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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Research

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Abstract

Background Up to 32% of patients with COVID-19 pneumonia may require ICU admission or mechanical ventilation(1, 2). Data from low- and middle-income countries for COVID-19 ARDS are limited. Groote Schuur Hospital in Cape Town, South Africa expanded its ICU service to support patients with COVID-19 ARDS requiring invasive mechanical ventilation (IMV). We report on patients' characteristics and outcomes from two pandemic waves.

Methods All adult patients with COVID-19 ARDS admitted to ICU for IMV were included in this prospective cohort study. Data were collected from 5th April 2020 to 5th April 2021. Ethical approval was granted (HREC: 362/2020).

Results Over the 12-month study period 461 patients were admitted to the designated COVID-19 ICU. Three-hundred-and-eighty patients met study criteria and 377 had confirmed hospital discharge outcomes. The median age of patients was 51 years (range 17–71), 50.5% were female and the median BMI was 32kg/m^2 (IQR 28–38). The median P/F ratio was 97 (IQR 71.5-127.5) after IMV was initiated. Co-morbidities 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 ICU length of stay of 19.5 days (IQR 9–36). Predictors of mortality after multivariate analysis were: male (OR:1.79), increasing age (OR:1.04), higher SOFA score (OR:1.29).

Conclusion In a resource limited environment, escalation of ICU IMV support achieved a 30.8% hospital survival in patients with COVID-19 ARDS. The ability to predict survival remains difficult given this complex disease.

Introduction

It is estimated that between 5 and 32% of patients hospitalised with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) require intensive care unit (ICU) admission or mechanical ventilation(1,2). The identification of prognostic factors in critically ill patients with COVID-19 infection 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.

The clinical characteristics and outcomes of infected patients requiring ICU in low- and middle-income countries (LMICs) are limited(3). Several countries in Asia, Europe, North and South America have published mortality outcomes ranging from 16.2%-94%(4-6) for patients admitted to the ICU for invasive mechanical ventilation (IMV) with COVID-19 ARDS. In South Africa, a middle-income country, over 1.55 million cases of SARS-CoV-2 have been confirmed over two pandemic waves with nearly 53 000 deaths as of 5th April 2021(7).

The aim of this study was to describe the clinical characteristics, course and outcomes of critically ill patients, with COVID-19 ARDS, admitted to ICU for IMV at Groote Schuur Hospital (GSH), Cape Town 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 (UCT).

Methods

Study design, population and time frame

The study is a prospective single-center cohort study of all intubated patients who received IMV, with laboratory-confirmed SARS-CoV-2 pneumonia and acute respiratory distress syndrome (ARDS). Patients admitted to the ICU during the first and second waves of the COVID-19 pandemic in South Africa (5th April 2020 to 5th April 2021) were recruited.

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 bedded patient-cluster. A regional ICU triage tool was in effect prior to the first wave (see Additional file 1).

COVID-19 ARDS was defined as a positive SARS CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab or tracheal aspirate as per WHO guidelines(8) in a patient with primary ARDS meeting the Berlin criteria(9) with an arterial oxygen partial pressure to fractional inspired oxygen ratio (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 (HREC: 362/2020) (see Additional file 2) ; additional departmental and hospital approval was also granted for this study (see Additional files 3 and 4). Consent was obtained for survivors and waived for patients who died.

Data collection

Patient clinical and outcome data were collected prospectively on a data collection form (see Additional file 5) from 5th April 2020 to 5th 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 performed to identify predictors of mortality. Data analysis was conducted

using GraphPad Prism for Mac V9.02, San Diego, California USA, www.graphpad.com. Data are presented using descriptive statistics.

Results

A total of 461 patients were admitted for IMV to the COVID-19 ICU service. Thirty-two patients did not meet criteria for laboratory confirmed SARS-CoV-2 infection and 23 patients did not meet the criteria for ARDS. Twenty-six patients were admitted with an alternative primary diagnosis and found to have co-incidental 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 (Figure 1).

