In the context of these restrictions, just over half of screening tools (n=31, 54.4%) are viable for use in LRS EUs; a smaller number (n=6, 26.1%) of triage and severity scoring (n=15, 27.8%) tools are also feasible. Many studies describing tools inappropriate for LRS EUs included imaging: 17 screening tools (29.8%), 16 triage tools (69.6%), and 14 (25.9%) severity scoring tools required a chest X-ray, chest CT and/or lung ultrasound. At least one laboratory value was included in seven screening (12.2%), six (26.0%) triage, and 28 severity scoring (51.9%) tools. Screening tools were proposed or implemented in six LMICs - 19 in China, two in India, and one each in Mexico, Timor-Leste, Turkey, and Uganda - with 16 (55.2%) of these tools were deemed feasible for LRS settings. Triage tools were proposed or implemented in four LMICs - three in China, and three in India, and one each in Timor-Leste and Turkey – with only four (17.4%) deemed feasible for LRS. Of the 25 severity scoring tools proposed or implemented in LMICs, 18 were from China, two were from Pakistan, and there was one each from Argentina, Brazil, Mexico, Turkey, and India; just three (5.6%) are likely feasible in LRS.

2.6 Discussion

This scoping review identified a wide range of tools being used to screen, triage, and predict the severity of suspected-positive COVID-19 patients worldwide. A disproportionate share of tools was described in three countries – China, the United States, and Italy: a reflection of the combination of early disease burden and host country research capacities. While more than half of screening tools provided some information about implementation, less than half of triage tools and no severity scoring tools did so. Overall manuscript quality was high, with nearly three-quarters from peer-reviewed publications. Uncertainty remains regarding the accuracy of these tools: Only one-quarter were validated, and variations in settings and reporting make it difficult to generalise and compare these data. Almost all studies providing both training and prospective validations showed substantial decreases in accuracy with prospective cohorts. There was also variance in accuracy of the same tools – such as the National Early Warning Score (NEWS) and National Early Warning Score 2 (NEWS2) – across different high-income and upper-middle-income settings.

Most of the tools identified were for screening, followed by severity scoring and triage. Tool length varied, though most were short (between four and five inputs). Identified tools with fewer inputs likely have more

utility in EUs, but only a small number of tools were purpose-designed for EUs. Available articles provide information on only 12 screening tools for EUs, and four triage tools. Despite the impact of severity scoring tools on informing appropriate patient interventions and disposition,⁵⁶ there was no literature available to guide the use of severity scoring tools in EUs. And, although there is substantial variance in presentations in children versus adults,⁶⁴ very few tools specified a target age group for utilisation. This, in combination with a lack of paediatric-specific tools, suggests a need for additional investigation into appropriate tools for identification and risk of poor outcomes in suspected COVID-19 in paediatric populations.

Screening is an essential means of separating patients with suspected illness from the general population on presentation to the health system. This is particularly critical in LRS, where laboratory testing for COVID-19 is limited,⁶⁵ and PPE and other resources need to be conserved for positive cases. Most of screening tools found in this review recommended conducting screening on patients using epidemiologic risk factors and symptoms consistent with the case definition of suspected COVID-19, such as cough and fever. Non-validated use of such tools could be problematic for multiple reasons. Firstly, it is well documented that there is poor, inaccurate self-reporting of epidemiologic risk factors, including exposure to other patients and travel history.⁶⁶ The impact of epidemiologic data in a tool is also limited by the establishment of widespread community transmission, since such transmission indicates that nearly all patients are at risk of exposure. Compounding this is the fact that a substantial portion of COVID-19 cases present atypically, without the commonplace symptoms that providers are screening for using these tools.⁶⁷ For example, one study of 1099 confirmed COVID-19 cases demonstrated that only 43.8% of COVID-19 positive cases presented with fever.⁶⁸ More than half of screening tools included fever as a symptom, and many of them considered it requisite to meet the suspect case definition. These challenges in capturing the correct epidemiologic data and meeting “typical” case definitions suggests that many screening tools may not effectively identify patients with COVID-19, lacking sensitivity. In addition, in many LRS settings where the infectious disease burden is high, using fever or cough alone for identification and isolation may be insufficiently specific and create excess burden of suspected cases, leading to delays in care and cross-contamination. Also of concern is that, despite the intention of screening as a rapid, first-pass method of identifying suspected COVID-19 patients, many published screening tools relied on laboratory investigations. It is likely that intensive precautions must be taken with these patients while awaiting diagnostic results since, even in the highest-resource settings, laboratory results take time. The resources to take these precautions are almost universally limited, and inaccurate screening may place healthcare workers and patients at unnecessary risk.

After screening, suspected COVID-19 patients should be triaged to determine symptom severity using a standard triage tool contextually validated.⁶⁹ Following this, patients should be further risk stratified using a severity scoring tool in order to guide clinical management and hospital disposition. Among both triage and severity scoring tools, there was a general lack of consensus about key inputs for prognosticating

COVID-19 patients. This is unsurprising, given the novelty of SARS-CoV-2 and the numerous typical and atypical presentations of COVID-19 disease. Despite emerging evidence that any comorbidity, as well as obesity, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, hypertension, and smoking history correlate with the likelihood of more severe COVID-19 disease,^{70 71} there was little agreement on which comorbidities to include in tools. Many triage and severity scoring tools included age as an input, congruent with large-scale data that age is a severity modifier. Fewer tools included male sex, despite similar evidence of its predictive value.^{70 71} Shortness of breath, cough, and fever were used in many tools. A concurrent meta-analysis identified that fever and shortness of breath were significant predictors of severe COVID-19 disease, while cough was not.⁷¹ A core set of five vital signs – heart rate, oxygen saturation, respiratory rate, systolic blood pressure, and temperature – were seen across triage and severity scoring tools. Although limited data are available on the utility of mental status in predicting COVID-19 illness severity, a majority of reporting studies do indicate that abnormal oxygen saturation, respiratory rate, systolic blood pressure, and temperature are significant predictors of poor outcome.⁷¹

Although many screening, triage, and severity scoring tools were described in the literature, LRS use is likely to be limited. More than half of the screening tools identified in this review are likely feasible in LRS, but only a small number of triage and severity scoring tools are. Of the 58 tools proposed for use in LMICs, only 23 – 16 for screening, four for triage, and three for severity scoring – were deemed feasible in LRS. The most notable of these was the integrated screening and triage process used by Howitt et al. in Timor-Leste.⁷² The algorithm was adapted from Ayebare et al. (Uganda) with the removal laboratory testing for COVID-19.⁷³ It uses well-supported inputs, including oxygen saturation and respiratory symptoms, to identify and prognosticate potentially positive COVID-19 patients in a rapid manner. The general lack of tools, specifically those for severity scoring, has led to the development of a contextually-appropriate COVID-19 mortality scale for LRSs.⁷⁴ Though not included in this study due to initial search parameters, the AFEM COVID-19 Mortality Score (AFEM-CMS) is a pragmatic tool which makes use of seven demographic, historical, and clinical inputs to evaluate potential risk of death in COVID-19 patients; a second tool includes pulse oximetry. While many LRS EUs lack pulse oximeters needed to evaluate for hypoxia,²⁰ these devices are becoming increasingly available. As such this review considered pulse oximetry feasible in LRS.

Limitations

Feasibility does not predict that a tool will be accurate or effective. Tools should be validated in the setting of intended use. This review found no tools validated in low- and lower-middle-income countries. Of those validated in upper-middle-income countries, nearly all were from well-resourced areas of China, substantially limiting generalisability to LRS. Without contextually appropriate validation data, it is difficult to predict if feasible tools are effective in identifying and risk stratifying COVID-19 patients.

Most of the tools discussed in this review were peer-reviewed publications or guidelines by reputable international organisations, with a smaller number in the form of editorials, published correspondence, and preprints. The latter forms of publication often lack peer-review and may be of lower quality. Furthermore, this review is likely missing several tools. Almost every health system worldwide maintains some form of screening and triage processes, along with processes for further decision-making around admission. While in use, both before and during the COVID-19 pandemic, these tools have not been formally published and cannot be described here. Feasibility in LRS was acknowledged if there was a well-described and low-input method of diagnosis available (e.g., case definition coupled with vital signs abnormalities) even if it was not necessarily the gold standard of diagnosis in high-resource settings. Risk of bias assessments could not be performed because most articles were in the form of descriptive reviews, rather than presentations of primary data.

2.7 Chapter summary

In LRS, where definitive diagnostic tests for COVID-19, such as RT-PCR, may not be easily accessible, screening, triage, and severity scoring of potential COVID-19 patients are critical system interventions. Rapid identification and prognostication of suspected COVID-19 patients in LRS EUs will allow for appropriate precautions and care to be rendered to all patients, helping with more appropriate use of limited resources, and potentially driving reductions in morbidity and mortality. At the time of this study, no screening, triage, or severity scoring tools had been designed and validated specifically for LRS. In the face of an enduring pandemic, it is critical that such tools be developed, validated, and made available, so that limited resources can be conserved for those in greatest need and unnecessary loss of life is prevented. This lack of tools for LRS motivated the next study, which investigated the predictive abilities of tool inputs that are feasible for collection in LRS.

Chapter 3: Clinical and historical features associated with severe COVID-19 infection: A systematic review and meta-analysis

3.1 Declaration by candidate

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	60

The following co-authors contributed to the work. Co-authors who are students at the University of Cape Town must also indicate the extent of their contribution in percentage terms. Co-author declaration forms for this study are provided in Appendix 3.1.

Name	Nature of contribution	Extent of contribution (%) (for student co-authors only)
Alexandra Friedman	Screened eligible full texts. Extracted data. Cross-checked all data extractions and assessed quality of included studies. Drafted manuscript and provided critical review of final article.	
Morgan Broccoli	Contributed to concept and study design. Screened eligible full texts. Extracted data. Provided critical review and contributed to final article.	
Sarah Hirner	Extracted data. Provided critical review and contributed to the final article.	
Vanessa Naidoo	Screened articles titles, abstracts, and full texts for inclusion. Extracted data. Provided critical review and contributed to the final article.	

Yasein Omer	Drafted manuscript and provided critical review of final article.	5
Swasthi Singh	Screened articles titles, abstracts, and full texts for inclusion. Extracted data. Provided critical review and contributed to the final article.	
Kalin Werner	Screened articles titles and abstracts for inclusion. Provided critical review and contributed to the final article.	5
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.	

Candidate's signature



3.2 Study overview

In LRS, a COVID-19 SST could ensure timely access to appropriate care and justify use of critically limited resources. However, as identified in the previous chapter, there existed no purpose-designed and validated tools for risk stratification in LRS. In order to develop a tool *de novo*, while minimizing the number of data points required for collection of derivation and validation data, it was necessary to determine what potential tool inputs (i.e., historical characteristics, clinical presentations, and lab and imaging investigations) feasible for collection in LRS EUs hold predictive value in prognosticating COVID-19 patients. As such, a systematic review was undertaken to identify all studies assessing potential associations between clinical and historical characteristic and investigations, and COVID-19 illness severity. Data for all variables that were statistically analysed in relation to COVID-19 disease severity were extracted, and meta-analyses were conducted on each variable to determine overall predictive capacity.

The proposal for this study (Appendix 3.2) received ethical approval from the University of Cape Town Human Research Ethics Committee (Appendix 3.3). This study has been submitted for publication. A

verbatim copy of the submitted manuscript, with citations, and table and figure numbers changed to align with the formatting of this dissertation, follows over the next 10 pages.

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3.3 Introduction

Despite containment efforts, the COVID-19 pandemic has persisted, placing severe strain on healthcare systems worldwide.¹⁵ Early recognition, resuscitation, and referral have proven key to effective COVID-19 responses, yielding lower mortality.¹⁷ 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.¹⁵ Many low-resource settings (LRS) have limited capacity to provide longitudinal responses to the pandemic: They have scarce critical care resources, with limitations in the availability of oxygen and other basic resources as well as healthcare provider shortages.^{19 20} Notwithstanding scarce resources, many LRS have maintained low levels of viral transmission during the COVID-19 pandemic;⁷⁵ this was accomplished largely through swift enactment of, and adherence to, public health measures such as lockdowns.⁷⁶ However, long-term lockdowns have serious negative impacts, and most LRS have since begun the process of reopening their economies and borders.⁷⁷ Increasing movement, particularly between territories with different levels of local transmission, leaves these regions at substantial risk of new surges of COVID-19. While ongoing emergency care system strengthening efforts are underway and showing impact in many of these settings, these systems may struggle to keep pace with enduring demand.⁷⁸ Immediate targeted efforts are needed to assist stressed healthcare systems around the globe in managing and treating large numbers of acutely ill COVID-19 patients.⁷⁸

Frontline providers in 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 – both existing and purpose-designed for COVID-19 – have been proposed for use in risk-stratifying COVID-19 patients.³¹ While these tools may have some utility in predicting COVID-19 patient severity, they are likely limited in this unique context: Many emerging COVID-19 prognostication tools involve resource-intensive investigations, including blood tests and imaging, that have very limited availability in LRS.³¹ Furthermore, no validation data exist confirming value of these tools in lower-middle-income or low-income countries.³¹

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. In order to identify or develop a severity assessment tool appropriate for COVID-19 patients, factors contributing to, and

predictive of, patient severity must first be understood. This study aimed to systematically evaluate existing literature for relationships between COVID-19 illness severity, and historical characteristics, clinical presentations, and investigations measurable in LRS, to inform the development of a context-appropriate severity scoring tool.

3.4 Methods

A systematic review and meta-analysis were conducted to evaluate potential associations between demographics, comorbidities, clinical presentations and investigational studies, and COVID-19 illness severity. The PRISMA guidelines were adhered to throughout this process (Appendix 3.4).⁷⁹ This review was registered with PROSPERO, registration number CRD42020178098.

Search strategy and selection criteria

Three online databases (PubMed, Scopus, and Web of Science) were searched using a combination of free-text phrases and medical subject headings. Results were restricted to those in the English, Spanish, and Mandarin languages, published between December 01, 2019 to June 01, 2020. 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”) were 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 3.5 for full search strategy.

All publications in the WHO Database of Publications on Coronavirus Disease (COVID-19) were also included.⁸⁰ Reference lists of all texts eligible full texts were reviewed to identify additional relevant literature.

Duplicates were manually removed. All articles were screened for inclusion by two independent reviewers (JLP, KW, SS, AVN), after which a third reviewer (AF, JLP, MB, SS, AVN) retrieved each eligible full-text and considered it for inclusion. Eleven discrepancies in agreement were resolved through discussion.

This study included all full-text manuscripts, both pre-print and published, that provided 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. A range of definitions and parameters of illness severity were 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 intensive care unit (ICU) admission⁸¹. Manuscripts that did not include statistical analyses evaluating significance were excluded. There were no restrictions to study design. Studies evaluating exclusively pregnant populations were excluded. Those not directly evaluating primary data, including literature reviews and meta-analyses, were excluded, as were opinion and editorial pieces, case reports, and clinical management guidelines.

Data extraction

Data extracted from each article included 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 were considered significantly associated with illness severity. One reviewer (JLP, AF, MB, SH, SS, AVN) extracted data, and second reviewer (JLP and AF) cross-checked all extractions. All extracted variables were documented categorically as 'significant', 'not significant' or 'not reported'.

The eight-question Newcastle-Ottawa Scale Quality Assessment Scale for Cohort Studies (NOS) was used to evaluate quality of included studies.⁸² Two reviewers (AF and JLP) scored each study, reaching consensus via discussion when necessary.

Data analysis

First, a descriptive analysis of the number of papers that reported each variable as significantly associated with illness severity was conducted.

In line with this study's aim to identify features usable in LRS tools, we conducted a meta-analysis to evaluate the effects on severity of only those features feasible for rapid evaluation in LRS EUs. LRS feasibility was determined based on interrogation of key literature, including the Disease Control Priorities, Third Edition, and the AFEM 2013 consensus statement describing the status of emergency care capacity on the continent^{32 33}. As with any other setting, LRS have hospitals of varying capacities. In this review, feasibility was targeted towards district level hospitals, as it is these facilities that the majority of patients are likely to initially present to.³² This literature suggests that demographics, comorbidities, signs and symptoms, some vital signs, and blood glucose testing are considered feasible at district level hospitals; other vital signs and laboratory investigations, and imaging, generally are not.¹⁹

All feasible features with data in the form of binary categorical variables were included in the meta-analysis. Data for each of these features were aggregated across all studies. pORs, and associated 95% confidence intervals (CIs) and p-values were calculated. Variables generating PORs with a p-value <0.05 were considered significant. The number of patients with each outcome (severe or not severe) and the prevalence of each feature across the two outcome groups was also calculated.

Between-study heterogeneity was assessed using the I^2 test.⁸³ A binary random-effects model (DerSimonian-Laird) was used when significant heterogeneity is identified across studies, indicated by an I^2 value >50% (moderate or high heterogeneity)⁸⁴; where this variance is not significant, a fixed model (Mantel-Haenszel) was used. Funnel plots were evaluated for symmetry to identify potential publication bias.⁸⁴ Forest plots were used to display point estimates of individual studies and a summary estimate for each feature studied.⁸⁴

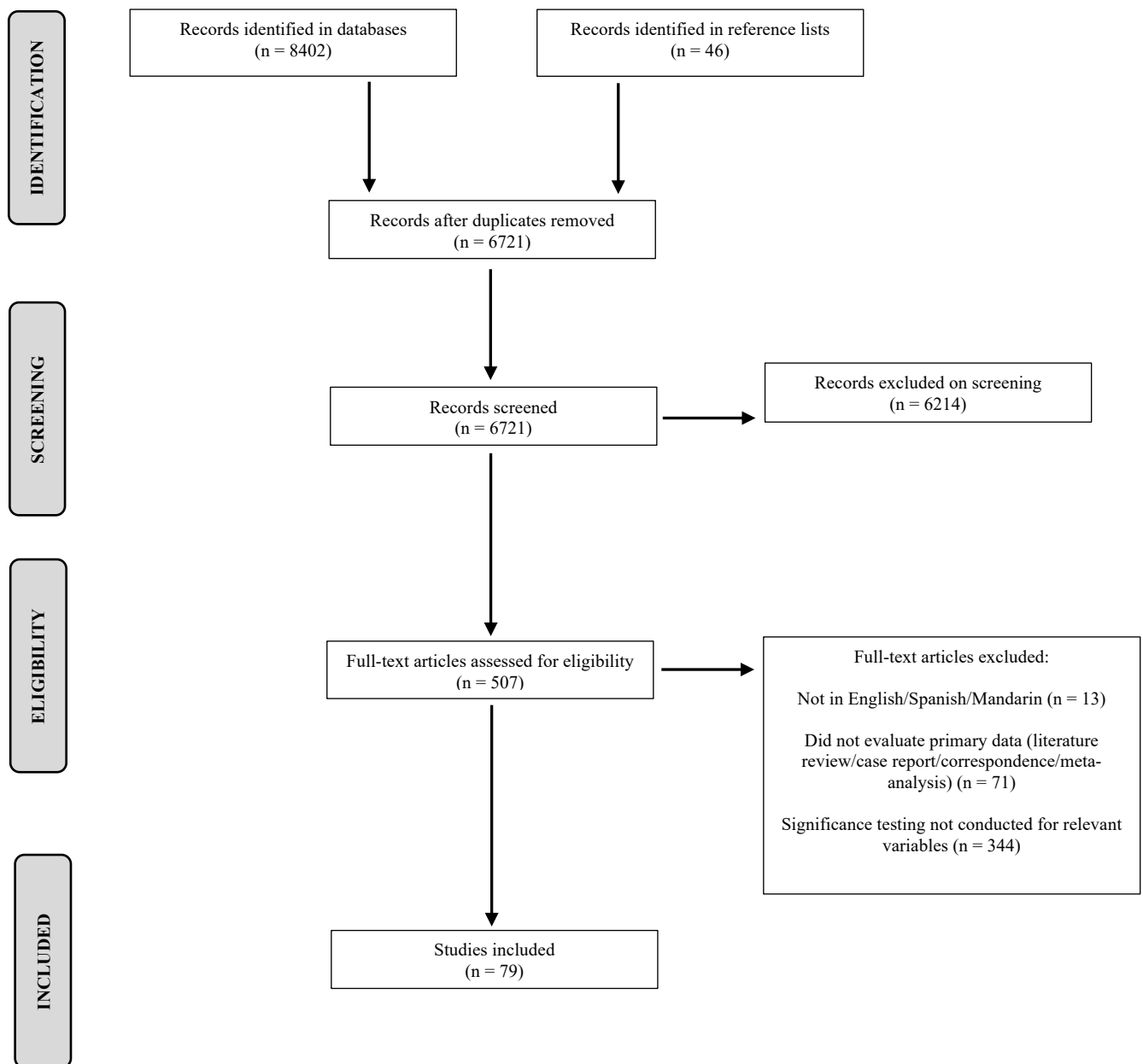
Patient and public involvement

Given the nature of this review, it was not appropriate to involve patients or the public in this study's design or execution.

3.5 Results

The literature search identified 8402 articles across four databases (Figure 3.1). A review of these articles' reference lists generated an additional 46 relevant publications. After removing duplicates, 6721 studies remained; title and abstract screening led to the removal of 6214 (92.5%) of these as they did not meet inclusion criteria.

Figure 3.1: PRISMA flow diagram.



Seventy-nine articles were eligible for inclusion following full-text review (Appendix 3.6). The majority (n=72, 91.1%) were from China and in English (n=75, 94.9%). Most were observational cohort studies: 69 (87.3%) retrospective and six (7.6%) prospective. Due in large part to study design, nearly all (n=62, 98.4%) studies were of moderate quality (Appendix 3.7).

Together, these studies analysed data from 27713 patients diagnosed with COVID-19 by laboratory technique (polymerase chain reaction (PCR) or RT-PCR). Sample sizes in these studies ranged from 16 to

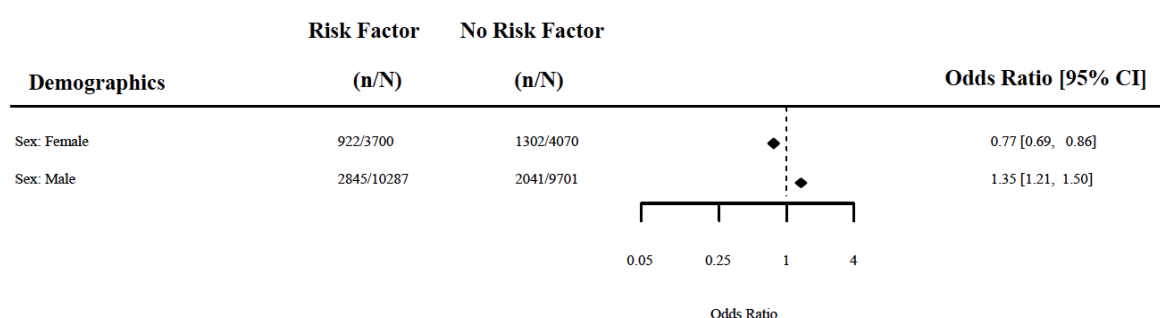
5771 patients, with a mean of 350.8 patients. Of the 76 publications reporting sex, a median 53.8% patients were male. Median ages ranged from 38.0 to 67.5 across 65 reporting studies. Most studies (n=67, 84.8%) included only adult patients; four (5.1%) included patients of all ages and one (1.3%), only children.

Just under half (n=37, 46.8%) of publications defined illness severity by the National Health Committee of the People's Republic of China's (NHC) guidelines (Appendix 3.6).⁸⁵ Thirteen studies (16.5%) evaluated inpatient mortality, and another five (6.3%) studied ICU admission. A total of 207 features were identified that were analytically studied in relation to illness severity in COVID-19 patients (Appendix 3.8).

Of the 207 features identified in this study, 82 (40.1%) were deemed appropriate for assessment in LRS EUs: All demographics, comorbidities, signs and symptoms, and vital signs identified were considered feasible in such settings, while all laboratory and imaging investigations (except blood glucose) were considered impractical under such time and resource constraints.^{19 20 32 33} Appropriate data were available for meta-analysis of 44 of these variables (53.7%), coming from 70 of the originally included studies. Meta-analysis of two demographic features, 21 comorbidities, and 21 presenting signs and symptoms identified 19 significant predictors of severe COVID-19 disease (Figures 3.2-3.4). All features were fit with random effects models due to substantial between-study heterogeneity identified when data from all studies were pooled together.

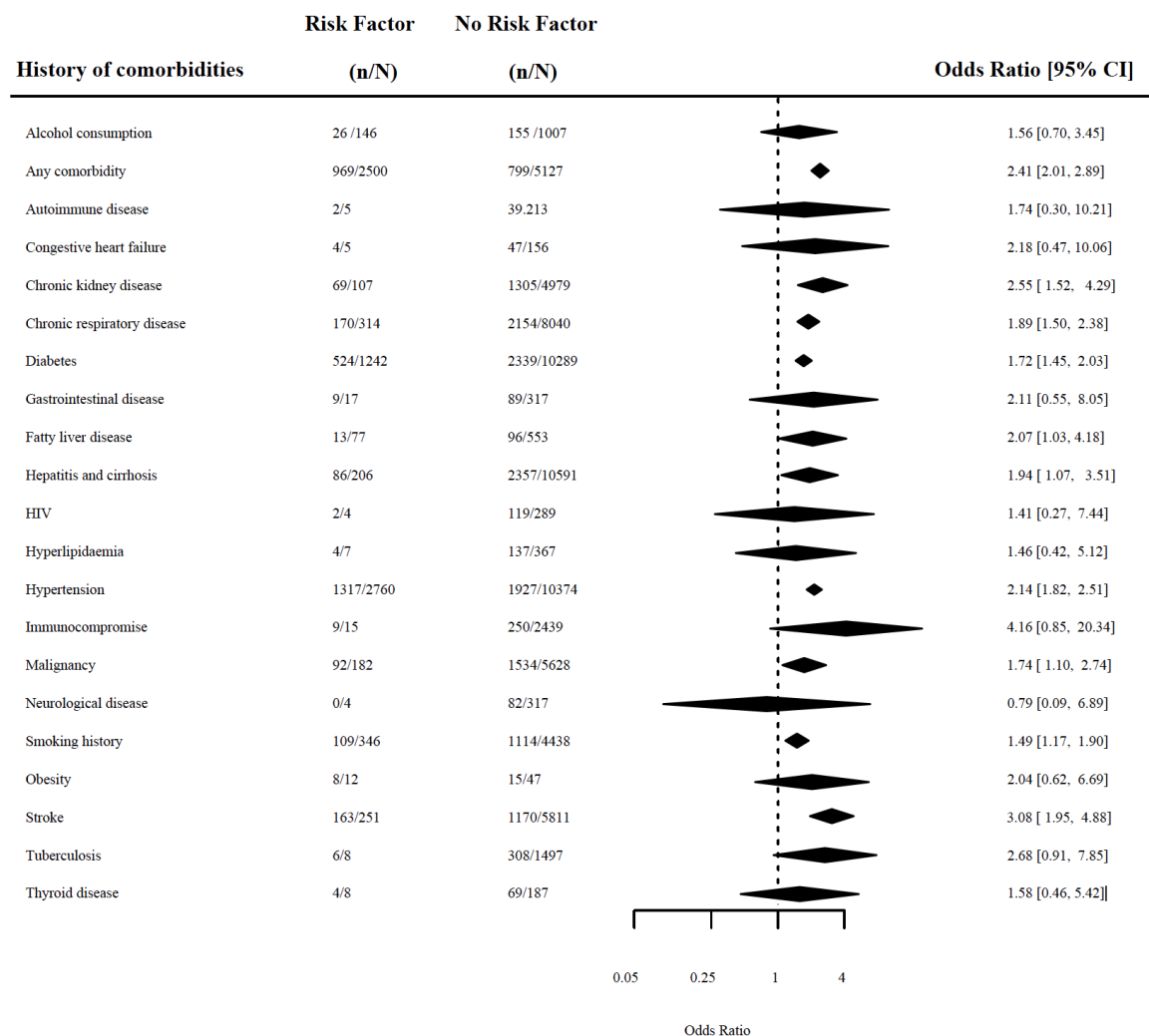
Male sex was the only demographic feature found to increase the odds of having severe COVID-19 disease (pOR: 1.35 (95% CI [1.21-1.50])) (Figure 2).

Figure 3.2: Meta-analysis of demographic features potentially associated with severe COVID-19 disease.



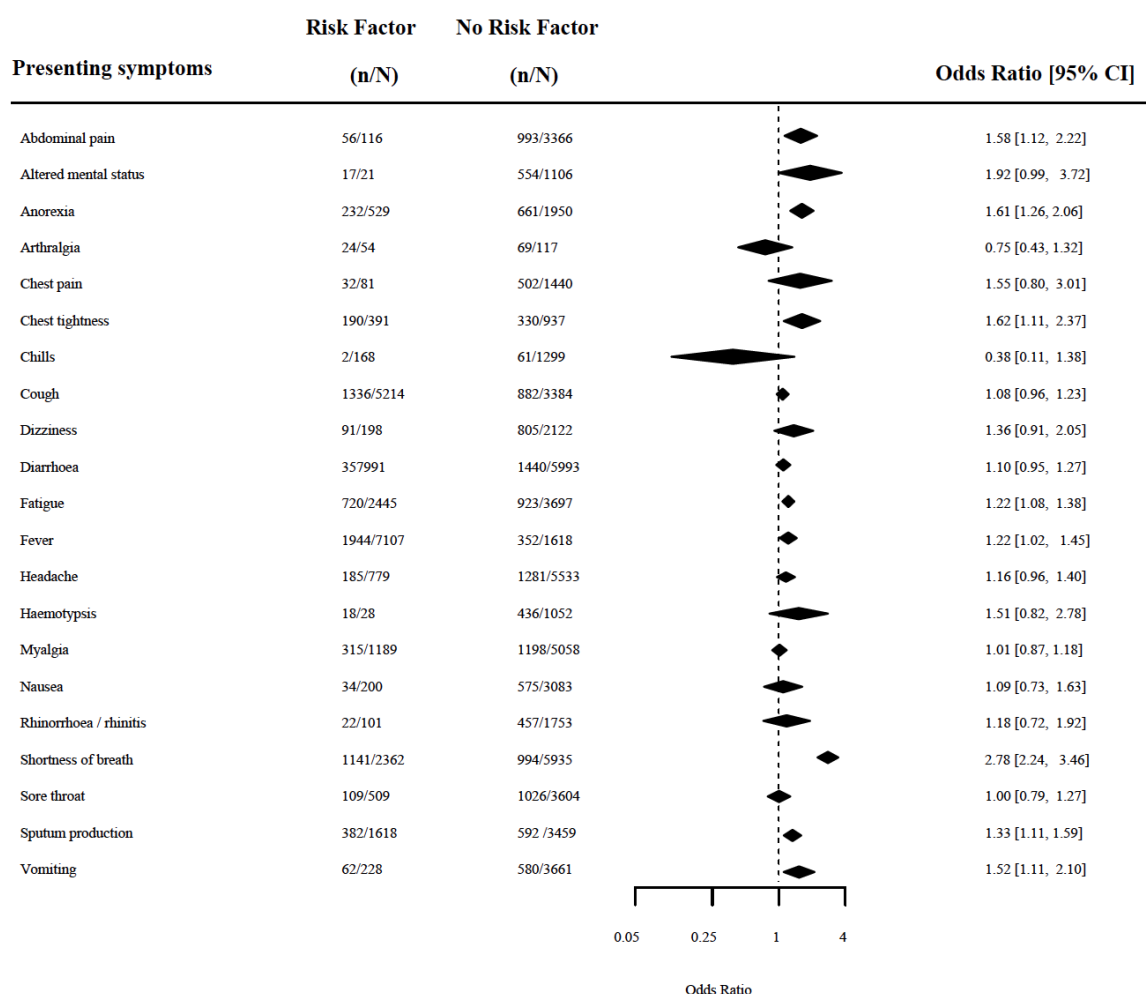
Odds were also significantly higher in patients with one of 10 comorbidities, including stroke (pOR: 3.08 (95% CI [1.95, 4.88])), chronic kidney disease (pOR: 2.55 (95% CI [1.52-4.29])), and hypertension (pOR: 2.14 (95% CI [1.82, 2.51])) (Figure 3).

Figure 3.3: Meta-analysis of comorbidities potentially associated with severe COVID-19 disease.



Additionally, eight presenting signs and symptoms were found to be significant predictors of severe COVID-19 disease, including shortness of breath (pOR: 2.78 (95% CI [2.24-3.46])), chest tightness (pOR: 1.62 (95% CI [1.11-2.37])), and anorexia (pOR: 1.61 (95% CI [1.26-2.06])) (Figure 4).

Figure 3.4: Meta-analysis of presenting signs and symptoms potentially associated with severe COVID-19 disease.



Outcomes of pooled analyses for individual features, including forest and funnel plots, are available in Appendix 3.9.

It was not possible to conduct an analysis of the remaining 37 variables feasible in LRS (45.7%) due to inconsistent nature of reporting parameter-based inputs: Many were reported with varying cut-offs for values, making these data incomparable across studies.

3.6 Discussion

The novelty of SARS-CoV-2 infection has led to many hypotheses regarding potentially significant predictors of severe illness. This study aimed to provide clarity around potential predictors by presenting a systematic review and meta-analysis of the variables associated with COVID-19 illness severity in the

context of their feasibility in LRS. The available literature evaluates a broad range of clinical characteristics and investigations and suggests that many variables may significantly associated with illness severity, including age and sex, history of pre-existing medical conditions, various signs and symptoms upon presentation, and a range of blood and imaging tests. However, only 40% of these features are realistically feasible for use in LRS EUs: Upon review, no laboratory and imaging investigations were considered practical for rapid evaluation in contexts with scarce resources.

Meta-analysis identified 19 predictors of severe COVID-19 disease that are readily-collectible in LRS. Interestingly, most features identified to be predictive of severe COVID-19 disease in the meta-analysis were not found to be predictive in the systematic review by a majority of the individual studies that evaluated them. All but three meta-analysis features – any comorbidity, chest tightness, and fatty liver disease – were deemed to have no significant potential to predict severe disease in most studies, yet these features were found to be predictive when data were aggregated across studies. This result is likely due in large part to the much larger numbers of patients included in these aggregate analyses.

Existing meta-analyses related to the severity of COVID-19 disease have been small in scope and focused only a portion of all potentially predictive features. Despite variations in defining illness severity across these studies, the majority report results very similar to those reported here. In line with results from this study, other meta-analyses have identified cerebrovascular disease, diabetes, hypertension as significant predictors of severe COVID-19 disease.⁸⁶⁻⁹⁰ Similar to our study, Fang *et al.* identified that male sex and the presence of any comorbidity were significant predictors of severe disease, and that smoking was not.⁷⁰ Contrastingly, Zhao *et al.* did find smoking to be a significant predictor. Their study did, however, align with our findings that chronic obstructive pulmonary disease was linked to severe COVID-19 disease.⁹¹

Some discrepancies exist between our findings and calculators currently being used to evaluate COVID-19 patients that have feasibility in LRS. For example, individual studies have reported that qSOFA was predictive of COVID-19 illness severity,⁹²⁻⁹³ indicating that altered mental status, tachypnoea, and systolic blood pressure ≤ 100 mmHg could be predictive in a severity scoring tool. This is also the case with the Modified Early Warning Score (MEWS) and NEWS2, which are feasible in LRS and include mental status evaluations⁹⁴⁻⁹⁵. While our systematic review identified that respiratory rate and systolic blood pressure may play a role in risk-stratifying patients, altered mental status was not a significant predictor in the meta-analysis. The discrepancies between our analysis and the clinical calculators of illness severity being used in this pandemic warrant ongoing development and validation of context-specific COVID-19 calculators based on the emerging evidence rather than single-institution experience to facilitate illness severity stratification.

A simultaneous study evaluating the feasibility of tools being proposed for screening, triage, and prognostication of COVID-19 patients identified 41 tools with likely feasibility in LRS: 29 for screening, five for triage, and nine for severity scoring.³¹ These tools rely a range of easily-collectible demographics, historical features, concurrent acute conditions, signs and symptoms, and vital signs. Only two comorbidities included across these tools – chronic kidney disease and hypertension – were found to be predictive in our meta-analysis. The most commonly included signs and symptoms were cough, fever, and shortness of breath. While fever and shortness of breath were significant predictors of severe COVID-19 disease in our meta-analysis, cough was not. No vital signs were evaluated in this meta-analysis; however, individual studies' data suggest that respiratory rate, temperature, oxygen saturation, and systolic blood pressure may have significant roles in predicting patient outcomes. All four of these were prominent features in most tools, as was heart rate, though this may have less predictive use. Results of this meta-analysis do suggest that many simple-to-collect and significantly predictive inputs are missing from tools that may be implemented in LRS. Although age and male sex are linked to disease severity across this and many other studies, these demographic features were rarely included in existing tools feasible in LRS.³¹ Eight of ten of the comorbidities identified as predictive are not present in any of these tools, as are six of seven signs and symptoms. The inclusion of an input that evaluates for the presence of any comorbidity may be particularly useful, as it is simple to collect in comparison to asking patients about a long list of potential comorbidities.

Limitations

Given the emergent nature of the COVID-19 pandemic, rapid efforts are being made to publish any available information. This review included pre-print articles alongside peer-reviewed publications. However, nearly all studies performed well against NOS criteria. Included studies may also be at risk of publication bias. Funnel plots used to evaluate these risks were largely symmetrical (Appendix 3.7), suggesting that publication bias may be of minimal concern;^{84 96} however, the interpretation of funnel plots is limited, particularly in analyses with fewer than 10 studies.⁹⁷

An overwhelming majority of studies originated in China; this suggests that there may be increased homogeneity in the data and that results might not be translatable to other settings. I^2 tests did, however, suggest substantial heterogeneity across all samples.¹⁹

Numerous definitions for, and proxy measures of, illness severity were presented in the primary literature included in this review. Given the novelty of SARS-CoV-2, this variation in defining severe cases of COVID-19 disease is unsurprising and unavoidable.

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3.7 Chapter summary

This systematic review and meta-analysis present the variables most associated with COVID-19 illness severity based on significance of reporting publications and analysis of aggregate data. The meta-analysis component was extremely robust, including separate meta-analyses for 44 individual variables. To our knowledge, we provide the first systematic review and meta-analysis tailored to evaluate the demographic, historical, clinical, and diagnostic features associated with severe COVID-19 infection in the context of LRS. The 19 identified predictors could be developed into a tool to aid frontline providers in determining how to allocate scarce resources, namely oxygen and mechanical ventilation, in a timely and appropriate manner for the rapidly increasing volume of COVID-19 patients around the world, especially in LRS. It is, however, important to note that these findings are based upon data from studies available during the first six months of the study and may no longer be as useful. Given the substantial impacts of COVID-19, it was essential to move forward with these results to develop the SST in a timely manner. In the next study, these predictors were evaluated for inclusion in a LRS-specific SST using machine learning against a Sudanese dataset.

Chapter 4: Derivation of a contextually appropriate COVID-19 mortality scale for low-resource settings

4.1 Declaration by candidate

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design and all data analysis and interpretation. The candidate wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	80

The following co-authors contributed to the work. Co-authors who are students at the University of Cape Town must also indicate the extent of their contribution in percentage terms. Co-author declaration forms for this study are provided in Appendix 4.1.

Name	Nature of contribution	Extent of contribution (%) (for student co-authors only)
Yasein Omer	Led data collection efforts. Drafted and provided critical review of the final article.	15
Lee Wallis	Provided critical review and contributed to final article.	

Candidate's signature



4.2 Study overview

In many LMICs, where vaccinations will be delayed and healthcare systems are underdeveloped, the COVID-19 pandemic will continue for the foreseeable future. Severity scoring tools can aid frontline providers in LRS in risk-stratifying patients and planning for their likely clinical needs, so that limited resources can be directed towards those in greatest need and unnecessary loss of life is prevented. While many prognostication tools have been developed for, or applied to, COVID-19 patients, no tools to-date have been purpose-designed for, and validated in, LRS. This study aimed to develop a pragmatic tool to

assist LRS frontline providers in evaluating in-hospital mortality risk, using only easy-to-obtain demographic and clinical inputs identified as predictive of severe COVID-19 in the previous chapter's meta-analysis. It leverages machine learning techniques to develop a predictive SST that is flexible for settings that do and do not have consistent access to a clinical input that is only sometimes available in LRS EUs: pulse oximetry.²⁰

The proposal for this study (Appendix 4.2) received ethical approval from the University of Cape Town Human Research Ethics Committee and the Sudanese Ministry of Health (Appendix 4.3). This study has been published (Pigoga et al., 2021⁷⁴). A verbatim copy of the published manuscript, with citations and table and figure numbers changed to align with the formatting of this dissertation, follows over the next 17 pages. Note that some statistics, such as COVID-19 vaccination rates, may now be out-of-date.

4.3 Introduction

Initial reports suggested that LMICs, whose health systems are generally categorised as underdeveloped,⁹⁸ would face the brunt of COVID-19 cases and fatalities;^{99 100} however, present data suggest that these concerns may have been premature. When compared to their HIC counterparts, many African LMICs have fared well, with substantially fewer recorded infections.¹⁰¹ Some of this difference may be accounted for in underreporting, since LMICs are more likely to have limitations in testing and reporting capacities.^{102 103} Younger populations and pre-existing immunity due to overall higher rates of infectious diseases, including other coronaviruses, may also have contributed to lower rates of infection.⁷⁵ It is also likely that the swift implementation and strong enforcement of effective public health practices such as lockdowns, along with previous experiences in responding to other outbreaks, aided these countries in stemming the early spread of COVID-19 disease.²⁴ While employing public health tactics proved effective in the medium-term, buying these health systems valuable time to build capacity for larger responses, these strategies have resounding social, economic, and health-related impacts and are not sustainable in the longer term.²⁵ As lockdowns are loosened around the globe, these regions have experienced an uptick in cases.²⁶

In LMICs, only 20% of the population is forecasted to receive vaccination against COVID-19 this calendar year,²⁷ and cases are likely to remain high. This lack of vaccinations, in combination with previously low infection rates and nascent healthcare systems, means that the pandemic may continue for the foreseeable future in African LMICs.²⁸ Clinicians and health system planners need to be able to allocate limited healthcare resources as cases inevitably rise. Establishing an early understanding of a patient's likely outcome is integral to decreasing mortality in LRS, with previous evidence suggesting that risk stratification can improve patient outcomes from a range of illnesses and injuries, while reducing resource utilisation.²⁹

³⁰ While many prognostication tools have been developed for, or applied to, COVID-19 patients, no tools to-date have been purpose-designed for, and validated in, truly LRS. A recent review identified 39 risk stratification scores (including severity and mortality indices) being used for COVID-19 prognostication. Only two of these tools were deemed feasible for use in LRS, where laboratory and imaging are not readily available, and neither was intended for such a setting or validated in it.^{19 31-33} The enduring impacts of the COVID-19 pandemic on LMICs make it essential that clinical decision-making tools with the potential to reduce mortality be made widely available. A mortality scale holds promise in aiding frontline providers in LRS in managing the pandemic SARS-COV-2 infection and COVID-19 disease by allowing them to allocate potential resources that a patient will need throughout the duration of both EU and hospital stays based on mortality likelihood.

This study aimed to develop a pragmatic tool to assist facility-based healthcare providers in LRS in evaluating in-hospital mortality risk, using only demographic and clinical inputs that are readily obtainable upon arrival in EUs.

4.4 Methods

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. Tool derivation and reporting followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) guidelines (Appendix 4.4).¹⁰⁴

Study setting

The Republic of the Sudan, Africa's third largest nation, is home to 41.8 million.¹⁰⁵ The country's population is young, with 80% of citizens under the age of 40 and an average life expectancy at birth of 64 years.^{105 106} Sudan's health system is strained by a number of causes of morbidity and mortality, including road traffic injuries and cardiovascular conditions, and there are also persistent challenges in maternal and child mortality.^{105 106} 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. Throughout the COVID-19 pandemic, however, these facilities have been providing similar levels of care, regardless of their designation as a district or referral hospital. Data for this study were obtained from two government referral hospitals in Sudan's most populous region, Khartoum State.

