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Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study

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Summary

Background The first wave of COVID-19 in South Africa peaked in July, 2020, and a larger second wave peaked in January, 2021, in which the SARS-CoV-2 501Y.V2 (Beta) lineage predominated. We aimed to compare in-hospital mortality and other patient characteristics between the first and second waves.

Methods In this prospective cohort study, we analysed data from the DATCOV national active surveillance system for COVID-19 admissions to hospital from March 5, 2020, to March 27, 2021. The system contained data from all hospitals in South Africa that have admitted a patient with COVID-19. We used incidence risk for admission to hospital and determined cutoff dates to define five wave periods: pre-wave 1, wave 1, post-wave 1, wave 2, and post-wave 2. We compared the characteristics of patients with COVID-19 who were admitted to hospital in wave 1 and wave 2, and risk factors for in-hospital mortality accounting for wave period using random-effect multivariable logistic regression.

Findings Peak rates of COVID-19 cases, admissions, and in-hospital deaths in the second wave exceeded rates in the first wave: COVID-19 cases, 240.4 cases per 100 000 people vs 136.0 cases per 100 000 people; admissions, 27.9 admissions per 100 000 people vs 16.1 admissions per 100 000 people; deaths, 8.3 deaths per 100 000 people vs 3.6 deaths per 100 000 people. The weekly average growth rate in hospital admissions was 20% in wave 1 and 43% in wave 2 (ratio of growth rate in wave 2 compared with wave 1 was 1.19, 95% CI 1.18–1.20). Compared with the first wave, individuals admitted to hospital in the second wave were more likely to be age 40–64 years (adjusted odds ratio [aOR] 1.22, 95% CI 1.14–1.31), and older than 65 years (aOR 1.38, 1.25–1.52), compared with younger than 40 years; of Mixed race (aOR 1.21, 1.06–1.38) compared with White race; and admitted in the public sector (aOR 1.65, 1.41–1.92); and less likely to be Black (aOR 0.53, 0.47–0.60) and Indian (aOR 0.77, 0.66–0.91), compared with White; and have a comorbid condition (aOR 0.60, 0.55–0.67). For multivariable analysis, after adjusting for weekly COVID-19 hospital admissions, there was a 31% increased risk of in-hospital mortality in the second wave (aOR 1.31, 95% CI 1.28–1.35). In-hospital case-fatality risk increased from 17.7% in weeks of low admission (<3500 admissions) to 26.9% in weeks of very high admission (>8000 admissions; aOR 1.24, 1.17–1.32).

Interpretation In South Africa, the second wave was associated with higher incidence of COVID-19, more rapid increase in admissions to hospital, and increased in-hospital mortality. Although some of the increased mortality can be explained by admissions in the second wave being more likely in older individuals, in the public sector, and by the increased health system pressure, a residual increase in mortality of patients admitted to hospital could be related to the new Beta lineage.

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Introduction

South Africa, a temperate country in the southern hemisphere, had recorded the most COVID-19 cases in Africa as of June, 2021.¹ The country has a high burden of non-communicable diseases and obesity, HIV, and tuberculosis. According to the 2016 Demographic and Health Survey, 41% of adult women and 11% of men had obesity, 46% of women and 44% of men had hypertension, and 13% of women and 8% of men had diabetes.² In 2019, 7.5 million people were estimated to be living with

HIV in South Africa, of whom 2.3 million (31%) were not receiving treatment.³ In 2018, 301 000 new cases of tuberculosis were diagnosed in South Africa.⁴ South Africa has a dual health system with a publicly funded district health system that serves about 84% of the population, and a private health system largely funded by private health insurance schemes.⁵

South Africa reported its first case of PCR-confirmed SARS-CoV-2 infection on March 5, 2020, and since then has experienced a first wave, which peaked in July, 2020,

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Research in context

Evidence before this study

Most countries have reported higher numbers of COVID-19 cases in the second wave but lower case-fatality risk, in part due to new therapeutic interventions, increased testing, and better prepared health systems. South Africa experienced its second wave, which peaked in January, 2021, in which the variant of concern, SARS-CoV-2 501Y.V2 (Beta), predominated. New variants have been shown to be more transmissible and, in the UK, to be associated with increased admission to hospital and mortality rates in people infected with variant B.1.1.7 (Alpha) compared with infection with non-Alpha viruses. There are currently limited data on the severity of lineage Beta. We did separate literature searches on PubMed using the following terms: "COVID-19", "wave", and "mortality"; "COVID-19", "variant", and "mortality"; and "COVID-19", "mortality", and "trend". All searches included publications from Dec 1, 2019, to May 5, 2021, without language restrictions. Additionally, we did two literature searches on MedRxiv using the terms "COVID-19", "wave", and "mortality"; and "COVID-19", "variant", and "mortality" from April 25, 2020, to May 5, 2021, without language restrictions.

Added value of this study

We analysed data from the DATCOV national active surveillance system for COVID-19 admissions to hospital, comparing in-hospital mortality and other patient characteristics between the first and second waves of COVID-19. The study revealed

that after adjusting for age, sex, race, comorbidities, health sector, province, and weekly COVID-19 hospital admissions, there was a 31% increased risk of in-hospital mortality in the second wave. Our study also describes the demographic shift from the first to the second wave of COVID-19 in South Africa and quantifies the impact of overwhelmed hospital capacity on in-hospital mortality.

