# Comparison of patients with severe COVID-19 admitted to an intensive care unit in South Africa during the first and second wave of the COVID-19 pandemic

**U Lalla,**[1] MB ChB, MMed (Int), FCP (SA), Cert Crit Care (SA) Phys;
**C F N Koegelenberg,**[1] MB ChB, MMed (Int Med), FCP (SA), FRCP (UK), Cert Pulm (SA), PhD;
**B W Allwood,**[1] MB ChB, FCP (SA), Cert Pulm (SA), PhD; **L N Sigwadhi,**[2] MSc (Biostatistics);
**E M Irusen,**[1] MB ChB, FCP (SA), PhD; **A E Zemlin,**[3] MB ChB, FCPath (SA) Chem, MMed (Chem), PhD; **T E Masha,**[4] PhD, MSc, BSc;
**R T Erasmus,**[3] MB BS, FMC Path, FACB, DABCC, DHSM; **Z C Chapanduka,**[5] MB ChB, FCPath (SA) Haem, MBA;
**H Prozesky,**[6] MB ChB, MMed (Int); **J Taljaard,**[6] MB ChB, MMed (Int); **A Parker,**[6] MB ChB, FCP (SA), MMed (Int), Cert ID (SA);
**E H Decloedt,**[7] MB ChB, BSc Hons, FCCP (SA), MMed (Clin Pharm), PhD; **F Retief,**[8] MB ChB, MMed (Anaesth);
**T P Jalavu,**[3] MB ChB, MMed ChemPath, FCPath Chem; **V D Ngah,**[2] BNS, PGD, MScMed; **A Yalew,**[2,9,10] MSc, BSc;
**J L Tamuzi,**[2] MD, MSc, MPH; **N Baines,**[1] BSc; **M McAllister,**[2] MB ChB, MSc; **A Zumla,**[11] PhD, MB ChB, KBE, FRCP, FRCPath, FRSB;
**P S Nyasulu,**[2,12] PhD Epi, MSc Epi, PGDip Epi, ADDV, DipClin Med, MACE; for the COVID-19 Rapid Research Response Collaboration

[1] *Division of Pulmonology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa*
[2] *Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*
[3] *Division of Chemical Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and National Health Laboratory Service (NHLS) Tygerberg Hospital, Cape Town, South Africa*
[4] *Faculty of Health and Wellness Sciences, Peninsula University of Technology Bellville Campus, Cape Town*
[5] *Division of Haematological Pathology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University and NHLS Tygerberg Hospital, Cape Town, South Africa*
[6] *Division of Infectious Diseases, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa*
[7] *Division of Clinical Pharmacology, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa*
[8] *Department of Anaesthesia and Critical Care, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa*
[9] *Department of Statistics, College of Natural and Computational Sciences, Addis Ababa University, Ethiopia*
[10] *National Data Management Centre for Health, Ethiopian Public Health Institute, Addis Ababa, Ethiopia*
[11] *Division of Infection and Immunity, Centre for Clinical Microbiology, University College London, Royal Free Campus, London, UK; NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK*
[12] *Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

***Corresponding author**: P Nyasulu (pnyasulu@sun.ac.za)*

**Background.** The second wave of coronavirus disease 2019 (COVID-19), dominated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Beta variant, has been reported to be associated with increased severity in South Africa (SA).
**Objectives.** To describe and compare clinical characteristics, management and outcomes of COVID-19 patients admitted to an intensive care unit (ICU) in SA during the first and second waves.
**Methods.** In a prospective, single-centre, descriptive study, we compared all patients with severe COVID-19 admitted to ICU during the first and second waves. The primary outcomes assessed were ICU mortality and ICU length of stay (LOS).
**Results.** In 490 patients with comparable ages and comorbidities, no difference in mortality was demonstrated during the second compared with the first wave (65.9% v. 62.5%, $p$=0.57). ICU LOS was longer in the second wave (10 v. 6 days, $p$<0.001). More female admissions (67.1% v. 44.6%, $p$<0.001) and a greater proportion of patients were managed with invasive mechanical ventilation than with non-invasive respiratory support (39.0% v. 14%, $p$<0.001) in the second wave.
**Conclusions.** While clinical characteristics were comparable between the two waves, a higher proportion of patients was invasively ventilated and ICU stay was longer in the second. ICU mortality was unchanged.
**Keywords**. COVID-19; SARS-CoV-2; ICU; waves; management; mortality; clinical characteristics; outcomes.