Data collection

Existing resource constraints have delayed implementation of an electronic COVID-19 patient registry in Sudan, and most facilities continue to rely on traditional paper-based charting systems. For the purposes of this study, on-site data collectors retrospectively logged deidentified historical and clinical information for patients presenting to the two study sites from paper records into a secure electronic Microsoft Excel (© Microsoft, Redmond, WA, USA) database stored locally. Data were randomly split into two cohorts – 80% for training and 20% for testing - for derivation purposes.

Study population

All patients were adults 18 years and over, who presented to study sites between 01 April to 01 September 2020, met WHO criteria for a suspected, probable, or confirmed case of SARS-CoV-2 infection,¹⁰⁷ and had a recorded disposition of either death or discharge.

Primary outcome

The primary outcome of this study was in-hospital mortality due to SARS-CoV-2 infection.

Candidate predictor variables

A set of potentially predictive variables was defined *a priori* based on a review of validation data for previously designed pneumonia and sepsis scores, and purpose-designed COVID-19 indices, in COVID-19 populations (Appendix 4.5). This list was generated in the context of the results of two studies - a scoping review and systematic review and meta-analysis – that evaluated the feasibility and significance of a range of variables in predicting severe COVID-19 in LRS.^{31 71} These potential candidate predictor variables comprise demographic and historical data, presenting signs and symptoms, and vital signs and associated parameters consistently identified to be clinically important in COVID-19 cohorts. In order to be included in model development, a potential predictor variable needed to be included in risk stratification tool validated in a COVID-19 population or evidenced as an independent predictor of COVID-19 severity.

Available literature suggests that demographics, comorbidities, signs and symptoms, vital signs, and blood glucose testing can feasibly be collected in most LRS EUs, while laboratory investigations and imaging generally are not.^{19 32 33} Peripheral oxygen saturation - highlighted in many studies to be a key indicator of poor outcomes in COVID-19^{108 109} – has mixed but increasing availability.^{19 20 110} In line with this study's aim to develop a mortality scale that is widely applicable across LRS, no laboratory and imaging data were considered for inclusion in this scale. Although pulse oximetry is limited in some LRS, it is available in Sudanese referral hospitals, and local stakeholders requested its consideration for inclusion in this scale. As such, an *a priori* decision was to include peripheral oxygen saturation in model development, but - should

it be included in the final scale – use identical methods to develop a second scale using identical methodology that does not consider this as a potential input.

Where evidence was unavailable to support inclusion, variables were excluded. Variables with greater than 33% missingness were also excluded. Comorbidities were collapsed into clinically relevant categories by local clinicians. These categories were viewed as binary, with patients either having one or more of the included comorbidities, or none.

Given the limited size of this dataset, we elected to use the following predefined parameters for continuous predictors included in the final model (Table 4.1).

Table 4.1: Predefined parameters for continuous candidate predictor variables.

Candidate predictor variable	Parameter(s)
Age	≥ 65 years ¹¹¹
Number of comorbidities	0, 1, ≥ 2 ¹¹²
Glasgow Coma Scale	< 15 ^{112 113}
Systolic blood pressure	≤ 100 mmHg ¹²
Respiratory rate	20-29 breaths/min, ≥ 30 breaths/min ¹¹²
Heart rate	> 90 beats/min ⁹³
Peripheral oxygen saturation on room air	$< 92\%$ ¹¹²
Temperature	$> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$ ⁹³

Data missingness

Multiple imputation by chained equations (MICE) was used for predictors in instances where less than 33% of data points were missing. Data were assumed to be missing completely at random. A total of 10 iterations of MICE were conducted, with predictive mean matching as the designated method for continuous variables and binary logistic regression for two-level variables. Distributions of missing and observed data were reviewed for each predictor and Rubin's rules were used to combine results.¹¹⁴

Model development

A criterion-based method of model selection, similar to that used by Knight and colleagues,¹¹² was utilised to build a model for predicting in-hospital mortality risk due to COVID-19. Generalised additive models (GAMs) were used to assess the deviance explained by independent predictors, with variables generating $> 1\%$ change in deviance explained included in the final model.

Least absolute shrinkage and selection operator (LASSO) logistic regression on a multiply imputed dataset was used for coefficient estimation. LASSO was selected to prevent overfitting due to the large number of predictor variables. A 10-fold cross-validation was performed to identify the optimal value of lambda, from which L1 penalised coefficients were generated. These L1 penalised coefficients were then proportionally scaled to create a usable scoring scale for the AFEM-CMS. Scatter plots distributions comparing scores

and case fatality rates were visually inspected by local clinicians to determine clinically meaningful cut-off points for risk groups.

Model performance in the derivation dataset was assessed using the C-index (area under the receiver operator curve (AUROC)) in the testing dataset.

All analyses were performed in R (version 4.0.2, © The R Foundation) using the *dplyr*, *finalfit*, *glmnet*, *mice*, *pROC*, *rmda*, and *tidyverse* packages.

4.5 Results

Characteristics of the study population

A total of 467 patients met the inclusion criteria and were included in this study (Table 4.2). Only one-third of the cohort (n=177) had recorded results for PCR testing, of which 75.1% were positive. All remaining patients were diagnosed via chest CT scan. All patients met the WHO case definition for suspected, probable, or confirmed SARS-CoV-2 infection.¹⁰⁷ The overall case fatality rate for these admitted patients was 51.2%. Survivors had a median age of 61 years (interquartile range (IQR)): 21.3) years; this was slightly younger than non-survivors' median age of 70 (IQR: 16) years. A majority of patients - 63.4% of survivors (n=149) and 74.9% of non-survivors (n=179) – were male. More than three-quarters of patients (n=341, 77.3%) had at least one comorbidity. The most prevalent comorbidities in these cohorts were hypertension (present in 36.2% of survivors and 57.4% of non-survivors) and diabetes (33.9% of survivors and 52.0 (n=116) of non-survivors). Shortness of breath was the most common self-reported symptom, seen in 68.0% of patients, followed by cough (34.5%) and fever (30.7%). Median Glasgow Coma Scale (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 4.2: Characteristics of study population.

Characteristic	Overall cohort (N = 467)		Survivor cohort (N = 228)		Non-survivor cohort (N = 239)	
	n (%) or median (IQR)	Total no patients (%)	n (%) or median (IQR)	Total no patients (%)	n (%) or median (IQR)	Total no patients (%)
In-hospital mortality	239 (51.2)	467 (100.0)	0 (0.0)	228 (100.0)	239 (100.0)	239 (100.0)
Positive PCR testing result	133 (75.1%)	177 (37.9)	74 (81.3)	91 (39.9)	59 (68.6)	86 (40.0)
DEMOGRAPHICS						
Age (years)	65 (19)	467 (100.0)	61 (21.3)	228 (100.0)	70 (16)	239 (100.0)
Male sex at birth	328 (70.2)	-	149 (63.4)	-	179 (74.9)	-
COMORBIDITIES*						
Alcohol use	10 (2.3)	441 (21.8)	5 (2.3)	218 (95.6)	5 (2.2)	223 (93.3)
Cardiovascular disease	50 (11.3)	-	26 (11.9)	-	24 (10.8)	-
Chronic respiratory disease	39 (8.8)	-	19 (8.7)	-	20 (9.0)	-
Rheumatic/connective tissue disease	4 (0.9)	-	1 (0.4)	-	3 (1.3)	-
Chronic neurological disease	32 (7.3)	-	14 (6.4)	-	18 (8.1)	-
Cirrhosis	5 (1.1)	-	3 (1.4)	-	2 (0.9)	-
Chronic kidney disease	34 (7.7)	-	17 (7.8)	-	17 (7.6)	-
Diabetes (type 1 and 2)	190 (43.1)	-	74 (33.9)	-	116 (52.0)	-
Hypertension	207 (49.6)	-	79 (36.2)	-	128 (57.4)	-
Hypothyroid	3 (0.7)	-	2 (0.9)	-	1 (0.4)	-
Malignancy	16 (3.6)	-	5 (2.3)	-	11 (4.9)	-
Current or former smoker	30 (6.8)	-	10 (4.6)	-	20 (9.0)	-
Current pregnancy**	1 (0.7)	82 (59.0)	0 (0.0)	37 (46.8)	1 (1.6)	45 (75.0)

Total no. comorbidities						
0	100 (22.7)	441 (94.4)	66 (30.3)	218 (95.6)	34 (15.2)	223 (93.3)
1	150 (34.0)	-	80 (36.7)	-	70 (31.4)	-
≥2	191 (43.3)	-	72 (33.0)	-	119 (53.4)	-
PRESENTING SIGNS & SYMPTOMS						
Abdominal pain and/or distention	12 (3.0)	394 (84.4)	10 (5.1)	196 (86.0)	2 (1.0)	198 (82.8)
Anorexia, nausea, and/or vomiting	33 (8.4)	-	18 (9.2)	-	15 (7.6)	-
Chest pain or tightness	11 (2.8)	-	5 (2.6)	-	6 (3.0)	-
Convulsions	4 (1.0)	-	1 (0.5)	-	3 (1.5)	-
Cough	136 (34.5)	-	66 (33.7)	-	70 (35.4)	-
Diarrhoea	12 (3.0)	-	7 (3.6)	-	5 (2.5)	-
Fatigue	58 (14.7)	-	31 (15.8)	-	27 (13.6)	-
Fever	121 (30.7)	-	67 (34.2)	-	54 (27.3)	-
Headache	34 (8.6)	-	19 (9.7)	-	15 (17.6)	-
Internal bleeding***	9 (2.3)	-	4 (2.0)	-	5 (2.5)	-
Myalgia	10 (2.5)	-	5 (2.6)	-	5 (2.5)	-
Shortness of breath	268 (68.0)	-	125 (63.8)	-	143 (72.2)	-
Sore throat	25 (6.3)	-	14 (7.1)	-	11 (5.6)	-
VITAL SIGNS						
Glasgow Coma Scale score	15 (1.0)	375 (80.3)	15 (0.0)	179 (78.5)	14 (3.3)	196 (82.0)
Heart rate (beat/min)	96 (24.0)	375 (80.3)	93 (21.0)	195 (85.5)	100.0 (22.0)	180 (75.3)
Peripheral oxygen saturation (%)****	91 (11.3)	372 (79.7)	94 (7.0)	186 (81.6)	87 (17.0)	186 (77.8)
Systolic blood pressure (mmHg)	130 (29.5)	367 (78.6)	131 (24.8)	195 (85.5)	123.5 (39.0)	173 (72.4)
Respiratory rate (breaths/min)	28 (12.0)	409 (87.6)	25 (9.0)	194 (85.1)	30 (14.5)	215 (90.0)
Temperature (°C)	36.9 (1.5)	62 (13.3)	36.6 (1.4)	27 (11.8)	36.9 (1.6)	35 (14.6)

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.

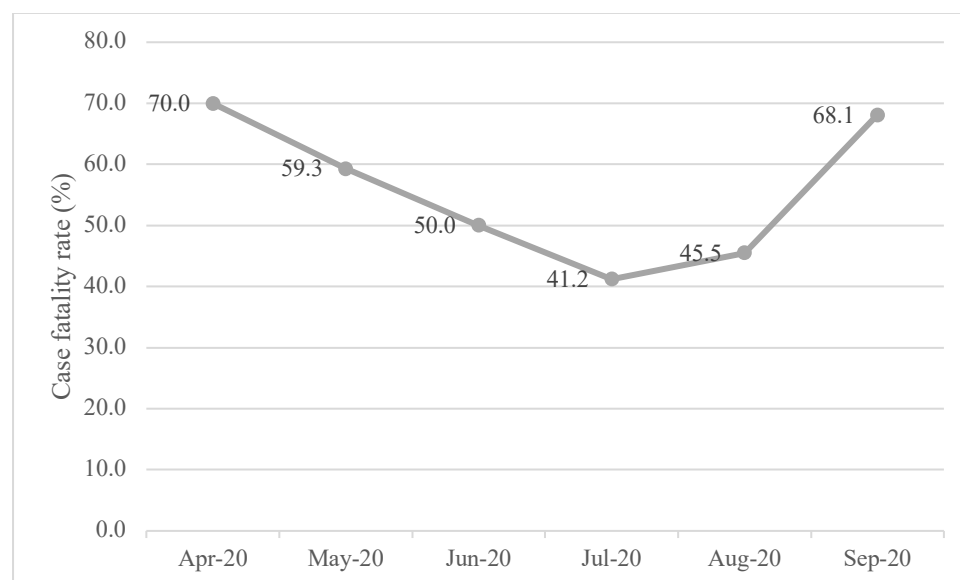
** Considered in female subpopulation only (n=139).

*** Internal bleeding includes one or more of the following: gastrointestinal bleeding, haematuria, or haemoptysis.

**** Peripheral oxygen saturation obtained on room air.

Case fatality rates varied over time, with peaks near 70% in April and September 2020 and a low point of 41.2% in July 2020 (Figure 4.1).

Figure 4.1: COVID-19 case fatality rates at two government referral hospitals in Sudan from April to September 2020.



Model development

This record review identified 34 potential predictors of mortality measurable in LRS EUs. Some data were missing for all predictors except sex at birth, age, and final disposition. Current pregnancy and temperature were excluded from model development due to excessive missingness (missing in 41.0% and 86.7% of cases, respectively). An additional five presenting signs and symptoms and one comorbidity were removed due to lack of evidence supporting inclusion in a COVID-19 risk stratification tool. Comorbidities were collapsed into a composite variable reflecting the patient's total number of comorbidities. Inclusion decisions for model fitting, including *a priori* evidence and data missingness, are described in detail in Appendix 4.5.

17 variables were included in the model fitting process, which used GAMs on the multiply imputed datasets to identify significant independent predictors of COVID-19 mortality. Male sex at birth, age, number of comorbidities, total number of comorbidities, GCS, systolic blood pressure, respiratory rate, and peripheral oxygen saturation on room air were found to be predictive (Appendix 4.5). LASSO regression was used to generate a usable scoring system, with all variables retained in the model (Appendix 4.6 and Table 4.3a).

Table 4.3a: AFEM COVID-19 Mortality Scale (AFEM-CMS) for in-hospital mortality due to COVID-19 in low-resource settings *with* access to pulse oximetry.

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

*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.

In line with this study's aim to generate a flexible but pragmatic tool for LRS, a second analysis was run excluding of peripheral oxygen saturation as a predictor. In this analysis, seven variables - male sex at birth, age, number of comorbidities, total number of comorbidities, GCS, systolic blood pressure, respiratory rate, and heart rate - were identified as important predictors of mortality (Appendix 4.5) and included in a second scale that is not reliant on pulse oximetry (Appendix 4.6 and Table 4.3b).

Table 4.3b: AFEM COVID-19 Mortality Scale (AFEM-CMS) for in-hospital mortality due to COVID-19 in low-resource settings *without* access to pulse oximetry.

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.

Analysis of scatter plots distributions comparing mortality scale scores and case fatality rates (CFRs) (Figures 4.2 and 4.3) led to the designation of clinically meaningful cut-off points that categorised patients into three mortality risk groups, as defined in Table 4.4.

Figure 4.2: Comparison of AFEM COVID-19 Mortality Scale (AFEM-CMS) scores to case fatality rates in derivation cohort, for settings *with* access to pulse oximetry.

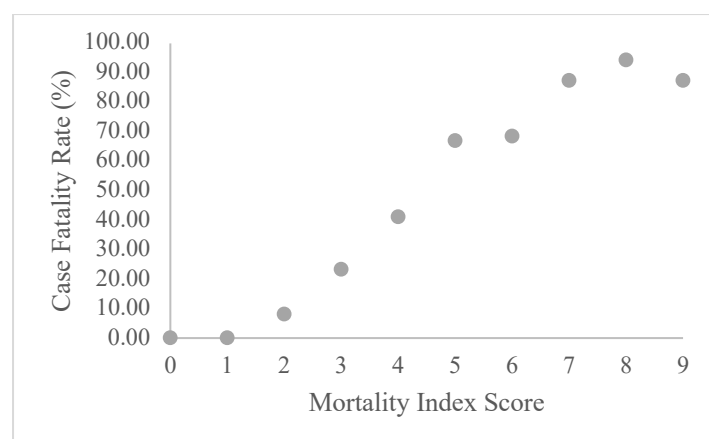


Figure 4.3: Comparison of AFEM COVID-19 Mortality Scale (AFEM-CMS) scores to case fatality rates in derivation cohort, for settings *without* access to pulse oximetry.

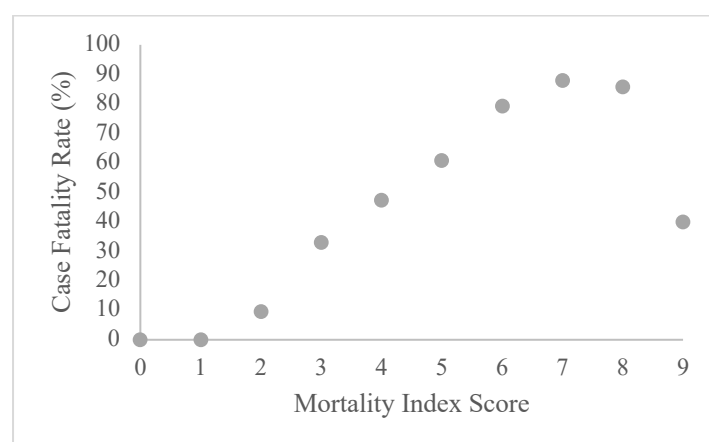


Table 4.4: Mortality risk stratification based on AFEM COVID-19 Mortality Scale (AFEM-CMS) scores.

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

Model assessment

In both versions of the scale, most patients - 47.3% (n=221) in the tool with pulse oximetry, and 57.2% (n=267) in the one without - were estimated to have between 33% and 66% risk of death. Distributions of scores are shown in Table 4.5, and Figures 4.4a and 4.4b.

Table 4.5. Comparison of mortality risk rates by mortality risk group for 467 COVID-19 patients used to train the AFEM COVID-19 Mortality Scale (AFEM-CMS).

Mortality risk group	Score	AFEM-CMS without pulse oximetry score			AFEM-CMS with pulse oximetry score		
		No. patients	No. fatalities	CFR (%)	No. patients	No. fatalities	CFR (%)
< 33%	0 to 2	68	5	7.4	84	5	6.0
33% to 66%	3 to 5	267	124	46.4	221	103	46.6
> 66%	6 +	132	110	83.3	162	131	80.9

*CFR: Case fatality rate.

Figure 4.4a: Distribution of patients across AFEM COVID-19 Mortality Scale (AFEM-CMS) scores in derivation cohort, for resource settings with access to pulse oximetry.

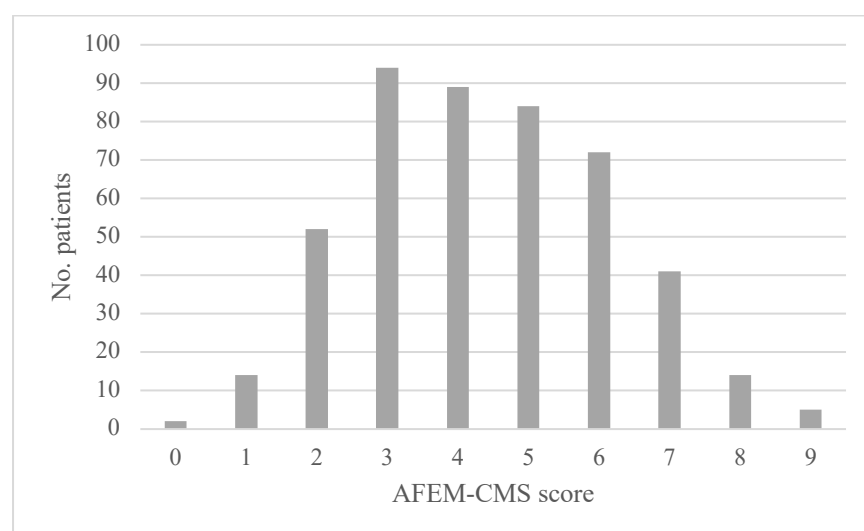
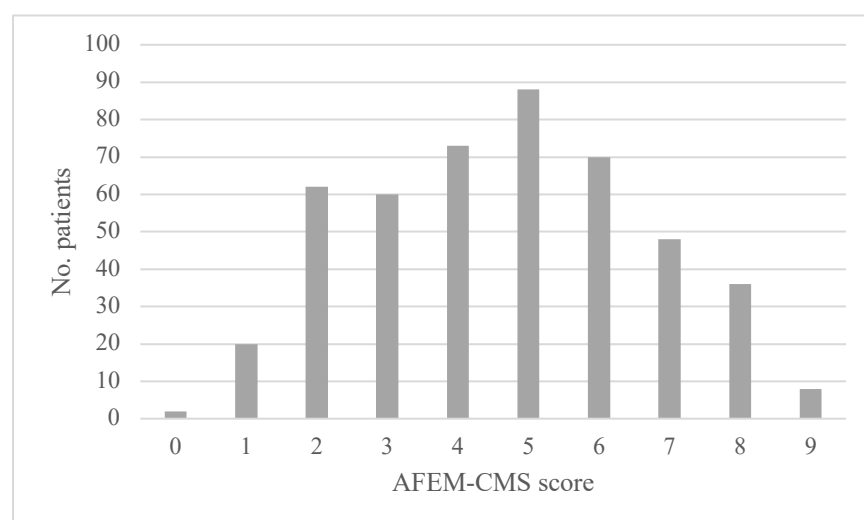


Figure 4.4b: Distribution of patients across AFEM COVID-19 Mortality Scale (AFEM-CMS) scores in derivation cohort, for resource settings without access to pulse oximetry.



Both versions of the mortality scale showed good discrimination. The model including pulse oximetry, had a C-statistic of 0.780 (95% CI: 0.740 – 0.820) in the training set and 0.775 (95% CI: 0.737 – 0.813) in the testing set. For the model excluding pulse oximetry, the C-statistic was 0.732 (95% CI: 0.686 – 0.778) in the training set and 0.719 (95% CI: 0.678 – 0.760) in the testing set.

4.6 Discussion

This study led to the successful generation of the AFEM-CMS, a pragmatic mortality scale purpose-designed for frontline clinicians in extremely LRS. Two versions of the tool exist, each using seven demographic, historical, and clinical inputs to evaluate potential risk of death in COVID-19 patients. The tool is intended for frontline use and, as such, does not include clinical inputs that may take significant time to obtain or be completely unavailable in LRS EUs, such as laboratory and imaging investigations. One version of the AFEM-CMS does, however, include pulse oximetry, has been found to be a strong predictor of poor outcomes in COVID-19 patients, but has variable availability in LMICs ^{19 20 108-110} Both versions of the tool have good discriminatory power, although associated CIs are somewhat wide. While the C-statistic for the scale including oxygen saturation is somewhat higher than for the one excluding it, their CIs do overlap. Given this, it is difficult to state with certainty that the model including oxygen saturation is better and should be prioritised for use in whenever possible. Some settings may have the capacity to perform pulse oximetry but have a limited number of monitors to do so; in these instances, it may be detrimental to slow down the assessment process in efforts to obtain a patient's oxygen saturation for use with the AFEM-CMS. It will be crucial that recommendations for AFEM-CMS implementation address such issues and emphasise that current data do not suggest significantly poorer discrimination in the tool without oxygen saturation.

Data from 34 independent predictors were available; however, two of these were not included in model fitting due to excessive missing data points and another six due to lack of evidence that they are predictive of mortality in COVID-19 disease. Presenting signs and symptoms accounted for eight of the 17 variables considered in our model. Despite evidence suggesting that these variables may be predictive of severe disease, no signs or symptoms were included in the final model. The case was the same for smoking, which has been identified in multiple meta-analyses as predictive of disease progression.

The AFEM-CMS shares many similarities with existing risk stratification tools for COVID-19 but is unique in its combination of variables and weightings. Similar to many other COVID-19 specific tools, such as A-DROP¹¹⁵ and the 4C Mortality Score³³, and pneumonia severity indices, such as PSI¹¹⁶, both

age and male sex at birth were identified as significant predictors of in-hospital mortality due to COVID-19 in both versions of the AFEM-CMS. Comorbidities were also a key predictor of mortality in both models. But, unlike in the 4C Mortality Score, from which our parameters for this variable – the presence of 0, 1, or ≥ 2 comorbidities – were chosen, mortality was only predicted by the presence of two or more comorbidities; one comorbidity was only slightly more predictive than zero.

In the version of the AFEM-CMS including pulse oximetry measurements, all vital signs except heart rate were included in the final model. In the absence of oxygen saturation measurements, however, heart rate became significantly predictive. Heart rate is likely serving as a proxy for decreased oxygenation in the model without pulse oximetry, as it will typically increase to compensate for decreasing blood oxygen levels. Three other vital signs are included in both models: systolic blood pressure, GCS, and respiratory rate. Decreases in systolic blood pressure and consciousness are late indicators of clinical deterioration and indicate increased potential for mortality. Respiratory rate has been characterised as a key predictor in nearly all existing COVID-19 risk stratification scores and, although cut-points for significance have varied, most tools consider rates greater than approximately 20 breaths per minute as abnormal. We originally sought to stratify patients into three classes – <20 , 20–29, and ≥ 30 – as is seen in the 4C Mortality Score; however, the penalised coefficients for the 20–29 and ≥ 30 classes were extremely similar and generated the same weighting in both models. This led to our tools having only one cut-point for respiratory rate.

We sought to generate a scale that categorised patients into one of three clinically meaningful levels of mortality risk. Most three-level mortality indices for COVID-19 and pneumonia described in the literature use standardised mortality-risk cut-points to classify patient severity.^{111 112 117 118} For example, in the COVID-19-specific 4C Mortality Score, a mortality rate below 2% represents low risk, a rate between 2% and 14.9% represents intermediate risk, and a rate 15% and above represents high risk.¹¹² Our original intention was to align our scale with these widely used cut points; however, analysis of the distribution of fatalities across AFEM-CMS scores suggested that case fatality rates (CFRs) for COVID-19-patients in Sudanese hospitals were much too high for the aforementioned cut-point values to have any clinical utility. As such, substantially higher but much more clinically relevant cut-points were selected that categorise patients into mortality risks of below 33%, 33% to 66%, and above 66%.

The Sudanese population was facing healthcare and political crises even before the pandemic, and COVID-19 has only worsened health and economic statuses.^{102 119} The healthcare system is vulnerable, with limited capacity to respond to the COVID-19 surge.⁷⁸ Calls have been made for unique, tailor-made approaches to managing the pandemic in Sudan,¹¹⁹ but it is difficult to respond to such requests without data to inform potential solutions. This study, which represents the largest record review of Sudanese COVID-19 patients admitted to hospitals in the literature to-date, provides key information

about hospitalised patients in the country that may be of use to researchers and systems planners. It describes an extremely ill cohort of patients: A majority have at least one comorbidity, the median age is higher than the nation's general life expectancy, and most presented with some abnormal vital signs. More than half of this cohort died in-hospital. Unfortunately, it is expected that patients presenting to hospitals in Sudan with COVID-19 are very sick and at high risk of death. While mortality rates have varied widely, both geographically and temporally, in Sudan, the country has been noted to have one of the highest infection fatality rates in the Arab world – 5.7%.¹⁰³ Sudan has some of the poorest physical access to healthcare for adults in sub-Saharan Africa, with 40.9% of adults 60 years or older traveling longer than six hours to the nearest hospital.¹²⁰ Given that this age demographic comprises the bulk of those with severe COVID-19 disease, it is unsurprising that they are not able to reach definitive care until their illness has worsened substantially.

Data from this study build upon, and largely align with, the one previous cohort study conducted on COVID-19 patients in Sudan. Omar et al. evaluated 88 COVID-19 patients at a Sudanese government hospital in Eastern Sudan between April and July 2020.¹²¹ As in our study, the majority of the cohort was male, and non-survivors tended to be older than their survivor counterparts. In both studies, cough, fever, and shortness of breath were the most common presenting signs and symptoms. Their work also identifies that age and peripheral oxygen saturation on room air at time of admission were significantly associated with in-hospital mortality, although only one comorbidity – diabetes mellitus – was found to be predictive. The in-hospital CFR in this study was slightly lower, at 37.5%, though this may be attributable to differences in geographic and resource constraints.

Limitations

There are several limitations to this study, the most important of which is the generalisability of its results. CFRs varied over time throughout this study, with an initial decrease followed by an increase to the original rate. The AFEM-CMS was developed based on the average of these rates and may perform differently when CFRs are consistently higher or lower. Additionally, given the urgency of the pandemic, only a small dataset could be obtained from just two facilities that had the capacity to participate in this work. These patients were extremely ill and tended to be older than Sudan's general population. As such, the AFEM-CMS's generalisability is likely very limited outside of similar extremely LRS settings, such as those nations listed on the Development Assistance Committee's list of Least Developed Countries,¹²² and its broader use cannot be recommended until additional validation work has been undertaken.

There is also potential that use of these two facilities' datasets may have inflated CFRs to rates higher than seen more broadly in Sudan, which are reported to be closer to the rates reported by Omar and colleagues. The hospitals included in this study are referral hospitals, whose advanced care attracts

sicker patients whose infections may be more likely to be fatal. To evaluate this further, future validation work will also include data from lower-level facilities.

All patients included in this study met the WHO definitions of suspected, probable, or confirmed COVID-19 infection; however, only one-third of patients received PCR testing to confirm infection. Although this deficit in testing aligns with previously-described testing challenges in LMICs,^{102 103} it does limit the results of this study: More than half of patients were diagnosed with COVID-19 using only WHO clinical and epidemiologic criteria,¹⁰⁷ and, without laboratory confirmation, it cannot be known that all of these patients were actually infected with SARS-CoV-2. The decision to include patients meeting all levels of the WHO COVID-19 case definition was made due to the urgent need for a reasonable volume of data to inform the response.

Some self-reported information, including age, specific comorbidities, and presenting signs and symptoms, may have gone undocumented, especially in instances where patients were very ill at the time of presentation. In the Sudanese setting, where paper records are used at government facilities, it is nearly impossible to link to patients' prior medical records to obtain historical information, and clinicians must rely solely on the narrative interview data gathered at the time of information. This information was missing at slightly higher rates in the non-survivor cohort but does not appear to be extremely different than in the survivor cohort, suggesting that such scenarios were uncommon and would not significantly influence results.

Development of the AFEM-CMS may also be limited by the use of predefined parameters for continuous clinical measurements: Although these cut-off points have been established and validated across a number of other risk stratification tools, including some for COVID-19, they may not be reliable for use in LRS. In future studies, analysis of the local distribution of these parameters will be undertaken to ensure that the current cut-off points are ideal.

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4.7 Chapter summary

To our knowledge, the AFEM-CMS was the first purpose-designed tool for mortality prediction of COVID-19 patients by frontline providers in LRS. It is intended for rapid use at the frontlines of the response, in EUs and other receiving areas of healthcare facilities where laboratory and imaging investigations are limited or unavailable. Despite its relatively small derivation dataset, the tool appears to have good discriminatory power to identify severe COVID-19 cases. In the face of an enduring

pandemic in many LMICs, the AFEM-CMS could serve as a practical solution to aid frontline providers in effectively allocating limited healthcare resources.

However, the tool's generalisability is likely limited outside of Sudan and similar LRS with similarly high fatality rates. Validation - both internal and external to the Sudanese setting - is essential. In the following study, internal validation was conducted using a second, more recently collected dataset from Sudan.

Chapter 5: Validation of a contextually appropriate COVID-19 mortality scale for low-resource settings

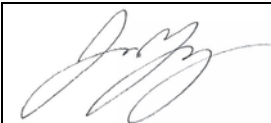
5.1 Declaration by candidate

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design and all data analysis and interpretation. The candidate wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	80

The following co-authors contributed to the work. Co-authors who are students at the University of Cape Town must also indicate the extent of their contribution in percentage terms. Co-author declaration forms for this study are provided in Appendix 5.1.

Name	Nature of contribution	Extent of contribution (%) (for student co-authors only)
Yasein Omer	Led data collection efforts. Drafted and provided critical review of the final article.	15
Lee Wallis	Provided critical review and contributed to final article.	

Candidate's signature



5.2 Study overview

The previous study provided a description of the derivation of the AFEM-CMS, a tool that is, to our knowledge, the first COVID-19 mortality risk predictor designed for LRS. Prior to rollout of the tool, additional validation in this setting was essential. In this chapter, a validation study is described in which a larger, more recent dataset collected in similar settings in Sudan is used to internally validate the AFEM-CMS.

The proposal for this study (Appendix 5.2) received ethical approval from the University of Cape Town Human Research Ethics Committee (Appendix 5.3). This study has been submitted for publication. A verbatim copy of the submitted manuscript, with citations, and table and figure numbers changed to align with the formatting of this dissertation, follows over the next 13 pages.

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5.3 Introduction

With only 0.8% of the eligible population of LICs vaccinated against SARS-CoV-2 to-date, the COVID-19 pandemic continues to impact some of the most vulnerable LRS across the globe.^{22 23 123 124} LMICs' rapid implementation and enforcement of public health practices such as lockdowns were effective in stemming the early spread of COVID-19, buying time to build healthcare capacity in LMICs,²⁴ but these lockdowns had severe social, economic, and health-related costs that are not sustainable in the long term.²⁵ LMICs that were resource constrained to begin with have been pressured to further ease lockdowns, and as lockdowns are loosened, there have been rises COVID-19 cases.²⁶⁻²⁸ Unfortunately, these enduring effects seen in LMICs are a stark contrast to HICs, where vaccination rates are substantially higher, and cases and fatalities have decreased to some of the lowest levels seen since the pandemic was declared.^{23 124 125}

LMIC settings tend to have underdeveloped healthcare systems that are exceptionally vulnerable to the strain of an outbreak such as SARS-COV-2. Prior to the pandemic, healthcare systems, including ECSs, in LRS were already described as overwhelmed and underdeveloped.¹¹ Clinicians in LRS contexts were, and continue to be, strained by the additional demands that COVID-19 has placed on their systems: In addition to the burden of COVID-19 itself, clinicians are also now beginning to see the impacts of interruptions in healthcare on chronic disease populations.^{126 127} Clinicians and health system planners must prepare already-constrained ECS to manage these increases in demand for urgent healthcare provision, allocating limited healthcare resources across a range of acute conditions. A cornerstone of any large-scale response is equipping clinicians in frontline settings, such as EUs, with triage and assessment tools that have been purpose-designed to aid in evaluating the severity of incoming patients: If effective and contextually-appropriate, such tools can be used by clinicians to rapidly assess patients, ensuring timely access to appropriate care and justified use of critically limited resources, such as beds, medications, or providers.^{29 30} However, while some tools have been developed and applied to the COVID-19 response, none were specifically designed for and validated in LRS.^{19 31-33}

The likely prolonged course of the COVID-19 pandemic on LMICs make it essential that LRS-specific tools be widely available to help reduce the sustained impact of COVID-19 in LMICs. In a previous

study, machine learning was leveraged to develop a pragmatic tool – the AFEM CMS - to assist LRS EU providers in evaluating in-hospital mortality risk, using only demographic and clinical inputs identified as predictive of severe COVID-19 that are readily available in LRS EUs. The AFEM-CMS is flexible for settings that do and do not have consistent access to a potentially high-resource clinical input: pulse oximetry. Both versions of the tool showed good discriminatory power in identifying those patients at greatest risk of death. However, prior to broader rollout nationwide, internal validation of the tool was essential. In this study, we aimed to validate the previously developed AFEM-CMS in the same setting, using data from COVID-19 patients presenting to Sudanese government hospital EUs.

5.4 Methods

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. Validation and reporting processes adhered to the TRIPOD guidelines (Appendix 5.4).¹⁰⁴

Study setting

The Republic of the Sudan is Africa's third largest nation and home to nearly 42 million.¹⁰⁵ Nearly half of Sudanese citizens live below the poverty line and two-thirds reside in rural areas.⁴⁶ The country's population is relatively young: 80% of citizens are under the age of 40 years old. The average life expectancy at birth is just 66.5 years, and the infant mortality rate remains high at 41.8 per 1,000 live births.⁴⁶

The impact of COVID-19 in Sudan has been substantial, with severe effects on the country's economy, health status, and social programs.^{128 129} Unfortunately, these ramifications are expected to persist, as only a small proportion of its population – 0.2% - has been vaccinated against COVID-19 to-date, representing one of the lowest vaccination rates worldwide.¹²³ 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.³⁴⁻³⁷ When the COVID-19 pandemic reached Sudan, its already strained healthcare system had to use its ECS to play a vital role in the pandemic response. Frontline EUs became a catch-all for the majority of potentially positive COVID-19 patients. Despite these challenges, recent pre-pandemic investments in EC 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.

Data collection

Data for this study were collected from four government referral hospitals in Sudan's Khartoum State. 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 were stored locally and shared with study investigators via a secure, cloud-based sharing platform (© Dropbox, San Francisco, CA, USA).

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,¹⁰⁷ and had a recorded ultimate disposition of either death or discharge from hospital.

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.⁷⁴ 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).

Data missingness

Missing datapoints were managed using 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.¹¹⁴

The AFEM-CMS model

The AFEM-CMS was derived in a previous study using a criterion-based method of model selection.⁷⁴ 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 5.1a* and 5.1b*, and mortality risk predictions are shown in relation to AFEM-CMS scores in Table 5.2.

Table 5.1a: AFEM COVID-19 Mortality Scale (AFEM-CMS) for in-hospital mortality due to COVID-19 in low-resource settings *with* access to pulse oximetry.⁷⁴

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 5.1b: AFEM COVID-19 Mortality Scale (AFEM-CMS) for in-hospital mortality due to COVID-19 in low-resource settings *without* access to pulse oximetry.⁷⁴

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 5.2: Mortality risk stratification based on AFEM COVID-19 Mortality Scale (AFEM-CMS) scores.⁷⁴

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

AFEM-CMS model validation

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.

5.5 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 5.3). All of these included cases met the WHO definitions for suspected, probable, or confirmed SARS-CoV-2 infection,¹⁰⁷ and a large majority of patients (82.6%) had a positive PCR testing result. PCR testing results were not available for 9.1% of patients. 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 5.3). 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, more than three-quarters (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, 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 5.3: 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)	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.)	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 score	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.

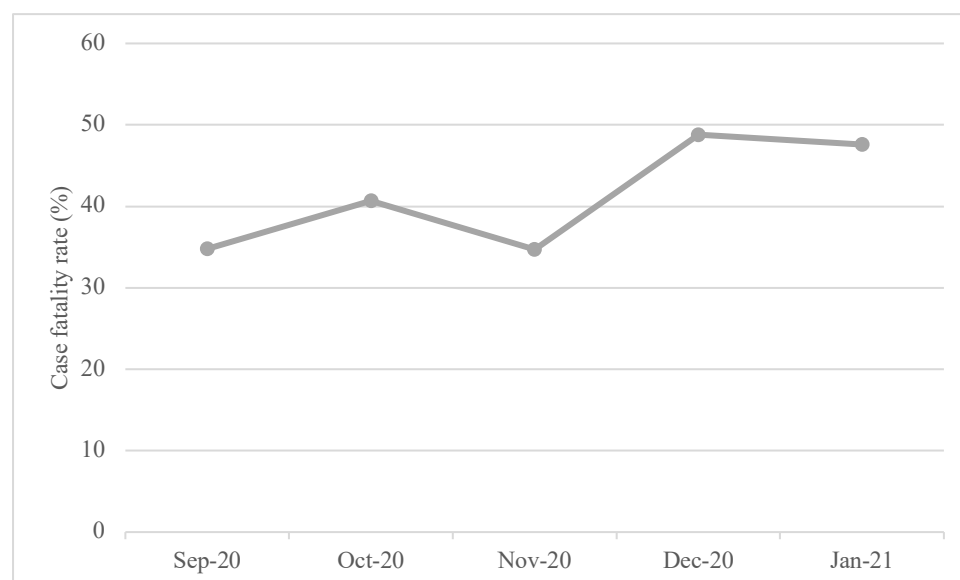
Rheumatic/connective tissue disease includes one or more of the following: gout, lupus, and rheumatoid arthritis.

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 5.1). 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 5.1: 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 5.4, and Figures 5.2a and 5.2b.

Table 5.4. Comparison of mortality risk rates by mortality risk group for 936 COVID-19 patients used to validate the AFEM COVID-19 Mortality Scale (AFEM-CMS).

Mortality risk group	Score	AFEM-CMS without pulse oximetry score			AFEM-CMS with pulse oximetry 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 5.2a: Distribution of patients across AFEM COVID-19 Mortality Scale (AFEM-CMS) scores in validation cohort, for resource settings with access to pulse oximetry.

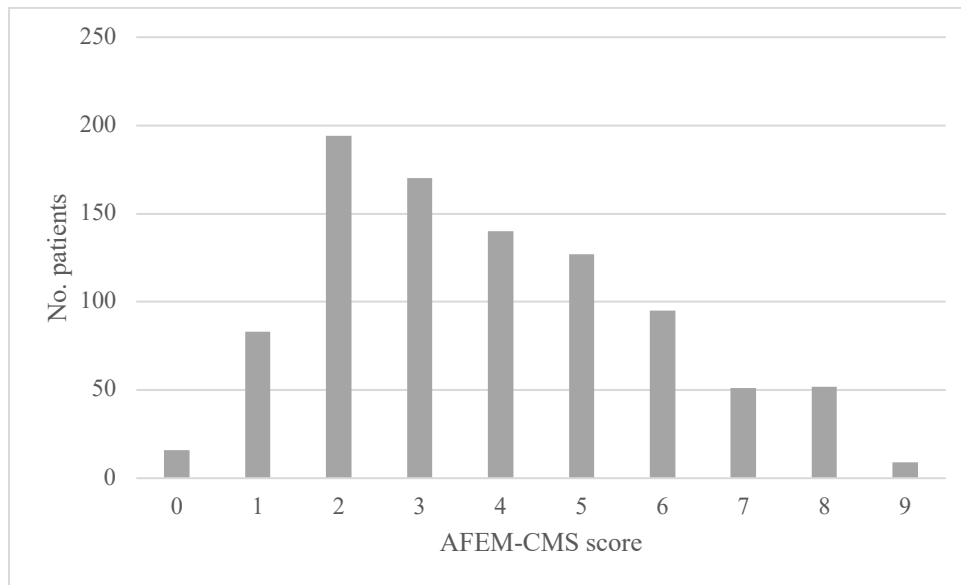
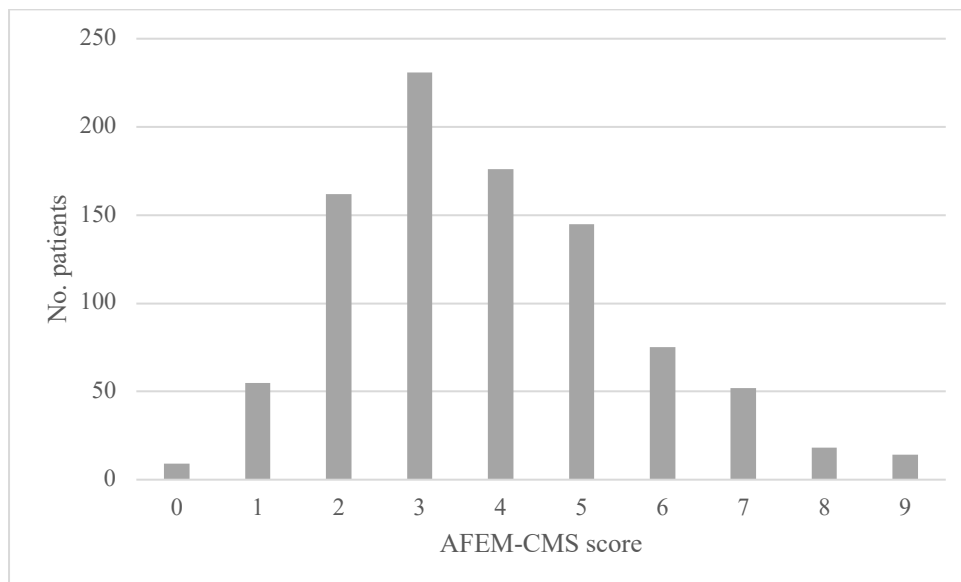


Figure 5.2b: Distribution of patients across AFEM COVID-19 Mortality Scale (AFEM-CMS) scores in validation cohort, for resource settings without access to pulse oximetry.