Implications of all the available evidence

Our data suggest that the new lineage (Beta) in South Africa might be associated with increased in-hospital mortality during the second wave. However, the findings should be interpreted with caution because our analysis is based on a comparison of mortality in the first and second wave as a proxy for dominant lineage and we did not have individual-level data on lineage. Individual-level studies comparing outcomes of people with and without the new lineage on the basis of sequencing data are required. We need to conduct surveillance and studies of new lineages to monitor their transmissibility and severity. Our data also suggest that overwhelmed hospital capacity was associated with increased in-hospital mortality during the first and second waves. With South Africa having entered the third wave of the pandemic in June, 2021, we require a combination of strategies to prevent high mortality, to slow the transmission of SARS-CoV-2, and to spread out the peak of the epidemic, which would prevent hospital capacity from being breached, as well as to increase access to vaccination.

a larger second wave, which peaked in January, 2021,⁶ and from June, 2021, has entered the third wave. A new lineage of SARS-CoV-2 detected in Eastern Cape province in September, 2020,⁷ was reported to be the predominant lineage of initially tested samples in each of the Eastern Cape (154 of 157, 98%), Western Cape (137 of 174, 79%), KwaZulu-Natal (244 of 252, 97%), and Gauteng (126 of 150, 84%) provinces between December, 2020, and February, 2021.^{8,9} This lineage, named 501Y.V2 or Beta, contains several mutations that were not identified in SARS-CoV-2 viruses from South Africa before September, 2020. Two of these mutations are within the receptor-binding domain, shown to enhance binding to the human ACE2 receptor.¹⁰

Preliminary data suggest that SARS-CoV-2 Beta might be more transmissible than other lineages^{7,11} and escape the immune response from preceding infection with earlier SARS-CoV-2 lineages.^{12,13} The UK reported increased admission to hospital and mortality rates in people infected with variant B.1.1.7 (Alpha) compared with infection with non-Alpha viruses.^{14,15} Data on the severity of lineage Beta are few. Determining the severity of disease during South Africa's second wave with Beta lineage predominance is important to better understand the burden of COVID-19 mortality and effect on health-care services.

We aimed to describe the demographic and clinical characteristics of individuals admitted to hospital with laboratory-confirmed COVID-19 throughout South Africa in the first and second waves, and assess risk factors for in-hospital mortality.

Methods

Study design and participants

We did a prospective cohort analysis of COVID-19 hospital surveillance data in South Africa. We accessed summary data on SARS-CoV-2 cases from national epidemiological reports.¹⁶ A secondary data analysis was done of the DATCOV national hospital surveillance database between March 5, 2020, and March 27, 2021. DATCOV is an active surveillance system for COVID-19 admissions, established in March, 2020, which has achieved comprehensive coverage of all hospitals in South Africa that have admitted a patient with COVID-19. As of March 27, 2021, a total of 644 facilities had submitted data on COVID-19 patients admitted to hospital: 393 from the public sector and 251 from the private sector. DATCOV contains data on all individuals who had a positive real-time RT-PCR assay for SARS-CoV-2 or a person who had a positive SARS-CoV-2 antigen test, with a confirmed duration of stay in hospital of one full day or longer, regardless of age or reason for admission. This included

patients who had COVID-19 symptoms, were admitted for isolation, acquired nosocomial COVID-19 infection, or tested positive incidentally when admitted for other reasons. The case reporting form was adapted from the WHO COVID-19 case reporting tool and contains the following variables: basic demographic data (age, sex, and race which was self-defined by the patient as Black African, White, Mixed or Indian); exposures such as occupation; and potential risk factors such as obesity, comorbid diseases, and pregnancy status. Socioeconomic variables are not collected. Additional variables included data on level of treatment (ward, high dependency, or intensive care unit), complications, treatment, and outcomes of hospital admission (discharged, transferred to another hospital, or died).

The Human Research Ethics Committee (Medical), University of the Witwatersrand, approved the project protocol as part of a national surveillance programme (M160667).

Procedures

Data collection was either through direct entry onto the DATCOV online platform, or through import of electronic data from health information systems into the database. Data imports contained validation checks to identify data errors. Data management described were done routinely and not for this study.

Case-fatality risk was calculated among individuals with in-hospital outcome (ie, COVID-19 deaths divided by COVID-19 deaths plus COVID-19 discharges, excluding individuals who were still admitted to hospital at the time of analysis).

The wave periods were determined using national hospital admission data. Using the admission date, we defined the incidence risk of admissions as the total number of new admissions divided by the population at risk at the beginning of the observation period (Statistics South Africa mid-year population estimates for 2020 were used).¹⁷ The wave periods were defined from the time the country recorded a weekly incidence risk of 5 admissions per 100 000 people at the start of the wave to the same incidence risk at the end of the wave. For the analysis of factors associated with in-hospital mortality, the COVID-19 epidemic was divided into five periods. The first was pre-wave 1 (weeks 10–23 of 2020; March 5–June 6, 2020); the second was wave 1 (weeks 24–34 of 2020; June 7–Aug 22, 2020); the third was post-wave 1 (weeks 35–46 of 2020; Aug 23–Nov 14, 2020); the fourth was wave 2 (week 47 of 2020–week 5 of 2021; Nov 15, 2020–Feb 6, 2021); and the fifth was post-wave 2 (weeks 6–12 of 2021; Feb 7–March 27, 2021). Pre-wave 1 was the period from the start of the epidemic to the start of wave 1, post-wave 1 was the period from the end of wave 1 to the start of wave 2, and post-wave 2 was the time from the end of wave 2 to the end of the analysis period.

The primary outcome was risk factors for mortality, investigating whether wave period was associated with

mortality; and the secondary outcome was wave period, exploring the changes in demographic and other characteristics between wave 1 and wave 2.