*Afr J Thoracic Crit Care Med* 2021;27(4):156-162. https://doi.org/10.7196/AJTCCM.2021.v27i4.185

Several countries worldwide have experienced multiple waves of coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In South Africa (SA), the first confirmed case of COVID-19 was reported on 5 March 2020, followed by the first wave of the pandemic that peaked in July 2020. The second wave started in November 2020 and exceeded the peak infection rate of the first wave (240.1/100 000 v. 138.1/100 000).[1]

Globally, patients admitted to an intensive care unit (ICU) in the second wave have been reported to have had a lower case fatality rate and shorter hospital stay than those in the first wave.[2-5] Contrary to other parts of the world, comparative studies of hospitalised and ICU patients in SA reported a higher patient mortality rate during the second wave than the first.[1,6]

The Beta variant was identified as the leading contributor of the rapid rise in infections in the second wave in SA.[7] This SARS-CoV-2 variant has E484K, K417N and N501Y mutations,[8,9] conferring the potential of increased disease severity based on hospitalisations and case fatality rates,[10,11] the potential to be more transmissible than the Alpha variant and the original wild-type Wuhan strain,[11-13] and the ability to escape previously acquired immunity.[14] Local reports have suggested that the increased mortality may potentially be explained by the admission of older individuals to the public sector and the increased health system pressure, with the residual increase in mortality of hospitalised patients related to the Beta lineage.[7]

Despite the increased virulence of the Beta variant, clinical experience gained and rapidly emerging evidence during the first wave may have contributed to improve management and outcomes among critically ill COVID-19 patients hospitalised in the second. However, there is a paucity of evidence to support this hypothesis.

The aim of the present study was to describe and compare the clinical characteristics, management and outcomes of two cohorts of COVID-19 patients admitted to ICU during the first and second waves of the pandemic.

# Methods

## Study population

This prospective, descriptive, cohort study included all patients over 18 years of age with severe COVID-19 admitted to the designated COVID-19 ICU at Tygerberg Hospital during the first two COVID-19 waves in SA: 27 March 2020 to 29 October 2020 (first) and 4 November 2020 to 10 February 2021 (second). Tygerberg Hospital is a 1 380-bed hospital in Cape Town, SA, providing tertiary services to ~3.5 million people from Western Cape Province. The study was approved by the Stellenbosch University Health Research Ethics Committee and the Ethics Research Committee of Tygerberg Hospital (ref. no. N20/04/002_COVID-19), and a waiver of consent was approved. The research project was conducted according to the ethical principles of the Declaration of Helsinki.[15] Patient confidentiality was ensured by labelling data with a unique episode number.

Admission to ICU is contingent on the availability of critical care resources and patients are triaged according to provincial guidelines.[16] Commercially available reverse transcriptase-polymerase chain reaction (RT-PCR) assays using nasopharyngeal swabs or lower respiratory tract aspirates were used to confirm the diagnosis of SARS-CoV-2 infection.

The wave periods were determined from national hospital admission data and 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. The incidence risk of admissions was defined 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).[1,17]

## Data collection

Data including sociodemographic (age, sex) characteristics and pre-existing comorbidities associated with severe COVID-19 (hypertension, diabetes mellitus and hyperlipidaemia) were captured prospectively using photographs of clinical notes at the bedside, which were securely stored electronically. Clinical data were entered remotely by data capturers into a Redcap database. Serum samples were collected on ICU admission from all study participants and analysed in the National health Laboratory Service (NHLS) Chemical Pathology Laboratory on the Roche Cobas 6000 analyser (Roche, Switzerland) according to the manufacturer's recommendations. A Siemens ADVIA 2120i haematology analyser (Siemens Healthcare Diagnostics, Germany) was used to load haematological samples. Biochemical data were imported from the NHLS Laboratory Information System (TrakCare Lab Enterprise) into the database. Data were quality checked by VDN and NB to ensure that data entered were of good quality and reliable.

Lactate dehydrogenase (LDH) was determined enzymatically, C-reactive protein (CRP) was determined immunoturbidimetrically and high-sensitivity troponin T (hs-TnT), *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), procalcitonin (PCT) and glycated haemoglobin (HbA1c) were determined using electrochemiluminescent immunoassay methodology. The pH, partial pressure of oxygen ($PaO_2$), partial pressure of carbon dioxide ($PaCO_2$), standard bicarbonate ($HCO_3$std) and arterial oxygen saturation ($SaO_2$) were recorded from arterial blood gas on ICU admission.

The mode of respiratory support was reported as invasive mechanical ventilation or non-invasive respiratory support which encompassed continuous positive airway pressure and pressure support ventilation (CPAP-PSV) and high-flow nasal oxygen (HFNO). The primary outcomes of interest were the proportion of patients who died in ICU and the days to ICU death or discharge (ICU length of stay (LOS)).

## Statistical analysis

Continuous variables were expressed as the mean with standard deviation for normally distributed data and median with interquartile range for non-normal data. Categorical variables were expressed using frequencies and percentages. Univariate characteristics between the two cohorts, namely the first and second waves, were compared using the $\chi^2$ test for categorical variables and Wilcoxon's rank-sum test for continuous variables. Probability of surviving curves up to 60 days were computed for the first and second waves, and the first and second wave trends were drawn separately. We used 60 days as we had our last event at 61 days to calculate the restricted mean survival time (RMST) for the same truncation time. Cox regression and restricted mean survival time were used. Schoenfeld residuals and the Cox proportional hazards test were used to assess the proportional hazards assumption.