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).

5.6 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.⁷⁴ 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. 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.¹²¹ 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-19.¹³⁰ 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.^{112 131 132} 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.¹²² 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.⁴⁶ 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.¹⁰⁷ 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.

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5.7 Chapter summary

In this chapter, the mortality risk prediction tool described in Chapter 4 is validated. To our knowledge, this is the first validation of a COVID-19 mortality prediction tool intentionally designed for frontline providers in LRS. This study provides the assurance needed to confirm that the AFEM-CMS holds value in the Sudanese setting and can serve as motivation for its rollout in clinical settings throughout the country. Future research efforts will focus on external validation of the tool in other similar LRS, to understand if its utility extends beyond this limited Sudanese setting.

Chapter 6: Discussion of thesis

6.1 Implications of the research

Derivation of the AFEM-CMS

This dissertation exemplifies a specific case of how existing review and machine learning methods can be merged to develop an effective tool for risk-stratifying COVID-19 patients in LRS.

It was important to first evaluate the existing landscape of COVID-19-related tools, many of which were reported on within the first few months of the pandemic, to ensure that efforts were not being duplicated. Many of these published tools were actually applications of existing risk-stratification tools for conditions such as pneumonia or sepsis to COVID-19 patients, and most were from high-resource settings. Had a LRS-appropriate tool been identified, work may have instead focussed on realigning and testing the tool in African LRS. However, since such a tool did not exist, this motivated our work to develop one. Only following this review could we be more confident that we were not repeating other groups' efforts.

It is important to note that the availability of a carefully-collected dataset is essential to machine learning, and to the development of a tool such as the AFEM-CMS. While some amount of data can be filled in using predictive methods such as multiple imputation, this increases error in results and should be avoided wherever possible. Initial plans for this study assumed that a complete dataset would not be available from an LRS setting in Africa with enough lead time to develop and implement a tool. In LRS, clinical information is typically recorded on paper and medical records are not linked electronically. It can often take years to collect a large dataset to inform any single clinical tool, and the process must be repeated to validate it. As such, the original proposal for tool derivation outlined a review consensus process, whereby a systematic review would identify significant predictors of COVID-19 and clinician input would form these predictors into a quantifiable scoring system. However, it was soon realised that existing data collection systems in Sudanese EUs could pivot to collect frontline COVID-19 data. And, by identifying significant predictors of COVID-19 through a robust systematic review, fewer datapoints were required in collection; this made for substantial savings in time and cost and allowed us to implement a machine learning instead.

The derivation methodology selected for this study is relatively basic in the context of what some other research groups have used to develop COVID-19 risk stratification tools.^{112 133-135} This decision to use a simplistic criterion-based method of model selection was made for many reasons, including newness of the researchers to this methodology and the desire to generate a tool within a reasonable amount of time. But the straightforwardness of this methodology has longer term implications, as it can serve as a pragmatic

and easy-to-implement model for future researchers developing tools in times of surge. It is also extremely functional, reliant on relatively small datasets instead of the large ones that many advance machine learning techniques, such as neural networks, require.¹³⁶

Prior to this work, there were no COVID-19 risk stratification tools made for, and validated in, LRS. While further validation studies are required, the AFEM-CMS has the potential to serve as a modifiable tool for others in like settings. Similar to our research team's original plan, other researchers may choose to validate this tool in their setting and tweak it as needed, instead of developing their own tool *de novo*. In the context of a pandemic, where implementing a tool as quickly as possible can generate real-time reductions in morbidity and mortality, the availability of the AFEM-CMS as a modifiable tool could have positive impacts.

Utility of machine learning in health emergencies

This dissertation's work is just one of hundreds of studies that have highlighted the use case for machine learning in response to the COVID-19 pandemic. The COVID-19 pandemic is not unique in that very little was known about the illness's spread, clinical course, or potential treatments as it spread across the globe: This experience is shared with numerous other pandemics, including the 1918 and 2009 influenza pandemics.¹³⁷ What was unique, however, was the availability of machine learning technology as a tool in its response.^{138 139} Machine learning can improve the response to a pandemic by increasing the accuracy and speed of diagnosing true cases, as it can learn detailed patterns from large datasets in a fraction of the time that human analysis would take.¹⁴⁰ Furthermore, it can be leveraged to track and predict future cases, conducting analysis that take hours instead of months or years.¹⁴⁰ This reduction in manpower required to generate clinical tools and inform the response increases available capacity to actually care for patients, thus amplifying machine learning's positive impacts.¹⁴⁰

Although machine learning has existed since the mid-1900's, it remained out-of-reach of most researchers until the last decade.¹⁴¹ Interest in applying machine learning techniques to the life sciences began to increase approximately 30 years ago, and has become an indispensable facet of biomedical research within the last 10 years.¹³⁹ Prior to the advent of machine learning, researchers and clinicians relied on less statistical methods, such as consensus building, to develop clinical tools. Now, by simply feeding a dataset into programming software with appropriate code, more robust tools with stronger predictive capabilities can be generated. This newer process is not only faster, but also more cost effective: Fewer research staff are needed, and clinicians need not be pulled from their work to provide insight into a subjective tool.

In light of the growth of machine learning, a large body of academicians were equipped with the knowledge and skills to deploy machine learning techniques in response to the COVID-19 pandemic. There was also substantial interest in doing so, as many funders identified machine learning efforts as a priority when

funding COVID-19 work. To-date, machine learning has been used for a wide variety of applications to the COVID-19 clinical response worldwide: screening and diagnosing patients with COVID-19, predicting risk of ICU admission and death, and allocating scarce resources (e.g., medications and ventilators) to those with the best chances of survival.¹⁴² It has also been leveraged in the broader public health sphere, where it has improved epidemiological efforts such as contact tracing and infection modelling.¹⁴² Machine learning has additional implications on predicting and understanding the wider effects of COVID-19, through applications to social and economic studies.¹⁴²

Of course, nearly all of these machine learning applications occurred in HICs and high-resource settings, where data collection mechanisms, research capacity, and available technology allowed for rapid implementation of these methods.¹⁴² Machine learning can be low-cost, particularly when being applied to a singular health problem in a limited population.¹⁴³ Many analyses can be run using free, open-access programs such as R statistical software (© RStudio, Boston, MA, USA), and there are countless freely-accessible training videos available online. The limiting factors in many LRS environments will be technology and time. Learning the skills necessary to implement these methods can take time, which is already extremely limited for many clinician-researchers – especially during a health emergency. Available researcher time also limits the potential for collection of datasets, which are essential to using machine learning.¹⁴³ Additionally, technology restricts potential to implement machine learning methodologies: Even with free software and training, more powerful computers and additional storage space are often necessary.¹⁴³ If structures are not already in place to provide trained personnel time and sufficient computing power, it may be impossible to develop these capacities during a crisis. However, if these items are developed, machine learning has the potential to ultimately minimise the human workload required to generate useful clinical tools.¹⁴⁰

Given the utility of these methods in generating morbidity- and mortality-reducing clinical tools,¹⁴⁰ it is essential that machine learning capacity be developed in LRS – ideally, prior to the advent of future health emergencies. Funders should consider prioritising training in the field, as well as increasing the availability of electronic medical records and technology essential to machine learning analytics - this dissertation and other bodies of work have exemplified that these would be worthwhile investments.¹⁴³

6.3 Future work

In line with the ever-changing COVID-19 situation, the development of the AFEM-CMS was fast-paced and responsive. This section describes areas that should be considered in future efforts, both to advance use of the AFEM-CMS and to explore additional questions that were identified during the initial research process.

Recommendations for future research

In this work, the AFEM-CMS was both derived from, and validated against, data on COVID-19 patients presenting to government referral hospital EUs in Sudan. Using such a limited dataset had advantages, as it was cost- and time-effective to collect and allowed for more rapid generation of a much-needed SST. However, it also limits the utility of the AFEM-CMS. The patients captured in the derivation and validation cohorts tended to be older than the general population of Sudan, and they may have been more ill than others with COVID-19 that did not present to these advanced hospitals. In order to inform use of the AFEM-CMS outside of Sudanese government referral hospitals, additional validation work must be conducted. It is recommended that validation studies, ideally prospective, be undertaken in other LRS, to understand the generalisability of the tool outside of the Sudanese setting. The tool may be best applied to countries with similar health, political, and socioeconomic statuses as Sudan, and nations listed on the Development Assistance Committee's list of Least Developed Countries are likely ideal for additional validation work.¹²²

Findings of this dissertation's scoping and systematic reviews suggest deficits in COVID-19-related research efforts in LRS and align with other evidence suggesting that LRS- and LMIC-based research has been insufficient during the pandemic.^{144 145} Retrospective investigations into the pandemic in LRS are necessary to understand its short- and long-term impacts in these regions and to prepare for responses to similar emergencies. In the wake of the pandemic, funding bodies should prioritise supporting such work, while also working to develop the capacity for rapid research to be conducted in future surges.

Recommendations for implementation

Of course, it is also essential that, in the Sudanese setting where validation has occurred, the AFEM-CMS is implemented in a usable and effective manner. First, the format of the tool must be finalised, including its visual layout, and space must be added for manual scoring. Depending on funding, the tool may also be developed virtually, either on a web-based platform or local mobile application. To encourage broad use, the AFEM-CMS will be made available in locally-appropriate languages, including Arabic and English.

An implementation package must then be developed to provide the necessary context and training for providers to use the tool in their EUs. AFEM intends to develop an implementation toolkit to provide rapid, on-the-job training to tool users. Given that the tool should be disseminated as quickly as possible, it is likely that a train-the-trainer method will be employed: A small number of lead trainers will be selected at each hospital to participate in a short, virtual training from AFEM on AFEM-CMS use and implementation. These trainers will then be instructed to provide AFEM-CMS use training to all other target users in their EUs. A rapid reference guide will also be developed to support use of the AFEM-CMS, copies of which can be kept in EUs near laminated copies of the tool for long-term use. Training materials will also provide a range of suggestions of how clinicians can implement the results of the tool in real-time in their EUs, potentially including guidance on score-based resource allocation and prioritisation of care.

The tool was intentionally developed to have a pragmatic scoring system that the researchers believe can be easily used by a range of staff and clinicians in LRS EUs. However, it is essential to understand whether or not the scoring system and tool layout are usable in real-world settings. Thus, additional research is a cornerstone of the implementation process: In addition to ongoing prospective validation of the tool in the Sudanese setting, is recommended that usability of the AFEM-CMS is evaluated through survey, time-based, or qualitative studies.

6.4 Conclusion

Despite efforts to mitigate the impacts of the pandemic, LRS have fared worse throughout the past 15 months than their high-resource counterparts.^{125 126 146-148} Already-strained healthcare systems in LMICs have struggled to care for surges of COVID-19 patients,^{52 149-155} and the health of broader populations in these regions has been negatively affected overall due to effects on other essential health services.^{149-151 156-158} The sheer volume of morbidity and mortality in LRS due to COVID-19 motivates exploration of how future responses can be planned for and improved upon, to prevent loss of life and wellbeing. Unfortunately, this will be challenging: It has been well-documented that it is challenging to collect data and conduct research in LRS health systems even in normal times,¹⁵⁹ and recent studies have shown that LRS are disproportionately underrepresented in the body of available COVID-19 evidence.^{144 145} This dissertation provides a rare insight into the impacts of, and response to, COVID-19 in a LRS.

In this dissertation, a flexible and responsive methodology for developing clinical risk prediction tools in the midst of a global health emergency is outlined. These methods are purpose-designed for LRS, where human resources, academic capacity, and technology are likely to be limited, especially during times of surge. In the first study, a scoping review established that there had been little focus on LRS in the development of clinical tools for managing COVID-19 patients, motivating the need for the development of a SST *de novo*. Study two's systematic review showed that there were no datasets being published in LICs early in the pandemic and went on to identify clinical and historical predictors of severe COVID-19 disease using the datasets that were available from higher-resourced countries. Existing data collection structures were then quickly leveraged to gather COVID-19 data in the Sudanese setting, so that a SST could be derived using machine learning in the third study. Finally, this tool was validated in the same setting in study four. This work has exemplified the utility of machine learning in response to emergencies and suggests that machine learning can be a game-changer in the development of clinical management tools in LRS at all times. It is our hope that, in future health crises, LRS-based researchers can refer these techniques to inform contextually appropriate clinical tools in a timely manner.

Appendices

Appendix 2.1: Co-author declarations for “*Clinical and historical features associated with severe COVID-19 infection: a systematic review and meta-analysis*”

Declaration by co-authors

Hirner S, **Pigoga, JL**, Naidoo V, Calvello Hynes EJ, Omer YO, Wallis LA, Bills CB. Potential solutions for triage, screening, and severity scoring of potentially-positive COVID-19 patients in low-resource settings: A scoping review. (Submitted and under review with BMJ Open)

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and contributed study design, searching, screening, and data extraction and analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	50%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Sarah Hirner	Contributed to concept and study design. Performed literature searches. Screened article titles, abstracts, and full-texts for inclusion, and extracted data. Cross-checked all data extractions. Drafted manuscript, and provided critical review of final article.
Vanessa Naidoo	Screened articles titles, abstracts, and full-texts for inclusion. Screened article titles, abstracts, and full-texts for inclusion, and extracted data. Drafted manuscript, and provided critical review of final article.
Emilie Calvello Hynes	Led study conceptualization and design, and oversaw research process. Provided critical review and contributed to the final article.
Yasein Omer	Provided critical review and contributed to the final article.
Lee Wallis	Provided critical review and contributed to the final article.
Corey Bills	Led study conceptualization and design, and oversaw research process. Provided critical review and contributed to the final article.

The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according these criteria.

Co- Author Name: Corey Bills

Co-Author Signature



Date January 20, 2021

Declaration by co-authors

Hirner S, **Pigoga, JL**, Naidoo V, Calvello Hynes EJ, Omer YO, Wallis LA, Bills CB. Potential solutions for triage, screening, and severity scoring of potentially-positive COVID-19 patients in low-resource settings: A scoping review. (Submitted and under review with BMJ Open)

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Vanessa Naidoo	Screened articles titles, abstracts, and full-texts for inclusion. Screened article titles, abstracts, and full-texts for inclusion, and extracted data. Drafted manuscript, and provided critical review of final article.
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Yasein Omer	Provided critical review and contributed to the final article.
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- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according these criteria.

Co- Author Name Emilie J Calvello Hynes

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Date 1/28/2021



Declaration by co-authors

Hirner S, **Pigoga, JL**, Naidoo V, Calvello Hynes EJ, Omer YO, Wallis LA, Bills CB. Potential solutions for triage, screening, and severity scoring of potentially-positive COVID-19 patients in low-resource settings: A scoping review. (Submitted and under review with BMJ Open)

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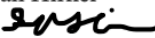
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- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according these criteria.

Co- Author Name Sarah Hirner

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Date 1/20/2021

Declaration by co-authors

Hirner S, **Pigoga, JL**, Naidoo V, Calvello Hynes EJ, Omer YO, Wallis LA, Bills CB. Potential solutions for triage, screening, and severity scoring of potentially-positive COVID-19 patients in low-resource settings: A scoping review. (Submitted and under review with BMJ Open)

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- (4) There are no other authors of the publication according these criteria.

Co- Author Name Yasein O Omer

Co-Author Signature



Date 21/1/20

Declaration by co-authors

Hirner S, **Pigoga, JL**, Naidoo V, Calvello Hynes EJ, Omer YO, Wallis LA, Bills CB. Potential solutions for triage, screening, and severity scoring of potentially-positive COVID-19 patients in low-resource settings: A scoping review. (Submitted and under review with BMJ Open)

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- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according these criteria.

Co- Author Name Lee A Wallis



Co-Author Signature
Date 21/1/21

Appendix 2.2: Search strategy

Search date: 01/06/20, 4/26/21

Search limits: 01/12/19 to 04/01/21, English only, publications only

Database	Search string	No. results
PubMed	("COVID-19" [TIAB] OR "SARS-CoV-2" [TIAB]) AND (Triage [MeSH] OR "Triage" [TIAB] OR "Screening" [TIAB] OR (("Risk" [TIAB] OR "Severity" [TIAB]) AND ("Stratification" [TIAB] OR "Prediction" [TIAB] OR "Tool" [TIAB] OR "Index" [TIAB] OR "Scor*" [TIAB])))	1953
Scopus	TITLE-ABS-KEY("COVID-19" OR "SARS-CoV-2") AND TITLE-ABS-KEY("triage" OR "screening" OR (("Risk" OR "Severity") AND ("Stratification" OR "Prediction" OR "Tool" OR "Index" OR "Scor*")))	1790
Web of Science	TS=("COVID-19" OR "SARS-CoV-2") AND TS=("triage" OR "screening" OR (("Risk" OR "Severity") AND ("Stratification" OR "Prediction" OR "Tool" OR "Index" OR "Scor*")))	734
Embase	('covid 19'/exp OR 'covid 19' OR 'sars cov 2'/exp OR 'sars cov 2') AND ('triage'/exp OR 'triage' OR 'screening'/exp OR screening OR (('Risk' OR 'Severity') AND ('Stratification' OR 'Prediction' OR 'Tool' OR 'Index' OR 'Scor*')))	2759
Ovid	("COVID-19" OR "SARS-CoV-2") AND ("Triage" OR "Screening" OR (("Risk" OR "Severity") AND ("Stratification" OR "Prediction" OR "Tool" OR "Index" OR "Scor*"))). ti, ab	279

Appendix 2.3: Screening, triage, and severity scoring tool study characteristics

Table 1: Screening tool study characteristics (n=57).

Title	First author	Year	Study location	Study setting income level	Study setting	Age group	No. tool inputs	Has the tool been proposed or implemented?
Preparing for emerging respiratory pathogens such as SARS-CoV, MERS-CoV, and SARS-CoV-2 ¹⁶⁰	Al-Tawfiq	2020	Dhahran, Saudi Arabia	High-income	Not specified	All ages	7	Proposed
Correlation Between the COVID-19 Respiratory Triage Score and SARS-COV-2 PCR Test ¹⁶¹	Aldobyany	2020	Makkah, Saudi Arabia	High-income	Not specified	Not specified	14	Implemented
Guidance for building a dedicated health facility to contain the spread of the 2019 novel coronavirus outbreak ^{162 163}	Argawal	2020	Pune, India	Lower-middle-income	Not specified	Not specified	4	Proposed
Rapid response infrastructure for pandemic preparedness in a tertiary care hospital: lessons learned from the COVID-19 outbreak in Cologne, Germany, February to March 2020 ¹⁶⁴	Augustin	2020	Cologne, Germany	High-income	Not specified	Not specified	3	Implemented
Adoption of COVID-19 triage strategies for low-income settings ⁷³	Ayebare	2020	Uganda	Low-income	Outpatient / general practitioner	Not specified	6	Proposed
Development, evaluation, and validation of machine learning models for COVID-19 detection based on routine blood tests ¹⁶⁵	Cabitzza	2021	Italy	High-income	Hospital	Not specified	23	Proposed
Hospital Emergency Management Plan During the COVID-19 Epidemic ¹⁶⁶	Cao	2020	Chengdu, China	Upper-middle-income	Hospital	Not specified	3	Implemented
Hospital surge capacity in a tertiary emergency referral centre during the COVID-19 outbreak in Italy ¹⁶⁷	Carenzo	2020	Milan, Italy	High-income	Hospital	Not specified	4	Implemented

Standard Operating Procedure for Triage of suspected COVID-19 patients in non-US Healthcare settings ¹⁶⁸	Centers for Disease Control and Prevention	2020	United States	High-income	Not specified	Not specified	4	Proposed
Enhancing the triage and cohort of patients in public primary care clinics in response to the coronavirus disease 2019 (COVID-19) in Hong Kong: an experience from a hospital cluster ¹⁶⁹	Chan	2020	Hong Kong, China	Upper-middle-income	Outpatient / general practitioner	Not specified	3	Implemented
Infection control measures of a Taiwanese hospital to confront the COVID-19 pandemic ¹⁷⁰	Chang	2020	Kaohsiun, Taiwan	High-income	Hospital	Not specified	3	Implemented
Fangcang shelter hospitals: a novel concept for responding to public health emergencies ¹⁷¹	Chen	2020	Wuhan, China	Upper-middle-income	Hospital	Not specified		Implemented
Escalating infection control response to the rapidly evolving epidemiology of the coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 in Hong Kong ¹⁷²	Cheng	2020	Hong Kong, China	Upper-middle-income	Not specified	Not specified	4	Implemented
Onsite telemedicine strategy for coronavirus (COVID-19) screening to limit exposure in ED ¹⁷³	Chou	2020	Texas, United States	High-income	Hospital-based emergency care	Not specified	3	Implemented
Mobilization and Preparation of a Large Urban Academic Center During the COVID-19 Pandemic ¹⁷⁴	Chowdhury	2020	Pennsylvania, United States	High-income	Hospital	Not specified	13	Implemented
Revised Triage and Surveillance Protocols for Temporary Emergency Department Closures in Tertiary Hospitals as a Response to COVID-19 Crisis in Daegu Metropolitan City ¹⁷⁵	Chung	2020	Daegu, Korea	High-income	Hospital-based emergency care	Not specified	7	Proposed
Infection control practices in children during COVID-19 pandemic: differences from adults ¹⁷⁶	Devrim	2020	Izmir, Turkey	Upper-middle-income	Not specified	Paediatric	4	Implemented
Calculated Decisions: Brescia-COVID Respiratory Severity Scale (BCRSS)/Algorithm Triage decision-making at the time of COVID-19 infection: the Piacenza strategy ¹⁷⁷	Duca	2020	United States	High-income	Hospital-based emergency care	Not specified	1	Implemented
	Erika	2020	Piacenza, Italy	High-income	Hospital-based emergency care	Not specified	4	Implemented
Lung Ultrasound vs. Chest X-Ray Study for the Radiographic Diagnosis of COVID-19 Pneumonia in a High-Prevalence Population ¹⁷⁸	Gibbons	2021	United States	High-income	Not specified	Not specified	7	Proposed

Immersion in an emergency department triage center during the Covid-19 outbreak: first report of the Liège University hospital experience ¹⁷⁹	Gilbert	2020	Liège, Belgium	High-income	Hospital-based emergency care	Not specified	5	Implemented
An effective screening and management process in the outpatient clinic for patients requiring hospitalization during the COVID-19 pandemic ¹⁸⁰	Guo	2020	Beijing, China	Upper-middle-income	Outpatient / general practitioner	Not specified	4	Proposed
How to transform a general hospital into an "infectious disease hospital" during the epidemic of COVID-19 ¹⁸¹	He	2020	China	Upper-middle-income	Hospital	Not specified	2	Implemented
Screening and triage at health-care facilities in Timor-Leste during the COVID-19 pandemic ⁷²	Howitt	2020	Timor-Leste	Lower-middle income	Not specified	Not specified	2	Implemented
Application and effects of fever screening system in the prevention of nosocomial infection in the only designated hospital of coronavirus disease 2019 (COVID-19) in Shenzhen, China ¹⁸²	Huang	2020	Shenzhen, China	Upper-middle-income	Hospital	Not specified	5	Implemented
The role of emergency medical services in containing COVID-19 ¹⁸³	Jaffe	2020	Israel	High-income	Prehospital emergency care	Not specified	2	Implemented
An algorithmic approach to diagnosis and treatment of coronavirus disease 2019 (COVID-19) in children: Iranian expert's consensus statement ¹⁸⁴	Karimi	2020	Tehran, Iran	Upper-middle-income	Not specified	Paediatric	9	Proposed
2019-nCoV: The Identify-Isolate-Inform Tool Applied to a Novel Emerging Coronavirus ¹⁸⁵	Koenig	2020	United states	High-income	Not specified	Not specified	3	Proposed
Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0): Working Group of 2019 Novel Coronavirus, Peking Union Medical College Hospital ¹⁸⁶	Li	2020	Beijing, China	Upper-middle-income	Not specified	Not specified	1	Proposed
A Double Triage and Telemedicine Protocol to Optimize Infection Control in an Emergency Department in Taiwan During the COVID-19 Pandemic: Retrospective Feasibility Study ¹⁸⁷	Lin	2020	Taipei, Taiwan	High-income	Hospital	Adult	3	Implemented

Optimizing screening strategies for coronavirus disease 2019: A study from Middle China ¹⁸⁸	Liu	2020	Changsa, China	Upper-middle-income	Not specified	Not specified	3	Proposed
A COVID-19 Risk Assessment Decision Support System for General Practitioners: Design and Development Study ¹⁸⁹	Liu	2020	Hangzhou, China	Upper-middle-income	Outpatient / general practitioner	Not specified	36	Proposed
Reorganization of a large academic hospital to face COVID-19 outbreak: The model of Parma, Emilia-Romagna region, Italy ¹⁹⁰	Meschi	2020	Parma, Italy	High-income	Hospital-based emergency care	Not specified	3	Implemented
How emergency departments prepare for virus disease outbreaks like COVID-19 ¹⁹¹	Möckel	2020	Germany	High-income	Hospital-based emergency care	Not specified	3	Implemented
Clinical Triage in Cough Clinic Alleviates COVID-19 Overload in Emergency Department in India ¹⁹²	Nayan	2020	West Bengal, India	Lower-middle-income	Hospital	Not specified	8	Implemented
A Pediatric Emergency Department Protocol to Avoid Interhospital Spread of SARS-CoV-2 during the Outbreak in Bergamo, Italy ¹⁹³	Nicastro	2020	Bergamo, Italy	High-income	Hospital	Paediatric	3	Implemented
The ultrasound guided triage: a new tool for prehospital management of COVID-19 pandemic ¹⁹⁴	Piliego	2020	Italy	High-income	Not specified	Not specified	7	Proposed
Screening and managing of suspected or confirmed novel coronavirus (COVID-19) patients: experiences from a tertiary hospital outside Hubei province ¹⁹⁵	Pu	2020	Chengdu, China	Upper-middle-income	Hospital	Not specified	2	Implemented
Reorganising the emergency department to manage the COVID-19 outbreak ¹⁹⁶	Quah	2020	Singapore	High-income	Hospital-based emergency care	Not specified	7	Implemented
Diagnostic accuracy of symptoms as a diagnostic tool for SARS-CoV 2 infection: a cross-sectional study in a cohort of 2,173 patients ¹⁹⁷	Romero-Gameros	2021	Mexico City, Mexico	Upper-middle-income	Hospital-based emergency care	Not specified	11	Proposed
Can You Catch It? Lessons Learned and Modification of ED Triage Symptom- and Travel-Screening Strategy ¹⁹⁸	Schwedhelm	2020	Nebraska, United States	High-income	Hospital-based emergency care	Not specified	4	Implemented
Emergency Responses to Covid-19 Outbreak: Experiences and Lessons from a General Hospital in Nanjing, China ¹⁹⁹	Shen	2020	Nanjing, China	Upper-middle-income	Hospital	Not specified	5	Implemented
A quickly, effectively screening process of novel corona virus disease 2019 (COVID-19) in children in Shanghai, China ²⁰⁰	Shi	2020	Shanghai, China	Upper-middle-income	Hospital	Paediatric	3	Implemented

The response of Milan's Emergency Medical System to the COVID-19 outbreak in Italy ²⁰¹	Spina	2020	Milan, Italy	High-income	Prehospital emergency care	Not specified	2	Implemented
Reducing hospital admissions for COVID-19 at a dedicated screening centre in Singapore ²⁰²	Tan	2020	Singapore	High-income	Hospital	Not specified	3	Implemented
The role of triage in the prevention and control of COVID-19 ²⁰³	Wang	2020	Xi'an, China	Upper-middle-income	Hospital	Not specified	7	Implemented
Providing uninterrupted care during COVID-19 pandemic: experience from Beijing Tiantan Hospital ²⁰⁴	Wang	2020	Beijing, China	Upper-middle-income	Hospital	Not specified	4	Implemented
Containing COVID-19 in the Emergency Department: The Role of Improved Case Detection and Segregation of Suspect Cases ²⁰⁵	Wee	2020	Singapore	High-income	Hospital-based emergency care	All ages	2	Implemented
Redesigning emergency department operations amidst a viral pandemic ²⁰⁶	Whiteside	2020	United States	High-income	Hospital-based emergency care	Not specified	3	Proposed
Clinical Management of COVID-19 Interim Guidance ²⁰⁷	World Health Organization	2020	Not applicable	Not applicable	Not specified	All ages	4	Proposed
Strategies for qualified triage stations and fever clinics during the outbreak of COVID-2019 in the county hospitals of Western Chongqing ²⁰⁸	Wu	2020	Western Chongqing, China	Upper-middle-income	Outpatient / general practitioner	Not specified	17	Implemented
Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics ²⁰⁹	Zhang	2020	Wuhan, China	Upper-middle-income	Outpatient / general practitioner	Not specified	10	Implemented
Analysis and suggestions for the preview and triage screening of children with suspected COVID-19 outside the epidemic area of Hubei Province ²¹⁰	Zhang	2020	Chongqing, China	Upper-middle-income	Outpatient / general practitioner	Paediatric	5	Implemented
COVID19: A Systematic Approach to Early Identification and Healthcare Worker Protection ²¹¹	Zhao	2020	Shanghai, China	Upper-middle-income	Not specified	Not specified	4	Proposed
Primary stratification and identification of suspected Corona virus disease 2019 (COVID-19) from clinical perspective by a simple scoring proposal ²¹²	Zhou	2020	Gansu, China	Upper-middle-income	Not specified	Not specified	10	Proposed
Proposed Clinical Indicators for Efficient Screening and Testing for COVID-19 Infection from Classification and Regression Trees (CART) Analysis ²¹³	Zimmerman	2020	Pennsylvania, United States	High-income	Outpatient / general practitioner	Not specified	5	Proposed

Application of Critical Care Ultrasound in Patients With COVID-19: Our Experience and Perspective ²¹⁴	Zou	2020	Chengdu, China	Upper-middle-income	Not specified	Not specified	7	Proposed
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Table 2: Triage tool study characteristics (n=23).

Title	First author	Year	Study location	Study setting income level	Study setting	Age group	No. tool inputs	Has the tool been proposed or implemented?
Point-of-Care Ultrasound in the Evaluation of COVID-19 ²¹⁵	Abrams	2020	United States	High-income	Hospital	Not specified	1	Proposed
Emergency Department COVID-19 Severity Classification ²¹⁶	American College of Emergency Physicians	2020	United States	High-income	Not specified	Adults	41	Proposed
Fangcang shelter hospitals: a novel concept for responding to public health emergencies ¹⁷¹	Chen	2020	Wuhan, China	Upper-middle-income	Hospital	Not specified	12	Implemented
Mobilization and Preparation of a Large Urban Academic Center During the COVID-19 Pandemic ¹⁷⁴	Chowdhury	2020	Pennsylvania, United States	High-income	Hospital	Not specified	16	Implemented
Revised Triage and Surveillance Protocols for Temporary Emergency Department Closures in Tertiary Hospitals as a Response to COVID-19 Crisis in Daegu Metropolitan City ¹⁷⁵	Chung	2020	Daegu, Korea	High-income	Hospital-based emergency care	Not specified	8	Proposed
Early prediction of the risk of severe coronavirus disease 2019: A key step in therapeutic decision making ²¹⁷	Côté	2020	Quebec, Canada	High-income	Not specified	Not specified	21	Proposed
Infection control practices in children during COVID-19 pandemic: differences from adults ¹⁷⁶	Devrim	2020	Izmir, Turkey	Upper-middle-income	Not specified	Paediatric	5	Implemented
Using Lung Point-of-care Ultrasound in Suspected COVID-19: Case Series and Proposed Triage Algorithm ²¹⁸	Duggan	2020	United States	High-income	Not specified	Not specified	1	Proposed
Simple, fast and affordable triaging pathway for COVID-19 ²¹⁹	Eggleton	2020	United Kingdom	High-income	Not specified	Not specified	1	Proposed
How is COVID-19 affecting South Korea? What is our current strategy? ⁹⁵	Her	2020	South Korea	High-income	Not specified	Not specified	2	Implemented

Screening and triage at health-care facilities in Timor-Leste during the COVID-19 pandemic ⁷²	Howitt	2020	Timor-Leste	Lower-middle income	Not specified	Not specified	4	Implemented
An algorithmic approach to diagnosis and treatment of coronavirus disease 2019 (COVID-19) in children: Iranian expert's consensus statement ¹⁸⁴	Karimi	2020	Tehran, Iran	Upper-middle-income	Not specified	Paediatric	15	Proposed
Diagnosis and clinical management of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection: an operational recommendation of Peking Union Medical College Hospital (V2.0): Working Group of 2019 Novel Coronavirus, Peking Union Medical College Hospital ¹⁸⁶	Li	2020	Beijing, China	Upper-middle-income	Hospital	Not specified	11	Proposed
A Double Triage and Telemedicine Protocol to Optimize Infection Control in an Emergency Department in Taiwan During the COVID-19 Pandemic: Retrospective Feasibility Study ¹⁸⁷	Lin	2020	Taipei, Taiwan	High-income	Hospital	Adult	8	Implemented
CLUE: COVID-19 lung ultrasound in emergency department ²²⁰	Manivel	2020	Sydney, Australia	High-income	Hospital-based emergency care	Not specified	1	Proposed
Proposed Modifications in the 6-minutue Walk Test for Potential Application in Patients with mild Coronavirus Disease 2019 (COVID-19): A Step to Optimize Triage Guidelines ²²¹	Mantha	2020	India	Lower-middle income	Not specified	Not specified	6	Proposed
Reorganization of a large academic hospital to face COVID-19 outbreak: The model of Parma, Emilia-Romagna region, Italy	Meschi	2020	Parma, Italy	High-income	Hospital-based emergency care	Not specified	8	Implemented
A Dynamic Bayesian Model for Identifying High-Mortality Risk in Hospitalized COVID-19 Patients ²²²	Momeni-Boroujeni	2021	New York, United States	High-income	Hospital	Not specified	11	Proposed
The ultrasound guided triage: a new tool for prehospital management of COVID-19 pandemic ¹⁹⁴	Piliego	2020	Italy	High-income	Not specified	Not specified	9	Proposed
Pattern recognition of high-resolution computer tomography (HRCT) chest to guide clinical management in patients with mild to moderate COVID-19 ²²³	Rajalingam	2021	South Tamilnadu, India	Lower-middle-income	Outpatient/general practitioner	Not specified	1	Proposed

COVID-19 Outpatient Screening: A Prediction Score for Adverse Events ²²⁴	Sun	2020	Massachusetts, United States	High-income	Outpatient / general practitioner	Adult	20	Proposed
Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province ¹⁷	Sun	2020	Nanjing, China	Upper-middle-income	Not specified	Not specified	6	Implemented
Clinical Management of COVID-19 Interim Guidance ^{207 225}	World Health Organization	2020	Not applicable	Not applicable	Not specified	All ages	18	Proposed

Table 3: Severity scoring / prognostication tool study characteristics (n=54).

Title	First author	Year	Study location	Study setting income level	Study setting	Age group	No. tool inputs	Has the tool been proposed or implemented?
Isaric 4c Mortality Score As A Predictor Of In-Hospital Mortality In Covid-19 Patients Admitted In Ayub Teaching Hospital During First Wave Of The Pandemic ²²⁶	Ali	2021	Abbottabad, Pakistan	Lower-middle-income	Hospital	Not specified	8	Proposed
Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-Cov-2 infection: a multicenter cohort study (PREDI-CO study) ²²⁷	Bartoletti	2020	Bologna, Italy	High-income	Hospital	Not specified	8	Proposed
Lung ultrasonography for risk stratification in patients with COVID-19: a prospective observational cohort study ²²⁸	Brahier	2020	Switzerland	High-income	Hospital	Not specified	1	Proposed
Prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count ²²⁹	Bi	2020	Taizhou, China	Upper-middle-income	Hospital	Not specified	2	Proposed
Chest X-ray in new Coronavirus Disease 2019 (COVID-19) infection: findings and correlation with clinical outcome ²³⁰	Cozzi	2020	Florence, Italy	High-income	Hospital	Not specified	1	Proposed
Predicting CoVID-19 community mortality risk using machine learning and development of an online prognostic tool ²³¹	Das	2020	South Korea	High-income	Not specified	Not specified	3	Proposed
A novel simple scoring model for predicting severity of patients with SARS-CoV-2 infection ²³²	Dong	2020	Wuhan, China	Upper-middle-income	Hospital	Not specified	3	Proposed
Correlation between the variables collected at admission and progression to severe cases during hospitalization among patients with COVID-19 in Chongqing ²³³	Duan	2020	Chongqing, China	Upper-middle-income	Not specified	Not specified	3	Proposed
A multipurpose machine learning approach to predict COVID-19 negative prognosis in São Paulo, Brazil ²³⁴	Fernandes	2021	São Paulo, Brazil	High-income	Upper-middle-income	Not specified	5	Proposed

The utility of established prognostic scores in COVID-19 hospital admissions: a multicentre prospective evaluation of CURB-65, NEWS2, and qSOFA ²³⁵	Frost	2020	Liverpool, England	High-income	Hospital	Not specified	2	Proposed
A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: An observational cohort study ²³⁶	Galloway	2020	London, United Kingdom	High-income	Hospital	Not specified	10	Proposed
Prognostic Accuracy of the SIRS, qSOFA, and NEWS for Early Detection of Clinical Deterioration in SARS-CoV-2 Infected Patients ²³⁷	Geol Jang	2020	Daegu, Korea	High-income	Not specified	Not specified	3	Proposed
Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection ²³⁸	Gidari	2020	Perugia, Italy	High-income	Hospital	Not specified	1	Proposed
A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China ²³⁹	Gong	2020	Guangzhou, China	Upper-middle-income	Hospital	Not specified	7	Proposed
Development and validation of a prognostic model based on comorbidities to predict COVID-19 severity: a population-based study ²⁴⁰	Gude-Sampedro	2021	Galicia, Spain	High-income	Not specified	Not specified	10	Proposed
Evaluation of the clinical profile, laboratory parameters and outcome of two hundred COVID-19 patients from a tertiary centre in India ²⁴¹	Gupta	2020	India	Lower-middle-income	Not specified	Not specified	12	Proposed
Development and validation of the quick COVID-19 severity index (qCSI): a prognostic tool for early clinical decompensation ²⁴²	Haimovich	2020	Connecticut, United States	High-income	Not specified	Not specified	3	Proposed
Predictive Value of 5 Early Warning Scores for Critical COVID-19 Patients	Hu	2020	Wuhan, China	Upper-middle-income	Hospital-based emergency care	Not specified	5	Proposed
COVID-19 Severity Index: predictive score for hospitalized patients ²⁴³	Huespe	2020	Buenos Aires, Argentina	Upper-middle-income	Hospital	Not specified	16	Proposed

COVID-19: Symptoms, course of illness and use of clinical scoring systems for the first 42 patients admitted to a Norwegian local hospital ²⁴⁴	Ihle-Hansen	2020	Viken county, Norway	High-income	Hospital	Not specified	1	Proposed
Clinical Characteristics and Prognostic Factors for Intensive Care Unit Admission of Patients With COVID-19: Retrospective Study Using Machine Learning and Natural Language Processing ²⁴⁵	Izquierdo	2020	Castilla-La Mancha, Spain	High-income	Not specified	Not specified	3	Proposed
Development and validation of a model for individualized prediction of hospitalization risk in 4,536 patients with COVID-19 ²⁴⁶	Jehi	2020	Guangzhou, China	Upper-middle-income	Not specified	Not specified	8	Proposed
The association of chest radiographic findings and severity scoring with clinical outcomes in patients with COVID-19 presenting to the emergency department of a tertiary care hospital in Pakistan ²⁴⁷	Kaleemi	2021	Pakistan	Lower-middle-income	Adult	Hospital-based emergency care	1	Proposed
The performance of the National Early Warning Score and National Early Warning Score 2 in hospitalised patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ²⁴⁸	Kostakis	2020	United Kingdom	High-income	Hospital	Not specified	1	Proposed
Clinical Frailty Scale for risk stratification in patients with SARS-CoV-2 infection ²⁴⁹	Labenz	2020	Mainz, Germany	High-income	Hospital	Not specified	1	Proposed
Triage tool for suspected COVID-19 patients in the emergency room: AIFELL score	Levenfus	2020	Zurich, Switzerland	High-income	Hospital	Not specified	6	Proposed
A simple algorithm helps early identification of SARS-CoV-2 infection patients with severe progression tendency ²⁵⁰	Li	2020	Shanghai, China	Upper-middle-income	Not specified	Not specified	3	Proposed
Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19 ¹³²	Liang	2020	Guangzhou, China	Upper-middle-income	Not specified	Not specified	10	Proposed
Early triage of critically ill COVID-19 patients using deep learning ²⁵¹	Liang	2020	Guangzhou, China	Upper-middle-income	Not specified	Not specified	10	Proposed
Development and validation of a risk stratification model for screening suspected cases of COVID-19 in China ²⁵²	Ma	2020	Wuhan, China	Upper-middle-income	Not specified	Not specified	23	Proposed

National Early Warning Score 2 (NEWS2) on admission predicts severe disease and in-hospital mortality from Covid-19 - a prospective cohort study ⁹⁴	Myrstad	2020	Oslo, Norway	High-income	Hospital	Not specified	1	Proposed
A score combining early detection of cytokines accurately predicts COVID-19 severity and intensive care unit transfer ²⁵³	Nagant	2020	Brussels, Belgium	High-income	Hospital	Not specified	3	Proposed
A nomogram to predict the risk of unfavourable outcome in COVID-19: a retrospective cohort of 279 hospitalized patients in Paris area ²⁵⁴	Nguyen	2020	Paris, France	High-income	Hospital	Not specified	7	Proposed
Automated EHR score to predict COVID-19 outcomes at US Department of Veterans Affairs ²⁵⁵	Osborne	2020	California, United States	High-income	Not specified	Adult	25	Proposed
NEWS can predict deterioration of patients with COVID-19 ²⁵⁶	Peng	2020	Huazhong, China	Upper-middle-income	Not specified	Not specified	2	Proposed
Examining the utility of extended laboratory panel testing in the emergency department for risk stratification of patients with COVID-19: a single-centre retrospective service evaluation ²⁵⁷	Ponsford	2021	Cardiff, United Kingdom	High-income	Hospital	Adult	8	Proposed
Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study ²⁵⁸	Sablerolles	2021	Europe	High-income	Hospital	Adult	1	Proposed
Performance of pneumonia severity index and CURB-65 in predicting 30-day mortality in patients with COVID-19 ¹¹⁶	Satici	2020	Istanbul, Turkey	Upper-middle-income	Hospital	Not specified	2	Proposed
Model-based Prediction of Critical Illness in Hospitalized Patients with COVID-19 ²⁵⁹	Schalekamp	2020	Amersfoort, The Netherlands	High-income	Not specified	Not specified	7	Proposed
Scoring systems for predicting mortality for severe patients with COVID-19 ²⁶⁰	Shang	2020	Wuhan, China	Upper-middle-income	Hospital	Not specified	5	Proposed
Evaluating a Widely Implemented Proprietary Deterioration Index Model Among Hospitalized COVID-19 Patients ²⁶¹	Singh	2020	Michigan, United States	High-income	Not specified	Not specified	1	Proposed

