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Prim, Brent Tyler Aloysius

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COVID-19: An Evaluation of Predictive Scoring Systems in South Africa

Brent Tyler Aloysius Prim

A Research Report Submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2023

I. Dedication

To Jen and Astrid for their support and patience as time keeps moving on.

To my brothers, Sherwin and Lyle, for being what brothers should be.

To my mother, Gail Walters, for providing me with the tools.

To Jarrod Zamparini and Farzahna Mohamed

– How you put up with me is a mystery

I am truly grateful.

II. Permissions

Permission to conduct this study was obtained from Prof. A. Mahomed (Head of Department, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital), Charlotte Maxeke Johannesburg Academic Hospital Research Committee and the Medical Human Research Ethics Committee of the University of the Witwatersrand [M220116].

III. Acknowledgements

Guidance from the following mentors in the writing of this research report is thankfully acknowledged.

Dr Farzahna Mohamed

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Mrs Beza Eshetu Yirdaw

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1. Chapter 1: Protocol and Literature review

1.1 Background

1.2 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belonging to the genus of beta coronaviruses, which causes coronavirus disease 2019 (COVID-19) has resulted in a global health pandemic. More than 100 million cases worldwide have been reported with the cumulative number of reported cases in South Africa reaching over 2.8 million affected individuals as of September 2021 [1,2]. These cases range from asymptomatic viral infection to severe illness, requiring hospitalisation, and death. The overall burden is likely to increase over time and is potentially further exacerbated as social gatherings recommence during the easing of lockdown restrictions nationally throughout 2021, with potential 'super spreader events' increasing cases [3]. The pandemic has thus prompted the development of scoring systems to evaluate patient severity as they present to healthcare services. These standardised systems, both novel to COVID-19 and established in the setting of acute respiratory illness, predict severity and mortality outcomes in patients with COVID-19 [4–9]. Scoring systems allow healthcare workers to triage patients with severe COVID-19 early on, using physiologic parameters available to healthcare personnel at the bedside and limited special investigations, to offer the most appropriate level of care [8–10]. In the absence of COVID-19, the NEWS2 score is highly predictive of mortality in sepsis, and an aggregate score of five is associated with a 23% risk of mortality [11]. The NEWS2 score incorporates six physiological parameters for assessment of illness severity: respiratory rate, pulse rate, oxygen saturation, systolic blood pressure, level of consciousness and temperature. These parameters, as expressed in Supplementary Table 1, are interpreted as an individual threshold parameter or aggregate score to define a clinical risk group and assign an appropriate response level. While the NEWS2 score is directed by physiological parameters, other predictive tools have incorporated patient demographics and biochemical data such as the ISARIC WHO Clinical Characterization Protocol 4C Mortality score (4C Mortality Score) and CURB-65 pneumonia severity score. The 4C Mortality Score uses eight parameters: age, sex at birth, number of comorbidities, respiratory rate, peripheral oxygen saturation on room air, Glasgow Coma Scale score, urea and C-reactive protein observed in Supplementary Table 1. The cumulative 4C score with weighted variables is then stratified into risk groups with the low-risk group, score 0-3, corresponding to a mortality of 1.2% while the very high-risk group, score 15 or greater, corresponding to a mortality rate of 61.5% [12].

The CURB-65 score is a commonly used severity assessment model for stratifying adult patients with community acquired pneumonia (CAP) into treatment groups to predict 30-day mortality based on five parameters: new onset confusion, urea above 7 mmol/L, respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg and age ≥ 65 years observed in Supplementary Table 1 [13]. CURB-65 defines three specific severity grades: non-severe low risk, non-severe moderate risk, and severe with predicted mortality for each grade.

Performance of the above-mentioned scores among patients with COVID-19 admitted across various hospitals, in Northwest England, have shown limited utility in predicting adverse outcomes, with mixed results for their use compared to traditional indications and all scores were poorly predictive for ICU admission [14]. Preliminary data in a multi-hospital cohort using the NEWS2 score for COVID-19 was shown to have greater negative predictive value for early mortality outcomes [14]. While Bradley *et al* described limited utility in predicting critical outcomes in COVID-19, De Socio *et al* compared outcomes of NEWS2 and COVID-GRAM, a predictive scoring system which incorporates radiologic, clinical, and biochemical parameters. In this study a NEWS2 score > 4 had a positive predictive value of 2.9 for critical illness. However, such scoring systems have not been validated in Southern Africa where a larger burden of HIV and Tuberculosis is present among the population. Research validating such scoring systems is needed to reduce mortality and direct healthcare services effectively and equitably in a region with limited resources. Retrospective analysis of the CURB-65 before the pandemic at a South African institution, albeit a modest cohort, highlighted its use in limiting hospital admissions at point of emergency care in CAP [8].

Utility scores have shown benefit in treatment decisions involving high flow nasal canula oxygenation where traditional practices involving early intubation may not be feasible due to limited availability of intensive care services [7]. Further research of the use of these scores in implemented clinical context is required to develop these tools in aiding accurate and rapid patient care [15].

1.3 **Study aims and Objectives**

1.3.1 **Aims**

This study aims to evaluate the utility of international scoring systems for risk stratifying patients with COVID-19 in South Africa.

1.3.2 **Primary objectives**

To evaluate the utility, in predicting clinical severity, of the following scoring systems in South African patients with confirmed COVID-19:

i. NEWS2 score
ii. CURB-65 score
iii. 4C Mortality score

The NEWS2 score was chosen for its widespread use, in COVID-19, across multiple National Health Service (NHS) centres in the United Kingdom [14]. The CURB-65 score has been used in studies predicting clinical severity of CAP in South Africa, while the 4C score is a validated scoring system for use in COVID-19 with integration of biochemical testing [13, 12].

1.4 **Methodology**

1.4.1 **Study design**

Retrospective single-centre observational study.

1.5 **Study setting**

COVID-19 medical wards within Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

1.6 **Study population**

1.6.1 **Inclusion criteria**

Patients with Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) confirmed COVID-19 admitted to the medical wards at CMJAH between 6 March 2020 and 6 September 2020.

1.6.2 **Exclusion criteria**

i. Pregnant patients.
ii. Patients ≤ 18 years of age.

1.7 **Sample size**

The COVID-19 database includes 676 patients admitted during the period above. In order to achieve a 95% confidence level with a 5% margin of error, and accounting for the possibility of missing data to calculate the scores above, the aim is to include at least 245 patients in the final analysis. However, all patients with complete data will be included.

1.8 **Study tools**

The CMJAH COVID-19 database will serve as the primary database. Selective data, as per the attached data collection sheet, will be captured electronically in tabulated format using Microsoft Excel. Data will be provided in a fully anonymised format by the CMJAH COVID-19 Database gatekeeper with no ability for the primary researcher to link any data back to the patients concerned.

1.9 **Statistical analysis**

Data will be exported from the CMJAH COVID-19 database to Microsoft Excel 16.3 (Microsoft Corporation, Redmond, USA) and analysed. Statistical tests will be appropriately chosen depending on the distribution of the data. Continuous variables will be presented as medians with an interquartile range (IQR) and categorical variables as numbers and percentages. The Mann-Whitney test and the Kruskal-Wallis test will be used to compare continuous variables between two groups and 3 groups respectively. The Pearson's chi-square test will be used to analyse categorical data between the groups and if the frequency was ≤5, a Fisher's exact (two-tailed) test will be used. A p-value < 0.05 will be considered statistically significant.

1.10 **Ethical Considerations**

i. Ethical approval will be requested from the University of the Witwatersrand Human Research Ethics Committee (Medical).
ii. Approval to conduct the study will be requested from the CMJAH Research Committee.
iii. Permission from the gatekeeper of the CMJAH COVID-19 Database will be obtained to obtain patient data.
iv. The retrospective nature of the study does not require individual patient consent.
v. No patient identifying details will be provided from the CMJAH COVID-19 database to maintain anonymity.

1.11 **Study strengths**

i. Large sample size

ii. No such study has been done in South Africa thus providing necessary input for future research and healthcare system integration of mortality risk stratification tools in a primarily non-European population.

iii. The sample population is representative of the provincial demographics based on inclusion of all medical adult patients presenting to the hospital with COVID-19.

