Outcomes of patients with COVID-19 acute respiratory distress syndrome requiring invasive mechanical ventilation admitted to an intensive care unit in South Africa

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Background. Up to 32% of patients with COVID-19 pneumonia may require intensive care unit (ICU) admission or mechanical ventilation. Data from low- and middle-income countries on COVID-19 acute respiratory distress syndrome (ARDS) are limited. Groote Schuur Hospital in Cape Town, South Africa, expanded its intensive care service to support patients with COVID-19 ARDS requiring invasive mechanical ventilation (IMV).
Objectives. To report on patients' characteristics and outcomes from the first two pandemic waves.
Methods. All patients with COVID-19 ARDS admitted to the ICU for IMV were included in this prospective cohort study. Data were collected from 5 April 2020 to 5 April 2021.
Results. Over the 12-month study period, 461 patients were admitted to the designated COVID-19 ICU. Of these, 380 met the study criteria and 377 had confirmed hospital discharge outcomes. The median (range) age of patients was 51 (17 - 71) years, 50.5% were female, and the median (interquartile range (IQR)) body mass index was 32 (28 - 38) kg/m^2. The median (IQR) arterial oxygen partial pressure to fractional inspired oxygen (P/F) ratio was 97 (71 - 128) after IMV was initiated. Comorbidities included diabetes (47.6%), hypertension (46.3%) and HIV infection (10.5%). Of the patients admitted, 30.8% survived to hospital discharge with a median (IQR) ICU length of stay of 19.5 (9 - 36) days. Predictors of mortality after adjusting for confounders were male sex (odds ratio (OR) 1.74), increasing age (OR 1.04) and higher Sequential Organ Failure Assessment (SOFA) score (OR 1.29).
Conclusions. In a resource-limited environment, the provision of IMV support in the ICU achieved 30.8% hospital survival in patients with COVID-19 ARDS. The ability to predict survival remains difficult given this complex disease.

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It is estimated that 5 - 32% of patients hospitalised with severe COVID-19 require intensive care unit (ICU) admission or mechanical ventilation.[1,2] Identification of prognostic factors in critically ill patients with COVID-19 is vital to guide decision-making, especially in resource-constrained environments with limited ability to expand critical care capacity. Ethical allocation of resources with early effective triaging of patients is dependent on local data to ensure equitable and appropriate admission to critical care services.

Information on the clinical characteristics and outcomes of COVID-19 patients requiring ICU admission in low- and middle-income countries (LMICs) is limited.[3] Several countries in Asia, Europe and North and South America have published mortality outcomes ranging from 16.2% to 94%[4-6] for patients with COVID-19 acute respiratory distress syndrome (ARDS) admitted to the ICU for invasive mechanical ventilation (IMV). In South Africa (SA), a middle-income country, >1.55 million cases of COVID-19 had been confirmed over two pandemic waves, with nearly 53 000 deaths, as of 5 April 2021.[7]

Objectives

To describe the clinical characteristics, course and outcomes of critically ill patients with COVID-19 ARDS admitted to the ICU for IMV at Groote Schuur Hospital (GSH), Cape Town, SA, during the first two waves of the COVID-19 pandemic. GSH is a 991-bed, public sector tertiary-level teaching hospital affiliated to the University of Cape Town.

Methods

Study design, population and time frame

This was a prospective, single-centre cohort study of all patients with laboratory-confirmed SARS-CoV-2 pneumonia and ARDS who were intubated and received IMV. Patients admitted to the ICU between 5 April 2020 and 5 April 2021 were entered into the study. This period covers the first and second waves of the COVID-19 pandemic in SA.

As per the hospital response plan, admission to the COVID-19 ICU was only for intubated patients requiring IMV. Standard hospital wards were repurposed to provide supplemental oxygen, including high-flow nasal oxygen (HFNO), outside of the ICU.

COVID-19 ICU bed capacity was dynamic and expanded to accommodate extra patients as needed. At maximum capacity, 43 COVID-19 ICU beds were managed by 3 intensivist-led ICU teams, with 2 registered nurses and 2 nursing assistants allocated to each 6-bed patient cluster. A regional ICU triage tool was in effect prior to the first wave (Appendix 1, available online at http://samj.org.za/public/sup/16115.pdf).