The Kaplan-Meier survival curve was plotted and the log-rank test was used to compare the two groups. Comparisons between the two cohorts with $p<0.05$ were considered statistically significant. All statistical analyses were performed using Stata version 16 (StataCorp., USA) and R version 4.1.0 (R Core Team, Austria) with R Studio V.1.3 (R Studio Team, Austria) statistical software.

# Results

## Clinical and laboratory characteristics

A total of 490 patients were admitted to ICU during the first ($n$=408) and the second ($n$=82) wave. Age and the presence of pre-existing comorbidities were comparable between the cohorts (Table 1). However, significantly more females were admitted during the second wave (67.1% v. 44.6%; $p<0.001$).

A higher admission median $PaO_2$ (8 kPa v. 7.2 kPa; $p=0.015$) and a higher median $PaCO_2$ (5.5 kPa v. 4.8 kPa; $p<0.001$) were observed in the second wave. The median P/F ratio, however, was similar between waves (72 mmHg v. 76 mmHg; $p=0.53$). The median pH (Table 2) was lower during the second wave than the first (7.45 v. 7.47; $p=0.02$) despite a higher median standard bicarbonate during this wave (28.4 mmol/L v. 26.5 mmol/L; $p=0.003$).

The median CRP on admission was significantly lower during the second wave (147 mg/L v. 182 mg/L; $p=0.003$). However, other haematological and biochemical analytes were similar.

## Clinical management

The proportion of patients managed with non-invasive respiratory support (CPAP-PSV or HFNO) was higher in the first wave (61.0% ($n$=50/82) v. 86.0% ($n$=351/408); $p<0.001$), while significantly more patients required invasive mechanical ventilation in the second wave (39.0% ($n$=32/82) v. 14.0% ($n$=57/408); $p<0.001$).

There was less empirical antibiotic (co-amoxiclav, azithromycin, meropenem, vancomycin and colistin) and antiviral (oseltamivir) therapy administered in the second wave compared with the first (18.5% v. 72.1%; $p<0.001$ and 2.5% v. 21.4%; $p<0.001$). No vitamin C was administered (0% v. 58.9%; $p<0.001$) and less thiamine was prescribed in the second wave (6.1% v. 80.1%; $p<0.001$) (Table 1).

## ICU mortality and length of stay

The proportional hazards assumption was met as shown on the Schoenfeld residuals plot (Fig. 1) where the pattern looks around 0 and proportional hazards test shows a $p$-value=0.086. There was no difference in mortality during the second wave compared to the first (65.9% v. 62.5%, $p=0.57$). The median LOS in the ICU (Table 2) during the second wave was 4 days longer than that of the first (6 days v. 10 days, $p<0.001$).

The probability of ICU survival was higher during the second wave than the first ($p=0.0031$) (Fig. 2). The probability of survival of the first 25 days of ICU admission was greater in the second wave than

**Table 1. Comparison of patient demographics, comorbidities and baseline treatment between COVID-19 patients admitted to ICU during the first ($N$=408) and second ($N$=82) waves**

| Variables | First wave ($n$=408), $n$ | Second wave ($n$=82), $n$ | First wave, $n$ (%)* | Second wave, $n$ (%)* | $p$-value |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age at admission (years), median (IQR) | 408 | 82 | 54.1 (45.7 - 61.7) | 53.8 (46.4 - 59.7) | 0.35 |
| Gender: female | 408 | 82 | 182 (44.6) | 55 (67.1) | <0.001 |
| Current smoker | 219 | 54 | 8 (3.7) | 3 (5.6) | 0.79 |
| Comorbidities | | | | | |
| Hypertension | 398 | 68 | 237 (59.5) | 39 (57.4) | 0.73 |
| Asthma | 398 | 68 | 22 (5.5) | 2 (2.9) | 0.55 |
| Diabetes mellitus (type 1 or type 2) | 398 | 68 | 199 (49.9) | 34 (50.0) | 0.98 |
| Ischaemic heart disease | 398 | 68 | 12 (3.0) | 0 (0.0) | 0.15 |
| Hyperlipidaemia | 398 | 68 | 43 (10.8) | 5 (7.4) | 0.39 |
| Immunodeficiency (including HIV) | 398 | 68 | 3 (0.8) | 0 (0.0) | 1 |
| Chronic lung disease | 397 | 67 | 13 (3.3) | 0 (0.0) | 0.23 |
| Chronic kidney disease | 397 | 68 | 19 (4.8) | 0 (0.0) | 0.091 |
| Baseline treatment administered in ICU | | | | | |
| Antibiotics | 387 | 81 | 279 (72.1) | 15 (18.5) | <0.001 |
| Antifungals | 387 | 81 | 4 (1.0) | 1 (1.2) | 0.87 |
| Antivirals | 387 | 81 | 83 (21.4) | 2 (2.5) | <0.001 |
| Anticoagulants | 387 | 81 | 357 (92.2) | 70 (86.4) | 0.092 |
| Corticosteroids | 387 | 81 | 332 (85.8) | 66 (81.5) | 0.32 |
| Vitamin C | 387 | 82 | 228 (58.9) | 0 | <0.001 |
| Thiamine | 387 | 82 | 310 (80.1) | 5 (6.1) | <0.001 |
| Zinc | 387 | 82 | 4 (1.0) | 0 | 1 |
| Losartan | 387 | 82 | 13 (3.4) | 4 (4.9) | 0.51 |
| Simvastatin | 387 | 82 | 53 (13.7) | 7 (8.5) | 0.2 |