The demographics and clinical characteristics of all COVID-19 ARDS patients are shown in Table 1. The median age of patients was 51 years (Interquartile Range (IQR) 43-58) with a range of 17 to 71 years. Co-morbidities were common with nearly 80% of patients having at least one co-morbid condition, the most frequent being diabetes mellitus (DM) (47.6%) and hypertension (46.3%). Obesity was common (62.6%), with a median Body Mass Index (BMI) of 32 kg/m^2 (IQR 28-38). Over 75% of female patients were obese with a median BMI of 35kg/m^2 compared to males 29kg/m^2 ($p<0.001$). Forty patients (10.5%) had HIV co-infection with generally preserved CD4 counts: median 258 (IQR 166.8-440). Male and female patients were similar in baseline characteristics, except for BMI.

Clinical characteristics and outcomes are detailed in Table 2. Of the 380 patients, 3 were still in ICU at the time of data analysis; of the 377 patients with known hospital outcomes, there were 116 (30.8%) survivors. Survivors had a median age of 48 years (IQR 40-55) vs. non-survivors (median age 53 years (IQR 45.5-59); $p<0.001$). The survival rate in males, 23.7% (44/185) was lower than in females 37.5% (72/192); $p=0.011$. Twenty-five of the female patients were peripartum, with an appreciably better survival of 48% (12/25) compared to non-peripartum females 35.9% (60/167); $p=0.02$. Male survival remained lower than females even when excluding the peripartum group ($p=0.041$).

There were no statistically significant differences in comorbidities between survivors and non-survivors (Table 2).

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 (Figure 2). The duration of symptoms prior to the need for IMV was significantly shorter in survivors compared to non-survivors (8 days vs. 10 days); $p<0.02$. A receiver operator characteristic (ROC) curve analysis (AUC 0.6) cut-off of 20 days 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 length of ICU stay was 19.5 days (IQR 9-36) for survivors vs. 7 days (IQR 3-13) for non-survivors (p-value <0.001) (Table 2). All ICU survivors (121) were followed up until hospital discharge. Five patients died in hospital, post ICU discharge.

A total of 299 patients (79.3%) failed HFNO prior to requiring IMV and admission to the ICU. The median P/F ratio was 97 (IQR 71.5-127.5) after IMV was initiated, on day 1 of ICU. The day 1 median Sequential Organ Failure Assessment (SOFA) score was 4 (IQR 4-7). Survivors were younger, [48 years (IQR 40-55) vs. 53 years (IQR 45-58.3) p=0.001], and had lower SOFA scores, Haemoglobin A1c (HbA1c) levels, and higher day 1 P/F ratios. No differences in laboratory characteristics [including White Cell Count (WCC), D-Dimer or C-reactive protein (CRP)] 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 3). 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 (OR:1.79), 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 reporting on outcome data for COVID-19 ARDS patients admitted to the ICU requiring IMV from an LMIC in Africa. We included all patients admitted to the ICU and have hospital outcomes for over 99% of patients.

Our paper is unique as the data analysis only includes patients receiving IMV. This makes interpretation of our outcomes challenging in relation to published international experience. Most studies to date include a combination of invasive and non-invasive mechanical respiratory support in the ICU, not IMV cohorts alone. Early in the global pandemic, mortality rates were reported from 0%(10) (expressed as 30-day hospital mortality); to as high as 97% for patients receiving IMV(11). In studies with outcome data for patients receiving IMV, mortality rates vary widely from 11.1% to 91.4%[(11-17)]. However, in these studies, the mortality rates were not consistently reported for the whole cohort or subgroup requiring IMV (see additional fie 6). Comparisons of outcomes is further complicated by lack of reporting on staffing ratios, bed capacity and resource availability; including RRT, tracheostomy and ECMO.

To give context to our reported cohort, only patients who required IMV were admitted to ICU. No patients received HFNO or any other form of non-invasive (NIV) 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). Patients who failed HFNO and fulfilled triage criteria were referred to the ICU. The fact that most 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, which is substantially lower than reported by other groups internationally (see additional file 6). The late initiation of IMV for HFNO failures may have a negative impact on survival.

Unfortunately, there are no prospective randomised trials comparing HFNO to IMV for COVID-19 ARDS. 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 (CCSSA) (19), and was modified by the regional Department of Health(20) 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 multi-organ 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(21). 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.