COVID-19 ARDS was defined as a positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction assay of a nasopharyngeal swab or tracheal aspirate as per World Health Organization guidelines[8] in a patient with primary ARDS meeting the Berlin criteria[9] with an arterial oxygen partial pressure to fractional inspired oxygen (P/F) ratio of <300 measured on day 1 of ICU admission.

Ethics approval for this study was granted by the University of Cape Town Human Research Ethics Committee (ref. no. 362/2020). Consent was obtained for survivors and waived for patients who died.

Data collection

Patient clinical and outcome data were collected prospectively from 5 April 2020 to 5 April 2021. Data were collected on the daily ward round and from the electronic laboratory and radiological systems.

Data were captured for all patients admitted, and no imputation was conducted for missing variables. Data were entered on an anonymised and password-protected database. Comparisons between groups were performed using appropriate parametric and non-parametric analyses, and stepwise multivariate logistic regression modelling was performed to identify predictors of mortality. Data analysis was conducted using GraphPad Prism for Mac V9.02 (Apple, USA; www.graphpad.com). Data are presented using descriptive statistics.

Results

A total of 461 patients were admitted to the COVID-19 ICU service for IMV, of whom 32 did not meet the criteria for laboratory-confirmed SARS-CoV-2 infection, 23 did not meet the criteria for ARDS, and 26 were admitted with an alternative primary diagnosis and found to have coincidental SARS-CoV-2 infection. These patients were excluded from the study. Data from all 380 patients with confirmed COVID-19 ARDS were included in the final analysis (Fig. 1).

The demographics, clinical characteristics and outcomes of all COVID-19 ARDS patients are shown in Table 1. The median (interquartile range (IQR)) patient age was 51 (43 - 58) years, with a range of 17 - 71 years. Comorbidities were common, with nearly 80% of patients having at least one comorbid condition, the most frequent being diabetes mellitus (47.6%) and hypertension (46.3%). Obesity was common (62.6%), with a median (IQR) body mass index (BMI) of 32 (28 - 38) kg/m^2. Over 75% of female patients were obese, with a median BMI of 35 kg/m^2 compared with 29 kg/m^2 for males (p<0.001) (not shown in the table). Forty patients (10.5%) had HIV co-infection, with generally preserved CD4 counts (median (IQR) 258 (166.8 - 440) cells/μL). Male and female patients were similar in baseline characteristics, except for BMI.

Of the 380 patients, 3 were still in the ICU at the time of data analysis; of the 377 patients with known hospital outcomes, there

