Risk factors for in-hospital related COVID-19 deaths in Mpumalanga province - June 2020 – June 2022

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Field Epidemiology

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September 2024

DECLARATION

I, Lethukuthula Zondi, declare that this Research Report is my original own, unaided work. It is being submitted for the Degree of Master of Science in Field Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been previously submitted for any degree or examination at any other University.

Signature: 

27th day of September 2024 in Johannesburg

DEDICATION

I would like to express gratitude to God and the universe for unfolding their plan so beautifully and miraculously, leading me to this journey that is an absolute dream come true.

I dedicate this dissertation to everyone in my life who has poured into me. To my late biological mother, Rose Maria Zondi, not a single day goes by without thinking about you; you are dearly missed. And to my other mother, Roseline Sophie Thini, you have been a godsend in my life, and I thank the universe for your existence and presence. Thank you both for all the sacrifices you've made for me to reach this point in my life—both the sacrifices I know of and all the others that I may never know.

I extend my gratitude to my maternal grandmother, Josephine Thini, and paternal grandmother, Ntombi Anna Zondi, and aunts, Kholekile Zondi and Thembi Nzuza who have left me with fond memories and consistently spoken life into my dreams. I will cherish that forever. To our small family (Lerato, Wandi, Sibongile, Sizwe, Hloni, Sihle, Nstiki, Lungile, Hlumi, Hlelo), thank you for your love and unwavering support.

Lastly, I want to thank my partner, Simphiwe Innocent Mabunda, who has believed in me and been my biggest cheerleader. Your ability to care for others is a sight to behold, one that is appreciated and cherished.

ABSTRACT

Background: South Africa was among the African countries heavily impacted by COVID-19, reporting significant case numbers and deaths. This study aimed to assess the demographic and clinical characteristics of hospitalized COVID-19 patients in Mpumalanga Province. We also analysed the factors associated with COVID-19 deaths in Mpumalanga Province.

Methods: We performed a retrospective cohort study using surveillance data of COVID-19 hospitalisations from Mpumalanga Province between June 2020 and June 2022, extracted from the DATCOV Surveillance System. Clinical severity was defined by the need for oxygen therapy, ventilation, or admission to High Care or Intensive Care Units. Kaplan-Meier survival analysis and Cox regression were used to estimate survival probabilities and identify risk factors for in-hospital mortality. Adjusted Hazard Ratios (aHR) with 95% Confidence Intervals (CI) were reported.

Results: Of the 20,960 hospitalized COVID-19 patients, 4,467 (21.6%) died. The majority were female (56%), and females accounted for 51.6% of the deaths. The median time to death was 25 days (IQR: 11–66). The overall mortality rate for this cohort was 21.6%. After adjusting for age, sex, comorbidities, and clinical severity, factors significantly associated with increased risk of in-hospital mortality included admission in Ehlanzeni [aHR 1.10; 95% CI 1.01–1.19] and Gert Sibande [aHR 1.20; 95% CI 1.10–1.30] districts, and during the second wave [aHR 1.09; 95% CI 1.02–1.18]. Protective factors included admission during the fourth wave [aHR 0.80; 95% CI 0.70–0.92], clinical severity [aHR 0.74; 95% CI 0.69–0.80], and private healthcare admission, which reduced mortality risk by 87%.

Conclusion: In-hospital mortality was significantly higher for patients admitted to hospitals located in Ehlanzeni and Gert Sibande districts, and during the second wave of the pandemic. Admission during the fourth wave, in private hospitals, and in clinically severe cases were associated with decreased mortality risk. Strenghtening the province's healthcare system, such as early identification of vulnerable groups to target vaccination campaigns, and improving healthcare infrastructure and access to underserved districts, low-density areas and in public hospitals could reduce in-hospital mortality in similar future pandemics.

Keywords: COVID-19, hospitalisation, in-hospital, mortality, factors, Mpumalanga

ACKNOWLEDGEMENTS

I wish to express my gratitude to the organizations and individuals, listed in no particular order, who have played a crucial role in the successful completion of this degree. Special recognition goes to the National Institute for Communicable Diseases (NICD), the South African Field Epidemiology Training Programme (FETP), and the University of the Witwatersrand (WITS) for their generous funding support.

I also extend my appreciation to the Mpumalanga Provincial Department of Health, specifically the Public Health Directorate, with a special mention to the Communicable Disease Prevention and Control (CDC) Unit. I am grateful for the support and collaboration provided by my supervisors Ms Hluphi Mpangane, Mr Khuliso Ravhuhali and Dr Innocent Maposa. In addition, thank you to Ms. Thembekile Zwane, Leigh Jonhstone, Mrs Hetani Mdose, Dr Lazarus Kuonza the other FETP and WITS faculty staff members. Their continued support, mentorship, and guidance have been instrumental in my academic journey.

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LIST OF ABBREVIATIONS & ACRONYMS

CoV - Coronavirus

COVID-19 – Coronavirus disease 2019

DATCOV – Covid-19 Surveillance System

DRC – Democratic Republic of Congo

EC – Eastern Cape

IHR – International Health Regulations

ICU – Intensive Care Unit

HIV – Human Immunodeficiency Virus

MERS – Middle Eastern Respiratory Syndrome

PHEIC – Public Health Emergency of International Concern

RNA – Ribonucleic Acid

RT- PCR – Real-time polymerase chain reaction

RR – Relative Risk

TB – Tuberculosis

SARS-CoV-1 – Severe Acute Respiratory Syndrome Coronavirus

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

SA – South Africa

WHO – The World Health Organization

UN – United Nations

CHAPTER 1: INTRODUCTION

1.1 Introduction

This chapter provides a background on the COVID-19 global pandemic and provides a comprehensive review of relevant literature. We examine the literature on the most commonly reported factors associated with in-hospital COVID-19-related mortality and summarize the study's problem and justification for conducting the study.

1.2 Background

The emergence of the COVID-19 pandemic, first identified in Wuhan, Hubei Province, China, was declared a pandemic on 11 March 2020[1] and placed considerable strain on healthcare systems worldwide[2]. Initially termed 2019-nCoV, the virus underwent a subsequent name change to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19), the widely recognized terms used today[3]. As of 03 March 2024, WHO reported approximately 774 834 251 cumulative COVID-19 cases globally, resulting in 7 037 007 deaths[4]. In the African region, 9 576 323 cumulative cases and 175 502 deaths were reported, and South Africa accounted for 4 072 636 cumulative cases and 102 595 global deaths[4]. More than three years later, the WHO Director announced the end of the COVID-19 pandemic on 05 May 2023[1].

1.3 Literature Review

1.3.1 SARS-CoV-2

SARS-CoV-2, identified as a pathogenic betacoronavirus, is responsible for causing COVID-19[3,5]. Classified within the coronavirus (CoV) family alongside the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV)[3], CoVs are enveloped spherical, positive-sense, single-stranded ribonucleic acid (RNA) viruses[6]. Belonging to the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae[3,6], CoVs typically infect humans through zoonotic transmission, with civets, raccoon dogs, camels, and possibly pangolins serving as intermediate hosts[6]. However, the natural reservoirs for human CoVs are identified as bats and rodents[7].

1.3.2 COVID-19 in South Africa

As of 3 March 2024, South Africa holds the 37th position in the world cumulative infections reported[4]. Among, sub-Saharan African countries, South Africa was the most severely affected, despite having fewer infections and fatalities even if the region was the least impacted in terms of the quantity of infections and fatalities compared to Europe, the Americas, and Asia[4]. The first case of COVID-19 in South Africa was reported on 5 March 2020 and soon after the country entered into a strict level 5 national lockdown on 27 March 2020[8,9]. The national lockdown was imposed to reduce the rate of transmission of infections as well as to alleviate the pressure on the healthcare system[9,10,11]. Lockdown measures included the full closure of childcare facilities, primary and higher education intuitions, and all public leisure activities, and severe physical distancing, among other things[8,9,11]. The implemented preventive measures managed to decrease the transmission rate[10]. However, as the stringent lockdown measures were relaxed, the country observed a gradual increase in cases, marking the onset of the nation's first wave driven by the ancestral variant[9,12].

The pandemic unfolded through five district waves, each driven by different variants and interrupted by periods of low transmission[12-15]. These waves present unique challenges and result in varying patterns of hospital admissions[12,13,15]. The hospital-based surveillance system, DATCOV, has thoroughly documented the country's COVID-19 hospitalisations DATCOV[12-15]. South Africa faced various challenges during different waves, including strained healthcare systems and fluctuations in the availability of medical resources[10,11,16]. Citizens were advised to self-isolate or self-quarantine at home if they had mild symptoms, had been exposed to a case, or were subclinical to free up hospital bed space for patients with moderate to severe disease[17,18,19]. The strategy may have likely been put in place to free up bed space in hospitals for patients who experienced moderate to severe disease.

The COVID-19 waves in South Africa were characterized by varying proportions of hospital admissions. Overall, the proportion of hospitalisations was higher in the first three waves compared to the fourth wave[14,15]. The second wave, associated with the Beta variant (501Y.V2) saw increased infections, hospitalizations, and deaths compared to the first wave[12,20]. This variant was first detected in Nelson Mandela Bay in the Eastern Cape province and emerged between early July and the end of

August 2020[20,21]. The third wave, driven by the Delta variant (B.1.617.2), was first detected in India in October 2020[21,22]. This wave was the most prolonged and was characterised by the highest proportion of cases, hospital admissions, and deaths among all waves[14,15]. Lastly, the fourth and fifth waves were, fueled by the highly infectious Omicron variant, B.1.1.529 (lineages BA.1/BA.2 & BA.4/BA.5) [14,15,20], the variant first identified by South African scientists in November 2021[23]. The fourth wave pattern exhibited a rapid increase in cases followed by a quick decline[14,15]. Despite its rapid spread, this variant resulted in the least hospital admissions, severe cases, and deaths compared to previous waves[15].

South Africa had some successes as well as challenges during the pandemic. For instance, unlike other low- and middle-income countries (LMICs) like Brazil, Nigeria, and Mexico, South Africa did not experience an oxygen shortage crisis[24,25] . However, in anticipation of potential shortages of ventilators due to global market constraints and increasing demand from hospitals for severe COVID-19 cases, the government took proactive steps by procuring locally designed ventilators[26]. Furthermore, addressing the overarching challenge of insufficient health infrastructure, particularly the shortage of beds[27,28], South Africa responded by constructing and opening field hospitals in provinces such as Gauteng, Limpopo, and the Western Cape[28,29,30,]. However, the challenges and factors contributing to COVID-19 in-hospital mortality that were reported by researchers included issues related to both patients and the healthcare system. Namely, sub-standard emergency care, inefficiencies in the referral system, late presentation, advanced age, comorbidities and undiagnosed comorbidities, limited and inadequate staffing, and shortages of medical equipment such as personal protective equipment[11,32].

1.3.3 COVID-19 Transmission

The transmission of COVID-19 occurs through both direct and indirect contact between individuals[33]. Infected individuals, when sneezing, coughing, or speaking within proximity (<1m) to uninfected individuals, can immediately transfer the virus through expelled respiratory droplets[33]. These droplets, carrying the virus, can either enter through mucosal membranes or land in the surrounding environment[33]. Additionally, indirect transmission occurs when fomites in the immediate environment of an infected person become contaminated, and uninfected individuals come into

contact with these surfaces[33]. The research was conducted to comprehend the rapid spread of COVID-19 and to develop effective non-pharmaceutical interventions.