Development and validation of a simple risk score for diagnosing COVID-19 in the emergency room ²⁶²	Sung	2020	Maryland, United States	High-income	Hospital	Not specified	10	Proposed
Prediction of Sepsis in COVID-19 Using Laboratory Indicators ²⁶³	Tang	2021	Tongji, China	Upper-middle-income	Not specified	Not specified	7	Proposed
Development of a data-driven COVID-19 prognostication tool to inform triage and step-down care for hospitalised patients in Hong Kong: A population based cohort study ²⁶⁴	Tsui	2020	Hong Kong, China	Upper-middle-income	Hospital	Not specified	7	Proposed
Personalized predictive models for symptomatic COVID-19 patients using basic preconditions: Hospitalizations, mortality, and the need for an ICU or ventilator ²⁶⁵	Wollenstein-Betech	2020	Mexico	Upper-middle-income	Not specified	Not specified	9	Proposed
Development of a Clinical Decision Support System for Severity Risk Prediction and Triage of COVID-19 Patients at Hospital Admission: An International Multicenter Study ²⁶⁶	Wu	2020	Maastricht, the Netherlands	High-income	Hospital	Not specified	7	Proposed
Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019 ²⁶⁷	Xiao	2020	Guangzhou, China	Upper-middle-income	Not specified	Not specified	5	Proposed
Point-of-Care Lung Ultrasound for COVID-19: Findings and Prognostic Implications From 105 Consecutive Patients ²⁶⁸	Yasukawa	2021	Washington D.C., United States	High-income	Hospital	Not specified	1	Proposed
A Novel Scoring System for Prediction of Disease Severity in COVID-19 ²⁶⁹	Zhang	2020	Beijing, China	Upper-middle-income	Hospital	Not specified	5	Proposed
Development and validation of a risk factor-based system to predict short-term survival in adult hospitalized patients with COVID-19: a multicenter, retrospective, cohort study ²⁷⁰	Zhang	2020	Honghu, China	Upper-middle-income	Hospital	Not specified	1	Proposed
Lung Ultrasound Score in Evaluating the Severity of Coronavirus Disease 2019 (COVID-19) Pneumonia ²⁷¹	Zhao	2020	Shanghai, China	Upper-middle-income	Hospital	Not specified	1	Proposed
Development and validation a nomogram for predicting the risk of severe COVID-19: A multi-center study in Sichuan, China ²⁷²	Zhou	2020	Sichuan, China	Upper-middle-income	Not specified	Not specified	6	Proposed

Deep-learning artificial intelligence analysis of clinical variables predicts mortality in COVID-19 patients ²⁷³	Zhu	2020	New York, United States	High-income	Not specified	Not specified	5	Proposed
Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019 ²⁷⁴	Zou	2020	Wuhan, China	Upper-middle-income	Hospital	Not specified	1	Proposed

Appendix 2.4: Summary of validation data for tools being used to screen, triage, and prognosticate COVID-19 patients

Title	Validation endpoint	Tool training/development validation data					Validation type	Other validation data				
		AUC	Sensitivity	Specificity	PPV	NPV		AUC	Sensitivity	Specificity	PPV	NPV
A Novel Scoring System for Prediction of Disease Severity in COVID-19 ²⁶⁹	ICU admission						Retro-spective	0.91	0.71	0.89		
A novel simple scoring model for predicting severity of patients with SARS-CoV-2 infection ²³²	COVID-19 confirmed by RT-PCR						Retro-spective		0.8	0.79		
A quickly, effectively screening process of novel corona virus disease 2019 (COVID-19) in children in Shanghai, China ²⁰⁰	COVID-19 diagnosis		1	0.71	0.18	1						
A simple algorithm helps early identification of SARS-CoV-2 infection patients with severe progression tendency ²⁵⁰	Severe COVID-19 disease						Retro-spective		0.18	0.93	0.49	0.98
A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China ²³⁹	Severe COVID-19 disease	0.91	0.86	0.88								
Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019 ²⁷⁴	In-hospital mortality	0.97	0.96	0.86								

Clinical Characteristics and Prognostic Factors for Intensive Care Unit Admission of Patients With COVID-19: Retrospective Study Using Machine Learning and Natural Language Processing.	ICU admission	0.76											
Containing COVID-19 in the Emergency Department: The Role of Improved Case Detection and Segregation of Suspect Cases ²⁰⁵	COVID-19 confirmed by RT-PCR		0.842 (95% CI [0.736-0.919])	0.648 (95% CI [0.625-0.670])									
COVID-19 Outpatient Screening: A Prediction Score for Adverse Events ²²⁴	Hospitalisation, ICU care, need for mechanical ventilation, or death within 7 days of an outpatient medical encounter	0.80 (hospitalisation); 0.82 (critical illness); 0.87 (death)						Pro- spective	0.76 (hospitalisation); 0.79 (critical illness); 0.93 (death)				
Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19 ¹³²	Critical COVID-19 disease		72% (95% CI [65%-79%]) (at risk score >3)	86% (95% CI [89%-92%]) (at risk score >3)	74% (95% CI [67%-80%]) (at risk score >3)	89% (95% CI [85%-91%]) (at risk score >3)		Retro- spective	80% (95% CI [73%-85%]) (at risk score >3)	76% (95% CI [70%-81%]) (at risk score >3)	69% (95% CI [60%-74%]) (at risk score >3)	85% (95% CI [80%-89%]) (at risk score >3)	
Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-Cov-2 infection: a multicenter cohort study (PREDI-CO study) ²⁷⁵	Severe respiratory failure	0.89 (95% CI [0.86-0.92])											

Development and validation of a prognostic model based on comorbidities to predict COVID-19 severity: a population-based study.	Mortality	0.89										
Development and validation of a risk factor-based system to predict short-term survival in adult hospitalized patients with COVID-19: a multicenter, retrospective, cohort study ²⁷⁰	28-day mortality						Retro-spective	0.879 (95% CI [0.856-0.900])				
Development and validation of a risk stratification model for screening suspected cases of COVID-19 in China ²⁵²	COVID-19 confirmed by RT-PCR	0.86	0.83	0.78	0.32	0.97	Retro-spective	0.87	0.82	0.77	0.26	0.98
Development and validation of a simple risk score for diagnosing COVID-19 in the emergency room.	COVID-19 confirmed by RT-PCR											
Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019 ²⁶⁷	Severe COVID-19 disease						Retro-spective	0.86	0.85	0.76		
Development and validation of the quick COVID-19 severity index (qCSI): a prognostic tool for early clinical decompensation ²⁴²	Respiratory failure within 24 hours of admission						Retro-spective	0.91	0.94	0.82		
Development of a Clinical Decision Support System for Severity Risk Prediction and Triage of COVID-19 Patients at Hospital Admission: An International Multicenter Study ²⁶⁶	Severe or critical COVID-19 disease	0.88	0.85	0.74	0.75	0.85						

Development of a data-driven COVID-19 prognostication tool to inform triage and step-down care for hospitalised patients in Hong Kong: A population based cohort study ²⁶⁴	Severe COVID-19 disease	0.913 (Day-1 model) and 0.942 (Day-5 model)									
Evaluating a Widely Implemented Proprietary Deterioration Index Model Among Hospitalized COVID-19 Patients ²⁶¹	ICU-level care, mechanical ventilation, or in-hospital death				Retro-spective	0.79	0.39	0.91	0.74	0.9	
Examining the utility of extended laboratory panel testing in the emergency department for risk stratification of patients with COVID-19: a single-centre retrospective service evaluation.	28-day mortality	0.77									
Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province ¹⁷	Severe COVID-19 disease	0.96	0.955 (95% CI [0.772-0.999])	0.899 (95% CI [0.863-0.928])							
Lung Ultrasound Score in Evaluating the Severity of Coronavirus Disease 2019 (COVID-19) Pneumonia ²⁷¹	Refractory COVID-19 disease				Retro-spective	0.52	1	0.74			
Model-based Prediction of Critical Illness in Hospitalized Patients with COVID-19 ²⁵⁹	Critical COVID-19 disease				Retro-spective	0.77	0.5	0.88	0.79	0.66	
National Early Warning Score 2 (NEWS2) on admission predicts severe disease and in-hospital mortality from Covid-19 - a prospective cohort study ⁹⁴	Severe COVID-19 disease	0.82	0.8	0.84							

NEWS can predict deterioration of patients with COVID-19 ²⁵⁶	Severe and critical COVID-19 disease						Pro-spective	0.84	1	0.51		
Performance of pneumonia severity index and CURB-65 in predicting 30-day mortality in patients with COVID-19 ¹¹⁶	30-day mortality						Retro-spective	0.79 (CURB-65); 0.85 (PSI)	0.73 (CURB-65); 0.80 (PSI)	0.85 (CURB-65); 0.89 (PSI)	0.31 (CURB-65), 0.39 (PSI)	0.97 (CURB-65), 0.98 (PSI)
Personalized predictive models for symptomatic COVID-19 patients using basic preconditions: Hospitalizations, mortality, and the need for an ICU or ventilator.	Mortality	0.63										
Predicting CoVID-19 community mortality risk using machine learning and development of an online prognostic tool.	Mortality	0.83	0.692	0.968								
Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count ²²⁹	Severe COVID-19 disease		0.863 (95% CI [0.640–0.964])	0.593 (95% CI [0.485–0.694])	0.339 (95% CI [0.222–0.0.479])	0.9474 (95% CI [0.845–0.986])	Pro-spective		0.857 (95% CI [0.420–0.992])	0.429 (95% CI [0.226–0.556])	0.333 (95% CI [0.143–0.588])	0.9 (95% CI [0.541–0.994])
Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection ²³⁸	Severe COVID-19 disease						Retro-spective		0.89	0.66	0.63	0.9
Prognostic Accuracy of the SIRS, qSOFA, and NEWS for Early Detection of Clinical Deterioration in SARS-CoV-2 Infected Patients ⁹³	28-day mortality						Retro-spective	0.918 (NEWS); 0.760 (qSOFA); 0.744 (SIRS)	0.867 (NEWS≥5)	0.905 (NEWS≥5)	0.591 (NEWS≥5)	0.977 (NEWS≥5)

Proposed Clinical Indicators for Efficient Screening and Testing for COVID-19 Infection from Classification and Regression Trees (CART) Analysis ²¹³	COVID-19 confirmed by RT-PCR	0.78	0.96	0.53	0.14	0.99						
The utility of established prognostic scores in COVID-19 hospital admissions: a multicentre prospective evaluation of CURB-65, NEWS2, and qSOFA ²³⁵	30-day mortality						Pro-spective	0.75 (CURB-65 ≥2); 0.61 (CURB-65 ≥3); 0.78 (NEWS2 ≥5); 0.66 (qSOFA ≥2)	0.85 (CURB-65 ≥2); 0.61 (CURB-65 ≥3); 0.92 (NEWS2 ≥5); 0.45 (qSOFA ≥2)	0.47 (CURB-65 ≥2); 0.73 (CURB-65 ≥3); 0.31 (NEWS2 ≥5); 0.484(qS OFA ≥2)	0.12 (CURB-65 ≥2); 0.17 (CURB-65 ≥3); 0.10 (NEWS2 ≥5); 0.19 (qSOFA ≥2)	0.97 (CURB-65 ≥2); 0.96 (CURB-65 ≥3); 0.98 (NEWS2 ≥5); 0.94 (qSOFA ≥2)

Note: Only common, standardised measures of validation were extracted.

AUC = area under curve score; PPV = positive predictive value; NPV = negative predictive value

Appendix 2.5: Breakdown of inputs used tools used to screen, triage, and prognosticate COVID-19 patients.

Input	Feasible to evaluate or perform in low-resource setting emergency units?	Screening tools (n=57)		Triage tools (n=23)		Severity scoring tools (n=54)	
		No. tools using input	%	No. tools using input	%	No. tools using input	%
CONCURRENT ACUTE CONDITIONS (n=20)							
Acute renal failure	No	0	0.0%	0	0.0%	2	3.7%
Acute respiratory distress syndrome	No	0	0.0%	3	13.0%	0	0.0%
Animal/insect bites	Yes	0	0.0%	1	4.3%	0	0.0%
Bacterial coinfection	No	0	0.0%	2	8.7%	0	0.0%
Cardiac arrest	Yes	0	0.0%	2	8.7%	0	0.0%
Current level of physical fitness	Yes	0	0.0%	0	0.0%	2	3.7%
Encephalopathy	Yes	0	0.0%	1	4.3%	0	0.0%
Major trauma	Yes	0	0.0%	0	0.0%	0	0.0%
Metabolic acidosis	No	0	0.0%	1	4.3%	0	0.0%
Multilobe infiltrate	Yes	0	0.0%	0	0.0%	0	0.0%
Organ failure	No	0	0.0%	1	4.3%	2	3.7%
Pericarditis	No	0	0.0%	1	4.3%	0	0.0%
Pleural effusion	Yes	0	0.0%	0	0.0%	1	1.9%
Pneumonia	Yes	2	3.5%	3	13.0%	2	3.7%
Respiratory distress	Yes	1	1.8%	3	13.0%	2	3.7%
Pneumothorax	No	0	0.0%	3	13.0%	0	0.0%
Respiratory failure	Yes	0	0.0%	3	13.0%	4	7.4%
Septic shock	Yes	0	0.0%	3	13.0%	1	1.9%
Systemic inflammatory response syndrome (SIRS)	Yes	0	0.0%	1	4.3%	0	0.0%
Unknown clinical inputs (proprietary algorithm)	No	0	0.0%	0	0.0%	1	1.9%
CLINICAL INTERVENTIONS RECEIVED (n=5)							
Nasal intermittent positive pressure ventilation	No	0	0.0%	1	4.3%	0	0.0%
Need for supplemental oxygen	Yes	0	0.0%	1	4.3%	7	13.0%

High-flow nasal canula	No	0	0.0%	1	4.3%	0	0.0%
Mechanical ventilation	No	0	0.0%	1	4.3%	0	0.0%
Vasopressors	No	0	0.0%	1	4.3%	0	0.0%
DEMOGRAPHICS (n=7)							
Age	Yes	4	7.0%	9	39.1%	28	51.9%
Sex	Yes	2	3.5%	3	13.0%	12	22.2%
Ethnicity	Yes	0	0.0%	0	0.0%	2	3.7%
Marital status	Yes	0	0.0%	0	0.0%	1	1.9%
Pregnancy	Yes	0	0.0%	0	0.0%	1	1.9%
Race	Yes	0	0.0%	1	4.3%	1	1.9%
Welsh Index of Multiple Deprivation	Yes	0	0.0%	0	0.0%	1	1.9%
COMORBIDITIES (n=29)							
Amyotrophic lateral sclerosis	Yes	0	0.0%	1	4.3%	0	0.0%
Any comorbidity	Yes	2	3.5%	3	13.0%	2	3.7%
Asthma	Yes	0	0.0%	0	0.0%	1	1.9%
Atrial fibrillation	Yes	0	0.0%	0	0.0%	1	1.9%
Body mass index	Yes	1	1.8%	2	8.7%	6	11.1%
Chronic kidney disease	Yes	2	3.5%	1	4.3%	5	9.3%
Chronic obstructive lung disease	Yes	0	0.0%	2	8.7%	7	11.1%
Connective tissue disease	Yes	0	0.0%	0	0.0%	1	1.9%
Coronary artery disease / congestive heart failure	Yes	2	3.5%	1	4.3%	7	13.0%
Cystic fibrosis	Yes	0	0.0%	1	4.3%	0	0.0%
Dementia	Yes	0	0.0%	0	0.0%	1	1.9%
Depression	Yes	0	0.0%	0	0.0%	1	1.9%
Diabetes	Yes	0	0.0%	1	4.3%	6	11.1%
Functional disorder	Yes	0	0.0%	0	0.0%	1	1.9%
Hypertension	Yes	0	0.0%	3	13.0%	6	11.1%
Immunocompromise	Yes	3	5.3%	0	0.0%	4	7.4%
Liver disease	Yes	0	0.0%	0	0.0%	3	5.6%
Malignancy	Yes	0	0.0%	2	8.7%	6	11.1%
Malnutrition	Yes	0	0.0%	0	0.0%	1	1.9%
Myasthenia gravis	Yes	0	0.0%	1	4.3%	0	0.0%
Pancreatitis	Yes	0	0.0%	1	4.3%	0	0.0%
Peripheral vascular disease	Yes	0	0.0%	0	0.0%	1	1.9%

Psychiatric disorder	Yes	1	1.8%	0	0.0%	1	1.9%
Seizure disorder	Yes	0	0.0%	1	4.3%	0	0.0%
Smoking history	Yes	0	0.0%	2	8.7%	1	1.9%
Spinal muscular atrophy	Yes	0	0.0%	0	0.0%	1	1.9%
Stroke	Yes	0	0.0%	1	4.3%	1	1.9%
Transplant history	Yes	0	0.0%	0	0.0%	1	1.9%
Valvular heart disease	Yes	0	0.0%	0	0.0%	1	1.9%

LABORATORY INVESTIGATIONS (n=64)

Albumin	No	0	0.0%	1	4.3%	3	5.6%
Alanine aminotransferase	No	0	0.0%	2	8.7%	0	0.0%
Albumin/globulin ratio	No	0	0.0%	0	0.0%	1	1.9%
Alkaline phosphatase	No	0	0.0%	1	4.3%	0	0.0%
Arterial blood gas	No	0	0.0%	2	8.7%	1	1.9%
Aspartate aminotransferase	No	0	0.0%	1	4.3%	1	1.9%
Basophil count	No	3	5.3%	1	4.3%	0	0.0%
Blood urea nitrogen	No	0	0.0%	2	8.7%	5	9.3%
C-reactive protein	No	2	3.5%	7	30.4%	14	25.9%
Calcium	No	0	0.0%	0	0.0%	1	1.9%
Cardiovascular abnormalities	No	0	0.0%	2	8.7%	0	0.0%
CD3	No	0	0.0%	0	0.0%	1	1.9%
CD4	No	0	0.0%	0	0.0%	2	3.7%
Chloride	No	0	0.0%	0	0.0%	1	1.9%
Complete blood count	No	0	0.0%	1	4.3%	0	0.0%
Creatine kinase	No	0	0.0%	0	0.0%	1	1.9%
Creatinine	No	0	0.0%	4	17.4%	5	9.3%
D-dimer	No	0	0.0%	3	13.0%	5	9.3%
Direct bilirubin	No	0	0.0%	1	4.3%	4	7.4%
Eosinophil count	No	2	3.5%	2	8.7%	0	0.0%
Erythrocyte sedimentation rate	No	0	0.0%	0	0.0%	1	1.9%
Ferritin	No	0	0.0%	1	4.3%	0	0.0%
Fibrinogen to albumin ratio	No	0	0.0%	0	0.0%	1	1.9%
Globulin	No	0	0.0%	0	0.0%	1	1.9%
Glomerular filtration rate	No	0	0.0%	0	0.0%	1	1.9%
Glucose	Yes	0	0.0%	0	0.0%	1	1.9%

Haematocrit	No	2	3.5%	0	0.0%	3	5.6%
Haemoglobin	No	2	3.5%	0	0.0%	0	0.0%
IL-2R	No	0	0.0%	0	0.0%	1	1.9%
IL-6	No	0	0.0%	0	0.0%	2	3.7%
IL-8	No	0	0.0%	0	0.0%	1	1.9%
IL-10	No	0	0.0%	0	0.0%	1	1.9%
Immature granulocyte percentage	No	1	1.8%	0	0.0%	0	0.0%
Influenza test	No	1	1.8%	0	0.0%	0	0.0%
INR	No	0	0.0%	1	4.3%	0	0.0%
Lactate	No	0	0.0%	1	4.3%	0	0.0%
Lactate dehydrogenase	No	0	0.0%	3	13.0%	11	20.4%
Leukocyte count	No	2	3.5%	1	4.3%	1	1.9%
Lymphocyte count	No	6	10.5%	4	17.4%	1	1.9%
Lymphocyte percentage	No	0	0.0%	1	4.3%	1	1.9%
Mean corpuscular haemoglobin	No	2	3.5%	0	0.0%	0	0.0%
Mean corpuscular haemoglobin concentration	No	1	1.8%	0	0.0%	0	0.0%
Mean corpuscular volume	No	3	5.3%	0	0.0%	0	0.0%
Mean platelet volume	No	1	1.8%	0	0.0%	0	0.0%
Comprehensive metabolic panel	No	0	0.0%	3	13.0%	0	0.0%
Mononuclear cell count	No	2	3.5%	0	0.0%	1	1.9%
Neutrophil count	No	1	1.8%	2	8.7%	5	9.3%
Neutrophil to lymphocyte ratio	No	1	0.0%	2	8.7%	5	9.3%
Nucleated red blood cells	No	1	1.8%	0	0.0%	0	0.0%
pH	No	0	0.0%	0	0.0%	3	5.6%
Platelet count	No	3	5.3%	3	13.0%	5	9.3%
Platelet distribution width	No	2	3.5%	0	0.0%	0	0.0%
Platelet haematocrit	No	2	3.5%	0	0.0%	0	0.0%
Potassium	No	0	0.0%	0	0.0%	4	7.4%
Prealbumin	No	0	0.0%	0	0.0%	1	1.9%
Procalcitonin	No	0	0.0%	1	4.3%	1	1.9%
Red cell count	No	0	0.0%	1	4.3%	0	0.0%
Red cell distribution width	No	2	3.5%	1	4.3%	1	1.9%
SARS-CoV-2 RT-PCR	No	9	15.8%	1	4.3%	0	0.0%
Sodium	No	0	0.0%	0	0.0%	3	5.6%

Total protein	No	0	0.0%	0	0.0%	1	1.9%
Troponin	No	0	0.0%	3	13.0%	1	1.9%
Urea	No	0	0.0%	1	4.3%	3	5.6%
White blood cell count	No	0	0.0%	2	8.7%	2	3.7%
IMAGING INVESTIGATIONS (n=3)							
Chest X-ray	No	4	7.0%	8	34.8%	7	13.0%
Chest CT	No	9	15.8%	10	43.5%	3	5.6%
Lung ultrasound	No	5	8.8%	8	34.8%	2	3.7%
SIGNS AND SYMPTOMS (n=37)							
Abdominal pain	Yes	0	0.0%	1	4.3%	0	0.0%
Anosmia / agueisa	Yes	4	7.0%	0	0.0%	1	1.9%
Any COVID-related symptoms	Yes	10	17.5%	1	4.3%	0	0.0%
Any respiratory symptoms	Yes	26	45.6%	0	0.0%	0	0.0%
Arthralgia	Yes	1	1.8%	0	0.0%	0	0.0%
Chest distress	Yes	2	3.5%	0	0.0%	0	0.0%
Chest pain	Yes	3	5.3%	0	0.0%	0	0.0%
Chest tightness	Yes	1	1.8%	0	0.0%	0	0.0%
Chills	Yes	6	10.5%	0	0.0%	0	0.0%
Conjunctival congestion	Yes	1	1.8%	0	0.0%	0	0.0%
Constipation	Yes	0	0.0%	1	4.3%	0	0.0%
Convulsions	Yes	0	0.0%	1	4.3%	0	0.0%
Cough	Yes	23	40.4%	0	0.0%	2	3.7%
Cyanosis	Yes	0	0.0%	1	4.3%	0	0.0%
Diarrhoea	Yes	3	5.3%	1	4.3%	0	0.0%
Dizziness	Yes	1	1.8%	0	0.0%	0	0.0%
Duration of fever	Yes	2	3.5%	0	0.0%	0	0.0%
Duration of symptoms	Yes	0	0.0%	2	8.7%	1	1.9%
Fatigue	Yes	1	1.8%	0	0.0%	1	1.9%
Fever	Yes	31	54.4%	2	8.7%	3	5.6%
Frequency of cough	Yes	1	1.8%	0	0.0%	0	0.0%
Gastrointestinal symptoms	Yes	1	1.8%	0	0.0%	0	0.0%
Haematemesis	Yes	0	0.0%	2	8.7%	0	0.0%
Haemoptysis	Yes	0	0.0%	0	0.0%	2	3.7%
Headache	Yes	1	1.8%	1	4.3%	1	1.9%

Inability to breastfeed or drink	Yes	0	0.0%	1	4.3%	0	0.0%
Myalgia	Yes	5	8.8%	0	0.0%	0	0.0%
Nasal congestion	Yes	3	5.3%	0	0.0%	1	1.9%
Nausea	Yes	1	1.8%	1	4.3%	0	0.0%
Rash	Yes	1	1.8%	0	0.0%	0	0.0%
Rhinorrhoea	Yes	2	3.5%	1	4.3%	0	0.0%
Shortness of breath	Yes	16	28.1%	0	0.0%	5	9.3%
Sore throat	Yes	5	8.8%	0	0.0%	1	1.9%
Sputum production	Yes	2	3.5%	0	0.0%	0	0.0%
Unconsciousness	Yes	0	0.0%	1	4.3%	1	1.9%
Unspecified signs and symptoms	Yes	1	1.8%	1	4.3%	0	0.0%
Vomiting	Yes	1	1.8%	1	4.3%	0	0.0%

VITAL SIGNS (n=17)

Altered mental status	Yes	1	1.8%	3	13.0%	5	9.3%
AVPU scale	Yes	0	0.0%	1	4.3%	0	0.0%
Clinical gestalt	Yes	1	1.8%	1	4.3%	1	1.9%
Diastolic blood pressure	Yes	0	0.0%	3	13.0%	1	1.9%
Exertional oxygen saturation	Yes	0	0.0%	1	4.3%	0	0.0%
FiO2	Yes	0	0.0%	0	0.0%	1	1.9%
Glasgow Coma Scale	Yes	0	0.0%	4	17.4%	4	7.4%
Haemodynamic instability	Yes	1	1.8%	1	4.3%	0	0.0%
Heart rate	Yes	1	1.8%	4	17.4%	8	14.8%
Hypercapnia	No	1	1.8%	0	0.0%	0	0.0%
Oxygen saturation	Yes	9	15.8%	14	60.9%	8	14.8%
Pain severity	Yes	0	0.0%	1	4.3%	0	0.0%
PaO2/FiO2 < 300	No	0	0.0%	4	17.4%	0	0.0%
Respiratory rate	Yes	2	3.5%	13	56.5%	16	29.6%
Systolic blood pressure	Yes	1	1.8%	9	39.1%	9	16.7%
Temperature	Yes	17	29.8%	5	21.7%	13	24.1%
Altered mental status	Yes	1	1.8%	2	8.7%	5	9.3%

OTHER CHARACTERISTICS (n=7)

Ability to live and walk independently	Yes	1	1.8%	0	0.0%	0	0.0%
Abnormal ECG findings	No	0	0.0%	1	4.3%	0	0.0%
Score on the Braden scale	Yes	0	0.0%	0	0.0%	0	0.0%

Epidemiological history	Yes	36	63.2%	2	8.7%	2	3.7%
Nursing home resident	Yes	0	0.0%	1	4.3%	1	1.9%
Status as a healthcare worker	Yes	2	3.5%	0	0.0%	0	0.0%
Use of prescription medications	Yes	0	0.0%	1	4.3%	0	0.0%

Appendix 2.6: Overview of use of established prognostication tools for COVID-19.

Tool	No. inputs	Inputs	Feasible in low-resource settings?	No. studies using tool
APACHE II Score ²⁷⁶	15	• Acute renal failure • Age • Creatinine • FiO2 • Glasgow Coma Scale • Haematocrit • Heart rate • History of severe organ failure or immunocompromise • Mean arterial pressure • pH • Potassium • Respiratory rate • Sodium • Temperature • White blood cell count	No	1
Clinical Frailty Score	1	• Level of physical fitness	Yes	3
CURB-65 Score for Pneumonia Severity	5	• Age • Blood urea nitrogen • Confusion • Respiratory rate • Systolic or diastolic blood pressure	No	4
Deyo-Charlson Score ²⁷⁷	17	• AIDS • Any malignancy • Cerebrovascular disease • Chronic pulmonary disease • Congestive heart failure • Dementia • Diabetes with complications • Diabetes without chronic complications • Hemiplegia or paraplegia • Metastatic solid tumour • Mild liver disease • Moderate/severe liver disease • Myocardial infarction • Peptic ulcer disease • Peripheral vascular disease • Renal disease • Rheumatoid disease	Yes	1
Korean Triage and Acuity Scale ²⁷⁸	17	• Abdominal pain • Bites • Cardiac arrest • Chest pain • Constipation • Diarrhoea • Glasgow Coma Scale • Haematemesis • Headache	Yes	1

		• Major trauma • Nausea and/or vomiting • Prescription medications • Respiratory failure • Systolic blood pressure • Systemic inflammatory response syndrome (SIRS) • Temperature • Urinary tract infection		
Modified 6-Minute Walk Test ²⁷⁹	1	• Distance walked in 6 minutes	Yes	1
Modified Early Warning Score (MEWS) for Clinical Deterioration ²⁸⁰	5	• AVPU score • Heart rate • Respiratory rate • Systolic blood pressure • Temperature • Absolute lymphocyte count	Yes	1
MuLBSTA Score for Viral Pneumonia Mortality ²⁸¹	6	• Age • Bacterial coinfection • History of hypertension • Multilobe infiltrate • Smoking history	No	1
National Early Warning Score (NEWS) ²⁸²	5	• Need for supplemental oxygen • Oxygen saturation • Respiratory rate • Systolic blood pressure • Temperature	Yes	4
National Early Warning Score 2 (NEWS2) ²⁸³	7	• Consciousness • Heart rate • Hypercapnic respiratory failure • Need for supplemental oxygen • Respiratory rate • Systolic blood pressure • Temperature	Yes	5
Pneumonia Severity Index for Community Acquired Pneumonia ²⁸⁴	19	• Age • Altered mental status • Blood urea nitrogen • Glucose • Haematocrit • Heart rate • History of congestive heart failure • History of liver disease history • History of renal disease • Neoplastic disease • Nursing home resident • Partial pressure of oxygen • pH • Pleural effusion on X-ray • Respiratory rate • Sex • Sodium • Systolic blood pressure • Temperature	No	1
qSOFA (Quick SOFA) Score for Sepsis ²⁸⁵	3	• Glasgow Coma Scale • Respiratory rate • Systolic blood pressure	Yes	5

Appendix 3.1: Co-author declarations for “*Clinical and historical features associated with severe COVID-19 infection: a systematic review and meta-analysis.*”

Declaration by co-authors

Pigoga J, Friedman A, Broccoli M, Hirner S, Naidoo V, Singh S, Werner K, Omer YO, Wallis LA. Clinical and historical features associated with severe COVID-19 infection: A systematic review and meta-analysis. (Submitted and under review with BMJ Open)

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	60%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Alexandra Friedman	Screened eligible full-texts. Extracted data. Cross-checked all data extractions and assessed quality of included studies. Drafted manuscript, and provided critical review of final article.
Morgan Broccoli	Contributed to concept and study design. Screened eligible full-texts. Extracted data. Provided critical review and contributed to final article.
Sarah Hirner	Extracted data. Provided critical review and contributed to the final article.
Vanessa Naidoo	Screened articles titles, abstracts, and full-texts for inclusion. Extracted data. Provided critical review and contributed to the final article.
Yasein Omer	Drafted manuscript, and provided critical review of final article.
Swasthi Singh	Screened articles titles, abstracts, and full-texts for inclusion. Extracted data. Provided critical review and contributed to the final article.
Kalin Werner	Screened articles titles and abstracts for inclusion. Provided critical review and contributed to the final article.
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.

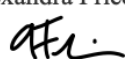
The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate’s contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according these criteria.

Co- Author Name Alexandra Friedman

Co-Author Signature

Date 22/01/2021



Declaration by co-authors

Pigoga J, Friedman A, Broccoli M, Hirner S, Naidoo V, Singh S, Werner K, Omer YO, Wallis LA. Clinical and historical features associated with severe COVID-19 infection: A systematic review and meta-analysis. (Submitted and under review with BMJ Open)

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	60%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Alexandra Friedman	Screened eligible full-texts. Extracted data. Cross-checked all data extractions and assessed quality of included studies. Drafted manuscript, and provided critical review of final article.
Morgan Broccoli	Contributed to concept and study design. Screened eligible full-texts. Extracted data. Provided critical review and contributed to final article.
Sarah Hirner	Extracted data. Provided critical review and contributed to the final article.
Vanessa Naidoo	Screened articles titles, abstracts, and full-texts for inclusion. Extracted data. Provided critical review and contributed to the final article.
Yasein Omer	Drafted manuscript, and provided critical review of final article.
Swasthi Singh	Screened articles titles, abstracts, and full-texts for inclusion. Extracted data. Provided critical review and contributed to the final article.
Kalin Werner	Screened articles titles and abstracts for inclusion. Provided critical review and contributed to the final article.
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.

The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according to these criteria.

Co- Author Name Kalin Werner

Co-Author Signature



Date January 20 2021

Declaration by co-authors

Pigoga J, Friedman A, Broccoli M, Hirner S, Naidoo V, Singh S, Werner K, Omer YO, Wallis LA. Clinical and historical features associated with severe COVID-19 infection: A systematic review and meta-analysis. (Submitted and under review with BMJ Open)

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The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	60%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Alexandra Friedman	Screened eligible full-texts. Extracted data. Cross-checked all data extractions and assessed quality of included studies. Drafted manuscript, and provided critical review of final article.
Morgan Broccoli	Contributed to concept and study design. Screened eligible full-texts. Extracted data. Provided critical review and contributed to final article.
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Yasein Omer	Drafted manuscript, and provided critical review of final article.
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Co- Author Name Lee A. Wallis

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Date 21/1/20

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Co- Author Name Morgan Broccoli

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Date 22/1/2021

Declaration by co-authors

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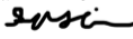
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Pigoga J, Friedman A, Broccoli M, Hirner S, Naidoo V, Singh S, Werner K, Omer YO, Wallis LA. Clinical and historical features associated with severe COVID-19 infection: A systematic review and meta-analysis. (Submitted and under review with BMJ Open)

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Date: 22 January 2021

Declaration by co-authors

Pigoga J, Friedman A, Broccoli M, Hirner S, Naidoo V, Singh S, Werner K, Omer YO, Wallis LA. Clinical and historical features associated with severe COVID-19 infection: A systematic review and meta-analysis. (Submitted and under review with BMJ Open)

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Co- Author Name Yasein O Omer



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Date 21/1/20

Appendix 3.2: University of Cape Town study proposal (FHS015)

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

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DECLARATION

I, Jennifer L Pigoga, 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:



Date: 18/11/20

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 severity scoring tool (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. 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 PhD aims to develop and validate a SST to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS.

A series of three studies is proposed. 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. The 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.

In this application, we are applying for UCT HREC approval for study one. While this is a systematic review and meta-analysis, it forms part of the PhD, and therefore requires UCT HREC approval. Study two has already been approved by UCT HREC (HREC REF: 450/2020) and study three is currently under review by HREC

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1. INTRODUCTION

1.1 Background

Despite containment efforts, COVID-19 has reached pandemic status. As of 18 November 2020, there are more than 54.6 million confirmed cases worldwide, with over 1.3 million deaths^{1 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.⁴ Mortality has varied across settings, but current data suggest a variable case fatality rate ranging from 0.5% to 4.5%.⁵⁻⁸

As COVID-19 spreads, healthcare systems worldwide are being strained.^{9 10} Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.¹¹ 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.^{9 10} It is increasingly likely that the countries with the most limited capacity to respond will be affected on a large scale.¹² Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.¹¹ 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.^{13 14} 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.¹⁵ 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.^{15 16} 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.¹⁷ High burdens of data entry seen in many tools can lead to increased time-to-decision making and frequent missing data points.¹⁸⁻²⁰ Some tools also

involve additional investigations, including blood tests and imaging, that have very limited availability in LRS.^{15 21-23}

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 continues to unfold in real time, profoundly impacting 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-2.²⁴ 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. 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 PhD 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 PhD has 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, HREC REF: 450/2020).
3. Validate the SST in the African setting using real-world data (study three, under review by HREC).

In this application, we are applying for UCT HREC approval for study one. While this is a systematic review and meta-analysis, it forms part of the PhD, and therefore requires UCT HREC approval.

2 METHODS

The aforementioned aim and objectives will be met via three studies.

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.²⁵

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.²⁶ 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.²⁷ 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 included, 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).²⁸ 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.¹³ 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.²⁹ All data will be in the form of binary categorical variables. Pooled odds ratios and associated 95% CIs 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.³⁰ 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).³¹ 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.³¹
³² Forest plots will be used to display point estimates of individual studies and a summary estimate for each feature studied.³¹

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.^{31 32}

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 PhD, 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: Derivation of a severity scoring tool for COVID-19 illness in low-resource settings.

This study has already received HREC approval (HREC REF: 450/2020)

2.3 Study three: Validation of a severity scoring tool for COVID-19 illness in low-resource settings.

This study is a separate application, currently under HREC review.

3. RESOURCES

There are no costs associated with study one of this PhD.

4. TIMELINE

YEAR	2020		2021				2022	
QUARTER	3	4	1	2	3	4	1	1
Ethical approvals								
Proposal development	X							
EMDRC	X							
HREC		X						
Study one								
Systematic review and meta-analysis		X						
Manuscript preparation		X	X					
Studies two and three		X	X	X	X	X		
Dissertation preparation					X	X	X	
Dissertation submission								X

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6. APPENDICES

Appendix 1A: Search strategy

PubMed

Search date: [TBC]

Restricted to studies published from 1/12/19 to-date.

#	Search terms	No. results
1	NCoV [TIAB] OR Coronavirus [MeSH] OR “severe acute respiratory syndrome coronavirus 2” [MeSH] OR “COVID*” [TIAB] OR “COVID-19” [TIAB] OR Coronavirus infections [MeSH] or “coronavirus” [TIAB]	
2	Severity of Illness Index [MeSH] OR “sever*” [TIAB] OR “critical*” [TIAB] OR Patient Admission [MeSH] OR Length of Stay [MeSH] OR Critical Illness [MeSH] OR Critical care [MeSH] OR Outcome* [TIAB] OR Mortality [MeSH] OR Death [MeSH] OR Morbidity [MeSH] OR Respiratory Insufficiency [MeSH] OR Respiratory Distress Syndrome, Adult [MeSH] OR Respiration, Artificial [MeSH] OR “ventilation” [TIAB]	
3	Demography [MeSH] OR “Age” [TIAB] OR “Sex” [TIAB] OR “Gender” [TIAB]	
4	Comorbidity [MeSH] OR “Co-morbid*” [TIAB] OR “Comorbid*” [TIAB] OR “Pre-exist*” [TIAB] OR “Condition*” [TIAB]	
5	Signs and Symptoms [MeSH] OR “symptom*” [TIAB] OR “characteristic*” OR “clinical” OR “presentation*” [TIAB]	
6	Diagnostic Techniques and Procedures [MeSH] OR "Imag*" OR "X-ray*" OR "Xray*" OR "CT" OR "Computed Tomography" OR "Radiograph"	
7	1 + 2 + 3	
8	1 + 2 + 4	
9	1 + 2 + 5	
10	1 + 2 + 6	

Scopus

Search date: [TBD]

Restricted to studies published from 1/12/19 to-date.

#	Search terms	No. results
1	TITLE-ABS-KEY(NCoV OR severe acute respiratory syndrome coronavirus 2 OR COVID* OR COVID-19 OR coronavirus)	
2	TITLE-ABS-KEY("severity of illness index" OR sever* OR critical* OR "patient admission" OR "length of stay" OR "critical illness" OR "critical care" OR outcome* OR mortality OR death OR morbidity OR respiratory AND insufficiency OR "respiratory distress syndrome" OR respiration OR ventilation)	
3	TITLE-ABS-KEY(demograph* OR age OR sex OR gender)	
4	TITLE-ABS-KEY(comorbidity OR co-morbid* OR comorbid* OR pre-exist* OR preexist OR condition*)	
5	TITLE-ABS-KEY("signs and symptoms" OR symptom* OR characteristic* OR clinical OR presentation*)	
6	TITLE-ABS-KEY(diagnostic OR techniques OR procedures OR invest*OR imag* OR X-ray* OR Xray* OR CT OR Computed Tomography OR radiograph*)	
7	1 + 2 + 3	
8	1 + 2 + 4	
9	1 + 2 + 5	
10	1 + 2 + 6	

Web of Science

Search date: [TBD]

Restricted to studies published from 1/12/19 to-date.

#	Search terms	No. results
1	TS=(COVID* OR NCoV OR Coronavirus* OR SARS-CoV-2)	
2	TS=(Sever* OR Critical* OR Admit* OR Admission* OR Length of stay* OR Critical Care OR Intensive Care OR Outcome OR Mortality OR Death OR Morbidity OR Respiratory Failure OR Respiratory Distress OR Respiration OR Ventilation)	
3	TS=(Demograph* OR Age* OR Gender* OR Sex*)	
4	TS=(Comorbid* OR Co-morbid* OR Preexist* OR Pre-exist* OR Condition*)	
5	TS=(Symptom* OR Sign* OR Characteristic* OR Clinical* OR Present*)	
6	TS=(Vital* OR Vital* Sign*)	
7	TS=(Blood* OR Blood Test* OR Laboratory* OR Investigat* OR Blood Count*)	
8	TS=(Imaging OR Image OR X-ray* or Xray* OR CT OR Computed Tomography OR Radiograph*)	
9	1 + 2 + 3	
10	1 + 2 + 4	
11	1 + 2 + 5	
12	1 + 2 + 6	
13	1 + 2 + 7	
14	1 + 2 + 8	

Appendix 1B: Newcastle – Ottawa Quality Assessment Scale for Cohort Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community*
 - b) somewhat representative of the average _____ in the community –
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non exposed cohort
 - a) drawn from the same community as the exposed cohort*
 - b) drawn from a different source
 - c) no description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (e.g, surgical records)*
 - b) structured interview*
 - c) written self report
 - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) yes
 - b) no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 - a) study controls for _____ (select the most important factor) *
 - b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

- 1) Assessment of outcome
 - a) independent blind assessment*
 - b) record linkage*
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes (select an adequate follow up period for outcome of interest) *
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for*
 - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
 - c) follow up rate < ____ % (select an adequate %) and no description of those lost
 - d) no statement

Wells, G. A, Shea, B., O'Connell, D. et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm 2009 Feb 1

Appendix 3.3: Ethical approval for “*Clinical and historical features associated with severe COVID-19 infection: a systematic review and meta-analysis.*”

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: 814/2020

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

Dear Prof Wallis

PROJECT TITLE: DERIVATION AND VALIDATION OF A SEVERITY SCORING TOOL FOR COVID-19 ILLNESS IN LOW-RESOURCE SETTINGS -PHD CANDIDATE-JENNIFER PIGOGA-SUB-STUYD LINKED 450/2020

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: - Jennifer Pigoga 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:814/2020sa

Appendix 3.4: PRISMA reporting checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4/5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl. Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7/8/App 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6/7/8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10/App 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	6

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 3.5: Search strategy.

