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Risk factors for COVID-19-related in-hospital mortality in a high HIV and tuberculosis prevalence setting in South Africa: a cohort study

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Summary

Background The interaction between COVID-19, non-communicable diseases, and chronic infectious diseases such as HIV and tuberculosis is unclear, particularly in low-income and middle-income countries in Africa. South Africa has a national HIV prevalence of 19% among people aged 15–49 years and a tuberculosis prevalence of 0·7% in people of all ages. Using a nationally representative hospital surveillance system in South Africa, we aimed to investigate the factors associated with in-hospital mortality among patients with COVID-19.

Methods In this cohort study, we used data submitted to DATCOV, a national active hospital surveillance system for COVID-19 hospital admissions, for patients admitted to hospital with laboratory-confirmed SARS-CoV-2 infection between March 5, 2020, and March 27, 2021. Age, sex, race or ethnicity, and comorbidities (hypertension, diabetes, chronic cardiac disease, chronic pulmonary disease and asthma, chronic renal disease, malignancy in the past 5 years, HIV, and past and current tuberculosis) were considered as risk factors for COVID-19-related in-hospital mortality. COVID-19 in-hospital mortality, the main outcome, was defined as a death related to COVID-19 that occurred during the hospital stay and excluded deaths that occurred because of other causes or after discharge from hospital; therefore, only patients with a known in-hospital outcome (died or discharged alive) were included. Chained equation multiple imputation was used to account for missing data and random-effects multivariable logistic regression models were used to assess the role of HIV status and underlying comorbidities on COVID-19 in-hospital mortality.

Findings Among the 219,265 individuals admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and known in-hospital outcome data, 51,037 (23·3%) died. Most commonly observed comorbidities among individuals with available data were hypertension in 61,098 (37·4%) of 163,350, diabetes in 43,885 (27·4%) of 159,932, and HIV in 13,793 (9·1%) of 151,779. Tuberculosis was reported in 52,823 (3·6%) of 146,381 individuals. Increasing age was the strongest predictor of COVID-19 in-hospital mortality. Other factors associated were HIV infection (adjusted odds ratio 1·34, 95% CI 1·27–1·43), past tuberculosis (1·26, 1·15–1·38), current tuberculosis (1·42, 1·22–1·64), and both past and current tuberculosis (1·48, 1·32–1·67) compared with never tuberculosis, as well as other described risk factors for COVID-19, such as male sex; non-White race; underlying hypertension, diabetes, chronic cardiac disease, chronic renal disease, and malignancy in the past 5 years; and treatment in the public health sector. After adjusting for other factors, people with HIV not on antiretroviral therapy (ART; adjusted odds ratio 1·45, 95% CI 1·22–1·72) were more likely to die in hospital than were people with HIV on ART. Among people with HIV, the prevalence of other comorbidities was 29·2% compared with 38·8% among HIV-uninfected individuals. Increasing number of comorbidities was associated with increased COVID-19 in-hospital mortality risk in both people with HIV and HIV-uninfected individuals.

Interpretation Individuals identified as being at high risk of COVID-19 in-hospital mortality (older individuals and those with chronic comorbidities and people with HIV, particularly those not on ART) would benefit from COVID-19 prevention programmes such as vaccine prioritisation as well as early referral and treatment.