1.3.3 Clinical Presentation

The spectrum of COVID-19 symptoms ranges from mild to severe, with early signs evolving from non-specific flu-like symptoms to more distinct features[3,33]. Commonly, individuals with COVID-19 experience a moderate illness, characterised by early signs such as fever, cough, myalgia, and shortness of breath[3,34-40] . Additionally, frequently observed symptoms include headache[34,35], anosmia, dysgeusia[3], sore throat[3,34], gastrointestinal symptoms[34-38,40], nasal congestion, and rhinorrhea[3]. Respiratory symptoms and objective indicators of respiratory impairment were often indicative of a serious illness or critical illness[41,42] including difficulty breathing, persistent chest pain or pressure, sudden confusion, challenges in maintaining consciousness, cyanosis, dsypnoea, and reduced oxygen saturation [34-37,39,41,42].

1.3.4 COVID-19 diagnosis and testing

Clinicians can suspect COVID-19 based on symptoms and exposure history, but laboratory confirmation is essential[33]. The two primary methods for detecting COVID-19 are antibody testing and real-time polymerase chain reaction (RT-PCR)[33,43]. RT-PCR involves collecting nasopharyngeal and oropharyngeal swabs from the respiratory system, and isolating viral DNA for confirmation of suspected cases[33]. While RT-PCR remains the gold standard, rapid antigen tests, which provide instant results using respiratory swabs, have been frequently employed in South Africa to manage high testing volumes during waves, despite taking several hours for results[44]. Essentially, clinicians rely on symptoms and exposure history to suspect COVID-19, and confirmation through laboratory testing, primarily RT-PCR or rapid antigen tests, is crucial in the diagnostic process.

1.3.5 Control and Prevention Strategies

In response to the COVID-19 outbreak, many countries globally enforced mandatory lockdowns. The South African government, aiming to curb the spread of the disease, implemented level-five lockdowns effective from 27 March 2022 to 26 April 2022[9]. This measure alleviated pressure on the healthcare system, contributing to a reduction in transmission rates, the number of cases, and fatalities[9,11]. Additional non-pharmaceutical measures included home isolation, travel restrictions, face mask

mandates, social distancing, and compulsory hand sanitization in public areas[9,10,11]. Lockdowns, in the long term, demonstrated impracticality, prompting the more effective preventive measure of swiftly developing a vaccine.

1.4 Factors

1.4.1 Biological Factors: Age & sex

Concerning biological factors such as sex and age, numerous studies have consistently identified advanced age and sex as significant predictors for COVID-19 mortality[34-,40,45].

Overall, the risk of COVID-19 mortality has been shown to increase with age[46,47]. Numerous studies carried out in Asia have revealed significant links between older age and higher COVID-19 mortality rates[34-37,39,40]. Similarly, a Korean study among elderly hospitalised patients (≥65) demonstrated a significant link between advanced age and a higher risk of mortality, with odd ratios of 77.0 (95%CI 73.0 – 83.0)[48]. While, an Italian study, after adjusting their model, also confirmed that older age (per ten years more) was associated with a higher risk of death[49]. Likewise, some researchers in sub-Saharan Africa found similar trends, a study in Nigeria reported that ages ≥51 years and older was associated with death[50] . These findings were also corroborated by a study conducted in the Democratic Republic of Congo (DRC) study where those aged 40-59 years (aHR: 4.45, 95% CI: 1.83-10.79), and ≥ 60 years (aHR: 13.63, 95% CI: 5.70-32.60) in the sample had an increased risk of death[51]., Contrasting findings were documented in the same study, documenting that individuals under the age of 20 had an elevated risk of COVID-19 compared to their counterparts aged 20-39[51].

Sex-based differences in COVID-19 mortality have been a subject of investigation. A North American study revealed that male individuals with COVID-19 had a higher risk of in-hospital death compared to their female counterparts (females vs. males 13.8% vs. 10.2%)[42]. Moreover, a systematic review and meta-analysis highlighted that morality and COVID-19 severity were more pronounced in males, with a relative risk (RR) of 1.29 (95%CI 1.19 – 1.40)[52]. Theories surrounding these sex-based differences have revolved around immunological and hormonal factors that may influence disease susceptibility and progression[52]. A study conducted in Nigeria,

done among community and hospitalised patients, where males accounted for 67.7% of the cases, showed that the male sex was associated with an increased risk of COVID-19 mortality[50]. The previously mentioned Chinese studies did not report any significant findings of sex differences in their studies[34-40] .

In South Africa, national study findings, that were performed throughout the COVID-19 pandemic were concordant with previous Asian, American, and sub-Saharan African studies where male sex and increased age were identified as risk factors among hospitalised private and public sector patients[12,14,13,53,54].

1.4.2 Clinical Characteristics: Comorbidities

The elevated mortality rate observed in individuals with COVID-19 is associated with their existing comorbidities[51,55,56,57]. A Chinese cohort of 1590 patients reported having at least one (25.1%) comorbidity, where the most prevalent comorbidities were hypertension (16.9%) and diabetes (8.2%)[58]. Patients with comorbidities such as COPD, diabetes, hypertension, and malignancy, had a higher risk of reaching composite end-points (admission to ICU, invasive ventilation, or death), with hazard ratios (HR) from 1.58 – 3.50[58]. The hazard ratio was 1.79 for patients with at least one comorbidity and 2.59 for patients with two or more comorbidities[58]. Underlying medical conditions were found in 63% of in-hospital fatalities and 41% in the discharge group had underlying disease. Patients with cardiovascular disease had a significantly increased risk of death when infected with SARS-CoV-2[58]. A study categorized patients into severity groups. The incidence of comorbidities was greater in the severe (43.6%) and critical (67.1%) categories compared to the moderate group (37.8%)[40]. Individuals diagnosed with COVID-19 are classified into disease severity categories. In the mild category, clinical symptoms remain mild, and no abnormal radiological findings are observed[40]. Progressing to moderate disease, patients experience fever, cough, and other symptoms alongside pneumonia detected on chest CT scans[40]. The disease will escalate to severe if any of the following conditions are met: respiratory distress with a respiratory rate exceeding 30 breaths per minute, oxygen saturation below 93% on room air at rest, or a partial pressure of oxygen in arterial blood/FIO2 less than 300 mm Hg[40]. Advancing to the critical category, patients experience respiratory failure necessitating mechanical ventilation, shock, or other organ dysfunction, which requires intensive care unit (ICU) monitoring and treatment[40].

In sub-Saharan Africa, a study done in the DRC reported that severe COVID-19 patients were more likely to have comorbidities, where 69% of those who died among the cases reported having an underlying health condition[59]. In the same country, a different study found that chronic kidney disease significantly increased the hazard of COVID-19 mortality[51]. In particular, hypertension (aOR 5.91; 95%CI 1.89-18.50], chronic lung disease (aOR 2.97 95%CI 1.65 – 5.37] and haematological disorders (aOR 3.10 95%CI 1.04 – 9.24) were identified as factors linked to these severe outcomes. An Ethiopian study found that diabetes (aRR: 2.00), cardiovascular disease (aRR: 2.53), and having a malignancy (aRR: 4.57) were significant risk factors for COVID-19 mortality[56]. Similarly, a Nigerian study identified several other comorbidities as predictors of death in COVID-19 patients, including hypertension (OR: 2.21), diabetes (OR: 3.69), renal disease (OR: 12.53), cancer (OR: 14.12) and HIV (OR: 2.21)[57]. Interestingly, a study reported contrasting results. The Sudanese study comprising 105 patients, 29% of which died, found no comorbidities to be significant predictors of COVID-19 mortality[60].

Generally, within the South African context, the presence of comorbid conditions was linked to in-hospital COVID-19 mortality[12-15, 62]. Explicitly, hypertension, diabetes, chronic cardiac disease, chronic kidney disease, malignancy, tuberculosis, and HIV were all significant predictors for COVID-19 morality[12-15,62] . In a national study, over half the sample (58.6%) presenting with two or more comorbidities resulted in deaths[61]. At a provincial level, the Western Cape to be specific, in three studies conducted, diabetes and chronic renal disease were identified consistently as significant predictors of death among those three studies in the province[53,54,63]. Other reported predictors included chronic obstructive pulmonary disease, congestive heart failure, and, HIV infection, and prior current TB infection, hypertension, were identified as notable factors, HIV[53,54,63].

1.4.4 Obesity

Obesity is linked to various comorbidities that can exacerbate the severity of COVID-19 and increase the likelihood of mortality[64,65].Obesity is often accompanied by metabolic conditions such as type 2 diabetes mellitus (T2DM), chronic inflammation, hypertension and pulmonary or chronic obstructive pulmonary disease (COPD)[64,65]. These conditions can weaken the body's immune response, making it less effective in fighting off viral infections like COVID-19[66].

A study in the United States of America (USA) indicated that obese patients, particularly those under the age of 50, have shown a higher likelihood of hospitalisation due to COVID-19[67]. They were at an increased risk of mortality or requiring mechanical ventilation during their hospital stay[67]. Those categorized as having Class III obesity were associated with a higher risk of in-hospital death, suggesting that individuals with class III obesity were more likely to experience fatal outcomes during their hospitalization[67]. Furthermore, the study explored the relationship between severe obesity (BMI ≥40 kg/m2) and in-hospital death further, specifically in individuals aged 50 years or younger[67]. In this subgroup, severe obesity was found to be associated with an increased risk of in-hospital death too[67]. This indicated that individuals with severe obesity, when younger than 50 years old, were at a heightened risk of experiencing fatal outcomes during their hospitalization overall[67].

In sub-Saharan Africa, one study found that in the DRC, the COVID-19 mortality rate was 2.30 times higher among hospitalized individuals classified as obese[51]. Although no studies conducted in South Africa have identified obesity as a predictor of death, however studies in other regions have clearly shown how is a significant predictor of COVID-19 mortality.

1.4.5 Socioeconomic determinants

In Brazil, two studies were conducted to highlight the income and ethnic disparities as they relate to COVID-19 mortality[68]. Pardo Brazilians had a 45% higher risk, and Black Brazilians had a 58% higher risk of COVID-19 mortality compared to White Brazilians[68] and another Brazilian study noted a large household size and income inequality (measured by Gini Index) were associated with increased risk of COVID-19 deaths in Brazil[69], while in the US Black non-Hispanic adults in the US were 6 times and Hispanic were 4 times more likely to die from COVID-19 compared to White non-Hispanic adults[70]. In the United Kingdom, Wales & England specifically, COVID-19 mortality was highest among individuals, identifying as Black and lowest among those identifying as White[71]. Moreover, Black individuals in these countries had a COVID-19 death rate of 3.13 times greater than White individuals, and the rate was also elevated for people of other ethnicities[71]. In the Colombian state, USA, a 1% increase in the proportion of the Hispanic or Black population was associated with a 0.65% and 1.57% increase in COVID-19 deaths[72].

In a Sweden population-based study, those of working age, and those within the lowest income tertile, were 5.4 times more likely to die from COVID-19[73]. Additionally, individuals with primary or secondary education were more than twice as likely to die compared to those with post-secondary education in working ages[73]. Immigrants from low and middle-income countries were approximately twice as likely to die as compared to individuals born in Sweden[73]. Patients with Medicare insurance in the US had 1.5 times, and those with unknown insurance coverage had 2.2 times higher risk of mortality than those with commercial insurance[74].

