MORTALITY TRENDS DURING THE FIRST THREE WAVES OF THE COVID- 19 PANDEMIC AT AN URBAN DISTRICT HOSPITAL IN KWAZULU-NATAL.

BY

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MANUSCRIPT AND PLAGIARISM DECLARATION

This Masters Dissertation consists of two manuscripts that are completed for submission to relevant academic medical journals. Author contributions are listed below respectively.

Manuscript 1: Hirachund O., Pennefather C., Naidoo M., Mortality trends during the Covid 19 pandemic at Wentworth Hospital, South Africa.
Author contribution: OH conceptualised the study and MN designed the data collection tool. OH and CP conducted the study and data collection. OH and CP performed the data analysis with assistance of the biostatistician (Cathy Connolly of UKZN). All authors contributed to drafting and production of the final manuscript.

Manuscript 2: Hirachund O., Pennefather C., Naidoo M., A retrospective and comparative analysis of mortality trends during the first three waves of the Covid 19 pandemic at Wentworth Hospital, South Africa.
Author contribution: As per manuscript 1, Dr Gill Hendry assisted with biostatistical analysis.

I Omishka Hirachund declare that:
1. That the work described in this dissertation has not been submitted to UKZN or any other institution for the purposes of an academic qualification, whether by myself or any other party.
2. That my contribution to the project is as follows: completion of the research proposal, obtaining ethics approval, data collection, data interpretation and writing of the manuscripts and thesis. The above was done by myself with the assistance of the individuals mentioned above. The data was collected during my lunch breaks at Wentworth Hospital or when I was post call. The other tasks were completed in my spare time.

[redacted] 31 July 2023

Omishka Hirachund Date

As the candidate's supervisor, I agree with all aspects of this Master's submission.

[redacted] 31 July 2023

Supervisor: Professor Mergan Naidoo Date

PRESENTATIONS

Poster presentation

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Poster and oral presentation

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DEDICATION

This thesis is dedicated to my beloved parents (Omesh and Mishy) for their ongoing support and faith in me – I would be nowhere without you. My sisters (Maru and Meha) and my love Nikhil: for their love and emotional support. To all the individuals who lost their lives during the C19 pandemic and lastly, to all the healthcare workers who worked tirelessly throughout mayhem – the world salutes you.

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ACRONYMS AND ABBREVIATIONS

- ACE — Angiotensin Converting Enzyme
- aHR — Adjusted Hazard Ratio
- ARDS — Acute Respiratory Distress Syndrome
- BMI — Body Mass Index
- C19 — Covid 19
- CFR — Case Fatality Rate
- CI — 95% Confidence Interval
- CKD — Chronic Kidney Disease
- CMJAH — Charlotte Maxeke Johannesburg Academic Hospital
- COPD — Chronic Obstructive Pulmonary Disease
- CPAP — Continuous Positive Airway Pressure
- CT Scan — Computerised Tomography Scan
- DATCOV — Daily Hospital Surveillance Tool
- DHs — District Hospitals
- DOH — Department of Health
- Hb — Haemoglobin
- HFNO2 — High Flow Nasal Cannula Oxygen
- HICs — High Income Countries
- HIV — Human Immunodeficiency Virus
- HT — Hypertension
- IQR — Inter Quartile Range
- INR — International Normalised Ratio
- KZN — Kwa-Zulu Natal
- LDH — Lactate Dehydrogenase
- LFTs — Liver Function Tests
- LMICs — Low- and Middle-Income Countries
- mMRC — Modified Medical Research Council
- NICD — National Institute for Communicable Diseases
- NYHA — New York Heart Association
- OR — Odds Ratio
- PCR — Polymerase Chain Reaction
- PTB — Pulmonary Tuberculosis
- SA — South Africa

➢ SAFPJ	South African Family Practice Journal
➢ SAMJ	South African Medical Journal
➢ SARS COV 2	Severe Acute Respiratory Syndrome Corona Virus 2
➢ SD	Standard Deviation
➢ SMR	Standardised Mortality Ratio
➢ SOFA	Sequential Organ Failure Assessment
➢ T2DM	Type 2 Diabetes Mellitus
➢ UE	Urea and Electrolytes
➢ WC	Western Cape
➢ WCC	White Cell Count
➢ WHO	World Health Organization
➢ WWH	Wentworth Hospital

ABSTRACT

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS COV 2) is the virus responsible for the COVID -19 (C19) pandemic. South Africa (SA) experienced multiple periods of increased transmission during which tertiary, regional and central hospitals were overwhelmed, resulting in a low acceptance rate of referrals from district hospitals (DHs). Thus, many severely ill, complex patients were managed at DHs while awaiting an Intensive Care Unit (ICU) bed. This study aims to describe mortality trends in a comparative analysis of the first three C19 waves at Wentworth Hospital (WWH).

Literature Review

Known risk factors for mortality are older age; male sex; Black African, Coloured and Indian compared to white race; admission in the public sector; comorbid diseases and obesity. Waves 2 and 3 had higher mortality rates compared to wave 1.

Methods

The study is a single-centre retrospective analysis of WWH's clinical records and included all patients infected with C19 (based on clinical, biochemical or radiological features suggestive of infection) who were admitted and subsequently demised in-hospital during the defined waves. Data was collected using a pre-piloted data extraction tool. Demographic and presenting features of the patients along with investigations and management strategies were compared by the primary investigator across the three waves.

Results

Wave one, two and three yielded case fatality rates of 14.5%, 27.6% and 6.3%, respectively, and crude fatality rates of 16.7%, 33.0% and 12.2%, respectively. Black Africans were less likely to demise during the third wave (odds ratio (OR) 0.54; 95% confidence interval (CI) 0.31 to 0.94). Obesity was most prevalent in the second wave (OR 1.87; CI 1.01 to 3.46). Patients in the second wave had clinical frailty scores of less than five (OR 2.51; CI 1.56 to 4.03). Severe ground glass appearance on chest radiographs was most common during the second wave (OR 2.37; CI 1.49 to 3.77).

Conclusion

The beta variant dominated the second wave and was the most virulent, as highlighted by the highest case- and crude fatality rates. This study identified the need to understand if case fatality

rates and mortality trends at a DH were significantly higher than those at regional or tertiary hospitals. It is hoped that this study will provide clinical and hospital managers, and provincial and national healthcare policy makers with insight into challenges faced in the health system in the public health sector and allow implementation of improved public health and planning strategies for future pandemics.

CHAPTER 1: INTRODUCTION

On March 11, 2020, the World Health Organisation (WHO) declared C19 a global pandemic[1] and estimated a global mortality rate of approximately three percent of confirmed cases.[1] Clinical presentation of the illness varied from mild, flu-like symptoms; to moderate symptoms or severe, pneumonia-like symptoms.[2] Individuals with severe and critical disease often require hospitalisation. About 20% of hospitalised patients subsequently develop acute respiratory distress syndrome (ARDS), of which 12% will meet the conventional intubation and mechanical ventilation indications.[2] In SA, advanced ventilation devices (invasive and non-invasive) such as ventilators, high flow nasal cannula oxygen devices and continuous positive airway pressure (CPAP) machines were not as readily available as in high-income countries (HICs), particularly at a DH level.[2] State-run and private healthcare facilities across the country were overwhelmed by the impact of C19.

Between March 1, 2020, to August 31, 2021, SA experienced three 'waves' (periods of increased transmission) of infection rates.[3] During the peak of each wave, multiple tertiary and regional hospitals functioned above their capacity resulting in low acceptance rates of referrals from DHs. The waves in SA occurred during periods defined by the National Institute of Communicable Disease (NICD). A differential pattern for these periods emerged for each province across the country. In KwaZulu-Natal (KZN), wave one occurred from week 26 to 34 in 2020, wave two from week 49 of 2020 to week five of 2021 and wave three from weeks 24 to 37 of 2021.[3] During these periods many DHs were compelled to manage patients with complex disease profiles who required intensive and specialised care.

Knowledge of mortality trends at DH and community hospitals during the pandemic was limited locally and internationally with mortality rates remaining high in mechanically ventilated C19 infected patients in SA at any level of care.[2] Globally, multiple independent risk factors have emerged as key contributors to developing severe disease and mortality. These risk factors include male sex; obesity; comorbidities such as hypertension (HT); type two diabetes mellitus (T2DM); cardiovascular disorders; malignancies; chronic obstructive pulmonary disease (COPD); pulmonary tuberculosis (PTB) and Human Immunodeficiency Virus (HIV).[4] In SA, differential patterns of C19 deaths by sex, age, comorbidities and province[5] emerged. Individuals with HT and DM risked mortality from C19[5] and require careful management. On April 1, 2020, the NICD developed the Daily Hospital Surveillance (DATCOV) database as a national surveillance system for C19 hospitalisations.[6] The surveillance system allowed

information regarding C19 hospitalisations to be collated. Notably, however, this system did not provide data analysis with institution-specific feedback and, thus, no identification of how to improve service provision.

Before the pandemic, most DHs functioned at their peak capacity and faced additional challenges of staff shortages, large service loads and under resourced facilities.[6] Sparse documentation combined with a lack of electronic records and no standardised protocols or guidelines during the first three waves resulted in limited published academic literature regarding managing C19 patients at DHs in SA. International data published from DHs were not comparable as these hospitals often offered specialist services and serve a different population profile. Therefore, the differences in mortality trends between the first three waves at all DHs in South Africa is poorly documented. Reports suggest that many DHs received insufficient support from higher levels of care, such as tertiary and regional hospitals, during surges in the infection rate.[6] This may have resulted in poorer outcomes for patients with severe C19; hence mortality trends are essential for future planning/risk stratification of patients. Further, it will aid DHs in being able to cope with large patient loads and critically ill patients which is useful in the event of future waves or pandemics and general functioning of the district health system. This study utilised WWH as an example of a DH in SA. WWH was selected as it is a busy DH in an urban setting which faced a high burden of C19 cases. WWH has access to family physicians and the on-call physicians at the referral centres.

Understanding the pattern of deaths from C19 in SA is critical to identifying individuals at high risk of dying from the disease.[5] In comparison to HICs, SA faces a quadruple burden of infectious diseases, maternal and child-health illnesses, non-communicable diseases and trauma.[2,4,5] The capacity of DHs, particularly WWH, in managing critically ill patients who require advanced ventilation interventions and in circumstances where critical nursing care is limited. Further, as access to technical/specialist medical expertise was insufficient, many DHs struggled to manage multimorbid, complex patients during the first three waves of C19 in SA.[2]

This study aimed to evaluate mortality trends associated with patients hospitalised with C19 at WWH in SA. Further, this study also compared the demographic, clinical profile and management strategies and risk factors for mortality among patients with C19 across the three waves.

CHAPTER 2: LITERATURE REVIEW

This literature review aimed to identify and critically review published literature regarding risk factors for mortality in patients with C19 both– globally and within a South African context. In doing so the literature aimed to identify biochemical indicators associated with increased mortality; and recognise mortality trends in current literature. The literature review is structured into five broad categories: demographic profiles, clinical information retrieved from the history and physical examination, investigations and management strategies which were implemented.

An independent search strategy was conducted on the August 30, 2022. An advanced search on PubMed using the following MeSH terms ("corona virus" [MeSH Terms] OR "sars cov 2"[MeSH Terms] OR "covid 19"[MeSH Terms]) AND "mortality"[MeSH Terms] yielded 4564 results, of which 249 articles were screened as relevant. No filters were used, and the search included books, documents, meta-analyses, reviews, systematic reviews and clinical trials with no language restrictions.

Risk factors for mortality in patients with C19

Demographic profile

Multiple risk factors are associated with an increase in mortality from C19. A systematic review and meta-analysis done by Parohan et al.[7] revealed that mortality risk increases with older age ≥65 years (pooled odds ratio (OR = 4, 59; p<0.001); and male gender (pooled OR = 1.5; 95% confidence interval (CI): 1.06-2.12. An article by Pillay-van Wyk and colleagues (2021)[5] stated the median age of death was 61 years (interquartile range (IQR) 52-71), with age being an independent risk factor for mortality. Males had a 1.5 times higher death rate than females and individuals with two or more comorbidities, accounting for 58,6% (CI 56.6-60.5) of deaths.[5] A hospital surveillance update published by the NICD discovered that factors associated with in-hospital mortality were: older age; male sex; Black African, Coloured and Indian compared to White race.[3] There is a knowledge gap on the management of C19 in LMICs – which serve a younger population with unique disease profiles; epidemics of both infectious (HIV and TB) and non-communicable diseases, coupled with an overburdened public health system.[5]

Clinical profile

Data published by the NICD determined that the following comorbidities increased the risk for mortality: HT (270% increase), DM (241% increase), cardiovascular diseases (372% increase), COPD (353% increase), malignancy (304% increase) and higher Sequential Organ Failure Assessment (SOFA)[6] scores. These findings were replicated in numerous other studies.[4,8,9] Ejaz et al.[4] also included obesity/increased body mass index (BMI) as a risk factor for severe disease or mortality. However, this same study stated that no significant correlation exists between developing disease and mortality in individuals with HIV, liver disease and asthma. A small retrospective study done in Saudi Arabia, with 352 patients, also deemed active smoking[10] to be linked to mortality - this was found in numerous other studies as well.[11,12,13] There is an association between comorbidities and the increase in mortality. A likely theory is that SARS COV 2 virus uses Angiotensin Converting Enzyme (ACE)-2 receptors to enter a cell.[14] Certain comorbidities result in an upregulation of ACE-2 receptor expression and increase the release of enzymes that facilitate viral entry into cells. Consequently, thorough clinical assessment is required when patients with these comorbid conditions present at hospital/outpatient facilities. Patients with poor prognostic features should be identified promptly and introduced to palliative care specialists or managed[15] holistically with a multi-disciplinary team. The limitations of the studies were as follows: most had small sample sizes and were retrospective; certain risk factors had inconclusive/conflicting information. Lastly, many of these studies were published in HICs with different population dynamics, disease profiles and healthcare systems to those in SA.

As of date of this dissertation while the amount of literature in a SA context has increased, data in respect of DHs remains limited. Admission in the public sector; and comorbid HT, DM, chronic cardiac disease, chronic renal disease, malignancy, HIV, current tuberculosis alone or both current and past tuberculosis, and obesity were associated with an increased risk for mortality and compared to wave 1, there was an increased risk of mortality in wave 2 and wave 3.[16] Pillay-van Wyk and colleagues (2021)[5] stated HT and DM were the most common comorbidities reported. HIV and TB were more common in individuals younger than 50 years. In addition, poor help-seeking behaviour/ seeking medical attention in advanced disease, low detection rates and limited capacity to manage critical cases have also proven to be risk factors for mortality in LMICs.[5] The study conducted by Mash et al. (2021)[17] in the Western Cape of South Africa correctly stated that "district hospitals supported primary care facilities and shielded tertiary hospitals" highlighting the increased burden placed on DHs. Healthcare-related constraints across sub-Saharan Africa range from inadequate medical equipment supplies to low

per capita capacity for isolation and treatment. A recent report estimated that the entire African continent has 1% of the ventilator capacity of the United States of America[6] highlighting the necessity to improve our healthcare systems. HIV and TB were associated with a moderately increased risk of in-hospital C19 mortality, with HIV-infected individuals with immunosuppression being at increased risk as opposed to those with CD4 counts ≥200.[6] These studies are limited as they had small sample sizes and did not distinguish between confirmed C19 and probable infection.

A multi-centre study conducted by the Western Cape (WC) Department of Health (DOH) and the NICD determined that C19 death was associated with male sex, increasing age, DM, HT, and chronic kidney disease (CKD). HIV was associated with C19 mortality (adjusted hazard ratio [aHR], 2.14; CI: 1.70–2.70), with similar risks across viral loads and immunosuppression strata. Current and previous diagnoses of TB were associated with C19 mortality (aHR, 2.70, CI, 1.81–4.04 and 1.51, CI, 1.18–1.93, respectively). The Standardised Mortality Ratio (SMR) for C19 death associated with HIV was 2.39 (CI, 1.96–2.86); the population attributable fraction was 8.5% (CI, 6.1–11.1).[18.]

A study of four district-level hospitals in the WC determined that out of 1376 patients of older age (OR 1.06 (CI 1.04 to 1.07)), male (OR 2.02 (CI 1.37 to 2.98)), overweight/obesity (OR 1.58 (CI 1.02 to 2.46)), T2DM (OR 1.84 (CI 1.24 to 2.73)), HIV (OR 3.41 (CI 2.06 to 5.65)), CKD (OR 5.16 (CI 2.82 to 9.43)) were significantly linked with mortality ($p<0.05$). Pulmonary diseases (TB, asthma, COPD, post-TB structural lung disease) were not associated with increased mortality.[17] A study conducted at Charlotte Maxeke Academic Hospital (CMJAH), a tertiary-level hospital in Johannesburg, concluded that their institution had the highest case fatality ratio (39.95%) during wave 2. Factors associated with hospitalisation included age groups 40–59 years (aOR: 2.14, CI: 1.08–4.27), 60–79 years (aOR: 2.49, CI: 1.23–5.02) and ≥ 80 years (aOR: 3.39, CI: 1.35–8.49). Factors associated with in–hospital mortality included age groups 60–79 years (aOR: 2.55, CI: 1.11–5.84) and ≥ 80 years (aOR: 5.66, CI: 2.12–15.08); male sex (aOR: 1.56, CI: 1.22–1.99); the presence of an underlying comorbidity (aOR: 1.76, CI: 1.37–2.26), as well as being admitted during post–wave 2 (aOR: 2.42, CI: 1.33–4.42).[19,20]

Covid-19 diagnosis initially posed a diagnostic dilemma as the clinical presentation can vary considerably.[21] Common initial symptoms are fever, fatigue, dry cough, sore throat and dyspnoea, pneumonia, sneezing, malaise, diarrhoea, headache and conjunctivitis, anosmia, and ageusia have also been reported.[21] The Cochrane database published a systematic review and

meta-analysis conducted by Talukder et al.[21], which described the relationship between presenting symptoms and disease severity. The findings of this meta-analysis suggested that patients with dyspnoea had twice the odds of having severe C19 illness at the time of hospital admission. No significant association was found between fever, cough, myalgia, fatigue, and headache with the severity of symptoms. Fever emerged as the most predominantly reported clinical manifestation in C19 confirmed cases. This was followed by cough, myalgia or fatigue and less proportionally dyspnoea and headache. The prevalence of fever was 87.89% (CI: 83.22–81.39). A higher SOFA score on admission was associated with higher odds of in-hospital death. (qSOFA (quick sequential organ failure assessment) is a score introduced by the United States Preventative Task Force for the detection of patients at risk of mortality from sepsis outside of intensive care units.[22.]

Investigations

Specific biochemical and radiological indicators have also been associated with increased mortality.[23] D-dimer levels greater than one microgram/millilitre, a raised serum Interleukin-6, high sensitivity cardiac troponin I, lactate dehydrogenase and lymphopenia (lymphocyte count <109/L) were more commonly seen in severe C19 illness.[24] Decreased PaO2/FiO2 (arterial oxygen partial pressure in mmHg divided by the fractional inspired oxygen) also known as the PF ratio, increased lactate, active smoking, and the prevalence of a pulmonary embolism were all poor prognostic factors in critically ill C19 patients.[25] Results associated with mortality were CD3+ CD8+ cell count ≤75 cells/microlitre, acute kidney injury (AKI) stage 2 and 3, proteinuria ≥1+, haematuria ≥1+, and peak serum creatinine ≥13.26 micromol/litre.[5] Merugu et al. (2021) described low haemoglobin (p=0.0046), elevated INR (p=0.0005), low platelets (p=0.0246), and an elevated procalcitonin (p=0.472) as being associated with an increase in mortality.[26] Radiological features were evident on chest x-ray and CT scan revealing bilateral ground glass opacities with variable pulmonary parenchymal consolidations were evident in patients with severe COVID pneumonia and were associated with increased mortality.[22]

Management

"The mainstay of treatment for mild cases of C19 is self-isolation, use of masks, proper.
hygiene practices, and symptomatic treatment such as antipyretics, analgesics, and appropriate rehydration. Antibiotic treatment or prophylaxis is explicitly not recommended."[27] Moderate C19 cases with suspected viral pneumonia are similarly managed; high-risk populations may

require hospitalisation – depending on the patient's clinical condition, and antibiotics are only recommended on clinical suspicion or laboratory confirmation of secondary bacterial infection. Escalation of medical treatment is recommended where there is clinical deterioration. Managing severe C19 pneumonia requires immediate administration of supplemental oxygen, conservative fluid management, and close monitoring for clinical deterioration with appropriate supportive care.[27] Empiric antimicrobial treatment covering all likely pathogens is recommended based on clinical judgment, patient host factors, and local epidemiology.[27] Antimicrobials should be administered as soon as possible (within 1 hour of initial assessment), ideally with blood cultures obtained first and assessed daily after that for de-escalation. Non-invasive ventilation is recommended in the first instance for ARDS management in critical C19 cases, followed by advanced oxygen/ventilator support upon acute hypoxemic respiratory failure and conservative fluid management.[27] Managing septic shock in critical C19 cases requires crystalloid fluid and vasopressors for resuscitation. Antimalarials, antivirals, immunomodulators, and convalescent plasma therapy are explicitly discouraged outside of clinical trials. Despite minimal robust evidence to support their use of antivirals, antimalarials, and antibiotics, singly and in combination, are currently being used to manage C19.[27] A retrospective cross-sectional study conducted by Mametja and colleagues[27] on a private healthcare database determined that from a population of 154,519 patients with C19, only 24% received in-hospital care. Among the hospitalised patients, 29% (n = 10,607) received oxygen therapy, and 18% (n = 6,795) were ventilated. Prescribed medications included antibiotics (43%), antivirals (9%), antifungals (1%), antimalarials (0.4%), and steroids (30%). The use of antivirals (aOR = 0.47; 95% CI= 0.40–0.54), and/or steroids (aOR = 0.46; 95% CI = 0.43–0.50) were associated with decreased death odds. The use of antibiotics in-hospital was not associated with increased survival (aOR = 0.97; 95% CI = 0.91–1.04). Antibiotics used include macrolides, such as azithromycin and erythromycin (28%), combinations of amoxicillin and clavulanic acid, (38%), third generation cephalosporins (15%), and fluoroquinolones (5%).[27.]