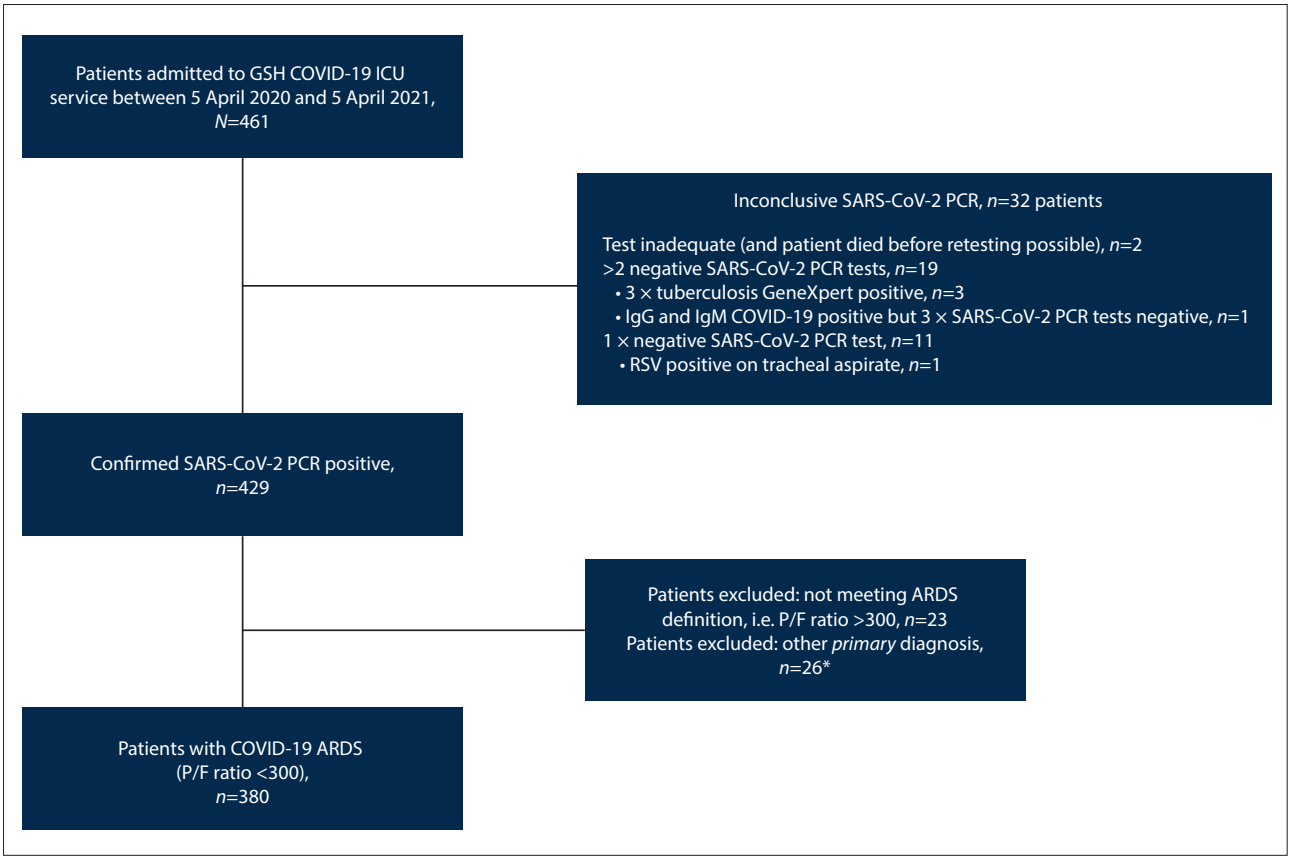

*Fig. 1. Consort diagram of patient inclusion and analysis. (ICU = intensive care unit; PCR = polymerase chain reaction; RSV = respiratory syncytial virus; ARDS = acute respiratory distress syndrome; P/F ratio = arterial oxygen partial pressure to fractional inspired oxygen ratio; *26 diagnoses: 3 × patients with multiple thoracoabdominal gunshot wounds; 2 × ethyl glycol poisoning with acute kidney injury; necrotising fasciitis of groin; bowel obstruction and septic shock; pituitary macroadenoma with acute hydrocephalus; gunshot head injury; thoracoabdominal polytrauma after motor vehicle accident; perforated diverticulitis with septic shock; penetrating head injury; lupus nephritis with septic shock, acute kidney injury and pulmonary oedema; mucormycosis; subarachnoid haemorrhage from mycotic aneurysm secondary to infective endocarditis; diabetic ketoacidosis in septic shock; stabbed heart injury; rheumatic heart disease admitted for valve replacement; 2 × acute severe pancreatitis; severe polytrauma after pedestrian-vehicle accident; gunshot wound to the chest; lymphoma in septic shock with acute kidney injury; penetrating neck injury; 2 × acute psychosis.)*

Table 1. Clinical and laboratory characteristics of patients admitted with severe COVID-19 ARDS to the ICU at Groote Schuur Hospital, Cape Town