One study conducted in South Africa aimed to highlight potential socio-economic disparities in COVID-19 outcomes in South Africa. The study investigated the interplay between age, sex, race, and socio-economic status in COVID-19 hospital admissions and deaths, and hospital admission[13]. Compellingly, this study used the health sector, as a proxy for socioeconomic status[13]. The study found that the case fatality rate was 8.1% higher in the public sector compared to the private sector (27% vs. 18.9%)[13]. They further reported admission in the public health sector had a 1.5 higher odds of being associated with an increased risk of mortality compared to admission in the private sector[13]. Additionally, those of Black African, mixed race, and Indian descent had higher odds of death relative to their white counterparts[13].

1.4.6 Vaccination status

In Spain, a study found that COVID-19 vaccines were found to significantly reduce the probability of death in patients with moderate to severe disease requiring oxygen therapy[75]. Firstly, the mortality rate was higher in the vaccinated group compared to the unvaccinated group[75]. However, after adjustment for the multiple comorbidities, the results, showed that the vaccinated group had decreased odds of death compared to those who were unvaccinated[75]. Particularly, the reduction in the risk of mortality was more pronounced among those who received the Pfizer vaccine followed by AstraZeneca, then Moderna, while the effect was lower with Sputnik[75].

A study in Iran comparing the mortality and length of ICU among vaccinated and unvaccinated hospitalised cases found that compared with the unvaccinated (39.3%), the first (8%), second (20%), and third (33%) doses of vaccine resulted in lower risk of ICU mortality in the adjusted model[76]. Moreover, the mean survival time was significantly shorter in the unvaccinated compared to the fully vaccinated

patients[76]. Furthermore, the duration of ICU stay was significantly shorter among the fully vaccinated than in the unvaccinated[80] group[76].

In Zambia, of the patients who had received ≥1 vaccine dose, fewer vaccinated (9.3%) patients died compared with the unvaccinated (24.2%) patients[77]. The vaccine effectiveness for progression to in-hospital mortality among hospitalized patients was 64.8%[77]. Locally, a South African study showed being partially, and fully, boosted and previous infection were associated with reduced risk of in-hospital mortality[15].

1.5 Problem Statement

Mpumalanga Province experienced a high number of in-hospital COVID-19-related deaths during the 2nd and 3rd waves[78] with a case fatality ratio (CFR) of 26.7%[12]. The province maintained the third-highest CFR (25.1%) after Eastern Cape and Limpopo provinces in the subsequent year, spanning the 3rd and 4th waves[13,14,15]. Furthermore, individuals hospitalized in Mpumalanga exhibited a 1.4-fold higher likelihood of in-hospital death when compared to those in the Western Cape[13,15]. Despite the high in-hospital COVID-19-related deaths and the persistent elevated case fatality ratios in Mpumalanga Province during the 2nd, 3rd, and 4th waves, there remains a lack of detailed understanding regarding the specific factors contributing to this trend. Further research is needed to explain the underlying reasons behind this persistent elevation in Mpumalanga. Identifying these factors could inform targeted interventions and strategies to improve outcomes and reduce mortality rates in Mpumalanga Province.

1.6 Justification

The existing body of literature has consistently identified certain factors that are associated with COVID-19 mortality, both on a global scale and within the specific context of South Africa.

However, there are limited studies examining survival outcomes and factors that can contribute to the mortality burden in patients hospitalised with COVID-19 in Mpumalanga Province. Describing the epidemiology and ascertaining risk factors of COVID-19 mortality in Mpumalanga will provide us with a better understanding of who is most afflicted by the disease in the province. The results from our study could be beneficial to help us determine the factors associated with in-hospital-related COVID-

19 deaths in a province where the cumulative cases, admissions, and deaths were ranked low in the country but with elevated in-hospital case fatality. This information could be beneficial to adopt existing policies for this population and help tailor future interventions around prevention and management in the province. Furthermore, this could also help direct the appropriate allocation of resources in the province and inform public health policies to reduce mortality rates and improve patient outcomes in the province for COVID-19 or future worldwide outbreaks.

1.7 Research Questions

1. What are the demographic and clinical characteristics of hospitalised COVID-19 patients in Mpumalanga Province, June 2020 – June 2022?
2. What is the time to death of hospitalised COVID-19 patients in Mpumalanga Province, June 2020 - June 2022?
3. What are the factors associated with mortality among hospitalised COVID-19 patients in Mpumalanga Province, June 2020 - June 2022?

1.8 Aim & Objectives

1.8.1. Aim

We aim to describe the characteristics of hospitalised COVID-19 patients, estimate the time to death and factors associated with mortality among -hospitalised COVID-19 patients in Mpumalanga Province, June 2020 – June 2022.

1.8.2. Objectives

1. To describe the demographic and clinical characteristics of hospitalised COVID-19 patients in Mpumalanga Province, June 2020 – June 2022.
2. To estimate the time to death among hospitalised COVID-19 patients in Mpumalanga Province, June 2020 – June 2022.
3. To determine the factors associated with mortality for COVID-19 hospitalised cases in Mpumalanga Province, June 2020 – June 2022.

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CHAPTER 2: MANUSCRIPT

This chapter introduces a manuscript prepared in accordance with the author guidelines for BMC Infectious Diseases journal. The paper explores the factors associated with in-hospital COVID-19 mortality in Mpumalanga Province. The formatting of this journal article may deviate from the rest of the research report to adhere to the author guidelines of the targeted journal for submission. A summary of the research aims, methods, findings, and conclusions will be given throughout this chapter. The appendices contain the specific guidelines provided by the journal **(Appendix 5)**.

Declaration

We, the undersigned authors of this article, hereby declare that the content presented within this manuscript is original and has not been published previously, nor is it under consideration for publication elsewhere. All authors have contributed to the conception, design, data acquisition, analysis, interpretation, drafting and review of this manuscript. Any sources of funding or conflicts of interest related to this research have been disclosed. Additionally, all ethical considerations and guidelines pertaining to human or animal subjects have been adhered to throughout the study. By submitting this article for publication, we affirm that it complies with the policies and standards of the journal and that all authors have read and approved the final version of the manuscript.

27 September 2024

Signature Date

Risk factors for in-hospital related COVID-19 deaths in Mpumalanga Province - June 2020 – June 2022: A Retrospective Observational Cohort Study

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Abstract

Background: South Africa was among the African countries heavily impacted by COVID-19, reporting significant case numbers and deaths. This study aimed to assess the demographic and clinical characteristics of hospitalized COVID-19 patients in Mpumalanga Province. We also analysed the factors associated with COVID-19 deaths in Mpumalanga Province.

Methods: We performed a retrospective cohort study using surveillance data of COVID-19 hospitalisations from Mpumalanga Province between June 2020 and June 2022, extracted from the DATCOV Surveillance System. Clinical severity was defined by the need for oxygen therapy, ventilation, or admission to High Care or Intensive Care Units. Kaplan-Meier survival analysis and Cox regression were used to estimate survival probabilities and identify risk factors for in-hospital mortality. Adjusted Hazard Ratios (aHR) with 95% Confidence Intervals (CI) were reported.

Results: Of the 20,960 hospitalized COVID-19 patients, 4,467 (21.6%) died. The majority were female (56%), and females accounted for 51.6% of the deaths. The median time to death was 25 days (IQR: 11–66). The overall mortality rate for this cohort was 21.6%. After adjusting for age, sex, comorbidities, and clinical severity, factors significantly associated with increased risk of in-hospital mortality included admission in Ehlanzeni [aHR 1.10; 95% CI 1.01–1.19] and Gert Sibande [aHR 1.20; 95% CI 1.10–1.30] districts, and during the second wave [aHR 1.09; 95% CI 1.02–1.18]. Protective factors included admission during the fourth wave [aHR 0.80; 95% CI 0.70–0.92], clinical severity [aHR 0.74; 95% CI 0.69–0.80], and private healthcare admission, which reduced mortality risk by 87%.

Conclusion: In-hospital mortality was significantly higher for patients admitted to hospitals located in Ehlanzeni and Gert Sibande districts, and during the second wave of the pandemic. Admission during the fourth wave, in private hospitals, and in clinically severe cases were associated with decreased mortality risk. Strenghtening the province's healthcare system, such as early identification of vulnerable groups to target vaccination campaigns, and improving healthcare infrastructure and access to underserved districts, low-density areas and in public hospitals could reduce in-hospital mortality in similar future pandemics.

Keywords: COVID-19, hospitalisation, in-hospital, mortality, factors, Mpumalanga

Background

A novel virus causing pneumonia of unknown origin was first discovered in Wuhan City, Hubei, China in December 2019[1,2]. The virus, later identified as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread rapidly in China and to other countries[2]. The World Health Organization (WHO) declared COVID-19 a public health crisis on 11 March 2020[3] according to the International Health Regulations (IHR) of 2005[3,4]. As of 10 March 2024, WHO has reported an estimated 774 889 074 confirmed cumulative global cases and 7, 038, 623 deaths[5]. In Africa, 9 576 544 cumulative confirmed cases including 175 381 deaths have also been reported[5]. South Africa accounted for 4 072 636 cumulative cases and 102 595 deaths[5].

While COVID-19 disease generally follows a self-limiting course, with individuals typically presenting with absent to moderate symptoms, a significant proportion may progress to severe or critical illness necessitating hospitalization[6]. Studies conducted in various countries have provided estimates of the proportion of COVID-19 infections leading to severe or critical cases. In China, these proportions were reported as 56% and 5.7% in separate studies[7,8], while in Italy, another study indicated a proportion of 38%[9]. Similarly, research conducted in the Democratic Republic of Congo (DRC) reported proportions of 30.6% and 24%[10.11]. Common factors identified as increasing the risk of severe or critical COVID-19 include chronic obstructive pulmonary disease (COPD), older age[12,13], and hypertension[10], Acute Respiratory Disease Syndrome (ARDS)/Respiratory Failure[13,14] and multiple organ dysfunction[15]. In a Chinese study focusing on estimated in-hospital severe cases, a staggering 67% of the cases resulted in death[7] and in-hospital mortality rate among critical patients was 41.1%[15]. Moreover, research consistently highlights older age, male gender, racial and ethnic disparities, socioeconomic status, obesity and underlying health conditions as key factors associated with adverse outcomes, such as severe illness and mortality, from COVID-19 globally[10,16-21]. However, it's essential to recognize that these factors may vary based on the population or setting[6,22].

In South Africa, many studies have researched risk factors in a specific population, namely, in-hospital mortality for COVID-19 on a national scale[6,12,13]. Several other studies have emanated from the Western Cape and Limpopo[23-32] in a similar study

population. The aforementioned and other studies in South Africa found factors associated with mortality include being non-white, being admitted to the public sector/low socioeconomic status, male sex, increasing age, comorbidities, wave, clinical severity, and variant [23-30]. Interestingly, countrywide studies consistently found that hospital admission in eight out of the nine South Africans had an increased risk of COVID-19 mortality[28,29]. Mpumalanga province was inclusive among the eight provinces although, it reported a lower number of cases, deaths, and hospitalisations in the country[33]. A study found COVID-19 cases hospitalised in Mpumalanga Province had 1.4 times higher odds of death compared to cases hospitalised in the Western Cape Province[29]. No study has been conducted in the province to further investigate this increased association with in-hospital mortality for COVID-19 found in the province. This study aimed to describe the demographic and clinical characteristics of all hospitalised COVID-19 patients and determine their time to death. We also analysed the factors associated with COVID-19 deaths in Mpumalanga Province.