PubMed

Search date: 01/06/20

Restricted to studies published from 01/12/19-01/06/20

#	Search terms	No. results
1	NCoV [TIAB] OR Coronavirus [MeSH] OR “severe acute respiratory syndrome coronavirus 2” [MeSH] OR “COVID*” [TIAB] OR “COVID-19” [TIAB] OR Coronavirus infections [MeSH] or “coronavirus” [TIAB]	5 581
2	Severity of Illness Index [MeSH] OR “sever*” [TIAB] OR “critical*” [TIAB] OR Patient Admission [MeSH] OR Length of Stay [MeSH] OR Critical Illness [MeSH] OR Critical care [MeSH] OR Outcome* [TIAB] OR Mortality [MeSH] OR Death [MeSH] OR Morbidity [MeSH] OR Respiratory Insufficiency [MeSH] OR Respiratory Distress Syndrome, Adult [MeSH] OR Respiration, Artificial [MeSH] OR “ventilation” [TIAB]	106 821
3	Demography [MeSH] OR “Age” [TIAB] OR “Sex” [TIAB] OR “Gender” [TIAB]	84 335
4	Comorbidity [MeSH] OR “Co-morbid*” [TIAB] OR “Comorbid*” [TIAB] OR “Pre-exist*” [TIAB] OR “Condition*” [TIAB]	18 804
5	Signs and Symptoms [MeSH] OR “symptom*” [TIAB] OR “characteristic*” OR “clinical” OR “presentation*” [TIAB]	20 966
6	Diagnostic Techniques and Procedures [MeSH] OR “Imag*” OR “X-ray*” OR “Xray*” OR “CT” OR “Computed Tomography” OR “Radiograph*”	43 618
7	1 + 2 + 3	391
8	1 + 2 + 4	247
9	1 + 2 + 5	303
10	1 + 2 + 6	291

Scopus

Search date: 01/06/20

Restricted to studies published from 01/12/19-01/06/20

#	Search terms	No. results
1	TITLE-ABS-KEY(NCoV OR severe acute respiratory syndrome coronavirus 2 OR COVID* OR COVID-19 OR coronavirus)	828
2	TITLE-ABS-KEY("severity of illness index" OR sever* OR critical* OR "patient admission" OR "length of stay" OR "critical illness" OR "critical care" OR outcome* OR mortality OR death OR morbidity OR respiratory AND insufficiency OR "respiratory distress syndrome" OR respiration OR ventilation)	24 468
3	TITLE-ABS-KEY(demograph* OR age OR sex OR gender)	132 302
4	TITLE-ABS-KEY(comorbidity OR co-morbid* OR comorbid* OR pre-exist* OR preexist OR condition*)	556 058
5	TITLE-ABS-KEY("signs and symptoms" OR symptom* OR characteristic* OR clinical OR presentation*)	1 001 095
6	TITLE-ABS-KEY(diagnostic OR techniques OR procedures OR invest*OR imag* OR X-ray* OR Xray* OR CT OR Computed Tomography OR radiograph*)	46 425
7	1 + 2 + 3	28
8	1 + 2 + 4	32
9	1 + 2 + 5	60
10	1 + 2 + 6	7

Web of Science

Search date: 01/06/20

Restricted to studies published from 01/12/19-01/06/20

#	Search terms	No. results
1	TS=(COVID* OR NCoV OR Coronavirus* OR SARS-CoV-2)	1 132
2	TS=(Sever* OR Critical* OR Admit* OR Admission* OR Length of stay* OR Critical Care OR Intensive Care OR Outcome OR Mortality OR Death OR Morbidity OR Respiratory Failure OR Respiratory Distress OR Respiration OR Ventilation)	625 363
3	TS=(Demograph* OR Age* OR Gender* OR Sex*)	397 718
4	TS=(Comorbid* OR Co-morbid* OR Preexist* OR Pre-exist* OR Condition*)	358 857
5	TS=(Symptom* OR Sign* OR Characteristic* OR Clinical* OR Present*)	1 363 307
6	TS=(Vital* OR Vital* Sign*)	24 207
7	TS=(Blood* OR Blood Test* OR Laboratory* OR Investigat* OR Blood Count*)	653 308
8	TS=(Imaging OR Image OR X-ray* or Xray* OR CT OR Computed Tomography OR Radiograph*)	260 291
9	1 + 2 + 3	165
10	1 + 2 + 4	59
11	1 + 2 + 5	442
12	1 + 2 + 6	12
13	1 + 2 + 7	203
14	1 + 2 + 8	57

Appendix 3.6: Characteristics of included studies.

Title	First author	Year	Newcastle-Ottawa Score*	Study location	Study design	Population	Gender (% male)	Median age	No. severe cases	No. non-severe cases	Definition of severe illness	Total no. study variables of interest** reported on (n)	No. study variables of interest** reported as significant (n)
Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019 ²⁷⁴	Zou	2020	7	Wuhan, China	Retrospective cohort study	154 patients with nCoV-19 infection admitted to the intensive care unit of Tongji Hospital from 10/01/20 to 10/02/20	43.5	60.68 (mean)	52	102	Mortality	45	29
Analysis of baseline liver biochemical parameters in 324 cases with novel coronavirus pneumonia in Shanghai area ²⁸⁶	Qian	2020	5	Shanghai, China	Retrospective cohort study	324 adult patients with nCoV-19 pneumonia admitted to Shanghai Public Health Clinical Center from 20/01/20 to 24/02/20	51.5	51.0	26	298	NHC - severe & critical***	12	7
Analysis of clinical characteristics of 29 cases of new type coronavirus pneumonia ²⁸⁷	Lei	2020	3	Wuhan, China	Retrospective cohort study	29 patients with nCoV-19 admitted to Tongji Hospital in January 2020	72.0	56.0	14	15	NHC - severe & critical	9	2
Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease ²⁸⁸	Liu	2020	3	Wuhan, China	Retrospective cohort study	78 adult patients with nCoV-19 admitted to three tertiary hospitals in Wuhan from 30/12/19 to 15/01/20	50.0	38.0	8	67	NHC - severe & critical	26	5
Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19 ²⁸⁹	Chen	2020	4	Wuhan, China	Retrospective cohort study	150 adult patients with nCoV-19 infection admitted to the fever clinic at Tongji Hospital from January 2020 to February 2020	59.0	59.0	24	126	NHC - severe & critical	9	7
Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy ²⁹⁰	Tang	2020	5	Wuhan, China	Retrospective cohort study	449 consecutive adult patients with nCoV-19 infection treated at Tongji Hospital from 01/01/20 to 13/02/20	59.7	65.1	134	315	Mortality	7	6

Association between clinical manifestations and prognosis in patients with COVID-19 ²⁹¹	Yu	2020	5	Guangdong Province, China	Retrospective cohort study	95 consecutive patients with nCoV-19 infection admitted to Dongguan People's Hospital and Nanfang Hospital of Southern Medical University from 01/01/20 to 28/02/20	55.8	NR	24	71	Acute Respiratory Distress Syndrome	14	5
Association of Obesity with Disease Severity among Patients with COVID-19 ²⁹²	Kalligeros	2020	8	Rhode Island, USA	Retrospective cohort study	103 consecutive adult patients with nCoV-19 infection admitted to Rhode Island Hospital, The Miriam Hospital, or Newport Hospital from 17/03/20 to 05/04/20	61.2	60.0	59	44	ICU admission within the first 10 days of hospital admission	7	2
Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China ²⁹³	Yuan	2020	6	Wuhan, China	Retrospective cohort study	27 consecutive adult patients with nCoV-19 admitted to Central Hospital of Wuhan	44.0	60.0	10	17	Mortality	13	6
Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy ²⁹⁴	Grasselli	2020	6	Lombardy, Italy	Retrospective case series	1591 critically ill patients with nCoV-19 infection admitted from 20/02/20 to 18/03/2020	82.0	63.0	405	1176	Mortality	2	2
C-reactive protein level may predict the risk of COVID-19 aggravation ²⁹⁵	Wang	2020	5	Changsha, China	Retrospective cohort study	209 adult patients with nCoV-19 infection admitted to the Public Health Treatment Center from 17/01/20 to 20/02/20	62.5	54.0	16	193	NHC - severe & critical	34	14
C-reactive protein correlates with CT findings and predicts severe COVID-19 early ²⁹⁶	Tan	2020	4	Hunan, China	Retrospective cohort study	27 consecutive adult inpatients with nCoV-19 infection admitted to Hunan Provincial People's Hospital from 18/01/20 to 10/02/2020	41.0	48.9	6	21	NHC - severe	6	3
Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience ²⁹⁷	Sun	2020	1	Beijing, China	Retrospective cohort study	63 patients with nCoV-19 infection in Beijing in 2020	58.7	47.0	19	44	Mild: Mild symptoms and normal or non-pneumonia findings on radiographic examination; Moderate: Respiratory symptoms and fever,	51	24

												with evidence of pneumonia on radiographic examination; Severe: Dyspnoea, respiratory frequency ≥ 30 /minute, blood oxygen saturation $\leq 93\%$, PaO2/FiO2 ratio < 300 , and/or lung infiltrates $> 50\%$ of the lung field within 24-48 hours; Critical: Respiratory failure and mechanical ventilation required, septic shock, and/or multiple organ dysfunction/failure and requires ICU monitoring and treatment.		
Characteristics of COVID-19 infection in Beijing ²⁹⁸	Tian	2020	5	Beijing, China	Retrospective cohort study	262 adult patients with nCoV-19 transferred to designated COVID hospitals by Beijing EMS from 20/01/20 to 10/02/20	48.5	47.5	46	216	Dyspnoea or respiratory failure	7	1	
Characteristics of Disease Progress in Patients with Coronavirus Disease 2019 in Wuhan, China ²⁹⁹	Ji	2020	4	Wuhan, China	Retrospective cohort study	101 patients with nCoV-19 infection admitted to Renmin Hospital of Wuhan University from 02/01/20 to 28/01/20, with follow-up through 08/02/20	48.0	51.0	51	70	NHC - severe & critical	26	16	
Characteristics of Liver Tests in COVID-19 Patients ³⁰⁰	Cai	2020	6	Shenzhen, China	Prospective cohort study	417 adult patients with nCoV-19 infection admitted to the Third People's Hospital of Shenzhen from 11/01/2020 to 21/02/2020	47.5	47.0	91	233	NHC - severe & critical	5	4	
Clinical and immunological features of severe and moderate coronavirus disease 2019 ³⁰¹	Chen	2020	5	Wuhan, China	Retrospective cohort study	21 patients with nCoV-19 infection admitted to Tongji Hospital through 27/01/20	81.0	56.0	11	10	Patients with pulse oximetry of 93% or lower, or respiratory rates of 30/min or greater on room air who required high-flow nasal cannula or non-invasive mechanical ventilation using BiPAP mode to correct hypoxaemia.	45	21	

Clinical and Transmission Characteristics of Covid-19: A Retrospective Study of 25 Cases from a Single Thoracic Surgery Department ³⁰²	Li	2020	6	Wuhan, China	Retrospective cohort study	25 adult patients with nCoV-19 infection from Tongji Hospital's Department of Thoracic Surgery, including 13 admitted patients and 12 healthcare staff, from 01/01/20 to 20/02/20	76.9	60.2	9	16	NHC - severe & critical	22	2
Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study ³⁰³	Chen	2020	7	Wuhan, China	Retrospective cohort study	203 older adult patients with nCoV-19 infection admitted to Zhongnan Hospital of Wuhan University from 01/01/20 to 10/02/2020	53.2	54.0	107	36	NHC - severe & critical	1	1
Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection ³⁰⁴	Lei	2020	7	Wuhan, China	Retrospective cohort study	34 adult patients with nCoV-19 infection admitted to Renmin Hospital, Zhongnan Hospital, Tongji Hospital and Central Hospital in Wuhan for elective surgeries from 01/01/20 to 05/02/20	41.2	55.0	15	19	ICU admission	21	4
Clinical characteristics and outcomes of patients with severe covid-19 with diabetes ³⁰⁵	Yan	2020	5	Wuhan, China	Retrospective cohort study	193 adult patients with nCoV-19 infection admitted to Tongji Hospital from 10/01/20 to 24/02/20	59.1	64.0	108	85	Mortality	49	27
Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China ³⁰⁶	Wang	2020	6	Wuhan, China	Retrospective case series	138 consecutive adult patients with nCoV-19 hospitalized in Zhongnan Hospital of Wuhan University from 01/01 to 28/01/20	54.0	56.0	36	102	ICU admission	42	22
Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China ³⁰⁷	Zhang	2020	6	Wuhan, China	Retrospective cohort study	140 adult patients with nCoV-19 infection No. 7 Hospital of Wuhan from 16/01/20 to 03/02/20	50.7	57.0	59	82	NHC - severe	20	2

Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China ³⁰⁸	Chen	2020	5	Taizhou, Zhejiang, China	Retrospective cohort study	145 patients with nCoV-19 infection admitted to Taizhou Public Health Medical Center through 11/03/20	54.5	47.5	43	102	NHC - severe	60	22
Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha ³⁰⁹	Zheng	2020	4	Hunan, China	Retrospective cohort study	161 adult patients with nCoV-19 infection admitted to the North Hospital of Changsha first Hospital (Changsha Public Health treatment Center) from 17/01/2020 to 7/02/2020	49.7	45.0	30	131	"Severe", without additional description	29	12
Clinical Characteristics of 30 Medical Workers Infected with New Coronavirus Pneumonia ³¹⁰	Liu	2020	5	Wuhan, China	Retrospective cohort study	30 adult hospital staff workers with nCoV-19 admitted to Jiangnan Hospital from 10/01/20 to 03/10/2020	50.0	35.0	4	26	NHC - severe & critical	8	8
Clinical Characteristics of 54 medical staff with COVID-19: A retrospective study in a single center in Wuhan, China ³¹¹	Chu	2020	3	Wuhan, China	Retrospective cohort study	54 adult medical staff with nCoV-19 infection from Tongji Hospital between 07/01/20 to 11/02/2020	66.7	47.0	43	11	NHC - severe & critical	7	2
Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020 ³¹²	Colaneri	2020	5	Pavia, North Italy	Retrospective cohort study	23 consecutive patients with nCoV-19 infection admitted to a teaching hospital in Pavia, Italy from 21/02/20 to 28/02/20, with follow-up through 04/03/20	63.6	67.5	17	27	Requirement for high-flow oxygen support	23	6
Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital ³¹³	Wang	2020	4	Wuhan, China	Retrospective cohort study	1012 non-critically ill adult patients with nCoV-19 infection admitted to Dongxihu Fangcang Hospital between 07/02 to 12/02/2020	51.8	50.0	100	912	Deterioration of COVID-19 defined as at least one of the following: (a) symptoms persisted or worsened for >7 days; (b) respiratory rate ≥ 30 or blood oxygen saturation 93%, at rest; (c) pulmonary imaging showed that the lesions progressed >50% within 48 hours; or (d) deterioration of co-morbidities or complications	23	11

mentioned in items (f) to (i) in manuscript.

Clinical Characteristics of Older Patients Infected with COVID-19: A Descriptive Study ³¹⁴	Niu	2020	6	Beijing, China	Retrospective cohort study	141 patients >50yo with nCoV-19 infection transferred from general hospitals to designated hospitals for special treatment by Beijing EMS from 20/01/20 to 29/02/20	56.7	NR	5	121	Mortality	1	1
Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study ³¹⁵	Zhao	2020	4	Hubei Province, China	Retrospective cohort study	91 patients with nCoV-19 infection admitted to Jingzhou Central Hospital from 16/01/20 to 10/02/20	53.8	46.0	30	61	"Severe", without additional description	21	4
Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China ³¹⁶	Mo	2020	6	Wuhan, China	Retrospective cohort study	155 consecutive adult patients with nCoV-19 infection at Zhongnan Hospital of Wuhan University from 01/01/20 to 05/02/20	55.5	54.0	85	70	Hospital stay <10 days	15	12
Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China ³¹⁷	Wang	2020	7	Wuhan, China	Retrospective case series	107 adult patients with nCoV-19 infection admitted to Zhongnan Hospital and Xishui Hospital through 10/02/20	53.3	51.0	19	88	Mortality	42	21
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study ⁹²	Zhou	2020	7	Wuhan, China	Retrospective cohort study	191 patients with nCoV-19 infection at Jinyintan Hospital and Wuhan Pulmonary Hospital through 20/01/20	38.0	56.0	54	137	Mortality	37	24
Clinical Features and Short-term Outcomes of 102 Patients with Corona Virus Disease 2019 in Wuhan, China ³¹⁸	Cao	2020	5	Wuhan, China	Retrospective cohort study	102 adult patients with nCoV-19 infection admitted to Wuhan University Zhongnan between 03/01/20 to 01/02/2020	51.0	54.0	17	85	Mortality	16	6
Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China ³¹⁹	Zhang	2020	5	Wuhan, China	Retrospective case series	221 patients with nCoV-19 infection admitted to Zhongnan Hospital of Wuhan University from 02/01/20 to 10/02/20	48.9	55.0	55	166	Community-acquired pneumonia	45	30

Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing ³²⁰	Wan	2020	6	Chongqing, China	Retrospective cohort study	135 adult patients with nCoV-19 hospitalized in Chongqing University Three Gorges Hospital from 23/01/20 to 08/02/20	53.0	47.0	40	95	NHC - severe & critical	17	15
Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China ³²¹	Wang	2020	6	Wuhan, China	Retrospective cohort study	69 adult patients with nCoV-19 hospitalized in Union Hospital from 16/01/20 to 29/01/20	46.0	42.0	55	55	Oxygen requirement <90%	46	15
Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients ³²²	Liu	2020	6	Hainan, China	Retrospective cohort study	56 patients with nCoV-19 infection treated at Hainan Provincial People's Hospital from 15/01/20 to 18/02/20	55.4	53.8	6	47	Mechanical ventilation	1	1
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China ³²³	Huang	2020	6	Wuhan, China	Prospective cohort study	41 adult patients with nCoV-19 admitted to a designated Wuhan Hospital from 16/12/19 to 02/01/20	73.0	49.0	13	28	ICU admission	42	16
Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China ³²⁴	Sun	2020	4	Beijing, China	Retrospective cohort study	55 patients with nCoV-19 infection admitted to Beijing302 Hospital from 20/01/20 to 15/02/20	56.4	44.0	15	40	NHC - severe & critical	21	11
Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States ³²⁵	Aggarwal	2020	7	Iowa, USA	Retrospective cohort study	16 adult patients with nCoV-19 infection admitted to an Iowa hospital from 01/03/20 to 04/04/20	75.0	67.0	8	18	Mechanical ventilation requirement, use of inotrope support, ICU admission or death	46	1
Clinical outcomes of COVID-19 cases and influencing factors in Guangdong province ³²⁶	Zhang	2020	1	Guangdong Province, China	Retrospective cohort study	1350 patients with nCoV-19 infection identified in the China Disease Prevention and Control Information System and the Guangdong Provincial Acute Infectious Disease Surveillance Information System through 04/03/20	NR	NR	229	1121	NHC - severe & critical	8	4

Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019 ³²⁷	Zhu	2020	4	Ningbo, Zhejiang Province, China	Retrospective cohort study	127 consecutive patients with nCoV-19 infection admitted to Hwa Mei Hospital of the University of Chinese Academy of Sciences from 23/02/20 to 20/02/20	35.4	50.9	16	111	Severe patients meet at least one of the following: shortness of breath with respiration rate (RR) 30 times/min, oxygen saturation 93% in resting state, partial pressure of arterial oxygen (PaO2)-to-fraction of inspired oxygen (FiO2) ratio 300 mm Hg. Obvious lesion progression >50% within 24-48 hours on pulmonary imaging were also recognized as severe cases. Critical cases were defined when one of the following conditions met: respiratory failure and require mechanical ventilation; shock; other organ failure and treated in intensive care unit. Mild and moderate cases were defined as non-severe group, while severe and critical patients were categorized as severe group in this study.	50	20
COVID-19 Coagulopathy in Caucasian patients ³²⁸	Fogarty	2020	5	Dublin, Ireland	Prospective cohort study	83 adult patients with nCoV-19 infection admitted to St James's Hospital from 13/03/20 to 10/04/20	66.3	64.0	33	50	ICU admission requiring ventilatory support or death	7	4
COVID-19 with Different Severities: A Multi-center Study of Clinical Features ³²⁹	Feng	2020	6	Wuhan, Shanghai and Anhui Provinces, China	Retrospective cohort study	476 adult patients with nCoV-19 infection admitted to three hospitals in China between 01/01/20 to 15/02/2020	56.9	53.0	124	352	NHC - severe & critical	46	32
CT characteristics of patients infected with 2019 novel coronavirus: association with clinical type ³³⁰	Wang	2020	4	China	Retrospective cohort study	93 patients with nCoV-19 infection admitted to multiple health centres in China from 24/01/20 to 07/02/20	61.3	NR	20	73	NHC - severe & critical	13	6
CT quantification of pneumonia lesions in early days predicts progression to severe illness in a cohort of COVID-19 patients ³³¹	Liu	2020	8	Shanghai, China	Retrospective cohort study	134 patients with nCoV-19 infection admitted to Shanghai Public Health Clinical Center from 20/01/20 to 03/02/20	47.0	51.5	19	115	Severe illness was defined as one major criterion, two or more minor criteria, or two criteria of additional organ dysfunction, as follows: (a) Major criteria: respiratory failure requiring mechanical ventilation; shock	24	5

High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation ³³⁷	Simmonet	2020	7	Lille, France	Retrospective cohort study	124 consecutive adult patients with nCoV-19 infection admitted to Roger Salengro Hospital at Centre Hospitalier Universitaire de Lille between 26/02/20 to 5/04/2020	73.0	60.0	85	39	Invasive mechanical ventilation	5	3
Hypolipidemia is associated with the severity of COVID-19 ³³⁸	Wei	2020	5	Wuhan, China	Retrospective cohort study	597 adult patients with nCoV-19 infection admitted to Cancer Center, Union Hospital of Tongji Medical College from 01/02/20 to 03/03/20	51.0	66.0	203	394	NHC - severe & critical	20	14
Kidney disease is associated with in-hospital death of patients with COVID-19 ³³⁹	Cheng	2020	7	Wuhan, China	Prospective cohort study	701 adult patients with nCoV-19 infection treated at Tongji Hospital from 28/01/20 to 11/02/20	52.0	63.0	113	588	Mortality	17	11
Longitudinal association between markers of liver injury and mortality in COVID-19 in China ³⁴⁰	Lei	2020	5	Hubei Province, China	Retrospective cohort study	5771 adult patients with nCoV-19 infection admitted to 10 hospitals in Wuhan, China from 20/12/19 to 08/03/20	47.2	56.0	1186	4585	NHC - severe	12	10
Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission ³⁴¹	Lighter	2020	6	New York, USA	Retrospective cohort study	3615 symptomatic adult patients with nCoV-19 infection who presented to New York University hospital system from 04/03/20 to 04/04/20	NR	NR	431	1853	ICU admission or need for invasive ventilation	1	1
Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19 ³⁴²	Yang	2020	6	Shenzhen and Beijing, China	Prospective cohort study	50 adult patients with nCoV-19 infection admitted to hospitals in Shenzhen and Beijing, China in 2020	58.0	62.0	25	14	NHC - severe	18	1
Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score ³⁴³	Ji	2020	5	Fuyang, China	Retrospective cohort study	208 consecutive adult patients with nCoV-19 infection admitted to Fuyang Second People's Hospital or Fifth Medical Center of Chinese PLA General Hospital between 20/01/20 to 22/02/2020	56.2	44.0	40	168	Progression to severe COVID-19 defined as at least one of the followings, respiratory rate ≥ 30 breaths/min, resting oxygen saturation $\leq 93\%$, PaO ₂ /FiO ₂ ≤ 300 mmHg or requirement of mechanical ventilation OR worsening of lung CT findings during the observation period.	10	5

Prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count ²²⁹	Bi	2020	7	Zhejiang Province, China	Retrospective cohort study	113 adult patients with nCoV-19 infection admitted to Taizhou Public Health Medical Center of Taizhou Hospital, from 23/01/20 to 04/02/20, with follow-up through 15/02/20	56.6	46.0	22	91	NHC - severe & critical	15	5
Predictive factors for disease progression in hospitalized patients with Coronavirus Disease 2019 in Wuhan, China ³⁴⁴	Zhang	2020	7	Wuhan, China	Retrospective cohort study	111 patients with nCoV-19 infection admitted to Cancer Center, Union Hospital of Tongji Medical College from 12/01/20 to 16/02/20	38.0	41.4	18	93	Disease deterioration, including transfer from isolation ward to ICU and all-cause death	42	20
Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study ³⁴⁵	Du	2020	6	Wuhan, China	Prospective cohort study	179 consecutive adult patients with nCoV-19 infection admitted to Wuhan Pulmonary Hospital from 25/12/19 to 07/03/2020	54.2	57.6	21	158	Mortality	38	18
Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19 ³⁴⁶	Liu	2020	5	Wuhan, China	Retrospective cohort study	140 adult patients with nCoV-19 infection admitted to General Hospital of Central Theater Command of People's Liberation Army from 18/01/20 to 12/03/20	35.0	65.5	33	107	NHC – severe & critical	20	9
Prognostic value of myocardial injury in patients with COVID-19 ³⁴⁷	Wang	2020	7	Wuhan, China	Retrospective cohort study	202 adult patients with nCoV-19 infection admitted to People's Hospital of Wuhan University from 31/01/20 to 05/02/2020	43.6	63.0	33	169	Mortality	21	11
Quantitative computed tomography analysis for stratifying the severity of Coronavirus Disease 2019 ³⁴⁸	Shen	2020	4	China	Retrospective cohort study	44 adult patients with nCoV-19 with CT images from 22/01/20 to 07/02/20	57.0	NR	9	35	NHC - severe & critical	2	1
Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study ³⁴⁹	Zhao	2020	5	Hunan, China	Retrospective cohort study	101 adult patients with nCoV-19 pneumonia from four institutions in Hunan, China	55.4	43	14	87	NHC - severe & critical	4	2

Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia ³⁵⁰	Pei	2020	6	Wuhan, China	Retrospective cohort study	333 adult patients with nCoV-19 infection admitted to Tongji Hospital from 28/01/20 to 09/02/20	54.7	NR	144	189	NHC - severe & critical	35	29
Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China ³⁵¹	Wu	2020	6	Wuhan, China	Retrospective cohort study	201 adult patients with nCoV-19 infection at Wuhan Jinyintan Hospital from 25/12/19 to 26/01/20	64.0	51.0	84	117	Acute Respiratory Distress Syndrome	34	23
Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus ³⁵²	Zhou	2020	6	Nanchang, China	Retrospective cohort study	17 adult patients with nCoV-19 infection admitted to the Ninth Hospital of Nanchang between 28/01/20 to 06/02/2020	35.3	41.5	5	12	Aggravation from admission: increased body temperature, more serious respiratory systems, and enlarging CT lung lesions.	14	1
Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China ³⁵³	Zhang	2020	6	Wuhan, China	Retrospective cohort study	663 patients with nCoV-19 infection admitted to Renmin Hospital of Wuhan University from 11/01/20 to 06/02/20	48.4	55.6	409	254	NHC - severe & critical	35	23
Risk factors for severe COVID-19: evidence from 167 hospitalized patients in Anhui, China ³⁵⁴	Wei	2020	0	Anhui, China	Retrospective cohort study	167 admitted patients with nCoV-19 infection	56.9	42.3	30	137	NR	39	14
Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan ³⁵⁵	Li	2020	5	Wuhan, China	Retrospective cohort study	548 adult patients with nCoV-19 infection admitted to Tongji Hospital from 26/01/20 to 05/02/2020, with follow up until 03/03/2020	50.9	60.0	269	279	NHC - severe & critical	47	30
Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China ³⁵⁶	Chen	2020	5	China	Retrospective cohort study	1590 adult patients with nCoV-19 infection admitted to 575 hospitals throughout China from 01/12/19 to 31/01/2020	NR	NR	50	1540	Mortality	7	5
SARS-CoV-2 viral load in sputum correlates with risk of COVID-19 progression ³⁵⁷	Yu	2020	5	Zhejiang Province, China	Retrospective cohort study	92 patients with nCoV-19 infection admitted to the First	62.0	55.0	11	51	"Severe", without additional description	28	14

Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China ³⁵⁸	Deng	2020	6	Wuhan, China	Retrospective cohort study	Affiliated Hospital of Zhejiang University from 19/01/20 to 12/03/20 112 adult patients with nCoV-19 infection admitted to Renmin Hospital of Wuhan University with symptom onset from 06/01/20 to 20/02/20	50.9	65.0	67	45	NHC - severe & critical	25	16
T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19 ³⁵⁹	Jiang	2020	1	Jiangxi, China	Retrospective cohort study	103 patients with nCoV-19 infection admitted to First Affiliated Hospital of Nanchang University from 30/01/20 to 16/02/20	56.3	46.0	17	86	ICU patients	7	5
The clinical course and its correlated immune status in COVID-19 pneumonia ³⁶⁰	He	2020	7	Wuhan, China	Retrospective cohort study	204 adult patients with nCoV-19 infection admitted to Renmin Hospital of Wuhan University between 10/01/20 to 13/02/2020	38.7	49.0	69	135	NHC - severe & critical	45	22
Using IL-2R/lymphocyte for predicting the clinical progression of patients with COVID-19 ³⁶¹	Hou	2020	5	Wuhan, China	Retrospective cohort study	389 adult patients with nCoV-19 infection admitted to Tongji Hospital from 21/01/20 to 15/02/20	51.4	61.3 (mean)	221	168	NHC - severe & critical	12	3

* Quality and bias were assessed using the Newcastle Ottawa Quality Assessment Form for Cohort Studies.³⁶²

** Study variables of interest were defined as those related to patient demographics and history, and clinical presentation and investigation.

***NHC = National Health Committee of People's Republic of China. NHC stratifies illness into three categories: **mild** (slight clinical symptoms, with few or no respiratory symptoms and no pneumonia manifestations on imaging); **severe** (respiratory distress, RR≥30 breaths/min, resting pulse oximetry ≤93%, and PaO₂/FiO₂ ≤300mmHg); and **critical** (respiratory failure, shock, and combined failure of other organs requiring mechanical ventilation and ICU-level care).⁸⁵

NR = not reported.

Appendix 3.7: Newcastle-Ottawa scale for assessment of quality of included studies, using the

Newcastle Ottawa Quality Assessment Form for Cohort Studies.³⁶²

(Note: Each asterisk represents if individual criterion within the subsection was fulfilled.)

DOMAIN	SELECTION				COMPARABILITY		OUTCOME		Overall quality score (maximum = 8)
Quality assessment criteria	Representative-ness of exposed cohort?	Selection of the non-exposed cohort?	Ascertainment of exposure?	Demonstration that outcome of interest was not present at start of study?	Study controls for age/sex?	Assessment of outcome?	Was follow-up long enough for outcome to occur?	Adequacy of follow-up of cohorts?	
Acceptable(*)	Representative of average member of community (age/sex/being at risk of disease)	Drawn from same community as exposed cohort	Secured records and/or structured interview	Only incident cases of COVID-19	Yes	Independent blind assessment and/or record linkage	Follow-up ≥ 14 days	Complete follow-up, or subjects lost to follow-up unlikely to introduce bias	
Acute Physiology and Chronic Health Evaluation II Score as a Predictor of Hospital Mortality in Patients of Coronavirus Disease 2019 ²⁷⁴	*	*	*	*	*	*		*	7
Analysis of baseline liver biochemical parameters in 324 cases with novel coronavirus pneumonia in Shanghai area ²⁸⁶	*	*		*		*		*	5
Analysis of clinical characteristics of 29 cases of new type coronavirus pneumonia ²⁸⁷		*		*				*	3
Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease ²⁸⁸		*		*				*	3
Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19 ²⁸⁹	*	*		*				*	4
Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy ²⁹⁰		*	*	*		*		*	5
Association between clinical manifestations and prognosis in patients with COVID-19 ²⁹¹	*	*	*	*		*			5
Association of Obesity with Disease Severity among Patients with COVID-19 ²⁹²	*	*	*	*	*	*	*	*	8
Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China ²⁹³	*	*	*	*			*	*	6
Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy ²⁹⁴	*	*	*	*	*			*	6

C-reactive protein level may predict the risk of COVID-19 aggravation ²⁹⁵	*	*	*	*	*					5
C-reactive protein correlates with CT findings and predicts severe COVID-19 early ²⁹⁶	*	*		*				*		4
Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience ²⁹⁷				*						1
Characteristics of COVID-19 infection in Beijing ²⁹⁸		*	*	*	*			*		5
Characteristics of Disease Progress in Patients with Coronavirus Disease 2019 in Wuhan, China ²⁹⁹			*	*	*			*		4
Characteristics of Liver Tests in COVID-19 Patients ³⁰⁰		*	*	*	*	*		*		6
Clinical and immunological features of severe and moderate coronavirus disease 2019 ³⁰¹	*	*	*	*	*					5
Clinical and Transmission Characteristics of Covid-19: A Retrospective Study of 25 Cases from a Single Thoracic Surgery Department ³⁰²	*	*	*	*	*			*		6
Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study ³⁰³	*	*	*	*	*	*	*	*		7
Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection ³⁰⁴	*	*	*	*	*	*	*	*		7
Clinical characteristics and outcomes of patients with severe covid-19 with diabetes ³⁰⁵	*	*	*	*	*					5
Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China ³⁰⁶	*	*	*	*	*	*		*		6
Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China ³⁰⁷	*	*	*	*	*	*		*		6
Clinical characteristics of 145 patients with coronavirus disease 2019 (COVID-19) in Taizhou, Zhejiang, China ³⁰⁸			*	*	*	*	*	*		5
Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha ³⁰⁹	*	*		*				*		4
Clinical Characteristics of 30 Medical Workers Infected with New Coronavirus Pneumonia ³¹⁰		*	*	*	*	*		*		5
Clinical Characteristics of 54 medical staff with COVID-19: A retrospective study in a single center in Wuhan, China ³¹¹		*		*				*		3
Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020 ³¹²	*	*	*	*	*	*				5
Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital ³¹³	*	*		*				*		4

Clinical Characteristics of Older Patients Infected with COVID-19: A Descriptive Study ³¹⁴	*	*	*	*	*		*	6
Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study ³¹⁵	*	*		*			*	4
Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China ³¹⁶	*	*	*	*	*		*	6
Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China ³¹⁷	*	*	*	*	*	*	*	7
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study ⁹²	*	*	*	*	*	*	*	7
Clinical Features and Short-term Outcomes of 102 Patients with Corona Virus Disease 2019 in Wuhan, China ³¹⁸	*	*		*		*	*	5
Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China ³¹⁹	*	*	*	*	*			5
Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing ³²⁰	*	*	*	*	*		*	6
Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China ³²¹	*	*	*	*	*		*	6
Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients ³²²	*	*		*	*	*	*	6
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China ³²³	*	*	*	*	*		*	6
Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China ³²⁴	*	*	*	*				4
Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States ³²⁵	*	*	*	*	*	*	*	7
Clinical outcomes of COVID-19 cases and influencing factors in Guangdong province ³²⁶				*				1
Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019 ³²⁷	*	*	*	*				4
COVID-19 Coagulopathy in Caucasian patients ³²⁸	*	*	*	*	*			5
COVID-19 with Different Severities: A Multi-center Study of Clinical Features ³²⁹	*	*	*	*	*		*	6
CT characteristics of patients infected with 2019 novel coronavirus: association with clinical type ³³⁰	*	*		*			*	4
CT quantification of pneumonia lesions in early days predicts progression to severe illness in a cohort of COVID-19 patients ³³¹	*	*	*	*	*	*	*	8
Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19 ³³²		*		*			*	3

Dysregulation of immune response in patients with COVID-19 in Wuhan, China ³³³	*	*	*	*		*		*	6
Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19) ³³⁴	*	*	*	*		*		*	6
Elevations of serum cancer biomarkers correlate with severity of COVID-19 ³³⁵		*		*		*			3
Epidemiological and Clinical Characteristics of 333 Confirmed Cases with Coronavirus Disease 2019 in Shanghai, China ³³⁶	*	*	*	*	*	*			6
High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation ³³⁷	*	*	*	*	*	*		*	7
Hypolipidemia is associated with the severity of COVID-19 ³³⁸	*	*	*	*				*	5
Kidney disease is associated with in-hospital death of patients with COVID-19 ³³⁹	*	*	*	*	*	*		*	7
Longitudinal association between markers of liver injury and mortality in COVID-19 in China ³⁴⁰	*	*	*	*	*				5
Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission ³⁴¹	*	*	*	*	*	*		*	6
Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19 ³⁴²		*	*	*		*	*	*	6
Prediction for Progression Risk in Patients with COVID-19 Pneumonia: the CALL Score ³⁴³	*	*	*	*				*	5
Prediction of severe illness due to COVID-19 based on an analysis of initial fibrinogen to albumin ratio and platelet count ²²⁹	*	*	*	*		*	*	*	7
Predictive factors for disease progression in hospitalized patients with Coronavirus Disease 2019 in Wuhan, China ³⁴⁴	*	*	*	*	*	*		*	7
Predictors of Mortality for Patients with COVID-19 Pneumonia Caused by SARS-CoV-2: A Prospective Cohort Study ³⁴⁵	*	*	*	*		*	*	*	6
Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19 ³⁴⁶	*	*	*	*		*			5
Prognostic value of myocardial injury in patients with COVID-19 ³⁴⁷	*	*	*	*		*	*	*	7
Quantitative computed tomography analysis for stratifying the severity of Coronavirus Disease 2019 ³⁴⁸	*	*		*				*	4
Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study ³⁴⁹	*	*	*	*				*	5
Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia ³⁵⁰	*	*	*	*		*		*	6
Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with	*	*	*	*		*		*	6

Coronavirus Disease 2019 Pneumonia in Wuhan, China ³⁵¹								
Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus ³⁵²	*	*	*	*	*		*	6
Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China ³⁵³	*	*	*	*	*		*	6
Risk factors for severe COVID-19: evidence from 167 hospitalized patients in Anhui, China ³⁵⁴								0
Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan ³⁵⁵	*	*	*	*			*	5
Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China ³⁵⁶	*	*	*	*	*			5
SARS-CoV-2 viral load in sputum correlates with risk of COVID-19 progression ³⁵⁷	*	*		*	*		*	5
Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China ³⁵⁸	*	*	*	*	*		*	6
T cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of COVID-19 ³⁵⁹				*				1
The clinical course and its correlated immune status in COVID-19 pneumonia ³⁶⁰	*	*	*	*	*	*	*	7
Using IL-2R/lymphocyte for predicting the clinical progression of patients with COVID-19 ³⁶¹	*	*	*	*	*			5

Appendix 3.8: Study variables' associations with illness severity.

Table 1: Demographic and historical variables significantly associated with illness Severity.* **

Variable	Reported as significant* (n (%))	Papers reporting variable (n)
DEMOGRAPHICS		
Age	58 (85.3)	68
Sex	24 (38.7)	62
HISTORY OF COMORBIDITIES		
Hypertension	30 (62.5)	48
Cardiovascular disease	24 (54.6)	44
Any comorbidity	21 (65.5)	32
Diabetes	20 (41.7)	48
Chronic respiratory/lung disease***	10 (27.8)	36
Stroke	8 (38.1)	21
Body mass index	7 (43.8)	16
Chronic kidney disease	5 (25.0)	20
Malignancy	4 (15.4)	26
Smoking history	2 (11.1)	18
Cardiomyopathy	1 (100.0)	1
Cerebral aneurysm	1 (100.0)	1
Endocrine disease****	1 (50.0)	2
Fatty liver disease	1 (50.0)	2
Hepatitis and cirrhosis	1 (4.6)	22
Immunocompromise	1 (25.0)	4
Inflammatory disease	1 (100.0)	1
Alcohol consumption	0 (0.0)	4
Arrhythmia	0 (0.0)	1
Atrial fibrillation	0 (0.0)	1
Autoimmune disease	0 (0.0)	2
Cholelithiasis	0 (0.0)	1
Chronic digestive disorders	0 (0.0)	1
Congestive heart failure	0 (0.0)	2
Gastrointestinal disease	0 (0.0)	3
Haematological diseases	0 (0.0)	1
HIV	0 (0.0)	2

Hyperlipidaemia	0 (0.0)	2
Neurological disease	0 (0.0)	2
Obesity	0 (0.0)	1
Peptic ulcer	0 (0.0)	1
Thyroid disease	0 (0.0)	1
Tuberculosis	0 (0.0)	5
Urinary system disease	0 (0.0)	2

*Significance denoted by $p < 0.05$ as related to illness severity by definition specified in paper.

**Note: All demographics and comorbidities identified in this study were deemed likely feasible in low-resource setting emergency units.

***Aggregate of chronic obstructive pulmonary disease, asthma, interstitial lung disease, and pulmonary hypertension

****Excluding diabetes

Table 2: Clinical presentation variables significantly associated with illness severity.* **

Variable	Reported as significant* (n (%))	Papers reporting variable (n)
SIGNS & SYMPTOMS		
Shortness of breath	31 (73.8)	42
Fever	11 (24.4)	45
Anorexia	6 (37.5)	16
Fatigue	5 (13.5)	37
Chest tightness	4 (50.0)	8
Diarrhoea	4 (11.4)	35
Nausea	4 (23.5)	17
Sputum production	3 (14.3)	21
Vomiting	3 (13.6)	22
Abdominal pain	2 (13.3)	15
Chills	2 (33.3)	6
Cough	2 (4.4)	45
Dizziness	2 (12.5)	16
Myalgia	2 (6.5)	31
Chest distress	1 (33.3)	3
Coma / unconsciousness	1 (50.0)	2
Altered mental status	1 (33.3)	3
Electrolyte imbalance	1 (100.0)	1
Headache	1 (3.5)	29
Palpitations	1 (100.0)	1
Respiratory failure	1 (100.0)	1
Sore throat	1 (5.0)	20
Anosmia	0 (0.0)	1
Arthralgia	0 (0.0)	2
Asymptomatic on admission	0 (0.0)	1
Belching	0 (0.0)	1
Bloating	0 (0.0)	1
Chest pain	0 (0.0)	9
Chest operation	0 (0.0)	1
Dysgeusia	0 (0.0)	1
Haemoptysis	0 (0.0)	4
Hypoacusis	0 (0.0)	1
Nasal congestion	0 (0.0)	1

Neurologic symptoms	0 (0.0)	1
Rhinorrhoea / rhinitis	0 (0.0)	6
Skin rash	0 (0.0)	1

VITAL SIGNS

Respiratory rate	11 (73.3)	15
Temperature (°C)	11 (64.7)	17
Oxygen saturation**	6 (75.0)	8
Systolic blood pressure	5 (55.6)	9
Heart rate	2 (15.4)	13
Diastolic blood pressure	1 (16.7)	6
Glasgow Coma Scale	1 (100.0)	1
Mean arterial pressure	0 (0.0)	6

*Significance denoted by $p < 0.05$ as related to illness severity by definition specified in paper.

**Note: All signs and symptoms, and vital signs identified in this study were deemed likely feasible in low-resource setting emergency units.