	All patients	Survivors	Non-survivors	*p*-value
Patients, *n* (%)	377 (100)	116 (30.8)	261 (69.2)	
Age (years), median (IQR)	51 (43 - 58)	48 (40 - 55)	53 (45.5 - 59)	<0.001*
Sex, *n* (%)				
Male	185 (49.5)	44 (37.9)	141 (54.0)	
Female	192 (50.5)	72 (62.1)	120 (46.0)	0.005
Peripartum	25 (13.0)	12 (16.7)	13 (10.8)	
Non-peripartum	167 (87.0)	60 (83.3)	107 (89.2)	0.002*
Comorbidities				
None, *n* (%)	69 (18.3)	22 (19.0)	47 (18.0)	0.885
Hypertension, *n* (%)	176 (46.3)	51 (44.0)	125 (47.9)	0.504
DM, *n* (%)	181 (47.6)	47 (40.5)	134 (51.3)	0.580
HbA1c (%) in known DM, median (IQR)	9.5 (7.1 - 11.8)	9.8 (6.8 - 12.4)	9.4 (7.3 - 11.7)	0.599
HIV infected, *n* (%)	40 (10.5)	9 (7.8)	31 (11.8)	0.280
CD4 count (cells/μL), (median, IQR)	258 (166.8 - 440)	278 (125 - 562)	249 (164 - 452)	0.886
BMI (kg/m^2), median (IQR)	32 (28 - 38)	33 (28 - 38.8)	31 (27.5 - 38)	0.296
Symptom onset to ICU admission (days), median (IQR)	9 (7 - 14)	8 (6 - 11)	10 (7 - 15)	0.002*
ICU length of stay (days), median (IQR)	10 (5 - 20)	19.5 (9 - 36)	7 (3 - 14)	<0.001*
Respiratory therapy prior to ICU admission, *n* (%)				0.412
HFNO	299 (79.3)	89 (76.7)	210 (80.5)	
Non-HFNO	78 (20.5)	27 (23.3)	51 (19.5)	
Day 1 SOFA score, median (IQR)	4 (4 - 7)	4 (3 - 5)	5 (4 - 8)	<0.001*
Day 1 P/F ratio, median (IQR)	97 (71 - 128)	109 (81 - 145)	90 (69 - 121)	<0.001*
Admission laboratory results† (median, IQR)				
Creatinine (μmol/L)	85.5 (66 - 109)	79.5 (60.3 - 109)	87 (68.5 - 109)	0.091*
WCC (× 10^9/L)	9.4 (7.0 - 14.4)	10.3 (7.5 - 15.7)	9.5 (7.3 - 14)	0.133*
Lymphocyte count (× 10^9/L)	1.2 (0.9 - 1.8)	1.37 (1 - 2)	1.2 (0.9 - 1.6)	0.092*
Platelet count (× 10^9/L)	248 (188 - 322)	251 (195 - 326)	244 (188 - 321)	0.490*
CRP (mg/L)	145 (76 - 260)	175 (98 - 258)	161 (86 - 279)	0.765*
D-dimers (mg/L)	0.67 (0.40 - 2.23)	0.7 (0.47 - 1.65)	0.76 (0.42 - 2.43)	0.994*
HbA1c (%)	6.8 (6.2 - 9.7)	6.5 (6 - 9.3)	6.9 (6.3 - 10.1)	0.009*
Additional ICU therapy, *n* (%)				
Vasopressor support	244 (64.2)	44 (37.9)	197 (75.5)	<0.001*
Renal replacement therapy	57 (15.0)	10 (8.6)	45 (17.2)	<0.001*
VV-ECMO	6 (1.6)	3 (2.6)	3 (1.2)	0.377*
Tracheostomy	78 (20.5)	53 (45.7)	25 (9.6)	<0.001*

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; DM = diabetes mellitus; BMI = body mass index; HFNO = high-flow nasal oxygen; SOFA = Sequential Organ Failure Assessment; P/F ratio = arterial oxygen partial pressure to fractional inspired oxygen ratio; WCC = white cell count; CRP = C-reactive protein; HbA1c = glycated haemoglobin; VV-ECMO = venovenous extracorporeal membrane oxygenation.
*All *p*-values <0.005 were considered significant.
†On presentation to hospital.

were 116 survivors (30.8%). Survivors had a median (IQR) age of 48 (40 - 55) years v. 53 (45.5 - 59) years for non-survivors (p<0.001). The survival rate for males (23.7%; n=44/185), was lower than that for females (37.5%; n=72/192) (p=0.011). Twenty-five of the female patients were peripartum, with an appreciably better survival of 48.0% (n=12/25) compared with non-peripartum females (35.9%; n=60/167) (p=0.02). Male survival remained lower than that for females even when excluding the peripartum group (p=0.041).