Methods

Study design and setting

We conducted a retrospective cohort study using data from the DATCOV Surveillance System. DATCOV is a national electronic hospital-based surveillance system that collected demographic and clinical information on COVID-19 admissions[34]. Patients admitted with suspected COVID-19 or other unrelated conditions were initially placed in a Person Under Investigation (PUI) ward, where they were swabbed and tested for COVID-19. If confirmed positive, they were transferred to a dedicated COVID-19 ward—general ward, High Care, or ICU—based on the attending clinician's assessment of their condition. Oxygen therapy and mechanical ventilation were provided as needed, depending on the severity of the patient's symptoms and clinical assessment. Patients were moved between levels of care, either escalated or de-escalated, as their condition worsened or improved, until recovery/ discharge or death.

Mpumalanga Province is located in South Africa and spans a surface area of 76 495 km^2 [35]. Mpumalanga Province occupies 6.3% of the country’s total area and is home to an estimated 4 743 584 people [35,36]. The province is separated into 3 districts (Nkangala, Ehlanzeni, and, Gert Sibande) and those districts are further divided into

6, 4, and 7 sub-districts. South Africa has a dual healthcare system[37], where the public health sector serves an estimated 71,1 % of its inhabitants while the private health sector serves approximately 27%[38]. The public health sector is state-funded and the private health sector is financed primary through health insurance. Mpumalanga has a total of 33 public and 9 private hospitals.

Study Population

The study was conducted among patients with COVID-19 admitted to private and public hospitals in Mpumalanga Province from June 2020 to June 2022 (**Figure 2.1**).

Inclusion criteria

- Patients with a laboratory-confirmed diagnosis of COVID-19by real-time reverse transcriptase polymerase chain reaction (RT-PCR) or Antigen test
- Patients admitted to hospitals (public or private) in Mpumalanga province due to COVID-19 infection during the study period (June 2020 to June 2022)

Exclusion criteria

- Any recent admission if a patient had multiple admissions during the study period
- Patients transferred to other hospitals in and out of the province
- Patients with incomplete information, including demographic data, comorbidities, treatment history, and outcomes during their hospital stay
- Patients who were confirmed to have died from other causes by an attending clinician
- Patients who were still hospitalized at the time of data export were also excluded from the study.

Sampling

We included records of all hospitalised COVID-19 patients for the period June 2020 to June 2022.

Data Collection and analysis

Data were extracted from the DATCOV surveillance system. We extracted sociodemographic and clinical characteristics variables such as age, sex, date of admission, comorbidities, treatment, and the study outcome in a password Microsoft Excel spreadsheet. The data was imported, cleaned, coded, and analysed using Statistical Software STATA version 17 (StataCorp, College Station, TX, Station). Two variables were used as proxies. Variable, wave period was created and used as a proxy for SARS-CoV-2 variants and health sector as a proxy for social economic status. Clinical severity was defined by the need for oxygen therapy, mechanical ventilation, or admission to High Care or the Intensive Care Unit.

Continuous variables were summarized using the median and interquartile range (IQR), while categorical variables were described with counts and proportions. Survival analysis was used to examine the time to death among hospitalized COVID-19 patients. A bivariate analysis was conducted, and the log-rank test was used to assess significant differences between exposure and outcome variables. Variables with a p-value below 0.25 in univariate analysis were considered for multivariable Cox regression analysis. Variables were selected *a prior* based on relevant literature and the availability of data in the surveillance system, which included age, sex, racial/ethnic background, comorbidities, and treatment interventions.

The outcome of the study was in-hospital mortality, measured from the date of admission to either discharge or recorded in-hospital death. Mortality data were captured through the COVID-19 hospital-based surveillance system, which tracked patient outcomes during hospitalization. The outcome was determined by reviewing medical records and confirming whether the patient was discharged alive or died during their hospital stay.

The Kaplan–Meier method was employed to calculate the median survival time among hospitalized COVID-19 patients. Cox regression analysis was applied to identify factors associated with death among hospitalized COVID-19 patients. The validity of the Cox proportional hazard assumptions for significant dependent variables was assessed using the Schoenfeld residuals global test. Due to the violation of these assumptions, extended Cox regression analysis was employed to

account for time-dependent variables. According to the Cox model, variables with a p-value less than 0.05 were deemed statistically significant.

Ethical Considerations

Ethical approval for this study was obtained from the Witwatersrand Human Research Ethics Committee (HREC) (Clearance certificate no: M230311). Permission to conduct the study was granted by the Mpumalanga Department of Health. The data was anonymized to protect the identifiable personal information of patients. The dataset was stored in a password-protected laptop, only known by the principal investigator.

Results

Recruitment of cases

Cases for our cohort were recruited through DATCOV, a hospital-based surveillance system. This involved identifying all hospitalised individuals who presented to the hospitals and were diagnosed COVID-19 positive. Those who met our inclusion criteria were included and those who did not were excluded.

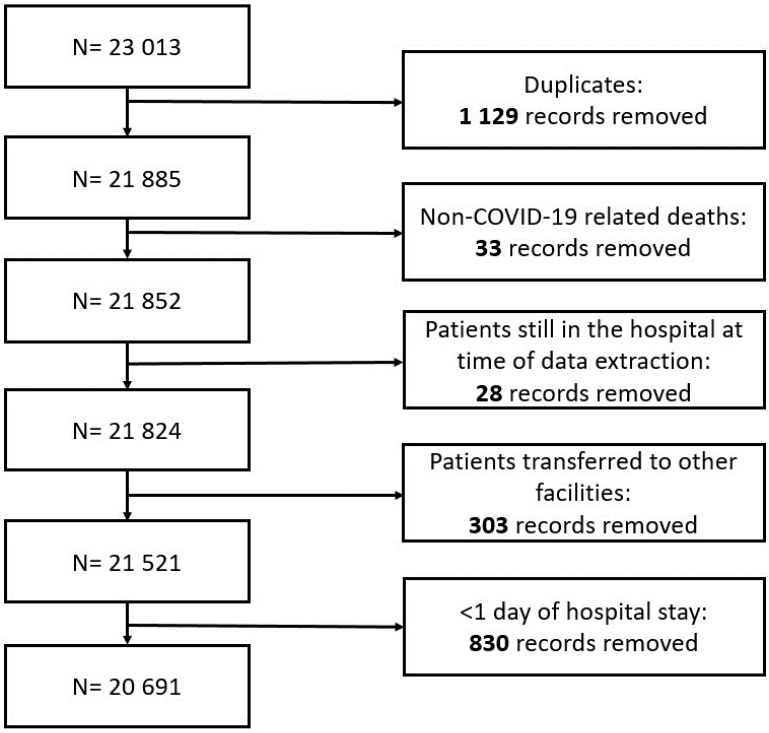

Figure 2.1: Flow diagram of participants included in COVID-19 in-hospital death analysis in Mpumalanga Province, June 2020 – June 2022. Covid-19=coronavirus disease 2019.

Demographic Characteristics

A total of 20 690 patient medical records were used for our study and 11 592 (56.1%) of COVID-19 admissions were female. The median age of the study population was 52 years (IQR: 36-64) and 12 401 (59.9%) admissions were Black African. Patients residing in Ehlanzeni district accounted for 7277 (35.2%) of the admissions and 11 218 (53.42%) cases were admitted to the private sector (53.9%). Of the 1338 admissions that provided a smoking history, 1 109 (83%) had never smoked (**Table 2.1**).

Clinical Characteristics

Over half, 4792 (53.6%) of the patients had at least one known comorbidity. The most common comorbidity recorded was hypertension, with 5 767 (27.9%) of the total patient population being hypertensive. Obese patients accounted for 295 (1.4%) of the admissions. Nine hundred and seventy-nine (4.7%) of patients required admission to an Intensive Care Unit (ICU). The majority, 10 921 (52.8%) of admissions received oxygen therapy, additionally, 1 575 (7.6%) were mechanically ventilated, 1 391 (6.7%) were admitted into High Care and 979 (4.7%) when they presented to the hospital. Most of the admissions (11 825/20 690; 57.2%) were clinically severe. Out of the 20 690 admissions, 4 467 (21.6%) died. Among those who died, the proportion of females (2 305/4 467, 51%) and those 60 years (2 594/4 467, 58.2%) of age and above were consistently the majority. Among the admissions that resulted in deaths, 11 155 (53.9%) patients were treated in the public sector but the public sector treated the majority of the 2 807 (62.8%) deaths, 3 403 (76.2%) admissions were admitted into a general ward upon presentation, and 3 025 (67.7%) of the deaths were initiated on oxygen therapy, while 3 578 (80.1%) deaths did not receive mechanical ventilation. Most admissions occurred during the third wave (delta variant), where 3 516 (78.7%) deaths presented as clinically severe (**Table 2.2**).

Median time-to-death of COVID-19 hospitalised cases

Figures 2.2 , 2.3 and 2.4 illustrate survival curves, and **Table 2.3** presents the median time to death for the study population. The overall median time to death was 25 days (IQR: 11 – 66). Females had a slightly higher survival time (26 days) compared to males (24 days). Age group 20-39 experienced increased median survival time (48 days) relative to ages 40-59 (29 days) and 60+ (17 days). Individuals of Indian descent had reduced median survival time (19 days) compared to mixed race (30 days), White

(28 days), and Black African descent (26 days). Median survival time varied across districts, with the lowest observed in Ehlanzeni (22 days), followed by Gert Sibande (26 days), and Nkangala (28 days). The private sector showed a higher median survival time (29 days) than the public sector (20 days). Current smokers had a higher median survival time (117 days) compared to former smokers (16 days) and non-smokers (25 days).

Figures 2.3 and 2.4 present Kaplan-Meier curves and **Table 2.3** displays median survival times for clinical predictors. Median survival time was higher for those without hypertension (28 days) and diabetes (28 days) compared to those with these conditions. A similar median survival time was observed for individuals with and without cardiovascular disease (27 days). Pulmonary disease admissions had a higher median survival time (18 days) than admissions without pulmonary disease (28 days). Patients with renal disease (11 days) had reduced median survival time compared to those without (27 days). HIV-positive individuals had a lower median survival time (21 days) than HIV-negative individuals (27 days). Active TB infection was associated with a higher median survival time (28 days) than those without TB (27 days). Obese individuals had a lower median time to death (15 days) than non-obese individuals (22 days). The second and third waves exhibited lower median survival times (22 days) compared to the first (29 days) and fourth waves (38 days).

Figure 2.4 displays Kaplan-Meier curves, and **Table 2.3** shows median survival times for treatment-related predictors. Patients ever admitted to a general ward had the highest median survival time (28 days) compared to High Care (22 days) or ICU (18 days). The median time-to-death for those receiving oxygen therapy (24 days) was lower than those not receiving it (28 days). Individuals who were never ventilated had a longer median survival time (29 days) compared to those ventilated (18 days). Median survival time was reduced for those experiencing severe disease (22 days) compared to those without severe disease (39 days).

Univariate Analysis

Demographic Characteristics

Table 2.3 presents findings from the univariate analysis of demographic clinical and treatment characteristics. The overall incidence rate of in-hospital mortality for the study population was 25.82 per 1000 person-years. Females had a significantly higher incidence rate (26.75 per 1000 person-years) than males. The age group 60+ (39.53 per 1000 person-years) exhibited a significantly higher incidence rate compared to age groups <20, 20-39, and 40-59. Individuals of Indian descent (36.92 per 1000 person-years) had a significantly higher incidence rate than those of Black African, mixed race, and White descent. Gert Sibande district (28.49 per 1000 person-years) had a significantly higher incidence rate than Ehlanzeni and Nkangala districts. The public sector (16.99 per 1000 person-years) showed a significantly higher incidence rate than the private sector. Former smokers had a non-significantly higher incidence rate compared to current smokers and those who never smoked.