Statistical analysis

We implemented post-imputation random-effect (on admission facility) multivariable logistic regression models to compare the characteristics of COVID-19 patients admitted to hospital in wave 1 and wave 2, and assess risk factors for in-hospital mortality accounting for wave period. Covariates included were chosen on the basis of biological plausibility and evidence from previous analysis. For the multivariable model comparing wave 1 and wave 2 as outcomes, covariates included were age, sex, race, health sector, and presence of comorbidity, also adjusting for weekly national COVID-19 admissions. The analysis included only data from wave 1 and wave 2, and not the other wave periods. For the multivariable model assessing risk factors for mortality, covariates included were age, sex, race, public or private health sector, and presence of comorbidity, including the wave period, and adjusting for weekly national COVID-19 admissions. In the mortality model, we included all five wave periods (pre-wave 1, wave 1, post-wave 1, wave 2, and post-wave 2). Weekly national COVID-19 numbers of admissions were used as a proxy of burden of COVID-19 cases on the health-care system and divided into four categories: low (<3500), medium (3500–5749), high (5750–7999), and very high (>8000) admissions. Only COVID-19 admissions were included because data on patients admitted with other illnesses were not available.

Obesity was not included in the model due to the high proportion of missing data. As the data can be assumed to be missing at random, for the main analysis, to account for incomplete or missing data on selected variables, we used multivariate imputation by chained equation (MICE—using the *mi impute chained* command in Stata) and generated ten complete imputed datasets that were used for subsequent analyses. The procedure involves a

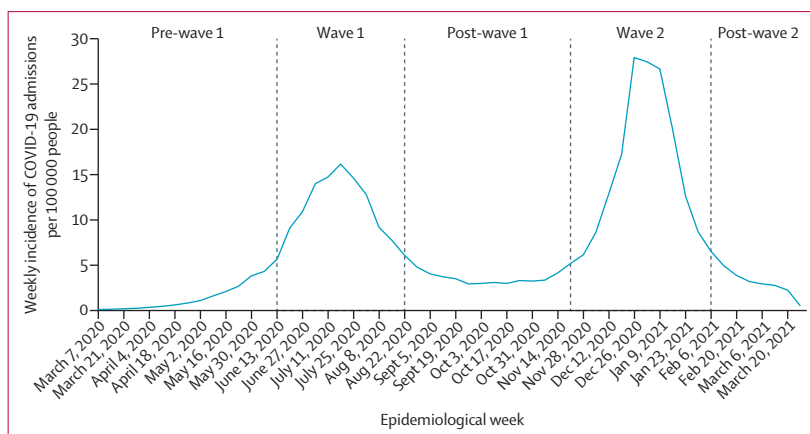


Figure 1: Weekly incidence per 100 000 people of COVID-19 admissions by epidemiological week in South Africa, March 5, 2020–March 27, 2021

Dashed lines show the time periods of the first and second waves.

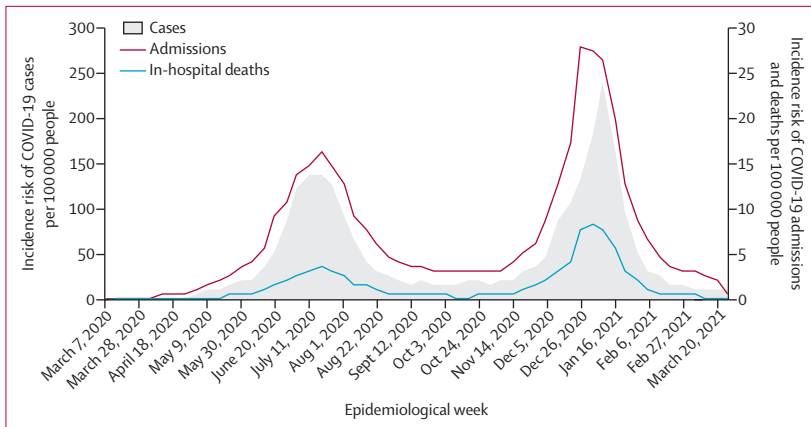


Figure 2: Incidence of reported SARS-CoV-2 cases, COVID-19 admissions, and in-hospital deaths by epidemiological week of diagnosis in South Africa, March 5, 2020–March 27, 2021

series of regression models being run, whereby each variable with missing data is modelled conditional upon the other variables in the dataset. Incomplete variables included sex, race, month of admission, and comorbidities. Complete variables included in the imputation process were age, province, health sector (ie, public or private), and in-hospital outcome (ie, discharged alive, or died, with transferred patients excluded from analysis).

A random effect on admission facility was included for all analyses to account for potential differences in the population served and the quality of care at each facility. For each multivariable model we assessed all variables that were significant at $p < 0.2$ on univariate analysis and dropped non-significant factors ($p \geq 0.05$) with manual backward elimination. Pairwise interactions were assessed by inclusion of product terms for all variables remaining in the final multivariable additive model. We did a sensitivity analysis to separately assess factors associated with in-hospital mortality among patients admitted in the private and public sectors on the imputed dataset; and a complete case analysis on the unimputed dataset for all variables included in both models. We used the χ^2 test to assess the difference in case-fatality risk at the peak of the first and second wave. Additionally, we compared the exponential growth rate of the first and the second wave. We estimated the exponential growth rate (from 5 admissions per 100 000 people at the start of the wave to the wave peak) for each wave using Poisson regression on count of weekly COVID-19 admissions (outcome variable) over time (weekly increases, dependent variable) and assessed the difference in the estimated weekly growth rate through the inclusion of an interaction term of weeks and wave in the model. The statistical analysis was implemented using Stata 15.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Number who died	Total outcomes	Case-fatality risk (95% CI)
2020			
March	45	400	11.25% (8.33–14.76)
April	185	1449	12.77% (11.09–14.60)
May	1072	5787	18.52% (17.53–19.55)
June	3698	18 209	20.31% (19.73–20.90)
July	8335	38 226	21.80% (21.39–22.22)
August	3707	19 671	18.85% (18.30–19.40)
September	1314	8851	14.85% (14.11–15.60)
October	1167	7735	15.09% (14.30–15.90)
November	2506	11 110	22.56% (21.78–23.35)
December	10 621	39 582	26.83% (26.40–27.27)
2021			
January	15 264	52 019	29.34% (28.95–29.74)
February	2380	11 940	19.93% (19.22–20.66)
March	737	4235	17.40% (16.27–18.58)

Data are absolute values (n), unless otherwise indicated.