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Introduction The first case of COVID-19 in South Africa was documented on March 5, 2020. By March 27, 2021, 154,5431 cases had been reported and the cumulative incidence was 2592·0 cases per 100,000 people.1 Meta-analyses have reported in-hospital mortality rates between 15% and 24%, with substantial global and temporal heterogeneity.2–4 Worldwide, studies have linked COVID-19-related mortality...
to older age, male sex, and underlying medical conditions, including cardiac disease, diabetes, cancer, chronic pulmonary disease, obesity, and kidney disease. Race or ethnicity and poverty were associated with increased risk of death in COVID-19 cases in large population cohorts and meta-analyses. Characterisation of populations at increased risk of COVID-19 mortality is important for prioritisation of interventions, particularly in low-income and middle-income countries, where resources are limited. However, available data on risk factors for severe COVID-19, including mortality, are mostly from high-income countries. High poverty rates, insufficient access to health care, and high prevalence of chronic communicable diseases, such as HIV and tuberculosis, are associated with mortality among patients admitted to hospital with COVID-19. South Africa is a middle-income country with co-occurring epidemics of non-communicable diseases and chronic infectious diseases (HIV and tuberculosis). In 2020, the prevalence of HIV among people aged 15–49 years was 19%, and tuberculosis prevalence was 0·7% for all ages. In 2019, 7·5 million people were estimated to be living with HIV in South Africa, of whom 2·3 million (31%) were eligible for, but not receiving, treatment. An understanding of whether HIV and tuberculosis are associated with mortality among patients admitted to hospital with COVID-19 is of huge importance for South Africa, and other countries in the region with large HIV and tuberculosis epidemics, to guide public health action around prevention and treatment of COVID-19. Early single-centre cohort studies and meta-analyses from high-income countries with relatively small numbers of people living with HIV did not find HIV to be a risk factor for severe COVID-19. Larger population cohorts and more recent meta-analyses found people with HIV to have an increased population risk of COVID-19-associated mortality. The interaction between non-communicable comorbidities, HIV infection, and COVID-19 in-hospital mortality is not well described. We aimed to examine the association between HIV infection, tuberculosis, non-communicable comorbidities, and in-hospital mortality among patients with COVID-19 mortality. No studies reported on the interaction between HIV infection and non-communicable comorbidities on COVID-19-associated mortality.
See Online for appendix laboratory-confirmed SARS-CoV-2 infection using data from a national surveillance programme in South Africa.

**Methods**

**Study design and data sources**

This cohort study was done in South Africa, which is administratively divided into nine provinces. South Africa has a dual health system, with a publicly funded district health system that serves approximately 84% of the population and a private health system largely funded by private health insurance schemes. In the absence of existing national COVID-19 hospital surveillance systems, the National Institute for Communicable Diseases established DATCOV as a national surveillance system for COVID-19 hospital admissions on April 1, 2020. DATCOV was adopted for national implementation by the South African Government on July 15, 2020, and by October, 2020, full coverage of all hospitals had been achieved. By March 27, 2021, 393 public-sector hospitals and 251 private-sector hospitals had reported COVID-19 admissions on DATCOV. Further details about the DATCOV surveillance system, including its implementation, data management, and data quality assurance, are described in the appendix (p 1).

The Human Research Ethics Committee (Medical) at the University of the Witwatersrand (Johannesburg, South Africa) approved the project protocol as part of a national surveillance programme (M160667). In South Africa, surveillance for notifiable medical conditions such as COVID-19 requires health facilities to submit data on all cases of emerging pathogens to national authorities. As such, individual consent for inclusion of their data to DATCOV is waivered. All personal identifying information was delinked for our analysis and stored in a secure server.

**Potential risk factors and covariates**

Age, sex, race or ethnicity, and comorbidities (hypertension, diabetes, chronic cardiac disease, chronic pulmonary disease and asthma, chronic renal disease, malignancy in the past 5 years, obesity, HIV, and past and current tuberculosis) were considered as potential risk factors for COVID-19 in-hospital mortality. Data on comorbidities (including HIV status, antiretroviral therapy (ART) status, and CD4 cell count and viral load in the past 12 months), obtained from patients’ written and electronic hospital records, were submitted to DATCOV by the hospitals. The DATCOV team did not independently verify these data or access laboratory records to obtain these data. The date of the most recent CD4 cell count or viral load was not documented. The level of virological control or immunosuppression was assessed based on last available viral load or CD4 cell count result within the past year and categorised as virologically suppressed (HIV RNA <1000 copies per mL) or viraemic (HIV RNA ≥1000 copies per mL), and immune reconstituted (CD4 count ≥200 cells per μL) or immunosuppressed (CD4 count <200 cells per μL). CD4 cell count is no longer routinely measured in all patients, in accordance with South African HIV care guidelines.