Clinical Characteristics

The incidence rate of in-hospital death was significantly higher among those with hypertension (31.04 per 1000 person-years) and diabetes (33.14 per 1000 person-years) diagnoses compared to those without. Individuals with cardiovascular disease (19.83 per 1000 person-years) had a significantly lower incidence rate than those without. Pulmonary disease (30.62 per 1000 person-years) patients had a significantly reduced incidence rate compared to those without a pulmonary diagnosis. Renal disease (57.11 per 1000 person-years) patients experienced a significantly higher incidence rate than those without renal disease. Those with cancer (34.35 per 1000 person-years) or HIV-positive (31.74 per 1000 person-years) diagnoses had significantly higher incidence rates than those without. Active TB (24.11 per 1000 person-years) infection and obesity were associated with significantly higher incidence rates of in-hospital mortality. The second (33.12 per 1000 person-years) wave had a significantly higher incidence rate than the third (28.85 per 1000 person-years), first (22.64 per 1000 person-years), and fourth (15.75 per 1000 person-years) waves **(Table 2.3)**.

Treatment Characteristics

Patients initially admitted to the ICU (35.36 per 1000 person-years) had a significantly higher incidence rate of in-hospital mortality than those in the High Care Unit (31.18 per 1000 person-years) or a general ward (24.08 per 1000 person-years). The incidence rate for those who received oxygen therapy (27.97 per 1000 person-years) was significantly higher than those who did not. Individuals who ever received mechanical ventilation (35.19 per 1000 person-years) experienced a significantly higher incidence rate compared to those who never ventilated. The incidence rate for those who experienced severe disease (29.44 per 1000 person-years) was significantly higher than those who did not.

Factors associated with time to death for COVID-19 mortality

Table 2.4 presents the main effects model of the Cox Regression model, along with the extended Cox regression model involving time-varying covariates interacting with the natural logarithm of time and factors identified as significantly associated with COVID-19 mortality. After controlling for all variables, there was a 1% reduction of hazards for COVID-19 mortality in females (aHR: 0.99; 95%CI: 0.94 – 1.06) compared to males although not significant. The hazard for mortality was non-significantly lower for ages 20-39 (aHR: 0.91; 95%CI: 0.67 – 1.23) and 40-59 (aHR: 0.93; 95%CI:0.70 - 1.23), while slightly higher for ages 60+ (aHR: 1.02; 95%CI: 0.77 – 1.35) compared to ages 19 and younger. District significantly influenced COVID-19 mortality, with Ehlanzeni district having a 1.10 times higher hazard (95%CI: 1.01 – 1.19) than Nkangala district. Gert Sibande district (aHR:1.20; 95%CI:1.10 – 1.30) exhibited significantly slightly higher hazards of mortality compared to Nkangala district as well. In the main effects model, individuals admitted to the private sector had a significantly lower hazard (81%) than those in the public sector (95%CI: 0.16 – 0.23) (**Table 2.4**). However, when we included the health sector as a time-varying covariate, there was a statistically significant 53% increase in mortality risk (95%CI: 1.42 – 1.64), resulting in an 87% significantly lowered hazard for each unit increase in time for private sector admissions compared to public sector admissions. The hazards of death for individuals with hypertension (aHR: 0.97; 95%CI: 0.88 – 1.07), diabetes (aHR: 1.07; 95%CI: 0.97 – 1.18), cardiovascular disease (aHR: 1.17; 95%CI: 0.82 – 1.68), and renal disease (aHR:1.11; 95%CI: 0.76 -1.63) were non-significantly lower than those without all the previous mentioned. Among those with HIV (aHR: 0.93; 95%CI: 0.79 –

1.10), the hazard of death was lower but showed no significance. Severe disease (aHR: 0.74; 95%CI: 0.69 – 0.80) was associated with a significantly lower hazard of mortality. The hazard of death was not significantly lower for individuals admitted during the first wave [Wild type/D614G] (aHR: 0.94; 95%CI: 0.84 – 1.05) compared to the third [Delta] but significantly lower during the fourth wave [Omicron] (aHR:0.80; 95%CI: 0.70 – 0.92). However, there was a significant increase in the hazard during the second wave Beta (aHR: 1.09; 95%CI: 1.02 – 1.18).

Discussion

We studied the demographic and clinical characteristics and outcomes of 20 690 COVID-19 patients hospitalised in Mpumalanga Province. Our analysis revealed that more than half of the admissions and deaths were among females, contrary to studies in the Americas and Asia where males dominated[17,39,40]. However, global reviews showed mixed results indicating an equal distribution between males and females[42]. South African studies mirrored our findings, reporting higher admissions and deaths among females[26,27,28,32] . The 40–59 age group had the highest admissions, while the ≥60 age group exhibited the most severe cases and deaths, aligning with local and global trends[17,26,27,43]. Moreover, deaths increased with age across sexes and races, consistently observed in the ≥60 age category in all waves. Furthermore, this aligns with Europe, the USA, and Asia, where older individuals had higher admission rates[41,42,43] .

In-hospital mortality was 21.6%, consistent with rates in sub-Saharan Africa, the Americas, and China, ranging from 2.8% to 67% [1,2,10,44-49]. Our study observed mortality exceeding 70% among clinically severe cases. Furthermore, mechanical ventilation was required for 8%, with 20% mortality in our study whereas a local study reported higher (54%) intubation and ventilation leading to a 62% mortality rate in the ICU[31].

Despite comorbidities in 23% of cases, mainly hypertension and diabetes, age and comorbidities were not significant mortality factors. Both diabetes and hypertension were more prevalent in the 40–59 and ≥60 age groups. Several prior studies have indicated that age constitutes a primary factor in hypertension and type 2 diabetes[50] .

Median survival time was 25 days, but longer than in an Ethiopian study (9 days). Expected risk factors like age and comorbidities from literature[10,27,28,40,51] were not significant in our analysis, instead admission in specific districts and wave influenced mortality risk. However, a smaller cohort in Sudan revealed that age and comorbidities were also not found to be associated with in-hospital COVID-19 mortality[47] .

Admission in specific districts influenced mortality risk, with Ehlanzeni and Gert Sibande districts showing higher risks than Nkangala, likely due to population density and healthcare infrastructure disparities. In Ehlanzeni, the presence of a tertiary hospital capable of delivering specialized care and advanced medical interventions may have contributed to the strain on the healthcare facility[52]. This strain could potentially be linked to two factors: an increased influx of COVID-19 cases from an already densely populated region as a Metro in the province and a surge in referrals from the neighbouring district of Gert Sibande. This strain could have further impacted various medical resources, such as staff, equipment, transportation, and hospital beds, potentially compromising the quality of care for COVID-19 patients[52]. Studies conducted in Algeria, India and South America found that larger metropolitan areas with dense populations had an increased risk for COVID-19 infection[53-57]. Moreover, COVID-19 mortality and a low-density population such as in Gert Sibande could be explained by insufficient healthcare infrastructure[57] . The absence of a tertiary hospital may result in reduced access to specialized care and advanced medical interventions, ultimately contributing to elevated hazards of COVID-19 mortality. A study conducted in France also supports this finding, indicating that low-density areas, like Gert Sibande, may have faced challenges associated with inadequate healthcare structures during the pandemic[57].

Regarding the intersection of socioeconomic status and COVID-19 in-hospital mortality, over 60% of admissions occurred in the private sector, accounting for nearly 40% of deaths. Importantly, admission to private hospitals significantly reduced the risk of mortality by 87%, a finding consistent with studies from the United States, Mexico, and South Africa[21,28,44,58]. This highlights the role of socioeconomic status in shaping COVID-19 outcomes within hospital settings, or at

the very least, highlights the complex relationship between healthcare access and mortality risk[21,28].

COVID-19 variants had a major impact on the trajectory of the pandemic in South Africa. Existing literature has consistently demonstrated significant associations between different waves of the pandemic and specific Variants of Concern (VOC) in the country[27,28,29,30,59,60]. The Beta variant, which dominated the second wave in the country, showed increased transmissibility and capacity to evade immune responses[60]. This wave, following the relaxation of lockdown measures after the first wave, led to a notable surge in both cases and deaths[18,61].

In contrast, the fourth wave, driven by the Omicron variant, dominated during the fourth wave in South Africa, proved to be highly contagious compared to the Delta and ancestral variants[29,30,62]. Contrary to its transmissibility, the Omicron variant resulted in decreased hospital admissions, severe disease and in-hospital deaths in both South Africa and Mpumalanga Province[28,29,30, 60,62,63] findings similary to studies in England and China[64,65]. Morover, the fourth wave demonstrated a lower proportion of individuals requiring ventilations or experiencing severe disease compared to previous waves[28,29,63]. This shift in disease trends and mortality rates is attributed to factors like previous infections and vaccination coverage in the South African population[29,30,66]. Despite South Africa's low COVID-19 vaccination uptake, the United States experienced a contrasting scenario during the Omicron wave. In the United States, the impact of Omicron on morbidity and mortality was still significant, and outcomes were heavily influenced by vaccine dose dependency[29,67,68] . Lastly, severe disease was associated with a 26% lower mortality risk in our study. A Chinese study revealed that 93.6% of those who died in-hospital experienced severe and critically disease[69] . It's important to note that many studies did not explicitly consider clinical severity as a predictor for mortality, as it often served as an endpoint or studied outcome[,10,69,15,70] . The definition of disease severity varied across studies, with some incorporating mortality as a parameter[10,69,15,70]. However, in the study, the presentation of clinical severity emerged as a protective factor for in-hospital COVID-19 mortality[10,29,58] . This discrepancy could be attributed to our approach of using treatment interventions to categorize clinical severity.

Several preventative measures are recommended to address the challenges identified and improve future pandemic responses. First, strengthening healthcare infrastructure, particularly in low-density areas like Gert Sibande, is crucial for enhancing access to specialized care and reducing mortality rates. Targeted public health interventions should be tailored to at-risk populations, such as older adults and those in underserved districts, to effectively address healthcare disparities. Furthermore, improving healthcare access for lower socioeconomic groups, particularly in public hospitals, is vital for mitigating mortality risks and ensuring more equitable health outcomes. Additionally, the early identification of vulnerable groups through research for vaccination campaigns is essential for bolstering population immunity and preventing severe outcomes. Implementing these measures will contribute to a more robust response to similar future pandemics and better safeguard public health.

Conclusion

This study offers a region-specific perspective on the demographic and clinical characteristics of COVID-19 hospitalizations in Mpumalanga Province. District-specific factors also influenced mortality, with higher risks in densely populated areas and those with limited healthcare infrastructure. Admission to private hospitals was associated with a substantial reduction in mortality, emphasizing the influence of socioeconomic status on health outcomes. The study further highlights the dynamic impact of COVID-19 variants, with the Beta variant linked to increased mortality and the Omicron variant associated with reduced disease severity and hospitalizations. To enhance future pandemic responses, it is essential to strengthen healthcare infrastructure, to improve access to specialized care and reduce mortality. Early identification of vulnerable groups for vaccination efforts through research to boost population immunity and preventing severe outcomes. Moreover, targeted interventions should address at-risk populations, while improving healthcare access for lower socioeconomic groups in public hospitals. These measures will strengthen pandemic preparedness and promote more equitable health outcomes for similar future pandemics.

Competing Interests

The authors confirm that the research was carried out without any commercial or financial affiliations that could be perceived as a conflict of interest.