Table 1: COVID-19 in-hospital case-fatality risk reported by month of admission in South Africa, March 5, 2020–March 27, 2021

Results

From March 5, 2020, to March 27, 2021, a total of 1 545 431 SARS-CoV-2 cases and 227 932 COVID-19 hospital admissions were reported in South Africa. Two wave periods were identified, and five wave periods defined: pre-wave 1, wave 1, post-wave 1, wave 2, and post-wave 2 (figure 1). Following the first wave peak in cases in epidemiological week 28, there was a resurgence beginning in the Eastern Cape province from week 40, followed by all other provinces subsequently, peaking in week 1 of 2021. Peak rates (per 100 000 people) of COVID-19 cases, admissions, and in-hospital deaths in the second wave exceeded the rates in the first wave (COVID-19 cases, 240.4 cases per 100 000 people vs 136.0 cases per 100 000 people; admissions, 27.9 admissions per 100 000 people vs 16.1 admissions per 100 000 people; deaths, 8.3 deaths per 100 000 people vs 3.6 deaths per 100 000 people; figure 2).

Of the 219 265 COVID-19 patients nationally with a recorded in-hospital outcome (died or discharged), 51 037 died and the in-hospital case-fatality risk was 23.28% across the whole study period. The case-fatality risk at the peak of the second wave in January, 2021 (29.34%, 95% CI 28.95–29.74) was significantly higher than that at the peak of the first wave in July, 2020 (21.80%, 95% CI 21.39–22.22; $p < 0.0001$; table 1).

The time it took from 5 admissions per 100 000 population to 15 admissions per 100 000 population in the first wave was 6 weeks and in the second wave was 5 weeks (figure 3). The estimated weekly growth rate from the start to the peak of the first wave was 1.20 (95% CI 1.19–1.20; 20% weekly average incidence risk increase from week to week); and in wave 2 was 1.43 (1.42–1.44; 43% weekly average incidence risk increase

from week to week). There was a significantly higher rate of increase in wave 2 (ratio of growth rate in wave 2 compared with wave 1 was 1.19, 95% CI 1.18–1.20).

For multivariable analysis, after adjusting for weekly hospital admissions, the factors more common in individuals admitted to hospital in the second wave were age 40–64 years (adjusted odds ratio [aOR] 1.22, 95% CI 1.14–1.31), and age 65 years and older (aOR 1.38, 1.25–1.52), compared with younger than age 40 years; admissions in individuals of Mixed race (aOR 1.21, 1.06–1.38) compared with White individuals; admission in the public sector (aOR 1.65, 1.41–1.92); and very high weekly admissions (>8000 admissions; aOR 2.31, 1.81–2.95) compared with low weekly admissions (<3500 admissions). The factors less common in the second wave were admissions in Black individuals (aOR 0.53, 95% CI 0.47–0.60) and Indian individuals (aOR 0.77, 0.66–0.91) compared with White individuals; presence of a comorbid condition (aOR 0.60, 0.55–0.67); and medium level of weekly admissions (3500–5749 admissions; aOR 0.80, 0.66–0.96) compared with low weekly admissions (<3500 admissions). We also observed provincial differences between the first and second wave with admissions more likely in Limpopo and less likely in Free State, Gauteng, and North West provinces, compared with the Western Cape province (table 2). The sensitivity analysis using unimputed complete case data showed similar associations (appendix p 4).

On multivariable analysis, after adjusting for weekly hospital admissions, we found an increased risk of in-hospital mortality in wave 2 (aOR 1.31, 95% CI 1.28–1.35) and decreased risk in the post-wave 1 period (aOR 0.85, 0.79–0.91), compared with wave 1. Other risk factors for in-hospital mortality included age 40–64 years (aOR 3.17, 95% CI 3.05–3.30), and age 65 years and older (aOR 7.89, 7.58–8.22), compared with younger than age 40 years; male sex (aOR 1.30, 1.27–1.33); Black race (aOR 1.18, 1.10–1.26), Mixed race (aOR 1.16, 1.07–1.26), and Indian race (aOR 1.30, 1.21–1.40) compared with White race; presence of a comorbid condition (aOR 1.67, 1.62–1.72); and admission in the public sector (aOR 1.39, 1.21–1.60). Compared with weeks with low numbers of national hospital admissions (<3500 admissions), there was an increased risk of mortality in weeks with high weekly admissions (5750–7999 admissions; aOR 1.08, 95% CI 1.01–1.15) and very high weekly admissions (>8000 admissions; aOR 1.24, 1.17–1.32). We also observed increased risk of mortality in Eastern Cape, KwaZulu-Natal, Limpopo, and Mpumalanga provinces, compared with the Western Cape province (table 3). The sensitivity analysis using unimputed data showed similar associations (appendix p 6).