Mash et al. (2021)[17] reported that: 558 out of 1376 patients (40.6%) received oxygen therapy and 0.8% were intubated. Those admitted were usually treated with oxygen, low molecular weight heparin (enoxaparin sodium) and antibiotics (ceftriaxone, azithromycin or co-amoxiclav), and far fewer patients were treated with proning or steroids. Proning was only used in 24% of those with severe or critical C19.[17] District hospitals reduced pressure on tertiary hospitals with ICU and critical care beds, particularly those with moderate and severe C19. Of those with moderate C19, only 9% were transferred to tertiary hospitals, and mortality was 7.5%. For those with severe disease, 17% were transferred, and mortality was 22%, which

compares favourably with reports from high-income settings. District hospitals could not manage critically ill patients, as they did not have ICU or critical care facilities.[17]

The second wave was dominated by the beta variant (501Y.V2 or B.1.351), which was characterised by rapid spread and higher infection rates, admissions, and mortality rates than the first wave. The beta strain of SARS-CoV-2 was first identified in SA in the last quarter of 2020. The virus developed multiple mutations in its protein structure, resulting in increased virulence (increased infectivity and decreased neutralisation by existing vaccines). The high crude- and case fatality rates in the second wave may be due to increased virulence of the beta variant, lack of vaccination among patients, and the overburdened hospital and healthcare workers. These results are like those published by the NICD, which stated, "Compared to wave 1, there was an increased risk of mortality in wave 2 (adjusted OR 1.5; 95% CI1.4-1.5) and wave 3 (adjusted OR 1.3, 95% CI 1.3-1.4)."[16] The Hospital Surveillance Report by the NICD estimated an overall facility case fatality rate of 22.5% across all four C19 waves in SA. Data published by the NICD - conducted on 666 facilities across the nine provinces of SA- concluded that factors associated with in-hospital mortality were older age and being of black African/Mixed/Indian race compared to White ethnicity. Comorbid HT, DM, chronic cardiac disease, chronic renal disease, malignancy, HIV, past and current TB, and obesity were also associated with mortality.[16]

As illustrated above multiple risk factors that have been associated with increased mortality due to C19. Despite evidence from a wider SA context, most studies were conducted in the WC. The WC has better developed infrastructure, family physician run DHs and a more robust health system than many of the other SA provinces, and the quality of care less than satisfactory in other parts of SA.[17] However, knowledge on the impact of the pandemic at a district-level hospital in KZN remains limited. DHs are crucial points of entry into the healthcare system for patients in the public sector and many acutely ill patients were managed at DH level prior to being referred to regional or tertiary level care. However, our experience in KZN was that most patients were managed at DHs because of the lack of capacity to accept large numbers of critically ill patients. There is a gap in the literature regarding C19 mortality trends in African countries as a whole and district hospitals in particular as these hospitals face many resource challenges. This study aimed to identify the similarities, differences, and overall mortality trends in the first three waves of C19 at a DH in KZN. The lack of resources and literature appropriate to KZN constantly hinders the ability to provide effective patient management, develop sustainable future practices and eventually eliminate the spread of the virus and its variants.

CHAPTER 3: METHODS

A) Methods

I. Study design

A retrospective audit was conducted on clinical records of patients who demised at the study site (WWH) between March 2020 and September 2021 after being admitted and subsequently demising from a severe COVID infection. The study aimed to evaluate mortality trends during the first three waves of the C19 pandemic and the study's specific objectives were as follows:

- To compare the demographic profile of patients who died from COVID-19 during the first three waves at WWH.
- To compare the clinical profile and management strategies of patients who died from COVID-19 during the first three waves at WWH.
- To identify risk factors for mortality among patients with COVID-19 during the first three waves at WWH.
- To identify areas requiring improvement with respect to holistic patient management.

2. Study setting

This study was conducted at Wentworth Hospital (WWH), an urban district hospital in KwaZulu-Natal, South Africa. WWH services the following catchment areas: Hillary, Seaview, Wentworth, Austerville, Yellowwood Park, Chesterville, Cato Manor, Bluff, Clairwood, Montclair, Jacobs, Lamontville, Umbilo, Woodlands and Merebank. WWH functions with a referral system, with patients being referred via their local clinics or walk-ins. This hospital was selected as it is very similar to other DHs in SA. It is a 230 bedded hospital that services the Durban South catchment population of approximately 407 000 as of 2013.[31] Wentworth Hospital provides ambulatory (general outpatients, antenatal care, HIV services and a Gateway Clinic), inpatient care (high care unit, medical, surgical, mental health, paediatric, nursery and obstetric wards), operative care, emergency care and has paramedical services (radiography, physiotherapy, speech therapy, occupational therapy and social work). District or primary hospitals in our setting are small, often rural or remote, and led by generalists or family physicians. These types of hospitals are rare in HICs, but an important part of African health systems.[17] The community of WWH was severely impacted during the C19 pandemic due to healthcare and socioeconomic issues in the area. Most data is published from HICs with access to advanced ventilation options, specialists, and critical care units as well as access to imaging modalities such as a CT scan and MRI.[17] However, little research exists in resource-limited

environments such as WWH. This hospital was chosen as the findings can be applied to other DH hospitals within SA and even resource-constrained hospitals internationally.

3. Study population

All inpatient files of adult patients (>18 years of age) admitted to WWH from March 2020 until August 31, 2021, who were diagnosed with C19 disease on admission and subsequently demised in-hospital during the admission as a sequela of the C19 disease.

Inclusion Criteria

- All adult patients (18 years or older) admitted to WWH with symptomatic COVID infection who subsequently demised between 1 March 2020 and 31 August 2021.

Diagnosis of C19 infection was based on the SARS COV 2 RT-PCR (reverse transcription polymerase chain reaction) test, which is the gold standard[28] for diagnosing C19 infection. Additionally, the C19 antigen test was used as an adjunct once it became available at the facility. In a small sample of patients, the RT-PCR yielded an inconclusive or negative result; consequently, clinical, biochemical, and radiological markers of infection were used to diagnose C19 infection. Specialist family physicians exclusively confirmed this diagnosis at the facility through discussion with the general internal medicine physicians or infectious disease physicians at the tertiary referral facility. Due to the long turnaround time for the C19 PCR test (up to 10 days), a locally devised clinical scoring system was used to identify patients who were strongly suspicious of having C19 disease. A score of 9 or greater (out of a total of 21) was deemed to be highly suggestive of C19. The PCR test later confirmed these results or, if the PCR test was negative, clinical judgement and biochemical and radiological markers were used to conclude the diagnosis of C19 using the probability score. The scoring system comprised of the following criteria: a history of positive contact (2 points); acute cough (1 point); fever ≥38°C (2 points); respiratory rate >25/min (1 point); pulse oximetry saturation (SpO2) < 95% (2 points); recent loss of taste/smell (3 points); high C-reactive protein (CRP) (2 points); high white cell count (WCC) (1 point); positive chest X-ray (ground glass (3 points) or pneumonia (2 points)); D-dimer >0.25 (2 points) and any diabetic emergency (hyper or hypoglycaemia) (2 points). This was an institutionally devised scoring system by two South African family physicians and an external international critical care specialist. A score of nine or more was highly indicative of C19. The tool had not been validated or utilised elsewhere.

Exclusion criteria:

- COVID-positive patients who died from unnatural causes e.g. trauma.

4. Study patients

All adult in-patients (>18 years of age) admitted to WWH from March 2020 until August 31, 2021, who were diagnosed with C19 disease on admission and subsequently demised in-hospital during the admission as a sequela of the C19 disease.

5. Data collection

An electronic data collection tool was designed to capture all data electronically and confidentially. The data was captured from inpatient files for March 1, 2020 – August 31, 2021. Please see Appendix 1: Data Collection Tool. Comprehensive data on multiple variables were retrieved, such as: age; SARS COV 2 PCR result; gender; ethnicity, symptoms; comorbid disease profile (such as HT, DM, Obesity (BMI > 30), HIV, current or previous TB, Asthma, COPD, malignancy, Chronic Kidney Disease, Ischaemic Heart Disease, Congestive Cardiac Failure, Dyslipidaemia); social habits such as ethanol use, smoking history/current smoker or illicit drug usage; class of dyspnoea according to the New York Heart Association (NYHA) Scale graded from 1-4; Clinical Frailty Score. Data regarding vital signs on admission such as systolic blood pressure; diastolic blood pressure; pulse rate; respiratory rate; SPO2 on room air; blood glucose; level of consciousness; the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen the patient is receiving (PaO2 / FiO2) (PF ratio)[29] on admission, were collected. Lastly, data regarding the presence of complications on admission, such as acute kidney injury, depressed level of consciousness, haemodynamic instability, liver enzyme abnormality, myocarditis, thrombo-embolic disease, diabetic ketoacidosis; chest radiograph features; ECG findings; urine dipstick findings; biochemical markers (white cell count; haemoglobin; urea, platelets, creatinine, eGFR, bilirubin, ALT, GGT, LDH, CRP and d-dimer); oxygen requirements, treatment prescribed and number of days spent admitted in the hospital was also included in the data collection tool.

At conception, the study was not based on any prior studies on mortality trends. However, the variables determining mortality, such as: comorbidities; clinical presentation; vital signs; and biochemical and radiological markers, were derived from current academic literature regarding risk factors for severe C19 disease and subsequently used to develop the data collection tool.

6. Data analysis

Data was captured via Google Form and transferred onto an Excel spreadsheet and imported into Stata v17[30], a statistical software package, for analysis. With respect to manuscript one

descriptive statistics were used to summarise the data. Frequencies and percentages were used for categorical data such as gender, ethnicity, and comorbidities. Frequency distributions of numeric variables were examined for normal distribution and mean (standard deviation (SD)) or median ((IQR) was used as appropriate. With respect to manuscript 2: odds ratios (ORs), 95% confidence intervals (CIs) and p-values were reported. A p-value < 0.05 was considered statistically significant. Stata v17[30] was used in the analysis. Analysis was done to determine if the continuous variable differs significantly across the three waves. This was done using either ANOVA for normally distributed results or Kruskal-Wallis tests for non-parametric results.

7. Funding

The study was self-funded.

8. Ethical considerations

Ethical clearance was obtained from the Biomedical Research Ethics Committee of the University of Kwa-Zulu Natal, BREC/00003680/2021; and the Provincial Department of Health NHRD Ref:KZ_202201_003. Additionally, institutional ethical clearance was received from the Wentworth Hospital Ethics Committee.

CHAPTER FOUR: FIRST MANUSCRIPT

Introduction:

The following article provides an overall analysis of the mortality trends between 1 March 2020 to 31 August 2021. During this period SA experienced three waves. This article aimed to establish risk factors associated with mortality for C19 at a SA, DH level as well as provide an overall comparison of the demographic and clinical profile and management strategies of the patients who demised during this period from C19. This directly addressed the aims and objectives of this dissertation. The manuscript was formatted according to published journal guidelines of the South African Family Practice Journal (SAFPJ). The manuscript was accepted for publication on March 7, 2023.

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A single-centred retrospective observational analysis on mortality trends during the COVID-19 pandemic

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Background: South Africa experienced high mortality during the COVID-19 pandemic. Resources were limited, particularly at the district hospital (DH) level. Overwhelmed healthcare facilities and a lack of research at a primary care level made the management of patients with COVID-19 challenging. The objective of this study was to describe the in-hospital mortality trends among individuals with COVID-19 at a DH in South Africa.

Methods: Retrospective observational analysis of all adults who demised in hospital from COVID-19 between 01 March 2020 and 31 August 2021 at a DH in South Africa. Variables analysed included: background history, clinical presentation, investigations and management.

Results: Of the 328 participants who demised in hospital, 60.1% were female, 66.5% were older than 60 and 59.6% were of black African descent. Hypertension and diabetes mellitus were the most common comorbidities (61.3% and 47.6%, respectively). The most common symptoms were dyspnoea (83.8%) and cough (70.1%). 'Ground-glass' features on admission chest X-rays were visible in 90.0% of participants, and 82.8% had arterial oxygen saturations less than 95% on admission. Renal impairment was the most common complication present on admission (63.7%). The median duration of admission before death was four days (interquartile range [IQR]: 1.5–8). The overall crude fatality rate was 15.3%, with the highest crude fatality rate found in wave two (33.0%).

Conclusion: Older participants with uncontrolled comorbidities were most likely to demise from COVID-19. Wave two (characterised by the 'Beta' variant) had the highest mortality rate.

Contribution: This study provides insight into the risk factors associated with death in a resource-constrained environment.

Keywords: severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; COVID-19; mortality trends; risk factors for mortality; district hospital; South Africa.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the COVID-19 pandemic. Clinical presentation of the illness ranges from mild, flu-like symptoms, moderate symptoms to severe, pneumonia-like symptoms.[1] During the first three waves and prior to the vaccination rollout, state-run and private healthcare facilities across the country were overwhelmed by the impact of COVID-19.[2] In a South African district hospital (DH) setting, ventilators, high-flow nasal oxygen (HFNO2) devices and non-invasive continuous positive airway pressure (CPAP) machines were scarce when compared to that in high-income countries (HICs).[2,3]

The South African public healthcare system consists of different levels of hospitals, namely district, regional, tertiary, provincial tertiary, central and specialised. District hospitals provide primary healthcare and unspecialised services and subsequently refer patients to regional or tertiary facilities should the patient require a higher level of care. All patients presenting to DHs are primary presentations or referrals from primary care clinics. Screening for COVID-19 is conducted at the entrance of the clinic or hospital. Patients are evaluated by a clinician and, if COVID-19 antigen or polymerase chain reaction (PCR) positive and deemed necessary, are admitted to the 'Person-Under-Investigation (PUI)' ward. Patients are subsequently transferred to the general COVID-19 ward (if clinically stable) or to the 'high-care' COVID-19 ward (if requiring a higher level of care or invasive ventilation). Those with a negative COVID-19 antigen or PCR test are transferred to the non-COVID-19 general ward or 'high care'. A locally devised probability scoring tool (defined below) was used when antigen testing was not yet

introduced in South Africa, and clinicians could not delay the focussed treatment of patients for the 10–14 days that it took for the PCR result to be ready.

During the peak of each wave, many tertiary, regional and central hospitals were running at maximum capacity, and intensive care unit (ICU) services were limited, resulting in poor acceptance rates or long waiting times for referrals from DHs. Consequently, many severely ill and complex patients were managed at primary care DHs. Under-resourced healthcare facilities, pandemic fatigue (among healthcare workers and other support staff), a lack of research at a district healthcare level and the quadruple burden of disease made the management of patients with COVID-19 and subsequent preparation for future waves or pandemics challenging – particularly at a DH level. Numerous studies regarding risk factors for mortality have been published internationally, and much is known about the socio-economical and health-related consequences of the pandemic on various countries worldwide.[4,5] There is limited mortality data from primary care facilities in both low- and middle-income countries (LMICs), particularly from DHs in a South African setting.[2,4]

The objective of the following study was to describe the in-hospital mortality trends among individuals with COVID-19 at Wentworth, a DH in South Africa. Determining these risk factors will assist with identifying high-risk populations, optimising future healthcare planning and preparing for subsequent waves or disease outbreaks. Additionally, it will allow healthcare providers to reflect on the impact of COVID-19 at a primary care level.

Methods

The study was a retrospective descriptive analysis of clinical records from Wentworth Hospital (WWH). Wentworth Hospital is a DH situated in the Wentworth district of Durban, South Africa. The target population included all adult participants over 18 years who were admitted to WWH and demised in hospital from COVID-19 disease between 01 March 2020 and 31 August 2021. During this period, South Africa experienced three waves (periods of increased transmission) as defined by the National Institute of Communicable Disease (NICD)[6]: wave 1 in KwaZulu-Natal is defined as week 26–34 (2020), wave 2 is defined as week 49–5 (2020–2021) and wave 3 is defined as week 24–37 (2021). The institutional crude fatality rate (institutional COVID-19 deaths/institutional COVID-19 admissions) for the entire study period, as well as for the defined waves of infection, was calculated.

The diagnosis of COVID-19 disease was based on clinical, laboratory or radiological features suggestive of SARS-CoV-2 infection. The PCR test was used to confirm the diagnosis of COVID-19, and only participants who demised in hospital because of COVID-19 were included in the study. Because of the long turnaround time for the COVID-19 PCR test (up to 10 days), a locally devised clinical scoring system was used to identify participants who were strongly suspicious of having COVID-19 disease. A score of 9 or greater (out of a total of 21) was deemed to be highly suggestive of COVID-19. The PCR test later confirmed these results or, if the PCR test was negative, clinical judgement, as well as biochemical and radiological markers were used to conclude the diagnosis of COVID-19 using the probability score. The scoring system comprised the following criteria: a history of positive contact (2 points), acute cough (1 point), fever > 38 °C (2 points), respiratory rate > 25/min (1 point), pulse oximetry saturation (SpO_2) < 95% (2 points), recent loss of taste taste or smell (3 points), high C-reactive protein (CRP) (2 points), high white cell count (WCC) (1 point), positive chest X-ray (ground glass [3 points] or pneumonia [2 points]), D-dimer > 0.25 (2 points) and any diabetic emergency (hyper or hypoglycaemia) (2 points). This was an institutionally devised scoring system by two South African family physicians and an external international critical care specialist whereby a score of nine or more was highly indicative of COVID-19. The tool was not validated or used elsewhere.

An electronic data collection tool was devised for the study. It was initially developed by one of the authors and was used as a mortality audit tool. Data were captured through a Google Form and presented at the monthly audit meetings. However, it required additional information to be added to the original tool as it was not comprehensive enough to answer the research objectives. Data from paper-based patient records were captured on a spreadsheet by the two principal investigators and analysed. The editor then checked the data. All the study objectives could be achieved with the modified data extraction tool and was subsequently used for data capture. The pilot study – which was conducted on the files of 54 participants who demised in August 2021 – allowed further adjustment of the data collection tool to extract meaningful, non-ambiguous data. The data collection tool included variables such as demographics, comorbidities, clinical presentation, biochemical findings, radiological markers and management. Race was captured from the COVID-19 admission clerking tool, as self-identified by participants. For those who were dead on arrival or too ill to communicate, race was reported by the next of kin of the deceased. The chest X-ray done on admission was evaluated by the admitting doctor and confirmed by the family physician in charge (as there was no radiologist available for reporting). This was documented on the COVID-19 admission clerking tool. Peripheral pulmonary infiltrates were classified as 'mild' changes, and 'ground glass appearance' or 'global consolidation' was classified as 'moderate/severe' changes.

Descriptive statistics were used to summarise the data. Frequencies and percentages were used for categorical data such as gender, ethnicity and comorbidities. Frequency distributions of numeric variables were examined for normality and mean (standard deviation [s.d.]) or median (interquartile range [IQR]) were used when appropriate. Stata® V15.1[7] was used for the analysis.

Results

Baseline characteristics

Of the 328 participants who demised from COVID-19, 197 (60.1%) were female (Table 1). The mean age of death was 64 years (standard deviation [s.d.]: 13.6), with the most significant proportion of deaths (n = 218; 66.5%) occurring in individuals older than 60 years. Most participants (n = 196; 59.6%) were of black African descent. Of those with documented clinical frailty scores (n = 312), 197 (63.1%) had a score of less than six, indicating good pre-morbid function. Hypertension was present in 201 (61.3%) participants and diabetes mellitus in 156 (47.6%) participants, with the majority (n = 115; 73.7%) of these having an haemoglobin A1c (HbA1c) greater than 8%. Of the total study population, 62 (18.9%) participants had a documented weight, all of whom had a body mass index (BMI) greater than 30, classifying them as 'obese'. Fifty-three (16.2%) participants had documented dyslipidaemia. Forty-five (13.7%) participants were human immunodeficiency virus (HIV)-positive, with 37 (82.2%) having unsuppressed/unknown viral loads. Most (n = 237; 72.3%) participants reported sober habits.

TABLE 1: Demographics and relevant clinical history of participants.

Variable (n = 328)	Number (n)	%	Mean	s.d.
Baseline characteristics				
Female	197	60.1	-	
Age (years)	-	-	63.5	13.6
> 60 years	218	66.5	-	-
< 60 years	110	33.5	-	-
Ethnic classification				
Black person	196	59.6	-	-
White person	50	15.2	-	-
Asian person	48	14.6	-	-
Mixed-race person	34	10.4	-	-
Clinical frailty score (n = 312)†				
≤ 5	197	63.1	-	-
> 5	115	36.9	-	-
Comorbidities				
Hypertension	201	61.3	-	-
Diabetes mellitus	156	47.6	-	-
Of which HbA1c less than 7% (n = 156)	8	5.1	-	-
Of which HbA1c 7-8 (n = 156)	33	21.2	-	-
Of which HbA1c greater than 8% (n = 156)	115	73.7	-	-
Obese (body mass index greater than 30)	62	18.9	-	-
Dyslipidaemia	53	16.2	-	-
HIV-positive	45	13.7	-	-
Of which viral load unsuppressed/ unknown (n = 45)	37	82.2	-	-
Current tuberculosis	10	3.0	-	-
Previous tuberculosis	13	4.0	-	-
Asthma	11	3.4	-	-
COPD	8	2.4	-	-
Chronic kidney disease	19	5.8	-	-
Ischaemic heart disease	31	9.5	-	-
Malignancy	9	2.7	-	-
Habits				
Sober habits	237	72.3	-	-
Current smoking	40	12.2	-	-
Ex-smoker	16	4.9	-	-
Current alcohol use	17	5.2	-	-
Illicit drug use	2	0.6	-	-

s.d., standard deviation; HbA1c, glycated haemoglobin; COPD, chronic obstructive pulmonary disease.
†, Except where specified.

Clinical presentation

The most frequent presenting symptoms were dyspnoea (83.8%) and cough (70.1%) (Table 2). Modified Medical Research Council (mMRC) dyspnoea grade 4 was evident in 143 (43.6%) participants on admission. Most participants (57.6%) were tachypnoeic (respiratory rate greater than 25 breaths per minute), and 55.8% were tachycardic (heart rate ≥ 100 beats per minute). The mean systolic blood pressure was 128.7 (s.d.: 26.4), and the mean diastolic blood pressure was 74.2 (s.d.: 18.2) mmHg. The mean SpO_2 on room air was 77.2% (s.d.: 18.8), with 82.8% of participants having an SpO_2

TABLE 2: Clinical presentation on admission of participants.

