

# BMJ Open Clinical evolution, management and outcomes of patients with COVID-19 admitted at Tygerberg Hospital, Cape Town, South Africa: a research protocol

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## ABSTRACT

**Introduction** The outbreak of the SARS-CoV-2 virus causing COVID-19, declared a global pandemic by the WHO, is a novel infection with a high rate of morbidity and mortality. In South Africa, 55 421 cases have been confirmed as of 10 June 2020, with most cases in the Western Cape Province. Coronavirus leaves us in a position of uncertainty regarding the best clinical approach to successfully manage the expected high number of severely ill patients with COVID-19. This presents a unique opportunity to gather data to inform best practices in clinical approach and public health interventions to control COVID-19 locally. Furthermore, this pandemic challenges our resolve due to the high burden of HIV and tuberculosis (TB) in our country as data are scarce. This study endeavours to determine the clinical presentation, severity and prognosis of patients with COVID-19 admitted to our hospital.

**Methods and analysis** The study will use multiple approaches taking into account the evolving nature of the COVID-19 pandemic. Prospective observational design to describe specific patterns of risk predictors of poor outcomes among patients with severe COVID-19 admitted to Tygerberg Hospital. Data will be collected from medical records of patients with severe COVID-19 admitted at Tygerberg Hospital. Using the Cox proportional hazards model, we will investigate the association between the survival time of patients with COVID-19 in relation to one or more of the predictor variables including HIV and TB.

**Ethics and dissemination** The research team obtained ethical approval from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University and Research Committee of the Tygerberg Hospital. All procedures for the ethical conduct of scientific investigation will be adhered to by the research team. The findings will be disseminated in clinical seminars, scientific forums and conferences targeting clinical care providers and policy-makers.

## Strengths and limitations of this study

- Our study will provide data about a unique population with different demographic characteristics (eg, younger age) from those already described in the current literature.
- Our population harbours a high burden of HIV with 7.7 million people living with HIV and tuberculosis (TB) incidence rate of 520 per 100 000 population; this gives us an opportunity to assess to the potential impact of COVID-19 in TB-infected and HIV-infected individuals.
- Cape Town harbours nearly 66% of the total number of COVID-19 cases; the bulk of these cases come from previously disadvantaged areas with high levels of poverty, malnutrition and where people live in overcrowded make shift communities. This allows us to investigate the socio-economic and demographic conditions of the population and its effect on patients with COVID-19 admitted to a hospital from such environments.
- A limitation of the research project is that as this is a novel infection and evolving rapidly, no sample size will be predetermined at this stage.
- This research project will collect data from Tygerberg Hospital and the surrounding feeder hospitals that account for a significant proportion but may not be entirely representative of the entire Western Cape Province, thereby limiting extrapolation of conclusions.

## BACKGROUND

The outbreak of *coronavirus* in South Africa is part of an evolving pandemic, which began when a large number of people were exposed to the wet animal market in Wuhan City, China. Current evidence points to this as the origin of the pandemic, which began in December 2019.<sup>1</sup> The infection primarily

targets the human respiratory system and is mainly transmitted by respiratory droplets and close contact. Initially, the virus was named 2019-nCov. Subsequently, experts from the International Committee on Taxonomy of Viruses renamed it SARS-CoV-2 virus, alluding to its similarity to the severe acute respiratory syndrome (SARS) outbreak associated with SARS-CoVs. The disease was eventually named COVID-19 by the WHO on 11 February 2020 and declared a pandemic with significant public health challenges.<sup>1</sup> As of 12 June 2020, official statistics from the WHO reports 7 410 510 million confirmed cases with 418 294 deaths representing 5.6% case fatality rate globally.<sup>2</sup> In South Africa, 55 421 cases have been reported as of 10<sup>th</sup> June 2020, with most cases being the Western Cape Province. Although most cases identified at the beginning of the epidemic were imported cases from overseas travellers, currently increasing numbers of cases are due to community transmission.<sup>3</sup> Active case detection is currently performed through mass screening in communities, hospitals as well as at various COVID-19 screening and testing centres. Individuals with COVID-19-positive test are followed-up regularly and advised to report to hospital should they develop symptoms of severe disease.