In the sensitivity analyses, we also separately analysed predictors of in-hospital death in the private sector and public sector (appendix p 8). Both analyses showed increased mortality in the second wave compared with

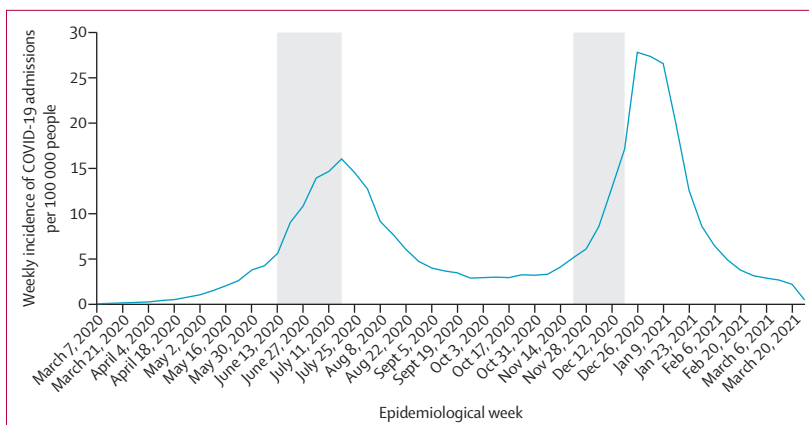


Figure 3: Incidence per 100 000 people of COVID-19 admissions by epidemiological week in South Africa, March 5, 2020–March 27, 2021

Shading shows the time period from 5 admissions per 100 000 population to 15 admissions per 100 000 population in the first and second waves.

the first wave, and similar trends and associations to those seen in the main combined analyses.

Discussion

The incidences of COVID-19 cases, admissions, and in-hospital deaths in the second wave exceeded the incidences in the first wave in South Africa. The weekly incidence of COVID-19 admissions also increased at a faster rate. Additionally, we found increased mortality in the second wave, partly explained by more admissions in older individuals and in the public sector, and by higher volumes of hospital admissions. Although we did not have individual-level data on infecting lineage for cases included in this analysis, the fact that Beta has been the predominant lineage in the second wave^{8,9} suggests that the residual 31% increased mortality could possibly be associated with the new lineage. Preliminary findings in the UK show increased case-fatality risk for individuals infected with variant Alpha, with mortality hazard ratio estimates ranging from 1.35 to 1.91.¹⁸ However, these were a series of matched case-control and population cohort studies comparing variant and non-variant cases,¹⁸ while ours was an unmatched analysis with wave as a proxy for lineage.

On the basis of global trends, in-hospital COVID-19 mortality in South Africa might have been expected to decrease in the second wave. In most countries, the second wave of COVID-19 had a higher number of cases but lower mortality.^{19–24} Improved outcomes during the second wave in these countries were probably a result of introduction of interventions such as remdesivir,²⁵ dexamethasone,²⁶ high-flow oxygen,²⁷ and increased use of thromboprophylaxis,²⁸ as well as non-pharmacological treatments such as placing the patient in the prone position.²⁰ Other possible suggestions for the lower case-fatality risk observed in the second wave in many countries are changes in demographic characteristics of cases, and the cohort or harvest effect whereby a large number of

See Online for appendix

	Percentage of patients in first wave (95% CI)	Percentage of patients in second wave (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Age, years					
<40	24.3% (24.0–24.6)	20.5% (20.3–20.8)	1 (ref)	1 (ref)	1 (ref)
40–64	51.2% (50.9–51.6)	50.7% (50.4–51.1)	1.17‡ (1.10–1.25)	1.29‡ (1.21–1.38)	1.22‡ (1.14–1.31)
≥65	24.5% (24.2–24.8)	28.7% (28.5–29.0)	1.39‡ (1.26–1.53)	1.46‡ (1.32–1.60)	1.38‡ (1.25–1.52)
Sex					
Female	55.8% (55.4–56.2)	55.5% (55.2–55.8)	1 (ref)
Male	44.2% (43.8–44.6)	44.5% (44.2–44.8)	1.01 (0.98–1.05)
Race					
White	9.2% (8.9–9.4)	11.6% (11.2–11.9)	1 (ref)	1 (ref)	1 (ref)
Black	78.6% (78.2–79.0)	68.1% (67.6–68.5)	0.69‡ (0.61–0.77)	0.56‡ (0.50–0.63)	0.53‡ (0.47–0.60)
Mixed	7.1% (6.8–7.3)	13.6% (13.3–13.9)	1.52‡ (1.29–1.80)	1.22‡ (1.07–1.39)	1.21‡ (1.06–1.38)
Indian	5.2% (5.1–5.4)	6.8% (6.6–7.0)	1.03 (0.90–1.18)	0.79‡ (0.67–0.93)	0.77‡ (0.66–0.91)
Presence of comorbidities					
No	39.3% (38.9–39.8)	45.0% (44.6–45.3)	1 (ref)	1 (ref)	1 (ref)
Yes	60.7% (60.2–61.1)	55.0% (54.7–55.4)	0.79‡ (0.71–0.89)	0.60‡ (0.55–0.66)	0.60‡ (0.55–0.67)
Health sector					
Private sector	51.6% (51.2–51.9)	47.1% (46.8–47.4)	1 (ref)	1 (ref)	1 (ref)
Public sector	48.4% (48.1–48.8)	52.9% (52.6–53.2)	1.20‡ (1.02–1.40)	1.63‡ (1.40–1.89)	1.65‡ (1.41–1.92)
Province					
Western Cape	16.5% (16.2–16.8)	22.4% (22.2–22.7)	1 (ref)	1 (ref)	1 (ref)
Eastern Cape	12.4% (12.2–12.6)	13.4% (13.2–13.6)	0.79 (0.59–1.06)	0.90 (0.66–1.24)	0.97 (0.71–1.34)
Free State	6.3% (6.1–6.5)	3.3% (3.2–3.5)	0.39‡ (0.28–0.55)	0.49‡ (0.34–0.70)	0.49‡ (0.34–0.70)
Gauteng	34.9% (34.5–35.2)	23.3% (23.0–23.5)	0.49‡ (0.37–0.64)	0.59‡ (0.44–0.78)	0.55‡ (0.41–0.74)
KwaZulu-Natal	18.1% (17.8–18.3)	23.5% (23.3–23.8)	0.96 (0.72–1.28)	1.21 (0.89–1.65)	1.14 (0.83–1.55)
Limpopo	1.9% (1.8–2.0)	5.2% (5.1–5.4)	2.00‡ (1.42–2.83)	2.60‡ (1.87–3.63)	2.41‡ (1.74–3.34)
Mpumalanga	3.0% (2.8–3.1)	3.9% (3.8–4.1)	0.97 (0.66–1.44)	1.32 (0.91–1.92)	1.30 (0.89–1.90)
North West	5.6% (5.4–5.7)	3.8% (3.6–3.9)	0.49‡ (0.33–0.73)	0.65‡ (0.43–0.99)	0.62‡ (0.41–0.95)
Northern Cape	1.4% (1.3–1.5)	1.1% (1.1–1.2)	0.59 (0.33–1.06)	0.60 (0.35–1.04)	0.62 (0.35–1.07)
Weekly national admission number					
Low (<3500)	4.7% (4.5–4.9)	3.0% (2.9–3.1)	1 (ref)	..	1 (ref)
Medium (3500–5749)	26.5% (26.2–26.8)	13.4% (13.2–13.6)	0.80‡ (0.65–0.97)	..	0.80‡ (0.66–0.96)
High (5750–7999)	19.5% (19.2–19.8)	14.7% (14.4–14.9)	1.18 (0.94–1.48)	..	1.22 (0.98–1.52)
Very high (>8000)	49.3% (48.9–49.6)	68.9% (68.7–69.2)	2.20‡ (1.71–2.85)	..	2.31‡ (1.81–2.95)

