The impact of COVID-19 infection on surgical mortality in Johannesburg, South Africa

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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GEMP 2/3 Research Projects 2022 – 2023

Research Protocol

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1. List of abbreviations

COVID-19: Corona virus disease 2019

SARS-CoV-1/2: Severe acute respiratory distress syndrome coronavirus 1/2

IHM: In-hospital mortality

CRP: C-reactive protein

BMI: Body mass index (kg/m^2)

HbA1c: Hemoglobin A1c

2. Introduction

2.1. The COVID-19 epidemic

COVID-19 is the pathological; phenotypic manifestation of SARS-CoV-2, a novel coronavirus strain initially identified in pneumonia-like patients in Wuhan, China (Chen et al., 2020). SARS-CoV-2 is a constituent of the family *Coronaviridae*; a group of relatively large enveloped, spherical virions consisting of a positive sense single stranded RNA genome (Goldsmith et al., 2004; Woo et al., 2010). This particular viral family is renowned for eliciting respiratory tract infections in humans; mimicking the morphology of acute respiratory distress syndrome (Sturman and Holmes, 1983). Epidemiologically, there have been 525,467,084 confirmed COVID-19 cases globally with 6,285,171 COVID-19 related deaths.

To date there have been approximately 9 000 000 confirmed COVID-19 cases in Africa with over 170 000 COVID-19 related deaths reported to the WHO. Of these, a significant proportion were localized in South Africa. The first case of COVID-19 in South Africa was reported by the Minister of Health, Dr. Zweli Mkhize, on 5 March 2020 (Mkhize, 2020). Since then, there have been approximately 4 000 000 confirmed COVID-19 cases in South Africa with over 100 000 COVID-19 related deaths reported to the WHO.

An essential public health approach to alleviate the burden of disease has been vaccinations. The WHO reports that approximately 5 billion people are fully vaccinated globally. To date, approximately 20 million South Africans are fully vaccinated. With a population of approximately 60 140 000 as indicated by the most recent South African census, less than one-third of the population are vaccinated against COVID-19. With the prevalence of adult hypertension and obesity in South Africa and alarming increase in obesity and cardiovascular risk factor in adolescents in sub-Saharan Africa, the lack of immunological protection against COVID-19 suggests there will be a continued burden of COVID-19 infection and mortality in South Africa (Choukem et al., 2020).

3. Literature review

3.1. Patient comorbidities and COVID-19 mortality

Throughout the course of the pandemic, it has been noted that individuals suffering with comorbidities have been disproportionately more likely to succumb to COVID-19 (Sanyaolu et al., 2020). It is important to get a better understanding of this to gain a better understanding of the potential outcomes of COVID-19 patients based on coexisting diseases they might have. There has been an association between in-hospital COVID-19 deaths and comorbidities such as an age above 65, cardiovascular disease, diabetes and obesity (Sanyaolu et al., 2020). There has also been a discrepancy between outcomes based on biological sex. Males appear to be at a greater risk of mortality when infected with SARS-CoV-19 (Kelada et al., 2020).

A recent study conducted has found that COVID-19 patients with elevated D-dimers, CRP and IL-6 experienced a worse disease state. This fact may be considered useful as by tracking these parameters one can potentially predict patient outcomes; given that CRP is a hallmark indication of the cytokine storm that frequently occurs with COVID-19 (Milenkovic et al., 2022). Another study provides such parameters. According to this study, CRP values greater than 100 mg/dL and D-dimer levels greater than 500 ng/ml during hospitalization may indicate increased chances of mortality (Ullah et al., 2020).

An increased BMI may also increase the risk of mortality when infected with SARS-CoV-19. Various mechanisms may exacerbate an infection in the case of obesity. Restricted breathing from an increased BMI, a proinflammatory state as well as increased difficulty intubating obese patients are some of the major factors underpinning a poorer COVID-19 prognosis (Nakeshbandi et al., 2020).