Although the global case fatality is around 5.6%, South Africa has recorded 1210 deaths as of 10 June 2020 representing a case fatality of 2.2%. Clinically, COVID-19 presents with influenza-like symptoms of fever, rhinorrhoea, sneezing, sore throat, dry cough, headache, productive cough, dyspnoea, general malaise and gastrointestinal symptoms such as diarrhoea.<sup>4 5</sup> Other clinical features include signs of pneumonia, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and acute cardiac injury.<sup>5-7</sup> The incubation period of COVID-19 infection averages 5.2 days; the most at-risk groups of developing severe disease include 'healthcare workers, individuals over the age of 60 years<sup>1</sup> and patients with other comorbidities such as diabetes, coronary heart disease, chronic kidney disease (CKD), autoimmune conditions, cancer and hypertension. In South Africa, the population is generally younger but potentially at higher risk of co-morbidities due to the non-communicable diseases highlighted earlier. In addition, our setting harbours the so-called 'colliding epidemics' of HIV, tuberculosis (TB) (both active and post-TB lung disease) and chronic obstructive pulmonary disease (COPD).<sup>8</sup> Data are scarce on the effect of HIV, TB, post-TB lung disease and other prevalent chronic medical conditions in a younger population with COVID-19.

Kidney involvement in patients with COVID-19 appears to be common. A study of 193 Chinese patients found that 59% had proteinuria, 44% had haematuria and 10% had elevated serum creatinine concentrations on admission.<sup>9</sup> Cheng *et al*<sup>10</sup> reported that among 710 hospitalised patients with COVID-19, 44% had proteinuria and haematuria and 26.7% had haematuria on admission. The prevalence of elevated serum creatinine was 15.5%. AKI is common and is an independent risk factor for

mortality. There is some evidence that SARS-CoV-2 infects the kidney directly, inducing AKI and contributing to viral spread in the body.<sup>11</sup> It is not clear whether urine can contain viable, infectious SARS-CoV-2. There has been a report from Guangzhou of the successful isolation of SARS-CoV-2 from the urine sample of an infected patient<sup>12</sup>; however, in a study of the detection of SARS-CoV-2 RNA in different clinical specimens, no virus was identified in the urine of 72 patients.<sup>13</sup> COVID-19 infection presents a special threat to our patients on chronic dialysis as they are immunocompromised and have an increased risk of transmission of infection, including to hospital staff and family members, as well as a risk of severe and critical diseases. At a single haemodialysis centre in Wuhan, 37 of 230 patients and 4 of 33 staff members developed COVID-19 infection between 14 January and 17 February 2020.<sup>14 15</sup>

SARS-CoV-2 poses significant challenges for patients with pre-existing cardiovascular conditions. Such patients have an increased risk of severe diseases and death. The infection also appears to cause cardiovascular-related complications, including acute myocardial injury, and myocarditis due to direct viral myocardial damage, hypoxia, venous thromboembolism and arrhythmias. Because treatment for COVID-19 is non-specific, patients might be subjected to treatment that may cause drug toxicity and inadvertently lead patients to suffer serious cardiovascular side effects. These are critical areas and very pertinent to the care of patients with COVID-19 that require thorough investigation.<sup>16 17</sup> Furthermore, over and above systemic and respiratory symptoms, SARS-CoV-2 appears to cause severe damage to the nervous system. Previous reports have documented the presence of coronavirus in the brain or cerebral spinal fluid; a high proportion of patients (~36.4%) with severe COVID-19 displayed neurological symptoms, that is, headache, reduced conscious level and paraesthesia; there was a case of viral encephalitis where genome sequencing of the cerebrospinal specimen revealed the presence of SARS-CoV-2 virus. It is therefore crucial to assess the neurological complications of COVID-19 in our patients.<sup>18 19</sup>