For this analysis, the outcome variable was admission to hospital during wave 2 (event) versus admission to hospital during wave 1 (control), and the exposures were the characteristics of patients admitted to hospital. ORs represent the odds of being admitted to hospital in wave 2 among patients in the given exposure category versus the odds of being admitted to hospital in wave 2 among patients in the reference exposure category. OR=odds ratio. *Unadjusted for weekly admissions. †Adjusted for weekly admissions. ‡Statistically significant estimates.

Table 2: Univariate and multivariate analysis of factors associated with admission to hospital in the first and second waves in South Africa, March 5, 2020–March 27, 2021

older people and those with health conditions (the clinically vulnerable groups) are likely to have died in the first wave.^{22,29,30} Additionally, improved testing capacities in the second wave could have resulted in more mild cases being identified,^{22,23,31,32} and health-care systems in many countries might have been better prepared in the second wave, offering timely treatment of severe cases.^{20,22,30}

The shifts in trend of admissions and deaths between the first and second wave in South Africa could also be explained by the different context of the epidemic when compared with other countries. South Africa experienced the first wave 2 months later than did other countries

and benefited from time for hospital preparedness and learning from other countries' experiences and the use of steroids, which were shown to improve clinical outcomes.³³ The country was less well prepared for the second wave, which was not predicted to have started as early as it did.

Regarding the multivariable analysis, an increased risk of mortality with admission load in South Africa was observed. In weeks with very high weekly admissions (>8000 admissions), mortality increased by 24%, compared with weeks with low weekly national admissions (<3500 admissions). The observed increase in

