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Clinical management of COVID-19 in hospitals and the community: A snapshot from a medical insurance database in South Africa

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ABSTRACT

Background: Little is known about the clinical care, use of medicines, and risk factors associated with mortality among the population with private health insurance with COVID-19 in South Africa.
Methods: This was a retrospective cross-sectional study using claims data of patients with confirmed COVID-19. Sociodemographics, comorbidities, severity, concurrent/progressive comorbidity, drug treatment, and outcomes were extracted from administrative data. Univariate and multivariate logistic regression models were used to explore the risk factors associated with in-hospital death.
Results: This study included 154,519 patients with COVID-19; only 24% were categorized as severe because they received in-hospital care. Antibiotic (42.8%) and steroid (30%) use was high in this population. After adjusting for known comorbidities, concurrent/progressive diagnosis of the following conditions were associated with higher in-hospital death odds: acute respiratory distress syndrome (aOR = 1.55; 95% CI = 1.44–1.68), septic shock (aOR = 1.55; 95% CI = 2.00–4.12), pneumonia (aOR = 1.35; 95% CI = 1.24–1.47), acute renal failure (aOR = 2.30; 95% CI = 2.09–2.5), and stroke (aOR = 2.09; 95% CI = 1.75–2.49). The use of antivirals (aOR = 0.47; 95% CI= 0.40–0.54), and/or steroids (aOR = 0.46; 95% CI = 0.43–0.50) were associated with decreased death odds. The use of antibiotics in-hospital was not associated with increased survival (aOR = 0.97; 95% CI = 0.91–1.04).
Conclusions: Comorbidities remain significant risk factors for death mediated by organ failure. The use of antibiotics did not change the odds of death, suggesting inappropriate use.

Introduction

Since the first report of the COVID-19, caused by the novel SARS-CoV-2 in Wuhan, China, in December 2019 (World Health Organization, 2020), there have been 378,460,745 cases and 5,674,493 deaths globally as of February 2, 2022 (Johns Hopkins University of Medicine, 2021).

COVID-19 is a viral respiratory tract infection with clinical manifestations ranging from asymptomatic and mild cases to critical cases. The vast majority of patients develop mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that require oxygen support, and 5% have critical disease that is characterized by complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury (World Health Organization, 2020). Adulthood, male gender, older age, location in urban and deprived areas, and smoking are demographic and lifestyle risk factors for the disease (de Lusignan et al., 2020). Underlying noncommunicable diseases, such as diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immune suppression, and cancer are clinical risk factors for severe disease and death (World Health Organization, 2020).

Mild cases are managed by self-isolation, use of masks, good hygiene practices, and symptomatic treatment such as antipyretics, analgesics, and appropriate rehydration. Antibiotic treatment or prophylaxis is explicitly not recommended. Moderate COVID-19 cases with suspected viral pneumonia are similarly managed; at-risk populations may require hospitalization, and antibiotics are only recommended on clinical suspicion or ideally laboratory confirmation of secondary bacterial infection. Escalation of medical care is recommended where there is clinical deterioration. The management of severe pneumonia in severe COVID-19 requires

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immediate administration of supplemental oxygen, cautious fluid management, and close monitoring for clinical deterioration with appropriate supportive care. Empiric antimicrobial treatment covering all likely pathogens is recommended on the basis of clinical judgment, patient host factors, and local epidemiology. Antimicrobials should be administered as soon as possible (within 1 hour of initial assessment), ideally with blood cultures obtained first and assessed daily thereafter for de-escalation. Noninvasive ventilation is recommended in the first instance for ARDS management in critical COVID-19 cases, followed by advanced oxygen/ventilator support upon acute hypoxemic respiratory failure, and conservative fluid management. The management of septic shock in critical COVID-19 cases requires crystalloid fluid and vasopressors for resuscitation. Antimalarials, antivirals, immunomodulators, and convalescent plasma therapy are explicitly discouraged outside of clinical trials (World Health Organization, 2020). Notwithstanding World Health Organization (WHO) guidance and despite minimal robust evidence to support their use of antivirals (Cao et al., 2020), antimalarials (Touret & de Lamballerie, 2020), and antibiotics (Molina et al., 2020), singly and in combination, are currently being used in the management of COVID-19.