Funding

The authors would like to acknowledge the funding support received for this research and related studies from The South African Field Epidemiology Training Programme.

Author's Contribution

The study questions were developed by Lethukuthula Zondi, Hluphi Mpangane, Khuliso Ravhuhali, and Dr. Innocent Maposa. The study protocol was reviewed and endorsed by all authors. Lethukuthula conducted the research, analyzed the data, and drafted the manuscript. Co-authors supervised the research process and provided feedback on the manuscript.

Acknowledgments

We would like to acknowledge the Mpumalanga Public Health Directorate and the South African Field Epidemiology for their continued support and mentorship.

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Table 2.1: Sociodemographic Characteristics of COVID-19 Admissions in Mpumalanga Province, June 2020 - June 2022.

Characteristics	**Total (n=20 690)**	**Alive (n=16 223)**	**Died (n=4 467)**	***p*-value**
Sex				<0.0001
Female	11 592	9 287 (57.2%)	2 305 (51.6%)	
Male	9 091	6 929 (42.7%)	2 162 (48.4%)	
Age, years, median (IQR)	52 (36 – 64)	48 (33 – 61)	63 (52 – 72)	<0.0001
< 20	1 635	1 581 (9.7%)	54 (1.2%)	
20 – 39	4 700	4 346 (26.8%)	354 (7.9%)	
40 – 59	7 424	5 963 (36.8%)	1461 (32.7%)	
60 +	6 931	4 333 (26.7%)	2 598 (58.2%)	
Race				<0.0001
Black	12 401	9 302 (57.3%)	3 099 (69.4%)	
Mixed	100	78 (0.5%)	22 (0.5%)	
Indian	97	61 (0.4%)	36 (0.8%)	
White	1 787	1 371 (8.5%)	416 (9.3%)	
Other	32	26 (0.2%)	6 (0.1%)	
Unknown	6 273	5 385 (33.2%)	888 (19.9%)	
Smoking (n=1 336)				0.094
Never smoked	1 109	818 (82.7%)	291(83.9%)	
Former smoker	71	47 (4.8%)	24 (6.9%)	
Current smoker	156	124 (12.5%)	32 (9.2%)	
Health Sector				<0.0001
Private	11 155	9 495 (58.5%)	1 660 (37.2%)	
Public	9 535	6 728 (41.5%)	2 807 (62.8%)	
District				0.247
Ehlanzeni	7 277	5 666 (34.9%)	1 611 (36.1%)	
Nkangala	6 531	5 119 (31.6%)	1 412 (31.6%)	
Gert Sibande	6 882	5 438 (33.5%)	1 444 (32.3%)	
Wave Period (Variant)				<0.0001
Wave 1 (DG14G)	1 972	1545 (9.5%)	427 (9.6%)	
Interwave 1	1 091	916 (5.6%)	175 (3.9%)	
Wave 2 (Beta)	3 870	2 712 (16.7%)	1 158 (25.9%)	
Interwave 2	2 119	1 648 (10%)	471 (10.5%)	

Wave 3 (Delta)	7 061	5 303 (32.7%)	1 758 (39.4%)	
Interwave 3	501	417 (2.6%)	84 (1.9%)	
Wave 4 (Omicron BA.1/BA.2)	2 624	2 363 (14.6%)	261 (5.8%)	

*IQR interquartile range, P values were calculated using χ2 test.

Table 2.2: Clinical Characteristics of COVID-19 admissions in Mpumalanga Province, June 2020 - June 2022.

Characteristics	**Total (N=20 690)**	**Discharged Alive (n=16 223)**	**Died in-hospital (n=4 467)**	***p*-value**
Length of stay, days, median (IQR)	6 (3 –10)	6 (3 – 9)	6 (2 – 12)	0.853
Obese				
No	1 809	1 385 (8.5%)	1 809 (40.5%)	<0.0001
Yes	295	175 (1.1%)	120 (2.7%)	
Unknown	18 585	14 662 (90.4%)	3 923 (87.8%)	
Comorbidities				
Hypertension				
No	8 293	7 124 (43.9%)	1 169 (26.2%)	<0.0001
Yes	5 767	4 053 (25.0%)	1 714 (38.4%)	
Unknown	6 630	5 046 (31.1%)	1 584 (35.4%)	
Diabetes				
No	9 609	8 162 (50.3%)	1 447 (32.4%)	<0.0001
Yes	3 581	2 430 (15.0%)	1 151 (25.7%)	
Unknown	7 500	5 631 (34.7%)	1 869 (41.8%)	
Cardiac Disease				
No	12 030	9 981 (61.5%)	2 049 (45.9%)	<0.0001
Yes	143	94 (0.6%)	49 (1.1%%)	
Unknown	8 517	6 148 (37.9%)	2 369 (53.0%)	
Chronic Renal Disease				
No	11 989	9 952 (61.3%)	2 037 (45.6%)	<0.0001
Yes	95	50 (0.3%)	45 (1.0%)	
Unknown	8 606	6 221 (38.3%)	2 385 (53.4%)	
HIV positive				
No	11 664	9 694 (59.8%)	1 950 (43.6%)	<0.0001
Yes				

Unknown	1 391	981 (6.0%)	410 (9.2%)	
	7 655	5 548 (34.2%)	2 107 (47.2%)	
Active Tuberculosis				<0.0001
No	11 893	9 813 (60.5%)	2 021 (45.2%)	
Yes	212	45 (0.3%)	26 (0.6%)	
Unknown	8 585	6 365 (39.2%)	2 420 (54.2%)	
Ward upon Admission				<0.0001
General Ward	18 320	14 923 (92.0%)	3 403(76.2%)	
High Care	1 391	932 (5.7%)	459 (10.3%)	
ICU	979	368 (2.3%)	611 (13.7%)	
Oxygen Therapy				<0.0001
No	9 768	15 536 (95.8%)	1 442 (32.3%)	
Yes	10 921	686 (4.2%)	3 025 (67.7%)	
Mechanical Ventilation				<0.0001
No	19 114	15 536 (95.8%)	3 578 (80.1%)	
Yes	1 575	686 (4.2%)	889 (19.9%)	
Clinical Severity				<0.0001
Not Severe	8 865	7 914 (48.8%)	951 (21.3%)	
Severe	11 825	8 309 (51.2%)	3 516 (78.7%)	

*IQR interquartile range, P values were calculated by Mann–Whitney U test, $\chi 2$ test, as appropriate. ICU intensive care unit, HIV Human Immunodeficiency Virus.

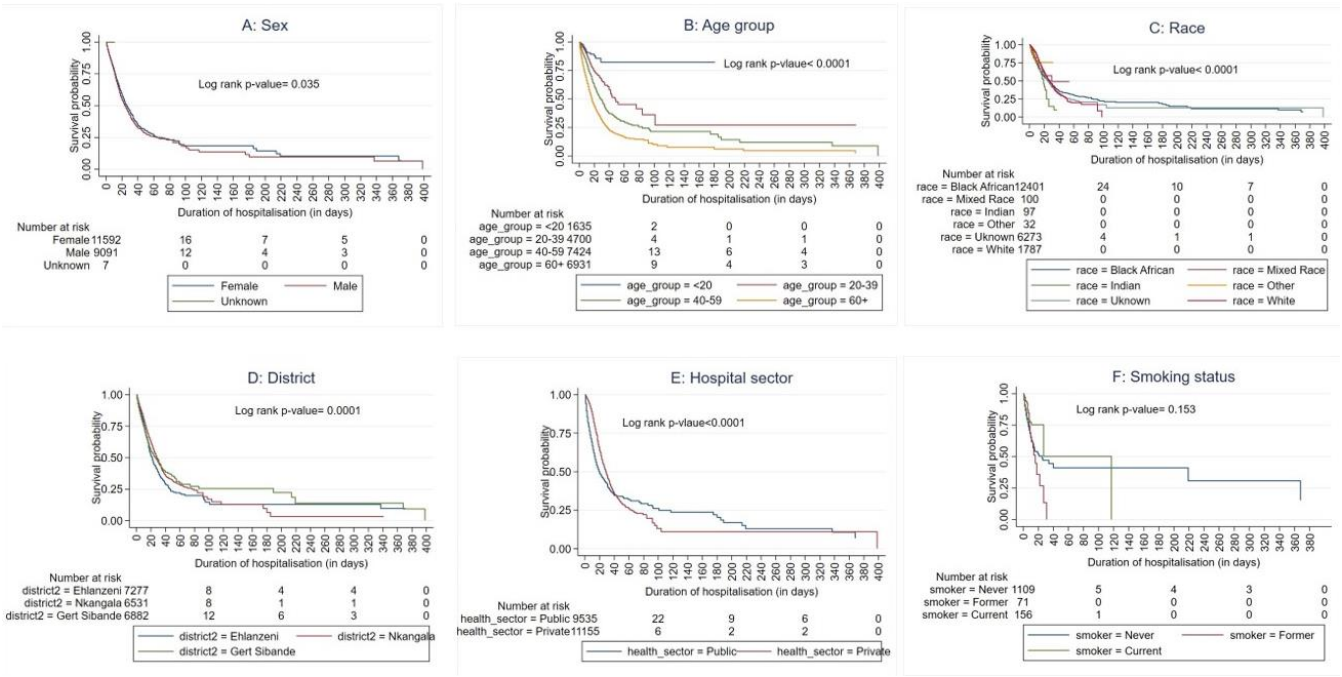

Figure 2.2: Illustrates Kaplan- Meier curves of Time to death among COVID-19 hospitalised cases stratified by sociodemographic information: (A) sex, (B) age group, (C) race, (D) district, (E) hospital sector and (F) smoking status in Mpumalanga Province from June 2020 – June 2022.

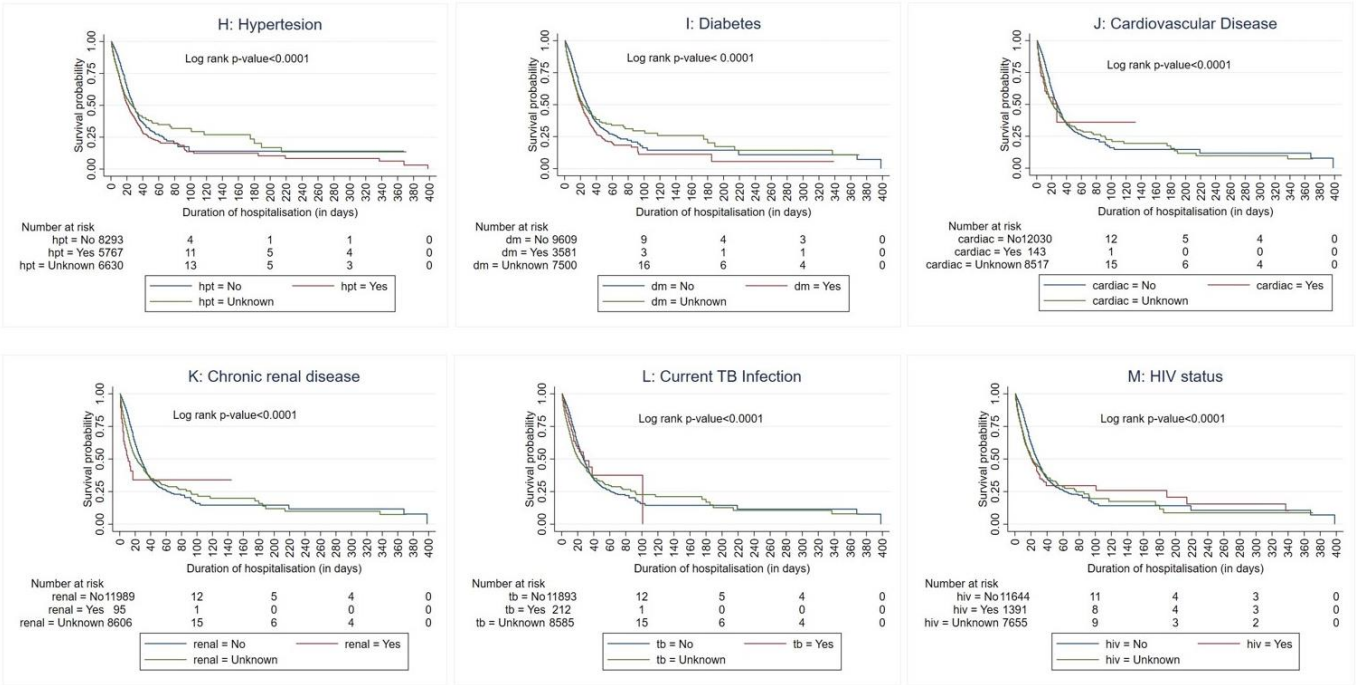

Figure 2.3: Illustrates Kaplan- Meier curves of Time to death among COVID-19 hospitalised cases stratified by clinical information: (H) hypertension, (I) diabetes, (J) cardiovascular disease, (K) chronic renal disease, (L) current TB infection and (M) HIV status in Mpumalanga Province from June 2020 – June 2022.