Both type 1 and 2 diabetes mellitus are independently associated with an increased chance of death when existing as a comorbidity in COVID-19 patients. Understanding diabetes as a coexisting disease in the context of COVID-19 is imperative given the poor COVID-19 prognosis in this group. This is supported by a study that analyzed this association across England (Barron et al., 2020). It was established that patients with type 1 diabetes had thrice the chance of an in-hospital death and patients with type 2 diabetes mellitus had twice the chance of an in hospital death compared to those without diabetes (Barron et al., 2020).

Additional factors worsening outcomes in COVID-19 patients include the presence of cardiovascular disease (CVD). It has previously been illustrated that CVD is associated with more severe clinical manifestations including an increased occurrence of pulmonary embolisms, tissue-damaging cytokine storms and lung injury (Li et al., 2020). It becomes clear that an array of comorbidities existent in various patient populations may worsen the prognosis of COVID-19 infection.
Furthermore, the literature suggests that in the context of the comorbidities outlined above, COVID19 infection is likely to worsen surgical prognosis and increase mortality.

3.2. COVID-19 infection and surgical mortality

COVID-19 affects the outcomes of patients receiving surgery. Globally, it is evident that COVID-19 infection increases surgical mortality (Haffner et al., 2021; Knisely et al., 2021). Evidence from a recent longitudinal cohort study performed internationally, illustrated that COVID-19 positive patients requiring surgery ferried an 18.9% risk of in-hospital mortality (IHM), compared to COVID-19 negative patients where a 3.6% risk for IHM was reported (Winter Beatty et al., 2021).

Interestingly, results reported in a recent investigation assessing surgical mortality and COVID-19 infection in an orthopedics ward in a South African population reported a 30-day mortality rate of only 2.5% (Waters et al., 2021). These results exist in contrast to a multicenter prospective study assessing patients undergoing elective and emergency orthopedic surgery, where the prevalence of deaths was significantly higher in COVID-19 positive patients (9.4%) compared to COVID-19 negative patients (0.43%) (Mohammadpour et al., 2022). This discrepancy may have been attributable to two factors: (1) None of the mortalities reported by Waters et al., 2021 were COVID19 related and (2) Approximately 10% of the patients assessed by Waters et al., 2021 were either lost to follow-up or had missing data possibly resulting in an underestimation of mortality.

Additional studies have suggested that COVID-19 related surgical mortality is ubiquitous across all surgical departments. In Chile, a similar association was found for patients that required general, gastroesophageal, hepatobiliary, and colorectal surgery. COVID-19 positive patients had a higher 30-day mortality rate (12.8%) compared to COVID-19 negative patients (1.4%) (Inzunza et al., 2021). Additionally, a European study exhibited that patients with Acute Coronary Syndrome (ACS) requiring invasive cardiac management, had an increased 30-day mortality rate in COVID-19 positive patients (23.1%) compared to COVID-19 negative patients (5%) (Salinas et al., 2021).

4. Rational, research question and hypothesis

4.1. Investigational rationale

It becomes clear that surgical mortality rate is increased in patients who are COVID-19 positive, perioperatively. The holistic mortality rate of surgery in South Africa is unknown but has previously been investigated by Moeng and Luvhengo, 2022 at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). In this study surgical mortality rate was 8.2% (862/10529) during the period of 2017-2018 (Moeng and Luvhengo, 2022). During the time of COVID-19 – defined temporally by 2020-2022 - the rate of surgical mortality in South Africa is unknown. Thus, the requirement arises to assess the effect of COVID-19 infection on surgical mortality during this time. This assessment is significant for three reasons: (1) It provides imperative prognostic value when considering surgical intervention in the setting of COVID-19 infection, (2) May provide evidence for surgical workflow alteration which is useful for the current and possible future pandemics (i.e. If surgical mortality increases, what alterations should be made to when and how surgery is performed?), and (3) The mortality milieu during COVID-19 aids in promoting and directing public health investment.

4.2. Research question

Is perioperative COVID-19 infection associated with a significant increase in surgical mortality?

4.3. Hypothesis

We hypothesize that perioperative COVID-19 infection has significantly increased surgical mortality during the period of 2020 to 2022 ubiquitously across all surgical departments.