ICU = intensive care unit; IQR = interquartile range.
*Unless otherwise specified.

in the first (19% v. 11%). From 26 days onwards, the probability was similar between the two waves. After approximately 37 days of admission to ICU, the probability for survival was worse in the second than in the first wave (6% v. 8%). From 15 days onwards, confidence intervals (CIs) between the two waves began to overlap. Patients in the first wave were 1.53 (95% CI 1.14 - 2.06; $p$=0.0048) times at risk of dying as compared with the second. However, at 60 days, the difference in restricted mean survival time (RMST) was 3.50 days. The point estimate indicated that patients in the second wave, on average, survived 3.50 (95% CI −0.93 - 7.93) days more than those in the first wave when following up the patients for 60 days, and no statistical significance was observed ($p$=0.122).

Although the mortality rate was not statistically different between the two waves, the trends in total mortality differed. During the first wave, total mortality fluctuated, reaching a peak of more than 20 deaths in weeks 13 and 15. In comparison, total mortality was consistent in the second wave, with a peak of 7 deaths in weeks 5 and 12. Similarly, the trend in the median ICU stay differed between waves, remaining constant from week 2 (less than 10 days) in the first wave as compared with the second, where ICU stay oscillated between 9 and 14 days from week 7 to 11.

## Discussion

We described the first comparative data from a low- to middle-income (LMIC) environment and demonstrated no significant difference in mortality between the first and second waves of the COVID-19 pandemic. However, the second wave was associated with significantly longer ICU stay. This could be explained by the higher percentage of intubated patients in the second wave, which may reflect a proxy of selection bias (delayed referral owing to less ICU capacity).

Our findings are consistent with studies conducted in France and the French West Indies that reported no significant difference between the two waves.[18,19] In contrast, two other studies conducted in SA and Greece reported a higher mortality rate [1,20] and a further study reported a lower mortality rate for the second wave as opposed to the first.[3] Our comparable mortality rate between the two waves may have been influenced by the adoption of COVID-19 evidence-based therapies in the ICU during the second wave, reflecting current literature.[21] Furthermore, varying centre-specific management protocols may have contributed to discrepancies seen in the mortality rates reported. In April 2020, our ICU changed its standard operating protocol from the initially recommended 'early intubation and ventilation' to the use of HFNO to avoid intubation if possible.[22] Hence, during the first wave, HFNO and mechanical ventilation were offered as respiratory support

**Table 2. Comparison of patient arterial blood gases, biochemical data and outcome of COVID-19 patients admitted to the ICU during the first ($N$=408) and second ($N$=82) waves**