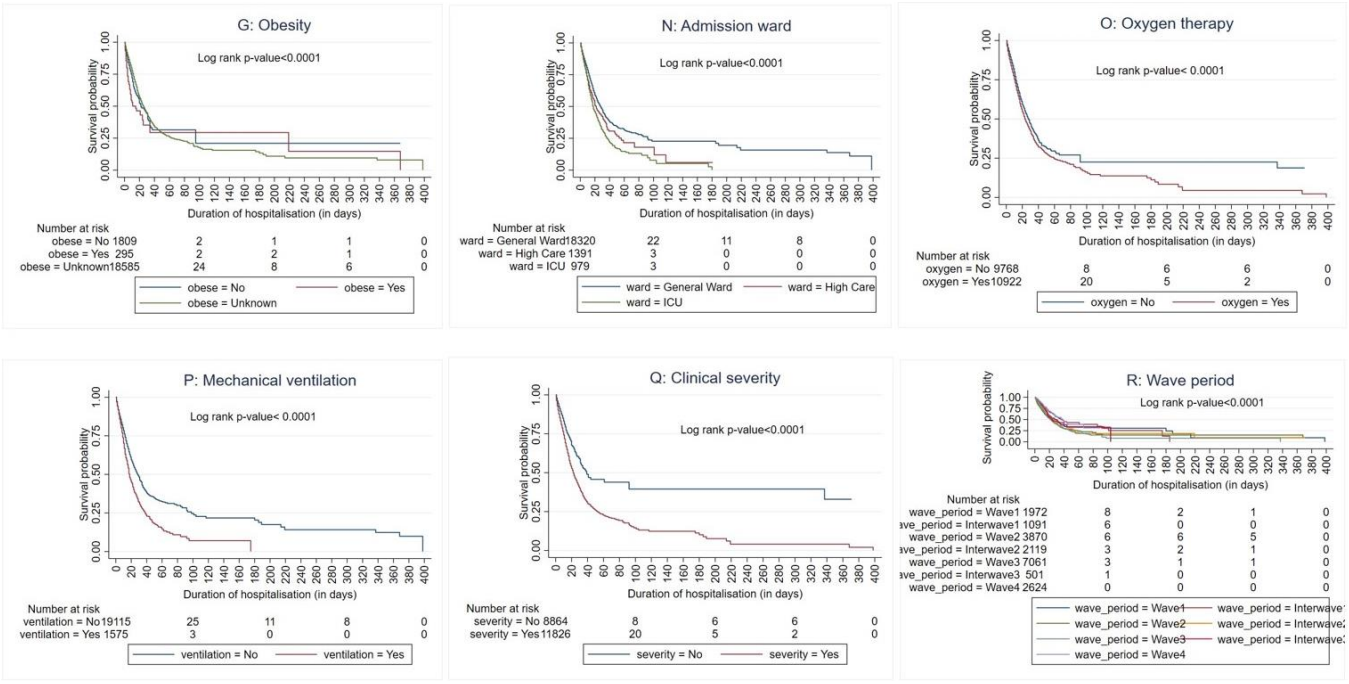

Figure 2.4: Illustrates Kaplan- Meier curves of Time to death among COVID-19 hospitalised cases stratified by clinical information: (G) obesity, (N) admission ward, (O) oxygen therapy, (P) mechanical ventilation, (Q) clinical severity and (R) wave period in Mpumalanga Province from June 2020 – June 2022

Table 2.3: Univariate survival analysis (Kaplan-Meier and log-rank test results) across possible predictor's groups for in-hospital COVID-19 admissions, in Mpumalanga Province, June 2020 - June 2022, (N= 20 690).

Characteristic	Number of admissions	Number of deaths	Time at risk	Incidence rate of in-hospital deaths per 1000 person-years (95% CI)	Median survival time – 50% percentile (IQR) [days]	p-value (Log-rank)
Overall	20 690	4 467	173,048	25.81 (0)	25 (11 – 66)	
Sex						<0.0001
Female	11 592	2 305	9, 217	26.75 (25.64 – 27.90)	26 (12 – 70)	
Male	9 091	2 162	8, 083	25.01 (24.01 – 26. 05)	24 (11 – 60)	
Age						<0.0001
<20	1 635	54	9, 112	5.93 (4.54 – 7.74)	-	
20-39	4 700	354	30, 169	11.73 (10.57 – 13.02)	48	
40-59	7 424	1 461	68, 049	21.47 (20.40 – 22.59)	29 (13 – 84)	
60+	6 931	2 598	65, 718	39.53 (38.04 – 41.08)	17 (7 – 38)	
Race						<0.0001
Black African	12 401	3 099	104, 415	29.68 (28.65 – 30.74)	26 (10 – 86)	
Mixed race	100	22	910	24.18 (15.92 – 36.72)	30 (11 – 30)	
Indian	97	36	975	36.92 (26.63 – 51.19)	19 (12 – 23)	
White	1 787	416	19, 701	21.12 (19.18 – 23.25)	28 (14 – 51)	
Other	32	6	276	21.74 (9.77 – 48.39)	-	
Unknown	6 273	888	46, 771	18.98 (17.78 – 20.28)	24 (14 – 55)	

District						<0.0001
Ehlanzeni	7 277	1 611	59, 043	27.29 (25.98 – 28.65)	22 (11 – 47)	
Gert Sibande	6 882	1 444	50, 687	28.49 (27.06 – 29.99)	26 (10 – 189)	
Nkangala	6 531	1 412	63, 318	22.30 (21.17 – 23.49)	28 (13 – 79)	
Health Sector						<0.0001
Private	11 155	1 660	97,690	37.25 (35.89 – 38.65)	29 (16 – 64)	
Public	9 535	2 807	75,358	16.99 (16.19 – 17.83)	20 (7 – 101)	
Hypertension						<0.0001
Yes	5 767	1 714	55,221	31.04 (29.60 – 32.54)	21 (10 – 47)	
No	8 293	1 169	64,972	17.99 (16.99 – 19.05)	28 (15 – 66)	
Unknown	6 630	1 584	52,855	29.97 (28.53 – 31.48)	26 (10 -175)	
Diabetes						<0.0001
Yes	3 581	1 151	34,730	33.14 (31.28 – 35.11)	21 (9 – 47)	
No	9 609	1 447	77,752	18.61 (17.68 – 19.59)	28 (15 – 66)	
Unknown	7 500	1 869	60,566	30.86 (29.49 – 32.29)	23 (9 – 175)	
Cardiovascular Disease						<0.0001
Yes	143	49	1 387	19.83 (18.99 – 20.71)	27	
No	12 030	2 049	103,327	35.33 (26.70 – 46.74)	27 (14 – 64)	
Unknown	8 517	2 369	68,334	34.67 (33.30 – 36.09)	27 (8 – 92)	
Pulmonary						<0.0001

Yes	503	129	4,213	30.62 (25.77 – 36.39)	18 (10 – 36)	
No	11 508	1 919	98,529	19.48 (18.62 – 20.27)	28 (15 – 64)	
Unknown	8 679	2 419	70,306	34.31 (33.06 – 35.81)	22 (8 – 92)	
Renal						<0.0001
Yes	95	45	788	57.11 (42.64 – 76.49)	11	
No	11 989	2 037	102,901	19.79 (18.95 – 20.67)	27 (14 – 62)	
Unknown	8 606	2 385	69,359	34.39 (33.03 – 35.79)	22 (8 – 92)	
Cancer						<0.0001
Yes	51	18	524	34.35 (21.64 – 54.52)	18	
No	11 990	2 051	102,946	19.23 (19.08 – 20.80)	27 (14 – 62)	
Unknown	8 649	2 398	69,578	34.47 (33.11 – 35.97)	22 (8 – 92)	
HIV						
Yes	1 391	410	12,919	31.74 (28.81 – 34.96)	21 (8 – 189)	<0.0001
No	11 644	1 950	99,935	19.51 (18.67 – 20.39)	27 (14 – 62)	
Unknown	7 655	2 107	60,194	35.00 (33.54 – 36.53)	22 (8 – 76)	
Current TB Infection						
Yes	212	57	2,364	24.11 (18.59 – 31.26)	28 (12 – 101)	<0.0001
No	11 893	2 017	101,910	19.79 (18.95 – 20.68)	27 (14 – 62)	
Unknown	8 585	2 393	68.774	34.79 (33.43 – 36.22)	22 (8 – 92)	
Obese						

Yes	295	120	2,679	44.79 (37.46 – 53.57)	15 (4 – 219)	<0.0001
No	1 809	242	13,572	31.24 (28.40 – 34.36)	22 (10 – 95)	
Unknown	18 585	3 923	156,795	25.02 (24.25 – 25.82)	25 (12 – 64)	
Wave period (N= 19 238)						<0.0001
Wave 1 (Wild type/ D614G)	1 972	427	18,865	22.64 (20.59 – 24.89)	29 (13 – 180)	
Interwave 1	1 091	175	9,727	17.99 (15.51 – 20.86)	37 (16 – 175)	
Wave 2 (Beta)	3 870	1 158	34,945	33.12 (31.28 – 35.10)	22 (8 – 59)	
Interwave 2	2 119	471	18,230	25.84 (23.61 – 28.28)	26 (12 – 55)	
Wave 3 (Delta)	7 061	1 758	60,932	28.85 (27.53 – 30.23)	22 (11 – 49)	
Interwave 3	501	84	4,136	20.31 (16.39 – 25.15)	24 (14 – 104)	
Wave 4 (Omicron-BA.1/BA.2)	2 624	261	16,571	15.75 (13.95 – 17.78)	38	
Admission Ward						<0.0001
General Ward	18 320	3 397	141,046	24.08 (23.29 – 24.91)	28 (12 – 92)	
High Care	1 391	459	14,720	31.18 (28.46 – 34.17)	22 (9 – 56)	
ICU	979	611	17,282	35.36 (32.66 – 38.27)	18 (9 – 37)	
Oxygen Therapy						<0.0001
Yes	10 922	3 025	108,164	27.97 (26.99 – 28.98)	24 (11 – 60)	
No	9 768	1 442	64,884	22.22 (21.11 – 23.40)	28 (12 – 92)	
Mechanical Ventilation						<0.0001
Yes	1 575	889	25,262	35.19 (32.95 – 37.58)	18 (9 – 38)	

No	19 115	3 578	147,786	24.21 (23.43 – 25.02)	29 (12 – 98)	
Clinical Severity						<0.0001
Severe	11 826	3 516	119,451	29.44 (28.48 – 30.42)	22 (10 – 52)	
Not severe	8 864	951	53,597	17.74 (16.65 – 18.91)	39	

Table 2.4: Multivariable Cox Regression model for factors associated with in-hospital related COVID-19 mortality in Mpumalanga Province, June 2020 – June 2022, N=19 231.