	Case-fatality risk (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)†
Age, years				
<40	7.2% (7.0–7.4)	1 (ref)	1 (ref)	1 (ref)
40–64	21.7% (21.5–22.0)	3.75‡ (3.62–3.90)	3.20‡ (3.08–3.32)	3.17‡ (3.05–3.30)
≥65	41.2% (40.8–41.6)	9.38‡ (9.03–9.75)	7.95‡ (7.63–8.28)	7.89‡ (7.58–8.22)
Sex				
Female	21.7% (21.5–21.9)	1 (ref)	1 (ref)	1 (ref)
Male	25.3% (25.0–25.5)	1.32‡ (1.29–1.34)	1.30‡ (1.27–1.33)	1.30‡ (1.27–1.33)
Race				
White	21.6% (20.8–22.3)	1 (ref)	1 (ref)	1 (ref)
Black	23.6% (23.4–23.8)	0.79‡ (0.74–0.84)	1.19‡ (1.11–1.27)	1.18‡ (1.10–1.26)
Mixed	22.6% (21.9–23.3)	0.89‡ (0.83–0.96)	1.17‡ (1.08–1.27)	1.16‡ (1.07–1.26)
Indian	23.9% (22.9–24.8)	1.07 (0.99–1.14)	1.31‡ (1.22–1.41)	1.30‡ (1.21–1.40)
Presence of comorbidities				
No	15.7% (15.4–15.9)	1 (ref)	1 (ref)	1 (ref)
Yes	28.9% (28.6–29.1)	2.23‡ (2.17–2.30)	1.67‡ (1.62–1.72)	1.67‡ (1.62–1.72)
Health sector				
Private sector	18.7% (18.5–19.0)	1 (ref)	1 (ref)	1 (ref)
Public sector	27.5% (27.2–27.7)	1.99‡ (1.70–2.33)	1.39‡ (1.21–1.60)	1.39‡ (1.21–1.60)
Province				
Western Cape	21.5% (21.1–21.9)	1 (ref)	1 (ref)	1 (ref)
Eastern Cape	32.6% (32.0–33.1)	2.32‡ (1.79–3.01)	2.14‡ (1.70–2.69)	2.16‡ (1.72–2.71)
Free State	22.3% (21.6–23.1)	1.14 (0.83–1.56)	1.29 (0.98–1.70)	1.29 (0.98–1.69)
Gauteng	20.0% (19.7–20.4)	0.76‡ (0.60–0.98)	1.08 (0.87–1.34)	1.07 (0.86–1.33)
KwaZulu-Natal	24.4% (24.0–24.8)	1.45‡ (1.13–1.86)	1.50‡ (1.21–1.87)	1.48‡ (1.19–1.84)
Limpopo	30.0% (29.0–31.0)	1.98‡ (1.44–2.72)	1.78‡ (1.34–2.35)	1.74‡ (1.32–2.30)
Mpumalanga	26.7% (25.7–27.6)	2.27‡ (1.62–3.20)	2.16‡ (1.61–2.92)	2.14‡ (1.59–2.86)
North West	14.6% (13.9–15.2)	0.73 (0.49–1.09)	0.93 (0.66–1.30)	0.92 (0.65–1.30)
Northern Cape	19.9% (18.6–21.3)	1.32 (0.84–2.08)	1.48 (0.99–2.21)	1.48 (0.99–2.20)
Wave period				
Pre-wave 1	18.0% (17.2–18.7)	0.79‡ (0.75–0.84)	0.88‡ (0.83–0.93)	0.99 (0.91–1.07)
Wave 1	20.8% (20.5–21.1)	1 (ref)	1 (ref)	1 (ref)
Pre-wave 2	16.4% (16.0–16.9)	0.70‡ (0.68–0.73)	0.76‡ (0.73–0.79)	0.85‡ (0.79–0.91)
Wave 2	27.8% (27.5–28.1)	1.34‡ (1.31–1.37)	1.37‡ (1.33–1.40)	1.31‡ (1.28–1.35)
Post-wave 2	18.6% (17.9–19.2)	0.80‡ (0.76–0.84)	0.90‡ (0.85–0.95)	1.02 (0.95–1.09)
Weekly national admission number				
Low (<3500)	17.7% (17.3–18.0)	1 (ref)	..	1 (ref)
Medium (3500–5749)	21.0% (20.6–21.5)	1.25‡ (1.20–1.29)	..	0.99 (0.93–1.05)
High (5750–7999)	23.0% (22.5–23.5)	1.44‡ (1.39–1.50)	..	1.08‡ (1.01–1.15)
Very high (>8000)	26.9% (26.6–27.1)	1.74‡ (1.69–1.79)	..	1.24‡ (1.17–1.32)

OR=odds ratio. *Adjusted OR including wave periods. †Adjusted for weekly admissions. ‡Statistically significant estimates.

Table 3: Univariate and multivariate analysis of factors associated with in-hospital mortality in South Africa, March 5, 2020–March 27, 2021

mortality of patients admitted to hospital at the peaks of the first and second waves reflects in part increasing pressure on the health system. In South Africa, the rising number of hospital admissions in the second wave required care to be rationed to those patients highest on triage lists.¹ Studies have shown that a strain on hospital capacity has been associated with increased mortality in non-pandemic settings.³⁴ COVID-19 mortality in hospitals appeared to be higher when the incidence of COVID-19 in the community was high or increasing^{35,36} and when the number of hospital admissions were highest.¹⁹

Additionally, the rapid escalation in cases resulted in hospital resource constraints affecting outcomes.³⁷ Furthermore, strains on critical care capacity were associated with increased COVID-19 mortality.^{37,38} In Brazil, a strained health-care system with regional differences in access to resources, compounded by overburdened hospital systems, contributed to greater in-hospital mortality.³⁹ Even the perception of a strained health system can lead to excess mortality from COVID-19 and other conditions, because individuals might avoid seeking care until their clinical condition has deteriorated

or might die at home.⁴⁰ Although we reported 51037 in-hospital COVID-19 deaths, in the same time period the South African Medical Research Council reported 151963 excess deaths above the numbers of deaths reported in previous years, estimating that at least 85% of the excess natural deaths are attributable to COVID-19.⁴¹ These data suggest that there might have been large numbers of individuals not accessing health care and dying at home. An important focus of the COVID-19 response in preparation for future waves should be efforts to strengthen health system readiness and prepare hospitals and critical care services with additional surge capacity.

In the second wave, individuals who had comorbidities and were of Black or Indian race were less likely to be admitted to hospital than they were during the first wave; while individuals who were older, of Mixed race, and presenting in public health-care facilities were more likely to be admitted. Similar findings of more admissions in older individuals less likely to have comorbidities in the second wave were reported from analysis of an individual hospital in the Eastern Cape.⁴² These differences observed between the first and second waves could have contradictory effects on mortality, with more admissions in older people and the public sector likely to result in increased mortality, and less admissions in individuals with comorbidities and of Black, Mixed, and Indian race (who have higher mortality) likely to result in reduced mortality.