The presence of comorbidities (81.7%), although associated with the development of severe disease, did not predict mortality in this cohort receiving IMV. This suggests that the number of co-morbidities is not discriminatory for outcome in this cohort. Our data suggests 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 2). Multivariate analysis indicated age, sex, and day 1 SOFA score as 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 respect to ICU admission.

The median length of ICU stay was 19.5 days (IQR 9-36) for survivors vs. 7 days (IQR 3-13) for non-survivors (Table 2). All ICU survivors (121) were followed up until hospital discharge. Five patients died in hospital, post ICU discharge. The long duration of ICU stay for survivors highlights the prolonged trajectory of recovery in patients requiring IMV for COVID-19 ARDS. In our setting patients were only discharged from 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(22). 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 due 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 18th December 2020 a new SARS-CoV-2 variant (501.V2) was identified as being the dominant strain in the second wave in South Africa(23). In our cohort, it is not possible to determine which variant of the

SARS-CoV-2 virus infected patients, and if this had an impact on outcomes. The Johnson & Johnson's Janssen COVID-19 vaccine roll out commenced in South Africa on 17th February 2021. As of 5th April 2021, less than 0.5% of the South African population had been vaccinated. Vaccination is unlikely to have had any impact on our cohort at all.

Limitations

This is a single-centre observational study, and unaccounted confounders may be present, and our findings may not be representative of other regions in South Africa or internationally. Inferences should, therefore, be made with caution. Our study only reports on the outcome of IMV in the first and second waves of the Covid-19 pandemic in South Africa. No long-term follow up data are available at the time of this publication but follow up studies are planned. Finally, our study did not foresee the development of the new SARS-CoV-2 variant (501.V2) that was reported on 18th December 2020 and, although data suggest that 501.V2 was the dominant strain in the second wave, virological subtyping was not performed and we are unable to comment on the impact that the new variant had on the mortality of our study population.

Conclusion

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 South Africa, had an overall hospital survival of 30.8% and survivors had a median length of stay in ICU of 19.5 days.

SARS-CoV-2 infected patients presenting with severe acute hypoxaemic respiratory failure require prolonged IMV, leading to high resource utilization. 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.

List Of Abbreviations

ARDS	Acute Respiratory Distress Syndrome
BMI	Body Mass Index
CRP	C-reactive protein
DM	Diabetes mellitus
GSH	Groote Schuur Hospital

HbA1c	Haemoglobin A1c
HFNO	High-flow nasal oxygen
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
IQR	Interquartile Range
LMIC	Low- and Middle-Income Countries
OR	Odds Ratio
PCR	Polymerase chain reaction
P/F ratio	Arterial oxygen partial pressure to fractional inspired oxygen ratio
ROC	Receiver Operator Characteristic
RRT	Renal Replacement Therapy
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SOFA	Sequential Organ Failure Assessment
UCT	University of Cape Town
VV-ECMO	Venovenous Extracorporeal Membrane Oxygenation
WC	Western Cape
WCC	White Cell Count
WHO	World Health Organization

Declarations

Availability of data and materials

The datasets generated and / or analysed during the current study are not publicly available but are available from the corresponding author, Dr Jenna Piercy, on reasonable request.

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Christel Arnold-Day, Jenna Piercy assisted with data collection. Christel Arnold-Day and Richard van Zyl-Smit 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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Ethics declarations

Ethics approval and consent to participate

Ethics approval for this study was granted by the University of Cape Town Human Research Ethics Committee (HREC: 362/2020). Consent was obtained for survivors and waived for patients who died.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Tables

Table 1: Demographics and baseline characteristics of COVID-19 ARDS patients admitted to the Intensive Care Unit at Groote Schuur Hospital