There were no statistically significant differences in comorbidities between survivors and non-survivors (Table 1).

The median duration of symptoms prior to ICU admission was 9 days, with a bimodal distribution with peaks at day 3 and day 7 and a long tail out to 41 days (Fig. 2). The duration of symptoms prior to the need for IMV was significantly shorter in survivors compared with non-survivors (8 days v. 10 days; p<0.02). A receiver operating characteristic curve analysis (area under the curve 0.6) cut-off of 20 days of symptom duration prior to the initiation of IMV was associated with a likelihood ratio for mortality of 2.3 (95.6% specificity, sensitivity 9.9%).

Overall ICU length of stay ranged from <1 day to 121 days. The median (IQR) length of ICU stay was 19.5 (9 - 36) days for survivors v. 7 (3 - 13) days for non-survivors (p<0.001) (Table 1). All ICU survivors (n=121) were followed up until hospital discharge. Five patients died in hospital after ICU discharge.

A total of 299 patients (79.3%) failed HFNO prior to requiring IMV and admission to the ICU. The median (IQR) P/F ratio was 97 (71 - 128) after IMV was initiated on day 1 in the ICU. The day 1 median (IQR) Sequential Organ Failure Assessment (SOFA) score was 4 (4 - 7). Survivors were younger than non-survivors (median (IQR) 48 (40 - 55) years v. 53 (45.5 - 59) years (p=0.001)), and had lower SOFA scores and glycated haemoglobin (HbA1c) levels, and

higher day 1 P/F ratios. No differences in laboratory characteristics (including white cell count, D-dimers and C-reactive protein) were noted between survivors and non-survivors.

The requirement for renal replacement therapy (RRT) or vasopressors was associated with poor outcomes.

In a univariate analysis, increasing age, male gender, lower day 1 P/F ratio, duration of symptoms prior to ICU admission and higher day 1 SOFA score were associated with mortality (Table 2). The presence of comorbidities (diabetes mellitus, hypertension, HIV infection), raised BMI and peripartum status were not predictors of mortality. After adjusting for confounders in a multivariate model, male gender (odds ratio (OR) 1.74), increasing age (OR 1.04) and higher day 1 SOFA score (OR 1.29) remained significant predictors of mortality.

Discussion

This is the first study to report on outcome data for COVID-19 ARDS patients admitted to the ICU requiring IMV from sub-Saharan Africa. We included all patients admitted to the ICU and had hospital outcomes for >99% of patients.

Our outcomes are challenging to interpret in relation to published international experience. Studies early in the global pandemic reported mortality rates from 0%[10] (expressed as 30-day hospital mortality) to as high as 97% for patients receiving IMV.[11] Most studies include a mixture of invasive and non-invasive mechanical respiratory support in the ICU, rather than IMV cohorts alone. In studies with outcome data for patients receiving IMV, mortality rates vary widely from 11.1% to 91.4%.[12-17] In these studies, the mortality rates were not consistently reported for the whole cohort or subgroup