Variable (n = 328)†	Number (n)	%	Mean	s.d.	Median	IQR
Symptoms						
Shortness of breath	278	83.8	-	-	-	-
Cough	230	70.1	-	-	-	-
Myalgia/body pain	128	39.0	-	-	-	-
Fever	96	29.3	-	-	-	-
Sore throat	59	18.0	-	-	-	-
Confusion	59	18.0	-	-	-	-
Recent loss of taste or smell	43	13.1	-	-	-	-
Diarrhoea	40	12.2	-	-	-	-
Chest pain	24	7.3	-	-	-	-
Headache	13	4.0	-	-	-	-
Other (unspecified)	45	13.7	-	-	-	-
mMRC grade 4 dyspnoea	143	43.6	-	-	-	-
Vital signs						
Respiratory rate	-	-	27.7	8.3	-	-
≥ 25 breaths per minute	189	57.6	-	-	-	-
< 25 breaths per minute	132	40.2	-	-	-	-
Heart rate	-	-	103	21.7	-	-
≥ 100 beats per minute	183	55.8	-	-	-	-
< 100 beats per minute	137	41.8	-	-	-	-
Systolic blood pressure	-	-	128.7	26.4	-	-
Diastolic blood pressure	-	-	74.2	18.2	-	-
SPO_2 on room air (n = 319)	-	-	77.2	18.8	-	-
< 95	264	82.8	-	-	-	-
> 95	55	17.2	-	-	-	-
Glasgow Coma Score						
15	235	71.6	-	-	-	-
10–14	69	21.0	-	-	-	-
3–9	16	4.9	-	-	-	-
Unspecified	8	2.4	-	-	-	-
Finger-prick blood glucose	-	-	-	-	8.3	6.6–15.6
≤ 11 mmol/L	206	62.8	-	-	-	-
> 11 mmol/L	115	35.1	-	-	-	-
Triage colour on admission						
Red	55	16.8	-	-	-	-
Orange	225	68.8	-	-	-	-
Yellow	36	11	-	-	-	-
Green	11	3.4	-	-	-	-
Clinical probability score on admission	-	-	10.76	2.49	-	-
Less than nine	48	14.6	-	-	-	-
Nine or more	275	83.8	-	-	-	-
Unspecified	-	1.5	-	-	-	-

mMRC, Modified Medical Research Council; s.d., standard deviation; IQR, interquartile range.
†, Except where specified.

< 95% on admission. The median finger-prick blood glucose on admission was 8.3 mmol/L (IQR: 6.6–15.6), and 206 (62.8%) participants had a blood glucose ≤ 11 mmol/L. On presentation to the emergency department, 235 (71.6%) participants had a Glasgow Coma Score (GCS) of 15, 69 (21.0%) had a GCS between 10 and 14, 16 (4.9%) had a GCS between three and nine and eight (2.4%) were unspecified. The majority (68.8%) of participants were triaged as an 'orange-code' on admission as defined by the South African Triage Scale (SATS), and a clinical probability score of nine or more was recorded in 275 (83.8%) participants.

Investigations

Of all the participants included in the study, 311 (94.8%) had a positive PCR test and 172 (76.1%) had a positive rapid antigen test (Table 3). A total of 329 (97.9%) participants were unvaccinated at the time of death. No participants were fully vaccinated at the time of death. Moderate/severe chest radiograph changes were evident in 278 (90.0%) participants. The median Horowitz Index[8] (ratio of arterial partial pressure of oxygen to fraction of inspired oxygen the patient is receiving: PaO_2/FiO_2) was 125 (IQR: 75–250), with 40.9% of participants having a Horowitz Index[9] less than or equal to 100, indicating severe acute respiratory distress syndrome (ARDS) on presentation. Biochemical derangements included a median urea of 9.4 (IQR: 5.9–17.1), median creatinine of 112 (IQR: 80–208) and a median glomerular filtration rate (GFR) of 47 (IQR: 25–82). The median CRP was 150.8 (s.d.: 65.94), median D-dimer was 0.69 (IQR: 0.33–1.18) and mean lactate dehydrogenase (LDH) was 1413.53 (s.d.: 621.56).

Complications

Complications noted on admission included renal impairment (63.7%), depressed level of consciousness (22.3%), haemodynamic instability (21.6%), liver enzyme abnormalities (18.6%) and thrombo-embolic disease (10.7%) (Table 4).

Management

With respect to medical management: 297 (90.5%), participants received Dexamethasone 6 mg intravenously (IVI); 240 (73.2%) received prophylactic low molecular weight heparin (LMWH) (40 mg daily subcutaneously); 60 (18.3%) received therapeutic LMWH (1.5 mg per kilogram daily); 194 (59.1%) received thiamine; 147 (44.8%) received vitamin D stat doses; 178 (54.3%) received vitamin B3; 195 (59.5%) received zinc; 304 (92.7%) received ceftriaxone and 287 (87.5%) received azithromycin (Table 4).

Most (n = 255; 77.5%) participants were oxygen requiring on admission, ranging from the nasal cannula to invasive ventilation, with 210 (66%) participants requiring oxygen for 1–6 days, and the median number of days for which oxygen was required being 3 (IQR: 1–7) (Table 4). Of the 88 participants (27.8%) discussed with higher levels of care, 73 (86.9%) were not accepted. Reasons for rejection included: 'no capacity at higher level of care' (referring to no bed space or ventilators), 'patient does not meet criteria for referral' (referring to poor indication for referral or does not meet other specific ICU criteria) or 'poor prognosis' (alluding to the justice principle where limited resources are reserved for patients with a good/moderate prognosis). The 11 referrals that were accepted demised prior to transfer, as they were either accepted very late or there was a major delay in the ambulance transfer.

TABLE 3: Investigations of participants.

Variable (n = 328)	Number (n)	%	Mean	s.d.	Median	IQR
Investigations						
COVID-19 data	-	-	-		-	-
Positive PCR	311	94.8	-		-	-
Positive antigen (n = 226)	172	76.1	-		-	-
Vaccinated fully	0	0	-		-	-
Partially vaccinated (one dose Pfizer)	2	0.6	-		-	-
Unvaccinated	321	97.9	-		-	-
Unknown vaccination status	5	-	-		-	-
Chest X-ray findings						
Changes on chest X-ray documented	309	94.2	-	-	-	-
Of which mild changes (n = 309)	31	10.0	-	-	-	-
Of which moderate to severe changes (n = 309)	278	90.0	-	-	-	-
Horowitz Index9 on admission (n = 254)	-	-	-	-	125	75–250
≤ 100	104	40.9	-		-	-
101–200	64	25.2	-		-	-
200–300	86	33.9	-		-	-
Urine dipstick						
Normal	5	1.5	-	-	-	-
Glucose	58	17.7	-	-	-	-
Protein	58	17.7	-	-	-	-
Ketones	26	7.9	-	-	-	-
Blood	19	5.8	-	-	-	-
Leukocytes	10	3.0	-	-	-	-
Not done/unspecified	220	67.1	-	-	-	-
Blood results						
Haemoglobin (n = 311)	-	-	12.45	2.49	-	-
White cell count (n = 311)	-	-	11.24	5.61	-	-
Platelets (n = 310)†	-	-	-	-	273	211; 357
Urea (n = 314)	-	-	-	-	9.4	5.9–17.1
Creatinine (n = 313)	-	-	-	-	112	80–208
GFR (n = 311)	-	-	-	-	47	25–82
≥ 60	123	39.5	-	-	-	-
< 60	188	60.5	-	-	-	-
Bilirubin (n = 290)	-	-	-	-	12	9–19
ALT (n = 288)	-	-	-	-	28	20–47
GGT (n = 286)	-	-	-	-	43	24–85
CRP (n = 310)	-	-	150.8	65.94	-	-
≥ 200	144	46.5	-	-	-	-
< 200	166	53.5	-	-	-	-
D-dimer (n = 278)	-	-	-	-	0.69	0.33–1.18
≥ 0.5	174	62.6	-	-	-	-
< 0.5	104	37.4	-	-	-	-
LDH (n = 40)	-	-	1413.53	621.56	-	-

PCR, polymerase chain reaction; Horowitz Index[9], ratio of arterial partial pressure of oxygen to fraction of inspired oxygen the patient is receiving (PaO_2 / FiO_2); IQR, interquartile range; s.d., Standard deviation; GFR, glomerular filtration rate; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; LDH, lactate dehydrogenase.
†, Except where specified.

TABLE 4: Complications and management of participants.

Variable (n = 328)	Number (n)	%	Median	IQR
Complications present on admission				
Renal impairment	209	63.7	-	-
Depressed level of consciousness	73	22.3	-	-
Haemodynamic instability	71	21.6	-	-
Liver enzyme abnormality	61	18.6	-	-
Thrombo-embolic disease	35	10.7	-	-
Diabetic keto-acidosis	29	8.8	-	-
Myocarditis	19	5.8	-	-
Other	12	3.7	-	-
No complication/unspecified	78	23.8	-	-
Management				
Treatment prescribed				
Dexamethasone	297	90.5	-	-
LMWH prophylaxis	240	73.2	-	-
LMWH therapeutic	60	18.3	-	-
Thiamine	194	59.1	-	-
Vitamin D stat doses	147	44.8	-	-
Vitamin B3	178	54.3	-	-
Zinc	195	59.5	-	-
Ceftriaxone	304	92.7	-	-
Azithromycin	287	87.5	-	-
Oxygen requirements on admission (n = 329)				
Room air	74	22.5	-	-
Nasal prongs	8	2.4	-	-
40% Venturi face mask	66	20.1	-	-
100% non-rebreather mask	114	34.7	-	-
Dual oxygen	32	9.7	-	-
High-flow nasal oxygen	22	6.7	-	-
Continuous positive airway pressure	12	3.6	-	-
Intubation and mechanical ventilation	1	0.3	-	-
Number of days on oxygen (n = 318)	-	-	3	1–7
0	22	7	-	-
1–6	210	66.0	-	-
≥ 7 days	86	27.0	-	-
Patient discussed with higher levels of care during admission				
No	229	72.2	-	-
Yes	88	27.8	-	-
Unknown	11	3.5	-	-
Number of referrals accepted (n = 88)				
No	73	86.9	-	-
Yes	11	13.1	-	-
Unknown	4	-	-	-

LMWH, low molecular weight heparin; IQR, interquartile range.
†, Except where specified.

Mortality trends

The median length of admission to WWH before death was 4 days (IQR: 1.5–8). Most participants (n = 196; 62.4%) demised after regular working hours (16:00–07:59). Eleven participants (3.4%) were dead on arrival (DOA), and 29 (8.8%) demised in the emergency centre (EC) within a few hours of arrival, precluding admission.

A total of 2138 were admitted to WWH from 01 March 2020 to 31 August 2021. During this period, 328 participants demised from COVID-19, yielding an institutional crude fatality rate of 15.3%. Of the total sample size (328), 311 deaths fell into the first three waves of the COVID-19 pandemic as described by the NICD. Fifty-nine (19.0%) of these fell into wave one, 189 (60.8%) fell into wave two and 63 (20.3%) fell into wave three. A total of 354, 573 and 517 patients were admitted to WWH with COVID-19 infection during wave one, two and three, respectively. The crude fatality ratio was therefore 16.7%, 33.0% and 12.2% for waves one, two and three, respectively (Figure 1).

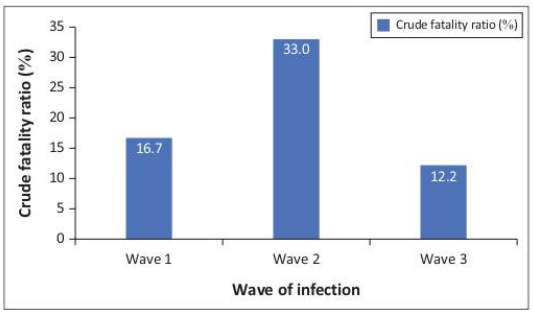

FIGURE 1: Institutional crude fatality ratios during the first three COVID-19 waves of infection.

Discussion

This study describes the demographics, as well as the clinical, biochemical and radiological presentation of 328 participants who demised from COVID-19 at WWH – a single DH – as well as their management. COVID-19 mortality was most frequent in the following participants: females; those older than 60 years; black Africans; obese individuals and those with comorbidities such as hypertension, diabetes mellitus and poorly controlled HIV. On admission, 63.1% participants had clinical frailty scores less than and/or equal to five, indicating good pre-morbid functioning. This highlights the isolated effect of COVID-19 on the immune system and suggests other pathogenic mechanisms for the development of severe infection and death.

The increased mortality rate in elderly individuals is a consistent finding across the published literature.[2,4,10] Suggested pathogenic mechanisms for this include age-related changes in innate and adaptive immunity and delayed presentation in older individuals because of concerns around exposure to COVID-19 in the hospital environment. An unbalanced, pro-inflammatory environment in elderly individuals can cause exacerbated inflammatory responses, resulting in a cytokine storm in older adults. Such dysregulation of the immune system is the basis of the development of ARDS as well as the involvement of other organ systems leading to multi-organ failure (MOF).[10]

Black African females made up most of the COVID-19-related deaths at WWH. The literature displays a complex interplay between gender, age and race and its associations with COVID-19-related death. A study conducted in the Eastern Cape of South Africa established that gender associations differed with race and age.[9] Indian males had a higher COVID-19-related death rate, while the lowest death rate was found in coloured females. Overall, females had a higher death rate than males in the black African and mixed race

populations, whereas males had a higher death rate than females in the Indian and white populations. The race profile of our participants was likely influenced by the demographic profile of the Wentworth community, which falls within the eThekwini Municipality and had a predominantly black African (74%) majority in the 2011 National Census.[11] Phaswana-Mafuya et al.[12] showed that white people were more likely to die at older ages compared to black Africans, mixed race people and Indian people. However, comparing each age group, the death rate was consistently highest among black Africans. These heterogeneous findings implicate complex pathophysiology relating to gender and race associations with COVID-19 death. In addition, poor help-seeking behaviour, a delay in seeking medical attention in advanced disease, low detection rates and limited capacity to manage critical cases have also proven to be risk factors for mortality in LMICs.[4] This is particularly relevant in this study setting: a resource-limited district hospital – managed mainly by junior medical officers – inundated with a sudden surge of critically ill patients with complex disease processes.

Hypertension, diabetes mellitus and immunocompromised status are reported in several studies (including ours) to be the most common comorbidities in severe COVID-19 infection.[3,5] The association between hypertension and severe COVID-19 illness and death is postulated to be because of myocardial damage and dysfunction.[13] This is implied by frequent findings of elevated troponin levels and electrocardiographic abnormalities in these patients. A significant proportion of our participants had diabetes mellitus, most of which had poorly controlled disease, as displayed by high HbA1c levels. The postulated reason for severe COVID-19 disease in participants with diabetes mellitus (primarily with poor glycaemic control) is a weakened innate and humoral immunity secondary to chronic hyperglycaemia, resulting in compromised host defence against SARS-CoV-2.[13] Diabetes mellitus is associated with low-grade chronic inflammation, making the participant vulnerable to an exaggerated inflammatory response, resulting in ARDS and MOF. Recent studies have also shown a direct damaging effect of SARS-CoV-2 on the pancreas, which worsens hyperglycaemia and possibly triggers the onset of diabetes mellitus in diabetes-naïve individuals.[14] Obesity is documented in several studies to be associated with severe COVID-19 disease.[5,14] Obesity was under-reported in our study because of poor documentation in participants' clinical records and the difficulty experienced by healthcare workers in weighing very ill patients. Nonetheless, all the participants in our study with a documented weight were obese. Most of the HIV-positive participants in our study had unsuppressed viral loads. Although not recorded in our study, the possible associated low CD4+ T-cell count in these participants is explained in a systematic review done by Chen et al.,[10] which found that lymphopenia (consisting of depletion of both CD4+ and CD8+ T-cells) and high neutrophil counts are helpful predictors for COVID-19 death. In contrast, high lymphocyte counts predict better clinical outcomes.

Most of our participants exhibited sober habits; however, the strongest association (albeit weak) was seen with current cigarette smoking. Alqahtani et al.[15] found that current smokers were 1.45 times more likely to have severe COVID-19-related complications and had a higher mortality rate of 38.5% compared to non-smokers and previous smokers. A study conducted on 4244 patients admitted with severe COVID-19 disease to ICUs across Switzerland, Belgium and France found that only 4% were active smokers.[5] Van Zyl-Smit et al.[16] postulated that increased susceptibility to infection in current smokers may be because of upregulation of the angiotensin-converting enzyme 2 (ACE2) receptor, which is the main receptor responsible for the entry of SARS-CoV-2 into the host's mucosa. It is still unclear as to whether modification of ACE 2 receptor availability affects COVID-19-related mortality.

The most common presenting symptoms were dyspnoea, cough, myalgia, fever, sore throat, confusion, loss of taste and/or smell and diarrhoea. A systematic review by Kumar Ochani et al.[17] delineated the most common symptoms reported by patients throughout the disease course, including all the symptoms mentioned above. These clinical presentations varied slightly between the different strains of SARS-CoV-2 viruses and different individuals; however, the core symptoms remained the same. Modified Medical Research Council grade four dyspnoea was present in many of our participants, highlighting the propensity for severe COVID-19 to cause ARDS, particularly in older individuals. This symptom is congruent with the chest X-ray changes on admission, most of which were classified as 'moderate-severe' with peripheral ground glass opacities – which has been evident in various other studies.[18,19] Furthermore, most of our participants were tachypnoeic with low arterial oxygen saturations on admission, likely because of ARDS.

On 17 February 2021, South Africa commenced its national vaccine rollout strategy, which was initially only available to healthcare workers.[20] People aged 60 years and older were only eligible to get the vaccine on 17 May 2021. People aged 50–59 years were only eligible to get the vaccine on 05 July 2021. Booster doses became available on 10 November 2021.[21] Even though vaccination was unavailable to most of the participants in our cohort, fewer than expected were partially vaccinated (only two participants) and none were fully vaccinated. This perhaps suggests a protective effect of vaccination against COVID-19-related death. Reasons for the initial lag in vaccination programme uptake likely include stigma/fear surrounding the vaccine, a lack of knowledge/health promotion around the topic, as well as a lack of access to vaccination facilities. Despite different dose requirements, efficacies, duration of immunity and side-effect profiles, approved vaccinations reduce the risk of COVID-19-associated deaths.[10]

The introduction of COVID-19 rapid antigen testing in KwaZulu-Natal in December 2020 improved the speed of COVID-19 diagnosis, making it a quick and reliable adjunct to diagnosing COVID-19. A recent Cochrane review on

antigen testing stated that in symptomatic patients, 'some rapid antigen tests are accurate enough to replace RT–PCR, especially for ruling in the presence of infection'.[22] Despite this, SARS-CoV-2 PCR is still the gold standard for diagnosis of COVID-19 infection with a recent meta-analysis stating a sensitivity of 86% on a nasopharyngeal swab.[18] Most participants in our study had a positive PCR result (94.8%), with a small proportion of participants included in the study despite a negative PCR result. These participants were included based on locally defined radiological and clinical criteria (high probability score) suggestive of COVID-19. This score allowed for rapid triage of patients with an increased probability of having COVID-19 to be admitted to the isolation wards, as the PCR turnaround time exceeded 10 days during the first two waves. Most participants had raised inflammatory- (CRP, LDH) and pro-thrombotic (D-dimer) markers, in keeping with the proposed pro-inflammatory and pro-thrombotic nature of COVID-19 disease. Chen et al.[10] explain the microvascular thrombosis and MOF seen in severe COVID-19 disease to be linked to the complement activation and endothelial dysfunction caused by immune and inflammatory markers, contributing to a dysregulation of the coagulation system. This is the basis for prophylactic administration of LMWH and intravenous immune globulin (IVIg) to patients with severe COVID-19.

The most frequent complication noted on admission was an impaired renal function; however, the chronicity of the renal dysfunction was not established. Because the derangements were present from admission, this could be indicative of the typical patient presenting with severe COVID-19 disease: multimorbid patient with established chronic kidney disease. Renal replacement therapy was needed in 28% of a cohort of patients admitted with severe COVID-19 disease to several ICUs in western Europe.[5] About one quarter of our participants had a decreased level of consciousness and haemodynamic instability on admission, indicating the systemic instability of patients with severe COVID-19 disease and proving useful clinical tools for predicting poor clinical outcomes and mortality. Thrombo-embolic complications were also common in patients with severe COVID-19 disease, as evident by this study and numerous other studies.[3,5,10] Ochani et al.[17] explain that micro thrombus formation is caused by the inflammation of lung tissue and pulmonary endothelial cells, which results in thrombotic complications such as pulmonary embolism, deep venous thrombosis (DVT), ischaemic stroke, myocardial injury and limb ischaemia. The pathogenesis of myocardial injury in patients with COVID-19 disease involves coronary spasm, hypoxic injury, microthrombi, hypercoagulability, hypoxic injury, direct vascular endothelial injury and atherosclerotic plaque instability, which increases the risk of acute myocardial infarction secondary to acute coronary occlusion.[13,14]

Almost all of our participants were prescribed antibiotics on admission (ceftriaxone with/without azithromycin). Antibiotics were prescribed in the institution as per the South African Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). Without a point-of-care confirmation of the diagnosis, admitted patients were treated for community-acquired pneumonia based on their severity assessment as per the STGs. Antibiotics were stopped once the COVID-19 antigen or PCR tests confirmed COVID-19 infection.

Most of our participants required oxygen supplementation on admission. The decision to start $HFNO_2$ and CPAP was based on the Horowitz index[9] and the clinical picture of the patient while using less advanced oxygen modalities, that is, whether they were able to maintain arterial oxygen saturations above 88% when a 100% non-rebreather mask was used at 15–20 litres per min. High-flow nasal oxygen and CPAP machines were commonly required modalities that were unavailable during the first wave. A few $HFNO_2$ and CPAP machines were acquired through private funding after the first wave of the COVID-19 pandemic. However, not every patient had the opportunity to go onto a device because of these resource constraints. Furthermore, many junior healthcare workers at the facility were untrained and inexperienced in using these devices, leading to poor utilisation of these devices and poor-quality management of patients on these devices. It is also possible that many patients who went on the $HFNO_2$ survived and are not included in this mortality study.

Most participants requiring such modalities were discussed with the tertiary-level referral hospital; however, because of limited ICU beds and ventilators, many of our participants were put on waiting lists and were not transferred to higher levels of care. Discussion with the tertiary referral facility was reserved for patients who fulfilled the criteria for ICU admission and for those that required invasive ventilation. This decision to discuss with tertiary care was made by senior members of staff – usually family medicine consultants – within 24 h of admission. The reality of the resource-limited situation at the regional and tertiary hospitals was also well known, and many patients were not discussed, as clinicians in the district-level hospitals saw this as pointless in the current circumstances. Many patients also had morbid obesity, an exclusion criterion for the ICU. The clinical probability score was used to assist with the clinical diagnosis and not to determine the prognosis. However, the clinical frailty score (included in the admission clerking notes) assisted clinicians in deciding who to discuss for ICU care: patients with higher clinical frailty scores (greater than five) were not considered for ICU. The median length of admission to WWH before demise was 4 days, similar to figures found at a tertiary facility in the Western Cape.[2]

A meta-analysis across multiple electronic databases noted that case fatality rates (CFR) (COVID-19 deaths/COVID-19 PCR tests) varied depending on the population at stake.[23] They found an overall pooled CFR of 10%, with a CFR of 13% in hospitalised patients, 37% in patients admitted to an ICU, 19% in patients older than 50 and only 1% in the general population. Our institutional crude fatality rate (institutional

COVID-19 deaths/institutional COVID-19 admissions) of 15.3% is slightly higher than the crude fatality ratio found in hospitalised patients in this meta-analysis. This could be accounted for because of the limitations of a district hospital in dealing with severely ill patients because of inadequate critical care facilities, healthcare workers, level of expertise at this level and inadequate medical equipment.[24] A study by Li et al.[25] identified a negative correlation between the mortality rate of COVID-19 and test numbers per 100 people, government effectiveness score and the number of hospital beds. Thus, the increased crude fatality ratio found in our study may be highlighting the strain on the healthcare system during this period. A limitation of our study was our inability to accurately describe a case fatality ratio based on the fact that patients may have had multiple PCR tests over the defined period and may have presented with PCR results from other facilities, falsely impacting the case fatality ratio. The crude fatality ratio is therefore a relatively accurate way of determining the mortality rate of patients hospitalised with COVID-19 at WWH over specified time periods. Wave two (as characterised by the 'Beta' variant – 501Y.V2 or B.1.351) had the highest crude fatality ratio, indicating increased virulence of the variant.[26] This is in keeping with the findings from multiple studies stating that the 'Beta' variant is more virulent than other COVID-19 strains because of its development of multiple protein mutations, causing increased infectivity of the strain and decreased neutralisation by existing vaccines.[27] Eleven participants were dead on presentation to WWF. This may be because of late presentation, stigma and fear surrounding COVID-19 and healthcare facilities. Twenty-nine participants demised in the EC within a few hours of presentation, indicating the severity of the disease on presentation to the healthcare facility, 423 and implying late presentation.