COVID-19 in-hospital mortality was defined as a death related to COVID-19 that occurred during the hospital stay and excluded deaths that occurred because of other causes or after discharge from hospital. Because the main outcome of the study was COVID-19 in-hospital
| Sex                  | People with HIV (n=13,793) | People without HIV (n=13,798) | Unadjusted OR (95% CI) unimputed | p value | Adjusted OR (95% CI) unimputed | p value | Unadjusted OR (95% CI) imputed | p value | Adjusted OR (95% CI) imputed | p value |
|----------------------|-----------------------------|--------------------------------|----------------------------------|---------|------------------------------|---------|--------------------------------|---------|------------------------------|---------|
| **Female**           |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Male                 |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Age, years**       |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| <20                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| 20–39                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| 40–59                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| 60–69                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| 70–79                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| ≥80                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Race or ethnicity**|                             |                                |                                  |         |                              |         |                                |         |                              |         |
| White                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Black                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Mixed                |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Indian               |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Hypertension**     |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| No                   |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Yes                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Diabetes**         |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| No                   |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Yes                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Chronic cardiac disease** |                       |                                |                                  |         |                              |         |                                |         |                              |         |
| No                   |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Yes                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Chronic pulmonary disease or asthma** |                  |                                |                                  |         |                              |         |                                |         |                              |         |
| No                   |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Yes                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Chronic renal disease** |                        |                                |                                  |         |                              |         |                                |         |                              |         |
| No                   |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Yes                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| **Malignancy in the past 5 years** |                    |                                |                                  |         |                              |         |                                |         |                              |         |
| No                   |                             |                                |                                  |         |                              |         |                                |         |                              |         |
| Yes                  |                             |                                |                                  |         |                              |         |                                |         |                              |         |

(Table 1 continues on next page)
mortality, all analyses included patients with laboratory-confirmed SARS-CoV-2 infection who had a known in-hospital outcome (ie, discharged alive or died) at the time of data extraction (March 27, 2021).

### Statistical analysis

We analysed DATCOV data from patients admitted to hospital with SARS-CoV-2 infection between March 5, 2020, and March 27, 2021. For the main analysis, to account for incomplete or missing data on selected variables, we used multivariate imputation by chained equation (MICE) and generated ten complete imputed datasets that were used for subsequent analyses. Variables analysed by use of MICE included sex, race or ethnicity, month of admission, and the following comorbidities: HIV infection, tuberculosis infection, hypertension, diabetes, chronic pulmonary disease and asthma, malignancy in the past 5 years, chronic cardiac disease, and chronic renal disease. ART status, HIV viral load, and CD4 cell counts were also incomplete and were conditionally imputed only among HIV-positive patients (either with observed or imputed HIV status). 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). Descriptive statistics such as frequencies and percentages were used for categorical variables, and continuous variables were expressed as mean with SD or median and IQR on the imputed datasets.

Table 1: Characteristics of people with HIV and HIV-uninfected people admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, South Africa (n=219 265)

| People with HIV (n=13 793) | People without HIV (n=137 986) | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|-----------------------------|---------------------------------|------------------------|----------|----------------------|----------|------------------------|----------|----------------------|----------|
| Never 780/1138 842 (7·5%)   | 131 035/138 842 (94·4%)        | 1 (ref)                | --       | 1 (ref)              | --       | 1 (ref)                | --       | 1 (ref)              | --       |
| Past 1207/2960 (40·8%)      | 1753/2960 (59·2%)              | <0·0001                | 4·88 (4·41–5·24) | <0·0001 | 4·24 (3·92–4·59) | <0·0001 | 3·55 (3·20–3·95) | <0·0001 |
| Current 360/954 (37·7%)     | 594/954 (62·3%)                | <0·0001                | 7·35 (6·07–8·92) | <0·0001 | 6·42 (5·55–7·42) | <0·0001 | 5·55 (4·64–6·65) | <0·0001 |
| Current and past 745/1259 (59·2%) | 514/1259 (40·8%) | <0·0001                | 6·84 (5·39–9·70) | <0·0001 | 14·30 (13·05–15·66) | <0·0001 | 11·19 (9·98–12·54) | <0·0001 |

**Table 1:** Characteristics of people with HIV and HIV-uninfected people admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, South Africa (n=219 265)
Figure 2: Multivariable analysis of factors associated with HIV infection
Dots represent adjusted odds ratios and error bars represent 95% CIs. See table 1 for 95% CI values.
We implemented three post-imputation random-effect (on admission facility) multivariable logistic regression models: first, to compare people with HIV and individuals who were HIV-uninfected; second, to determine the factors associated with COVID-19 in-hospital mortality, including ART status, HIV viral load, and CD4 cell count among HIV-positive individuals; and, third, to evaluate the combined effect of multiple non-HIV comorbidities on COVID-19 in-hospital mortality. A combined comorbidity variable categorised none, one, two, and three or more comorbidities among factors that were individually significantly associated with COVID-19 in-hospital mortality in the third model. We evaluated the effect of multiple comorbidities among all patients and among people with HIV and HIV-uninfected patients separately through stratification by HIV infection status. In addition, we assessed the potential differential effect (through the inclusion of an interaction term) of multiple or individual comorbidities on COVID-19 in-hospital mortality between people with HIV and HIV-uninfected individuals.