1.12 **Study Limitations**

i. Observer Bias: Being a retrospective observational study, data collection relies on the accuracy of written records, and it should be anticipated that important data may not be available.

ii. Selection Sampling Bias: The study population predominantly includes patients with moderate to severe COVID-19 that required admission to CMJAH COVID medical ward with a possible low external validity to mild disease.

1.13 **Time frame**

The study will commence on 01 December 2021 pending ethics approval. The expected duration is approximately 6 to 10 months.

The following Gantt chart shows the timeline of the study:

	March 2021	April 2021	May 2021	June 2021	July 2021	August 2021	September 2021	October 2021	November 2021	December 2021	January 2022	February 2022	March 2022
Literature review													
Protocol preparation													
Protocol Assessment													

Ethics application													
Data Collection													
Data Analysis													
Writing up paper													
Publication applications													

1.14 **Funding**

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WHO's International Clinical Trial Registry Platform
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Putting research into context

- All research papers (including systematic reviews/meta-analyses) submitted to any journal in *The Lancet* family must include a panel putting their research into context with previous work in the format outlined below (see *Lancet* 2014; **384**: 2176–77, for the original rationale). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy
- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.

Data sharing

From September 21, 2020, all submitted research Articles must contain a data sharing statement, to be included at the end of the manuscript. Data sharing statements must include:
- Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others ("undecided" is not an acceptable answer);
- What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set);
- Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form);
- When these data will be available (beginning and end date, or "with publication", as applicable);
- Where the data will be made available (including complete URLs or email addresses if relevant);
- By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism – eg, with or without investigator support, after approval of a proposal, with a signed data access agreement - or any additional restrictions).

See table for examples. Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. Mendeley Data is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.

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Clinical Pictures

- The ideal Clinical Picture provides visual information that will be useful to other clinicians. *The Lancet* rarely publishes pictures that just illustrate an extreme example of a medical condition.
- Clinical Pictures should be interesting, educational, and respectful of the patient.
- Authors must obtain signed informed consent for publication in print and electronically (see Patient and other consents). Do not use "blackout" bars or similar devices to anonymise patients: if you have taken consent appropriately, masking is not necessary.
- Use no more than 300 words, with no references or figures. The text should include a brief patient history and put the high

quality image in context, explaining what the image shows, why it is of interest to the general reader, and the outcome of the patient.
- The authors must have been involved in the care of the patient.
- Clinical Pictures will be prioritised around the 136 diseases included in The *Lancet* Clinic, which is based on Global Burden of Disease data and clinical need.
- Please also write a short single best answer question of approximately 20 words with four short answers to create an accompanying Picture Quiz. These questions should be appropriate for a non-specialist medical doctor within the first five years of practice. Clinical Pictures chosen for publication will be peer-reviewed, receive a DOI, and be submitted to the National Library of Medicine for PubMed listing. All Clinical Pictures are included in *The Lancet*'s table of contents and published online; a selection are also published in print.

Blue section (Comment, World Report, Perspectives, Correspondence, etc)

Editorial

Editorials are the voice of *The Lancet*, and are written in-house by the journal's editorial-writing team and signed "The Lancet"

Comment

- Most Comments are commissioned, but spontaneous Comments are welcome on a paper or other report or event within the past month or so, or in the near future
- Comments should be about 700 words and ten references
- The place to respond to something we have published is in our **Correspondence** section
- See **Conflict of Interest** guidelines for Comments

World Report

- *The Lancet* has a function as an international newspaper covering news about science, medicine, policy issues, and people
- Most of the writers of World Report articles are professional journalists, but an important event in your country that might be of wider interest can be brought to the attention of our World Report editors via editorial@lancet.com

Perspectives

- Reviews of books and other media, Lifelines, and art of medicine pieces are often commissioned, but suggestions for contributions are welcome via editorial@lancet.com

Obituaries

- Obituaries are written by our team of professional journalists, but we invite suggestions from readers for people whom we should feature—remarkable individuals who are internationally renowned for their contributions to medicine
- Please submit such suggestions within 3 weeks of an individual's death via editorial@lancet.com

Correspondence

- We welcome correspondence on content published in *The Lancet* or on other topics of interest to our readers
- Letters for publication in the print journal must reach us within 2 weeks of publication of the original item and should be no longer than 250 words
- Letters of general interest, unlinked to items published in the journal, can be up to 400 words long
- Correspondence letters are not usually peer reviewed (we rarely publish original research in this section), but the journal might invite replies from the authors of the original publication, or pass on letters to these authors
- Only one table or figure is permitted, and there should be no more than five references and five authors
- All accepted letters are edited, and proofs will be sent out to authors before publication
- Some letters might be chosen for online-only publication

Adverse drug reactions

- Reports of adverse drug reactions are peer reviewed and those we accept are published in the Correspondence section
- Length must not exceed 800 words, with only one table or figure, and no more than five references. No more than five authors are permitted

Department of Error

- Any substantial error in any article published in *The Lancet* should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight
- *The Lancet* journals have a policy for types of errors that we do and do not correct. We will always correct any error affecting a non-proprietary drug name, dose, or unit, any numerical error in the results, or any factual error in interpretation of results. Authorship format changes after publication to facilitate a different visualisation in MEDLINE/PubMed will not be done.

Green section (Seminars, Reviews, Therapeutics, Series, Viewpoints, etc)

Commissioned Seminars, Reviews, Therapeutics, and Series

- Seminars are disease-oriented clinically focused overviews for the generalist, covering epidemiology, pathophysiology, diagnosis, management, and prevention; whereas Reviews have a narrower remit for a more specialised audience. We aim to provide comprehensive balanced Review papers for clinicians and researchers on topics that we judge to be of widespread interest
- Therapeutics papers are up-to-date evidence-based reviews for clinicians on new and up-and-coming therapeutic options for diseases. The primary focus is on new drugs in a specific disease, but broad-based reviews on a drug class or on new non-pharmacological options will be commissioned; see *Lancet* 2019; **394:** 360
- Complete transparency about the choice of material included is important to any Review paper. Therefore, all Seminars and Reviews, Therapeutics papers, and some Series, should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers

The Lancet Clinic
http://www.thelancet.com/clinical/diseases

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should be comprehensive, we encourage citation of publications in non-English languages. An example is shown below:

Search strategy and selection criteria

Data for this Review were identified by searches of MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms "sentinel node", "breast cancer", and "axilla". Abstracts and reports from meetings were included only when they related directly to previously published work. Only articles published in English between 1995 and 2019 were included.

Formatting guidelines for text, tables, and figures
Guidelines on formatting of text, tables, and figures can be found at **https://www.thelancet.com/pb/assets/raw/Lancet//authors/artwork-guidelines.pdf**

- Seminars should be no more than 5000 words with a maximum of 140 references, and Reviews should be no more than 4500 words, with a maximum of 100 references. Therapeutics papers should be 3500-4500 words, with 5-6 figures, tables, or panels, and a maximum of 80 references. A 150 word unstructured summary should be included. These papers should include about five illustrations to aid the reader

Hypotheses

- A hypothesis paper describes a substantial jump in thinking that is testable but not so easily testable that readers will wonder why you have not already done it. New data are not part of a hypothesis, but you must include a section on how to test your idea
- Sharing a new idea takes courage and concision. If you cannot express your line of thought in 1500 words, 20 references, and a 150 word unstructured summary, it is not a hypothesis

Other departments

- Much of *The Lancet's* role in encouraging debate and opinion takes place in sections such as Public Health, Viewpoint, Essay, Reportage, and the Departments of Medical History, Ethics, Medicine and Art, and Literature and Medicine. 1500 words and 20 references are our general guidelines for papers in these sections

Commissions

- Topics for *The Lancet* Commissions are selected by our editors, who work with academic partners to identify the most pressing issues in science, medicine, and global health with the aim of producing recommendations to change public policy or improve practice. Projects usually last 2–3 years, and author groups will represent a broad range of international expertise. All *Lancet* Commissions are academic publications and are subject to the same rigorous peer review process as all other research papers published in our journals. *The Lancet* does not provide direct financial support to Commissioners for the research or writing of the reports. Funding is sought directly by authors, with oversight from our editors.

Formatting guidelines

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- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated with email and telephone details.