Strengths of the study include the provision of a thorough description of the risk factors for mortality in a generalisable health context: an overwhelmed, resource-constrained DH in an LMIC. This provides representative data that can be used to provide insights into risk factors for COVID-19 mortality as well as managements in a similar health setting. Apart from those already mentioned, limitations of the study include some paucity of data because of scanty record-keeping and a reliance on paper-based clinical notes. This may have resulted in under-reporting of certain risk factors. Furthermore, there is a risk of false-positive COVID-19 cases because of the clinical probability score being used for participants without a positive COVID-19 PCR test.

Conclusion

This study describes the COVID-19-related deaths during the first two years of the COVID-19 pandemic at a DH in South Africa. Many participants were female (60.1%), older than 60 (66.5%), of black African descent (59.6%), unvaccinated and had uncontrolled comorbidities. The institutional crude fatality rate was 15.3%, a value higher than that seen in many other hospitalised populations worldwide.[23] This is perhaps indicative of the strain placed on an under-resourced facility with a lack of specialist medical expertise and a lack of advanced medical equipment. The highest crude fatality rate was seen in wave two (33.0%), which was characterised by the 'Beta' variant, perhaps indicating increased virulence of this variant.

Recommendations for future research include the development of an electronic record-keeping system, to allow the capture of reliable, site-specific information that could be used for quality improvement projects and further research as well as doing further research into the impact of the National Vaccination Programme on country-wide mortality statistics.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

O.H. designed the study, and M.N. designed the data collection tool. O.H. and C.P. performed the study and collected the data. O.H. and C.P. performed the data analysis with the help of biostatistician (Cathy Connolly of UKZN) and wrote the first draft, and M.N. assisted with editing the final article.

Ethical considerations

This study was conducted after obtaining ethical clearance from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (BREC/00003680/2021). Ethical approval from the Health Research Committee – KwaZulu-Natal Department of Health (NHRD Ref: KZ_202201_003). Institutional approval was also granted by Wentworth Hospital Ethics Committee.

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Data availability

Patient data is strictly confidential, and data for the study are solely accessible by the authors involved.

Disclaimer

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CONCLUSION

Manuscript one described the C19-related deaths during the first two years of the C19 pandemic at a DH in South Africa. Most patients were female (60.1%), older than 60 (66.5%); of Black African descent (59.6%); unvaccinated and had uncontrolled comorbidities. The institutional crude fatality rate was 15.3%. The highest crude fatality rate was seen in wave two (33.0%), which was characterised by the 'Beta' variant, perhaps indicating increased virulence of this variant. Recommendations for future research include developing an electronic record-keeping system to capture reliable, site-specific information that could be used for quality improvement projects and further research. As well as doing further research into the impact of the National Vaccination Programme on country-wide mortality statistics.

CHAPTER 5: MANUSCRIPT TWO

Introduction

The findings related to the aim and objectives 1 to 4 of this dissertation are presented in manuscript format. The following article provides a detailed comparison of the three waves and mortality trends at a DH level during the first three waves of the C19 pandemic. The manuscript was formatted according to published journal guidelines of the South African Medical Journal (SAMJ) and has been submitted to the relevant journal.

The key study findings were as follows: Wave one, two and three yielded case fatality rates of 14.5%, 27.6% and 6.3%, respectively, and crude fatality rates of 16.7%, 33.0% and 12.2%, respectively. Black Africans were less likely to demise during the third wave (OR 0.54; 95% CI 0.31 to 0.94). Patients in the second wave had a clinical frailty score of less than five (OR 2.51; 95% CI 1.56 to 4.03). Obesity was most prevalent in the second wave (OR 1.87; 95% CI 1.01 to 3.46), and dyslipidaemia (OR 3.03; 95% CI 1.59 to 5.77) and ischaemic heart disease was most prevalent during the third wave (OR 3.77; 95% CI 1.71 to 8.33). Mild infiltrates on chest radiograph were most prevalent during the third wave (OR 2.41; 95% CI 1.09 to 5.34), moderate ground glass appearance was most common during the first wave (OR 3.12; 95% CI 1.74 to 5.59), and severe ground glass appearance was most common during the second wave (OR 2.37; 95% CI 1.49 to 3.77). Renal impairment was most prevalent during the first wave (OR 3.28; 95% CI 1.59 to 6.77), and thrombo-embolic phenomena were less common during wave three (OR 0.12; 95% CI 0.02 to 0.91).

2 May 2023

The Editor

South African Medical Journal

Mortality trends during the first three waves of the COVID-19 pandemic at an urban district hospital in South Africa: A retrospective comparative analysis

Dear Sir/Madam

We thank you for this opportunity to present our research to you. The study was set at a district level hospital in South Africa. The findings are as follows:

A total of 311 patients demised in hospital from COVID-19 (C19) during the first three defined waves: 59 in wave one, 189 in wave two and 63 in wave three. During the first three waves, 354, 573 and 517 patients were admitted with C19 infection to Wentworth hospital (WWH), yielding a crude fatality rate (institutional C19 deaths / institutional C19 admissions) of 16.7%; 33.0% and 12.2% for waves one, two and three respectively. Over these defined periods 408, 684 and 994 patients tested positive with the C19 PCR test, yielding a case fatality rate (institutional C19 deaths / institutional C19 positive PCR swabs) of 14.5%, 27.6% and 6.3% for waves one, two and three respectively.

The beta variant, which characterised the second wave, was the most virulent, as portrayed by the highest case- and crude fatality rates during this period. The characteristics of the patients who demised during the second wave were individuals with lower clinical frailty scores and more severe clinical presentations. Across the three waves, most patients were female and older than 60. Individuals of the black African race constituted most deaths across all three waves. However, this was significantly less during the third wave (OR 0.54; 95% CI 0.31 to 0.94). Caucasians made up a significantly smaller proportion of deaths during the first wave (OR 0.35; 95% CI 0.12 to 1.03) compared to the second and third waves. Hypertension and diabetes mellitus were present in a similar proportion of patients across all three waves. Most patients with diabetes mellitus across all three waves had an HBA1c greater than eight percent. Obesity was most prevalent in the second wave (OR 1.87; 95% CI 1.01 to 3.46) compared to the other two waves. Dyslipidaemia (OR 3.03; 95% CI 1.59 to 5.77) and ischaemic heart disease (IHD) (OR 3.77; 95% CI 1.71 to 8.33) were most prevalent during the third wave. IHD was least prevalent during the second wave (OR 0.42; 95% CI 0.19 to 0.91) compared to the other two

waves. Most patients reported sober habits, with current smoking being the most frequently reported social habit across all three waves.

Our study provides an extensive analysis of mortality data across the first three waves of the C19 pandemic at a district-level hospital (primary health care level) in South Africa. The crude and case fatality rates are similar to local and international figures. Furthermore, the risk factors for severe disease and death are similar to those found in local and international studies. Our research provides valuable data on the differences between the first three C19 waves of infection (which, by proxy, provides valuable comparative data on the alpha, beta and delta strains of SARS-CoV-2). Lastly, our study provides important information on the additional burden placed by C19 on an already resource-constrained environment. This information could assist in the development of healthcare policies for primary level healthcare facilities across the world. Recommendations include development of an electronic record-keeping system and further research into the broader socio-economical impacts of C19 on health facilities across South Africa.

Important mention must be made of a preceding study conducted by the same authors, commenting on the overall mortality trends of patients who died from C19 at Wentworth Hospital from 1 March 2020 to 31 August 2021. The main findings of this study were: Of the 328 patients who demised from C19, 197 (60.1%) were female. The mean age of death was 64 years (SD 13.6). Most patients (n = 196; 59.6%) were of black African descent. Of those with documented clinical frailty scores, 197 (63.1%) had a score of less than six, indicating good pre-morbid function. Hypertension was present in 201 (61.3%) patients and diabetes mellitus in 156 (47.6%) patients, with the majority (35.1%) having an HbA1c greater than 8%. Sixty-two patients (18.9%) had a body mass index (BMI) greater than 30, and 53 (16.2%) had dyslipidaemia. Forty-five (13.7%) patients were HIV-positive. There appeared to be no association between substance use and C19 death, with 237 (72.3%) patients reporting sober habits. Comparative analysis of the mortality data between the three defined waves of infection was not done. This study is awaiting publication.

From a developing country and primary healthcare perspective, we hope our study will provide useful comparative data on the mortality trends of the first three waves of the C19 pandemic.

Kind regards,
O Hirachund (Corresponding author)

Mortality trends during the first three waves of the COVID-19 pandemic at an urban district hospital in South Africa: A retrospective comparative analysis

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Abstract

Objectives

To compare mortality trends of patients who demised in hospital from SARS-CoV-2 infection during the first three waves of infection as defined by the National Institute of Communicable Diseases of South Africa.

Design

Retrospective cohort study.

Setting

District level hospital in South Africa.

Patients

311 adults who demised within the first three waves.

Main outcome measures

Case- and crude fatality rates, baseline characteristics, symptomatology, clinical presentation, and management of patients.

Results

Wave one, two and three yielded case fatality rates of 14.5%, 27.6% and 6.3% respectively; and crude fatality rates of 16.7%, 33.0% and 12.2% respectively. Black Africans were less likely to demise during the third wave (OR 0.54; 95% CI 0.31 to 0.94). Patients in the second wave had clinical frailty scores of less than five (OR 2.51; 95% CI 1.56 to 4.03). Obesity was most prevalent in the second wave (OR 1.87; 95% CI 1.01 to 3.46), and dyslipidaemia (OR 3.03; 95% CI 1.59 to 5.77) and ischaemic heart disease (OR 3.77; 95% CI 1.71 to 8.33) were most prevalent during the third wave. Severe ground glass appearance was most common during the second wave (OR 2.37; 95% CI 1.49 to 3.77). Renal impairment was most prevalent during the first wave (OR 3.28; 95% CI 1.59 to 6.77), and thrombo-embolic phenomena were less common during wave three (OR 0.12; 95% CI 0.02 to 0.91).

Conclusions

The beta variant was the most virulent with the highest case- and crude fatality rates.

What is known about this topic?

Since the start of the COVID-19 (C19) pandemic, there have been multiple studies worldwide. However, knowledge of mortality trends in developing countries - particularly at a district hospital level - is limited. Mortality remains high in multi-morbid ventilated patients with C19 in South Africa (SA) at any level of care.[1] Globally, multiple independent risk factors have been

identified as key contributors to the development of severe disease and mortality. These risk factors include male sex, obesity, and comorbidities such as hypertension (HT), type two diabetes mellitus (T2DM), cardiovascular disorders, malignancies, chronic obstructive pulmonary disease, pulmonary tuberculosis (PTB), and HIV.[2] Within SA, differential patterns of C19 deaths by sex, age, comorbidities, and province have emerged. However, individuals with HT and T2DM are reliably shown to be at high risk of death from C19.[3] On 1 April 2020, the National Institute for Communicable Diseases (NICD) developed the DATCOV database to serve as a national surveillance system for COVID-19 hospitalisations.[4] This system allowed for data to be collected regarding COVID-19; However, there is no official system to ensure regular analysis of this data within individual institutions to allow appropriate feedback to improve service provision. Little is known about the impact of the C19 pandemic on these facilities and the differences in mortality trends between the first three waves at all district hospitals (DH) in SA. Anecdotal reports suggest that many district hospitals had little support from higher levels of care (tertiary and regional hospitals) during surges in the infection rate.

What this study adds

Prior to the pandemic, most district hospitals in South Africa functioned at their peak capacity due to staff shortages and an increased service load.[3] Mortality trends are essential for future planning/risk stratification of patients. Most of the data published within SA has been conducted at a tertiary level - minimal evidence exists at a DH level. This is particular important to guide decision-making, especially in resource-constrained environments with limited ability to expand critical care capacity.[5] Ethical allocation of resources with early effective triaging of patients is dependent on local data to ensure equitable and appropriate admission to critical care services. This study utilises Wentworth Hospital (WWH) as an example of a DH in SA. The findings of this study may be generalised to other low-resourced facilities in low and middle-income countries (LMICs) or rural primary care facilities in high-income countries (HICs).

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS COV 2) is responsible for the COVID-19 (C19) pandemic. South Africa has experienced numerous periods of increased transmission, also known as 'waves ‘, of infection.[6] Variants or mutations of the original virus drove the surges in infection rates. The first wave was predominated by the ancestral strain with the Asp614Gly mutation, the beta variant (B.1.351) during the second wave and the delta variant (B.1.617.2) during the third wave.[4] Prior to the vaccination rollout, state-run and private healthcare facilities across the country were overwhelmed by the impact of C19.[1] South Africa's overall facility case fatality rate (CFR) was 21.5% during the first wave, 28.8% during the

second wave and 26.4% during the third wave.[4] Despite evidence existing from a South African context, most of the published studies were conducted in the Western Cape. The Western Cape has better infrastructure and a stronger healthcare system than many other provinces in the country; and therefore the mortality rates are likely to be lower than in other parts of South Africa.[7] Mortality rates were highest in patients over 60 and in those with comorbidities - especially obesity, hypertension and diabetes mellitus.[8] These results are in keeping with international findings.

The South African public healthcare system consists of various levels of hospitals: district, regional, tertiary, provincial tertiary, central and specialised.[9] District hospitals (DHs) provide primary health care and unspecialised services, and subsequently refer patients to regional or tertiary facilities should the patient require a higher level of care. During the peak of each wave, many tertiary, regional and central hospitals were inundated with large patient volumes resulting in poor acceptance rates of referrals from DHs. Consequently, many severely ill patients with complex presentations were managed at DHs. In KwaZulu-Natal (KZN), intensive care unit (ICU) services were limited, and many ill patients were placed on waiting lists for ICU beds. In the interim, these patients were managed at the DH level. The additional burden of increasing healthcare-worker infection rates - who required self-isolation - posed increased stressors to an already resource-constrained environment.[5] Contract staff were employed to bridge the gap of the service-burden during the C19 pandemic, but many of them were untrained in managing critically ill patients.

This study compared mortality rates, examined the risk factors for death, and explored differing clinical presentations of patients with SARS-CoV-2 infection between the first three defined waves of infection at an urban DH in KZN, South Africa. There is limited data from level-one hospital facilities in South Africa and thus limited insight into the effects of the pandemic at a primary care level.

Methods

Study design and setting

A single-centre retrospective observational analysis of Wentworth Hospital's (WWH) clinical records was performed. WWH is a DH in Durban, Kwa-Zulu Natal, South Africa. The target population included all patients admitted to WWH who subsequently demised from C19 disease in the hospital within the designated waves as defined by the National Institute of

Communicable Disease (NICD).[10] Wave one in KwaZulu Natal was from week 26 to 34 of 2020; wave two was from week 49 of 2020 to week five of 2021, and wave three was from week 24 to 37 of 2021.

Inclusion and exclusion criteria

All patients over 18 of age, infected with C19 (based on clinical, biochemical or radiological features suggestive of SARS-COV-2 infection) who were admitted and subsequently demised in-hospital during the defined waves were included in the study. The study excluded patients who demised outside of the defined waves. None of the patients were re-admissions and patients who were discharged and demised at home were not included in the study. The diagnosis of C19 disease was based on a positive polymerase chain reaction (PCR) test from a nasopharyngeal upper respiratory tract swab. A small subset of patients with negative PCR tests were included in the study based on the score attained in a locally devised clinical probability score. A score of 9 or greater (out of 21) was deemed "highly suggestive" of C19. Points were awarded as follows: a history of positive contact (2 points); acute cough (1 point); fever >38°C (2 points); respiratory rate >25/min (1 point); pulse oximetry saturation (SpO2) < 95% (2 points); recent loss of taste/smell (3 points); high C-reactive protein (CRP) (2 points); high white cell count (WCC) (1 point); positive chest X-ray [ground glass (3 points) or pneumonia(2 points)]; D-dimer >0.25 (2 points) and any diabetic emergency (hyper or hypoglycaemia) (2 points). The study excluded any non C19 related deaths i.e an incidental positive C19 finding in a patient who demised from injuries sustained in a motor vehicle accident.

Data sources and outcome measures

An electronic data collection tool was devised (this consisted of a Google form which converted the data into an Excel spreadsheet), and a pilot study was conducted on 54 files of patients who demised in August 2020 to validate the data collection tool and ensure that the study objectives were met. The data was gathered from paper-based records and then captured electronically by the two principal investigators. A crude fatality rate for each wave was calculated using admission data of patients who were admitted to WWH with C19 disease during each wave. A case fatality rate per wave was calculated using positive PCR test results from the National Health Laboratory Service (NHLS) at WWH. Further analysis was conducted on the baseline characteristics, comorbidities, clinical presentation and management of patients across all three waves. Race was recorded on admission as identified by patients or for those who were too ill to communicate or dead-on arrival, race was reported by the attending medical doctor and captured on the admission clerking tool. The admitting medical doctor described the radiological changes

evident on chest radiograph and these findings were confirmed by the consulting Family Physician, as no radiologist was available at the facility.

Quantitative variables and statistical methods

Descriptive statistics were used to summarise the data. Frequencies and percentages were used for categorical data such as gender, ethnicity, and comorbidities. Frequency distributions of numeric variables were examined for normality and mean (SD) or median (IQR) was used as appropriate. Odds ratios (ORs), 95% confidence intervals (CIs) and p-values were reported. A p-value < 0.05 was considered statistically significant. Stata v17[11] was used in the analysis. Analysis was done to determine if the continuous variable differs significantly across the three waves. This was done either using ANOVA or Kruskal-Wallis tests.

Patients and public involvement

Patients and the public did not personally partake in this research due to the retrospective, observational nature of the study. Ethical clearance was obtained from the Biomedical Research Ethics Committee BREC/00003680/2021; and the National Department of Health NHRD Ref: KZ_202201_003. Additionally, institutional ethical clearance was received from the Wentworth Hospital Ethics Committee.

Results

Patients and mortality data

Of the 311 total patients who demised within the defined waves, 59 (19.0%) demised in wave one, 189 (60.8%) demised in wave two and 63 (20.3%) demised in wave three. During the first three waves, 354, 573 and 517 patients were admitted to WWH with C19 infection, yielding a crude fatality rate (institutional C19 deaths / institutional C19 admissions) of 16.7%; 33.0% and 12.2% for waves one, and two and three respectively (Figure 1). Over these defined periods, 408, 684, and 994 patients tested positive for C19 using the PCR test, yielding an institutional case fatality rate (institutional C19 deaths / institutional C19 positive PCR swabs) of 14.5%; 27.6% and 6.3% for waves one, and two and three respectively.

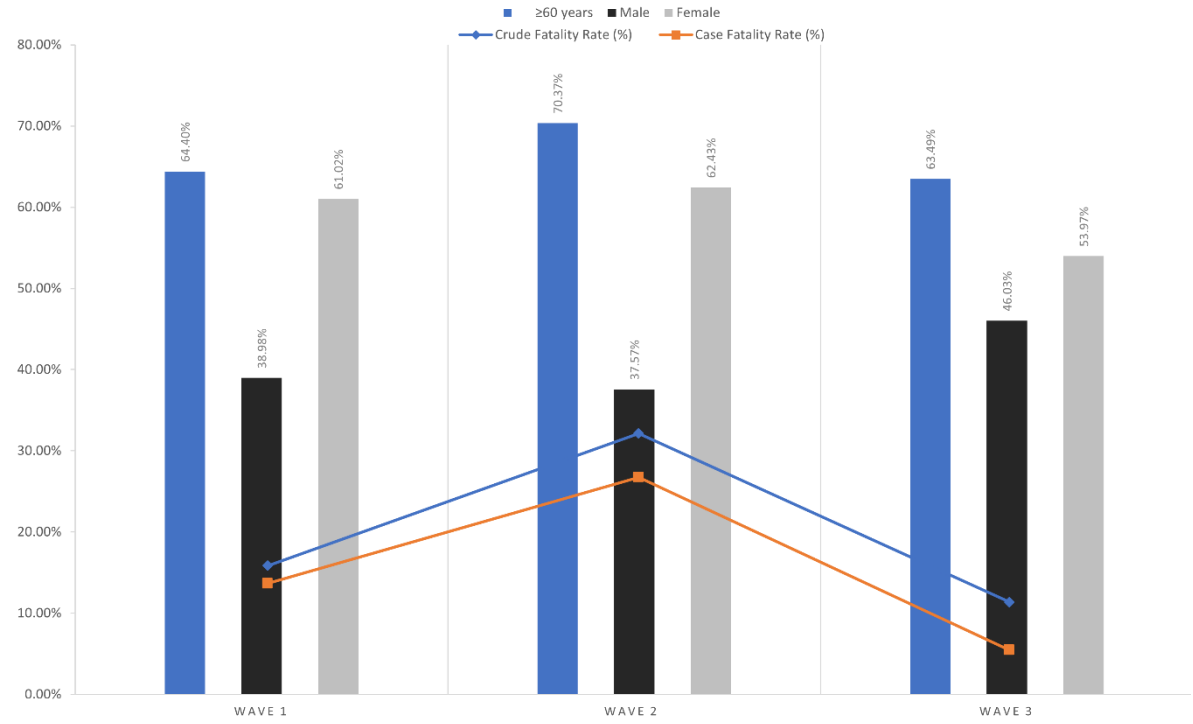

Figure 1: Bar graph depicting mortality rates in patients over 60, as well as males and females, over the first three waves. Line graph showing the crude- and case fatality rates over the first three waves.