The cumulative number of confirmed COVID-19 cases in South Africa as of September 11, 2021 was 2,858,195. Contrary to global reports of greater risk of disease among males and older people, female incidence per 100,000 persons was higher than that of males, and the 40–59 age group incidence per 100,000 persons was higher than all age groups. There were 90,174 deaths, equating to 3.2% (COVID-19 Weekly Epidemiology Brief, 2021). The country experienced 3 waves,; the first peaking in July 2020, the second in January 2021, and the third is currently underway at the time of reporting (National COVID-19 Daily Report, 2021). The second was predominated by the SARS-CoV-2 501Y.V2 lineage with reportedly higher incidence, hospital admissions, and in-hospital deaths. Patient demographics were also different in that hospitalized individuals were more likely to be older (40–64 years and ≥65 years, compared to <40 years in the first wave) and less likely to have comorbidities (Jassat et al., 2021).

There is minimal information on disease progression, clinical management, and outcomes of patients with COVID-19 in hospitals and the community in South Africa. Thus, we mined the database of the largest public-sector medical insurance scheme in South Africa to analyze the clinical management of COVID-19 in South African private facilities, with a particular emphasis on antimicrobial and steroid therapy in comparison with the latest WHO and the South African National Institute for Communicable Diseases guidelines. We also determined the predictors of mortality in hospitalized patients.

This medical scheme for government employees was established 14 years ago with the intention of improving healthcare coverage to the previously uninsured population and reducing inequities in health coverage. Contributions are income-based, and lower-income earners are fully subsidized by the government. Pensioners are further defaulted to the lowest contribution band irrespective of their income to ensure adequate financial protection.

Methods

This was a retrospective cross-sectional study that used claims data of the medical scheme beneficiaries who are cared for in private facilities in South Africa. All patients with confirmed COVID-19 on the basis of available positive reverse transcriptase-polymerase chain reaction (RT-PCR) results were identified and grouped according to mild-moderate (out-of-hospital care) and severe (in-hospital care) cases. Mild/moderate cases were described as cases that were managed at primary health care facilities; we excluded those who had claims for oxygen. Severe cases were described as cases that were treated in the hospital; criteria for hospital admission is at the discretion of the patient's clinician at the South African private health sector.

Demographics, income levels, clinical, treatment, and preexisting and copresenting medical conditions were extracted from member profiles and compared between survivors and nonsurvivors.

We applied univariate and multivariate logistic regression models to explore the risk factors associated with in-hospital death.

Data analysis was carried out using Microsoft Excel and STATA version 16. A descriptive analysis was performed to assess the distribution of patient clinical and demographic characteristics, medication use, hospital characteristics, and clinical outcomes by survival status (deceased vs survived) and treatment setting (outpatient vs inpatient). Categorical variables were expressed as counts and percentages. Continuous data were expressed as median (interquartile range [IQR]) or mean (standard deviation [SD]). The Mann–Whitney *U* test, independent *t* test, chi-square test, or Fisher exact test were used to evaluate differences between groups, as appropriate. Univariate and multivariate logistic regression models were used to explore the risk factors associated with in-hospital mortality, with 28-day mortality as the dependent variable. All tests were two-tailed, and all *P*-values reported were tested at a $\alpha = 0.05$ level.

Results

The study included 154,519 members of the medical scheme with confirmed SARS-CoV-2 infection, of whom 66% were female. At least 1 comorbidity was present in 29% of the participants. Only 36,893 (24%) were treated in the hospital. A total of 8359 (5.4%) individuals died, and 7596 (91%) of these deaths occurred in-hospital, translating to an in-hospital rate of 21%. The mean age was 54 and 43 years for in-hospital and out-of-hospital groups, respectively. Hospitalization was more common in patients with 1 or more comorbidities (38% vs 18%). Only 18% of patients who were treated out-of-hospital had pneumonia and 0.1% had ARDS. Hospitalized patients had the following diagnosis in addition to COVID-19: ARDS (18%), pneumonia (74%), pulmonary embolism (8%), stroke (2.1%), and acute renal failure (ARF) (11%).

Among the hospitalized patients, 29% (n = 10,607) received oxygen therapy and 18% (n = 6,795) were ventilated. Prescribed medications included antibiotics (43%), antivirals (9%), antifungals (1%), antimalarials (0.4%), and steroids (30%). The steroids were prescribed for all patient categories (i.e., in-hospital [38%] and out-of-hospital [28%]). The use of antimicrobial therapy in patients treated in the community was similar to patients treated in the hospital. (43% vs 44%), antivirals (9% vs 11%), and antifungals (1% vs 2%).

Only 44% of in-hospital and 2% of out-of-hospital patients receiving antibiotics were tested using 1 or more of blood, microscopy, culture and sensitivity (MC&S) tests (Table 2). The antiviral use in 11,000 (73%) patients was associated with chronic antiretroviral medications. For those who were not on the HIV program, antivirals include antiretrovirals (11%), oseltamivir ($n = 1356$, 11%), and acyclovir (3%). Antibiotics used include macrolides, such as azithromycin and erythromycin (28%), combinations of amoxicillin and clavulanic acid, (38%), third-generation cephalosporins (15%), and fluoroquinolones (5%).