| Variables | First wave ($n$=408), $n$ | Second wave ($n$=82), $n$ | First wave, $n$ (%)* | Second wave, $n$ (%)* | $p$-value |
|---|---|---|---|---|---|
| Arterial blood gases, median (IQR) | | | | | |
| pH | 391 | 82 | 7.47 (7.41 - 7.5) | 7.45 (7.39 - 7.49) | 0.02 |
| $PaO_2$ (kPa) | 391 | 82 | 7.2 (6 - 8.9) | 8 (6.8 - 8.8) | 0.015 |
| $PaCO_2$ (kPa) | 391 | 82 | 4.8 (4.3 - 5.5) | 5.5 (4.9 - 6.3) | <0.001 |
| $HCO_3$std | 368 | 49 | 26.55 (23.9 - 28.65) | 28.4 (25.6 - 29.9) | 0.003 |
| $SaO_2$ | 380 | 82 | 89 (82 - 94) | 91 (88 - 93) | 0.053 |
| P/F ratio (mmHg) | 388 | 82 | 76.036 (54 - 114.69) | 72.68 (56.25 - 96) | 0.53 |
| Baseline biochemical data on ICU admission | | | | | |
| *D*-dimer | 396 | 68 | 1.06 (0.46 - 4.35) | 1.03 (0.42 - 3.91) | 0.43 |
| Platelets | 406 | 76 | 295.5 (221 - 376) | 309 (240 - 383) | 0.42 |
| Neutrophils | 405 | 75 | 9.38 (6.89 - 12.36) | 9.21 (6.82 - 13.41) | 0.81 |
| Lymphocytes | 405 | 74 | 0.94 (0.63 - 1.29) | 0.93 (0.72 - 1.36 | 0.48 |
| hs-TnT | 361 | 58 | 14 (9 - 33) | 13 (6 - 27) | 0.19 |
| HbA1c | 302 | 72 | 6.7 (6.2 - 9.3) | 7.6 (6.3 - 8.8) | 0.22 |
| NT-proBNP | 366 | 54 | 352 (100 - 1 223) | 220 (102 - 845) | 0.28 |
| CRP | 401 | 73 | 182 (117 - 282) | 147 (96 - 221) | 0.003 |
| PCT | 399 | 70 | 0.44 (0.19 - 1.09) | 0.36 (0.13 - 1.12) | 0.19 |
| Serum creatinine | 406 | 76 | 77 (63 - 108) | 73.5 (64.5 - 99) | 0.660 |
| Neutrophil to lymphocyte ratio | 405 | 75 | 9.45 (6.24 - 16.24) | 8.69 (6.41 - 16.05) | 0.62 |
| Outcome in the ICU | | | | | |
| Non-invasive respiratory support | 408 | 82 | 351 (86.0) | 50 (61.0) | <0.001 |
| Time to ICU from admission, days | 408 | 82 | 1 (0 - 2) | 1 (0 - 3) | 0.15 |
| Length of ICU stay, days | 408 | 82 | 6 (3 - 10) | 10 (5 - 14) | <0.001 |
| Total hospital admission, days | 408 | 82 | 9 (6 - 14) | 12 (8 - 17) | 0.001 |
| Overall ICU mortality, $n$ (%) | 408 | 82 | 255 (62.5%) | 54 (65.9%) | 0.57 |

$PaO_2$ = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide; $HCO_3$std = standard bicarbonate; $SaO_2$ = arterial oxygen saturation; P/F ratio = arterial partial pressure of oxygen (mmHg)/inspired oxygen concentration; hs-TnT = high sensitivity troponin T; HbA1c = glycated haemoglobin; NT-proBNP = *N*-terminal pro-B-type natriuretic peptide; CRP = C-reactive protein; PCT = procalcitonin.
*Unless otherwise specified.