***Variable availability in low-resource settings.

Table 3: Clinical investigation variables significantly associated with illness severity.* **

Variable	Reported as significant* (n (%))	Papers reporting variable (n)
LABORATORY FINDINGS		
Lymphocyte (absolute count)	35 (70.0)	50
C-reactive protein	32 (74.4)	43
Lactate dehydrogenase	30 (83.3)	36
Leucocytes (absolute count)	28 (59.6)	47
Aspartate aminotransferase	27 (65.9)	41
D-dimer	25 (67.6)	37
Neutrophils (absolute count)	22 (64.7)	34
Albumin	20 (80.0)	25
Procalcitonin	19 (61.3)	31
Creatinine	17 (46.0)	37
Blood urea nitrogen (mg/dL)	16 (76.2)	21
Alanine aminotransferase	15 (36.6)	41
Interleukin 6	15 (71.4)	21
Creatine kinase	12 (46.2)	26
Platelets	12 (38.7)	31
Total bilirubin	11 (45.8)	24
CD4+ T lymphocyte count	10 (100.0)	10
Prothrombin time	10 (45.5)	22
Troponin	10 (66.7)	15
CD8+ T cells	9 (81.8)	11
Creatine kinase-MB	9 (69.2)	13
Ferritin	9 (90.0)	10
Erythrocyte sedimentation	7 (38.9)	18
Fibrinogen	7 (77.8)	9
CD3+ T cell count	6 (100.0)	6
High-sensitivity troponin	6 (85.7)	7
Interleukin 10	6 (60.0)	10
Lymphocyte (percentage)	6 (85.7)	7
N-terminal pro-B-type natriuretic peptide	6 (75.0)	8
PaO ₂ /FiO ₂	6 (85.7)	7
Acute kidney injury, proteinuria, haematuria	5 (71.4)	7
Neutrophil-to-lymphocyte ratio (NLR)	5 (100.0)	5
Partial thromboplastin time	5 (29.4)	17
Blood Glucose	4 (66.7)	6

Eosinophils (absolute count)	4 (66.7)	6
Interleukin 2 receptor	4 (57.1)	7
Prealbumin	4 (100.0)	4
BNP	3 (60.0)	5
Haemoglobin	3 (20.0)	15
Myoglobin	3 (75.0)	4
Neutrophils (percentage)	3 (75.0)	4
Potassium	3 (60.0)	5
Tumour necrosis factor- α	3 (27.7)	11
T lymphocyte count	3 (75.0)	4
α -hydroxybutyrate dehydrogenase	2 (100.0)	2
B lymphocyte (count)	2 (40.0)	5
Direct bilirubin	2 (50.0)	4
Eosinophils (percentage)	2 (66.7)	3
Globulin	2 (28.6)	7
High-sensitivity C-reactive protein	2 (66.7)	3
Interleukin 8	2 (40.0)	5
International normalised ratio	2 (100.0)	2
Low-density lipoprotein cholesterol	2 (100.0)	2
paO ₂	2 (100.0)	2
Total cholesterol	1 (100.0)	1
Thrombin time	1 (50.0)	2
Albumin to globulin ration	1 (100.0)	1
Bacterial coinfection	1 (100.0)	1
Basophils (percentage)	1 (100.0)	1
Complement 3	1 (50.0)	2
CD3 cell percentage	1 (100.0)	1
CD4/CD8 ratio	1 (100.0)	5
CD4 cell percentage	1 (50.0)	2
CD16+ 65+ count	1 (100.0)	1
Cholinesterase	1 (100.0)	1
Serum cystatin	1 (50.0)	2
Fibrinogen to albumin ration	1 (100.0)	1
Gamma-glutamyl transferase	1 (20.0)	5
High-density lipoprotein cholesterol	1 (100.0)	1
Haematuria	1 (100.0)	1
Immunoglobulin G	1 (33.3)	3
Immunoglobulin M	1 (33.3)	3

Interleukin 2	1 (20.0)	5
Interleukin 2R/lymphocyte	1 (100.0)	1
Interleukin 5	1 (100.0)	1
Indirect bilirubin	1 (100.0)	1
Interferon gamma	1 (25.0)	4
Lactate	1 (25.0)	4
Monocyte (absolute count)	1 (5.9)	17
Monocyte (%)	1 (100.0)	1
Myocarditis (possible)	1 (100.0)	1
Natural killer cell	1 (33.3)	3
Platelet-to-lymphocyte ratio	1 (33.3)	3
pCO2	1 (50.0)	2
Proteinuria	1 (100.0)	1
Regulatory T cells	1 (50.0)	2
Serum amyloid A	1 (50.0)	2
Sialic acid	1 (100.0)	1
Sodium	1 (20.0)	5
Triglycerides	1 (50.0)	2
Uric acid	0 (0.0)	3
Total protein	0 (0.0)	1
Adenovirus co-infection	0 (0.0)	2
Alkaline Phosphatase	0 (0.0)	6
Basophils (absolute count)	0 (0.0)	1
Complement component C4	0 (0.0)	2
Calcium	0 (0.0)	1
CD8 cell percentage	0 (0.0)	2
Cholesterol	0 (0.0)	1
Creatinine clearance	0 (0.0)	1
Creatine phosphokinase	0 (0.0)	1
Electrolyte disturbance	0 (0.0)	1
Fungal coinfection	0 (0.0)	1
gamma-interferon	0 (0.0)	1
Haemoglobin A1c	0 (0.0)	1
Immunoglobulin A	0 (0.0)	3
Immunoglobulin E	0 (0.0)	1
Interleukin 1 beta	0 (0.0)	6
Interleukin 4	0 (0.0)	4
Influenza A coinfection	0 (0.0)	2

Influenza B coinfection	0 (0.0)	1
Mycoplasma coinfection	0 (0.0)	1
parainfluenza virus co-infection	0 (0.0)	2
pH	0 (0.0)	2
Plasma thromboplastin antecedent	0 (0.0)	1
Red blood cell count	0 (0.0)	1
Renal function damage	0 (0.0)	1
SARS-CoV-2 nucleic acid test	0 (0.0)	1
Syncytial virus co-infection	0 (0.0)	2

IMAGING INVESTIGATIONS

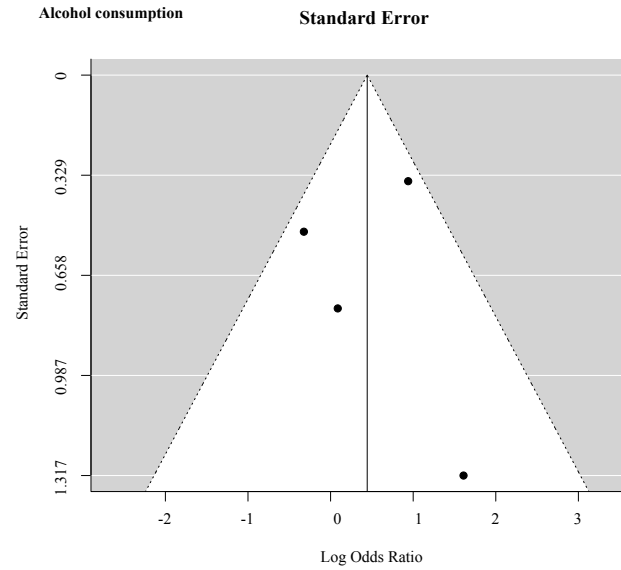
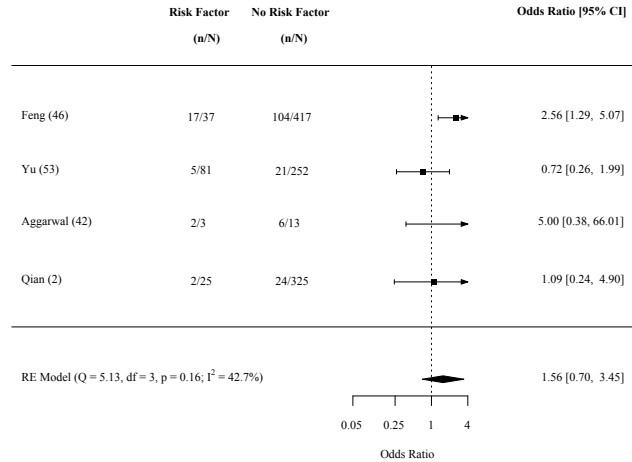
Any abnormality on chest CT	11 (42.3)	26
Any abnormality on chest X-ray	6 (40.0)	15
Normal CT	1 (25.0)	4

*Significance denoted by $p < 0.05$ as related to illness severity by definition specified in paper.

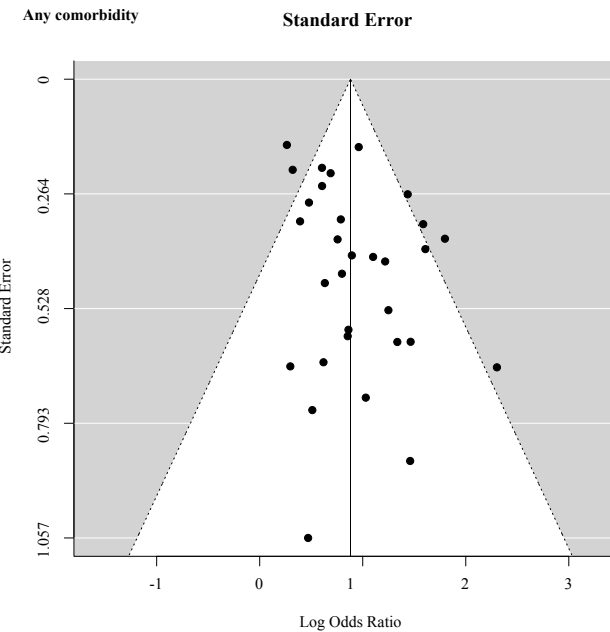
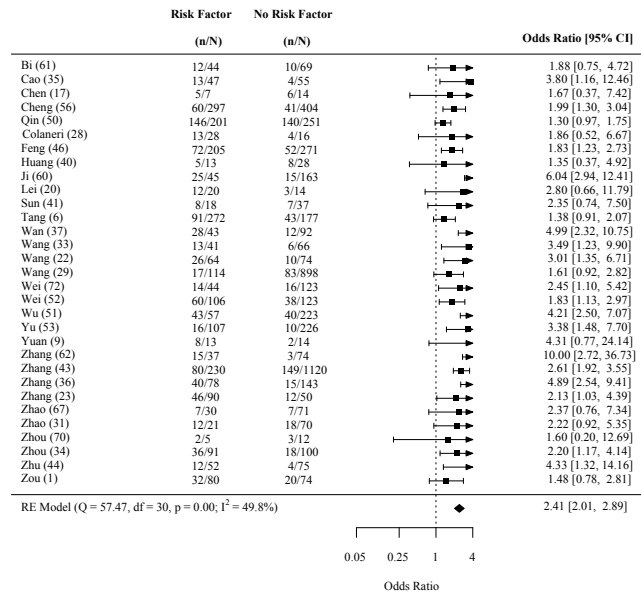
**Note: No laboratory or imaging investigations were deemed likely feasible in low-resource setting emergency units.

Appendix 3.9: Forest plots and funnel plots for individual features.

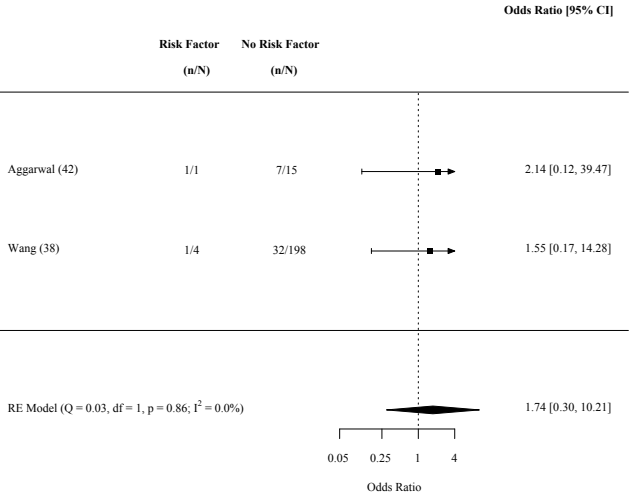
Alcohol consumption



Any comorbidity

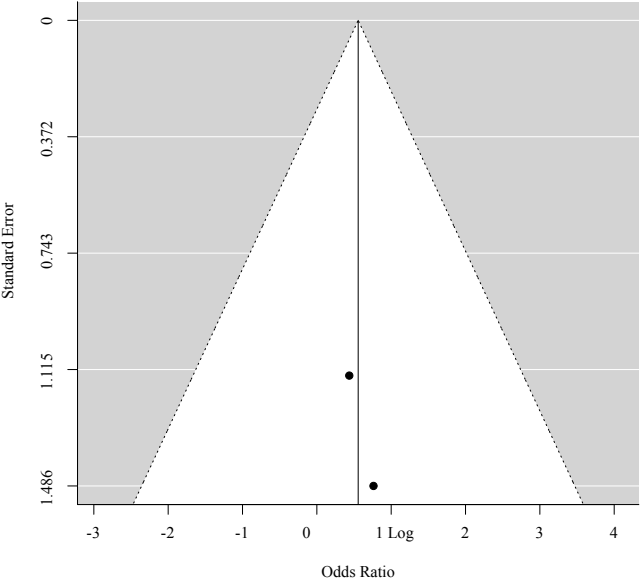


Autoimmune disease

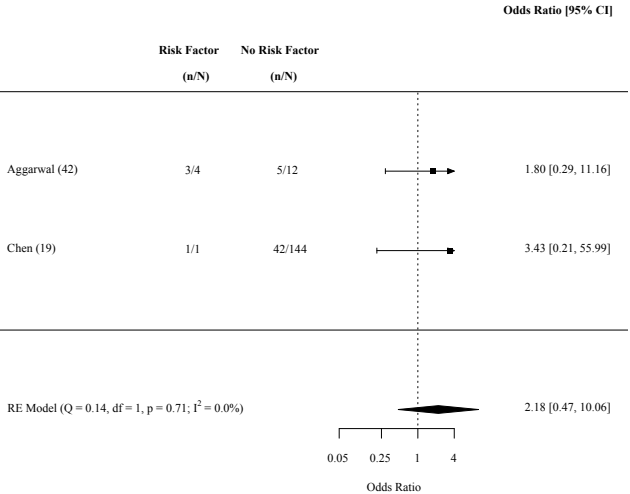


Autoimmune disease

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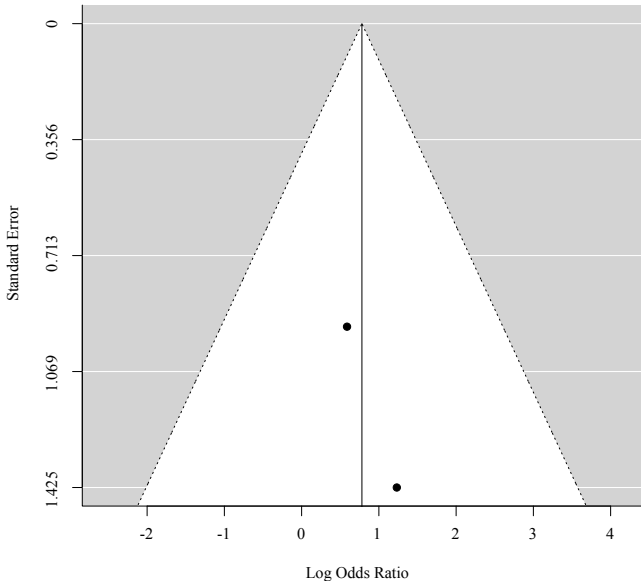


Congestive heart failure

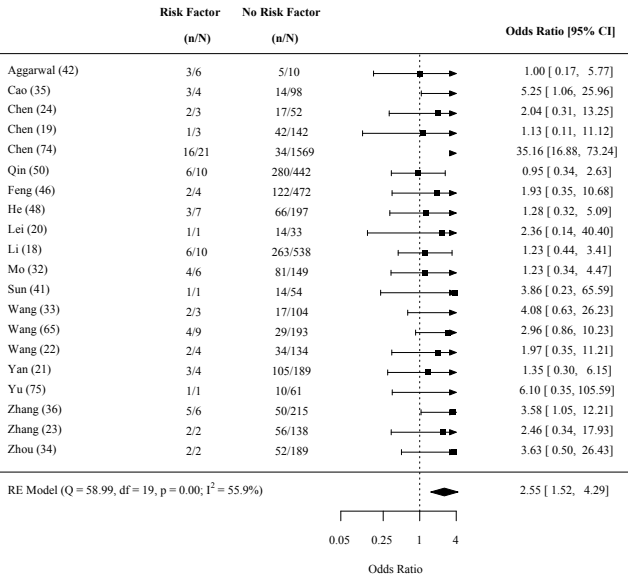


Congestive heart failure

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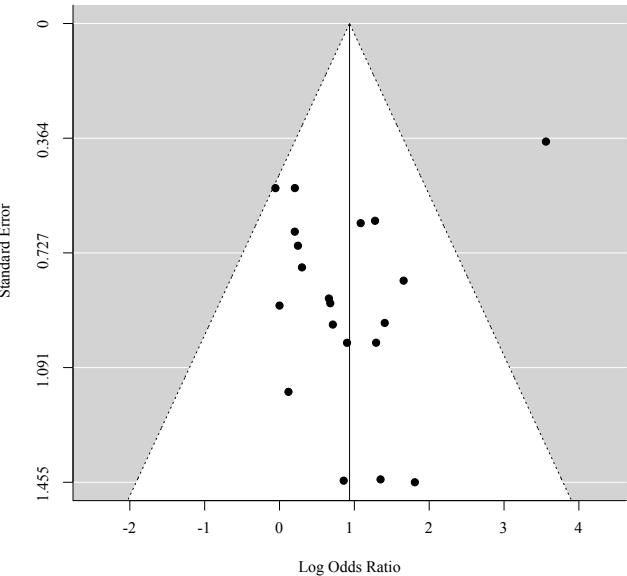


Chronic kidney disease

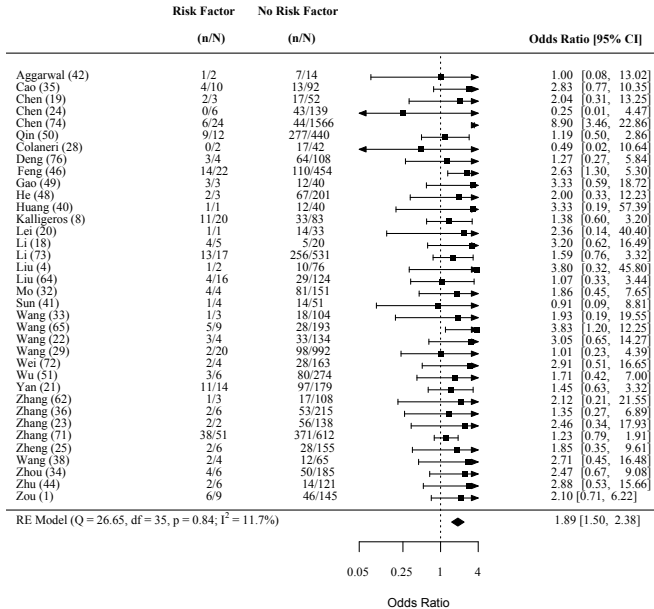


Chronic kidney disease

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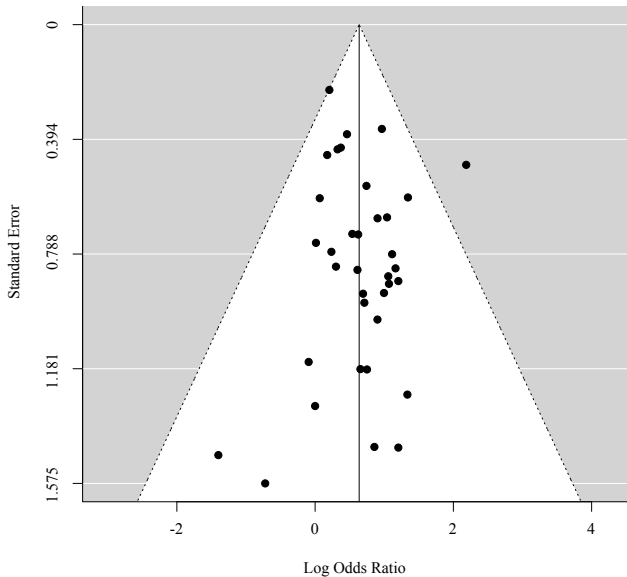


Chronic respiratory disease

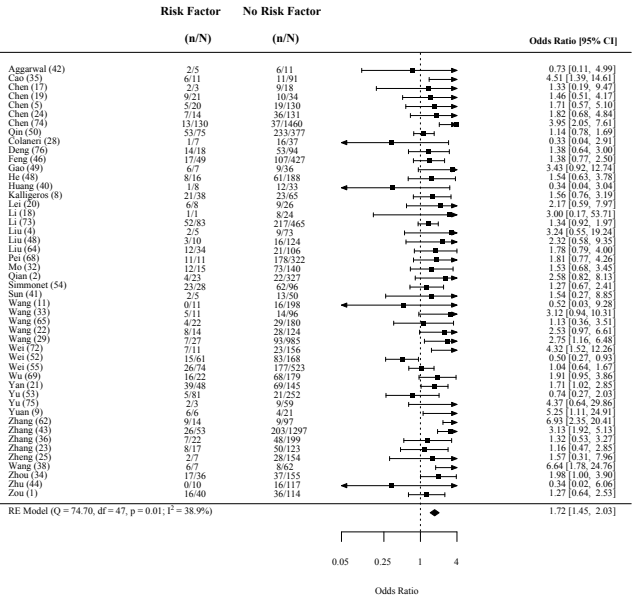


Chronic respiratory disease

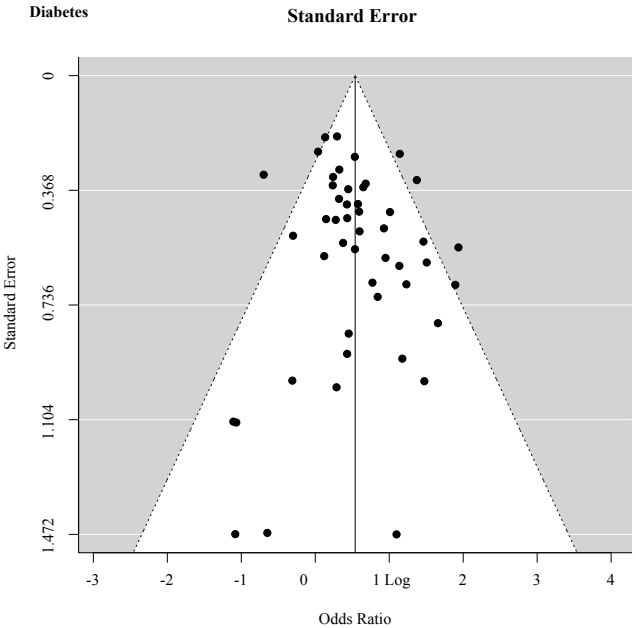
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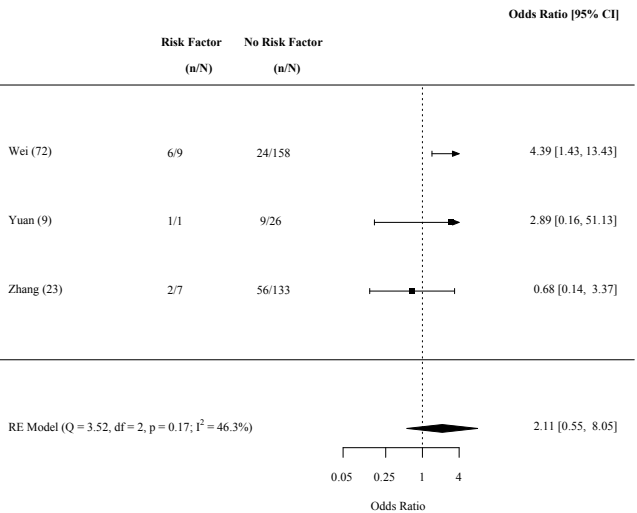
Diabetes