Descriptive data

Retrospective, descriptive analysis was conducted on the files of 311 patients whose dates of death fell into the specified waves of infection. This included 11 patients who were 'dead on arrival' and 28 patients who “demised within a few hours of admission”.

Background characteristics

Across the three waves, most patients were female and older than 60 (Table 1). Individuals of the black African race constituted most deaths across all three waves, however, they contributed significantly less to the total population during the third wave (OR 0.54; 95% CI 0.31 to 0.94; p-value 0.027). Caucasians made up a significantly smaller proportion of deaths during the first wave (OR 0.35; 95% CI 0.12 to 1.03; p-value 0.067) compared to the second and third waves. Patients were more likely to have clinical frailty scores less than five in the second wave (OR 2.51; 95% CI 1.56 to 4.03; p-value <0.001) compared to the other two waves, indicating better pre-morbid functioning of those who demised in wave two. Contrastingly, patients were more likely to have clinical frailty scores greater than/equal to five in the first wave (OR 2.25; 95% CI 1.24 to 4.07; p-value 0.007) and third wave (OR 1.82; 95% CI 1.03 to 3.21; p-value 0.037) compared to the second wave, indicating lower level of pre-morbid function in these patients.

Hypertension and diabetes mellitus was present in a similar proportion of patients across all three waves. Most patients with diabetes mellitus across all three waves had an HBA1c greater than eight percent. Although poorly reported, obesity was most prevalent in the second wave (OR 1.87; 95% CI 1.01 to 3.46; p-value 0.043) compared to the other two waves. Dyslipidaemia (OR 3.03; 95% CI 1.59 to 5.77; p-value 0.001) and ischaemic heart disease (IHD) (OR 3.77; 95% CI 1.71 to 8.33; p-value 0.001) were most prevalent during the third wave. Ischaemic heart disease was least prevalent during the second wave (OR 0.42; 95% CI 0.19 to 0.91; p-value 0.025) compared to the other two waves. HIV-positive patients with unsuppressed viral loads were most common in the first wave (OR 2.13; 95 % CI 0.95 to 4.79; p-value 0.061) compared to the other two waves. Most patients reported sober habits, with current smoking being the most frequently reported social habit across all three waves. Antigen testing was introduced at WWH towards the end of the first wave. The rapid antigen test yielded a positive result in 61.4% and 76.2% of patients who fit the inclusion criteria during the second and third waves, respectively. Most positive antigen tests were found during the third wave (OR 3.53; 95% CI 1.88 to 6.63; p-value <0.001). The PCR test was positive in all patients during the first wave, 178 (94.2%) patients during the second wave, and 58 (92.1%) patients during the third wave. None of the patients were fully vaccinated.

Table 1: Background characteristics of patients that died in the hospital.

Characteristics, n (%) except where specified	**Wave 1**		**Wave 2**		**Wave 3**	
	***n* = 59**	**OR (95% CI); p-value**	***n* = 189**	**OR (95% CI); p-value**	***n* = 63**	**OR (95% CI); p-value**
Background						
Female	36 (61.0%)	1.03 (0.58-1.84); 0.921	118 (62.4%)	1.23 (0.78-1.96); 0.373	34 (54.0%)	0.72 (0.41-1.25); 0.239
Age (years), mean (SD)	64.6 (14.4)		64.1 (13.1)		64.4 (13.2)	
≥60 years	38 (64.4%)	0.83 (0.46-1.50); 0.530	133 (70.4%)	1.34 (0.83-2.17); 0.235	40 (63.5%)	0.78 (0.44-1.40); 0.407
<60 years	21 (35.6%)	1.21 (0.67-2.20); 0.530	56 (29.6%)	0.75 (0.46-1.21); 0.235	23 (36.5%)	1.28 (0.72-2.28); 0.407
Ethnic classification						
Black	42 (71.2%)	**1.85 (1.00-3.43); 0.048**	114 (60.3%)	1.06 (0.66-1.68); 0.819	30 (47.6%)	**0.54 (0.31-0.94); 0.027**
White	4 (6.8%)	0.35 (0.12-1.03); 0.067	29 (15.3%)	1.05 (0.55-1.98); 0.887	14 (22.2%)	1.86 (0.93-3.74); 0.078
Asian	10 (16.9%)	1.31 (0.61-2.83); 0.493	21 (11.1%)	0.54 (0.28-1.02); 0.056	13 (20.6%)	1.82 (0.89-3.73); 0.098
Coloured/Mixed race.	3 (5.1%)	0.38 (0.11-1.29); 0.110	25 (13.2%)	1.91 (0.96-4.25); 0.106	6 (9.5%)	0.83 (0.33-2.09); 0.688
Clinical frailty score						
<5	18 (31.6%)	**0.44 (0.24-0.81); 0.007**	104 (57.1%)	**2.51 (1.56-4.03); <0.001**	22 (36.1%)	**0.55 (0.31-0.98); 0.042**
≥5	39 (68.4%)	**2.25 (1.24-4.07); 0.007**	78 (42.9%)	**0.40 (0.25-0.63); <0.001**	39 (63.9%)	**1.82 (1.03-3.21); 0.037**
Unspecified	2		7		2	
Comorbidities						
Hypertension	38 (64.4%)	1.11 (0.62-2.01); 0.721	111 (61.7%)	1.07 (0.67-1.70); 0.791	37 (58.7%)	0.82 (0.47-1.45); 0.503
Diabetes mellitus	31 (52.5%)	1.30 (0.74-2.29); 0.367	86 (45.5%)	0.83 (0.53-1.32); 0.438	30 (47.6%)	1.02 (0.59-1.77); 0.95
HbA1c < 7%	2 (3.4%)	1.73 (0.33-9.16); 0.512	2 (1.1%)	0.25 (0.05-1.31); 0.078	3 (4.8%)	3.05 (0.66-13.99); 0.132
HbA1c 7-8	4 (6.8%)	0.72 (0.24-2.18); 0.564	19 (10.1%)	1.59 (0.67-3.76); 0.285	4 (6.3%)	0.66 (0.22-1.99); 0.462
HbA1c > 8%	25 (42.4%)	1.44 (0.81-2.58); 0.211	62 (32.8%)	0.75 (0.47-1.21); 0.239	23 (36.5%)	1.06 (0.6-1.89); 0.832
Unknown	0 (0.0%)		3 (1.6%)		0 (0%)	
Body mass index > 30	8 (13.6%)	0.59 (0.26-1.32); 0.193	44 (23.3%)	**1.87 (1.01-3.46); 0.043**	9 (14.3%)	0.63 (0.29-1.36); 0.233
Dyslipidaemia	5 (8.5%)	0.39 (0.15-1.04); 0.052	28 (14.8%)	0.67 (0.37-1.22); 0.194	20 (31.7%)	**3.03 (1.59-5.77); 0.001**
Ischaemic Heart Disease	4 (6.8%)	0.66 (0.22-1.98); 0.455	12 (6.3%)	**0.42 (0.19-0.91); 0.025**	13 (20.6%)	**3.77 (1.71-8.33); 0.001**
HIV-positive	11 (18.6%)		1 (0.5%)		5 (7.9%)	
With viral suppression	1 (1.7%)	0.85 (0.10-7.43); 0.884	3 (1.6%)	0.64 (0.13-3.22); 0.585	2 (3.2%)	2.00 (0.36-11.17); 0.421
Virally unsuppressed/ unknown	10 (16.9%)	2.13 (0.95-4.79); 0.061	19 (10.1%)	0.94 (0.44-1.97); 0.864	3 (4.8%)	0.38 (0.11-1.28); 0.106
Habits						
Sober habits	42 (71.2%)	0.93 (0.50-1.75); 0.825	137 (72.5%)	1.02 (0.61-1.69); 0.945	46 (73.0%)	1.04 (0.56-1.94); 0.894
Current smoking	8 (13.6%)	1.16 (0.50-2.68); 0.727	24 (12.7%)	1.12 (0.56-2.26); 0.748	6 (9.5%)	0.71 (0.28-1.78); 0.465
Ex-smoking	1 (1.7%)	0.29 (0.04-2.27); 0.213	9 (4.8%)	0.97 (0.34-2.79); 0.950	5 (7.9%)	2.05 (0.68-6.23); 0.197
Current alcohol use	2 (3.4%)	0.65 (0.14-2.94); 0.568	9 (4.8%)	0.97 (0.34-2.79); 0.950	4 (6.3%)	1.46 (0.45-4.75); 0.527
Illicit drug use	0 (0.0%)	-	2 (1.1%)	1.65 (1.51-1.81); 0.254	0 (0.0%)	-
COVID-19 data						
Positive antigen	2 (3.4%)	**0.02 (0.00-0.08); <0.001**	116 (61.4%)	**2.29 (1.44-3.64); <0.001**	48 (76.2%)	**3.53 (1.88-6.63); <0.001**
Negative antigen	0 (0.0%)	-	36 (19.0%)	1.68 (0.88-3.22); 0.116	15 (23.8%)	1.84 (0.93-3.63); 0.075
Antigen not done.	57 (96.6%)	**165.61 (38.75-707.79); <0.001**	37 (19.6%)	**0.28 (0.17-0.46); <0.001**	0 (0.0%)	-
Positive PCR	59 (100.0%)	-	178 (94.2%)	0.69 (0.23-2.04); 0.502	58 (92.1%)	0.54 (0.18-1.61); 0.333
Negative PCR	0 (0%)	-	11 (5.8%)	1.45 (0.49-4.27); 0.502	5 (7.9%)	1.86 (0.62-5.55); 0.333

Vaccination history						
Partial (one dose)	0 (0.0%)	1.24 (1.17-1.30); 0.492	0 (0.0%)	0 (0-0); 0.052	2 (3.2%)	**1.21 (1.29-1.53); 0.005**
Unvaccinated	58 (98.3%)	1.90 (0.23-15.51); 0.542	184 (97.4%)	1.25 (0.33-4.74); 0.745	60 (95.2%)	0.5 (0.12-2.04); 0.322
Unknown	1		5		1	

Abbreviations: SD: Standard deviation; OR: Odd's ratio; CI: confidence interval; PCR: polymerase chain reaction

Clinical presentation

The most frequent presenting symptom across all three waves was shortness of breath, which was most prevalent during the second wave (OR 2.05; 95% CI 1.12 to 3.74; p-value 0.018). Headache (OR 0.62; 995% CI 0.35 to 1.09; p-value 0.019) and fever (OR 0.50; 95% CI 0.25 to 1.00; p-value 0.046) were significantly less prevalent in the third wave compared to the first and second waves. Tachypnoea (respiratory rate ≥25 breaths per minute) was considerably less prevalent in patients on admission in the first wave (OR 0.48; 95% CI 0.27 to 0.85; p-value 0.010) compared to the second and third waves. Tachycardia (heart rate of more than 100 beats per minute) was present in just over half of the patients across all three waves. A systolic blood pressure below 139 mmHg (OR 1.76; 95% CI 1.08 to 2.85; p-value 0.022) and a diastolic blood pressure below 90 mmHg (OR 2.6; 95% CI 1.49 to 4.53; p-value 0.001) was more common in the second wave. Most patients across all three waves had a normal Glasgow Coma Score (GCS) on admission. Patients in the second wave were least likely to have a high finger prick glucose ≥11 mmol/L (OR 0.61; 95% CI 0.38 to 0.97; p-value 0.036) compared to the first and third waves. Most patients had less than 95% oxygen saturation on admission across all three waves. There were significantly more "orange codes" present during the second wave (OR 1.80; 95% CI 1.11 to 2.93; p-values 0.017), and more "yellow codes" present during the first wave (OR 2.54; 95% CI 1.18 to 5.46; p-values 0.014), as per the validated South African Triage Scale (SATS)[12], which categorises patients into red (emergency), orange (urgent), yellow (semi-urgent), green (not urgent), or blue (dead), based on various criteria. The highest proportion of patients who were "dead on arrival" (DOA) was during the third wave (n = 3; 4.8%); however, the greatest proportion of patients to demise within a few hours of being seen in casualty (before admission) was during the second wave (n = 26; 13.8%). Most patients demised outside of standard working hours (between 16h00 and 8h00) across all three waves.

Table 2: Clinical presentation of patients on admission

Clinical presentation on admission	Wave 1		Wave 2		Wave 3	
	***n* = 59**	**OR (95% CI); p-value**	***n* = 189**	**OR (95% CI); p-value**	***n* = 63**	**OR (95% CI); p-value**
Symptoms						
Headache	0 (0.0%)	-	6 (3.2%)	1.29 (0.72-2.31); 0.441	6 (9.5%)	**0.62 (0.35-1.09); 0.019**
Fever	23 (39.0%)	1.73 (0.96-3.13); 0.068	56 (29.6%)	1.05 (0.63-1.73); 0.859	12 (19.0%)	**0.50 (0.25-1.00); 0.046**
Shortness of breath	45 (76.3%)	0.57 (0.29-1.14); 0.109	165 (87.3%)	**2.05 (1.12-3.74); 0.018**	49 (77.8%)	0.63 (0.32-1.26); 0.190
Sore throat	14 (23.7%)	1.51 (0.76-3.00); 0.234	36 (19.0%)	1.13 (0.62-2.05); 0.683	7 (11.1%)	0.50 (0.21-1.15); 0.097
Confusion	6 (10.2%)	0.45 (0.18-1.10); 0.072	37 (19.6%)	1.24 (0.68-2.26); 0.479	14 (22.2%)	1.36 (0.69-2.69); 0.371
Chest pain	4 (6.8%)	0.89 (0.29-2.73); 0.841	11 (5.8%)	0.57 (0.24-1.33); 0.186	8 (12.7%)	2.26 (0.91-5.60); 0.072
Diarrhoea	7 (11.9%)	0.96 (0.40-2.30); 0.926	20 (10.6%)	0.68 (0.35-1.35); 0.273	11 (17.5%)	1.73 (0.81-3.71); 0.155
Cough	44 (74.6%)	1.20 (0.63-2.28); 0.586	131 (69.3%)	0.74 (0.44-1.23); 0.244	48 (76.2%)	1.33 (0.70-2.53); 0.376
Anosmia/ageusia	9 (15.3%)	1.19 (0.54-2.65); 0.662	26 (13.8%)	1.06 (0.54-2.06); 0.872	7 (11.1%)	0.76 (0.32-1.80); 0.534
Myalgia	22 (37.3%)	0.95 (0.53-1.71); 0.864	74 (39.2%)	1.10 (0.69-1.76); 0.688	23 (36.5%)	0.91 (0.51-1.61); 0.748
Respiratory rate, mean (SD)	25.7 (7.3)		28.6 (8.8)		27.0 (7.9)	
≥25 breaths per minute	25 (42.4%)	**0.48 (0.27-0.85); 0.010**	115 (60.8%)	1.46 (0.92-2.30); 0.109	38 (60.3%)	1.17 (0.67-2.06); 0.580
<25 breaths per minute	33 (55.9%)	**2.17 (1.22-3.85); 0.007**	69 (36.5%)	0.66 (0.41-1.04); 0.073	24 (38.1%)	0.88 (0.50-1.55); 0.661
Unspecified	1		5		1	
Heart rate, mean (SD)	100.5 (21.4)		103.3 (20.0)		98.9 (25.0)	
≥100 beats per minute	32 (54.2%)	0.96 (0.55-1.70); 0.898	106 (56.1%)	1.12 (0.71-1.77); 0.627	33 (52.4%)	0.88 (0.50-1.53); 0.642
<100 beats per minute	26 (44.1%)	1.09 (0.61-1.92); 0.779	78 (41.3%)	0.88 (0.56-1.4); 0.602	28 (44.4%)	1.11 (0.63-1.93); 0.719
Systolic BP, mean (SD)	137.9 (29.4)		124.5 (25.3)		130.0 (28.7)	
Systolic BP <139	31 (52.5%)	**0.43 (0.24-0.78); 0.004**	138 (73.0%)	**1.76 (1.08-2.85); 0.022**	43 (68.3%)	1.01 (0.55-1.82); 0.987
Systolic BP ≥ 140	27 (45.8%)	**2.48 (1.38-4.45); 0.002**	46 (24.3%)	**0.55 (0.34-0.90); 0.018**	18 (28.6%)	0.96 (0.52-1.77); 0.893
Unknown	1		5		2	
Diastolic BP, mean (SD)	78.5 (23.3)		71.5 (15.6)		75.4 (21.3)	
Diastolic BP < 90	40 (67.8%)	**0.48 (0.26-0.91); 0.022**	161 (85.2%)	**2.60 (1.49-4.53); 0.001**	44 (69.8%)	0.54 (0.29-1.01); 0.052
Diastolic BP >90	18 (30.5%)	**2.40 (1.25-4.60); 0.007**	23 (12.2%)	**0.36 (0.20-0.65); <0.001**	16 (25.4%)	1.72 (0.89-3.32); 0.104
Unspecified	1		5		3	
GCS on admission, median (IQR)	15 (15-15)		15 (14-15)		15 (14-15)	
3-9	1 (1.7%)	0.29 (0.04-2.27); 0.213	8 (4.2%)	0.73 (0.26-2.06); 0.545	6 (9.5%)	2.80 (0.96-8.17); 0.051
10-14	10 (16.9%)	0.71 (0.34-1.50); 0.373	45 (23.8%)	1.50 (0.84-2.68); 0.165	11 (17.5%)	0.74 (0.36-1.52); 0.414
15	47 (79.7%)	1.72 (0.87-3.43); 0.118	131 (69.3%)	0.77 (0.46-1.28); 0.315	44 (69.8%)	0.91 (0.50-1.67); 0.762
Unspecified	1		5		2	
Finger-prick glucose, median (IQR)	10.1 (6.6-18)		8.3 (6.4-14.3)		10.3 (6.9-18.2)	
<11mmol/l	33 (55.9%)	0.76 (0.43-1.34); 0.337	124 (65.6%)	1.57 (0.98-2.50); 0.059	34 (54.0%)	0.68 (0.39-1.19); 0.174
≥11mmol/l	25 (42.4%)	1.37 (0.77-2.44); 0.284	60 (31.7%)	**0.61 (0.38-0.97); 0.036**	28 (44.4%)	1.53 (0.87-2.69); 0.134
Unspecified	1		5		1	
SP02 on room air on admission, median (IQR)	87.0 (76.0-94.3)		83.5 (61.3-92.0)		78.0 (55.5-89.0)	
<95%	44 (74.6%)	0.60 (0.31-1.18); 0.138	155 (82.0%)	1.12 (0.62-2.00); 0.710	54 (85.7%)	1.48 (0.68-3.20); 0.319

≥95%	14 (23.7%)	1.87 (0.93-3.74); 0.075	29 (15.3%)	0.87 (0.47-1.61); 0.661	7 (11.1%)	0.6 (0.25-1.40); 0.229
Unspecified	1		5		2	
Triage colour on admission						
Red	9 (15.3%)	0.85 (0.39-1.86); 0.685	31 (16.4%)	0.89 (0.49-1.63); 0.709	13 (20.6%)	1.35 (0.67-2.72); 0.396
Orange	36 (61.0%)	0.66 (0.37-1.19); 0.170	139 (73.5%)	**1.80 (1.11-2.93); 0.017**	38 (60.3%)	0.63 (0.36-1.13); 0.118
Yellow	12 (20.3%)	**2.54 (1.18-5.46); 0.014**	15 (7.9%)	**0.44 (0.22-0.90); 0.021**	8 (12.7%)	1.19 (0.51-2.76); 0.685
Green	1 (1.7%)	0.53 (0.06-4.29); 0.542	4 (2.1%)	0.51 (0.13-1.92); 0.309	4 (6.3%)	3.29 (0.86-12.65); 0.067
Missing	1		0		0	
Dead on Arrival	1 (1.7%)		7 (3.7%)		3 (4.8%)	
Demised within a few hours of presentation to hospital (in the emergency department)	2 (3.4%)		26 (13.8%)		0	
Demised between 16:00-8:00	38 (64.4%)	0.87 (0.48-1.58); 0.654	131 (69.3%)	1.32 (0.82-2.13); 0.257	39 (61.9%)	0.76 (0.43-1.35); 0.347

Abbreviations: SD: Standard deviation; OR: Odd's ratio; CI: confidence interval; IQR: inter-quartile range; BP: Blood pressure

Investigations

Mild infiltrates on chest radiograph appeared to be more frequent during the third wave (OR 2.41; 95% CI 1.09 to 5.34; p-value 0.026) compared to the first and second wave, moderate ground glass appearance was most common during the first wave (OR 3.12; 95% CI 1.74 to 5.59; p-value <0.001) compared to the other two waves, and severe ground glass appearance to be most common during the second wave (OR 2.37; 95% CI 1.49 to 3.77; p-value <0.001) compared to the other two waves (Table 3.1). The ratio of arterial partial pressure of oxygen to fraction of inspired oxygen the patient is receiving (PaO_2 / FiO_2) (PF ratio) was most commonly <100 on admission across all three waves, indicating severe respiratory distress of patients on admission. More patients in wave three (OR 1.91; 95% CI 1,01 to 3.61; p-value) had a PF ratio between 100 and 200, compared to waves one and two. There were no significant differences in urine dipstick findings across the three waves. There were no statistically significant differences in blood results across the three waves; however, urea and creatinine were highest during the first wave, with the corresponding lowest glomerular filtration rate (GFR) during the first wave (Table 3.2). D-dimer was highest in patients during the first wave. CRP and LDH were similarly elevated across all three waves.

Complications

Renal impairment was most common during the first wave (OR 3.28; 95% CI 1.59 to 6.77; p-value 0.001) and least common during the second wave (OR 0.6; 95% CI 0.37 to 0.97; p-value 0.038). Patients with "No specified complications" documented were less frequent during the first wave (OR 0.31; 95% CI 0.13 to 0.75; p-value 0.006) compared to the other two waves. Thrombo-embolic phenomena were significantly less common during wave three (OR 0.12; 95% CI 0.02 to 0.91; p-value 0.015). "Other" complications not described in this study were more common during the third wave (OR 4.25; 95% CI 1.32 to 13.65; p-value 0.009).

Management

The 100% non-rebreather mask was the most common oxygen requirement on admission for patients across all three waves (Table 3.1). High-flow nasal oxygen (HFNO) was most used during the third wave (OR 6.25; 95% CI 2.5 to 15.61; p-value <0.001) compared to the other two waves. The average duration of admission (in days) before demise was: four, four and three during the first, second and third waves, respectively.

Table 3.1 Investigations, complications and management of patients who died due to C19 across the first three waves.