Formatting of text

- Type a single space at the end of each sentence
- Do not use bold face for emphasis within text
- We use a comma before the final "and" or "or" in a list of items
- Type decimal points midline (ie, 23·4, not 23.4). To create a midline decimal on a PC: hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables
- Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph
- Do not use the automated features of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Please use page numbering
- Guidelines on formatting tables are available in the artwork guidelines

References

- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example:
  "…as reported by Saito and colleagues.[15]"
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC: hold down CTRL key and minus sign on the number pad, or on a Mac: ALT hyphen
- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text
- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule or "long" hyphen):
  "…15[tab]Saito N, Ebara S, Ohotsuka K, Kumeta J, Takaoka K. Natural history of scoliosis in spastic cerebral palsy. *Lancet* 1998; **351:** 1687–[en rule]92."
- Give any subpart to the title of the article. Journal names are abbreviated in their standard form as in Index Medicus
- If there are six authors or fewer, give all six in the form:

  surname space initials comma

- If there are seven or more give the first three in the same way, followed by et al
- For a book, give any editors and the publisher, the city of publication, and year of publication
- For a chapter or section of a book, also give the authors and title of the section, and the page numbers
- For online material, please cite the URL, together with the date you accessed the website

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- Online journal articles can be cited using the DOI number
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- Do not put references in the Summary or Research in context and Search strategy and selection criteria panels
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We have different criteria for photographic and illustrative files, the following notes are a summary of our ideal requirements, but a detailed description is in the artwork guidelines

- For images (photographs or photographic images) that are used as part of illustration or image composite figures we require a file that is no less than 300 dpi when set at its final printed size. Ideal file formats are TIF or JPG
- For trial profiles, study profiles, and CONSORT diagrams, please supply as an editable flow diagram in Word (.doc) or PowerPoint (.ppt) file
- For illustrations (all non-photographic line-work and general drawing) we require editable vector files that contain selectable geometry and fonts (editable text). The editability of files depends on the package they were created in, but as a rule we would prefer to receive any of the following: Adobe Illustrator (.ai) file; Adobe Illustrator or generic .eps files exported from a graphics program; vector-based PDF, PowerPoint, or Word file; or SVG file. If authors are unable to supply files in any these formats, our in-house illustrators can offer guidance on whether it is more economical to export or convert the file into another format, or to redraw from scratch. When files are exported to eps files, we would prefer text to be exported "as text" rather than "as objects", which is especially crucial for files such as forest plots in which there is a lot of text
- If your figures are annotated, please supply two copies of each of these figures as separate files (one annotated copy and one non-annotated and editable copy). Our in-house illustrators will annotate according to journal style using the annotated figures as a guide. For multi-part figures, please supply the individual parts as well as a combined version to be used as a guide for our illustrators to recreate the files
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Guidelines for supplementary material

All material should be submitted as one PDF (with a table of contents and numbered pages) with the paper and will be peer reviewed. Material will be published at the discretion of *The Lancet* journals' editors. For clinical trials, we encourage authors to include a copy of the study protocol. All material should be provided in English.

Text

- Main heading for the web extra material should be in 12 point Times New Roman font **BOLD**
- Text should be in 10 point Times New Roman font, single spaced
- Headings should be in 10 point **BOLD**

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- Main table heading should be in 10 point Times New Roman font **BOLD**
- Legends should be in 10 point, single spaced
- Tables should be in 8 point Times New Roman font, single spaced
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Data

- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- p values should be given to two significant figures, unless p<0·0001

Drug names

- Recommended international non-proprietary name (rINN) is required
- We encourage use of neuroscience-based nomenclature for psychotropic drugs

Drug names
For more on neuroscience-based nomenclature see **http://www.thelancet.com/pdfs/journals/lanpsy/PIIS2215-0366(17)30098-6.pdf**

References

- Vancouver style—eg,
  —Smith A, Jones B, Clements S. Clinical transplantation of tissue-engineered airway. *Lancet* 2008; **372:** 1201–09.
  —Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine. London: *Elsevier,* 2008: 230–47.
- Numbered in order of mention in Webappendix and numbered separately from references in the full paper

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- All images must have a minimum resolution of 300 dpi, width 107 mm
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- The paper to which the audio or video clip relates should be mentioned in the recording
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- Audio material submitted as an mp3 file, no larger than 50 Mb
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Audio
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- All video files can be submitted alongside your article in EM

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How *The Lancet* handles your paper

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- Receipt of your paper will be acknowledged by an email containing a reference number, which should be used in all future communications

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- All Seminars, Series, Reviews, Therapeutics papers, and other non-research material that we are interested in publishing will be checked by editors using CrossCheck (see *Lancet* 2011; **377**: 281–82). We expect that such papers are written in a way that

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- *The Lancet* operates a single-anonymised review process
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3 Chapter 3: Manuscript

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COVID-19: An Evaluation of Predictive Scoring Systems in South Africa

Prim BTA.[1], Zamparini J.[2]*, Mohamed F.[3]*

A Submission to *The Lancet* Journal

[1]Dr Brent Tyler Aloysius Prim, MBBch (WITS), Department of Internal Medicine, University of Witwatersrand, Johannesburg, 2193, South Africa. Email: brent.bta.prim@gmail.com. Telephone: +27(0)76-393-4618.

[2]Dr Jarrod Zamparini, FCP(SA), Department of Internal Medicine, University of Witwatersrand, Johannesburg, 2193, South Africa.

[3]Dr Farzahna Mohamed, Cert. Endo. & Metab. (SA), Department of Internal Medicine, Division of Endocrinology and Metabolism, University of Witwatersrand, Johannesburg, 2193, South Africa.

*Joint senior authors

Correspondence to: Dr Brent Tyler Aloysius Prim, **brent.bta.prim@gmail.com**

3.1 **Abstract**

Background | The Coronavirus Disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2, has resulted in more than 700 million cases worldwide. Sepsis and pneumonia severity scores assist in risk assessment of critical outcomes in patients with COVID-19. This allows healthcare workers to triage patients, by using clinical parameters and limited special investigations, thus offering the most appropriate level of care.

Methods | A retrospective cohort study of 605 adult patients hospitalised with moderate to severe COVID-19, at a tertiary state hospital in South Africa. Evaluating the utility of the CURB65, NEWS2 and ISARIC-4C Mortality Score, in predicting critical outcomes, using clinical characteristics on admission. Outcomes included in-hospital mortality, invasive mechanical ventilation, and intensive care unit admission (ICU). Performance of severity scores and risk factors was assessed by area under the receiver operator characteristics (AUROC) analysis and logistic regression.

Findings | A total of 605 records were used, 129 (21%) non-survivors, 101 (17%) ICU admissions and 77 (13%) requiring invasive ventilation. Greater odds of mortality was associated with moderate and severe risk groups of the CURB65, ISARIC-4C and NEWS2 score. Mortality AUROC curve analysis for the CURB65 score was 0·76 (95% CI: 0·71–0·8), 0·77 (95% CI: 0·73–0·81) for the ISARIC-4C and 0·77 (95% CI: 0·73–0·82) for the NEWS2 score. The CURB65 score had a sensitivity of 86% with 12·8% mortality, the ISARIC-4C score a sensitivity of 87·6% with 8% mortality and the NEWS2 score a sensitivity of 92·2% with 8·6% mortality.

Interpretation | In 605 hospitalised patients with moderate to severe COVID-19, predominantly infected by the ancestral strain, good performance of the NEWS2 and ISARIC-4C score in predicting in-hospital mortality was noted. The CURB65 score had a high mortality rate in its low-risk group suggesting unexplained risk factors, not accounted for in the score, thus limiting its utility in the South African setting.

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3.2 **Contributions**

[1]Prim BTA: conceptualisation, data curation, investigation, methodology, visualisation, formal analysis, writing–original draft, writing–review and editing.

[2]Zamparini J: supervision, methodology, conceptualisation, project administration, writing–review and editing.

[3]Mohamed F: supervision, methodology, conceptualisation, visualisation, project administration, writing–review and editing.