A random effect on admission facility was included for all analyses to account for potential differences in the service population and the quality of care at each facility. For each multivariable model, we assessed all variables that were significant at p values of less than 0.2 in the univariate analysis (to evaluate lack of significance in the univariate analysis after adjusting for potential confounders) and excluded non-significant factors (p≥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 implemented several sensitivity analyses separately, analysing risk factors for COVID-19 in-hospital mortality in the public and private sectors using post-imputation random-effect multivariable logistic regression models. We also reported the univariate and multivariate association of all covariates evaluated in the analyses described previously with HIV infection and COVID-19 in-hospital mortality using non-imputed data. The statistical analysis was implemented using Stata (version 15). We followed STROBE guideline recommendations.

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.

Results
From March 5, 2020, to March 27, 2021, 229154 individuals were admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and reported to DATCOV. Of these patients, 219265 had a known inhospital outcome and were included in analyses (appendix p 5). The percentage of missing data for the imputed variables varied and was highest for obesity (163570 [74.6%]), race or ethnicity (73389 [33.5%]), and for HIV-specific variables including HIV diagnosis (67486 [30.8%]), being on ART (5715 [41.4%] of 13793 known HIV-positive individuals), viral load (12077 [87.6%] of 13793), and CD4 cell count (11023 [79.9%] of 13793; appendix pp 6–7). Obesity was excluded from the analysis due to the high proportion of missing data.

South Africa experienced a first wave of SARS-CoV-2 infection, peaking at 10086 admissions per week in July, 2020, and a second wave peaking at 17976 admissions per week in January, 2021 (appendix p 8).

The median age of patients admitted to hospital with SARS-CoV-2 infection was 54 years (IQR 40–66), and 121937 (55.7%) of 218827 patients were female (appendix p 6). Among 145876 patients with available race information, 114571 (78.5%) were Black (appendix p 6). The public sector accounted for 113856 (51.9%) of 219265 hospital admissions reported to DATCOV (appendix p 7). 176272 (80.4%) of 219265 hospital admissions were recorded by hospitals in four provinces (Western Cape, Gauteng, KwaZulu-Natal, and Eastern Cape; appendix p 7).

After multiple imputation, the estimated proportion of individuals reporting at least one comorbidity was 60.5% (95% CI 59.8–61.2). The most prevalent comorbidities were hypertension (38.6%), diabetes (29.0%), and HIV (11.7%). The prevalence of non-communicable comorbidities increased with age, whereas HIV and tuberculosis were most prevalent in individuals aged 20–59 years (figure 1).

Of 151779 (69.2%) patients admitted to hospital with COVID-19 who had available data on HIV, 13793 (9.1%) were HIV positive (appendix pp 6–7). HIV prevalence was 20.4% in the public sector and 2.2% in the private sector (table 1; age-specific HIV prevalence for public and private sector is presented in the appendix p 9). A subset of the 13793 people with HIV had ART (8078 [58.6%]), viral load (1716 [12.4%]), and CD4 cell count (2770 [20.1%]) information available. 7483 (55% CI 59–61.2%) of 13793 people with HIV were receiving ART, and 443 (25.8%) of 1716 were viracemic (HIV RNA ≥1000 copies per mL), and 1080 (39.0%) of 2770 were immunosuppressed (CD4 count <200 cells per µL) based on the last available test.

Compared with HIV-uninfected patients admitted to hospital with SARS-CoV-2 infection, those with HIV were more likely to be aged 20–39 years, 40–59 years, and 60–69 years compared with younger than 20 years; be Black or mixed race compared with White race; be 60–69 years compared with younger than 20 years; be of Indian ancestry; and past and current tuberculosis; and die in hospital. People with HIV were less likely to be aged 70–79 years and 80 years or older; be male; be of Indian ancestry; and have comorbid chronic cardiac disease, chronic renal disease, malignancy in the past 5 years, current tuberculosis, past tuberculosis, and past and current tuberculosis; and die in hospital. People with HIV were less likely to be aged 70–79 years and 80 years or older; be male; be of Indian ancestry; and have comorbid hypertension, diabetes, and chronic pulmonary disease or asthma (table 1; figure 2). HIV prevalence among patients with COVID-19 varied, with lower prevalence in the Eastern Cape and Gauteng provinces and higher prevalence in the KwaZulu-Natal and Mpumalanga provinces (table 1).
Of the 219265 patients with recorded outcomes, 168228 (76·7%) were discharged alive and 51037 (23·3%) died. The unadjusted in-hospital case fatality ratio for people with HIV was 3407 (24·7%) of 13793 compared with 30697 (22·2%) of 137986 for HIV-uninfected individuals.