	All patients	Male	Female	p-value
Total	380	188 (49.5%)	192 (50.5%)	
Age, years; (median, IQR)	51 (43-58)	51.5 (44-58)	51 (42-57)	p=0.132
Comorbidities; n (%)				
▪ **None**	70 (18.4%)	42 (22.3%)	28 (14.6%)	p=0.636
▪ **Hypertension**	176 (46.3%)	83 (41.1%)	93 (48.4%)	p=0.412
▪ **Diabetes Mellitus**	181 (47.6%)	98 (52.1%)	83 (43.2%)	p=0.100
All patients HbA1c (med, IQR)	6.7 (6.1-9.0)	6.8 (6.3-9.6)	6.7 (6.1-9.75)	p=0.152
Known DM HbA1c (med, IQR)	9.5 (7.1-11.8)	9.0 (7.0-11.7)	10.1 (7.2-12.1)	p=0.356
▪ **HIV infected**	40 (10.5%)	17 (9.0%)	23 (11.9%)	p=0.405
CD4 (median, IQR)	258 (166.8-440)	198 (109-390)	302 (194-507)	p=0.089
Body Mass Index	32 (28-38)	29 (27-33)	35 (30-41)	
▪ **< 30 kg/m^2**	142 (37.3%)	95 (50.5%)	47 (24.5%)	**p<0.001**
▪ **≥ 30 kg/m^2**	238 (62.6%)	93 (49.5%)	145 (75.5%)	**p<0.001**

Table 2: Clinical and laboratory characteristics of patients admitted with severe SARS-CoV-2 ARDS to the ICU at Groote Schuur Hospital

	All patients	Survivors	Non-survivors	p-value
Number patients; (%)	377	116 (30.8%)	261 (69.2%)	
Age, years; (median, IQR)	51 (43-58)	48 (40-55)	53 (45.5-59)	p<0.001
Sex; n (%) ▪ Male ▪ Female	185 (49.5%) 192 (50.5%)	44 (37.9%) 72 (62.1%)	141 (54%) 120 (46%%)	p=0.005
Peripartum Non-peripartum	25 (13%) 167 (87%))	12 (16.7%) 60 (83.3%)	13 (10.8%) 107 (89.2%)	p=0.002
Comorbidities; n (%) one rpertension abetes Mellitus Known DM HbA1c (%) (median, IQR) V infected CD4 (median, IQR) MI kg/m^2 (median, IQR)	69 (18.3%) 176 (46.3%) 181 (47.6%) 9.5 (7.1-11.8) 40 (10.5%) 258 (166.8-440) 32 (28-38)	22 (19%) 51 (44%) 47 (40.5%) 9.8 (6.8-12.4) 9 (7.8%) 278 (125-562) 33 (28-38.8)	47 (18%) 125 (47.9%) 134 (51.3%) 9.4 (7.3-11.7) 31 (11.8%) 249 (164-452) 31 (27.5-38)	p=0.885 p=0.504 p=0.580 p=0.599 p=0.280 p=0.886 p=0.296
Symptom onset to ICU admission (days) (median, IQR)	9 (7-14)	8 (6-11)	10 (7-15)	p=0.002
ICU length of stay (days) (median, IQR)	10 (5-20)	19.5 (9-36)	7 (3-14)	p<0.001
Respiratory therapy prior to ICU admission: ▪ HFNO ▪ Non-HFNO	299 (79.3%) 78 (20.5%)	89 (76.7%) 27 (23.3%)	210 (80.5%) 51 (19.5%)	p=0.412
Day 1 SOFA score (median, IQR)	4 (4-7)	4 (3-5)	5 (4-8)	p<0.001
Day 1 P/F ratio (median, IQR)	97 (71-128)	109 (81.3-145)	90 (68.5-121)	P<0.001
Admission laboratory results* (median, IQR) eatinine (µmol/L) CC (x10□/L) mphocyte Count (x10□/L) atelets (x10□/L) RP (mg/L) dimer (mg/L) bA1c (%)	85.5 (66-109) 9.4 (7.0-14.4) 1.2 (0.9-1.8) 248 (188-322) 145 (76-260) 0.67 (0.40-2.23)	79.5 (60.3-109) 10.3 (7.5-15.7) 1.37 (1-2) 251 (195-326) 175 (98-258) 0.7 (0.47-1.65) 6.5 (6-9.3)	87 (68.5-109) 9.5 (7.3-14) 1.2 (0.9-1.6) 244 (188-321) 161 (86-279) 0.76 (0.42-2.43)	p=0.091 p=0.133 p=0.092 p=0.490 p=0.765 p=0.994 p=0.009