3.3 **Background**

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

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

In one study these scores showed limited utility in predicting adverse outcomes among patients with COVID-19 as all scores were poorly predictive for ICU admission.[13] Preliminary data in a multi-hospital cohort using the NEWS2 score for COVID-19 was shown to have a greater negative predictive value for early mortality outcomes.[13] Whilst the above study described limited utility in predicting critical outcomes in COVID-19, a subsequent study comparing outcomes of the NEWS2 score and COVID-GRAM, showed that a NEWS2 score of four had a positive likelihood ratio of 2·9 for critical illness.[14] A retrospective analysis of the CURB-65 score prior to the pandemic at a South

African institution, albeit a modest cohort, highlighted its use in reducing hospital admissions at point of emergency care in community acquired pneumonia.[6] Utility scores have shown benefit in treatment decisions involving high flow nasal cannula oxygenation where traditional practices involving early intubation may not be feasible due to limited availability of intensive care services.[5] Research validating these scoring systems is needed to reduce mortality and direct healthcare services effectively and equitably in a region with limited resources. To our knowledge, no studies in South Africa, have compared the effectiveness of these scoring systems in predicting outcomes in patients with moderate to severe COVID-19. Therefore, the aim of our study was to evaluate the utility of severity scoring systems for risk stratifying patients with COVID-19 in a low-middle income country (LMIC) setting.

3.4 **Methods**

3.4.1 **Study design and participants**

The study was a retrospective single centre cohort study. It included 605 adults admitted with moderate to severe COVID-19, during the period of March 2020 to September 2020, at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary state hospital in South Africa. The cohort included all adult inpatients diagnosed with COVID-19 by laboratory confirmed positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR), using oropharyngeal and naso-pharyngeal swabs, with the predominant variant of concern (VOC) being the ancestral variant, Asp614Gly mutation, according to published data by the National Institute of Communicable Diseases (NICD).[15] Exclusions of analysis were age <18 years, pregnancy, and outpatient observation. Approval for the study was obtained from the University of the Witwatersrand Medical Human Research Ethics Committee [M220116].

3.4.2 **Study data**

All relevant clinical data was anonymously extracted from a password protected electronic database and transferred to a local secure data research application. Demographic and clinical data necessary for calculating the NEWS2, ISARIC-4C and CURB-65 scores were documented. Parameters of each score are available in Supplementary Table 1. The NEWS2 score was calculated based on respiratory rate (breaths/min), peripheral oxygen saturation, systolic blood pressure (mmHg), pulse rate (beats/min), mental state, temperature (Celsius) and supplemental oxygen use.[9] The ISARIC-4C score

was based on age (years), gender, number of comorbidities, respiratory rate (breaths/min), peripheral oxygen saturation, Glasgow coma scale, urea (mmol/L) and C-reactive protein (mg/L).[10] Finally, the CURB-65 score which utilises age (years), mental state, urea (mmol/L), respiratory rate (breaths/min), systolic and diastolic blood pressure was calculated.[11] Demographic and clinical variables in the descriptive statistics were categorised based on scoring system factors. However, continuous variables with a low cell frequency were treated as continuous or re-categorized during inferential analysis. Based on the aggregate score, patients were classified into three risk groups: low, medium, and high risk, with an additional very-high risk category in the ISARIC-4C mortality score.

3.4.3 **Statistical analysis**

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

3.4.4 **Outcome measures**

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

3.5 **Findings**

3.5.1 **Baseline characteristics of CURB65, NEWS2 and ISARIC-4C score risk groups**

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

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

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

3.5.2 **Logistic regression analysis**

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

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

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

and high-risk temperature categories were combined for accuracy of odds calculation for the NEWS2 score model (Table 2).

3.5.3 **Area Under Receiver Operator Characteristics (AUROC) Curve analysis**

Performance in predicting in-hospital mortality for the CURB65, NEWS2 and ISARIC-4C score in Figure 2 shows an AUROC of 0·76 (0·71–0·80, p<0·001) for the CURB65 score, 0·77 (0·73–0·82, p<0·001) for the NEWS2 score and 0·77 (0·73–0·81, p<0·001) for the ISARIC-4C score based on a univariate classifier. The CURB65 score showed a sensitivity of 86% with a 12·8% mortality rate at a threshold of one whereas the NEWS2 score had a sensitivity of 92·2% with an 8·6% mortality rate at a threshold of six and the ISARIC-4C score a sensitivity of 87·6% with an 8% mortality rate at a threshold of seven (Table 3). In comparison multivariable models with the aforementioned amended regression parameters demonstrated AUROC values greater than 80% for the NEWS2 score (AUROC: 0·81) and ISARIC-4C score (AUROC: 0·83) whereas the CURB65 score achieved an AUROC of 0·77.

3.6 **Discussion**

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

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

be attributed to sparse event data in the very-high risk group, however, it is possible that the ISARIC-4C score is an overall poor predictor of ICU admission, as demonstrated by Martin et al where an AUROC of 0·62 was observed.[26]

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

In-hospital mortality predictions of the CURB65, ISARIC-4C and NEWS2 score by ROC observed comparable performance using AUC for aggregate scores. The NEWS2 score was the most sensitive predictor, at publication thresholds of five for urgent response, followed by the ISARIC-4C score. Mortality rates of the NEWS2 and ISARIC-4C score were approximately 8%, whereas the CURB65 score at a low-risk threshold was 12·8%. Recommendations for community acquired pneumonia, in literature prior to the pandemic, advised clinicians to consider home based care in low-risk groups of

the CURB65 score. These recommendations were based on observed mortality rates below 4%, however, a higher mortality rate in the low risk group in our study limits concession to such recommendations.[6,11,12] A number of studies have reported an increase in mortality risk in the low risk group of the CURB65 score with Bradley et al hypothesising endothelialitis, microthrombi and other SARS-CoV-2 cytokine mediated events as translatable measures by comparing models incorporating D-dimer and procalcitonin levels to the CURB-65 score and Pneumonia Severity Index (PSI).[28] Unfortunately, these markers were not associated with an improvement in critical outcome predictions and consistently observed a higher mortality among SARS-CoV-2 pneumonia patients. Richards et al, in a placebo arm study of the PROWESS trial prior to COVID-19, observed a similar mortality risk in non-SARS-CoV-2 pneumonia for the CURB65 score.[29] Thus far, no clinical prediction tools are present in the literature that translate biologic cytokine events to measurable prognostic mortality tools.

The limitations we identified in our study included a small sample size resulting in low cell frequency requiring the amendment of factors inherent to both the ISARIC-4C and NEWS2 score, especially in older age groups. The study was also conducted at a single centre in a LMIC, which may limit generalisability of findings with different resources. Predictions of end-point outcomes using first assessment data compared to dynamic changes during hospital stay is considered an inherent limitation of point estimation. In view of the heterogeneity of disease presentation associated with variations in COVID-19 mutations, data may not be generalisable with each wave. Consistency of mortality data in our study with national health surveillance data suggests that our findings may be representative of our broader population thus strengthening recommendations in the LMIC setting.

3.7 **Interpretation**

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

clinicians. However, therapeutic decisions in clinical practice should ultimately be guided by clinical judgement of healthcare providers.

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

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VIII. Appendices

Table 1. Risk severity grade according to CURB65, ISARIC-4C and NEWS2 score and association with in-hospital mortality, ICU admission and invasive ventilation

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

[a] COR: Crude odds ratio; [b] χ^2

Table 2. Multivariable logistic regression for in-hospital mortality using factors related to the CURB65, ISARIC-4C and NEWS2 score

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

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

Table 3. AUROC of CURB65, ISARIC-4C and NEWS2 scores to predict in-hospital mortality

	AUC	CI (95%)	Threshold	Sensitivity (%)	Specificity (%)	Mortality (%)
CURB65	0·76	0·71-0·8	1	86	50·8	12·8%
ISARIC-4C	0·77	0·73-0·81	7	87·6	49·8	8·0%
NEWS2	0·77	0·73-0·82	6	92·2	44·1	8·6%