Factors statistically associated with COVID-19 in-hospital mortality were increasing age 20–39 years, 40–59 years, 60–69 years, 70–79 years, and 80 years or older, compared with younger than 20 years; male sex; Black, mixed race, and Indian ancestry compared with White race; having comorbid hypertension, diabetes, chronic cardiac disease, chronic renal disease, malignancy in the past 5 years, HIV, past tuberculosis, current tuberculosis or both past and current tuberculosis; and being admitted in the public health sector. COVID-19 in-hospital mortality increased each month of the epidemic to the peak of the first wave in July, 2020, then decreased between waves and increased again to the peak of the second wave in January, 2021. COVID-19 in-hospital mortality was significantly higher in Eastern Cape, Free State, KwaZulu-Natal, Limpopo, and Mpumalanga, compared with Western Cape (table 2; figure 3). The unimputed multivariate analysis showed similar findings (table 2).

A sensitivity analysis of risk factors for COVID-19 in-hospital mortality in the public and private sectors (appendix pp 10–11) confirmed increased association

| Sex               | Case fatality ratio | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value | Unadjusted OR (95% CI) | p value | Adjusted OR (95% CI) | p value |
|-------------------|---------------------|------------------------|---------|----------------------|---------|------------------------|---------|----------------------|---------|
| Female            |                     |                        |         |                      |         |                        |         |                      |         |
| Male              | 26666/1213937 (21.7%) | 1 (ref)                | <0.0001 | 1 (ref)              | <0.0001 | 1 (ref)                | <0.0001 | 1 (ref)              | <0.0001 |
| Age, years        |                     |                        |         |                      |         |                        |         |                      |         |
| <20               | 300/8505 (3.5%)     | 1 (ref)                | <0.0001 | 1 (ref)              | <0.0001 | 1 (ref)                | <0.0001 | 1 (ref)              | <0.0001 |
| 20–39             | 3516/44605 (7.9%)   | 2·38 (2·11-2·70)       | <0.0001 | 2·60 (2·02-3·28)     | <0.0001 | 2·38 (2·11-2·70)       | <0.0001 | 2·15 (1·90-2·44)     | <0.0001 |
| 40–59             | 16285/86065 (18.9%) | 6·83 (6·11-7·76)       | <0.0001 | 6·90 (5·45-8·74)     | <0.0001 | 6·88 (6·11-7·76)       | <0.0001 | 5·32 (4·71-6·00)     | <0.0001 |
| 60–69             | 14472/10375 (75.1%) | 15·08 (13·28-17·01)    | <0.0001 | 14·41 (12·26-18·28)  | <0.0001 | 15·08 (13·38-17·01)    | <0.0001 | 11·29 (9·99-12·76)   | <0.0001 |
| 70–79             | 10509/24943 (42.1%) | 20·75 (18·38-23·42)    | <0.0001 | 20·85 (16·40-26·49)  | <0.0001 | 20·75 (18·38-23·42)    | <0.0001 | 15·93 (14·06-18·04)  | <0.0001 |
| ≥80               | 6065/23940 (43.1%)  | 24·85 (21·96-28·12)    | <0.0001 | 24·89 (22·62-36·89)  | <0.0001 | 24·85 (21·96-28·12)    | <0.0001 | 20·67 (18·19-23·48)  | <0.0001 |
| Race or ethnicity |                     |                        |         |                      |         |                        |         |                      |         |
| White             |                     |                        |         |                      |         |                        |         |                      |         |
| Black             |                     |                        |         |                      |         |                        |         |                      |         |
| Mixed             |                     |                        |         |                      |         |                        |         |                      |         |
| Indian            |                     |                        |         |                      |         |                        |         |                      |         |

(Table 2 continues on next page)
of COVID-19 in-hospital mortality with age, male sex, race, and comorbidities. Divergent findings in the health sector analysis included hypertension being associated with COVID-19 in-hospital mortality in the private but not the public sector; a stronger effect of age, sex, race, and comorbidities in the private sector; and a stronger effect of province and month of admission in the public sector, with a significant difference in COVID-19 in-hospital mortality observed only at the peak of the second wave.