Variables, n (%) except where specified	**Wave 1**		**Wave 2**		**Wave 3**	
	***n* = 59**	**OR (95% CI); p-value**	***n* = 189**	**OR (95% CI); p-value**	***n* = 63**	**OR (95% CI); p-value**
Investigations						
Chest X-ray findings						
Mild infiltrates	8 (13.8%)	1.56 (0.66-3.69) ; 0.306	12 (6.8%)	**0.37 (0.17-0.79) ; 0.008**	11 (19.0%)	**2.41 (1.09-5.34) ; 0.026**
Ground glass/moderate	31 (53.4%)	**3.12 (1.74-5.59) ; <0.001**	49 (27.7%)	**0.54 (0.33-0.88) ; 0.013**	17 (29.3%)	0.78 (0.42-1.44) ; 0.420
Ground glass/severe	19 (32.8%)	**0.34 (0.19-0.63) ; <0.001**	116 (65.5%)	**2.37 (1.49-3.77) ; <0.001**	30 (51.7%)	0.76 (0.44-1.32) ; 0.333
Unspecified	1		12		5	
PF ratio on admission						
≤100	18 (36.7%)	0.91 (0.49-1.68) ; 0.764	59 (31.2%)	0.90 (0.55-1.46) ; 0.660	23 (36.5%)	1.28 (0.72-2.28) ; 0.407
101 - 200	12 (20.3%)	1.06 (0.52-2.14) ; 0.876	31 (16.4%)	0.60 (0.34-1.06) ; 0.076	18 (28.6%)	**1.91 (1.01-3.61) ; 0.045**
>200	19 (32.2%)	1.46 (0.79-2.70) ; 0.231	49 (25.9%)	0.98 (0.59-1.65) ; 0.953	13 (20.6%)	0.69 (0.35-1.35) ; 0.273
Unspecified	10		50		9	
Urine dipstick						
Normal	1 (1.7%)	1.07 (0.12-9.74) ; 0.953	2 (1.1%)	0.42 (0.07-2.58) ; 0.338	2 (3.2%)	2.68 (0.44-16.38) ; 0.268
Glucose	15 (25.4%)	1.75 (0.89-3.44) ; 0.100	32 (16.9%)	0.83 (0.46-1.50) ; 0.539	9 (14.3%)	0.71 (0.33-1.55) ; 0.389
Protein	12 (20.3%)	1.21 (0.59-2.46) ; 0.604	30 (15.9%)	0.70 (0.39-1.25) ; 0.223	14 (22.2%)	1.40 (0.71-2.77) ; 0.329
Ketones	4 (6.8%)	0.76 (0.25-2.3) ; 0.626	16 (8.5%)	1.04 (0.45-2.36) ; 0.933	6 (9.5%)	1.2 (0.46-3.13) ; 0.709
Blood	5 (8.5%)	1.57 (0.54-4.56) ; 0.399	9 (4.8%)	0.56 (0.22-1.42) ; 0.217	5 (7.9%)	1.44 (0.5-4.16) ; 0.498
Leukocytes	2 (3.4%)	1.23 (0.25-6.07) ; 0.801	5 (2.6%)	0.80 (0.21-3.05) ; 0.745	2 (3.2%)	1.13 (0.23-5.57) ; 0.882
Not done/unspecified	37 (62.7%)	0.81 (0.45-1.46) ; 0.486	130 (68.8%)	1.29 (0.80-2.08) ; 0.301	40 (63.5%)	0.84 (0.47-1.50) ; 0.563
Complications present on admission.						
Renal impairment	49 (83.1%)	**3.28 (1.59-6.77); 0.001**	113 (59.8%)	**0.60 (0.37-0.97); 0.038**	38 (60.8%)	0.81 (0.46-1.42); 0.459
Depressed LOC	10 (16.9%)	0.67 (0.32-1.4); 0.282	42 (22.2%)	1.01 (0.58-1.74); 0.985	17 (27.0%)	1.39 (0.74-2.63); 0.305
Haemodynamic	17 (28.8%)	1.77 (0.92-3.37); 0.082	35 (18.5%)	0.73 (0.42-1.27); 0.263	12 (19.0%)	0.89 (0.44-1.78); 0.736
LFT abnormality	9 (15.3%)	0.75 (0.34-1.62); 0.457	38 (20.1%)	1.28 (0.71-2.33); 0.412	11 (17.5%)	0.90 (0.44-1.87); 0.786
Thrombo-embolic	9 (15.3%)	1.98 (0.86-4.58); 0.105	20 (10.6%)	1.33 (0.60-2.94); 0.487	1 (1.6%)	**0.12 (0.02-0.91); 0.015**
DKA	7 (11.9%)	1.48 (0.60-3.67); 0.394	14 (7.4%)	0.62 (0.28-1.34); 0.221	7 (11.1%)	1.35 (0.55-3.34); 0.513
Myocarditis	5 (8.5%)	1.70 (0.58-4.98); 0.326	12 (6.3%)	1.31 (0.48-3.59); 0.598	1 (1.6%)	0.22 (0.03-1.68); 0.110
Other	2 (3.4%)	0.85 (0.18-3.98); 0.836	4 (2.1%)	**0.31 (0.09-1.05); 0.047**	6 (9.5%)	**4.25 (1.32-13.65); 0.009**
Nil specified	6 (10.2%)	**0.31 (0.13-0.75); 0.006**	52 (27.5%)	1.73 (0.98-3.02); 0.055	16 (25.4%)	1.12 (0.59-2.11); 0.738
Oxygenation needs on admission:						
Room air	17 (28.8%)	1.56 (0.82-2.95); 0.174	43 (22.8%)	1.09 (0.63-1.89); 0.765	9 (14.3%)	0.52 (0.24-1.12); 0.091
Nasal prongs	1 (1.7%)	0.71 (0.08-5.99); 0.749	3 (1.6%)	0.48 (0.1-2.16); 0.326	3 (4.8%)	3.05 (0.66-13.99); 0.132
40% venturi mask	12 (20.3%)	1.06 (0.52-2.14); 0.876	36 (19%)	0.91 (0.52-1.61); 0.754	13 (20.6%)	1.08 (0.55-2.15); 0.819
100% non-rebreather	20 (33.9%)	0.92 (0.51-1.68); 0.793	73 (38.6%)	1.45 (0.89-2.35); 0.135	17 (27.0%)	0.62 (0.33-1.14); 0.119
Dual oxygen	6 (10.2%)	1.08 (0.42-2.76); 0.880	19 (10.1%)	1.13 (0.52-2.46); 0.762	5 (7.9%)	0.77 (0.28-2.10); 0.607
High-flow nasal oxygen	1 (1.7%)	0.20 (0.03-1.52); 0.085	8 (4.2%)	**0.37 (0.15-0.92); 0.028**	12 (19.0%)	**6.25 (2.5-15.61); <.001**
CPAP	2 (3.4%)	0.85 (0.18-3.98); 0.836	7 (3.7%)	0.90 (0.28-2.90); 0.86	3 (4.8%)	1.33 (0.35-5.06); 0.677
Intubation + ventilation	0 (0.0%)		0 (0%)		1 (1.6%)	

Number of days admitted, median (IQR)	4 (2-7)		4 (1-7)		3 (1-8)	
<5	40 (69.0%)	1.27 (0.69-2.34); 0.448	113 (61.4%)	0.69 (0.42-1.13); 0.138	43 (70.5%)	1.39 (0.76-2.56); 0.288
6-10	11 (19.0%)	0.77 (0.38-1.59); 0.480	45 (24.5%)	1.35 (0.77-2.38); 0.296	12 (19.7%)	0.81 (0.40-1.64); 0.562
>10	7 (12.1%)	0.91 (0.38-2.19); 0.839	26 (14.1%)	1.34 (0.66-2.73); 0.416	6 (9.8%)	0.69 (0.28-1.73); 0.428
Missing	1		5		2	

Abbreviations: SD: Standard deviation; OR: Odd's ratio; CI: confidence interval; IQR: inter-quartile range; n: Number of patients; PF ratio: Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen the patient is receiving (PaO_2 / FiO_2); AKI: Acute kidney injury: LOC: Level of consciousness; LFT: Liver function test; DKA: Diabetic keto-acidosis; CPAP: Continuous positive airway pressure; LMWH: Low molecular weight heparin; IV: Intra-venous

Table 3.2 Blood results of patients who died due to C19 across the first three waves.

Blood results	**Wave 1**		**Wave 2**		**Wave 3**		**p-value**
	N	**Mean, SD**	**n**	**Mean, SD**	**n**	**Mean, SD**	
Haemoglobin	57	12 (2.62)	179	12.6 (2.28)	59	12.9 (2.61)	0.079
White cell count	57	11.3 (5.41)	179	11 (5.86)	59	11.4 (5.00)	0.525
Platelets	57	298.3 (134.87)	178	288.9 (129.43)	59	265.8 (101.97)	0.339
Urea	58	17 (14.23)	181	12.6 (10.62)	59	14.1 (11.37)	0.114
Creatinine	58	265.6 (287.13)	181	173 (195.78)	58	188.8 (181.16)	0.130
GFR	56	44.1 (33.39)	181	55.4 (33.37)	58	52.6 (33.72)	0.088
Bilirubin	49	14.4 (6.79)	170	16 (12.65)	57	19.9 (21.9)	0.838
ALT	47	45.2 (57.46)	171	42.9 (43.27)	56	70.8 (182.65)	0.997
GGT	47	85.3 (100.85)	170	73.2 (83.48)	56	74.2 (134.44)	0.084
CRP	57	159.8 (61.96)	179	151.4 (66.13)	58	144.5 (66.16)	0.234
D-dimer	44	0.8 (0.59)	168	1.2 (2.26)	52	0.9 (1.49)	0.235
LDH	2	1242 (371.94)	28	1465.6 (593.85)	7	1628.1 (628.82)	0.684

Abbreviations: SD: Standard deviation; GFR: Glomerular filtration rate; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferase; CRP: C-reactive protein; LDH: Lactate Dehydrogenase

Discussion

Main findings

The study compares mortality trends between the first three waves of C19 at a DH. The institutional crude- and case fatality rates in wave 2 was the highest, highlighting increased mortality rates in wave two and increased virulence of the beta variant.

Across the three waves, females over 60 were identified as most likely to demise from C19. Mortality was most prevalent in individuals of the black African race across all three waves, particularly during the first wave. Individuals of White, Asian and Mixed races contributed to

more deaths during the second and third waves. Patients who died during the second wave had lower clinical frailty scores[8] than during the first and third waves. Hypertension had a similar prevalence across the first three waves. Diabetes mellitus and HIV were less prevalent during the second wave. Obesity was most prevalent during the second wave, and dyslipidaemia and ischaemic heart disease were most prevalent during the third wave. No patients were "vaccinated fully," defined as receiving initial and booster doses.

Shortness of breath was the commonest presenting symptom across all three waves; however, it was approximately 10% more common in the second wave. Headache and myalgia were also more common features of the second wave. Fever, sore throat, and loss of taste and smell were more common in the first wave. Confusion, chest pain and diarrhoea were more common features of the third wave. The second and third waves saw more severe consolidation on chest X-rays than the first wave. Approximately 80 to 90% of patients across all three waves required oxygen on admission. Elevated serum urea, creatinine, D-Dimer and LDH levels were the most significant serological findings. Most patients died outside of regular working hours, likely due to under-staffing of doctors (particularly senior, specialist doctors), nurses, radiographers, laboratory technicians, and other allied workers during these hours.

Comparison with other studies

The second wave was dominated by the beta variant (501Y.V2 or B.1.351) and was characterised by rapid spread, as well as higher infection rates, admissions, and mortality rates than the first wave.[13] The beta strain of SARS-CoV-2 was first identified in South Africa in late 2020. It developed multiple mutations in its proteins, making the virus more virulent (increased infectivity and decreased neutralisation by existing vaccines).[14] The high crude- and case fatality rates in the second wave may be due to increased virulence of the beta variant, lack of vaccination among patients, and the overburdened hospital and healthcare workers. These results are similar to those published by the NICD, which stated, "compared to wave 1, there was an increased risk of mortality in wave 2 (adjusted OR 1.5; 95% CI1.4-1.5) and wave 3 (adjusted OR 1.3, 95% CI 1.3-1.4)." The Hospital Surveillance Report by the NICD estimated an overall facility case fatality rate of 22.5% across all four C19 waves in South Africa. Data published by the NICD - conducted on 666 facilities across the nine provinces of South Africa - concluded that factors associated with in-hospital mortality were older age and being of black African/Mixed/Indian race compared to White ethnicity. Presence of comorbid hypertension, diabetes mellitus, chronic cardiac disease, chronic renal disease, malignancy, HIV, past and current tuberculosis, and obesity were also factors associated with mortality."[15]

Older age is widely documented as a risk factor for C19 death; however, a systematic review and meta-analysis conducted by Parohan et al. (2020)[16] identified male gender as a risk factor for mortality (pooled OR 1,5; 95% CI: 1.06-2.12). The increased mortality rate found in females in our study may be attributed to gender-based differences in access to healthcare across South Africa, with females forming a vulnerable part of the community and thus presenting later and with more advanced disease progression. A recent inter-sectional analysis conducted in South Africa, Malawi, and Nigeria reported a statistically significant decline in women's ability to see a healthcare provider during the pandemic but did not find this decline amongst men. This gender gap was more evident in those who did not have post-secondary education. South African women financially affected by the pandemic had a significant decline in seeking preventive care during the pandemic (OR = 0.23, P = 0.022).[17] As per the 2016 National Census, the population of KwaZulu-Natal consists of 52.1% females and 47.9% males, with a larger proportion of females (62.30%) contributing to the age group >60 compared to males.[18] Furthermore, Nglazi et al[19] determined that 60% of women of child bearing age were overweight and 35.2% were clinically obese. This could account for the gender differences seen in our study. The variation in mortality amongst racial groups could be attributed to race being an important determinant of health in South Africa. Historical differences in socioeconomic status and housing conditions render the black population in South Africa more vulnerable during a droplet-spread pandemic. Some further explanations for higher transmission rates and mortality in the Black population include multi-generational households with more persons per area, decreased access to healthcare, and decreased access to public health messaging regarding prevention, diagnosis, and treatment, resulting in delayed presentation.[20] Additional, as stated by Mash et. al: “poverty is also a major issue that impacts on access to healthcare as well as food security and malnutrition.”[17] During the initial months of the pandemic – strict nationwide lockdown was implemented resulting in a great deal of uncertainty regarding resumption of work and thus remuneration leading to further financial strain and barriers to accessing healthcare services.

The decreased prevalence of comorbidities during the second wave could indicate an increased virulence of the SARS-CoV-2 beta strain. However, Parohan et al.[16] suggest that the reduced prevalence of comorbidities in the second wave could also be due to differences in clinician practise, survival bias or changing manifestations in individuals without underlying illness, or simply due to under-reporting of comorbidities and other medical conditions at the peak of the second wave when hospitals were over-burdened and under-staffed. The higher prevalence of ischaemic heart disease in the third wave may be a combination of underlying cardiac disease or the cardiac effects of the delta variant.[21] SARS-CoV -2 causes many cardiovascular disorders,

including direct myocardial injury, arrhythmia, acute coronary syndrome (ACS) and venous thromboembolism (VTE). The higher incidence of chest pain in the third wave may be directly linked to the higher incidence of ischaemic heart disease in the third wave.[22]

There was a lack of data regarding antigen testing, as this method of detecting C19 was only introduced at WWH during the second wave. Despite this, availability of the antigen test during waves two and three contributed significantly to the earlier detection of C19 infection, allowing for earlier directed clinical management and more effective quarantining protocols. South Africa's national vaccine rollout strategy commenced on 17 February 2021, only available to healthcare workers.[23] The first vaccine became available to people over 60 on 17 May 2021, and available to those aged 50-59 on 5 July 2021. Booster doses only became available on 10 November 2021. The relatively late implementation of a nationwide vaccination rollout strategy and poor help-seeking behaviour of patients eligible to receive the vaccine is likely to have a pronounced effect on mortality rates – particularly in the first two waves. Poor help-seeking behaviour, traditional medicines and a lack of trust from the public as well as poor health literacy and the socio-economic climate at that time (high unemployment and job losses) also contributed with people having no resources to access healthcare. The initial lag in vaccination programme uptake could be attributed to stigmas and fears surrounding the vaccination and its side effects.[23]

A study conducted in India revealed that shortness of breath increased by 6% from the first to the second wave.[24] This resulted in an increased demand for oxygen support and mechanical ventilation and a subsequent mortality increase. Conflicting data from a study in Italy showed an increased incidence of early dyspnoea in the first wave compared to the second wave (13.4% vs 1.9%).[25] Differences in our findings may be explained by the fact that many of our patients presented late to health facilities due to socioeconomic challenges, fears of exposure to C19, and hypoxic unawareness,[26] which may account for the high death rate on arrival or shortly after the presentation to the facility.

Approximately 80% of C19 cases develop a mild fever, headache, sore throat and myalgia, and 15% develop severe disease characterised by dyspnoea, hypoxia and chest X-ray changes.[27] Only 5% become critically ill with ARDS, shock and multi-organ failure (MOF). Because our patients consisted only of those who died from C19 infection, dyspnoea was the commonest symptom of severity. Similarly, Portacci et al.[25] found a higher incidence of ageusia and fever in Italy's first wave of the SARS-CoV-2 epidemic. Furthermore, headache and myalgia were also found by Mukhurjee et al.[24] (2021) to be more common in the second wave in patients in India. It is proposed that SARS-CoV-2 causes gastrointestinal symptoms by direct viral invasion and

immune-mediated tissue injury.[28] Specific viral protein mutations in the "delta" variant cause an increased binding affinity of the virus to ACE-2 receptors in both type-2 alveolar cells and epithelial cells throughout the gastrointestinal tract. This may be the mechanism behind the higher incidence of diarrhoea in the third wave; however, improved symptom reporting may also significantly contribute to such a finding.

A cohort study conducted in Italy, describing the computed tomography (CT) chest findings of 461 patients across all four waves, found bilateral pulmonary disease in 100% of evaluated patients.[29] Typical patterns observed included "ground-glass" appearance, consolidation, and subpleural and parenchymal bands. They found "ground glass" appearance to be the predominant pattern during the second (91.6%) and third (100%) waves. Furthermore, they found pleural effusions to be more prevalent during the first wave (41.4%) compared to the second (20.4%) and third waves (32.8%).[30] Pleural effusion was not commonly reported in our study. Oxygen requirements were similar across all three waves; however, WWH was better equipped with advanced oxygenation devices during the second and third waves to accommodate these increased oxygen requirements. After the first wave, WWH acquired many HFNO2 and CPAP machines, allowing patients to be treated at WWH. The acquisition of CPAP and HFNO2 devices at WWH was vital in the survival of patients and positively impacted ARDS management during the second and third waves. Additionally, doctors' clinical knowledge and experience of C19 disease improved after the first wave, allowing for more prompt identification of ARDS and other C19-related complications, and better management of patients. The higher mortality rate seen during the second wave may also have been attributed to the overwhelmed healthcare system, shortage of healthcare workers, poor health literacy and misinformation surrounding the pandemic circulating on social media.

The cause of the renal impairment seen in patients in wave one was not well established. It may be a combination of acute kidney injury (AKI), underlying chronic kidney disease (CKD), and acute on-chronic kidney disease (AOCKD). A systematic review and meta-analysis of 31 studies found an overall AKI incidence of 26% in C19-infected patients.[30] The incidence was significantly higher in patients with concomitant ARDS (59%) compared to in those without ARDS (6%). Mortality in C19 patients with AKI was also significantly higher than in those without AKI (Risk ratio 4.46; 95% CI 3.31 to 6.00).[30] The potential mechanisms for kidney injury in C19 disease includes cytokine-induced damage, systemic effects (including deranged fluid balance status, haemodynamic instability, rhabdomyolysis, metabolic acidosis and hyperkalaemia), as well as "organ crosstalk", which denotes lung-kidney bidirectional damage as a result of cytokine overproduction.[31] Risk factors for the development of AKI include older

age and comorbidities such as diabetes mellitus and hypertension, which contributes to underlying CKD and kidney vulnerability.[29,30] This may explain why the incidence of renal impairment was highest in the first wave, where the incidence of comorbidities (especially diabetes mellitus) was also the highest.

Elevated D-dimers are in keeping with the pro-thrombotic state demonstrated in critically ill C19 patients.[32] Despite the fact that platelet numbers remained normal across all three waves in our study, Zhang et al.[32] showed that patients with C19 have increased mean platelet volume and hyperactivity, with an associated decrease in overall platelet count. They showed that SARS-CoV-2 directly enhances platelet activation and facilitates the release of coagulation and inflammatory factors, promoting the formation of leukocyte-platelet aggregates and thereby enhancing thrombus formation.[32] Elevated LDH levels found across all three waves are likely because of the direct effects of C19 on the liver, which is facilitated by the ACE-2 receptors in cholangiocytes, allowing for the retrograde transmission of the virus from the bile tree cells into the liver.[28] Furthermore, indirect causes of liver damage may result from certain drugs and the release of pro-inflammatory cytokines, causing tissue hypoxia and thrombosis, and thereby exacerbating underlying liver injury. Mild to moderate elevation of aminotransferases is a common finding, but severe liver injury is rare.[28]

Strengths and limitations of the study

Strengths of the study include the provision of a detailed comparison of the mortality rates, as well as the demographic and clinical profiles of patients who died from C19 across the first three waves of the C19 pandemic in a LMIC. Furthermore, we provide generalisable insights into the challenges faced by an over-burdened, under-resourced primary healthcare facility in a LMIC.

Limitations of the study include paucity of some data due to a reliance on paper-based clinical records, which may have contributed to the under-reporting of certain findings. Of note is that obesity was under-reported in our study due to poor documentation in clinical records, likely due to difficulties experienced by healthcare workers in weighing ill and immobile patients. Regardless, all patients with a documented weight had a BMI greater than 30, indicating a relatively high prevalence of this comorbidity. Furthermore, there is a possibility that false-positive C19 cases were included in the study due to the clinical probability tool being used as an adjunct to the PCR test. Lastly, genomic sequencing was not done on patients to confirm infection with a specific C19 variant; However, each of the three waves included in this study had a predominant variant as described by multiple national epidemiological studies, which

allowed for assumptions to be made about the dominant variant responsible for each defined wave of infection.

Conclusions and recommendations

The beta variant - which characterised the second wave - was the most virulent, as portrayed by the highest case- and crude fatality rates found during this wave, as well as the characteristics of its victims: Individuals with lower clinical frailty scores, fewer comorbidities, and more severe clinical presentations. Our study provides an extensive analysis of mortality data across the first three waves of the C19 pandemic at a district-level hospital in South Africa. The crude and case fatality findings are similar to those seen in other facilities locally and internationally. Risk factors for severe disease and death are identical to those reported elsewhere. Our study provides essential information on the additional burden placed by C19 on a resource-constrained environment. This information could assist in the development of healthcare responses for similar healthcare facilities across the world. Recommendations include the development of an electronic record-keeping system, as well as further research into the wider socio-economical impacts of C19 on health facilities across South Africa.