AUC: Area Under Curve; CI: Confidence Interval

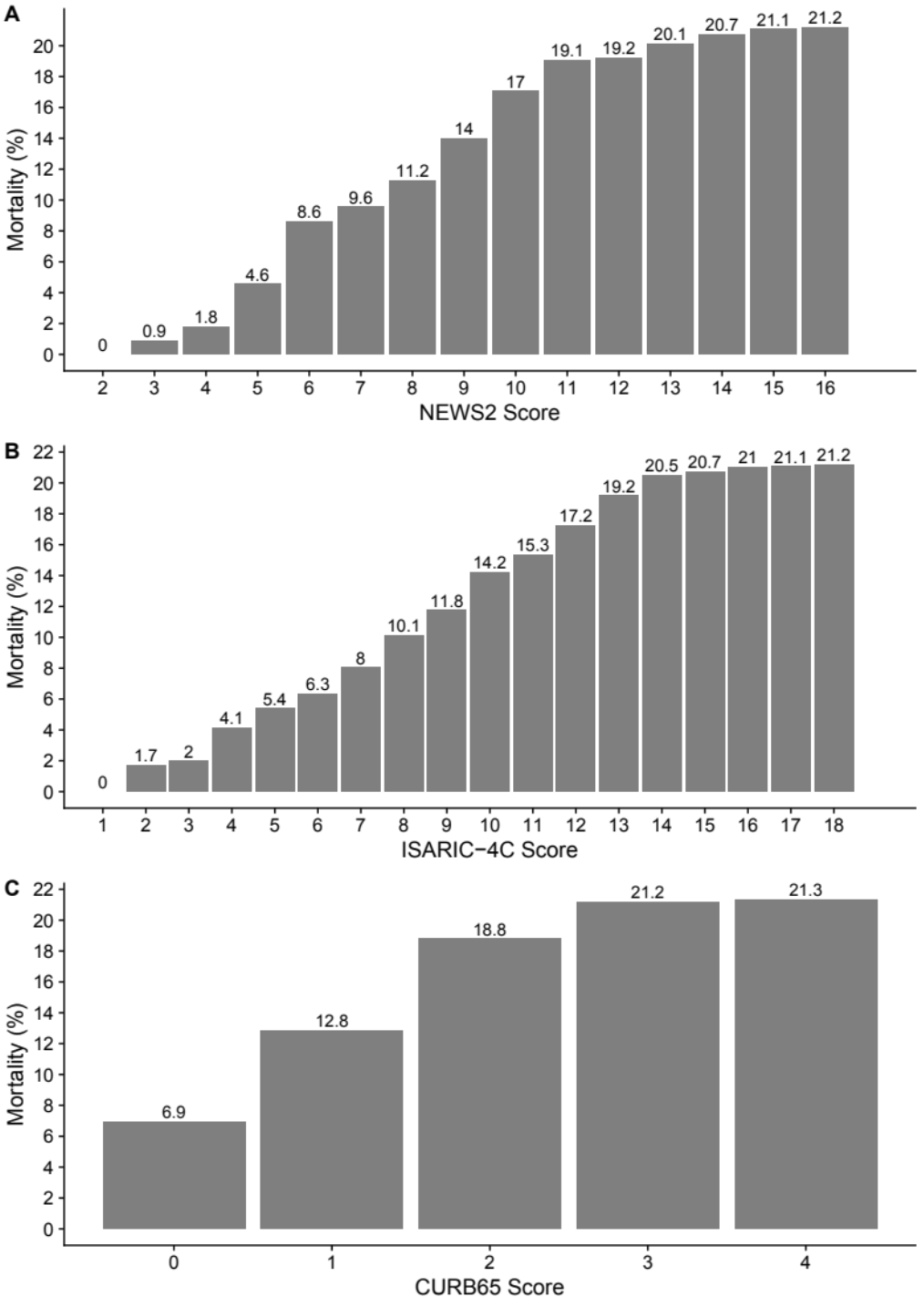

Figure 1. Mortality for various threshold values of (A) NEWS2 score, (B) ISARIC-4C score, (C) CURB65 score.

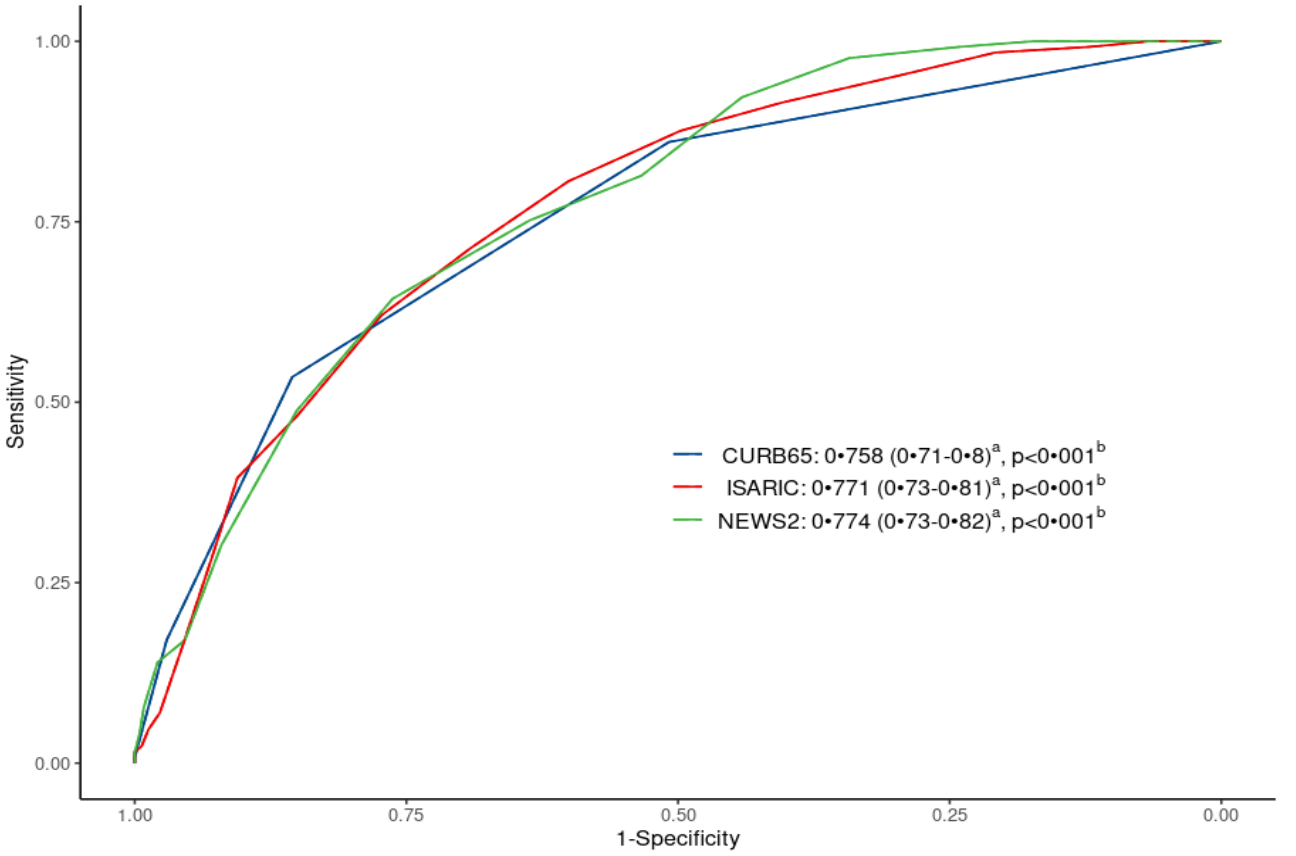

Figure 2. ROC curve showing efficacy of risk scores to predict in-hospital mortality. [a] DeLong method (95% CI); [b] Mann-Whitney-U statistic equivalent

IX. Supplementary Appendix A – Journal

COVID-19: An Evaluation of Predictive Scoring Systems in South Africa

Supplementary Appendix A

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Supplementary Table 1. NEWS2, ISARIC-4C and CURB65 Scoring Systems

CURB65 Score[1]

Parameter	Threshold	Points
Mental status	Confusion	1
Urea (mg/L)	≥ 7·0	1
Respiratory rate (breaths/min)	≥ 30	1
Blood pressure (mmHg)	Systolic ≤ 90 or Diastolic < 60	1
Age (years)	> 65 years	1

Aggregate Score	Risk	Mortality (%)
0 - 1	Low risk	0 – 4
2	Moderate risk	17
≥ 3	Severe risk	26 – 33

ISARIC-4C score[2]

Parameter	0	1	2	3	4	5	6	7
Age (years)	< 50		50-59		60-69		70-79	≥80
Sex at birth	Female	Male						
No. of comorbidities	0	1	≥ 2					
Respiratory rate (breaths/min)	<20	20-29	≥ 30					
SpO2 (%)	≥ 92		<92					
Glasgow coma scale	15		<15					
Urea (mmol/L)	<7	7-14		>14				
C-Reactive protein (mg/L)	<50	50-99	≥ 100					