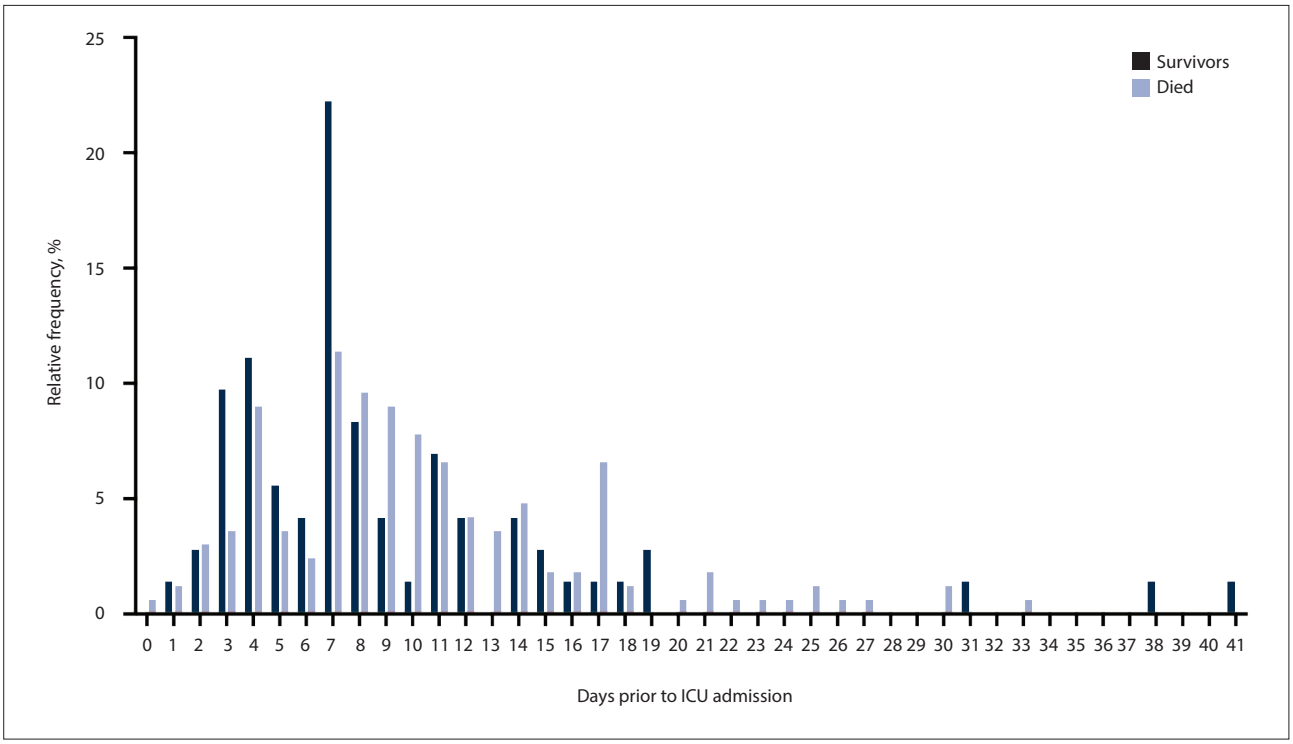

Fig. 2. Duration of symptoms prior to ICU admission by survival status. (ICU = intensive care unit.)

Table 2. Associations with mortality in COVID-19 ARDS

Variable	OR	95% CI
Univariate analysis		
Age	1.042	1.021 - 1.064
Male	1.923	1.234 - 3.022
HbA1c	1.060	0.972 - 1.161
Days from symptom onset to ICU admission	1.043	1.005 - 1.086
Day 1 ICU SOFA score	1.308	1.169 - 1.480
Estimated BMI	0.979	0.951 - 1.007
HIV	1.544	0.735 - 3.560
Day 1 ICU P/F ratio	0.992	0.987 - 0.997
Multivariate analysis		
Age	1.038	1.016 - 1.062
Admission SOFA score	1.287	1.153 - 1.453
Male gender	1.739	1.090 - 2.791

OR = odds ratio; CI = confidence interval; HbA1c = glycated haemoglobin; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment; BMI = body mass index; P/F ratio = arterial oxygen partial pressure to fractional inspired oxygen ratio.

requiring IMV. Comparisons of outcomes are further complicated by lack of reporting on staffing ratios, bed capacity and resource availability, including RRT, tracheostomy and extracorporeal membrane oxygenation (ECMO).

To give context to our reported cohort, only patients who required IMV were admitted to the ICU. No patients received HFNO or any other form of non-invasive or oxygen therapy on admission to the ICU. A medical team provided HFNO, self-proning and corticosteroid therapy to patients with severe hypoxia but not requiring intubation, in repurposed medical wards.[18,19] Patients who failed HFNO and fulfilled triage criteria were referred to the ICU. The fact that the majority of patients admitted to our ICU (79.5%) had failed HFNO implies that IMV was frequently initiated as a salvage therapy. This may account for our median day 1 P/F ratio of only 97. The late initiation of IMV for HFNO failures may have a negative impact on survival. At the time of data analysis, there were no prospective randomised controlled trials comparing HFNO with IMV for COVID-19 ARDS, but subsequent data from the RISC-19-ICU study have shown that in patients with COVID-19, a trial of HFNO appeared to be the most balanced initial respiratory support strategy, with reduced intubation rates and comparable ICU mortality rates compared with standard oxygen therapy and early IMV.[20] The stepwise escalation of oxygen therapy was driven by resource constraints in our setting.