Contributor and guarantor information

OH designed the study, MN designed the data collection tool. OH and CP performed the study and collected the data. OH and CP performed the data analysis with the help of biostatisticians (Ms Cathy Connolly of UKZN and Dr Gill Hendry) and wrote the first draft. MN assisted with editing of the final article. OH and CP are responsible for the overall content as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval

This study was conducted after obtaining ethical clearance from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal BREC/00003680/2021.

Transparency statement

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CHAPTER 6: SYNTHESIS

1) Main findings of the study

Of the 311 total patients who demised within the defined waves, 59 (19.0%) demised in wave one, 189 (60.8%) demised in wave two and 63 (20.3%) demised in wave three. During the first three waves: 354; 573 and 517 patients were admitted to WWH with C19 infection, yielding a crude fatality rate (institutional C19 deaths / institutional C19 admissions) of 16.7%; 33.0% and 12.2% for waves one, and two and three respectively. Over these defined periods, 408; 684; and 994 patients tested positive for C19 using the PCR test, yielding an institutional case fatality rate (institutional C19 deaths / institutional C19 positive PCR swabs) of 14.5%; 27.6% and 6.3% for waves one, and two and three respectively. The institutional crude- and case fatality rates in wave 2 were the highest, highlighting increased mortality rates in wave two and increased virulence of the beta variant.

Across the three waves, females over 60 were identified as most likely to demise from C19. Mortality was most prevalent in individuals of the Black African race across all three waves, particularly during the first wave. Individuals of White, Asian and Mixed races contributed to more deaths during the second and third waves. Patients who died during the second wave had lower clinical frailty scores than during the first and third waves. Hypertension had a similar prevalence across the first three waves. Diabetes mellitus and HIV were less prevalent during the second wave. Obesity was most prevalent during the second wave, and dyslipidaemia and ischaemic heart disease were most prevalent during the third wave. No patients were "vaccinated fully," defined as receiving both the initial and booster doses.

Shortness of breath was the most typical presenting symptom across all three waves; however, it was approximately 10% more common in the second wave. Headache and myalgia were also more common features of the second wave. Fever, sore throat, and loss of taste and smell were more common in the first wave. Confusion, chest pain and diarrhoea were more common features of the third wave. The second and third waves saw more severe chest X-ray consolidation than the first. Approximately 80 to 90% of patients across all three waves required oxygen on admission. Elevated serum urea, creatinine, D-Dimer and LDH levels were the most significant serological findings. Most patients died outside of regular working hours, likely due to the under-staffing of doctors (particularly senior, specialist doctors), nurses, radiographers, laboratory technicians, and other allied workers during these hours.

2) How the study met the aims and objectives

The study aimed to evaluate mortality trends associated with patients who were hospitalised for C19 at WWH in South Africa. This study successfully achieved this aim and identified that: the beta variant - which characterised the second wave - was the most virulent, as portrayed by the highest case- and crude fatality rates found during this wave, as well as the characteristics of its victims: individuals with lower clinical frailty scores, fewer comorbidities, and more severe clinical presentations. Our study provides an extensive analysis of mortality data across the first three waves of the C19 pandemic at a district-level hospital in South Africa. The crude and case fatality findings are similar to those seen in other facilities locally and internationally. Risk factors for severe disease and death are identical to those reported elsewhere. Our study provides essential information on the additional burden placed by C19 on a resource-constrained environment. This information could assist in the development of healthcare responses for similar healthcare facilities across the world.

The study's specific objectives were as follows:

1. To compare the demographic profile of patients who died from COVID-19 during the first three waves at WWH.

2. To compare the clinical profile and management strategies of patients who died from COVID-19 during the first three waves at WWH.

3. To identify risk factors for mortality among patients with COVID-19 during the first three waves at WWH.

4. To identify areas requiring improvement with respect to holistic patient management.

The study met objective 1, 2 and 3 by identifying that: across the three waves, females over 60 were identified as most likely to demise from C19. Mortality was most prevalent in individuals of the Black African race across all three waves, particularly during the first wave. Individuals of White, Asian, and Mixed races contributed to more deaths during the second and third waves. Patients who died during the second wave had lower clinical frailty scores than during the first and third waves. Hypertension had a similar prevalence across the first three waves. Diabetes mellitus and HIV were less prevalent during the second wave. Obesity was most prevalent during the second wave, and dyslipidaemia and ischaemic heart disease were most prevalent during the third wave. Shortness of breath was the commonest presenting symptom across all three waves; however, it was approximately 10% more common in the second wave. Headache and myalgia were also more common features of the second wave. Fever, sore throat, and loss of taste and smell were more common in the first wave. Confusion, chest pain and diarrhoea

were more common features of the third wave. The second and third waves saw more severe consolidation on chest X-rays than the first wave. 80 to 90% of patients across all three waves required oxygen on admission. With respect to medical management: 90.5%, patients received Dexamethasone 6 mg intravenously; 73.2% received prophylactic low molecular weight heparin (LMWH) (40 mg daily subcutaneously);18.3% received therapeutic LMWH (1.5 mg per kilogram daily); 59.1% received thiamine; 44.8% received vitamin D stat doses; 54.3% received vitamin B3; 59.5% received zinc; 92.7% received ceftriaxone and 87.5% received azithromycin.

Objective 4 was met as areas for improving holistic patient management were identified. These were as follows: involvement of a multidisciplinary team early on in patient care. This team will consist of a physiotherapist, social worker, psychologist (if available), family physician/medical officer, nursing staff and the patient's family. The importance of patients and their families' expectations on survival outcomes is vital to ascertain early on in the treatment process and adequate counselling of terminally ill patients and their families is crucial for optimal patient-centered care. During the pandemic routine visiting hours were not operational thus further emphasizing the importance of the healthcare worker in communicating effectively with patients' next of kins'. Additionally, assisting patients with post-discharge care such as outpatient physiotherapy, assessment for ambulatory oxygen services through an oxygen concentrator and education on symptoms of long C19 on discharge proved to be an important role in management.

3) Insights gained.

The study gave insight into mortality trends during the C19 pandemic and risk factors for mortality at a DH level in SA. It highlighted the demographic and clinical picture and management strategies of individuals at risk of mortality for C19. These individuals will be prioritised for urgent care, which includes referral to higher levels of care, in future respiratory pandemics. A sub-district/ district plan needs to be formulated to allow for the more efficient uptake of such patients to better-resourced facilities to prevent the burden on DH. In recognising severe symptoms and presenting early, community awareness may also help mitigate mortality.

4) Study strengths

This study provided comprehensive insight into mortality trends at a DH level during the first three waves of the pandemic. South Africa has the highest C19 infection and mortality rates, and DHs handled many C19 cases. This study had a large sample size broadly representative of the South African population demographic. The primary investigators, who are medical doctors, collected all the data. The findings demonstrated significant mortality at DHs outside of the WC highlights the need to capacitate DHs in line with the requirements of the National Health

Insurance. The results are probably similar to other hospitals in other LMICs. Manuscript 2, in particular, reinforced findings from many multi-centre studies conducted in the WC and internationally.

5) Study limitations

The study was a single-centre study and thus had findings limited to the Wentworth population. All patient records were paper-based, and the investigators relied on the recorded data. Information bias existed due to incomprehensible language, the scarcity of data and pages not in the incorrect order. There is the possibility of including false positives when the clinical scoring system was used as a diagnostic tool. Due to the study's retrospective nature, the data could not be retrieved and had to be captured as 'unspecified'. The study does not provide insight into the outcomes of patients discharged from the Emergency Department with mild disease. Some may have been re-admitted to and died in other hospitals or at home. There was no record that patients in the study were re-admissions. Wentworth Hospital is an academic hospital with family physicians overseeing the clinical work and has a newly developed C19 infrastructure. It may have provided a higher quality of care than an ordinary DH that does not have resident family physicians or such infrastructure.

6) Recommendations for practice and future research initiatives

This study recommends implementing an electronic record-keeping system at the DH level. This will allow patient records to be easily accessible, legible, and cost-effective long-term. Additionally, the study should be expanded to include other DHs in the Durban Metropolitan area and even interprovincially. This will be particularly useful in determining how WWH mortality rates compared to the other DHs. Furthermore, expanding the study to include regional and tertiary hospitals in the district would provide critical insight into the severity of illness and differences in clinical management at these referral centres. Moreover, further research should be conducted into the wider psychological and socio-economic impacts of C19 on health facilities and healthcare workers working in resource-limited settings. These findings should be utilised to strengthen our response to future pandemics/current epidemics such as trauma and HIV.

The hospital can perform ongoing research on healthcare interventions that mitigate C19, such as pharmacotherapy and vaccination. Early in the pandemic, the opportunity existed to investigate interventions such as chloroquine, ivermectin etc, in the South African setting. With proper development of the research resources, ongoing studies into long C19, healthcare worker burnout and resilience, vaccination, and the impact of C19 on non-communicable diseases could be undertaken.

Opportunistic health promotion measures should be done at DH and community hospital level whereby C19 vaccination is promoted and offered routinely in outpatient departments or on discharge, particularly in high-risk individuals. The multidisciplinary team management of C19 needs to be refined, as everyone has a vital role in managing this illness. Community engagement and mobilising community resources to deal with the pandemic is essential.

Conclusion

Wave 2 was the most severe wave with the highest crude and case fatality rates. Black Africans; females over the age of 60 and multimorbid patients were most likely to demise from C19 at WWH. Critically ill patients requiring intensive care were managed in a low resourced hospital with limited access to advanced ventilation options during a respiratory pandemic. The high mortality rates across each wave and the failure to urgently accommodate critically ill patients at better resourced, higher levels of care was a major public health crisis and policy makers need to have clear policies implemented for future pandemic responses to ensure person-centred holistic care.

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APPENDIX 1: RESEARCH PROTOCOL

MORTALITY TRENDS IN PATIENTS DURING THE FIRST THREE WAVES OF THE SARS COV 2 PANDEMIC AT WENTWORTH DISTRICT HOSIPTAL IN SOUTH AFRICA

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ABBREVIATIONS

DHs District hospitals

HIC High income countries.

SA South Africa/n

INTRODUCTION

What is the Problem?

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS COV 2) causes corona virus disease commonly known as COVID-19. December 2019 saw the emergence of the novel coronavirus or SARS COV2; when unexplained cases of pneumonia were identified in Wuhan, China.[1, 2] The positive-stranded RNA virus, belonging to the Coronaviridae family (a subgroup B βcoronavirus), was initially isolated at the Wuhan Huanan Seafood Wholesale Market and appears to have spread to humans through zoonotic transmission.[3] As time progressed it became evident that efficient human-human transmission from respiratory droplets occurred.[2] Since its inception it spread rapidly across the globe, sparking the beginning of a pandemic resulting in debilitating effects to healthcare systems globally. Clinical presentation of the illness ranges from: mild, flu-like symptoms; moderate symptoms or severe, pneumonia-like symptoms. Individuals with severe and critical disease often require hospitalisation, and about 20% of hospitalised patients with confirmed SARS COV 2 pneumonia will develop acute respiratory distress syndrome (ARDS), of which 12% will meet the conventional indications for intubation and mechanical ventilation." [4] In a South African setting ventilators, high flow nasal oxygen devices and non-invasive continuous positive airway pressure (CPAP) devices are not as readily available as they are in the high income countries.[4] The country's slow vaccination rollout coupled with the discovery of numerous highly infectious variants has led to the increase in infection rates; with many countries experiencing multiple waves. South Africa has already experienced a devastating first and second wave in 2020 and currently is at the end of the third wave in October 2021. Both state-run and private health care facilities, across the country, have been overwhelmed by the impact of COVID-19. During the peak of each wave, many tertiary and regional hospitals were running at capacity resulting in the poor acceptance rates for referrals from district hospitals. Consequently, many district hospitals (DHs) had to manage patients with complex disease profiles who required intensive care.

What is known so far?

Since the start of the pandemic, studies from countries around the world have been published. However, knowledge on mortality trends at district and community hospitals is limited in a SA setting. Mortality remains high in ventilated patients with COVID 19 in SA at any level of care.[4] Globally, multiple independent risk factors have been identified as key contributors to developing severe disease and mortality. These risk factors include male sex, obesity, comorbidities such as hypertension, type two diabetes mellitus, cardiovascular disorders, malignancies, chronic obstructive pulmonary disease, pulmonary tuberculosis and HIV.[5] Within SA, differential patterns of COVID-19 deaths by sex, age, comorbidities and province[6] have emerged, however individuals with "hypertension and diabetes mellitus are at high risk of dying from COVID-19 in SA[6] and consequently, require careful management. On the 1st of April 2020 the National Institute for Communicable Diseases (NICD) developed the DATCOV database to serve as a national surveillance system for COVID-19 hospitalisations.[7] This system allowed for data to be collected regarding COVID-19 however, there is no meaningful means of analysing the data for individual institutions with appropriate feedback to improve service provision. No evidence at the level of a DH in SA has been published thus far regarding mortality trends,

What needs to be known?

Prior to the pandemic, most DHs functioned at their peak capacity due to the staff shortages and a greater service load.[7] Little is known about how these hospitals managed COVID-19 and the differences in mortality trends between the first three waves at all DHs in SA as no information exists from this level of healthcare. Anecdotal reports suggest that many DHs had little support from higher levels of care such as tertiary and regional hospitals, during periods of surges in the infection rate. This may have resulted in severe consequences for patients with severe COVID-19 hence mortality trends are important for future planning/risk stratification of patients. This study will utilise Wentworth Hospital (WWH) as an example of a DH in SA.

Why is the problem important?

"Understanding the pattern of deaths from COVID-19 in SA is critical to identifying individuals at high risk of dying from the disease." [6] Unlike high income countries (HICs), SA faces a quadruple burden of disease such as: communicable diseases, maternal and child health complications, HIV, Tuberculosis, non-communicable diseases and a trauma epidemic.[4, 5, 6] This extensive disease burden, coupled with overwhelmed, poorly resourced district health facilities and the slow rate of vaccination could result in the country experiencing several more waves before herd immunity is achieved. The capacity of DHs, particularly WWH, in managing

critically ill patients who require advanced ventilation interventions and critical care nursing is limited. Additionally, access to technical/specialist expertise is reduced, yet many DHs were expected to manage such complex patients during the first three waves.[4] Consequently, there is a need to identify if the case fatality rates/ mortality trends at a district hospital is significantly greater than at regional or tertiary hospitals and thus measures to improve capacity at a district level should be considered. In addition, it will allow for DHs to identify potential areas of improvement, lead to the development of protocols/ standard operating procedures during a pandemic and address a public health issue.

How will the study solve the problem?

Identification of the mortality trends at WWH between the first three waves will highlight areas which require improvement with respect to patient management and allow for risk stratification of the population. Furthermore, information from this study may be applied to other district hospitals and community hospitals in SA. The study will make health management (at a district, provincial and national level) aware of the burden placed on DHs and take this into consideration when planning a pandemic response for future waves.

Research Question/Hypothesis

What were the mortality trends during the first three waves among patients admitted for COVID-19 at Wentworth hospital in Durban, Kwa Zulu Natal, South Africa?

AIM AND OBJECTIVES

Overall Aim

To evaluate mortality trends associated with patients who were hospitalised for COVID-19 at WWH in South Africa.

Specific Objectives

1. To compare the demographic profile of patients who died from COVID-19 during the first three waves at WWH.
2. To compare the clinical profile and management strategies of patients who died from COVID-19 during the first three waves at WWH.
3. To identify risk factors for mortality among patients with COVID-19 during the first three waves at WWH.
4. To identify areas requiring improvement with respect to holistic patient management.

LITERATURE REVIEW

On the 11th of March 2020 the World Health Organization (WHO) declared COVID-19 (disease caused by SARS COV2 virus) as a global pandemic.[8] By the 21st June 2021 178,360,849 confirmed cases of COVID-19 and 3,869,384 deaths worldwide were recorded.[9] SA has recorded 1 832 479 cases with 58 795 deaths since the 21st of June and is currently at the beginning of a third wave.[10] Overwhelmed healthcare facilities; pandemic fatigue (amongst both healthcare workers and non-healthcare workers) combined with a paucity of research in our population setting and the quadruple burden of disease makes the management of COVID-19 patients and subsequent preparation for future waves challenging - particularly at a DH level. In addition, delayed procurement of vaccines and vaccine hesitancy among the general population contribute to the rise in infection rate.

This literature review aims to identify and critically review articles regarding risk factors for mortality in patients with COVID 19 – globally and in a SA context; identify biochemical indicators associated with increased mortality and lastly to recognize mortality trends in current literature. All articles and literature pertaining to COVID 19 on the PubMed database are collated into a collection of resources called the SARS CoV 2 data (NCBI). By the 21st of June 2021, 147 072 PubMed articles and 5 974 clinical trials pertaining to COVID 19 had been carried out. An advanced search on PubMed on the 21 June 2021 using the following MeSH terms ("corona virus" [MeSH Terms] OR "sars cov 2"[MeSH Terms] OR "covid 19"[MeSH Terms]) AND "mortality"[MeSH Terms] yielded 2774 results, of which 21 articles were relevant. No filters were used and consequently included books, documents, met-analyses, reviews, systematic reviews and clinical trials with no language restrictions applied. Additionally, LitCovid (a curated literature hub for new information regarding COVID 19), was searched - using the above search terms - and yielded seven additional relevant articles. The majority of the research available to date comes from High income countries (HICs) with a lack of information from low- and middle-income countries (LMICs). Of the 28 articles, only four articles were related to COVID-19 and mortality in a SA context and only one of them conducted at the level of a rural hospital.

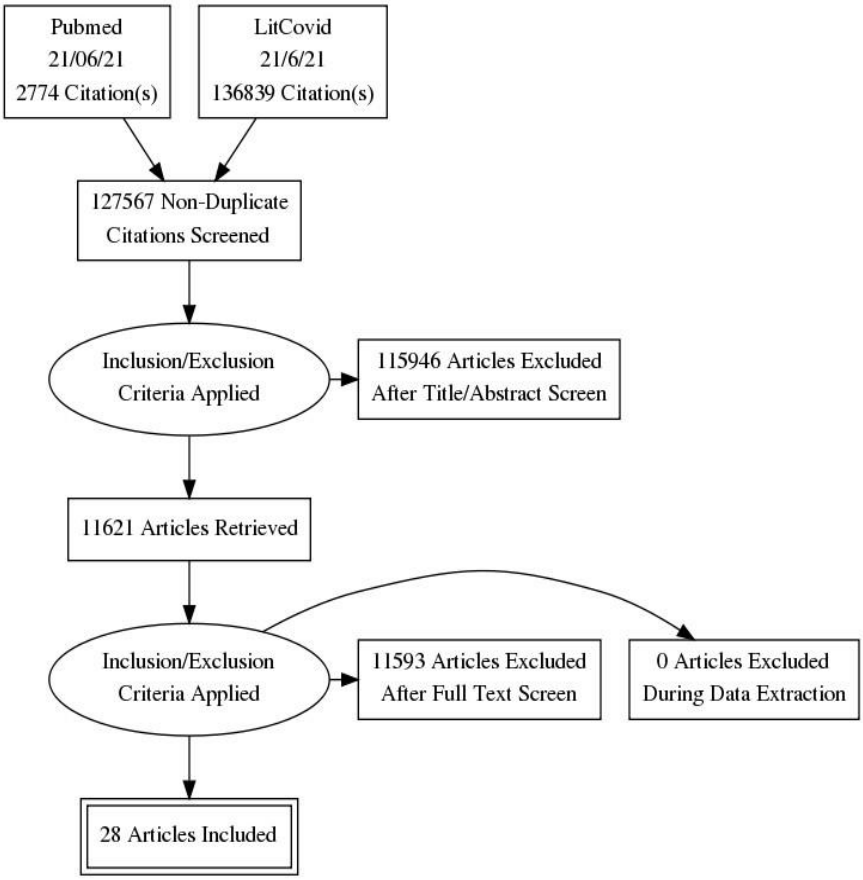

Figure 1: Prisma chart depicting study selection.

Risk factors for mortality in patients with COVID-19 (internationally)

Multiple risk factors have been associated with an increase in mortality from COVID – 19. A systematic review and meta-analysis done by Parohan et al.[11] found that mortality risk increases with older age ≥65 years (pooled ORs = 4, 59; 95% CI: 2.61-8.04; p<0.001); male gender[12] (pooled ORs = 1.5; 95% CI: 1.06-2.12. Hypertension (270% increase), Diabetes Mellitus (241% increase), cardiovascular diseases (372% increase), Chronic Obstructive Pulmonary Disease (353% increase), malignancy (304% increase) and higher Sequential Organ Failure Assessment (SOFA)[7] scores were associated with an increase in mortality. Ejaz et al.[5] (2020), also includes obesity/increased body mass index as a risk factor for severe disease or mortality. However, this same study stated that no significant correlation for developing disease or mortality exists in individuals with HIV, liver disease and asthma. A small retrospective study, done in Saudi Arabia, with 352 patients also deemed active smoking[13] to be linked to mortality - this was found in numerous other studies as well.[14,15,16,17] The association between comorbidities

and the increase in mortality is explained by the fact that SARS COV 2 virus uses ACE-2 receptors in order to enter a cell. Certain comorbidities result in an upregulation of ACE-2 receptor expression and increase the release of enzymes which facilitate viral entry into cells. Consequently, accurate evaluation and consideration is required when patients with these comorbid conditions present to hospital/outpatient facilities. Patients with poor prognostic features should be identified promptly and be introduced to palliative care specialists or managed holistically with the use of a multi-disciplinary team.

The above studies had a few limitations. Most had small sample sizes and were retrospective in nature. Also, certain risk factors had inconclusive/conflicting information. Lastly, many of these studies were published in HICs which have different population dynamics, disease profiles and healthcare systems to those in SA.