Aggregate Score	Risk	Mortality (%)
0-3	Low	1.2
4-8	Intermediate	9.9
9-14	High	31.4
≥ 15	Very-high	61.5

NEWS2 score[3]

Parameter	+ 3	+ 2	+ 1	0	+ 1	+ 2	+ 3
Respiratory rate (breaths/min)	≤ 8		9-11	12-20		21-24	≥ 25
Sp02 Scale 1 (%)	≤ 91	92-93	94-95	≥ 96			
Sp02 Scale 2 (%)	≤ 83 (Air)	84-85 (Air)	86-87 (Air)	88-92 or ≥ 93 (Air)	93-94 (oxygen)	95-96 (oxygen)	≥ 97 (oxygen)
Air or Oxygen		Oxygen		Air			
Systolic blood pressure (mmHg)	≤ 90	91-100	101-110	112-219			≥ 220
Pulse (beats/min)	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Mental status				Alert			Confusion
Temperature (ºC)	≤ 35		35·1-36	36·1-38	38·1-39	>39	

Aggregate Score	Risk	Response	Response team
0 - 4	Low	Ward-based response	General management
5 - 6	Medium	Threshold for urgent response	Management of acutely ill patients
≥ 7	High	Urgent or emergency response	Staff with critical care skills.

Supplementary Table 2. Univariate association between in-hospital mortality and CURB65 score risk factors

Risk factor	Survivor n (%)	Non-survivor n (%)	COR[a]	95% CI	P[b]
Age (years)					
< 65	402 (81·9)	89 (18·1)		Reference	**< 0·001**
≥ 65	74 (64·9)	40 (35·1)	2·44	1·56-3·82	
Respiratory rate (breath/min)					
< 30	434 (82·5)	92 (17·5)		Reference	**< 0·001**
≥30	42 (53·2)	37 (46·8)	4·16	2·53-6·82	
Mental status					
Alert	438 (82·5)	93 (17·5)		Reference	**<0·001**
Altered	38 (51·4)	36 (48·6)	4·46	2·68-7·41	
Urea (mmol/L)					
< 7	324 (87·3)	47 (12·7)		Reference	**<0·001**
≥ 7	152 (65·0)	82 (35·0)	3·72	2·47-5·58	
Blood pressure (mmHg)					
SBP ≥ 90 or DBP > 60	469 (79·1)	124 (20·9)		Reference	0·2
SBP < 90 or DBP ≤ 60	7 (58·3)	5 (41·7)	2·70	0·85-8·66	

[a]COR: Crude odds ratio, [b] χ^2

Supplementary Table 3. Univariate association between in-hospital mortality and ISARIC-4C score risk factors

Risk factor	Survived n (%)	Non-survived n (%)	COR[a]	95% CI	P[b]
Age (years)					
< 50	243 (86·5)	38 (13·5)		Reference	
50-59	109 (75·2)	36 (24·8)	2·11	1·27-3·51	
60-69	82 (71·9)	32 (28·1)	2·49	1·46-4·25	**< 0·001**
70-79	36 (65·5)	19 (34·5)	3·38	1·76-6·48	
≥ 80	6 (60·0)	4 (40·0)	4·26	1·15-1·81	
Gender					
Female	239 (82·4)	51 (17·6)		Reference	**0·037**
Male	237 (75·2)	78 (24·8)	1·54	1·04-2·29	
Respiratory rate					
< 20	163 (90·6)	17 (9·4)		Reference	
20-29	271 (78·3)	75 (21·7)	2·65	1·51-4·65	**< 0·001**
≥ 30	42 (53·2)	37 (46·8)	8·45	4·34-16·46	
Urea (mmol/L)					
< 7	320 (87·9)	44 (12·1)		Reference	
7-14	97 (67·4)	47 (32·6)	3·52	2·20-5·64	**< 0·001**
> 14	59 (60·8)	38 (39·2)	4·68	2·80-7·84	
Glasgow coma scale					
15	438 (82·5)	93 (17·5)		Reference	**< 0·001**
< 15	38 (51·4)	36 (48·6)	4·46	2·69-7·41	
C-reactive protein (mg/L)					
< 50	180 (91·4)	17 (8·6)		Reference	
50 -99	99 (78·6)	27 (21·4)	2·89	1·50-5·56	**< 0·001**
> 99	197 (69·9)	85 (30·1)	4·57	2·61-7·99	
SpO2 (%)					
≥ 92	206 (88·8)	26 (11·2)		Reference	**< 0·001**
< 92	270 (72·4)	103 (27·6)	3·02	1·89-4·82	
Number of comorbidities					
0	179 (82·1)	39 (17·9)		Reference	
1	173 (78·3)	48 (21·7)	1·27	0·79-2·04	0·20
≥ 2	124 (74·7)	42 (25·3)	1·55	0·95-2·54	

[a] COR: Crude odds ratio, [b] χ^2

Supplementary Table 4. Univariate association between in-hospital mortality and NEWS2 score risk factors

Risk factor	Survivor n (%)	Non-survivor n (%)	COR[a]	95% CI	P[b]
Supplemental Oxygen					
Air	233 (94·0)	15 (6·0)		Reference	**<0·001**
Oxygen	243 (68·1)	114 (31·9)	7·29	4·13-12·85	
Mental status					
Alert	438 (82·5)	93 (17·5)		Reference	**<0·001**
Altered	38 (51·4)	36 (48·6)	4·46	2·68-7·42	
Respiratory rate (breath/min)					
12-20	260 (90·6)	27 (9·4)		Reference	
21-24	108 (76·1)	34 (23·9)	3·03	1·77-5·27	**0·001**
≤ 8 or ≥ 25	108 (61·4)	68 (38·6)	6·06	3·68-9·99	
Pulse rate (beats/min)					
51-91	155 (86·6)	24 (13·4)		Reference	
41-50 or 91-110	185 (79·4)	48 (20·6)	1·68	0·98-2·86	**0·001**
111-130	107 (71·8)	42 (28·2)	2·54	1·45-4·43	
< 40 or ≥ 131	29 (65·9)	15 (34·1)	3·34	1·57-7·12	
Systolic blood pressure (mmHg)					
111-219	382 (78·8)	103 (21·2)		Reference	
101-110	56 (83·6)	11 (16·4)	0·73	0·37-1·44	0·4
91-100	24 (75·0)	8 (25·0)	1·24	0·53-2·83	
≤ 90	14 (66·7)	7 (33·3)	1·85	0·73-4·71	
SpO2 (%)					
≥ 96	103 (88·0)	14 (12·0)		Reference	
94-95	51 (86·4)	8 (13·6)	1·15	0·45-2·92	**<0·001**
92-93	52 (92·9)	4 (7·1)	0·57	0·18-1·81	
≤ 91	270 (72·4)	103 (27·6)	2·81	1·54-5·13	
Temperature (Celsius)					
36.1-38.0	365 (78·8)	98(21·2)		Reference	
35.1-36.0 or 38.1-39.0	94 (83·2)	19 (16·8)	0·75	0·44-1·29	**0·004**
>39	15 (68·2)	7 (31·8)	1·74	0·69-4·38	
≤35	2 (28·6)	5 (71·4)	9·31	1·78-48·72	

[a] COR: Crude odd ratio; [b] χ^2

References

[1] G. Barlow, D. Nathwani, P. Davey, The CURB65 pneumonia severity score outperforms generic sepsis and early warning scores in predicting mortality in community-acquired pneumonia, Thorax. 62 (2007) 253. https://doi.org/10.1136/thx.2006.067371.