A consensus triage guidance tool was drafted by the Critical Care Society of Southern Africa,[21] and was modified by the regional Department of Health[22] to assist in allocating the use of ICU resources during the COVID-19 pandemic. This triage tool, implemented by the ICUs at GSH and across the region, excluded patients with poor functional status or severe multiorgan failure prior to admission. The triage tool was based on the Ventilator Allocation Guidelines drafted by the New York State Task Force on Life and the Law, by the New York State Department of Health.[23] The New York document, from a high-income country, was modified as there were no available triage guidelines from LMIC countries at the beginning of the COVID-19 pandemic.

At the height of the COVID-19 waves, pressure on resources resulted in a limited supply of ICU beds, necessitating tighter triaging and the admission of patients who were assessed as being the highest priority for ventilatory support only. Later in the pandemic, as the number of referrals waned, triaging was less strict and patients assessed as being intermediate priority for ventilatory support were considered for ICU admission, in accordance with the consensus triage tool and the availability of resources. Fig. 3A - D illustrates the graphical data for the first two waves, nationally as well as provincial data for Western Cape Province. These graphs also depict the start of the third wave being experienced in SA at the time of writing (data analysis does not include patients from the third wave).

The presence of comorbidities (81.7%), although associated with the development of severe disease, did not predict mortality in this cohort receiving IMV. This finding suggests that the number of comorbidities was not discriminatory for outcome in this cohort. Our data suggest that although many factors are perceived to be associated with poorer outcomes, we identified no biochemical parameters prior to ICU admission that help to predict outcome in the individual patient (Table 1). Multivariate analysis indicated age, sex and day 1 SOFA score to be statistically significant for predicting mortality. However, these three factors are of little clinical use to guide the physician facing the need to make triage decisions with regard to ICU admission.

The median (IQR) length of ICU stay was 19.5 (9 - 36) days for survivors v. 7 (3 - 14 days for non-survivors (Table 1). All ICU survivors (n=121) were followed up until hospital discharge. Five patients died in hospital after ICU discharge. The long duration of ICU stay for survivors highlights