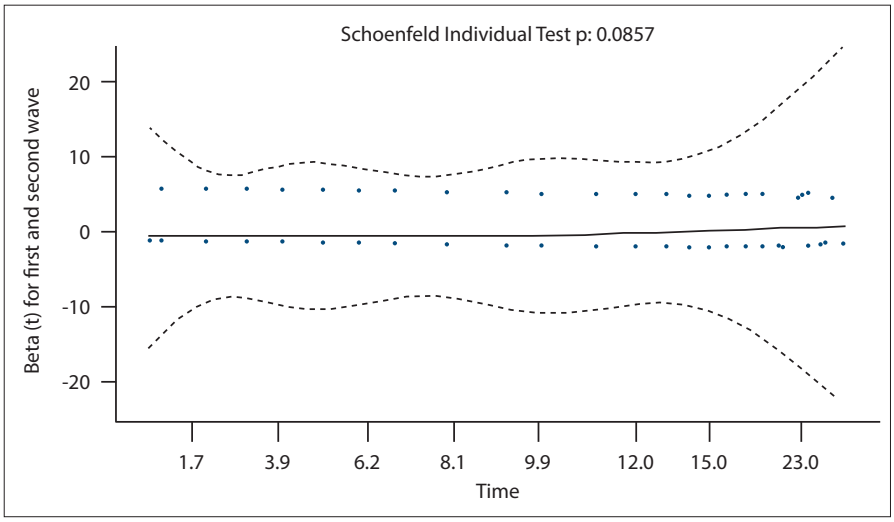


*Fig. 1. Assessing proportional hazards function using Schoenfeld residuals.*

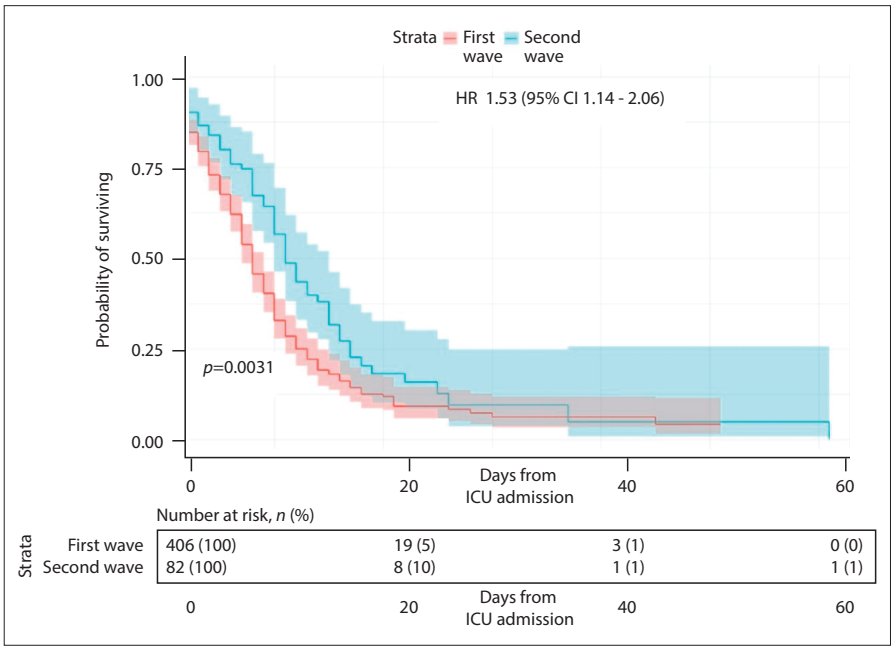


*Fig. 2. Probability of survival curve of COVID-19 patients admitted in the ICU: first v. second wave. (HR = hazard ratio.)*

in our ICU whereas, during the second wave, the cohort predominantly comprised patients requiring invasive mechanical ventilation. This practice may, additionally, provide a plausible explanation for the significantly increased length of ICU stay observed in the second wave. In other centres, during the second wave, patients were more often treated with non-invasive mechanical ventilation and corticosteroids, and less often with invasive mechanical ventilation, conventional oxygen therapy and anticoagulants.[3,7]

We observed an increased proportion of female patients admitted to ICU during the SARS-CoV-2 second wave. This sex-specific COVID-19 severity distribution contrasted with a systematic review of nine studies with a total of 2 025 critical COVID-19 cases showing a male predominance toward greater severity and mortality risks.[23] Possible explanations for the lower case fatality risk observed in males during the second wave may include changes in case demographic characteristics owing to the new variant. Evidence suggests that variants of concern occurred more frequently in younger adults, healthier individuals, infants and pregnant or postpartum women.[3]

We did not observe significant biochemical differences between the two waves, despite the Beta variant's potential for more severe disease.[10,11] A recent study describing 56 of our ICU patients in the first wave reported that the presence of an alkalaemia in most patients and a higher pH was associated with survival.[24] In the present study, although the median $HCO_3$std was significantly higher during the second wave, the median pH was significantly lower. In addition, the median CRP, a nonspecific acute-phase biomarker and inflammatory protein, was statistically lower in the second wave. The clinical significance of these findings remains unclear and may reflect, in part, more astute triage decisions made in the second wave and the revision of the ICU admission protocol during this period. Lastly, although a higher initial median $PaO_2$ was demonstrated in the second wave, both cohorts had similar P/F ratios in keeping with severe acute respiratory distress syndrome. A plausible explanation for this finding may be that the P/F ratio remains a highly variable parameter which depends on the fraction of inspired oxygen and the ventilator strategy utilised. However, the P/F ratio remains an independent risk factor of mortality for COVID-19 patients.[25,26]

Our study clearly demonstrates the evolution of the COVID-19 pharmacological protocols in our ICU over time. In the first wave, prior to robust evidence for or against use in COVID-19, management included the prescription of empirical antibiotics (meropenem, vancomycin, co-amoxiclav, azithromycin and colistin), antiviral (e.g., oseltamivir), and adjunctive therapies including vitamin C and thiamine. A systematic review of 30 studies including 3 834 patients did not support the routine use of antibiotics in the management of confirmed COVID-19 infection.[27] Of concern, combination antibiotic therapy may predispose COVID-19 patients to secondary infections[28,29] with most pathogenic organisms found in COVID-19 patients being multidrug-resistant (MDR) nosocomial organisms.[30] Adjunctive therapy with vitamin C and thiamine is currently not routinely advised in the management of severe COVID-19, with the former having no proven efficacy against the disease.[31,32]

Almost five times more patients were admitted to ICU in the first wave than in the second. This does not reflect a lower burden of critical illness in the second wave,

but rather resource constraints associated with critical care services. During the first wave, there was a fourfold increase in the number of critical care beds, enabled by the near-complete de-escalation of non-COVID-19 services to emergency services. Furthermore, stringent national restrictions resulted in a significant reduction in the demand for non-COVID-19 critical care capacity. The relaxation of these measures during the second wave was accompanied by the need to accommodate the usual non-COVID-19 burden, limiting resources available to patients with COVID-19 requiring critical care. Further explanations for this striking difference may be the shorter duration of the second wave and the accompanying longer ICU stay, limiting the overall number of patients admitted to ICU.

The consistency of patient age and comorbid disease as well as COVID-19 disease severity between both waves is a strength of the present study, making outcomes comparable between the waves. The prospective design and performance in the same ICU environment with the same team of intensivists over both periods, could potentially be considered an additional strength. Furthermore, we utilised corticosteroids very early in the first wave.