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X. Supplementary Appendix B – Permissions and Declarations

COVID-19: An Evaluation of Predictive Scoring Systems in South Africa

Supplementary Appendix B

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Supplementary Figure 1. Plagiarism Declaration



PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I ____BRENT TYLER ALOYSIUS PRIM_____ (Student number: __306488_) am a student

registered for the degree of _MASTERS of MEDICINE (RESEARCH REPORT)_in the academic year_FOUR__.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: _____12-06-2023_____

Supplementary Figure 2. Human Research Ethics (Medical) Clearance Certificate [M220116]

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr B Prim

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220116

NAME: (Principal Investigator)	Dr B Prim
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	*COVID-19: An evaluation of predictive scoring systems within South Africa*
DATE CONSIDERED:	2022/01/28
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs J Zamparini and F Mohamed
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/02/28

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and therefore reports and re-certification will be due in the month of **January** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

2022/3/03
Date

Supplementary Figure 3. Charlotte Maxeke Johannesburg Academic Hospital Site Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms. TT Mahlangu*
Email: Thandi.Mahlangu4@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
10 March 2022

GP_202201_037

Dear Brent Prim

RE: FINAL APPROVAL OF STUDY

TITLE: COVID-19: AN EVALUATION OF PREDICTIVE SCORING SYSTEMS WITHIN SOUTH AFRICA

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

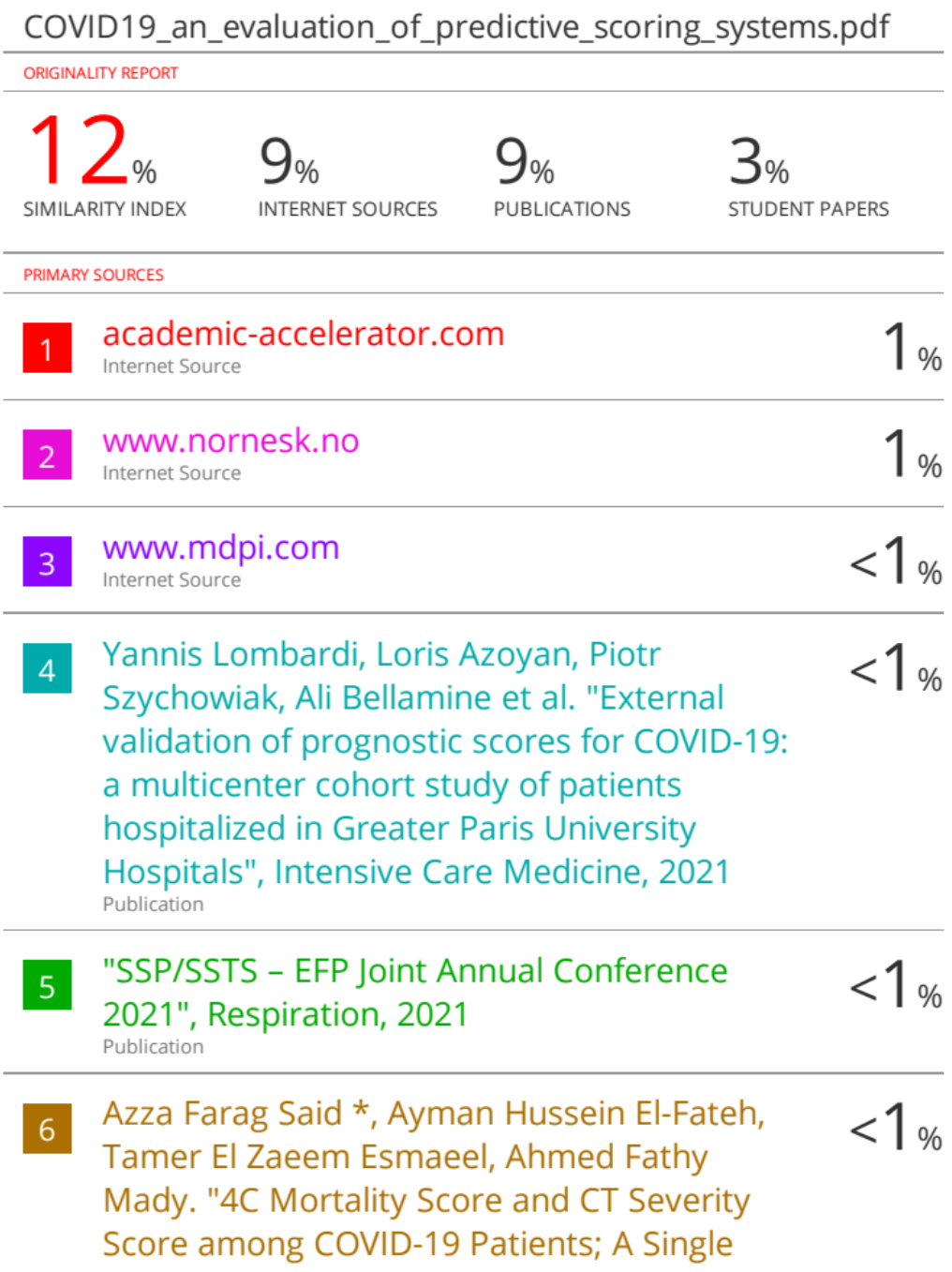
Supported/~~Not Supported~~
Signed by:Jayshina Punwasi
Signed at:2022-03-09 11:23:11 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director

Approved/~~Not Approved~~

Ms. G Bogoshi
Chief Executive Officer

Supplementary Figure 4. Similarity report for 'COVID-19: An Evaluation of Predictive Scoring Systems in South Africa', page 1



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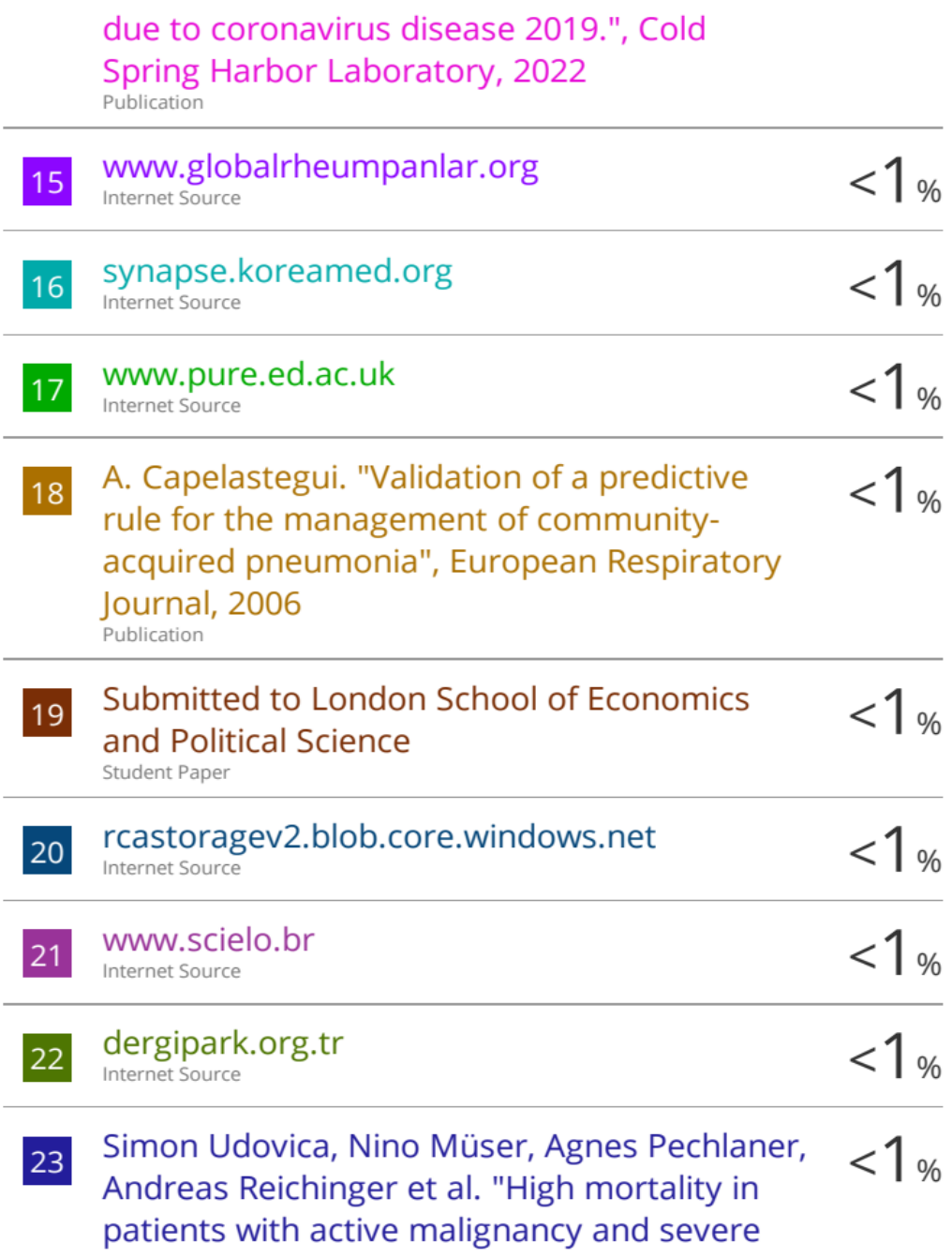