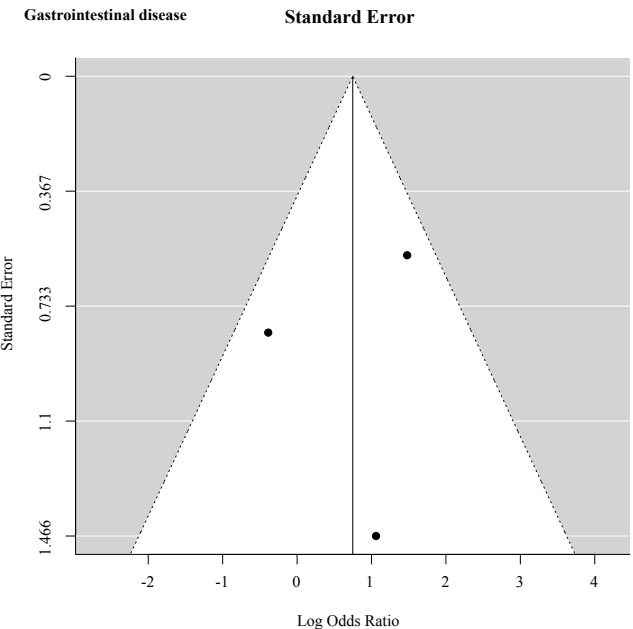
Diabetes



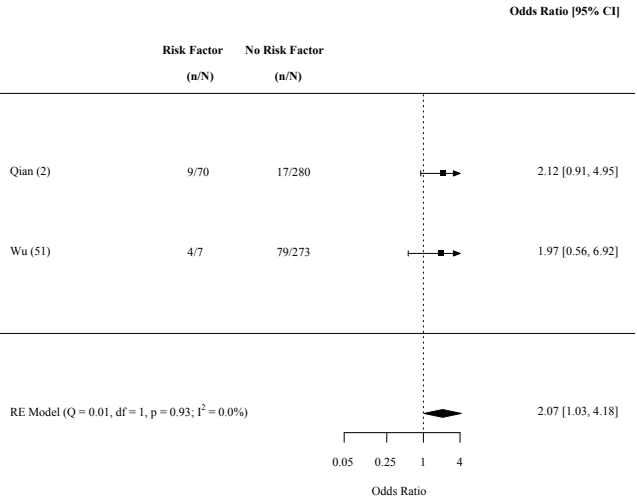
Gastrointestinal disease



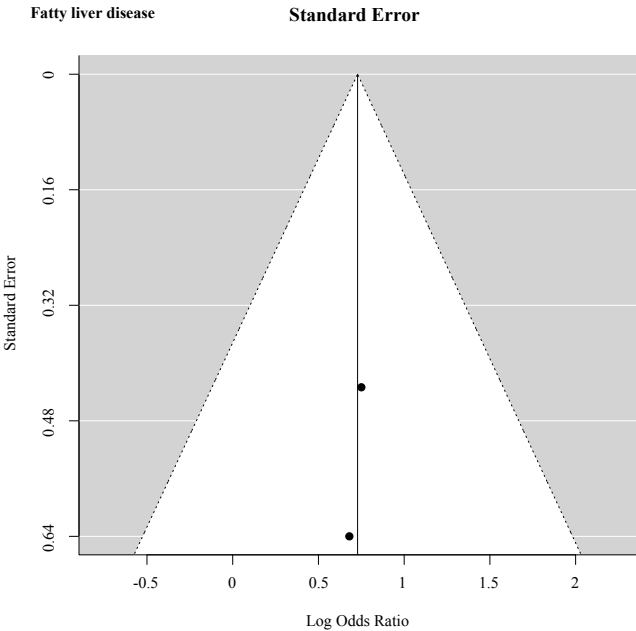
Gastrointestinal disease



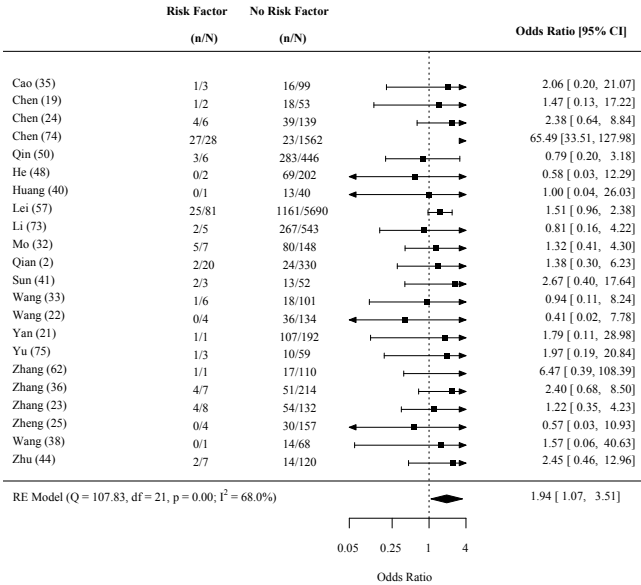
Fatty liver disease



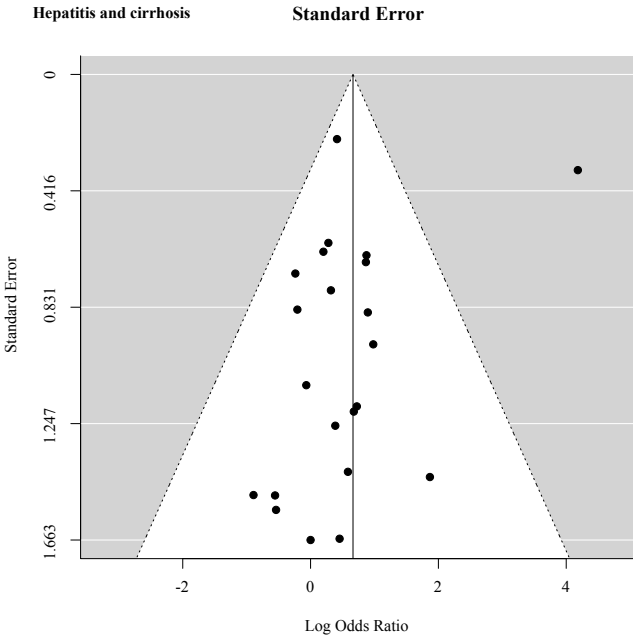
Fatty liver disease



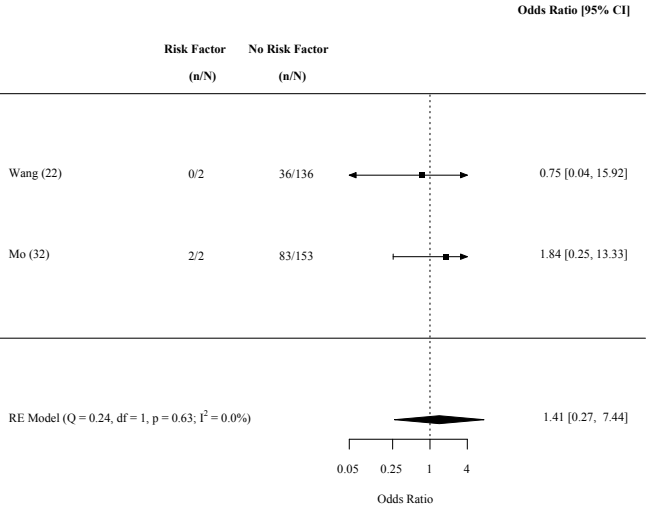
Hepatitis and cirrhosis



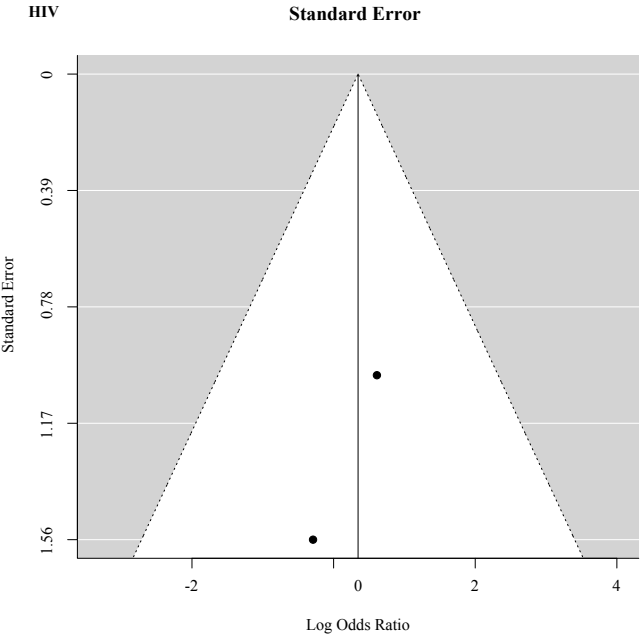
Hepatitis and cirrhosis



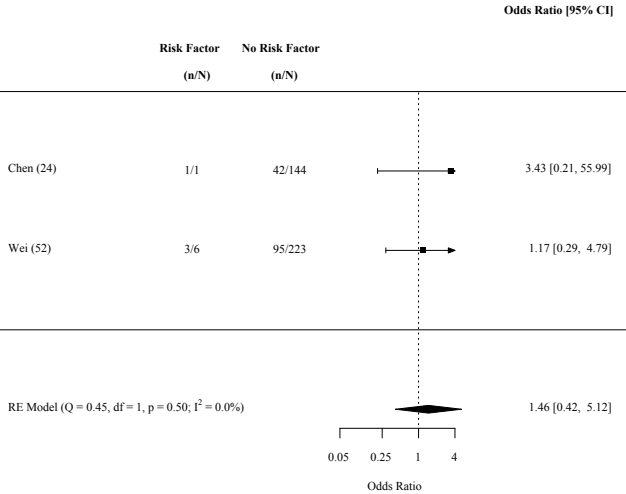
HIV



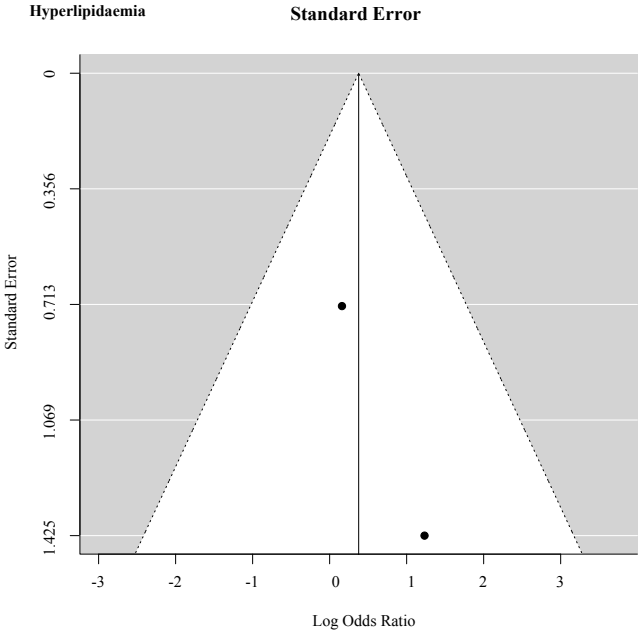
HIV



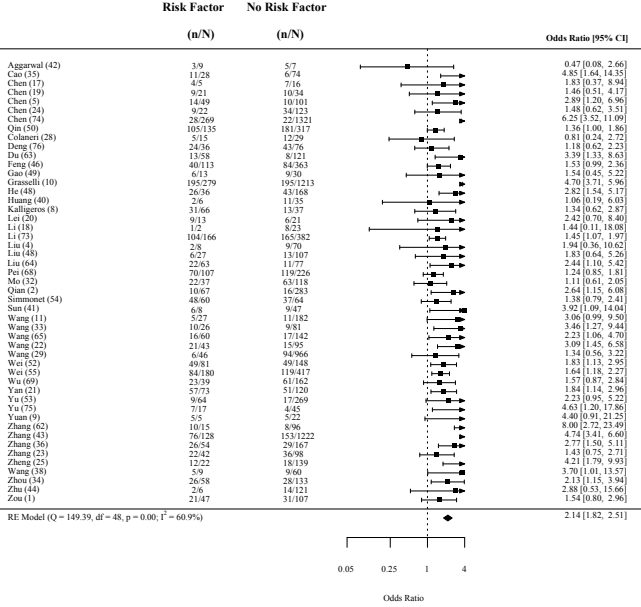
Hyperlipidaemia



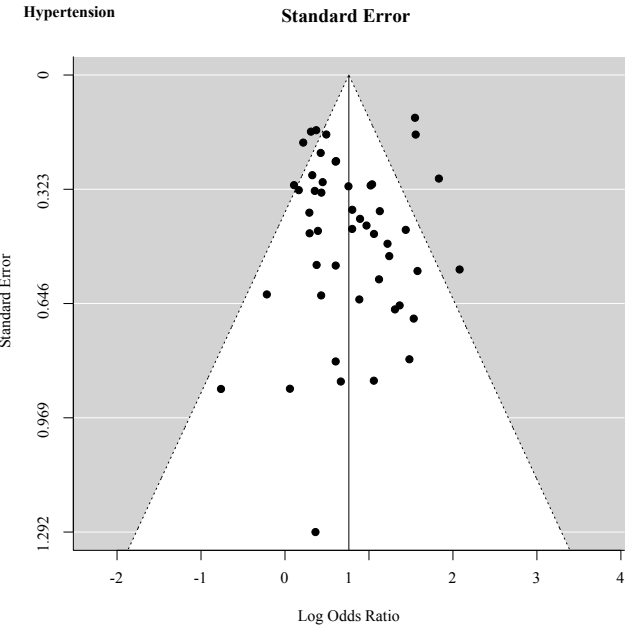
Hyperlipidaemia



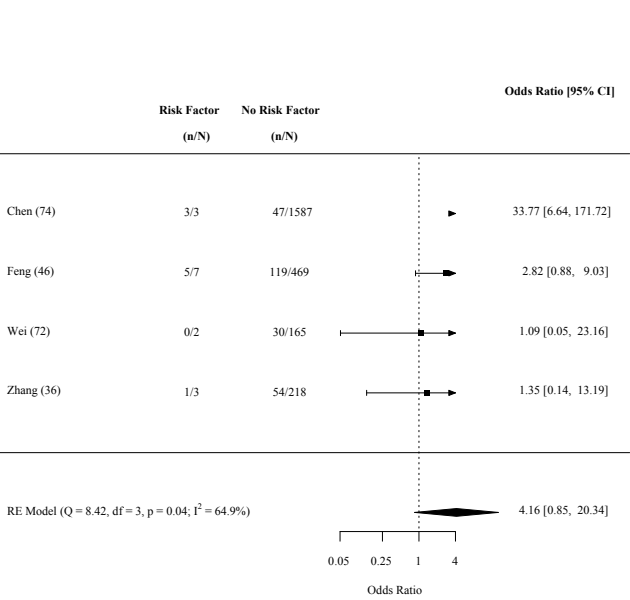
Hypertension



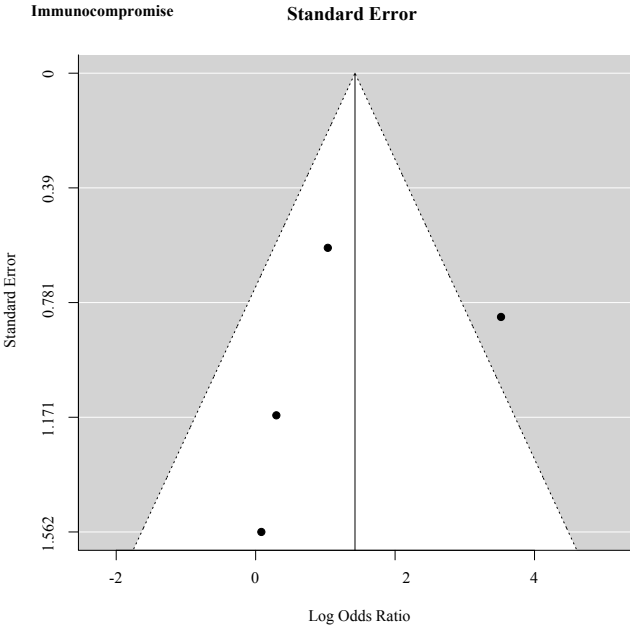
Hypertension



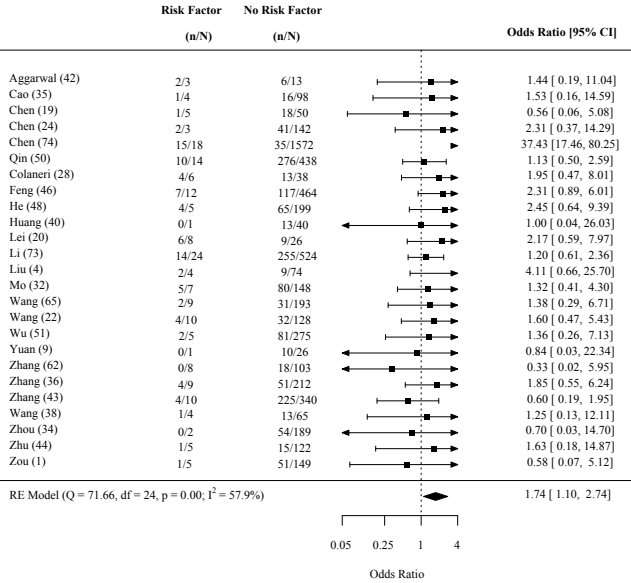
Immunocompromise



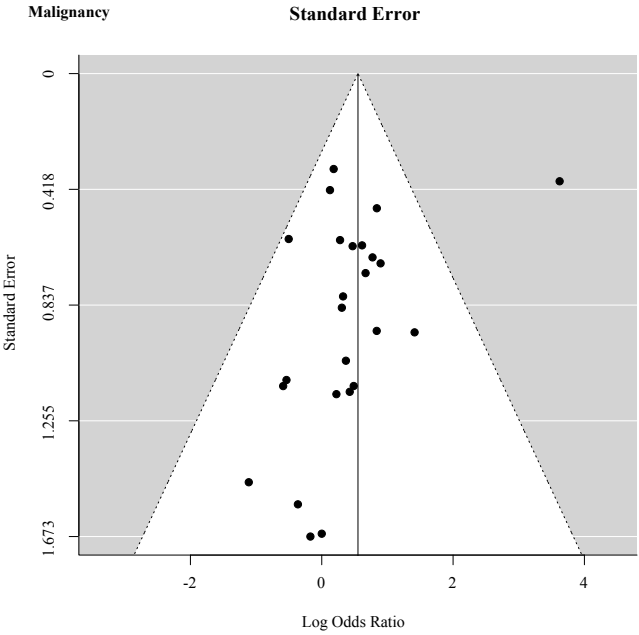
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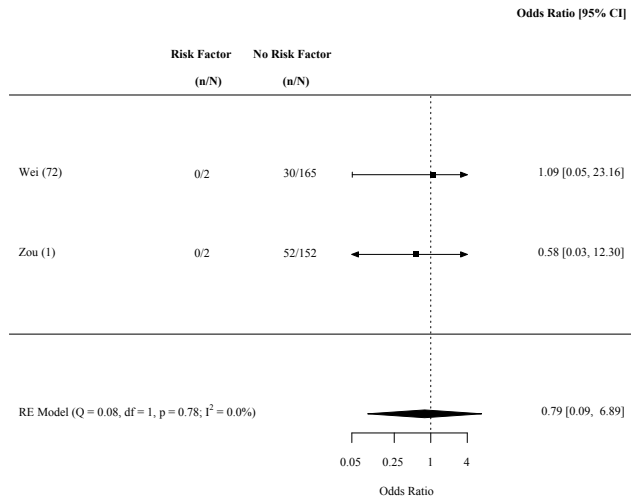
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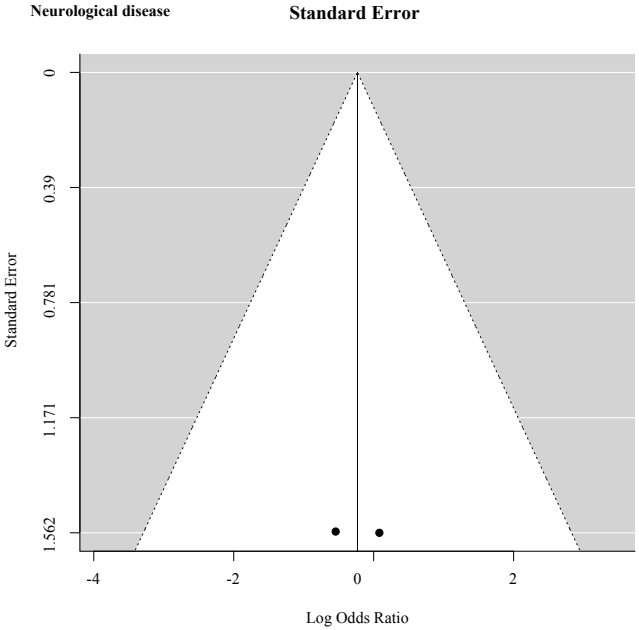
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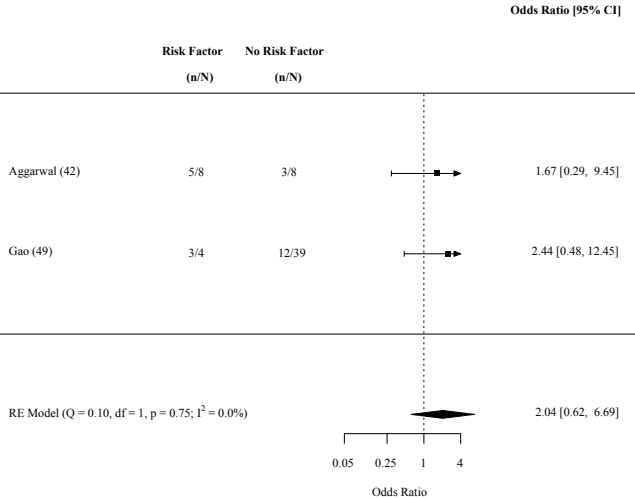
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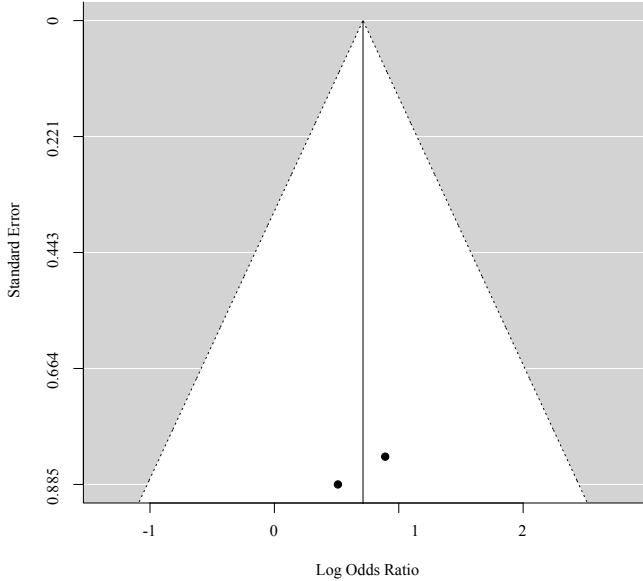
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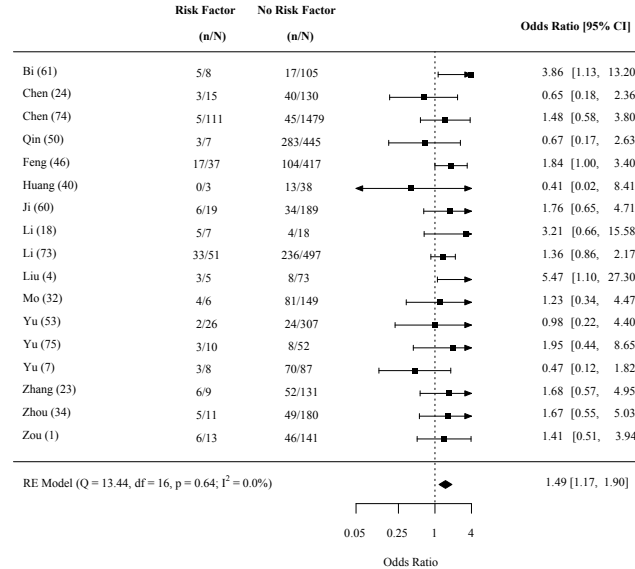
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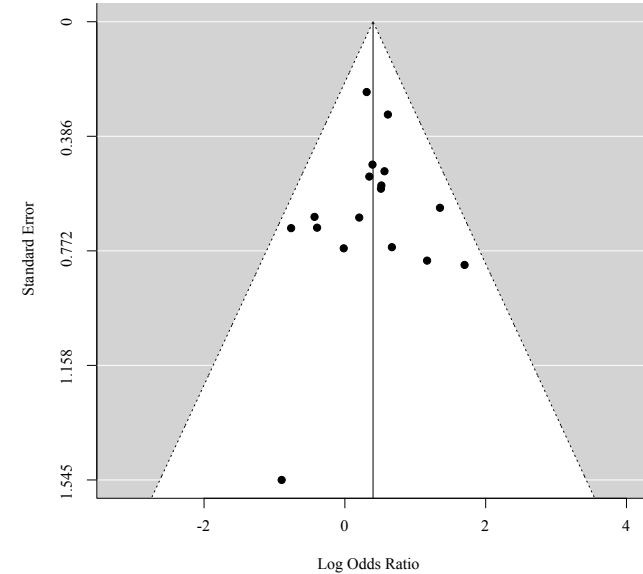
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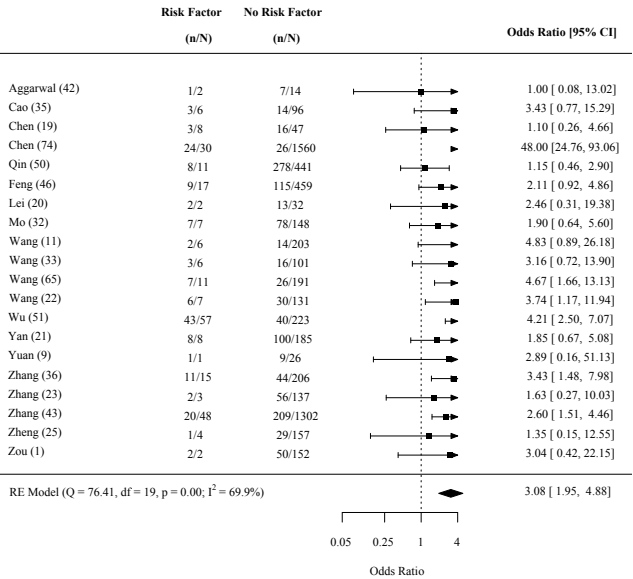
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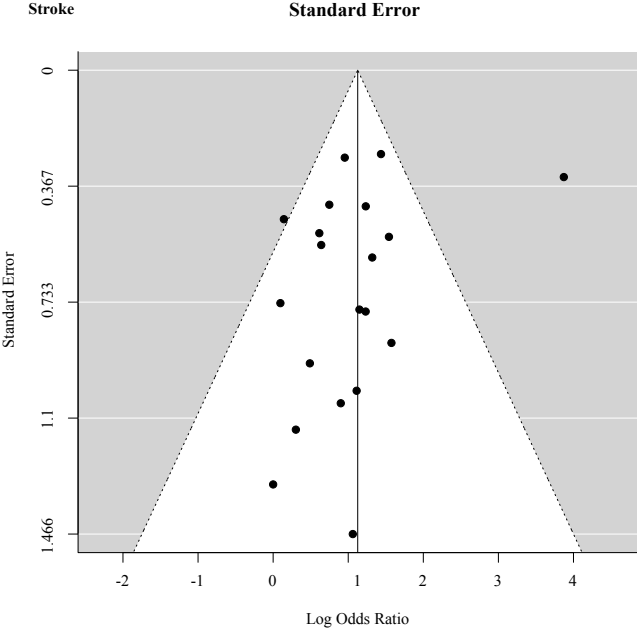
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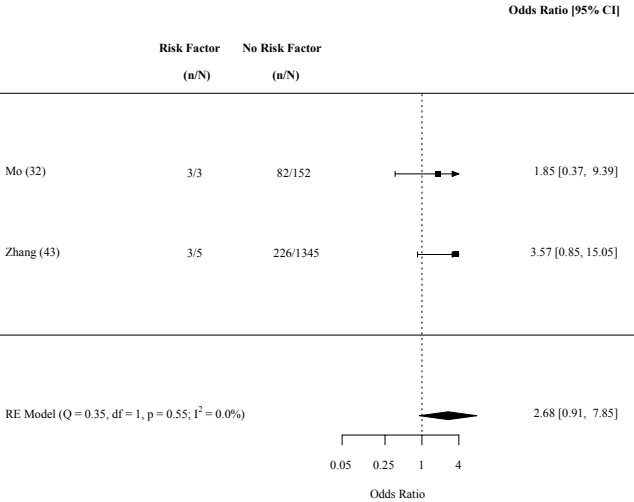
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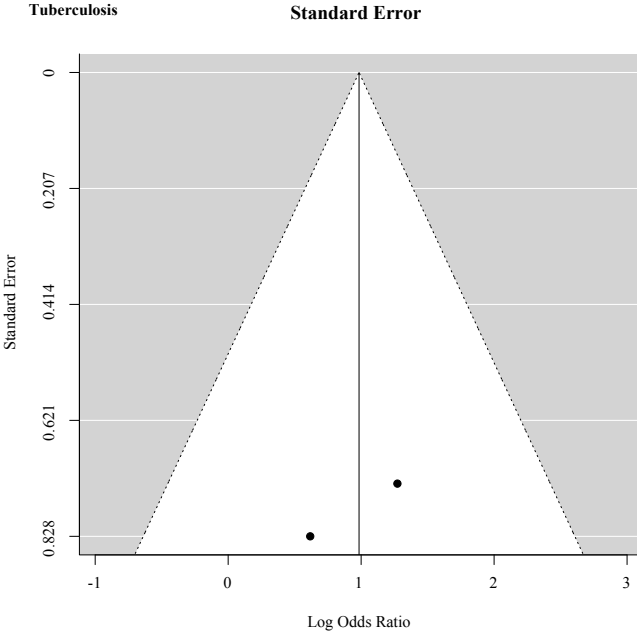
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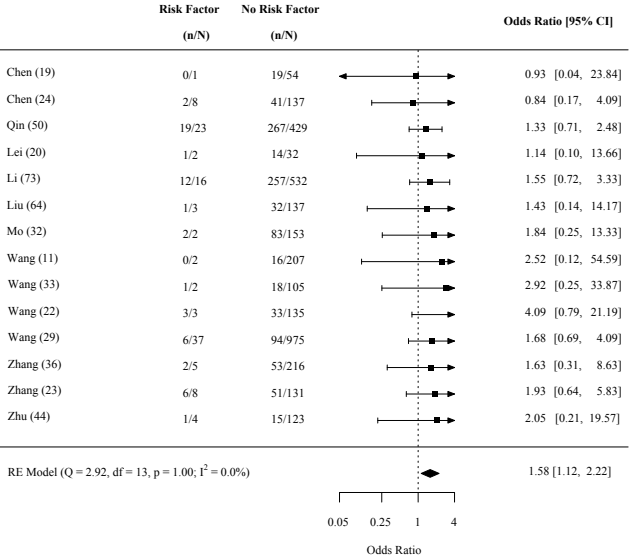
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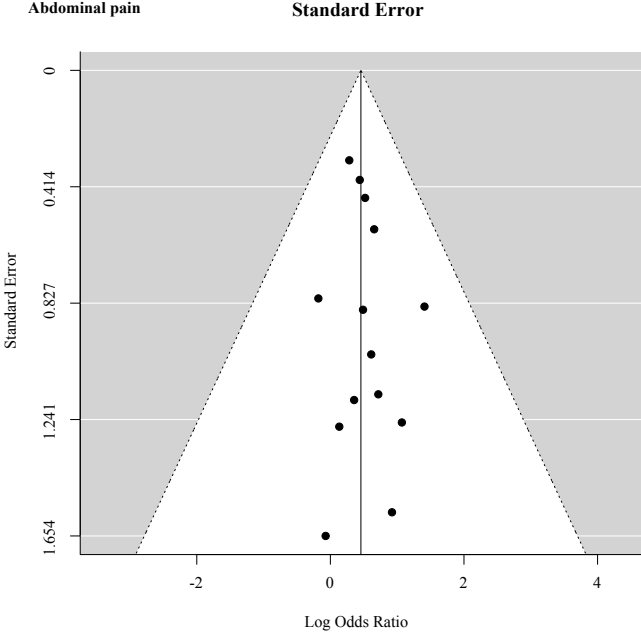
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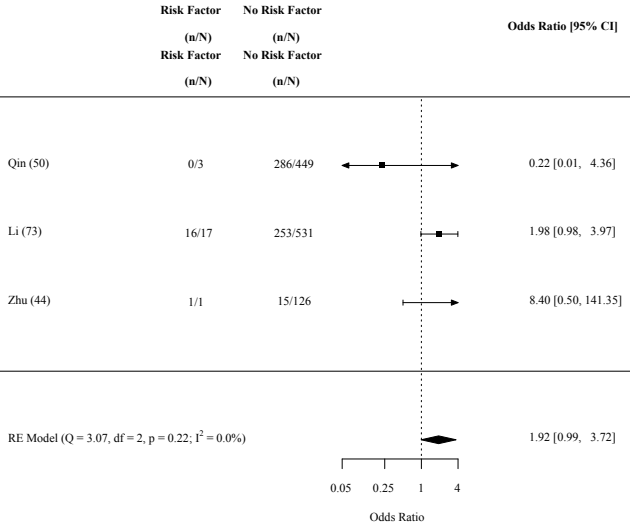
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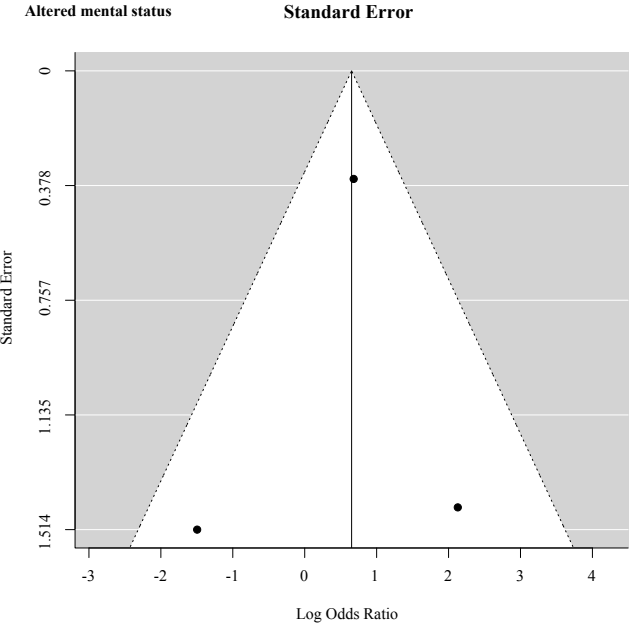
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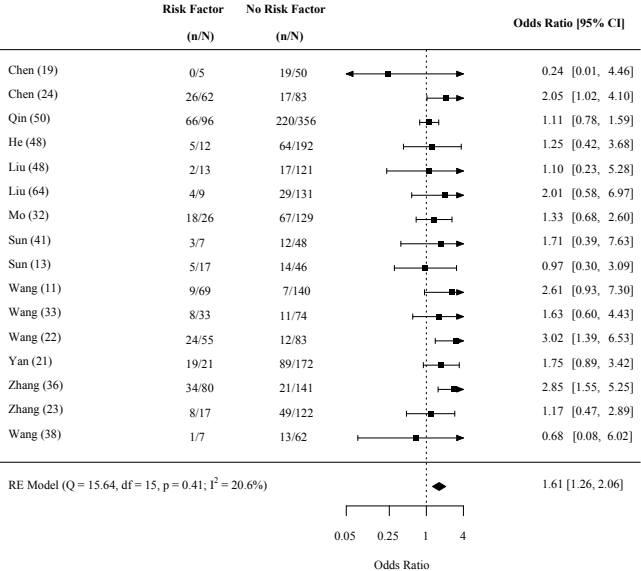
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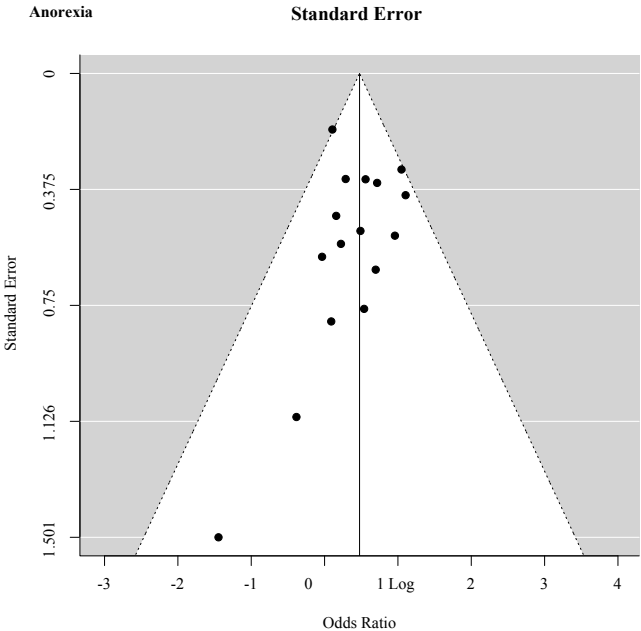
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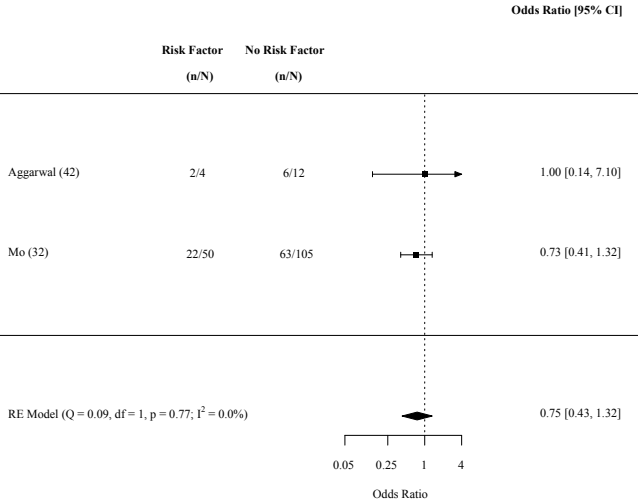
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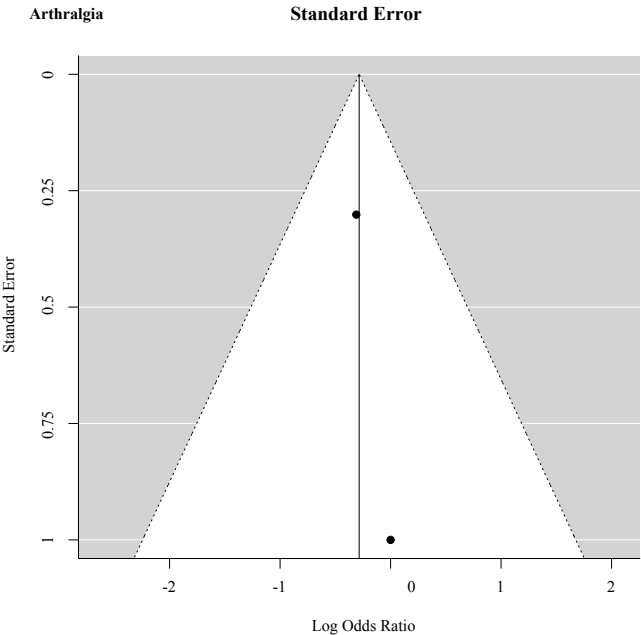
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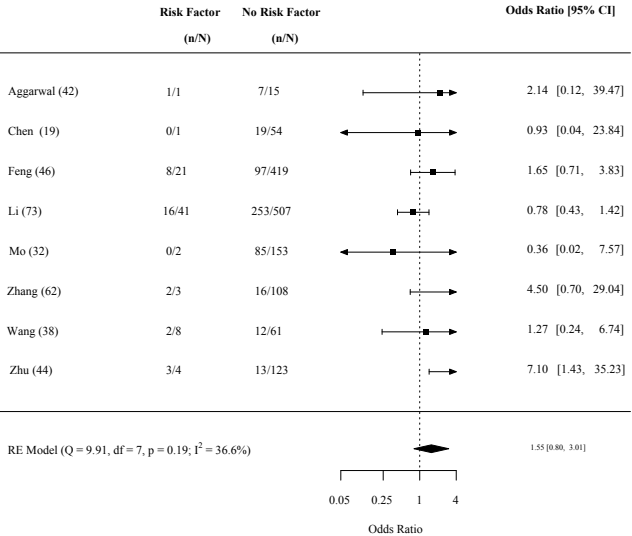
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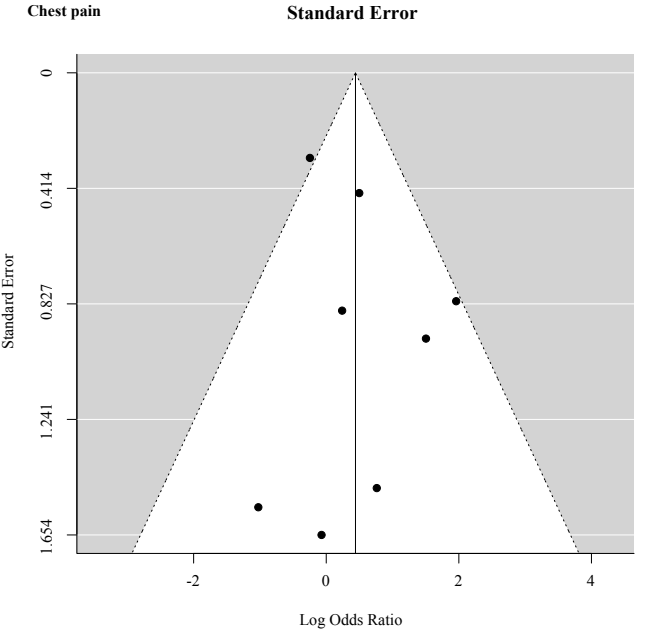
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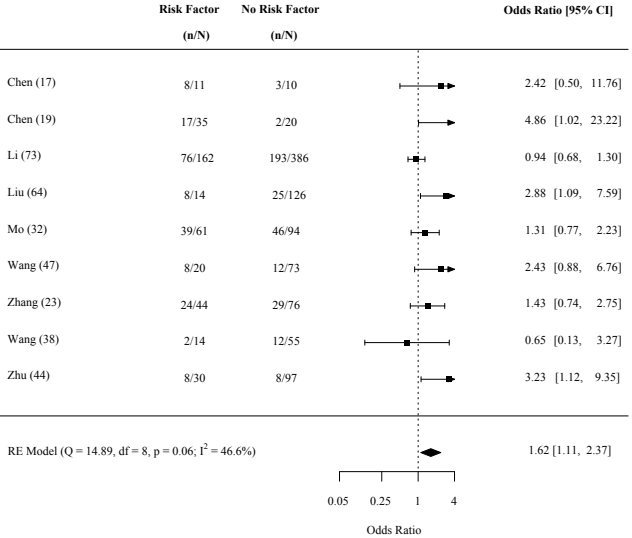
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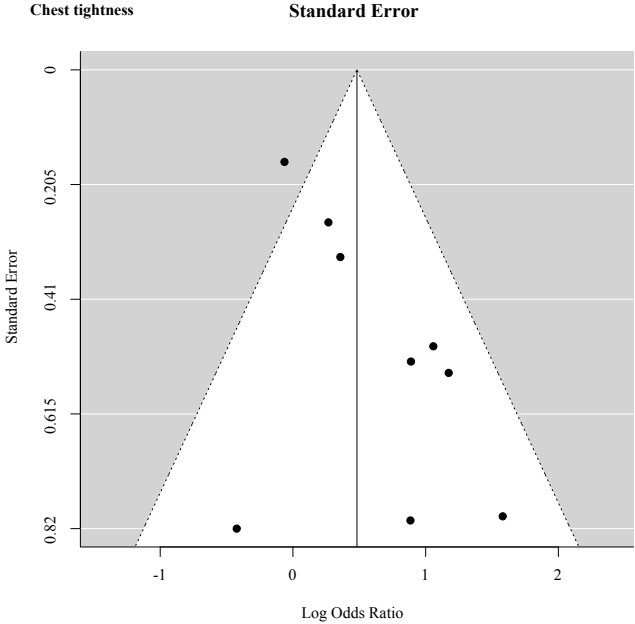
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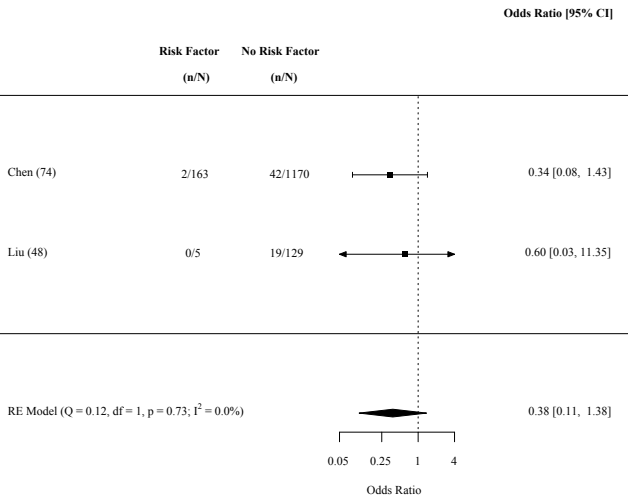
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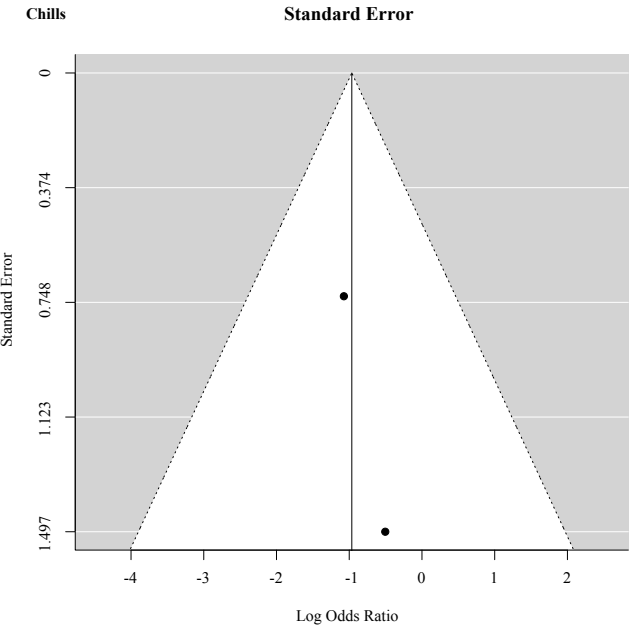
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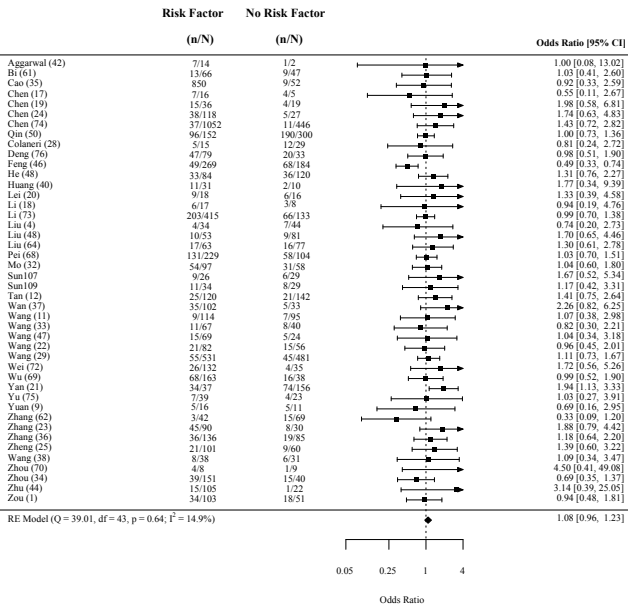
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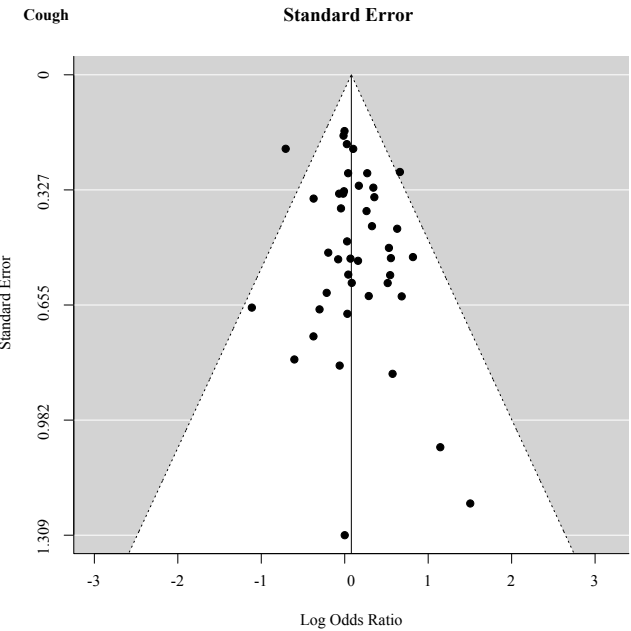
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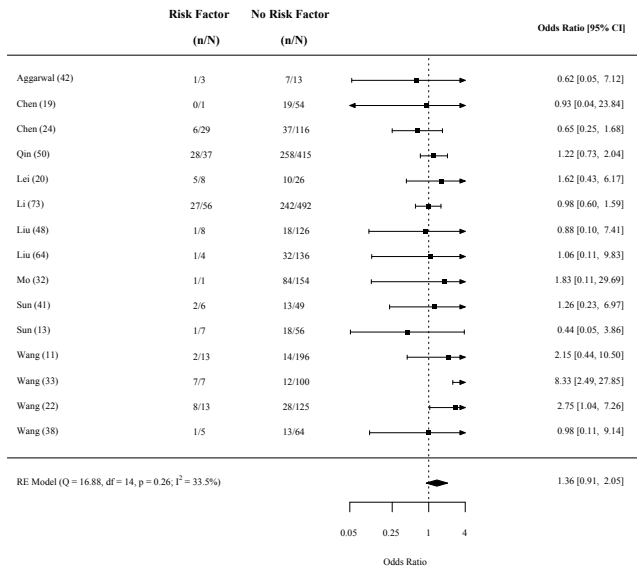
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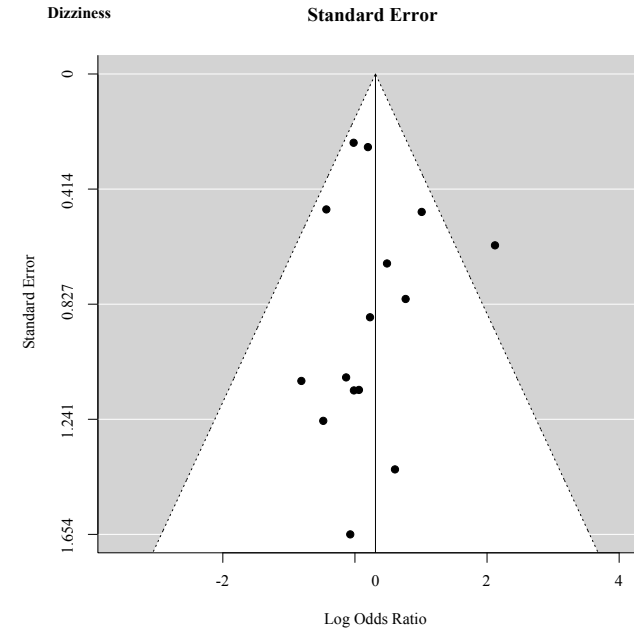
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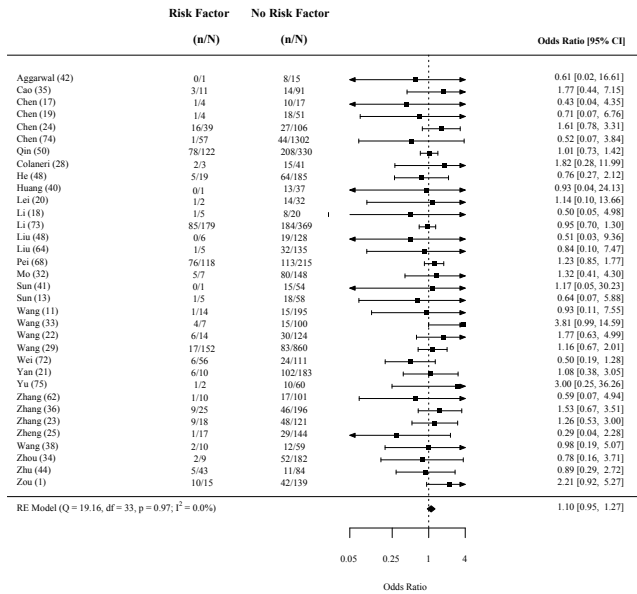
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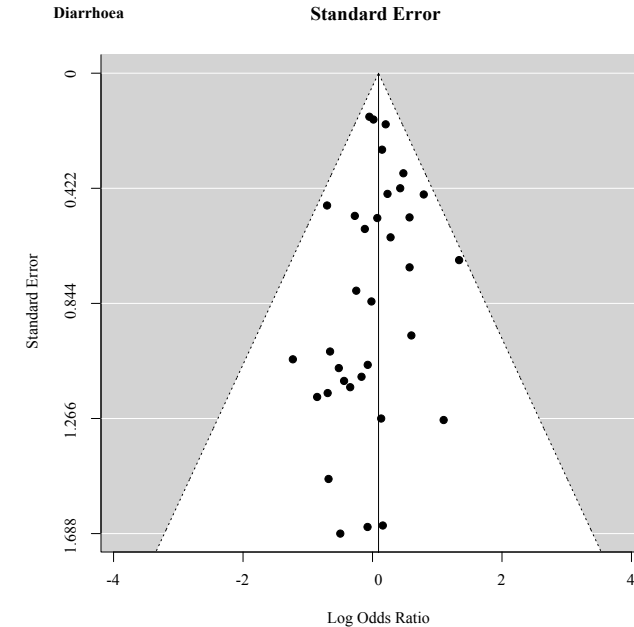
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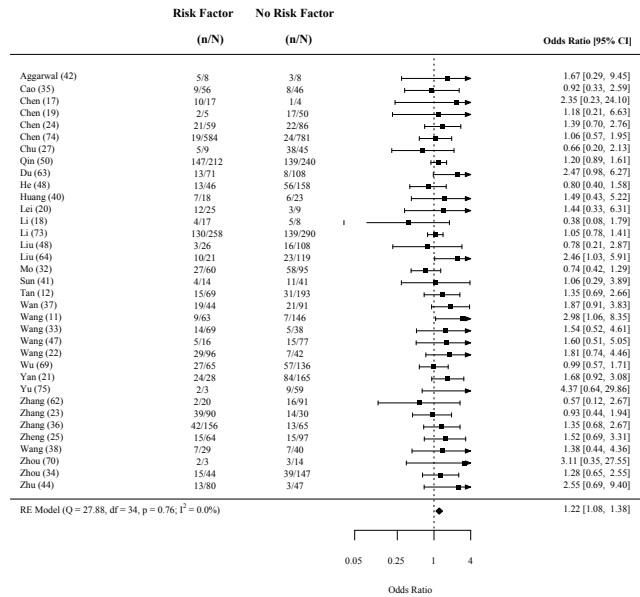
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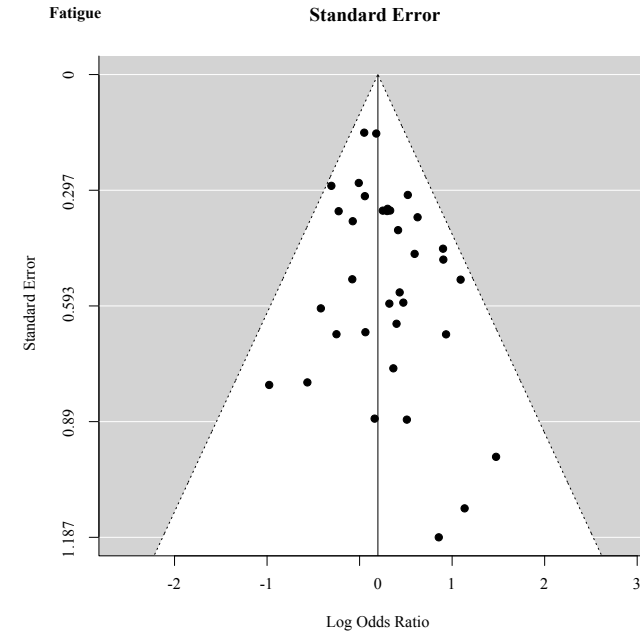
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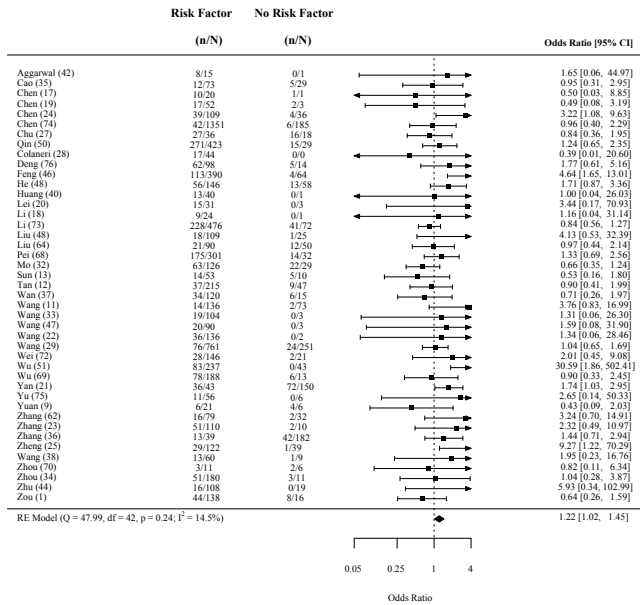
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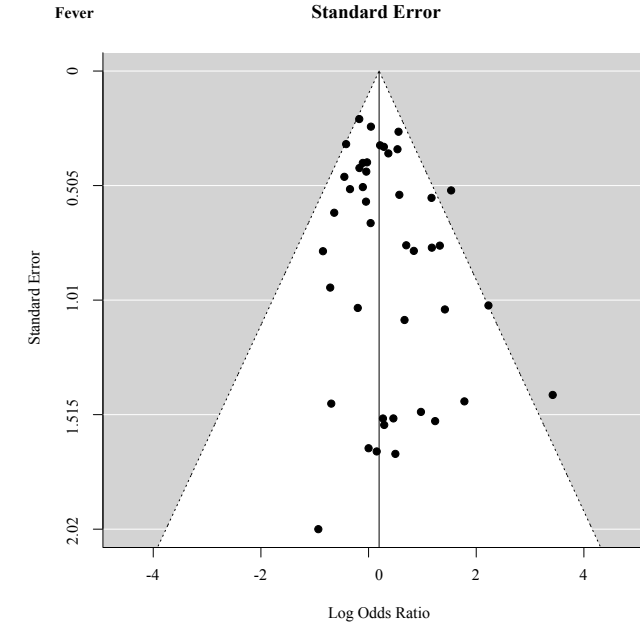
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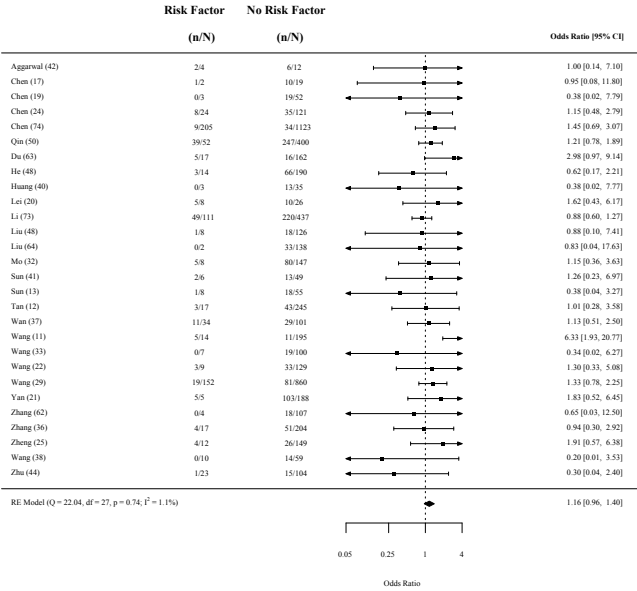
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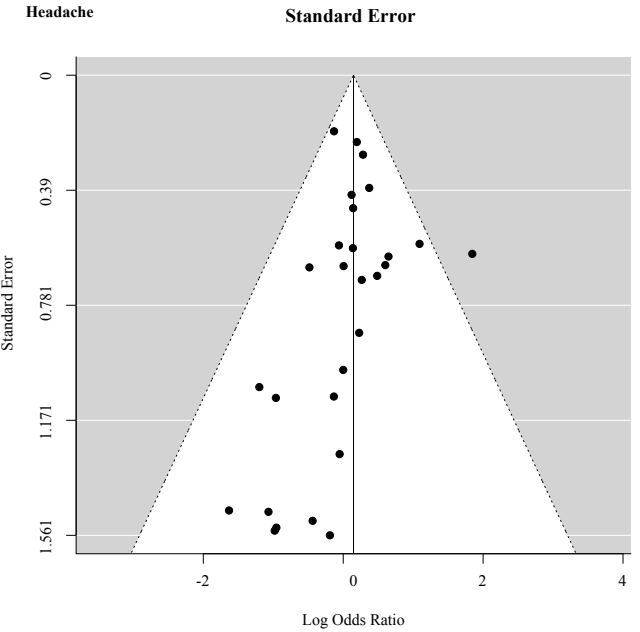
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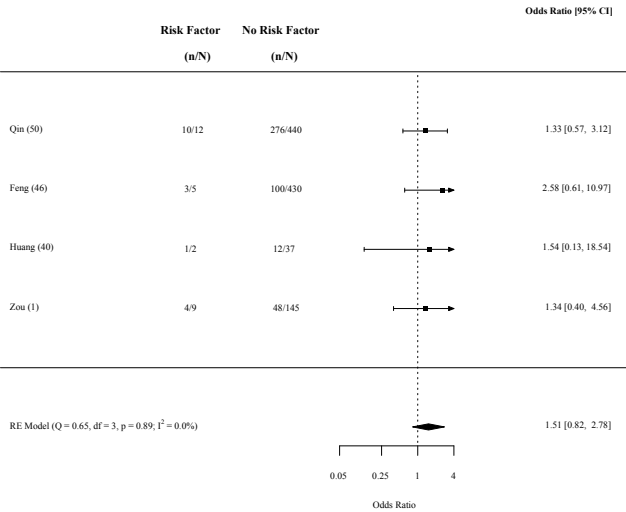
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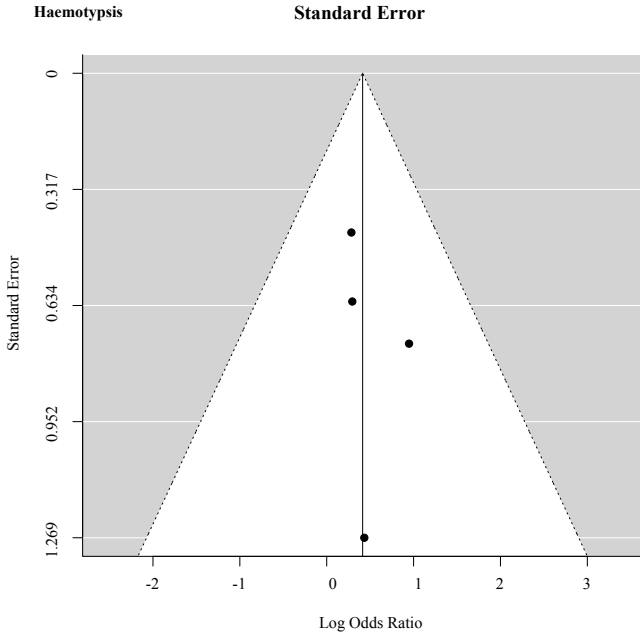
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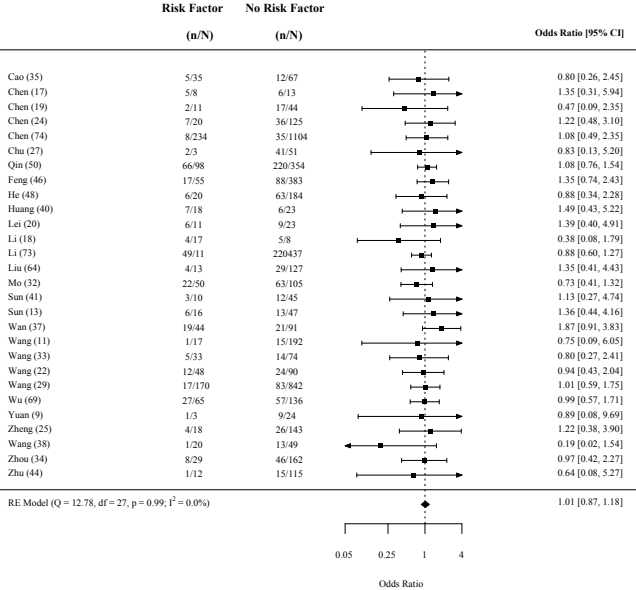
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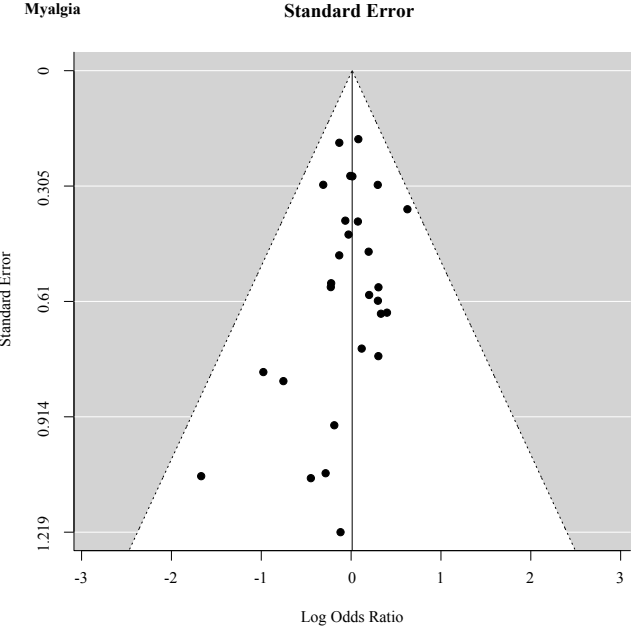
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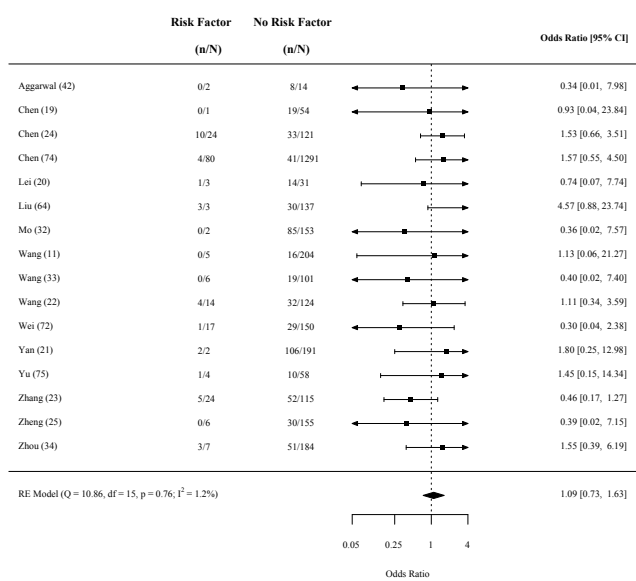
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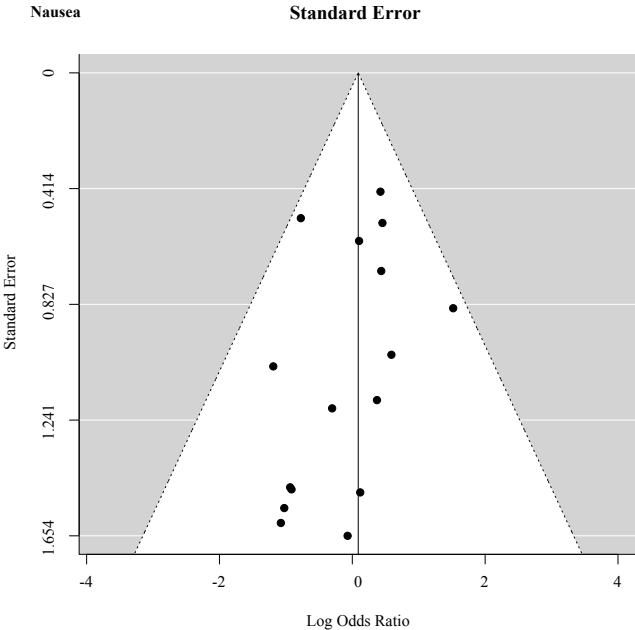
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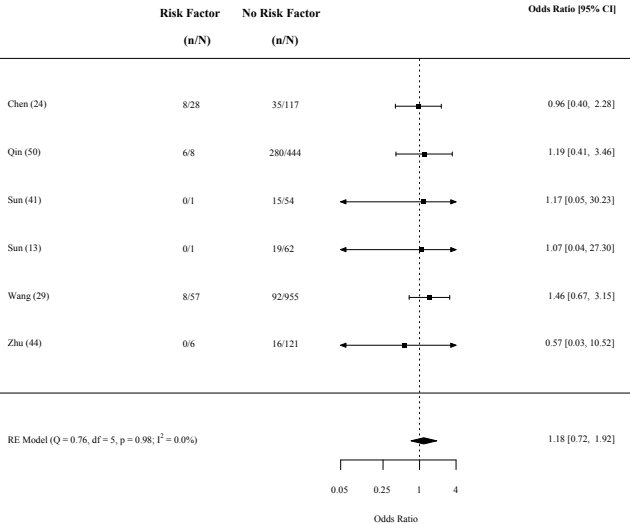
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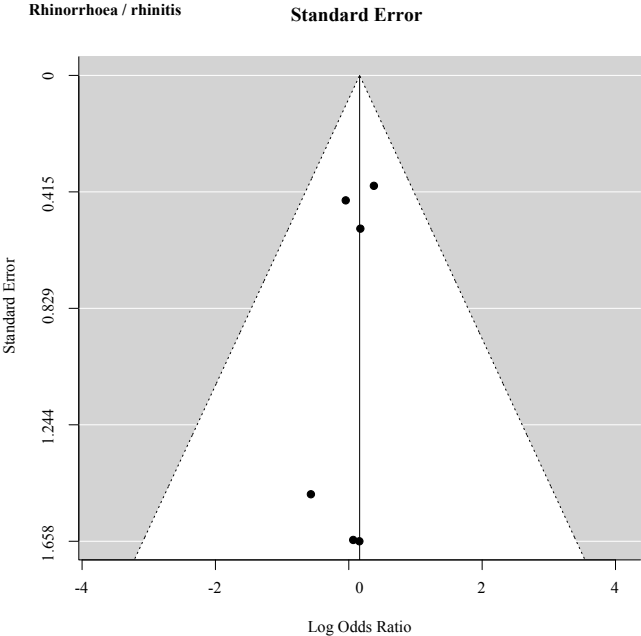
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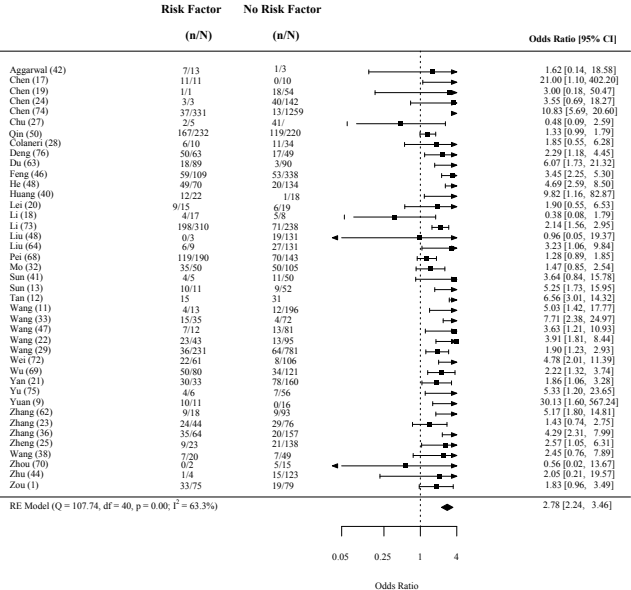
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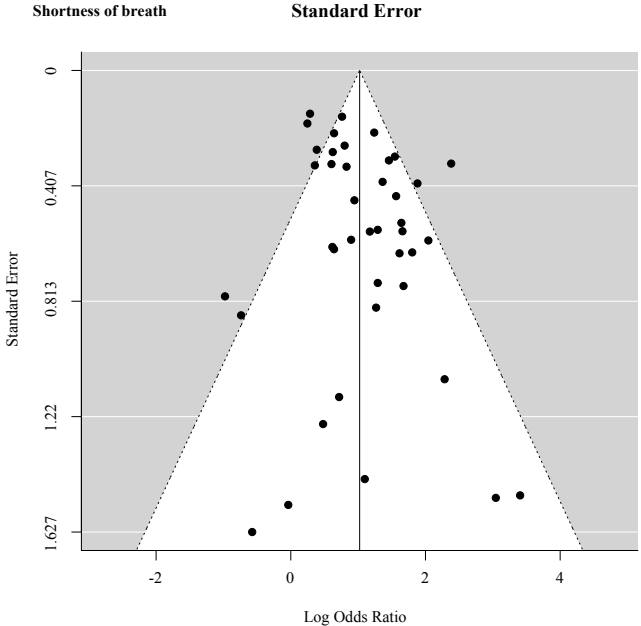
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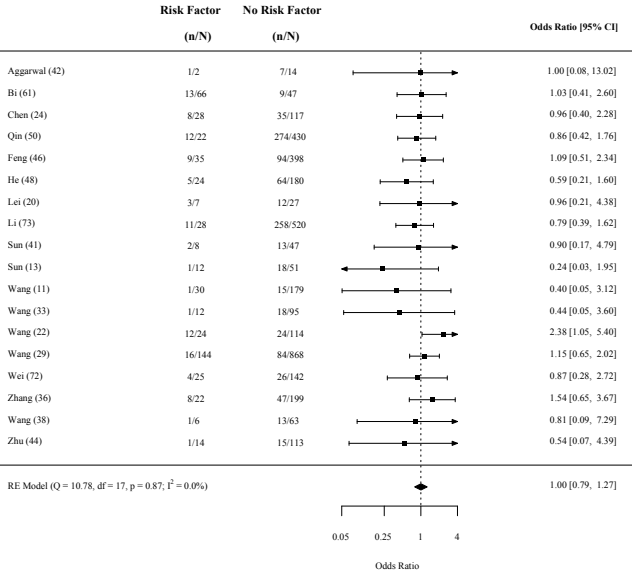
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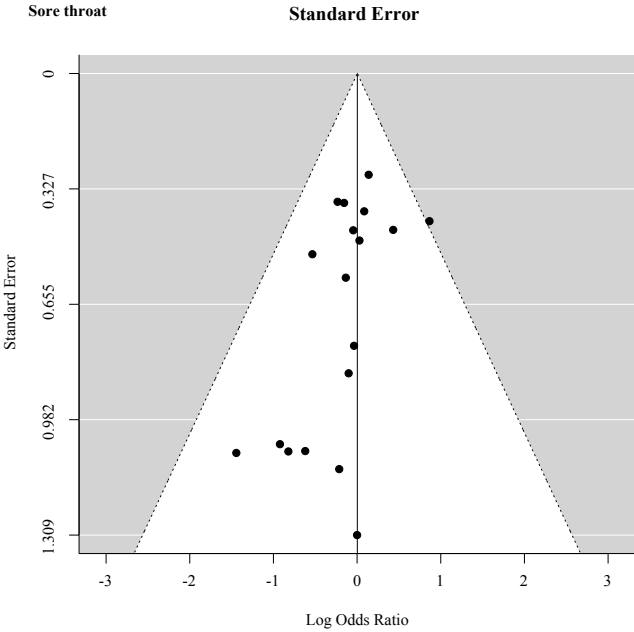
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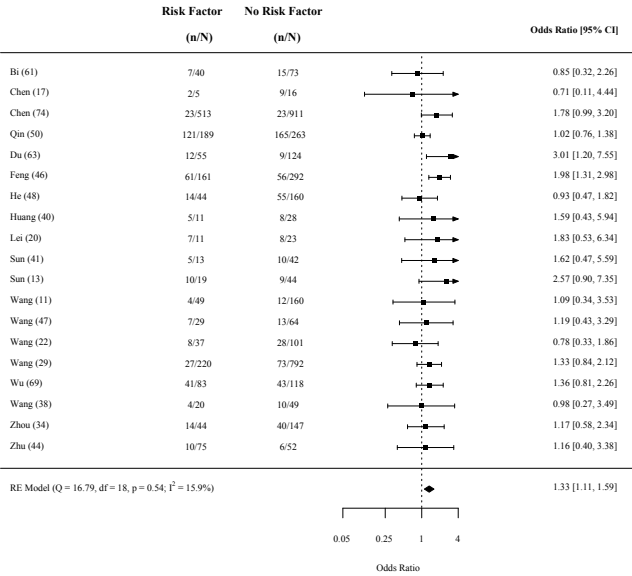
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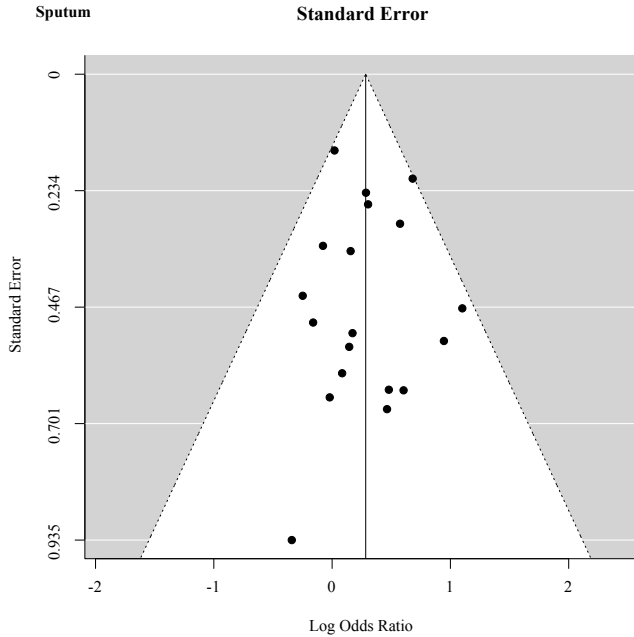
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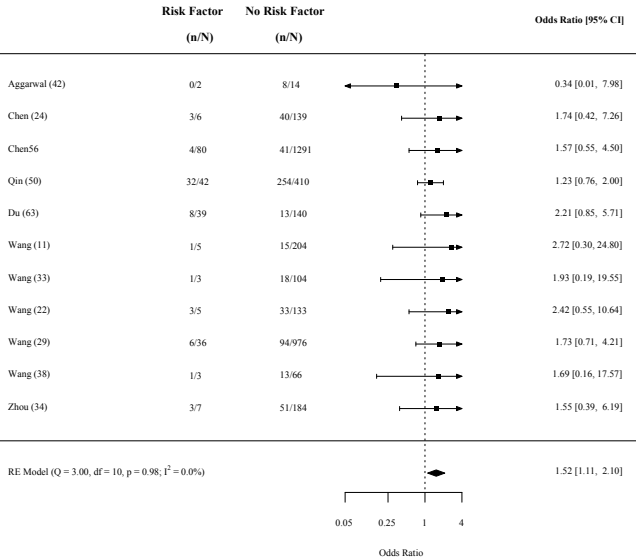
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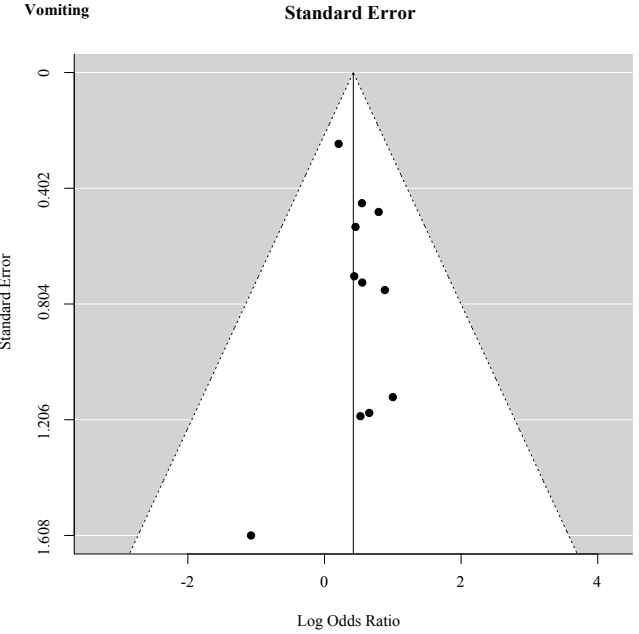
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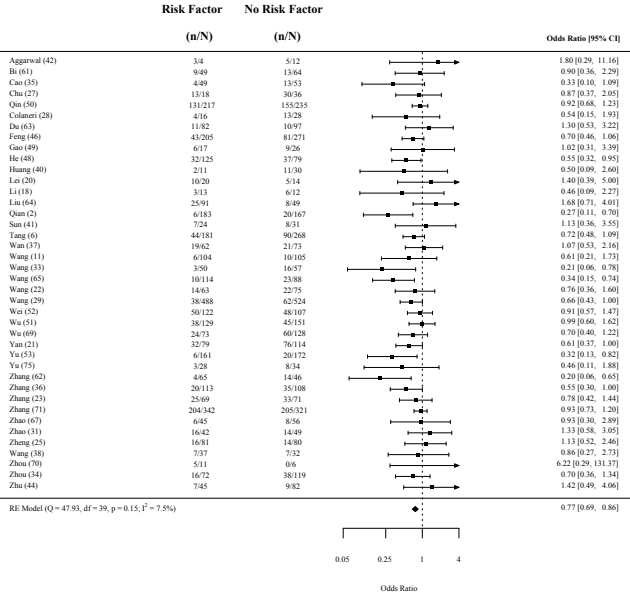
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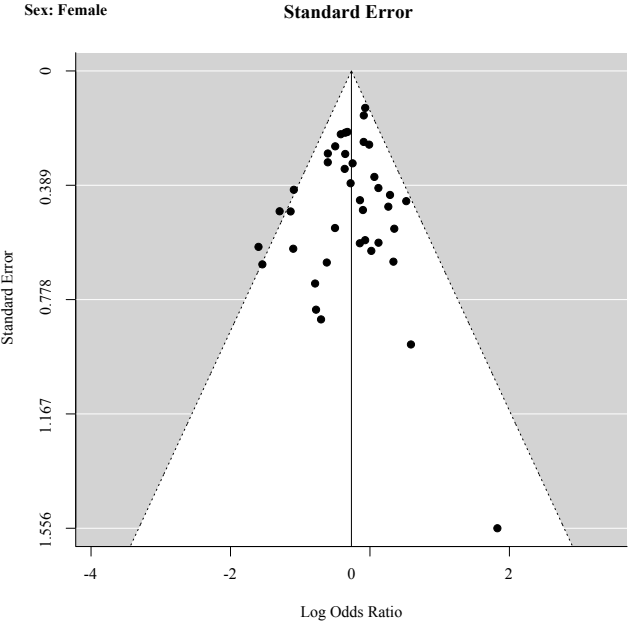
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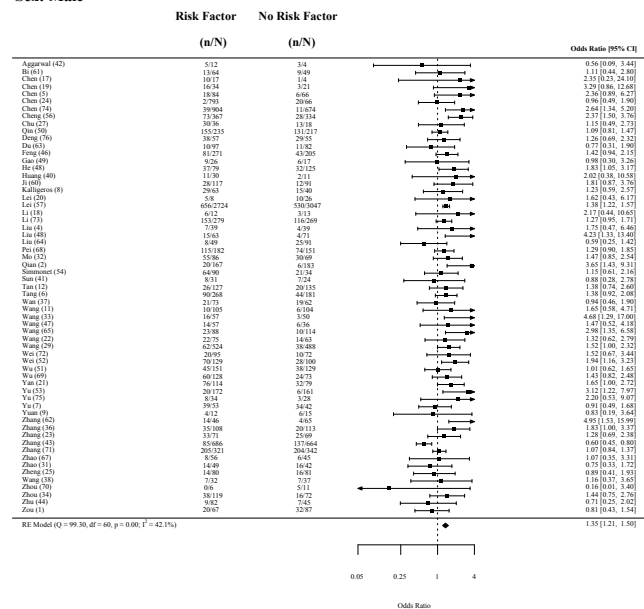
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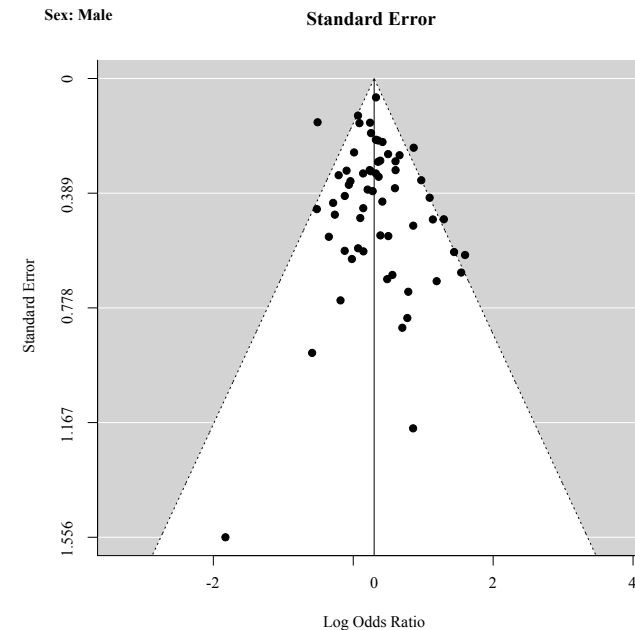
Sex: Female