5. Aims and objectives

5.1. Aim

To determine the influence of COVID-19 infection on surgical mortality by performing a retrospective analysis of surgical outcomes at CMJAH, Helen Joseph Academic Hospital (HJH) and Chris Hani Baragwanath Academic Hospital (CHBAH).

5.2. Objectives

Based on the above aim, an array of objectives arise:

5.2.1. To determine the demographic and clinical pathological data of COVID-19 positive and negative patients who were admitted and operated on during study period.

5.2.2. To compare demographics and clinical pathological findings of surgical patients between COVID-19 positive and negative in patients who survived and died.

5.2.3. To compare the demographics and clinical pathological findings of covid positive and negative patients who survived or died during the time frame of the study.

5.2.4. To build a step-wise regression model to statistically test the effect COVID-19 infection on surgical mortality.

6. <u>Research methodology and data analysis</u>

6.1. Methodology

6.1.1 Research design

We will conduct a retrospective data analysis of patients that have been admitted to the surgical department during the COVID-19 pandemic (March 2020 to March 2022) and have died, enabling a comparison to previously published surgical mortality literature.

6.1.2 Study site

The investigation will be performed in the surgical departments of CMJAH, HJH and CHBH. These institutions were selected for two reasons: (1) They are all tertiary hospitals with high surgical admissions enabling a sufficient data load for viable statistical analysis and (2) They are all located in different regions of the Johannesburg metropolitan and thus, may provide representative data which is prospectively applicable to all surgery in Johannesburg within the public healthcare sector.

6.1.3 Study population, sampling, inclusion/exclusion criteria

The patients that will be included in this study will be those that have undergone emergency or elective surgery from March 2020 to March 2022 and have survived or have died within a 30 day timeframe after surgery. As outlined in *section 6.2.1* below, a minimum sample size of 876 (438 COVID-19 positive and 438 COVID-19 negative) will be required.

Patient sampling will be carried out using a data collection sheet, outlining all patient and surgical information intended to be recorded (included in *Appendix, Section 9, table 1*). To maintain patient confidentiality, participant study numbers are functionally arbitrary (i.e. not related to patient admission or ID numbers) and labelled in such a way to: (1) Reduce redundancy in data collection and (2) Gain an understanding of total patient numbers.

Patients deemed 'COVID-19' positive are those who tested positive for COVID-19, perioperatively. Perioperative COVID-19 infection is considered a single positive COVID-19 test 7 days before or 30 days after surgery, consistent with previously published literature (Inzunza et al., 2021).

The primary exclusion criteria of patients from the study were as follows: (1) Patients in the surgical department who did not receive surgery or died before receiving surgery, (2) Patients who were referred to other departments after surgery and subsequently died and (3) Patients with unknown COVID-19 status. Point (1) above amplifies the rigour in assessing the effect of COVID-19 infection of surgical mortality and point (2) reduces confounding of mortality aetiology related to other departments. By default, patients whose data on REDCap was incomplete will be excluded. This ensures dilution of comorbidity-defined patient strata is avoided. Supplementary exclusion criteria includes patient deaths not directly related to COVID-19-associated surgical complications or outcome such as: late-stage cancer, acute traumatic brain injury, established sepsis, serious burn trauma, late-stage HIV/AIDs, as well as irreversible organ failure.

6.1.4 Data collection tool and collection process

REDCap, an electronic data capture software, will be used as the main source of data. The data that is captured on this program includes: patients' demographics, admission diagnosis, comorbidities, surgical procedures, intraoperative adverse events (Moeng and Luvhengo, 2022). Additionally, where necessary, data will be collected from discharge summaries and theatre records. Data collection will be mediated by the use a data sheet (*Appendix, Section 9, table 1*), enabling initial stratification and summarization. Information obtained on data collection sheets will be amalgamated on Microsoft Excel and compiled in various patient strata for various patient variables. This will enable data summarization and description as outlined in *section 6.2.2* below.