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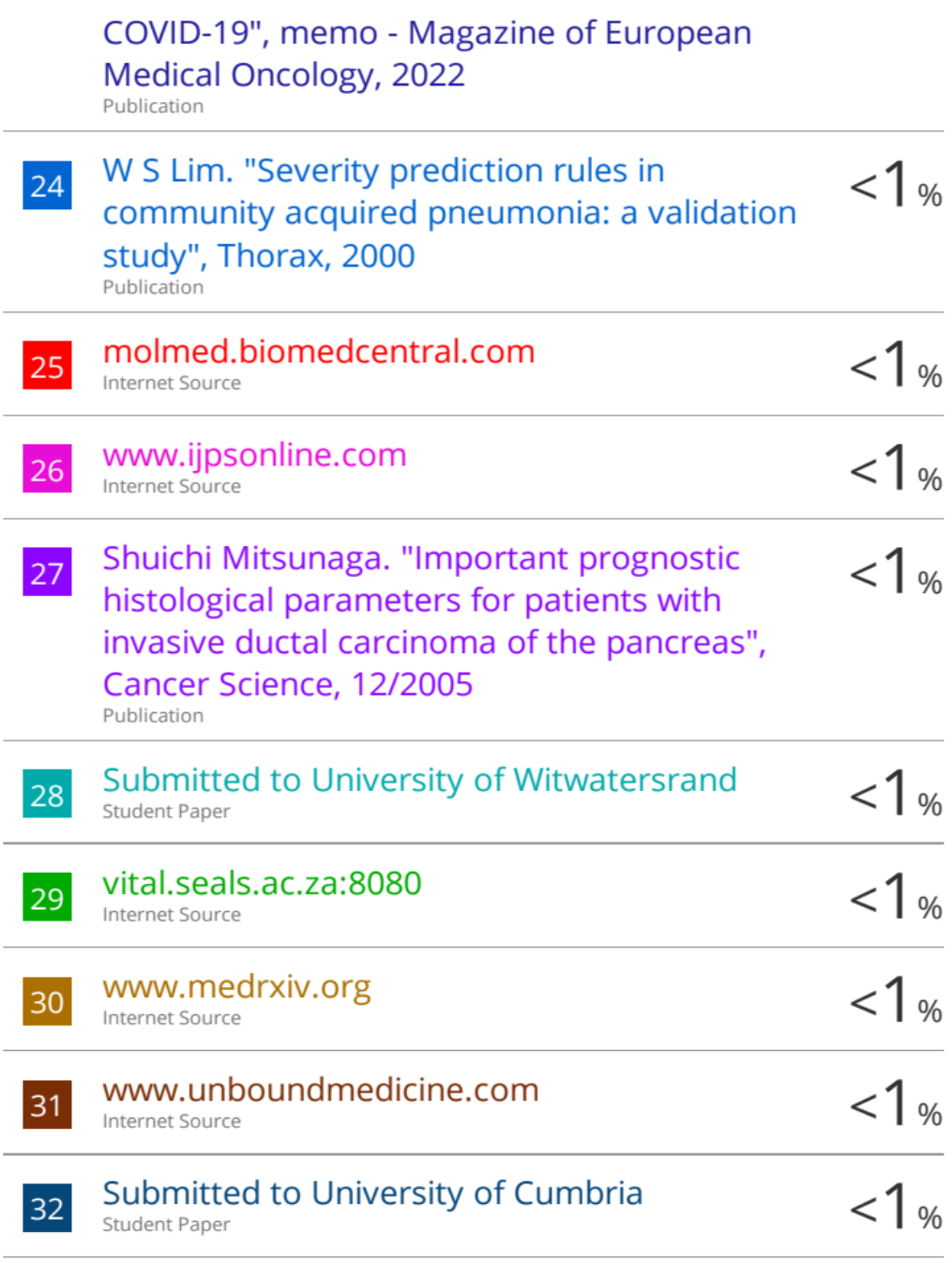

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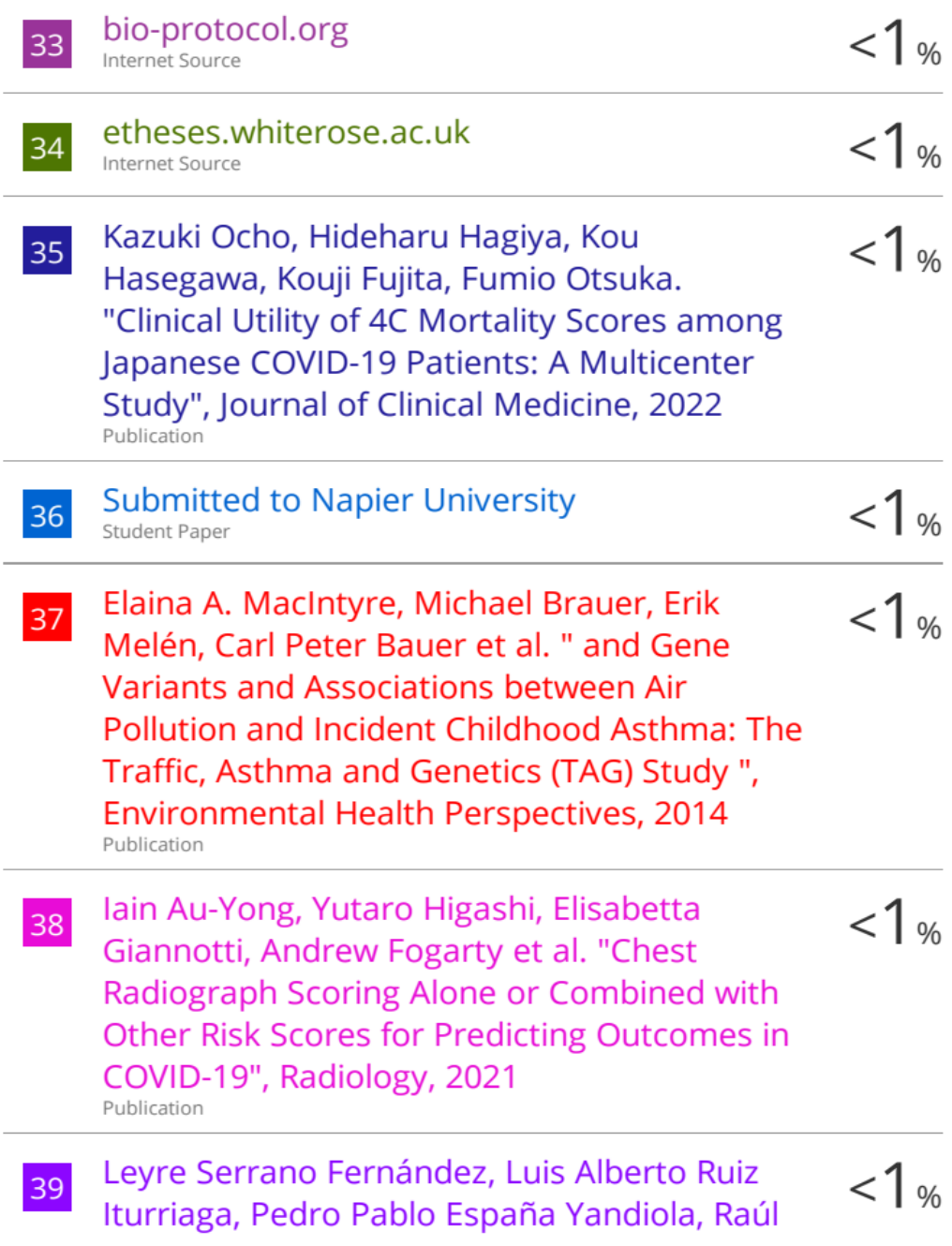

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