Autoimmune conditions including rheumatoid arthritis and systemic lupus erythematosus are typically associated with an increased risk of infections.<sup>20 21</sup> The increased risk is related to the condition itself, as well as the use of immunosuppressive therapies including corticosteroids, cyclophosphamide and synthetic (including chloroquine) or biological disease-modifying antirheumatic drugs.<sup>22 23</sup> Many features of the disease (fever, raised inflammatory markers and low lymphocytes in severe cases) overlap with those of autoimmune disease, making the diagnosis challenging.<sup>24</sup> Data are limited on the incidence and outcome of COVID-19 in patients with autoimmune rheumatic conditions. Being immunocompromised with an altered cytokine profile, patients with severe rheumatological conditions are expected to be at increased risk of severe COVID-19.<sup>25 26</sup> The effect of chronic immunosuppressive therapies including the

**Table 1** Description of outcome and exposure factors and their specific measurements

**Outcome variables**

Outcomes	Measurements
1.Primary outcome	▶ In-hospital survival/mortality
2.Secondary outcomes	▶ Disease progression after admission requiring critical care ▶ In survivors, time to discharge from the ICU and hospital ▶ In those who have died and time to death ▶ Incidence of AKI, need for dialysis and recovery of kidney function

**Exposure variables**

Exposure factors	Measurements
1.Clinical	▶ Will include 'fever, disease severity, presence of ARDS, presence of HIV infection and presence of other comorbidities (diabetes, obesity, heart failure, hypertension, existing cancer, chronic obstructive pulmonary disease, post-tuberculous structural lung disease)'
2.Laboratory	▶ Will include 'leucopenia, lymphopenia, thrombocytopenia, neutrophil as lymphocyte ratio, elevated serum creatinine, elevated C-reactive protein', D-dimer, procalcitonin, CD4 and HIV viral load
3.Social demographic	▶ Will include 'age, sex, area of residence and occupation'
4.Epidemiological	▶ Cases could imported, local transmission, isolated or disease clustering, and duration of contact with a symptomatic individual before symptoms
5.Medication	▶ COVID-19-supportive therapy, COVID-19-directed therapy, antiretroviral treatment (ART) and, other antivirals, any other concurrent medication for any other indication

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ART, antiretroviral treatment; ICU, intensive care unit; REDCap, Research Electronic Data Capture.

potential beneficial effect of chloroquine on these conditions should be documented.

### Rationale of the study

The number of incident cases of COVID-19 is increasing at a rapid rate in South Africa and, being a new infection, it is unclear how it will evolve in the context of a population with a high burden of other infectious diseases such as TB and HIV, and high levels of poverty, malnutrition and overcrowding. It is therefore important to describe the clinical spectrum of COVID-19 in our setting, including its complications and its outcomes, focussing on the moderate to severely ill patients who require admission to hospital and who may need critical care. Furthermore, the findings of this study have the potential hypothesis-generation that could be tested in further studies; in addition, data-generating could give on the development of appropriate public health interventions that could be effective at curbing the spread of COVID-19.

### Objectives

The main objective of this study is to investigate the clinical presentations of patients and healthcare workers admitted with COVID-19 in our setting, the evolution of their disease, the management and the outcomes. The specific objectives and expected measurements are detailed in [table 1](#).

The specific objectives of the study are as follow:

1. Identify baseline factors associated with the outcome of the diseases (eg, HIV viral loads and immunological markers, use of antiretrovirals for HIV treatment, CKD, healthcare worker, TB or previous TB, hypertension, cardiovascular disease, autoimmune rheumatic conditions, diabetes and other comorbidities).
2. Develop a risk score to predict the outcome of COVID-19 based on baseline factors appropriate for a low-income and middle-income setting.
3. Assess supportive and COVID-19-directed therapeutic interventions.
4. Assess the effect of COVID-19 on individual organ systems.

### METHODOLOGY

#### Study design

The study will use multiple approaches because of the evolving nature of the COVID-19 pandemic. These approaches are as follow:

- ▶ Case series will provide detailed reports of the symptoms, signs, diagnosis, treatment and follow-up of patients admitted with COVID-19.
- ▶ A prospective observational design will be applied to study risk predictors of poor outcome. The primary outcome is in-hospital mortality.
- ▶ Detection of virus in urine and kidney: RNA will be extracted from clinical specimens and SARS-CoV-2

genome detected by real-time PCR, using WHO-approved protocols. Positive samples will be analysed to determine the viral RNA concentration (viral load) by quantitative PCR and used to inoculate Vero cell cultures to detect infection-competent virus, using established protocols in a biosafety level three facility. In kidney tissue, in situ expression of viral nucleocapsid protein antigen will be detected by immunohistochemistry.<sup>11</sup>