When adjusting for age, sex, race or ethnicity, health sector, province, month of admission, non-com municable diseases, and past or current tuberculosis, compared with HIV-negative individuals, people with HIV not on ART were more likely to die in hospital than those on ART; people with HIV with a history of immune suppression (CD4 count <200 cells per μL) were more likely to die in hospital than those with CD4 counts of 200 cells or more per μL; and people with HIV with a history of a viral load of 1000 copies per mL or more were more likely to die in hospital than those with a viral load of less than 1000 copies per mL (table 3).

Among people living with HIV, the prevalence of other comorbidities was 29·2% compared with 30·8% among HIV-uninfected individuals. In a multivariable model adjusting for age, sex, race or ethnicity, HIV (for the non-stratified model on HIV status only), health sector, province, and month of admission, there were increasing odds of COVID-19 in-hospital mortality for individuals with multiple non-HIV comorbidities, irrespective of HIV status (table 4). There was no statistical evidence of interaction between the presence of other multiple comorbidities and HIV infection status on COVID-19 in-hospital mortality (table 4). No interaction was found for individual comorbidities and HIV infection status on COVID-19 in-hospital mortality (appendix p 12).

**Discussion**

Among a large cohort of patients admitted to hospital with SARS-CoV-2 infection in a high HIV and tuberculosis prevalence setting, although age was the strongest
predictor of COVID-19 in-hospital mortality, we found that HIV and tuberculosis were associated with a moderately increased risk of COVID-19 in-hospital mortality, similar to the increased risk associated with other underlying conditions such as diabetes, chronic renal disease, and malignancy in the past 5 years.
Table 3: Effect of ART, CD4 cell count, and HIV viral load on COVID-19 in-hospital mortality among people with HIV admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, South Africa

| ART status | Case fatality ratio (95% CI) unimputed | Case fatality ratio (95% CI) imputed | Unadjusted OR (95% CI) imputed | p value | Adjusted OR (95% CI) imputed* | p value | Adjusted OR (95% CI) imputed* | p value |
|------------|--------------------------------------|-------------------------------------|--------------------------------|---------|-------------------------------|---------|-------------------------------|---------|
| HIV negative | 30.69/132.986 (22.2%) | 23.1% (22.9–23.3) | 1 (ref) | - | 1 (ref) | - | 0.77 (0.72–0.82) | <0.0001 |
| HIV positive on ART | 24.6% (23–25.4) | 0.85 (0.80–0.90) | <0.0001 | 1.20 (1.22–1.39) | <0.0001 | 1.20 (1.22–1.39) | <0.0001 |
| HIV positive not on ART | 28.1% (25.2–31.2) | 0.99 (0.86–1.15) | 0.98 | 1.85 (1.60–2.23) | <0.0001 | 1.45 (1.22–1.72) | <0.0001 |
| CD4 count | | | | | | | | |
| HIV negative | 30.69/132.986 (22.2%) | 23.1% (22.9–23.3) | 1 (ref) | - | 1 (ref) | - | 1.06 (0.93–1.20) | 0.37 |
| HIV positive CD4 count, ≥200 cells per µL | 19.7% (17.2–21.7) | 0.64 (0.57–0.73) | <0.0001 | 0.95 (0.83–1.08) | 0.37 | 1 (ref) | - |
| HIV positive CD4 count, <200 cells per µL | 32.2% (29.9–34.5) | 1.23 (1.09–1.38) | 0.0023 | 2.19 (1.92–2.49) | <0.0001 | 2.31 (1.82–2.93) | <0.0001 |
| Viral load | | | | | | | | |
| HIV negative | 30.69/132.986 (22.2%) | 23.1% (22.9–23.3) | 1 (ref) | - | 1 (ref) | - | 0.83 (0.76–0.90) | 0.0002 |
| HIV positive viral load, <1000 HIV RNA copies per mL | 24.7% (23.0–26.4) | 0.86 (0.78–0.94) | 0.0029 | 1.21 (1.11–1.32) | 0.0002 | 1 (ref) | - |
| HIV positive viral load, ≥1000 HIV RNA copies per mL | 25.2% (21.9–25.9) | 0.85 (0.69–1.05) | 0.23 | 1.88 (1.53–2.31) | <0.0001 | 1.55 (1.20–2.01) | 0.0029 |

Model adjusted for age, sex, race or ethnicity, health sector, province, month of admission, non-communicable comorbidities, and past or current tuberculosis. ART=antiretroviral therapy. OR=odds ratio.
*Output from the same model but with different reference categories to assess the effect of the predictors compared with HIV-uninfected individuals (model 1) or individuals on ART, with high CD4 count, or with low viral load (model 2).