Patient characteristics	Adjusted Hazard ratio (95% CI)	*p*-value
Main model		
Sex		
Female	Ref	Ref
Male	0.99 (0.94 – 1.06)	0.944
Age		
<20	Ref	Ref
20-39	0.91 (0.67 – 1.23)	0.538
40-59	0.93 (0.70 – 1.23)	0.598
60+	1.02 (0.77 – 1.35)	0.909
Race		
Black African	1.09 (0.96 – 1.23)	0.187
Mixed race	1.42 (0.92 – 2.19)	0.112
Indian	1.03 (0.72 – 1.48)	0.853
White	Ref	Ref
Other	1.89 (0.84 – 4.27)	0.122
Unknown	1.32 (1.15 – 1.52)	<0.0001
District		
Ehlanzeni	1.10 (1.01 – 1.19)	0.028*
Gert Sibande	1.20 (1.10 – 1.30)	<0.0001*
Nkangala	Ref	Ref
Health Sector		
Private Sector	0.19 (0.16 – 0.23)	<0.0001*
Public Sector	Ref	Ref
Hypertension		
Yes	0.97 (0.88 – 1.07)	0.547
No	Ref	Ref
Unknown	0.97 (0.85 – 1.11)	0.644
Diabetes		

Yes	1.07 (0.97 – 1.18)	0.170
No	Ref	Ref
Unknown	1.06 (0.94 – 1.20)	0.354
Cardiovascular Disease		
Yes	1.17 (0.82 – 1.68)	0.388
No	Ref	Ref
Unknown	1.13 (0.83 – 1.52)	0.439
Chronic Renal Disease		
Yes	1.11 (0.76 – 1.63)	0.578
No	Ref	Ref
Unknown	0.81 (0.59 – 1.10)	0.177
HIV Status		
Yes	0.93 (0.79 – 1.10)	0.412
No	Ref	Ref
Unknown	1.06 (0.89 – 1.24)	0.512
Current TB Infection		
Yes	0.91 (0.67 – 1.24)	0.553
No	Ref	Ref
Unknown	1.07 (0.83 – 1.39)	0.598
Wave period		
Wave 1 (Wild type/D614G)	0.94 (0.84 – 1.05)	0.267
Interwave 1	0.88 (0.75 – 1.03)	0.105
Wave 2 (Beta)	1.10 (0.84 – 1.18)	0.018*
Interwave 2	0.94 (0.84 – 1.04)	0.195
Wave 3 (Delta)	Ref	Ref
Interwave 3	0.78 (0.62 – 0.97)	0.026
Wave 4 (Omicron-BA.1/BA.2)	0.80 (0.70 – 0.92)	0.001*
Clinical Severity		
Severe	0.74 (0.69 – 0.80)	<0.0001*
Not severe	Ref	
Time-varying coefficient model		

Health sector x ln(t)		
Private	1.53 (1.42 – 1.64)	<0.0001*
Public	Ref	

Sex, age, race, health sector, comorbidities, treatment, and classification were included in the final model. The combined effect of the health sector, treatment, and clinical severity was calculated using the main model and time-varying coefficients (i.e. for health sector: $1- e^{(-1.646 - 0.424)} = 0.874$). p-values were obtained by multivariable Cox regression analysis *Significant difference noted ($p < 0.05$) HR hazards ratio, CI confidence interval. Bold values are the statistically significant p defining the variables (factors) associated with mortality.

CHAPTER 3: CONCLUSION AND RECOMMENDATIONS

In this chapter, we provide a summary of the key findings from our study along with their interpretations. We also acknowledge the study's limitations and suggest areas for further research based on the results. Finally, we conclude by presenting several recommendations that could inform future research in similar contexts.

3.1 Conclusion

Our study presented a different region-specific perspective on the impact of the COVID-19 virus in Mpumalanga Province. Our findings identified factors influencing mortality risk, such as the district of admission and the sector (public or private) of healthcare. Ehlanzeni and Gert Sibande districts showed higher mortality risks than Nkangala, suggesting the influence of population density and healthcare infrastructure disparities on outcomes. Admission to the private sector significantly lowered mortality risk, emphasizing the impact of socioeconomic status on COVID-19 outcomes. The role of variants, particularly the Beta variant in the second wave and the Omicron variant in the fourth wave, highlights the dynamic nature of the virus and its varying impact on mortality risk. Severe disease was associated with a reduced mortality risk, providing insights into the relationship between COVID-19 severity and outcomes.

The findings highlight the importance of considering local factors in COVID-19 management strategies, and informing policymakers and healthcare professionals to tailor interventions effectively. The study serves as a valuable resource for understanding regional patterns and refining public health responses in the ongoing battle against the COVID-19 pandemic in Mpumalanga and similar contexts.

3.2. Recommendations

Recommendations include:

- Performing several imputation techniques to handle missing data
- Include community COVID-19 cases in the analysis

- Conduct studies on immunity and vaccination status among the Mpumalanga population
- The identification of vulnerable groups through research for vaccination campaigns and prioritisation is essential for bolstering population immunity, to effectively address healthcare disparities.
- Strengthening healthcare infrastructure, particularly in low-density areas like Gert Sibande.
- Improving healthcare access for lower socioeconomic groups, particularly in public hospitals, is vital for mitigating mortality risks and ensuring more equitable health outcomes.

APPENDICES

Appendix 1: Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I, Lethukuthula Zondi (Student number: 670478) am a student registered for the degree of Master of Science in Field Epidemiology in the academic year 2024 .

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: 27/09/2024

Appendix 2: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms L Zondi
School of Public Health
Division of Epidemiology and Biostatistics
Medical School
University

E-mail: lethukuthulazondi18@gmail.com

CC: Supervisor: Ms HD Mpanagane; Mr K Ravhuhali; Dr I Maposa <HluphuiM@mpuhealth.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/05/10

REF: R14/49

PROTOCOL NO: **M230311** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Risk factors for COVID-19 related in-hospital deaths in Mpumalanga Province, June 2020-June 2022*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms L Zondi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230311

NAME: (Principal Investigator)	Ms L Zondi
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	*Risk factors for COVID-19 related in-hospital deaths in Mpumalanga Province, June 2020-June 2022*
DATE CONSIDERED:	2023/03/31
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:	Ms HD Mpanagane; Mr K Ravhuhali; Dr I Maposa
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/05/10

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 **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

Date 2023/06/17

Appendix 3: Provincial Research Permission Letter

health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

Indwe Building, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
Private Bag X11285, Mbombela, 1200, Mpumalanga Province
Tel I: +27 (13) 766 3429, Fax: +27 (13) 766 3458

Litiko Letemphilo | Departement van Gesondheid | UmNyango WezeMaphilo

Enq: 013 766 3766
Ref: MP_202307_004

Research Permission Letter

MS L ZONDI
PRINCIPAL INVESTIGATOR
1978 MLONZI STREET, PROTEA NORTH,
JOHANNESBURG
1818

Dear Ms Zondi

STUDY TITLE: RISK FACTORS FOR COVID-19 RELATED IN-HOSPITAL DEATHS IN MPUMALANGA PROVINCE – JUNE 2020 – JUNE 2022

The Mpumalanga Provincial Health Research and Ethics Committee (MPHREC) has approved your research proposal in the latest format you sent, and hereby grant you permission to conduct your research as detailed below.

- Approval Reference Number: **MP_202307_004**
- Data Collection Period: **01/08/2023 to 30/12/2024**
- Approved Data Collection Facilities:

*MPUMALANGA PROVINCE PROVINCIAL OFFICES

Kindly ensure that conditions mentioned below are adhered to, and that the study is conducted with minimal disruption and impact on our staff, and also ensure that you provide us with a soft or hard copy of the report once your research project has been completed.

Conditions:
- *Researchers not allowed to make copies, take pictures of medical records or administer medicine to patients at the facility.*
- *Kindly notify the facility manager **a week BEFORE** you start with data collection to ensure that conditions are conducive in the facility.*
- *The FINAL RESEARCH FINDINGS must be uploaded on the NHRD website*

Kind regards

DR C NELSON
MPHREC CHAIRPERSON
DATE: 14/08/2023

Appendix 4: Turnitin Report

For Turnit Report-4.docx

ORIGINALITY REPORT

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Appendix 5: BMC Infectious Disease Research Article Guidelines

https://bmcinfectdis.biomedcentral.com/submission-guidelines/preparing-your-manuscript

Research article

Criteria

Research articles should report on original primary research or new experimental or computational methods, test or procedure. Research articles may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines. Non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered.

Studies reporting descriptive results from a single institution or region will not be considered unless analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

BMC Infectious Diseases strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's data repository guidance. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.

Authors who need help depositing and curating data may wish to consider contacting our Research Data Support Helpdesk.

Please note that for outbreak reports and intervention studies of nosocomial infection we endorse the ORION guidelines.

Cropped gels and blots can be included in the main text if it improves the clarity and conciseness of the presentation. In such cases, the cropping of the blot must be clearly evident and must be mentioned in the figure legend. Corresponding uncropped full-length gels and blot must be included in the supplementary files. These uncropped images should indicate where they were cropped, be labelled as in the main text and placed in a single supplementary figure. The manuscript's figure legends should state that 'Full-length blots/gels are presented in Supplementary Figure X'. Further information can be found under 'Digital image integrity' which is detailed on our Standards of Reporting page.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

present a title that includes, if appropriate, the study design e.g.:

"A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

or for non-clinical or non-research studies a description of what the article reports

list the full names and institutional addresses for all authors

if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below

Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it

accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.

indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

Background: the context and purpose of the study

Methods: how the study was performed and statistical tests used

Results: the main findings

Conclusions: brief summary and potential implications

Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

the aim, design and setting of the study

the characteristics of participants or description of materials

a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

Ethics approval and consent to participate

Consent for publication

Availability of data and materials

Competing interests

Funding

Authors' contributions

Acknowledgements

Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

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include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner.

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If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

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All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

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Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article [and its supplementary information files].

The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

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More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central strongly encourages the citation of any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

If you wish to co-submit a data note describing your data to be published in *BMC Research Notes*, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing.

Co-published data notes will be linked to the research article the data support (example).

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All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

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Acknowledgements

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Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

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Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

Article within a journal supplement

Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan. Blood 1979;59 Suppl 1:26-32.

Book chapter, or an article within a book

Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

OnlineFirst chapter in a series (without a volume designation but with a DOI)

Saito Y, Hyuga H. Rate equation approaches to amplification of enantiomeric excess and chiral symmetry breaking. Top Curr Chem. 2007. doi:10.1007/128_2006_108.

Complete book, authored

Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html (1999). Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt (1999). Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org (2006). Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, et al. Genome data from sweet and grain sorghum (Sorghum bicolor). GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.

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