### Study setting

The study will be carried out at Tygerberg Hospital, a 1380-bed tertiary hospital in the Eastern Metropole of Cape Town. The hospital provides tertiary services to approximately 3.5 million people from the Western Cape Province. Much of the population serviced by the hospital is from low-income areas, with a significant proportion living in low-cost and informal settlements, where overcrowding, shared ablution and shared water facilities make social distancing and the advocated hygiene methods difficult. Additionally, unlike current northern hemisphere registries, South Africa is about to enter our peak annual influenza season with the usual anticipated rise in pneumonia admissions. The impact of this on the COVID-19 epidemic locally is still unknown.

### Sampling and sample size

As this is, a novel infection and evolving rapidly, no sample size will be predetermined at this stage. Power calculations will be performed for objectives that are inferential. The team will work with *all identifiable* cases to develop an optimal approach to clinical care and establish an epidemiological profile of COVID-19 in the region.

### Data collection and management

Data will be collected over a period of 6 months from June to November 2020. Data will be extracted from the medical records of all suspected and confirmed cases and entered into Research Electronic Data Capture (REDCap),<sup>27</sup> a secure, web-based, electronic database designed to support data capture for research. The variables of interest are described further. REDCap facilitates easy and accurate data entry through the use of drop-down lists, radio buttons and checkboxes, and data validation. For example, date fields have a calendar control and will only accept valid dates. Another example is the setting of maximum valid values for analyte concentrations. Data capturers will be trained on the REDCap system using PDF versions of the online data capture forms and the data dictionary as training materials. Other measures to improve data quality include double data entry, and data cleaning through checking for inconsistencies, numerical errors and missing parameters, among others. Where discrepancies are observed, data entered will be verified with the primary data source. Where possible, data will be validated by comparing a certain percentage of data in our database with that of another database. Once data

cleaning is complete, data will be exported to Stata V.16 (StataCorp Limited) for the analysis.

### Variables measurements

The variables to collect and measure in this study are outlined and defined in [table 1](#).

Baseline exposure measurements will be assessed on the admission of patients to guide the risk profile as well as the severity of COVID-19 such as age  $\geq 60$  years, high fever, presence of ARDS, comorbidities and diagnostic biomarkers such as leucopenia, high serum creatinine and so on. Disease progression will be monitored and assessment of organ function regularly done through conducting repeated tests including radiographic examinations while the patient is admitted in the hospital.

### Assessment and diagnosis

#### Severity grading

Cases of COVID-19 are clinically divided into mild (influenza-like symptoms and mild pneumonia), severe (presenting with dyspnoea, respiratory frequency  $\geq 30$ /min and blood oxygen saturation ( $SpO_2$ )  $\leq 93\%$ ) and critical cases (presenting with respiratory failure, septic shock, and with or without multiple organ failure). Patients with '>50% lesions progression within 24–48 hours in pulmonary radiographic imaging' should be treated as severe cases<sup>28</sup> hence admitted for clinical care in the ICU.

#### Diagnostic criteria

Two categories shall be defined: (a) 'suspected cases' and (b) 'confirmed cases'.

(a) *Suspected cases* are those patients who meet any one of the epidemiological exposure history as well as any two of the clinical manifestations (1) fever and respiratory symptoms; (2) features of pneumonia; (3) a decrease of total white blood cell count or lymphocyte count. Second, suspected cases include patients who have no definite epidemiological exposure history but have the following three clinical manifestations: (1) fever and/or respiratory symptoms; (2) features of pneumonia; (3) decrease of total white blood cells count or lymphocyte count. (b) *Confirmed cases* are patients with a positive test result of the SARS-CoV-2 RNA by real-time fluorescence reverse transcription-PCR, or where the virus gene sequence is highly homologous to the SARS-CoV-2. Sputum, nasopharyngeal/oropharyngeal swab or secretions from the lower respiratory tract in intubated patients where relevant will be collected and tested.<sup>28 29</sup>

#### Therapeutic interventions

Data will be collected on all therapeutic interventions, both supportive and directed therapy. Supportive therapy includes medications, such as vasopressors and antibiotics, and interventions, such as mechanical ventilation and dialysis, prescribed as part of the standard of care. Directed therapy will include any therapy used to lower the COVID-19 viral load or suppress the cytokine storm. We will record the specific medicine used, dose, start and

stop dates and any adverse events considered related to intervention.