This cohort included 13793 people with HIV and 5282 patients with tuberculosis, and in addition 2312 patients co-infected with SARS-CoV-2, HIV, and tuberculosis. Describing mortality risk among these groups is important because studies have shown that among patients with SARS-CoV-2 infection, those who also had HIV and tuberculosis had altered T-cell functions and were at risk of more severe disease. Large population cohorts from the Western Cape province of South Africa and the UK and more recent meta-analyses found people with HIV to have an increased risk of COVID-19 mortality, with increased in-hospital mortality reported in the Western Cape and UK studies. Our study, however, could not conclude that HIV is a risk factor at the population level.

We describe an increased risk of COVID-19 in-hospital mortality in people with HIV not on ART, with increasing HIV-associated immunosuppression, and with higher viral load, although missing data limited inference. Few studies have explored the effect of the association between ART status, increased immunosuppression, and viraemia on COVID-19 mortality among people with HIV. A Western Cape public sector study found no association with the presence of high viral load or immunosuppression, using latest CD4 cell count and viral load assessment within the past 18 months through linkage with laboratory information systems. This finding could be explained by the fact that our study used a larger dataset over a longer time period, including data from the private sector, and from other provinces with different levels of access to care and treatment and different HIV and tuberculosis burden.

The HIV prevalence in our study was 2-2% in the private sector and 20-4% in the public sector, due to socioeconomic differences in the populations served by each sector. The lower prevalence of HIV (11.7%) in individuals admitted to hospital with SARS-CoV-2 infection in our study, than in the population among adults (19%), is probably because of the under-representation of private sector COVID-19 admissions and possible under-reporting of comorbidities in the public sector.

The prevalence of other comorbidities, including tuberculosis, malignancy in the past 5 years, and chronic cardiac and renal disease, was high among people with HIV included in our analysis. This high prevalence could be due to antiretroviral drugs. For example, tenofovir disoproxil fumarate, which is part of the first-line ART regimen in South Africa, has new or worsening renal failure as one of its side-effects and other antiretroviral drugs have side-effects that include hyperlipidaemia, cardiovascular disease, diabetes, and liver disease. Additionally, because people with HIV who are on ART live longer, the risk of developing non-communicable diseases increases with age. HIV-positive people with immunosuppression are also more likely to develop tuberculosis and HIV-related malignancies. Increasing numbers of comorbidities were associated with increased risk of COVID-19 mortality, possibly because of poorer overall health status, more compromised immunity, and presence of chronic inflammatory state, which could create a pathway for severe COVID-19. The effect was similar in people with HIV and HIV-uninfected individuals.

Age was the strongest predictor of COVID-19 in-hospital mortality, as is reported in meta-analyses. In our cohort, 67% of patients who died were younger than 70 years. A review of 27 countries showed a greater proportion of deaths in low-income and middle-income countries occur at younger age, with people younger...
than 70 years constituting 63% of deaths attributed to COVID-19 in low-income and middle-income countries on average, versus 13% in high-income countries. Lower recovery rates in middle-aged people are thought to be driven by high prevalence of pre-existing conditions in younger people in low-income and middle-income countries, and limited access to hospitals and intensive care. In low-income and middle-income countries, younger people with comorbidities should also be prioritised for vaccination along with older people.

Although increasing age was the strongest predictor, male sex, non-White race, and chronic underlying illness were associated with increased COVID-19 in-hospital mortality in our study population, as reported in meta-analyses. For non-communicable diseases, immune function impairment, severe hypoxaemia, inflammatory activation, and hypercoagulability might be contributory mechanisms for increased mortality. Increased mortality associated with non-White race could be related to burden of infection and prevalence of comorbidities in non-White races. Race as a potential proxy for poverty has been shown in other studies as an additional risk factor for higher COVID-19 in-hospital mortality and has been suggested to be related to structural discrimination towards marginalised populations, translating to inequities in the delivery of care and barriers to accessing care.

The COVID-19 in-hospital mortality rate of 23·3% observed among patients in our analysis was at the upper bounds of the range of 15% and 24% reported in meta-analyses. Observed variation in case fatality ratios at different times during the epidemic and between regions and health sectors might be a result of population demographics and prevalence of comorbidities, varying population levels of COVID-19, changes in admission practices, the severity of illness in admitted cases, limited access to care, higher numbers of admissions overwhelming services, improved care and treatment options as the pandemic progressed, health services' effectiveness, and completeness of death reporting.