	6.8 (6.2-9.7)		6.9 (6.3-10.1)	
Additional ICU therapy ▪ **Vasopressor support; n (%)** ▪ **Renal Replacement Therapy; n (%)** ▪ **Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO); n (%)** ▪ **Tracheostomy; n (%)**	244 (64.2%) 57 (15%) 6 (1.6%) 78 (20.5%)	44 (37.9%) 10 (8.6%) 3 (2.6%) 53 (45.7%)	197 (75.5%) 45 (17.2%) 3 (1.2%) 25 (9.6%)	**p<0.001** **p<0.001** **p=0.377** **p<0.001**

*On presentation to hospital

Table 3: Associations with mortality in COVID-19 ARDS

Variable	OR	95% CI
Univariate Analysis		
Age	**1,042**	**1,021 to 1,064**
Male	**1,923**	**1,234 to 3,022**
HbA1c	1,060	0,972 to 1,161
Days from symptom onset to ICU admission	**1,043**	**1,005 to 1,086**
Day 1 ICU SOFA score	**1,308**	**1,169 to 1,480**
Est BMI	0,979	0,951to 1,007
HIV	1,544	0,735 to 3,56
Day 1 ICU P/F ratio	**0,992**	**0,987 to 0,997**
Multivariate Analysis		
Age	**1,038**	**1,016 to 1,062**
Admission SOFA score	**1,287**	**1,153 to 1,453**
Male gender	**1,739**	**1,090 to 2,791**