Predictors of death among in-hospital patients

We performed univariate logistic regression analyses to investigate possible risk factors associated with COVID-19 in-hospital mortality. We included only the variables that were significantly associated with mortality in the univariate logistic regression in a multivariate logistic regression model (Table 3) where we noted that the risk for in-hospital mortality increased with age (aOR = 1.05; 95% CI = 1.06–1.08), the odds of death were 15% higher in males (aOR = 1.59; 95% CI = 1.08–1.23). Likewise, we found a significant positive association between in-hospital death and comorbidity (diabetes [aOR = 1.19; 95% CI = 1.10–1.27], chronic renal failure [aOR = 1.04; 95% CI = 1.01–1.23], and HIV [aOR = 2.05; 95% CI = 1.79–2.34]). Understandably, patients presenting with concurrent/progressive diagnosis of the following conditions had a higher mortality rate: ARDS (aOR = 1.55; 95% CI = 1.44–1.68), septic shock (aOR = 1.55; 95% CI = 2.00–4.12], pneumonia (aOR = 1.35; 95% CI = 1.24–1.47), concurrent diagnosis with ARF (aOR = 2.30; 95% CI = 2.09–2.5), and stroke (aOR=2.09; 95% CI = 1.75–2.49).

Patients who used antivirals (aOR = 0.47; 95% CI = 0.40–0.54) and/or steroids (aOR = 0.46; 95% = 0.43–0.50] were associated with decreased odds of death. On the other hand, the use of antibiotics in-hospital was not associated with decreased odds of death (aOR = 0.97; 95% CI = 0.91–1.04).

Discussion

Of the 154,519 patients, 24% of patients had appeared to have severe symptoms and were treated in-hospital. Among the hospitalized patients, only 47% were put on oxygen and/or ventilation as per the insurance claim. The lower-than-expected use of oxygen can be ascribed to inappropriate hospitalization induced by clinicians. The in-hospital case fatality rate was 21%, which was higher than the overall South African in-hospital case fatality rate of 11% (Jassat et al., 2021). This is because the population included in the study had better access to testing in the private sector than the rest of the population who accessed testing in the public sector; thus, a more approximate estimation of case fatality rate was achieved.

In the multivariate analysis, we found that the male gender, age, diabetes, HIV, chronic renal failure, and concurrent presentation with heart failure, stroke, pneumonia, and ARDS increased the risk of death. Treatment with antivirals and steroids was associated with reduced mortality. We did not find any significant association between death and income, cancer, coronary artery disease, tuberculosis (TB), and hypertension.

The male gender is thought to be related to severe COVID-19 outcomes due to the overexpression of angiotensin-converting enzyme (ACE) 2 receptors and different immunological responses to the virus (Aggarwal et al., 2020; Li et al., 2020; Yang et al., 2020). However, males are also known not to seek medical help and may typically have undiagnosed or uncontrolled comorbidities, such as HIV and diabetes (Johnson et al., 2015; Kipp et al., 2010).

Similar to British (Chedid et al., 2021; Geretti et al., 2020) and other South African studies (Davies, 2020; Jassat et al., 2020), HIV was associated with increased odds of mortality. However, we noted that the use of antiviral therapy, in which 73% of patients received ART as chronic treatment, was associated with lower mortality. Thus, it is possible that mortality was high in those patients with HIV who chose not to undergo chronic treatment. We did not identify any association between TB and COVID-19 mortality, probably due to the under-representation of TB in these groups because TB is treated in the public sector.

In our study, we found almost double the odds of death in patients with diabetes. This association is hypothesized to be due to coagulation dysfunction, reduced immune response, and inflammatory response, which contribute to increased disease severity. In addition, poor access to routine health care has been associated with severe outcomes in patients with COVID-19 (Gupta et al., 2020). We did not compare outcomes on the basis of the diabetic control of patients.

Our analysis suggests that ARF and stroke are associated with increased odds of mortality. A similar finding in other studies suggests that the cause of death in patients with COVID-19 can be a result of multiorgan failure, which may be a result of increased levels of inflammatory mediators, endothelial dysfunction, coagulation abnormalities, and infiltration of inflammatory cells into the organs (Alessandri et al.; Elezkurtaj et al., 2021; Mokhtari et al., 2020). The etiology of stroke in the majority of patients with COVID-19 has been found to be cryptogenic (undetermined origin) (Ramos-Araque et al., 2021).