Risk factors for mortality in patients with COVID-19 (African/South African context)

There is limited research on the risk factors for mortality and mortality trends with respect to COIVD-19 within our population. Nonetheless, the existing research supports the evidence mentioned above with regards to patient demographics and comorbidities.[4,18] As stated by Pillay-van Wyk et al. (2020) the median age of death was 61 years (interquartile range 52-71). Males had a 1.5 times higher death rate compared with females and individuals with two or more comorbidities accounted for 58,6% (95% CI 56.6-60.5) of deaths. Hypertension and diabetes mellitus were the most common comorbidities reported, and HIV and tuberculosis were more common in individuals aged <50 years.[6] In addition, poor help-seeking behavior/ seeking medical attention in advanced disease, low detection rates and limited capacity to manage critical cases have also proven to be risk factors for mortality in LMICs.[17] Healthcare-related constraints across sub-Saharan Africa range from inadequate supplies of medical equipment to low per capita capacity for isolation and treatment. A recent report estimated that the entire African continent has 1% of the ventilator capacity of the United States of America,[17] highlighting the need to upgrade our healthcare systems. Furthermore, our population demographics vary greatly from HICs with most of our population being younger and having a unique disease profile particularly with respect to HIV and Tuberculosis.[7] HIV and TB were associated with a moderately increased risk of in-hospital COVID-19 mortality with HIV infected individuals with immunosuppression being at [increased risk] as opposed to those with CD4 counts ≥200. [18] These studies are limited as they had small sample sizes and did not distinguish between confirmed COVID-19 and probable infection, while another study used a simulated case analysis. However, as stated by Jassat et al. (2020) there is a knowledge gap in

LMIC – in which there is a younger population, unique disease profile with epidemics of both infectious (HIV and TB) and non-communicable diseases, and an overburdened public health system.[7]

Certain biochemical and radiological indicators have been associated with increased mortality.[19] Older age, d-dimer levels greater than 1 microgram/milliliter, and higher SOFA (Sequential Organ Failure Assessment) score on admission were associated with higher odds of in-hospital death. Additionally, elevated levels of blood IL-6, high sensitivity cardiac troponin I, and lactate dehydrogenase and lymphopenia (lymphocyte count $<10^9$/L) were more commonly seen in severe COVID-19 illness.[2] Decreased SpO_2/FiO_2 ratio, increased lactate, active smoking and the prevalence of a pulmonary embolism were all poor prognostic factors in critically ill COVID patients.[12] Results associated with mortality were: CD3+ CD8+ cell count ≤75 cells/microliter, AKI stage 2 and 3, proteinuria ≥1+, haematuria ≥1+, and peak serum creatinine ≥13.26 micromol/litre.[18] Merugu et al[20] (2020) described low haemoglobin (p=0.0046), elevated INR (p=0.0005), low platelets (p=0.0246), and an elevated procalcitonin (p=0.472) as being associated with an increase in mortality.[20] Radiological features on a chest x-ray and a CT scan showing bilateral ground glass opacities with variable pulmonary parenchymal consolidations[12] were evident in patients with a severe COVID pneumonia and was associated with increased mortality. Limited evidence exists from a SA context. This study aims to identify the similarities and differences in mortality in the first three waves of the COVID -19 at a DH in KZN. Healthcare systems internationally have been disrupted by the COVID-19 pandemic. Lack of resources and literature appropriate to our setting constantly hinders our ability to provide effective patient management, developing sustainable future practices and eventually eliminating the spread of the virus and its variants.

RESEARCH DESIGN AND METHODS

Overview

1. Study Setting

This study is set at Wentworth Hospital (DH), Durban, Kwa Zulu Natal, South Africa.

Wentworth Hospital services the following catchment areas: - Hillary, Seaview, Wentworth, Austerville, Yellowwood Park, Chesterville, Cato Manor, Bluff, Clairwood, Montclair, Jacobs, Lamontville, Umbilo, Woodlands and Merebank. Wentworth Hospital operates on a referral system with patients being referred via their local clinics or regional hospitals. This hospital was

selected as it is very similar to other DH in SA. It has minimal facilities and staffing yet services a vast population – many of whom have complex disease processes. The community of WWH was particularly hard-hit during the COVID-19 pandemic with respect to healthcare and socioeconomic issues in the area. There is a great deal of data published from the first world that have access to advanced ventilation, specialist and critical care units as well as access to imaging modalities such as a CT scan and MRI. However, little research exists in resource constricted environments such as WWH. This hospital was chosen as results and findings can be applied to other DH hospitals within SA and even resource-constrained hospitals internationally.

2. Study Design

This study design is an observational retrospective analytical study in which mortality trends will be identified based on retrospective analysis of data.

3. Target Population

All adult patients regardless of age admitted to public hospitals in KZN with COVID-19 during the first three waves.

4. Study population

All adult patients (>18 years of age) admitted to WWH since March 2020 until the 31st of September 2021, who had COVID-19 disease on admission based on clinical, biochemical, or radiological features suggestive of SARS COV 2 infection and demised during their hospital admission due to COVID-19.

5. Inclusion / Exclusion criteria Inclusion criteria:

Inclusion criteria

a) Admission to Wentworth Hospital due to a severe COVID infection
b) 18 years or older regardless of demographics such as gender, race, ethnicity, severity of disease on admission or comorbid disease profile
c) Positive SARS COV 2 PCR or in the event of a negative PCR a strong clinical suspicion by the treating doctors based on **clinical, biochemical, or radiological** features of SARS COV 2 infection. WWH used a clinical scoring system out of a total of 21 – in which a score of >9 was strongly suspicious of COVID. The scoring system comprised of the following criteria: a history of positive contact, acute cough, fever >38, RR > 25/min, SpO2 <95%, recent loss of taste/smell, high CRP, high WCC, positive CXR (ground glass or pneumonia), D-dimer >0.25 and any diabetic emergency. Please review Appendix 2.
d) Death related to COVID-19 during hospital admission.

Exclusion criteria:

a) Death not attributable to COVID infection, for example patients who demised due to trauma with an incidental positive SARS COV 2 PCR
b) Age: there is no age restriction applied to this study Sampling
c) Method of selecting sample: All files of patients who died from COVID-19 at WWH will be sampled from March 2020 until the 31st of August 2021.

6. Data sources

Measurement instruments / Data Collection Techniques

The source of data for this research is the inpatient files of all the patients admitted for SARS COV 2 and subsequently demising between the period of March 2020 to 31 August 2021. A data collection tool has been devised and is attached as Appendix 1.

7. Measures to ensure validity.

Internal

Selection bias: All files will be sampled.

Information bias: This may an issue as information from clinical files may be scanty and files/parts of files may be lost. A pilot study will be conducted to validate the data collection instruments and to ensure that the study objectives are met.

External:

The study is generalisable to other district hospitals in South Africa.

8. List of Variables to be measured.

- Age
- SARS COV 2 PCR result
- Gender
- Ethnicity
- Symptoms
- Comorbidities such as: Hypertension, Diabetes Mellitus, Obesity (BMI > 30), HIV, current or previous TB, Asthma, COPD, malignancy, Chronic Kidney Disease, Ischemic Heart
- Disease, Congestive Cardiac Failure, Dyslipidaemia
- Social habits: ethanol use, smoking history/current smoker, illicit drug usage
- Class of dyspnoea according to the New York Heart Association Scale graded from 1-4

- Clinical Frailty Score
- Systolic Blood Pressure
- Diastolic Blood Pressure
- Pulse rate
- Respiratory rate
- SPO2 on room air
- Blood glucose on admission
- Level of consciousness
- PF ratio on admission
- Presence of complications on admission such as: acute kidney injury, depressed level of consciousness, haemodynamic instability, liver enzyme abnormality, myocarditis, thromboembolic disease, diabetic keto-acidosis
- Chest Xray features
- ECG findings
- Urine dipstick findings
- Biochemical markers: White cell count, haemoglobin, urea, platelets, creatinine, eGFR, bilirubin, ALT, GGT, LDH, CRP, d-dimer, oxygen requirements, treatment prescribed, number of days in the hospital.

9. Plan for Data collection

The data required will be collected and captured electronically using the data collection tool. This study is not based on any previous study for mortality trends: however, the factors determining mortality, as highlighted in the literature review, such as: comorbidities, clinical presentation, vital signs, biochemical and radiological markers have been used to develop the data collection tool.

10. Plan for Data handling/processing

The data will be stored secured on the principal investigator's laptop which is password protected. Data will be extracted from files at WWH, and the files will not be taken offsite. All paper-based data will be stored in a locked-up cupboard in the supervisor's office. Data will be destroyed five years after study completion.

11. Statistical methods

Descriptive statistics will be used to summarise the data. Frequencies and percentages will be used for categorical data such as gender, ethnicity, and comorbidities. Frequency distributions of numeric variables will be examined for normality and means (SD) or median (IQR) used as

appropriate. Categorical variables will be compared between the two waves using Chi Square or Fisher's exact tests. Numeric variables will be compared using t-tests or Mann Whitney tests as appropriate. A logistic model will be used to identify independent factors differing between the two groups. Odds ratios, 95% confidence intervals and p values will be reported. Stata V15.1 will be used for the analysis.

12. List of associations to be measured.

The association between mortality and factors such as: age; gender; ethnicity; time of death, vaccination status, the number of comorbidities and risk of death, presence of hypertension, diabetes mellitus and level of control, obesity (BMI > 30), HIV and level of immune compromise, current or previous TB, asthma, COPD, malignancy, chronic kidney disease, ischaemic heart disease, congestive cardiac failure, dyslipidaemia and the risk of death; Clinical Frailty Score; triage colour and risk of death, TEWS score and the risk of death; PF ratio on admission; Chest Xray features; Troponin levels, eGFR, d-dimer, CRP, urine dipstick findings, Abnormal LFT vs normal LFTs.

ETHICAL CONSIDERATIONS

When conducting medical research of any nature or on any scale one must always consider the 4 basic principles of medical ethics, namely: benefice, non-maleficence, justice and autonomy. Since this study is retrospective in nature it respects patient autonomy without doing any harm. Informed consent from every patient will not be required as no personal information of any nature will be disclosed. Each patient will be allocated a code known only to the research to ensure that their records will be kept strictly confidential and private. Since the proposed research is a study of mortality trends the study group on whom the data was collected is a vulnerable population group, however as emphasized above patient personal data will be kept entirely confidential. As a healthcare practitioner it is important to advocate for your patients. This research project aims to identify mortality trends and the areas which require improvement in the district health care system in order to provide better quality patient centered health care overall.

Approval from the Biomedical Research Ethics Committee and the Institutional and Provincial DoH committees will be obtained prior to study commencement.

WORK PLAN

The budget for this study is R50 0000.[1] These funds will be utilized for paying a data capturer, stationary, publication and printing purposes.

The above study and write up will be done over two years: from the 1 June 2021 to the 1st of June 2023. Details regarding the project completion are elaborated in the Gantt chart below.

MMEDSci GANTT Chart													
Activity	**Jun**	**Jul**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**April**	**May**	**Jun**
Part 1													
Meeting with research supervisor: finalisation of research topic													
Protocol development													
Meeting with biostatistician													
Submission of final protocol													
Ethics approval (RIG)													
Pilot study													
Data collection													
Data analysis													
Part 2													
Writing of first report													
Submission to supervisor													
Editing													
Final Submission													

Figure 2: GANTT Chart illustrating project timeline.

1 The study will be self-funded until further alternative funding becomes available.

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APPENDIX 1: CLINICAL PROBABILITY SCORE

Clinical probability Score	Score:
1. History of confirmed Covid contact	2
2. Acute cough	1
3. Fever ≥ 38° C	2
4. RR >25 breaths per minute	1
5. SPO_2 < 95% on room air	2
6. Recent loss of taste or smell	3
7. High CRP	2
8. High WCC	1
9. Positive Chest X-ray – ground glass (3 points) or pneumonia (2 points)	2/3
10. D-dimer >0.25	2
11. Any diabetic emergency	2
Total:	21

APPENDIX 2: DATA COLLECTION TOOL

Mortality Trends Data Collection Tool

The data was collected by the primary investigator electronically via a Google Form

---

1. Patient number

_____

2. Month of demise

☐ January
☐ February
☐ March
☐ April
☐ May
☐ June
☐ July
☐ August
☐ September
☐ October
☐ November
☐ December

3. Year of demise

☐ 2020
☐ 2021

4. Results of SARS CoV2 Antigen Test

*Only mark one square

☐ Positive
☐ Negative

5. Results of SARS CoV2 PCR test

*Only mark one square

☐ Positive
☐ Negative

6. If the answer to the above is negative, what was the basis for being deemed COVID positive? *Only mark one square

☐ Clinical

☐ Radiological features suggestive of a COVID pneumonia

☐ Biochemical indicators

7. Was the patient vaccinated?

*Only mark one square

☐ Yes – the patient is fully vaccinated.

☐ No

☐ Partially vaccinated.

☐ Unknown

8. If the patient is fully vaccinated, which vaccine did they receive?

*Only mark one square

☐ Johnson and Johnson (single dose)

☐ Pfizer (both doses

*At inception of this question, additional booster doses were not available

9. Age (in years)

_____

10. Time (please specify am/pm)

_____

11. Triage colour on admission (according to the South African Triage Scale)

*Only mark one square

☐ Red

☐ Orange

☐ Yellow

☐ Green

12. TOO score on admission.

_____

13. Sex

*Only mark one square

☐ Male

☐ Female

14. Ethnic classification

*Only mark one square

- ☐ Black African
- ☐ Indian/Asian
- ☐ White
- ☐ Coloured
- ☐ Other

15. History obtained from patient regarding presenting symptoms:

- ☐ Contact with confirmed case of C19.
- ☐ Cough
- ☐ Fever
- ☐ Sore throat
- ☐ Shortness of breath
- ☐ Recent loss of taste or smell
- ☐ Myalgia/body pain
- ☐ Diarrhoea/GIT disturbance
- ☐ Confusion
- ☐ Chest pain
- ☐ Headache
- ☐ Other

16. Comorbidities present:

- ☐ Nil
- ☐ Hypertension
- ☐ Diabetes Mellitus HbA1C <7
- ☐ Diabetes Mellitus HbA1C 7-8
- ☐ Diabetes Mellitus HbA1C >8
- ☐ Obesity BMI >30
- ☐ HIV with viral suppression
- ☐ HIV without viral suppression/Unknown viral load
- ☐ Current TB
- ☐ Asthma
- ☐ COPD

- ☐ Malignancy
- ☐ Chronic Kidney Disease
- ☐ Ischaemic Heart Disease
- ☐ Dyslipidemia
- ☐ Other

17. Social habits

- ☐ Current smoker
- ☐ Ex-smoker
- ☐ Current alcohol use
- ☐ Illicit drug use
- ☐ Not documented
- ☐ Sober habits

18. NYHA Class of dyspnoea

*Only mark one square

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ Not recorded

19. Clinical frailty

*Only mark one square

☐ 1- very fit

☐ 2 - well often, active occasionally

☐ 3 – managing well – routine walking

☐ 4 - vulnerable symptoms limit activity but still independent

☐ 5 – Mildly frail, needs help with higher order ADLs e.g., housework

☐ 6 – Moderately frail, needs help with all outside activity e.g., bathing

☐ 7 – Severely frail, totally dependant

☐ 8 – Very severely frail, completely dependent – approaching end of life

☐ 9 – Terminally ill – approaching end of life

☐ 10 – Not documented

20. Systolic blood pressure in mmHg

_____

21. Diastolic blood pressure in mmHg

_____

22. Heart rate in beats per minute

_____

23. Respiratory rate in breaths per minute

_____

24. SPO_2 on room air on admission

_____

25. PF Ratio on admission

_____

26. Blood glucose on admission

_____

27. GCS (/15)

_____

28. Complications present

- ☐ Acute kidney injury
- ☐ Decreased level of consciousness
- ☐ Haemodynamic instability
- ☐ Liver enzyme abnormality
- ☐ Myocarditis
- ☐ Thromboembolic disease
- ☐ Diabetic ketoacidosis/diabetic emergency
- ☐ Other

29. Chest Xray features (confirmed by admitting doctor/consultant in charge) *no radiologist available on site for formal reporting.

- ☐ Normal
- ☐ Pulmonary infiltrates (mild)
- ☐ Ground glass appearance OR peripheral consolidation (moderate)
- ☐ Ground glass appearance AND peripheral consolidation (severe)

30. ECG findings

_____

31. Urine dipstick findings

- ☐ Not done
- ☐ Normal
- ☐ Glucose present
- ☐ Protein present
- ☐ Blood present
- ☐ Leukocytes present
- ☐ Other abnormalities e.g., ketones

32. Haemoglobin (g/dL)

_____

33. White cell count

    _____

34. Platelets

    _____

35. Urea

    _____

36. Creatinine

    _____

37. eGFR

    _____

38. Bilirubin

    _____

39. ALT

    _____

40. GGT

    _____

41. LDH

    _____

42. CRP

    _____

43. D-dimer

    _____

44. Oxygen used at the time of admission.

*Only mark one square

- ☐ Room air
- ☐ Nasal prongs
- ☐ Venturi Facemask 40%
- ☐ Nonrebreather mask
- ☐ Dual oxygen
- ☐ High flow nasal oxygen
- ☐ Continuous positive airway pressure
- ☐ Intubation and mechanical ventilation

45. Treatment prescribed:

*Mark as appropriate

- ☐ Dexamethasone 6 mg intravenously
- ☐ Clexane 40 mg subcutaneously (prophylactic)
- ☐ Clexane 80 mg subcutaneously (therapeutic)
- ☐ Thiamine
- ☐ Vitamin D stat dose
- ☐ Vitamin B3
- ☐ Zinc
- ☐ Rocephin
- ☐ Azithromycin

46. Were oxygen needs escalated after admission? If so, to what?

*Only mark one square

- ☐ Oxygen needs were less after admission.
- ☐ Oxygen needs remained the same.
- ☐ Nasal prongs with a higher flow
- ☐ Venturi face mask
- ☐ Non-rebreather
- ☐ Dual oxygen
- ☐ High Flow Nasal Cannula Oxygen
- ☐ Continuous Positive Airway Pressure
- ☐ Intubation and mechanical ventilation

47. If on High Flow Nasal Cannula Oxygen, how many days was the patient on it for?

_____

48. Number of days on oxygen in total

_____

49. Number of days admitted to Wentworth Hospital

_____

50. During their admission was the patient discussed with higher levels of care such as Inkosi Albert Luthuli Central Hospital or King Edward VIII Hospital?

*Only mark one square

- ☐ Yes
- ☐ No

51. If the answer to the above was yes, was the referral accepted?

*Only mark one square

- ☐ Yes
- ☐ No

52. If the referral was not accepted, what was the reason for non-acceptance?

*Only mark one square

☐ Patient does not meet the referral criteria.

☐ No accepting capacity at higher level of care (i.e., no bed space available/ no available ventilators)

☐ Patient not for escalation of care due to poor premorbid functioning

☐ Patient was accepted but demised while awaiting transport/en route to another facility.

☐ Other reason, please specify: _____

53. Time of death *please specify am/pm.

_____

APPENDIX 3: NATIONAL HEALTH RESEARCH DATABASE APPROVAL

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202201_003

Dear Dr O. Harichund
(UKZN)

Approval of research

1. The research proposal titled **'Mortality trends in patients during the first three waves of the SARS 2 pandemic at Wentworth District Hospital in South Africa'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Wentworth Hospital.

2. You are requested to take note of the following:
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 03/02/2022.

Fighting Disease, Fighting Poverty, Giving Hope

APPENDIX 4: BIOMEDICAL RESEARCH ETHICS COMMITTEE APPROVAL

28 April 2022

Dr Omishka Hirachund (221121569) School of Nursing & Public Health Howard College

Dear Dr Hirachund,

Protocol reference number: BREC/00003680/2021

Chapter 1 Project title: Mortality Trends in Patients during the First Three Waves of the SARS Cov 2 Pandemic at Wentworth District Hospital in South Africa

Degree: MMedSc

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 28 April 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Amended_Lockdown_Level_1_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 28 April 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of patients, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 10 May 2022. Yours sincerely,

Prof D Wassenaar

Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee Chair: Professor D R Wassenaar

UKZN Research Ethics Office Westville Campus, Govan Mbeki Building Postal Address: Private Bag X54001, Durban 4000

Email: BREC@ukzn.ac.za

Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

APPENDIX 5: WENTWORTH HOSPITAL INSTITUTIONAL APPROVAL

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

WENTWORTH HOSPITAL
PRIVATE BAG
JACOBS 4026

22/12/2021

UKZN BREC Reference No	BREC/00003680/2021
Full (Scientific) title	**Mortality trends in patients during the first three waves of the SARS COV 2 pandemic at Wentworth District Hospital in South Africa**

Dear Dr Hirachund
Principal Investigator

Re: Letter of Support to conduct a clinical trial

The Ethics Committee- WWH supports this study and therefore grant Gateway Permission to access Wentworth Hospital for the conduct of such study, subject to:
Prior to the study commencing, please produce "Gateway Permission" from KZNDOH-Ethics
Please adhere to ALL COVID-19 Protective measures in place at the hospital.
Please share the results of your study once completed.
Wishing you every success with your study
Yours sincerely
Dr Ruben Naidoo
Chairman- Wentworth Ethics Committee

K Naidoo

Dr K Naidoo- MbChB(Natal);MMED-FamMed (Natal);LLM-Medical Law(UKZN); FCFP(SA); PhD-Medicine (UKZN)
Lecturer/ Head of Clinical Unit- Dept. of Family Medicine/ Wentworth Hospital
Master of Laws-Medical Law
School of Nursing and Public Health
Nelson R Mandela School of Medicine
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E-mail: naidook@ukzn.ac.za
Website: http://familymedicine.ukzn.ac.za
Website: http://www.kznhealth.gov.za/familymedicine.htm

APPENDIX 6: SAFPJ ACCEPTANCE

Ref. No.: 5700

Manuscript title: Mortality trends during the COVID-19 pandemic at Wentworth Hospital South Africa: A retrospective observational analysis

Journal: South African Family Practice

****

Dear Dr Hirachund

Thank you for your revised manuscript. We have reached a decision regarding your submission. I am pleased to inform you that your manuscript has now been accepted for publication.

The Editorial Office will contact you by 14 March 2023. If you need any assistance, kindly contact the Editorial Office at submissions@safpj.co.za with any questions or concerns.

Thank you for submitting your interesting and important work to the South African Family Practice.

Kind regards,

Assoc. Prof. Von Pressentin

Division of Family Medicine, Department of Family, Community and Emergency Care (FaCE), University of Cape Town

APPENDIX 7: CLINICAL PROBABILITY SCORE

Clinical Probability Score	Score:
1. History of confirmed Covid contact	2
2. Acute cough	1
3. Fever ≥ 38° C	2
4. RR >25 breaths per minute	1
5. SPO_2 < 95% on room air	2
6. Recent loss of taste or smell	3
7. High CRP	2
8. High WCC	1
9. Positive Chest X-ray – ground glass (3 points) or pneumonia (2 points)	2/3
10. D-dimer >0.25	2
11. Any diabetic emergency	2
Total:	21

APPENDIX 8: SOUTH AFRICAN MEDICAL JOURNAL ACCEPTANCE

SAMJ Editor Decision

2023-07-31 06:10 AM

Dear Omishka Hirachund, Camilla Pennefather, Mergan Naidoo

We have reached a decision regarding your submission to South African Medical Journal, "Mortality trends during the first three waves of the COVID-19 pandemic at an urban district hospital in South Africa: A retrospective comparative analysis".

Our decision is to: Accept Submission

Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@samedical.org

Thank you for submitting your work to the journal.

Kind regards

Bridget