### Radiological examination

Chest radiography will be used to assess signs of progressive pulmonary infiltrates. Data will be collected from radiographic and or ultrasound reports that were requested as part of standard clinical care for patients with COVID-19 admitted to the hospital. The chest radiograph has shown to be a less sensitive diagnostic test in the early stages of the disease; however, one notes that the chest CT scan has been reported to be more sensitive at identifying pulmonary abnormalities associated with coronavirus.<sup>30</sup> Trans-thoracic ultrasound will be documented, particularly of the B-lines and evidence of consolidation as per the standard technique.<sup>31</sup>

### Statistical analysis

The primary outcome of the study defined as in-hospital mortality will be categorised as dead (yes/no). Furthermore, we will assess time to event (death) or censored (alive at discharge); diseases progression during hospitalisation in the intensive care unit (from severe to critical/ or death). Frequency tabulations will be produced for social-demographic characteristics (age, sex, socioeconomic status, smoking, alcohol and area of residence); and clinical characteristics (number of actual days on treatment prior to outcome, HIV status, Antiretroviral therapy (ART), definite or presumed COVID-19 diagnosis, treatment given prior to admission, treatment given while admitted, mechanical ventilation, dialysis, comorbidities (hypertension, diabetes, Cerebrovascular accident (CVA), Cardiovascular disease (CVD), COPD, cancer, asthma, TB and so on) and pre-existing chronic medication). To investigate whether significant associations exist between demographic, clinical factors and treatment outcome (death: yes/no), the  $\chi^2$  test and multivariable logistic regression will be used. To determine the influence of clinical variables on disease progression, the  $\chi^2$  test and multivariable logistic regression will be used. Log-rank test and Kaplan-Meier plots will be used to assess the association between time to event (discharge/death) and the explanatory variables. Causal diagrams will be used to select variables to be included in the multivariable logistic regression models. Factors showing a significant association with the outcome defined at a conservative 10% significance level will be selected for inclusion in the multivariable logistic regression model.<sup>32</sup> The logistic regression analysis will determine independent factors associated with COVID-19 treatment outcomes. Using the Cox proportional hazards model, we will investigate the association between the survival time of patients with COVID-19 in relation to one or more of the predictor variables outlined earlier. Here we will assume that the effect of any of the covariate described above does not change over time. We will use scaled Schoenfeld residuals to assess for any of the violations of the proportional hazards assumptions.<sup>33</sup> To investigate longitudinal measures and

outcomes describing the impact of COVID-19 on individual organ systems, we will use a Generalised Estimating Equation method. A two-sided level of significance of 5% will be considered. All statistical analyses will be performed using Stata V.16 statistical software.

### Ethics and dissemination

The research team obtained ethical approval from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University and Research Committee of the Tygerberg Hospital. All procedures for the ethical conduct of scientific investigation will be adhered to by the research team. The findings will be disseminated in clinical seminars, scientific forums and conferences targeting clinical care providers and policy-makers using virtual platforms such as webinars or zoom.

### Patient and public involvement

There was 'no patient involved' in the conceptualisation of this proposal. The results will be shared with the department of health where the Minister of Health will release the findings to the public.

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**Correction notice** This article has been corrected since it was published.

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**Collaborators** N/A.

**Contributors** BWA, CFK, EI, UL conceptualised the idea; MRD, YC, RDT, AV contributed the section on renal pathology and autoimmune rheumatic conditions;

RD, HP, JT, AP, ED, PJ, SL, RM, NS contributed to drafting the objectives and measurements to be undertaken, RE, BA contributed to methods and aligning to objectives. PSN put together the first draft of the protocol. All authors made a significant contribution to the development of this research protocol. After the first draft, the protocol went through several iterations with substantial input and appraisal from all of the authors. All authors approved the final version of the manuscript.

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