Figures

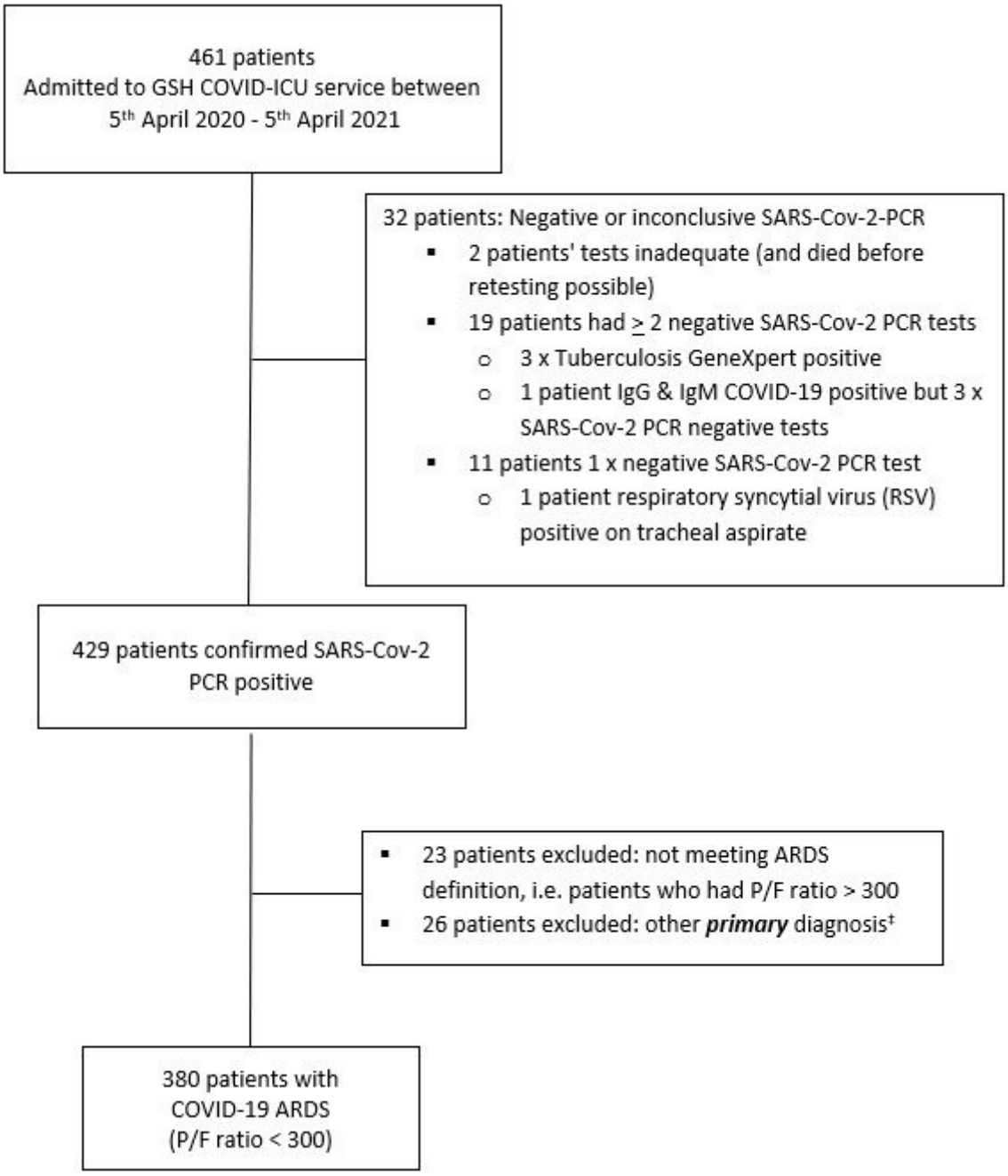

Figure 1

Consort diagram of patient inclusion and analysis ‡26 diagnoses: 3 x patients with multiple thoracoabdominal gunshot wounds / 2 x ethyl glycol poisonings 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 x patients with acute severe pancreatitis / severe polytrauma after a pedestrian-vehicle accident / gunshot wound to the chest /

lymphoma in septic shock with acute kidney injury / penetrating neck injury / 2 x patients with acute psychosis

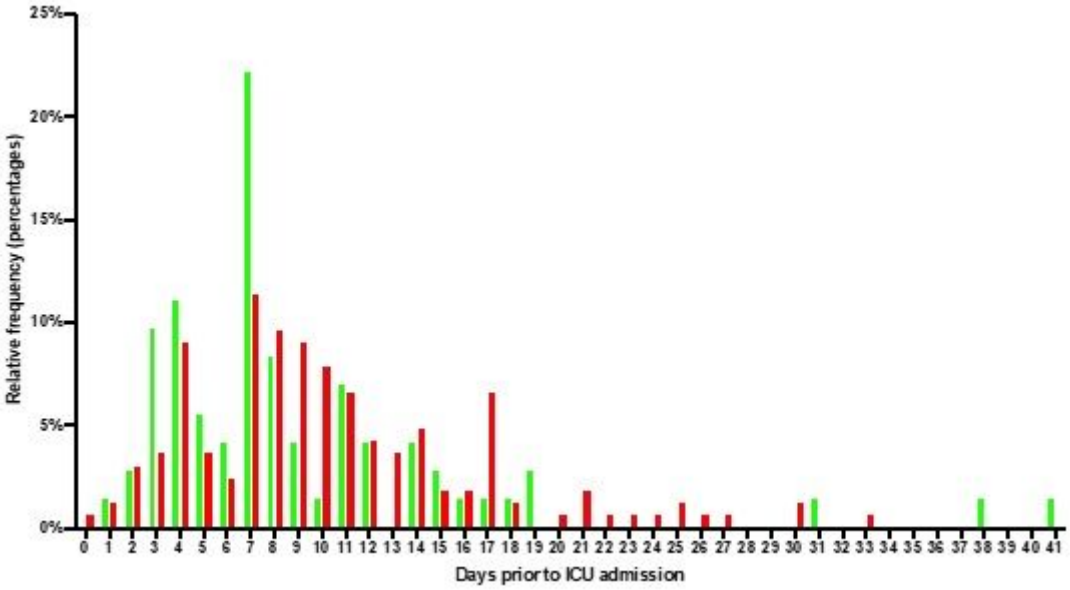

Figure 2

Duration of symptoms prior to ICU admission by survival status

Supplementary Files

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- Additionalfile1.docx
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