Data collected of COVID-19 positive and negative patients who underwent surgery and survived or died will be of either a categorical or continuous nature. Categorical data include and is limited to: COVID-19 status, biological sex, HIV status, surgical urgency (emergency or elective), surgical department, oxygen administration indicated by respiratory abnormality (7 days before or 30 days after surgery), mortality preventability (Moeng and Luvhengo, 2022), smoking, hypertension status, diabetic status and COPD status. Continuous data includes and is limited to: C-reactive protein (CRP), D-dimer, HBA1c, body-mass-index (BMI) and blood pressure.

A data collection flow chart will be developed and included to summarize the process and ensure investigational transparency. This will include the initial and final number of surgical mortalities included for statistical analysis with the numbers of excluded cases accompanied by appropriate rationalization of exclusion.

6.1.5 Sources of bias

By collecting data from only three hospitals our data could possibly reflect selection bias, failing to be a complete representation of all the surgical mortalities in Johannesburg, South Africa. Our literature review may suggest that we were English language bias, as only articles written in English were read and reviewed. As we will rely on data instruments, some measurement bias could be evident in our data.

6.1.6 Ethics and ethical considerations

Permission will be obtained from the Research Review Board of CMJAH, this includes permission from the hospital Chief Executive Officer (CEO), and the Deputy Head of the Surgical Department of the hospital. For CHBAH, we will obtain permission to perform the study from the Medical Advisory Board. For HJH, permission will be obtained from the Research Review Board. We will apply for ethics approval at the Human Research Ethics Committee (Medical) of University of the Witwatersrand. Ethical considerations include:

- Maintenance of confidentiality through the exclusion of all aspects directly associated with patient identity such as patient admission number, name and ID number.
- Non-distribution of data to individuals without ethical clearance for the research.
- Research and protocol transparency by detailing the process of data capture and analysis including reasoning for patient exclusion where appropriate.

6.2. Data analysis

The data analysis of our investigation entails description and summarization of our data. Subsequently, association or independence between various patient strata of respective variables will be determined and used to direct a step-wise regression model. All statistical tests will be performed utilizing Rstudio (version 4.2.1).

6.2.1 Sample size calculation

To determine the sample size necessary to investigate our aim, we used the surgical mortality rate of 8.2% previously established in the surgical unit as the baseline for the power proportion test (Moeng and Luvhengo, 2022). This test was two-sided, performed at an 80% power and 5% significance level. It was determined that to illustrate a 4% increase in surgical mortality due to COVID-19 infection (or illustrate an increase in surgical mortality at an odds ratio of 1.5), a sample size of 876 (438 COVID-19 positive and 438 COVID-19 negative) will be required. A sample size of 876 is attainable considering 10529 surgeries were performed at CMJAH alone from 2017 to 2018.

6.2.2 Descriptive statistics

Data collected will be of a categorical and continuous nature. Categorical data will be summarised in terms of percentages and/or contingency tables. For continuous data specifically, normality will be assessed we will also assess whether it is normally distributed using a Kolmogrov-Smirnov test. Parametric continuous data will be summarised using means and standard deviations while nonparametric data will be summarized using the median and interquartile range.

6.2.3 Test(s) for association

To test for association between various patient strata for each variable, both categorical and continuous data will be considered. This allows for an assessment of which patient variables may confound the effect of COVID-19 infection on surgical mortality.

6.2.3.1.1 Chi-Squared test

The association between various patient strata of the categorical variables outlined in *section 4.1.4* will be assessed using a Chi-squared test (α = 0.1%; df = *category specific*) determining independence or association. In the event that a patient stratum of a particular variable contains less than 5 entries, appropriate patient strata will be amalgamated until statistical viability is assumed.

6.2.3.1.2 Unpaired Student's t-test and/or Mann-Whitney U test

The continuous variables outlined in *section 4.1.4* may be of a parametric or non-parametric nature. To test for association between patient strata of parametric, continuous data; an unpaired Student's t-test (two-sided; $\alpha = 0.05$) comparing means will be employed. The association or independence of between patient strata of non-parametric, continuous data will be determined by employing a MannWhitney U test (two-sided; $\alpha = 0.05$).