Empiric antimicrobial treatment covering all likely pathogens is recommended on the basis of clinical judgment, patient host factors, and local epidemiology. Antimicrobials should be administered as soon as possible (within 1 hour of initial assessment), ideally with blood cultures obtained first and assessed daily thereafter for de-escalation. However, in our study, antibiotic use was very high, and there was little blood culture testing in out-of-hospital settings. Only 2% of mild/moderate cases of COVID-19 treated out-of-hospital had microscopy and blood culture. Contrary to the WHO and South African guidelines which recommended against the use of antibiotics (National institute for Communicable Diseases, 2021), the use of antibiotics was high in this study, even in those who did not have a diagnosis of pneumonia. The antibiotics used were predominately azithromycin and amoxicillin. The inappropriate use of antibiotics in COVID-19 has not been associated with improved outcomes and instead has been associated with increased risk of allergic reaction and antimicrobial resistance (Chedid et al., 2021; Liu et al., 2021). Similar to these studies, the use of empirical antibiotic therapy did not reduce the odds of death in hospitalized cases.

Although the South African guidelines recommended the use of steroids only for patients on oxygen supplementation and ventilation (Chu et al., 2021; National Department of Health, 2020), in this study, we found that steroids were used for patients with COVID-19 who did not meet the aforementioned criteria. The use of steroids was associated with a 45% lower mortality rate in patients treated in the hospital. A meta-analysis suggests that the use of corticosteroids can delay or even prevent mechanical ventilation; however, inappropriate use can result in delayed viral clearance (van Paassen et al., 2020). In our study, prednisone and not dexamethasone was used in 99% of patients (National Deparment of Health, 2020). The high use of steroids in the out-of-hospital setting is concerning. Use of corticosteroids has been associated with delayed viral clearance.

The inappropriate use of steroids and antimicrobial therapy in this group is largely due to healthcare arrangements in South Africa, where clinicians practicing in the private sector have discretion for prescription of medicines, which may be contrary to the national guidelines.

Although TB, hypertension, coronary artery disease, and cancer were associated with increased odds of death in univariate analysis, this was not the case in the multivariate analysis. This is contrary to other South African studies (Jassat et al., 2020) When adjusted for additional risk factors, hypertension alone does not seem to increase the risk of death from COVID-19 (Williamson et al., 2020). The other negative associations could be a result of the small sample. The number of people with TB is underrepresented because most patients with TB receive free treatment from the government (Podestà et al., 2021). The lack of association between CRF and mortality can be a result of high collinearity between diabetes mellitus and CRF.

Unlike other studies (Jung et al., 2021), we found that the level of income was not a driver of mortality in this insured population. To eliminate differences in care, the Minister of Health amended the Medical Schemes Act Regulations to include COVID-19 as a prescribed minimum benefit, gazetting that all health insurances registered with the Council for Medical Schemes in the country cover all individuals irrespective of option plan, contributions, etc (*Medical Schemes Act No.131 OF 1998, Regulations Amendment*, 2020). Therefore, gazetting proequity legislation eliminated the gaps in access to health care. In addition to the legislation, the mandate of this scheme is to eliminate inequities in access to healthcare through efficient age and income cross-subsidies.

Limitations of the study

The study relied on claims data for reimbursement. We did not have access to patient records. The study was also retrospective and cross-sectional, and thus a high risk of misclassification for severity as well as care was possible if the claims were not submitted. Although we have assumed that copresenting conditions are complications of COVID-19, it is difficult to ascertain temporality in retrospective and cross-sectional studies.

Conclusion

The study has shown that comorbidities and concomitant diagnosis with ARF and stroke are associated with a high risk of in-hospital mortality in patients with COVID-19. This highlights the inappropriate use of antibiotics in this medically insurance population. South African clinicians should be encouraged to prescribe antimicrobials on the basis of diagnostic stewardship and only for confirmed secondary bacterial or fungal infections to prevent the unintended consequences of antimicrobial resistance.

Ethical approval statement

Ethical approval was obtained from a subcommittee of the biomedical Research Ethics Committee of the University of KwaZulu Natal (Reference No. BREC/00001589/2020).

Author contributions

Selaelo Mametja: drafting of protocol, study design, interpretation of data, and writing. Sabiha Yusuf Essack: drafting of protocol, literature review, interpretation, and review of the final manuscript. Lundi Matoti and Mabatlo Semenya: data management. Zelalem Getahun: data analysis. Stan Moloabi: conceptualizations of the study, interpretation, and proofreading. Selaelo Mametja, Lundi Matoti, and Zelalem Getahun have accessed and verified the underlying data.

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Declaration of Competing Interest

The authors declare no competing interests.

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