The higher proportion of older people admitted in the second wave in South Africa could be due to changes in preventive behaviour and transmission dynamics or increased susceptibility to the new lineage. Across Europe, North America, the Middle East, and southeast Asia, a shift towards younger cases with fewer comorbidities and less severe disease has been observed and was considered to be due to public health measures to reduce transmission in clinically vulnerable groups.^{22,23,30,43–45} The lower proportion of reported comorbidities in the second wave, even accounting for the age distribution of patients, could reflect differences in clinician practice, survival bias, or changing manifestation in individuals without underlying illness. It could also be due to variation in reporting of comorbidities, with underascertainment of other medical conditions at the peak of the wave more likely when hospitals were busy.

Differences in race could reflect Black individuals being more greatly affected in the first wave due to historical differences in socioeconomic status and housing conditions, which is supported by data showing higher seroprevalence in Black individuals than in other race groups in South Africa.⁴⁶ It could also be due to greater aversion to seeking health care by Black, Mixed, and Indian groups in the second wave, as described in other settings during the pandemic.⁴⁷ Some explanations for higher transmission and mortality in Black and Asian people have been suggested in the literature, including

their over-representation in front-line occupations; higher incidences of multigenerational households; differences in access to health care; and public health messaging regarding prevention, early diagnosis, and treatment of COVID-19 being less effective in these groups, resulting in later presentation.¹⁹

The increased COVID-19 mortality in the public sector is in keeping with well described differences in the level of resourcing, standard of care, and outcomes between the public and private health sectors in South Africa.⁴⁸ Provincial-level differences might reflect differences in testing, health seeking behaviour, health systems, clinical practice, and underlying population characteristics. Such regional differences have also been observed in other countries such as Brazil.³⁹ The findings identify provinces less likely to have admissions in the second wave (Free State, Gauteng, and North West), suggesting that they might have earlier resurgences or larger third waves. Before the country entered the third wave, these provinces were prioritised for support by the national government, to be on alert and to ensure strong prevention and control responses.

Notably, even after adjusting for older age, higher admissions in the public sector, and higher hospital loads, a significant independent residual increase in in-hospital COVID-19 mortality was observed in wave 2, which was not accounted for by other factors.

Strengths of this study include the use of comprehensive electronic health record data on all COVID-19 hospital admissions at all 644 public and private hospitals in the country, thus minimising selection or surveillance bias and maximising generalisability. The study includes a diverse patient population, complete study outcomes, and a lengthy period of investigation of 13 months, with in-hospital follow-up until occurrence of discharge or death.

The allocation of wave time periods, categorisation of weekly hospital admissions, and risk factor analyses were performed at a national level. However, the timing of the waves differed by provinces and districts within provinces, and the national categories might not fit all provinces perfectly. Sensitivity analyses by sector found similar results to the national-level analysis, and analyses at provincial and district level in the Western Cape (unpublished) and at individual hospital level⁴² have confirmed moderately increased mortality in the second wave.

The high proportion of missing data, particularly for fields such as race (32%) and comorbidities (22%) is a limitation of a routine national surveillance system. Obesity was excluded from the analysis due to 75% of individuals having missing data. There are also no routine data available on socioeconomic status because this is not collected in DATCOV.

Additional limitations of this analysis were the lack of individual-level lineage type data, and possible residual confounding because we could not adjust for several factors. We adjusted for COVID-19 admissions but were

not able to adjust for weekly hospital admission volumes for people under investigation and non-COVID-19 admissions. We were not able to adjust for differences between the first and second wave related to the level of national restrictions or lockdowns, and to individual preventive behaviours. The analysis includes only in-hospital deaths and any differences between the two waves in the proportions of patients who did not or could not access care and those who died outside of hospital are not accounted for in the analysis. There have been changes in treatment protocols with better COVID-19 treatment regimens including steroid use and high-flow oxygen. These have probably decreased mortality rates as the epidemic progressed. The numbers of hospitals reporting to DATCOV increased in October, 2020, and while all hospitals were required to back-capture historic admissions, they might not have done this completely, leading to reporting bias with possible under-reporting in the first wave. The characteristics of those patients who died in the first wave (such as old age, comorbidities, and obesity) might have differed from the survivors and those who were not infected with SARS-CoV-2. Therefore, the characteristics of patients admitted to hospital in the second wave might be different to those of the first wave as a result of survival bias. Thresholds for hospital admission might also have changed over time.

Although much of the increased mortality in the second wave was explained by more admissions in older individuals and in the public sector, and by increasing pressure on the health system, the finding of a residual 31% increase in mortality even after accounting for these factors suggests that the new lineage (Beta) might have contributed to increased in-hospital mortality during the second wave. However, the findings should be interpreted with caution because our analysis is based on a comparison of mortality in the first and second wave as a proxy for dominant lineage and we did not have individual-level data on lineage. Individual-level studies comparing outcomes of people with and without the new lineage on the basis of sequencing data are needed. As new variants continue to emerge across the globe, surveillance to identify them and studies to determine their transmissibility and severity are important. To prevent high mortality in the third wave, we advocate a so-called flattening the curve approach, which requires a combination of strategies to slow the spread of COVID-19, to spread out the peak of the epidemic, which would prevent hospital capacity from being breached.³¹

Contributors

WJ and LO contributed to the literature search. WJ, CC, M-AD, LO, and CM contributed to the study design and refining the methods of analysis. CM, ST, CC, and WJ contributed to data analysis, and creation of tables and figures. WJ, CC, ST, and CM contributed to data interpretation and initial drafting of the manuscript. WJ drafted the initial manuscript and all other coauthors contributed scientific inputs equally towards the interpretation of the findings and the final draft of the manuscript. WJ, CM, LO, and ST have verified the underlying data. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The dataset analysed for the manuscript is available upon reasonable request. The data dictionary is available on request to the corresponding author: waasilaj@nicd.ac.za

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