Limitations of our study include the sample size in the second wave compared with the first and the single-centre nature of the study. Moreover, not all variables were available for all patients and 'obesity' was based on clinical impression rather than formal measurements. Furthermore, routine subtyping (Beta v. wild type) during either wave was not accessible and some patients during the first wave may have been infected with the Beta variant. Additional limitations include the difference in ICU capacity during the two waves and the fact that only the highest form of respiratory support was captured and analysed.

## Conclusion

While clinical characteristics were comparable between the two waves, a higher proportion of patients were invasively ventilated and ICU stay was longer in the second. ICU mortality was unchanged. Our results also clearly demonstrate that the management of COVID-19 patients in the ICU differed between the two waves. As more evidence-based therapies became available, drugs that lacked evidence of efficacy in the management of severe COVID-19 patients were used less frequently in the second wave.

**Declaration.** None.

**Acknowledgements.** Professor Alimuddin Zumla is Co-principal Investigator of PANDORA-ID-NET, the Pan-African Network for Rapid Research, Response, Relief and Preparedness for Infectious Disease Epidemics, supported by the European and Developing Countries Clinical Trials Partnership (EDCTP). He is in receipt of a UK National Institutes of Health Research, Senior Investigator Award and is a Mahathir Foundation Science Award laureate.

**Author contributions.** PSN: project initiation and coordination. PSN, UL, BA and CFK: study design. VDN, NB, AZ and LNS: data acquisition. LNS and AY: statistical analyses. UL, CFK PSN, JLT and LNS: drafting of manuscript. EI, AEZ, TEM, RTE, ZCC, HP, JT, AP, EHD, FR, TRJ, VDN, AY, JLT, NB, MMA, AZ and PSN: reviewed and revised the manuscript. All authors read and approved the final manuscript.

**Funding.** This work was carried out under the COVID-19 Africa Rapid Grant Fund supported under the auspices of the Science Granting Councils Initiative in Sub-Saharan Africa (SGCI) and administered by South Africa's National Research Foundation (NRF) in collaboration with Canada's International Development Research Centre (IDRC), the Swedish International Development Cooperation Agency (Sida), South Africa's Department of Science and Innovation (DSI), the Fonds de Recherche du Québec (FRQ), the United Kingdom's Department of International Development (DFID), United Kingdom Research and Innovation (UKRI) through the Newton Fund, and the SGCI participating councils across 15 countries in sub-Saharan Africa.

**Conflicts of interest.** None.

1. Jassat W, Mudara C, Ozougwu L, et al. Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: A cohort study. Lancet Glob Health 2021;9:e1216-1225https://doi.org/10.1016/S2214-109X(21)00289-8
2. -Fan G, Yang Z, Lin Q, Zhao S, Yang L, He D. Decreased case fatality rate of COVID-19 in the second wave: A study in 53 countries or regions. Transbound Emerg Dis 2021;68(2):213-215. https://doi.org/10.1111/tbed.13819
3. Iftimie S, López-Azcona AF, Vallverdú I, et al. First and second waves of coronavirus disease-19: A comparative study in hospitalised patients in Reus, Spain. PLoS One 2021;16(3):e0248029.https://doi.org/10.1371/journal.pone.0248029
4. Karagiannidis C, Windisch W, McAuley DF, Welte T, Busse R. Major differences in ICU admissions during the first and second COVID-19 wave in Germany. Lancet Respir Med 2021;9(5):e47-e48. https://doi.org/10.1016/s2213-2600(21)00101-6
5. Saito S, Asai Y, Matsunaga N, et al. First and second COVID-19 waves in Japan: A comparison of disease severity and characteristics. J Infect 2021;82(4):84-123. https://doi.org/10.1016%2Fj.jinf.2020.10.033
6. Maslo CI, Messina A, Laubscher A, et al. COVID-19: A comparative study of severity of patients hospitalised during the first and the second wave in South Africa, 2021. medRxiv https://doi.org/10.1101/2021.05.11.21257033
7. Jassat W, Mudara C, Ozougwu L, et al. Increased mortality among individuals hospitalised with COVID-19 during the second wave in South Africa, 2021. Lancet Glob Health 2021;9(9):e1216-e1225. https://doi.org/10.1016/S2214-109X(21)00289-8
8. Khateeb J, Li Y, Zhang H. Emerging SARS-CoV-2 variants of concern and potential intervention approaches. Crit Care 2021;25(1):244. https://doi.org/10.1186/s13054-021-03662-x
9. Tegally H, Wilkinson E, Giovanetti M, et al. Detection of a SARS-CoV-2 variant of concern in South Africa. Nature 2021;592(7854):438-443. https://doi.org/10.1038/s41586-021-03402-9
10. Horby P, Huntley C, Davies N, et al. NERVTAG note on B.1.1.7 severity. New & Emerging Threats Advisory Group, 2021. https://www.gov.uk/government/publications/nervtag-note-on-b117-severity-20-january-2021 (accessed 19 October 2021).
11. Centers for Disease Control. SARS-CoV-2 Variant Classifications and Definitions. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (accessed 19 October 2021).
12. American Society of Microbiology. How dangerous is the Delta variant (B.1.617.2)? https://asm.org/Articles/2021/July/How-Dangerous-is-the-Delta-Variant-B-1-617-2
13. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England, 2020. medRxiv. https://doi.org/10.1126/science.abg3055
14. Are EB, Colijn CB. Projected spread of COVID-19's second wave in South Africa under different levels of lockdown 2021. medRxiv https://doi.org/10.1101/2021.01.22.21250308
15. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191-2194. https://doi.org/10.1001/jama.2013.281053
16. Critical Care Society of Southern Africa. Allocation of scarce critical care resources during the COVID-19 pandemic health emergency in South Africa. 2020. https://criticalcare.org.za/covid-9/ (accessed 28 July 2021).
17. Statistics South Africa. SADHS: South African Demographic and Health Survey 2016: Key Indicator Report. 2016. statssa.gov.za/publications/Report%2003-00-09/Report%2003-00-092016.pdf (accessed 19 October 2021).
18. Contou D, Fraissé M, Pajot O, Tirolien J-A, Mentec H, Plantefève G. Comparison between first and second wave among critically ill COVID-19 patients admitted to a French ICU: No prognostic improvement during the second wave? Crit Care 2021;25(1):3. https://doi.org/10.1186/s13054-020-03449-6
19. Pommier JD, Martino F, Bleakley K, et al. A tale of a two waves epidemic: Characteristics and mortality risk factors for COVID-19 ICU patients in the French West Indies. J Biol Today's World 2021;10(3):1-6.