The main strengths of this analysis are that DATCOV is nationally representative across all provinces, has 100% coverage of hospitals in the public and private health sector in South Africa, and contains close to 220000 hospital admissions for SARS-CoV-2 infection.

There were several limitations related to the study population and data completeness. Patients with SARS-CoV-2 infection reported to DATCOV had COVID-19 mortality rates similar to those reported in other studies. Although probably a result of high pressure for hospital beds, such individuals would have made up a small proportion of included cases.

Hospitals reported a small number of deaths (219; appendix p 5) from causes other than COVID-19; however, we have little information on the process used by the hospital for classification of cause of death other than that it is done by the attending clinician. It is possible that other deaths reported to DATCOV have not undergone similar review and might have been misclassified as COVID-19 deaths. It is also possible that some COVID-19 admissions have not been reported to the surveillance system.

Patients who were transferred to other hospitals and had no further records of admission, and those still in hospital at the time of the analysis were excluded. We do not know whether the case fatality ratio among excluded patients would differ from that of included patients, possibly introducing biases. However, given the small number of the excluded patients (1-8%), the effect of biases would be limited.
Private-sector hospital admissions are over-represented because of a lower threshold for admission to private hospitals, resulting in similar proportions of patients with COVID-19 admitted to hospitals in the public and private sector even though they serve 84% and 16% of the population, respectively. This might explain why the HIV prevalence in the overall cohort (11.7%) was lower than the population prevalence of HIV in South Africa (14%).

However, HIV prevalence among patients aged 20–59 years admitted to hospitals in the public sector was similar to the population HIV prevalence in this age group (appendix p 9).

Data quality in a surveillance system is dependent on the information submitted by health-care institutions. The data on comorbidities were submitted to DATCOV by the hospital based on information contained in the patient’s written or electronic hospital record, and were not independently verified because there are no systematic information systems that would verify pre-existing comorbidities. We used multiple imputation to address missing data; however, the validity of the imputed data relies on the assumption that data were missing at random. Fields with the highest proportion of incomplete data included race (33.5%) and comorbidities (25.5–32.2%). The level of control of non-communicable diseases such as diabetes, using objective measures such as glycated haemoglobin, was not consistently reported. Other data have shown that individuals with poorly controlled non-communicable diseases were at greater risk of COVID-19 mortality.

The most recent CD4 cell count and viral load results in the past year were submitted by the hospital based on information contained in the patients’ hospital records and not obtained from laboratory information systems. These fields had a high degree of missing data, which is an important limitation given that this analysis focuses on outcomes in people with HIV. Moreover, the hospital did not record the date of the CD4 cell count and viral load tests, so we are not able to calculate the median time between the test and COVID-19 hospital admission, or to be certain that the status of immunosuppression or viraemia had not changed, which might also have introduced measurement bias. It must be noted that DATCOV is a new surveillance system that has not yet been developed to link to other data sources and allow, for example, linkage of laboratory records to the hospital record.

This study confirmed age as the strongest predictor of COVID-19 in-hospital mortality in South Africa, as well as sex, race, and comorbid disease. The demonstration of modest increases in COVID-19 in-hospital mortality for individuals with HIV and tuberculosis (particularly those who were not on ART) are important, given the high prevalence of these diseases in South Africa. People with HIV, particularly those with additional comorbidities, would benefit from COVID-19 prevention programmes such as vaccine prioritisation, as well as early referral and treatment programmes that include prioritising linkage and retention to HIV care, ART adherence, virological suppression, and subsequent immune restoration. The increased case fatality ratio in the public sector, in certain provinces, and during the peaks of the epidemic require further interrogation for resources and support to be directed where they are found to be required, ahead of a possible resurgence of cases.

Contributors
DS, SG, and WJ contributed to the literature search. WJ, MM, and CC contributed to the study design and data collection. WJ, PM, and ST contributed to data analysis, and creation of tables and figures. WJ, ST, PM, and MM verified all the underlying data in the study. WJ, ST, CC, TK, SW, and LB contributed to data interpretation and writing. WJ drafted the manuscript and all other authors contributed scientific inputs equally to drafts of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
Data used in this manuscript are available upon reasonable request to the corresponding author. Individual participant data that underlie the results reported in this Article, after de-identification (test, tables, figures, and appendices), will be shared with investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose. To gain access, data requestors will need to sign a data access agreement. The request will have to be approved by the South African National Department of Health.

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