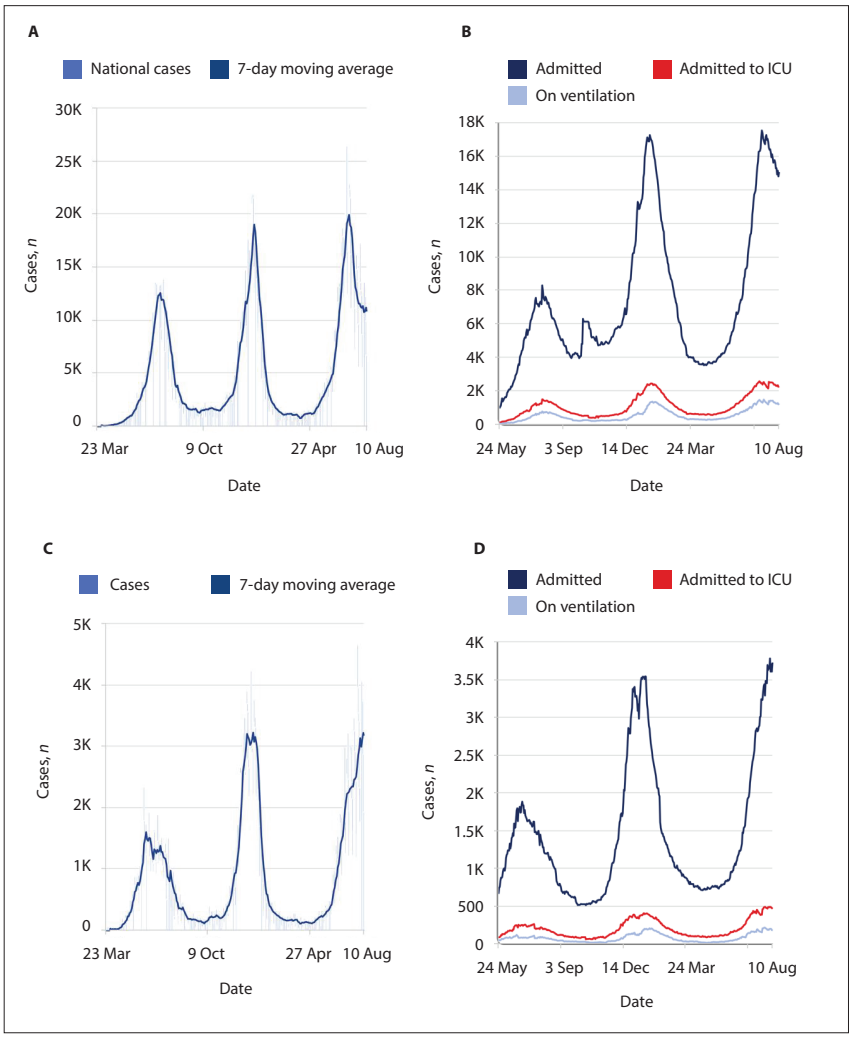

Fig. 3. Data for the first two waves of COVID-19 in South Africa, 2020/2021 (the start of the third wave is also depicted). (A) National daily new COVID-19 cases (7-day moving average); (B) national hospitalisations of COVID-19 cases; (C) daily new COVID-19 cases (7-day moving average) in Western Cape province; (D) hospitalisations of COVID-19 cases in Western Cape. Figures adapted with permission from News24's COVID-19 dashboard,[24] data source National Department of Health and National Institute for Communicable Diseases. (ICU = intensive care unit.)

the prolonged trajectory of recovery in patients requiring IMV for COVID-19 ARDS. In our setting, patients were only discharged from the ICU once liberated from IMV.

Our management strategies included lung protective ventilatory strategies,[9] the use of neuromuscular blocking agents, sedation, and the liberal use of prolonged prone positioning (for periods of up to 16 hours). Anticoagulant therapy, using mainly low-molecular-weight heparin, was guided by anti-Xa levels. The use of dexamethasone was instituted shortly after the positive data from the RECOVERY trial were released.[25] Prior to this, corticosteroid use was at the discretion of the treating physician. Despite international controversy, no patients received hydroxychloroquine, remdesivir, tocilizumab, ivermectin, convalescent plasma or other experimental therapy.

GSH is a designated regional ECMO referral centre. ECMO was available for patients with COVID-19 ARDS, but owing to high resource demands, particularly nursing, the use of ECMO was severely limited. Each patient receiving ECMO is cared for by a dedicated registered nurse, putting further pressure on nursing capacity.

On 18 December 2020, a new SARS-CoV-2 variant (501.V2) was identified as being the dominant strain in the second wave in SA.[26] In our cohort, it is not possible to determine which variant of the SARS-CoV-2 virus infected patients, and whether this had an impact on outcomes. The Johnson & Johnson's Janssen COVID-19 vaccine roll-out commenced in SA on 17 February 2021. As of 5 April 2021, less than 0.5% of the SA population had been vaccinated. Vaccination is unlikely to have had any impact on our cohort at all.

Conclusions

Patients with COVID-19 ARDS who required IMV admission to a tertiary ICU in Cape Town during the first and second wave of the pandemic in SA had an overall hospital survival of 30.8%, and survivors had a median length of ICU stay of 19.5 days.

SARS-CoV-2-infected patients with severe acute hypoxaemic respiratory failure require prolonged IMV, leading to high resource utilisation. In an African LMIC setting with strict triage criteria, we were unable to identify clinically useful prognostic factors in patients admitted for IMV. Interpretation of critical care patient outcomes during a pandemic that overwhelms healthcare systems is challenging. Larger standardised data sets may help shed light on strategies to improve patient selection and outcome. Crucial would be uniformity in defining the context in which critical care was delivered, including IMV and the reporting of standardised ICU and hospital outcomes.

Declaration. None.

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Author contributions. CA-D and JLP assisted with data collection. CA-D and RNvZ-S analysed data. All authors had access to the data set, assisted with data review and manuscript preparation, and approved the final manuscript.

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Conflicts of interest. None.

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