6.2.4 Step-wise regression

In an attempt to explicitly elucidate whether COVID-19 infection significantly increases surgical mortality in our patient groups, a step-wise regression model will be developed taking all confounding categorical and continuous variables into account. A Multi-Way ANOVA ($\alpha = 0.05$; power = 80%) may be employed for this purpose.

7. Limitations

The limitations of our investigation regard the nature of our data and the setting from which the data will be obtained. Based on the above, the following limitations arise:

a) CRP and D-dimer levels increase in other disease states unrelated to COVID-19. Thus, the use of CRP and D-dimer levels as indicators of COVID-19 severity is rudimentary.
b) The clinical sensitivity of the COVID-19 RT-PCR test is moderate at best (Kortela et al., 2021). Thus, the potential for false positives overestimating the effect of COVID-19 infection on surgical mortality, arises.
c) The Chi squared test requires a frequency higher than five per multi-parameter. This may limit the statistical malleability of the study as a number of parameters assessed in the context of COVID-19 surgical mortality are narrowed dependent on the abundance of data available.
d) All elective surgeries were postponed during the initial period of COVID-19. This may exist as a confounding factor as mortality may have been attributable to the severity of ailment requiring emergency surgery in addition to COVID-19 infection.
e) In April 2021, a fire at CMJAH prompted the evacuation of ~840 patients. Thus, surgical mortality data may be under-reported as (1) Many patients who were scheduled to receive surgery may have received surgery at a later date at a different public hospital and (2) Patients who received surgery may have been moved and subsequently died at a different institution.

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9. Timeline

	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan 2023	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Preparing protocol																		
Ethics course																		
Protocol presentation																		
Protocol submission																		
Ethics application																		
Collecting data																		
Data analysis																		
Writing final paper																		
Final paper submission																		

10. Budget

Expense	Amount (R)
Transport	150 per day to and from campus per person twice a month for 15 months (**4500**)
Printing, photocopying, paper and other stationery	**1200**
Data and airtime	200 pm for 15 months (**3000**)
Total	**8700**

11. Appendix

Table 1: The data collection sheet employed in the investigation

<table>
<tr><td>Participant study number</td><td colspan="3"></td></tr>
<tr><td>COVID-19 + or -</td><td colspan="3"></td></tr>
<tr><td>CRP (mg/L)</td><td colspan="3"></td></tr>
<tr><td>D-Dimer (μg/mL)</td><td colspan="3"></td></tr>
<tr><td>HbA1c (highest)</td><td colspan="3"></td></tr>
<tr><td>HbA1c (admission)</td><td colspan="3"></td></tr>
<tr><td>BMI
(mass (kg) / height (m^2)</td><td>BMI:</td><td>Height:</td><td>Mass:</td></tr>
<tr><td>Blood pressure (highest average)</td><td colspan="3"></td></tr>
<tr><td>Age (years)</td><td colspan="3"></td></tr>
<tr><td>Sex (tick applicable)</td><td>Male:</td><td>Female:</td><td>Other:</td></tr>
<tr><td>Surgical urgency (tick applicable)</td><td>Elective:</td><td>Emergency:</td><td></td></tr>
<tr><td rowspan="2">Surgery (tick applicable)</td><td>General:</td><td>Trauma:</td><td>Vascular:</td></tr>
<tr><td>Transplant:</td><td>Other (specify department):</td><td></td></tr>
<tr><td colspan="4">Fill in one option below:</td></tr>
<tr><td>Preventable</td><td colspan="3">Reason:</td></tr>
<tr><td>Potentially preventable</td><td colspan="3">Reason:</td></tr>
<tr><td>Non preventable</td><td colspan="3">Reason:</td></tr>
<tr><td rowspan="3">Co-morbidity/risk factor (Yes or no)</td><td>Hypertensive:</td><td>DM type 1:</td><td>DM type 2:</td></tr>
<tr><td>Smoking:</td><td>COPD:</td><td>HIV:</td></tr>
<tr><td>Oxygen administrated:</td><td colspan="2"></td></tr>
</table>