20. Chalkias A, Pantazopoulos I, Papagiannakis N, et al. Clinical course and outcomes of critically ill COVID-19 patients in two successive pandemic waves. medRxiv. https://doi.org/10.1101/2021.02.26.21251848
21. World Health Organization. COVID-19 Clinical management: living guidance, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1 (accessed 19 October 2021).
22. Lalla U, Allwood BW, Louw EH, et al. The utility of high-flow nasal cannula oxygen therapy in the management of respiratory failure secondary to COVID-19 pneumonia. S Afr Med J 2020;110(6):432. https://doi.org/10.7196%2FSAMJ.2020.v110i6.14882
23. Galbadage T, Peterson BM, Awada J, et al. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. Front Med (Lausanne) 2020;7:348. https://doi.org/10.3389%2Ffmed.2020.00348
24. Bezuidenhout MC, Wiese OJ, Moodley D, et al. Correlating arterial blood gas, acid-base and blood pressure abnormalities with outcomes in COVID-19 intensive care patients. Ann Clin Biochem 2021;58(2):95-101. https://doi.org/10.1177/0004563220972539
25. Santus P, Radovanovic D, Saderi L, et al. Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: A prospective observational multicentre study. BMJ Open 2020;10(10): e043651. https://doi.org/10.1136/bmjopen-2020-043651
26. Gu Y, Wang D, Chen C, et al. $PaO_2/FiO_2$ and IL-6 are risk factors of mortality for intensive care COVID-19 patients. Sci Rep 2021;11(1):7334. https://doi.org/10.1038/s41598-021-86676-3
27. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: A systematic review and meta-analysis. J Infect 2020;81(2):266-275. https://doi.org/10.1016/j.jinf.2020.05.046
28. Castle A. Secondary infections may increase morbidity and mortality in COVID-19 patients. Massachusetts Gen Hosp. 5 May 2020. https://advances.massgeneral.org/research-and-innovation/article.aspx?id=1193 (accessed 19 October 2021).
29. Khurana S, Singh P, Sharad N, et al. Profile of co-infections & secondary infections in COVID-19 patients at a dedicated COVID-19 facility of a tertiary care Indian hospital: Implication on antimicrobial resistance. Ind J Med Microbiol 2021;39(2):147-153. https://doi.org/10.1016/j.ijmmb.2020.10.014
30. Moolla MS, Reddy K, Fwemba I, et al. Bacterial infection, antibiotic use and COVID-19: Lessons from the intensive care unit. S Afr Med J 2021;111(6):575-581. https://doi.org/10.7196/SAMJ.2021.v111i6.15590
31. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, et al. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: A randomised open-label clinical trial. Eur J Med Res 2021;26(1):20. https://doi.org/10.1186/s40001-021-00490-1
32. Al Sulaiman K, Aljuhani O, Saleh KB, et al. Ascorbic acid as an adjunctive therapy in critically ill patients with COVID-19: A propensity score matched study. Sci Rep 2021 24;11(1):19433. https://doi.org/10.1038/s41598-021-96703-y

*Accepted 25 November 2021.*