Sex: Male



Sex: Male



Appendix 4.1: Co-author declarations for “Derivation of a contextually appropriate COVID-19 mortality scale for low-resource settings.”

Declaration by co-authors

Pigoga, JL, Omer, YO, Wallis, LA. Derivation of a Contextually-Appropriate COVID-19 Mortality Scale for Low-Resource Settings. Annals of Global Health, 2021; doi: <http://dx.doi.org/10.5334/aogh.3278>

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	80%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Yasein Omer	Drafted manuscript, and provided critical review of final article.
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.

The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according to these criteria.

Co- Author Name Yasein Omer



Co-Author Signature

Date 12/6/21

Declaration by co-authors

Pigoga, JL, Omer, YO, Wallis, LA. Derivation of a Contextually-Appropriate COVID-19 Mortality Scale for Low-Resource Settings. *Annals of Global Health*, 2021; doi: <http://dx.doi.org/10.5334/aogh.3278>

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	80%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Yasein Omer	Drafted manuscript, and provided critical review of final article.
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.

The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according to these criteria.

Co- Author Name Lee A Wallis

Co-Author Signature

Date 12/6/21



Appendix 4.2: University of Cape Town study proposal (FHS015).

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

Student:

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PhD Candidate in Emergency Medicine

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DECLARATION

I, Jennifer L Pigoga, 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: 

Date: 14/10/20

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 both Sudan and Tanzania 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 PhD aims to develop and validate a severity scoring tool (SST) to assist frontline providers in rapidly predicting severe COVID-19 disease in LRS.

A series of three studies is 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 two low-income countries in 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.

We are currently seeking HREC approval of an amendment to the methodology for study two (HREC ref: 450/2020).

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2. INTRODUCTION

2.4 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 deaths^{1 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.⁴ Mortality has varied across settings, but current data suggest a variable case fatality rate ranging from 0.5% to 4.5%.⁵⁻⁸

As COVID-19 spreads, healthcare systems worldwide are being strained.^{9 10} Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.¹¹ 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.^{9 10} It is increasingly likely that the countries with the most limited capacity to respond will be affected on a large scale.¹² Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.¹¹ 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.^{13 14} 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.¹⁵ 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.^{15 16} 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.¹⁷ High burdens of data entry seen in many

tools can lead to increased time-to-decision making and frequent missing data points.¹⁸⁻²⁰ Some tools also involve additional investigations, including blood tests and imaging, that have very limited availability in LRS.^{15 21-23}

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.

2.5 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-2.²⁴ 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 both Sudan and Tanzania 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.

2.6 Aim and objectives

This PhD 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 PhD has 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).

We are currently seeking HREC approval of an amendment to the methodology for study two (HREC ref: 450/2020), which meets objectives two.

3 METHODS

3.1 Study two: Development of a severity scoring tool for COVID-19 patients using machine learning.

3.1.1 Aim and objectives

This study aims to use machine learning develop a tool to predict severity of illness progression in COVID-19 patients that is usable in frontline environments in LRS.

It has the following objectives:

1. Identify the features most predictive of severe COVID-19 disease, and
2. Develop a classification algorithm for predicting severe COVID-19 disease.

3.1.2 Study design

Analytic statistics will first be used to identify the features most predictive of severe COVID-19 disease. Following this, 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.

The SST is intended to utilise predictors of illness severity to inform a patient's likelihood of needing resource-heavy interventions, specifically, oxygen and mechanical ventilation. It will be designed to stratify potentially-positive COVID-19 patients into three categories: mild/moderate, severe, and critical. Mild/moderate patients are less likely to need oxygen; severe patients are likely to need oxygen but less likely to need mechanical ventilation; and critical patients are likely to need mechanical ventilation.

3.1.3 Study population and sample size

The Khartoum State Ministry of Health (MOH) is currently collecting a robust dataset on all potentially positive COVID-19 patients presenting to Sudanese healthcare facilities through its regional COVID-19 database. This study will utilise the first 1000 consecutive adult patients recorded in the database (estimated to be patients presenting through 01 August 2020); remaining patient data will be used in future validation studies.

Existing literature suggests a minimum sample size of 560 patients be included when developing classification algorithms via machine learning,²⁵ and other COVID studies have used even fewer numbers of records – likely due in part to the time constraints that the pandemic presents. For example, one recent study to derive a COVID-19 severity detection tool obtained 82% accuracy using just 137 patients,²⁶ and another achieved 90% accuracy with 375 patients.²⁷ A sample size of 1000 patients should be sufficient for the algorithm development in this study, while preserving some data for validation work.

3.1.4 Data collection and management

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.

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 included in study three's validation process.

3.1.5 Data analysis

A two-step process will be undertaken to develop the SST using the data collected from the Sudanese registry.

After data cleaning, the training dataset will be analysed to identify highly predictive features of severe COVID-19. A tool that uses fewer features is preferred in time- and staff-constrained EUs and is unlikely to have significantly reduced performance in comparison to more complicated models.²⁸⁻³⁰ An algorithm using the student t-test will be run to identify those features that are significantly associated with disease severity.^{26 31 32} Features with p-values below 0.05 will be considered to have significant predictive ability and included in algorithm derivation.

Several classification algorithms - all of which have been used in previous emergency care related tool development studies - will be tested to identify the most predictive model: chi-square automatic interaction

detection (CHAID), logistic regression (LR), random forest (RF), and support vector machine (SVM).^{26 32-34 35 36} Model performance will be assessed using the area under the receiver operating characteristic curve as the key indicator for overall prognostic accuracy.³⁷ A set of additional performance characteristics - sensitivity and specificity; positive predictive value (PPV) and negative predictive value (NPV); and over- and under-triage³⁸ - will also be evaluated. The most predictive model will be selected for use as the SST.

3.1.6 Limitations

The final model may be limited in accuracy by the sample size used to train it; however, other studies suggest this sample will be sufficient and it is essential that additional data be saved for local validation purposes. Additionally, while the Khartoum State MOH has worked tirelessly to capture all relevant data for patients in its COVID-19 registry, some values may be missing. Assuming that a characteristic - for example, a comorbidity such as diabetes - was not present simply because it was not captured may bias the dataset. To reduce this, multiple imputation will be used where possible to account for missing data.

The dataset used to train the SST is likely limited in its generalisability to other settings. Validation of the tool in study three with datasets generalisable to the broader target population after derivation will allow for evaluation of the tool prior to recommendation of its use and dissemination occurring.

3.1.7 Ethical considerations

Study two 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).

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 or made available to the researchers. All electronic data will be extracted by Khartoum State MOH personnel in deidentified form and shared in encrypted, password-protected files. Only study personnel will have access to these data. Analyses will be conducted anonymously and at the aggregate level.

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 then entered into the national database by administrators. This study therefore places no additional burden on frontline providers.

This study will benefit the Sudanese population, 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 continue suffering COVID-19 outbreaks and whose emergency care systems are severely burdened. 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.

3.1.8 Reporting and implementation of results

Study two will generate a preliminary version of the SST; this will then be validated using data collected in study three. 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.

3. RESOURCES

There are no costs associated with study two.

4. STUDY TWO TIMELINE

YEAR	2020		2021			
QUARTER	3	4	1	2	3	4
Proposal development	X					
EMDRC	X					
HREC	X	X				
Sudan FMoH approval	X					
SST derivation		X	X			
Manuscript preparation			X	X		

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6. APPENDICES

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

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

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 4.3: Ethical approvals for “Derivation of a contextually appropriate COVID-19 mortality scale for low-resource settings.”

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 6626
Email: hrec-enquiries@uct.ac.za

Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18th September 2020

HREC REF: 450/2020

Prof L Wallis

Division of Emergency Medicine

Department of Surgery

Email: lee.wallis@uct.ac.za

Dear Prof Wallis

PROTOCOL TITLE: DEVELOPMENT AND VALIDATION OF A SEVERITY SCREENING TOOL FOR COVID-19 ILLNESS IN LOW-RESOURCE SETTINGS (PhD candidate: Jennifer Pigoga)

Thank you for submitting your response dated 31st August 2020 to the comments raised by the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved Study Two: Development of a screening severity tool for COVID-19 patients using a Delphi and expert consensus processes.**

This approval is subject to the following conditions:

1. Please provide the HREC with the recruitment letter that will be sent to members of the African Federation for Emergency Medicine database.
2. Please amend the consent statement for the Modified Delphi Consensus Process to include a participant and investigator declarations and signatures, as has been provided for the consent statement for the Expert Consensus Tool Development Process. Please provide the HREC with the updated informed consent form for the Modified Delphi Consensus Process.
3. Sudanese Ministry of Health approval is required for the expert consensus process.

This approval is also subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID-19, dated 17th March 2020 and 6th July 2020.

Approval is granted for one year until 30th September 2021.

The HREC acknowledge that the PhD candidate, Jennifer Pigoga, is involved in this study.

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

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 4.4: Transparent Reporting of a Multivariable Prediction Model for Individual Prediction or Diagnosis (TRIPOD) guidelines for “*Derivation 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.	3
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.	4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
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.	5
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	Describe eligibility criteria for participants.	5
	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.	5
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
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.	6-8
	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.	8
Model development	14a	Specify the number of participants and outcome events in each analysis.	8
	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).	10
	15b	Explain how to use the prediction model.	10
Model performance	16	Report performance measures (with CIs) for the prediction model.	11
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	14-15
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	13-14
Implications	20	Discuss the potential clinical use of the model and implications for future research.	13-15
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.	15

Appendix 4.5: Evidence for inclusion of candidate variables.

Variable	Evidence	Inclusion decision
DEMOGRAPHICS		
Age (years)	A-DROP ¹¹⁵ , APACHE II ²⁷⁴ , COVID-GRAM ¹³² , CURB-65 ^{116 363} , MuLBSTA ³⁶⁴ , PSI ¹¹⁶ , SMART-COP ³⁶⁵ , 4C ^{112 363}	Included
Male sex at birth	A-DROP ¹¹⁵ , PSI ¹¹⁶ , 4C ^{112 363} , pOR: 1.35 (95% CI [1.21-1.50]) ⁷¹	Included
COMORBIDITIES*		
Alcohol use	pOR: 1.56 (95% CI [0.70, 3.45]) ⁷¹	Included in composite "Total no. comorbidities" variable
Cardiovascular disease	PSI (congestive heart failure) ¹¹⁶ , 4C (chronic cardiac disease) ^{112 363}	Included in composite "Total no. comorbidities" variable
Chronic respiratory disease	4C (chronic pulmonary disease, excluding asthma) ^{112 363} , pOR for chronic obstructive pulmonary disease, asthma, interstitial lung disease, and pulmonary hypertension: 1.89 (95% CI [1.50, 2.38]) ⁷¹ ; pOR for tuberculosis: 2.68 (95% CI[0.91, 7.85]) ⁷¹	Included in composite "Total no. comorbidities" variable
Chronic neurological disease	PSI (cerebrovascular disease) ¹¹⁶ , pOR for stroke: 3.08 (95% CI[1.95, 4.88]) ⁷¹	Included in composite "Total no. comorbidities" variable
Cirrhosis	PSI ¹¹⁶ , 4C (liver disease) ^{112 363} , pOR: 1.94 (95% CI [1.07, 3.51]) ⁷¹	Included in composite "Total no. comorbidities" variable
Chronic kidney disease	PSI ¹¹⁶ , 4C ^{112 363} , pOR: 2.55 (95% CI [1.52-4.29]) ⁷¹	Included in composite "Total no. comorbidities" variable
Current or former smoker	MuLBSTA ³⁶⁴ , pOR: 1.49 (95% CI [1.17, 1.90]) ⁷¹	Included in composite "Total no. comorbidities" variable
Current pregnancy	No evidence identified	Excluded due to lack of evidence and excessive missingness in derivation dataset (65.4% missing for females)
Diabetes (types 1 and 2)	4C ^{112 363} , pOR: 1.72 (95% CI [1.45, 2.03]) ⁷¹	Included in composite "Total no. comorbidities" variable
Hypertension	MuLBSTA ³⁶⁴ , pOR: 2.14 (95% CI[1.82, 2.51]) ⁷¹	Included in composite "Total no. comorbidities" variable
Hypothyroid	COVID-GRAM ¹³² , pOR for thyroid disease: 1.58 (95% CI [0.46, 5.42]) ⁷¹	Included in composite "Total no. comorbidities" variable

Malignancy	PSI ¹¹⁶ , 4C ^{112 363} , pOR: 1.74 (95% CI[1.10, 2.74]) ⁷¹	Included in composite "Total no. comorbidities" variable
Rheumatological/connective tissue disease	No evidence identified	Excluded due to lack of evidence
Total no. comorbidities	COVID-GRAM ¹³² , 4C ^{112 363} , pOR: 2.41 (95% CI [2.01, 2.89]) ⁷¹	Included
PRESENTING SIGNS & SYMPTOMS		
Abdominal pain and/or distention	pOR: 1.58 (95% CI [1.12, 2.22]) ⁷¹	Included
Anorexia, nausea, or vomiting	pOR for anorexia: 1.61 (95% CI [1.26, 2.06]) ⁷¹ ; pOR for vomiting: 1.52 (95% CI [1.11, 2.10]) ⁷¹	Included
Anosmia	No evidence identified	Excluded due to lack of evidence
Chest pain or tightness	pOR for chest tightness: 1.62 (95% CI [1.11, 2.37]) ⁷¹ ; pOR for chest pain: 1.55 (95% CI [0.80, 3.01]) ⁷¹	Included
Convulsions	No evidence identified	Excluded due to lack of evidence
Cough	A-DROP ¹¹⁵ , pOR: 1.08 (95% CI [0.96, 1.23]) ⁷¹	Included
Diarrhoea	pOR: 1.10 (95% CI [0.95, 1.27]) ⁷¹	Included
Fatigue	pOR: 1.22 (95% CI [1.02, 1.45]) ⁷¹	Included
Fever	pOR: 1.22 (95% CI [1.08, 1.38]) ⁷¹	Included
Headache	No evidence identified	Excluded due to lack of evidence
Internal bleeding	COVID-GRAM ¹³² , pOR for haemoptysis: 1.51 (95% CI [0.82, 2.78]) ⁷¹	Included
Myalgia	No evidence identified	Excluded due to lack of evidence
Shortness of breath	COVID-GRAM ¹³² , pOR: 2.78 (95% CI [2.24, 3.46]) ⁷¹	Included
Sore throat	No evidence identified	Excluded due to lack of evidence
VITAL SIGNS		
Glasgow Coma Scale	APACHE II ²⁷⁴ , NEWS2 ⁹⁴ , PSI ¹¹⁶ , qSOFA ^{112 237 363} , 4C ^{112 363}	Included
Heart rate (beats/min)	APACHE II ²⁷⁴ , NEWS ^{112 237 363} , NEWS2 ⁹⁴ , PSI ¹¹⁶ , SIRS ²⁴⁶ , SMART-COP ³⁶⁵	Included

Peripheral oxygen saturation	A-DROP ¹¹⁵ , BCRSS ^{12,13} , NEWS ^{112 237 363} , NEWS2 ⁹⁴ , qCSI ¹⁶⁵ , 4C ^{112 363}	Included
Systolic blood pressure (mmHg)	CURB-65 ^{116 363} , NEWS ^{112 237 363} , NEWS2 ⁹⁴ , PSI ¹¹⁶ , qSOFA ^{5,8,11} , SMART-COP ³⁶⁵	Included
Respiratory rate (breaths/min)	APACHE II ²⁷⁴ , BCRSS ^{177 366} , CURB65 ^{116 363} , NEWS ^{112 237 363} , NEWS2 ⁹⁴ , PSI ¹¹⁶ , qCSI ¹⁶⁵ , qSOFA ^{112 237 363} , SIRS ²⁴⁶ , SMART-COP ³⁶⁵ , 4C ^{112 363}	Included
Temperature (°C)	APACHE II ²⁷⁴ , NEWS ^{112 237 363} , NEWS2 ⁹⁴ , PSI ¹¹⁶ , SIRS ²⁴⁶	Excluded - excessive missingness in derivation dataset (86.7% missing)

Appendix 4.6: Variable selection using generalised additive models.

Variable	Model for settings <i>with</i> access to pulse oximetry					Model for settings <i>without</i> access to pulse oximetry				
	Deviance explained (%)	Deviance explained (%)	Deviance explained (%)	Deviance explained (%)	Deviance explained (%)	Deviance explained (%)	Reduction in deviance explained on removal from full model (%)	R ²	Area under receiver operator curve	Inclusion in final model
ALL CANDIDATE VARIABLES	45	35.9	35.9	35.9	35.9	35.9	-	0.471	0.879	
Male sex at birth	44.3	34.7	34.7	34.7	34.7	34.7	0.7	0.466	0.877	Include
Age (years)	42.8	32.8	32.8	32.8	32.8	32.8	2.2	0.45	0.869	Include
Number of comorbidities*	43.5	34.4	34.4	34.4	34.4	34.4	1.5	0.456	0.873	Include
Current or former smoker	44.9	35.9	35.9	35.9	35.9	35.9	0.1	0.472	0.879	Exclude
Abdominal pain and/or distention	44.6	35.8	35.8	35.8	35.8	35.8	0.4	0.468	0.877	Exclude
Anorexia, nausea, and/or vomiting	44.6	35.8	35.8	35.8	35.8	35.8	0.4	0.468	0.877	Exclude
Chest pain or tightness	44.7	35.8	35.8	35.8	35.8	35.8	0.3	0.469	0.878	Exclude
Cough	44.6	35.7	35.7	35.7	35.7	35.7	0.4	0.469	0.876	Exclude
Diarrhoea	44.6	35.8	35.8	35.8	35.8	35.8	0.4	0.468	0.877	Exclude
Fatigue	44.7	35.9	35.9	35.9	35.9	35.9	0.3	0.471	0.878	Exclude
Internal bleeding**	44.9	35.9	35.9	35.9	35.9	35.9	0.1	0.473	0.879	Exclude
Shortness of breath	44.8	35.7	35.7	35.7	35.7	35.7	0.2	0.469	0.879	Exclude
Glasgow Coma Scale score	40.8	30.7	30.7	30.7	30.7	30.7	4.2	0.439	0.861	Include
Heart rate (beat/min)	44.6	33.9	33.9	33.9	33.9	33.9	0.4	0.466	0.876	Exclude
Systolic blood pressure (mmHg)	42.2	34.6	34.6	34.6	34.6	34.6	2.8	0.446	0.869	Include
Respiratory rate (breaths/min)	39.9	26.7	26.7	26.7	26.7	26.7	5.1	0.419	0.856	Include
Peripheral oxygen saturation (%)***	36	-	-	-	-	-	9	0.382	0.839	Include
FINAL MODEL	42.4	34.2	34.2	34.2	34.2	34.2	2.6	0.461	0.868	-

*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.

**Internal bleeding includes one or more of the following: gastrointestinal bleeding, haematuria, or haemoptysis.

***Peripheral oxygen saturation obtained on room air.

Appendix 4.7: Penalised regression coefficients from LASSO regression.

Variable	Level	Model for settings <i>with</i> access to pulse oximetry		Model for settings <i>without</i> access to pulse oximetry	
		Penalised coefficient	Penalised coefficient	Penalised coefficient	Penalised coefficient
Intercept	-	-0.157	-0.354	-0.354	-0.157
Sex at birth	Male	0.117	0.143	0.143	0.117
Age (years)	≥65	0.113	0.139	0.139	0.113
No. of comorbidities*	1	0.003	0.004	0.004	0.003
	≥2	0.088	0.098	0.098	0.088
Glasgow Coma Scale score	<15	0.233	0.276	0.276	0.233
Heart rate (beats/min)	>90	-	0.079	0.079	-
Systolic blood pressure (mmHg)	<100	0.112	0.238	0.238	0.112
Respiratory rate (breaths/min)	20-29	0.069	0.087	0.087	0.069
	≥30	0.076	0.092	0.092	0.076
Peripheral oxygen saturation (%)**	<92	0.304	-	-	0.304

*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.

**Peripheral oxygen saturation obtained on room air.

Appendix 5.1: Co-author declarations for “*Validation of a contextually appropriate COVID-19 mortality scale for low-resource settings.*”

Declaration by co-authors

Pigoga J, Omer YO, Wallis LA. Validation of a contextually-appropriate COVID-19 mortality scale for low-resource settings. (Submitted and under review with Annals of Global Health)

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	80%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Yasein Omer	Drafted manuscript, and provided critical review of final article.
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.

The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate’s contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according to these criteria.

Co- Author Name Yasein Omer



Co-Author Signature
Date 12/6/21

Declaration by co-authors

Pigoga J, Omer YO, Wallis LA. Validation of a contextually-appropriate COVID-19 mortality scale for low-resource settings. (Submitted and under review with Annals of Global Health)

Nature of contribution	Extent of contribution (%)
The candidate was the primary author and responsible for study design, data searching, screening, and data extraction and meta-analysis. The candidate co-wrote all drafts of the manuscript while under the supervision of the co-authors. The candidate accepts overall responsibility for the publication.	80%

The following co-authors contributed to the work and the nature of their contribution is provided below.

Name	Nature of contribution
Yasein Omer	Drafted manuscript, and provided critical review of final article.
Lee Wallis	Contributed to concept and study design. Provided critical review and contributed to the final article.

The undersigned hereby certify that:

- (1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
- (2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
- (3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication; and
- (4) There are no other authors of the publication according these criteria.

Co- Author Name Lee A Wallis

Co-Author Signature

Date 12/6/21



Appendix 5.2: University of Cape Town study proposal (FHS015).

**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:

A handwritten signature in black ink, appearing to be 'Yasein Omer', written in a cursive style.

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.

We are currently seeking HREC approval for study three. Study two was previously approved (HREC ref: 450/2020).

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3. INTRODUCTION

3.2 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 deaths^{1 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.⁴ Mortality has varied across settings, but current data suggest a variable case fatality rate ranging from 0.5% to 4.5%.⁵⁻⁸

As COVID-19 spreads, healthcare systems worldwide are being strained.^{9 10} Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.¹¹ 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.^{9 10} It is increasingly likely that the countries with the most limited capacity to respond will be affected on a large scale.¹² Early recognition, resuscitation and referral have proven key to effective responses, yielding lower mortality.¹¹ 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.^{13 14} 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.¹⁵ 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.^{15 16} 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.¹⁷ High burdens of data entry seen in many

tools can lead to increased time-to-decision making and frequent missing data points.¹⁸⁻²⁰ Some tools also involve additional investigations, including blood tests and imaging, that have very limited availability in LRS.^{15 21-23}

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.

3.3 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-2.²⁴ 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.

3.4 Aim and objectives

This MSc aims to 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. Derive the SST using data from a LRS (study two, not part of this MSc).
3. Validate the SST in the African setting using real-world data (study three).

We are currently seeking HREC approval for study three. Study two was previously approved (HREC ref: 450/2020).

4 METHODS

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

4.1.1 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.

4.1.2 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.^{25 26} 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.²⁵ 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.²⁵ 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.

4.1.3 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.

4.1.4 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%.²⁷ 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.

4.1.5 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.

4.1.6 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.^{25 26} As previously mentioned, while clinical vignettes are often considered a better standard for triage tool validation^{25 26}, 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-triage²⁸ - AUROC for overall prognostic accuracy²⁹
Comparison of SST performance characteristics across sites and countries	- Pearson's χ^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) ²⁸.

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

4.1.7 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.

4.1.8 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.

4.1.9 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 study three.

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	X	X	X					
Study three								
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 A: Ethical approval for use of Sudanese data from the Khartoum State MOH.

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

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 5.3: Ethical approvals for “Validation of a contextually appropriate COVID-19 mortality scale for low-resource settings.”

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

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

Dear Professor Blockman:

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

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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 5.4: 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 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

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