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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DECLARATION

I, ***Christel Arnold-Day***, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signature: ..... Signed by candidate

Date: 29 April 2021

DEDICATION

To my husband, children, parents and family for their never ending support, encouragement, sacrifices and love.

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My co-supervisor, Professor Richard van Zyl-Smit, you are a master of not only medicine and research but of life in general. You inspire me to be a better doctor, student and person - you define professional transcendence, and you make it look easy. Thank you so much for your wisdom, time, patience, guidance and for re-doing the statistics for this project a million times over with no complaints.

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I would also like to thank the University of Cape Town as well as Groote Schuur Hospital for granting me permission to use patients' records to complete this research project.

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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

Chapter 1 Introduction

1.1 Context

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). 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.

1.2 Ethical considerations

Ethics approval for this study was granted by Groote Schuur Hospital's Department of Surgery Research Committee (2020/089 - appendix 3) as well as the University of Cape Town Human Research Ethics Committee (HREC: 362/2020- appendix 4). Consent was obtained for survivors and waived for patients who died.

1.3 Author guidelines of the Journal

Chosen journal: Intensive Care Medicine

Intensive Care Medicine is a journal covering the categories related to Critical Care and Intensive Care Medicine. It is published by Springer Verlag. The overall rank of

Intensive Care Medicine is 466. According to SCImago Journal Rank (SJR), this journal is ranked 3.654. Intensive Care Medicine has an h-index of 176. ISSN of this journal is/are 03424642. The impact factor of Intensive Care Medicine is 8.61.

Journal Instructions to Authors for Original Papers (see appendix 6)

- Abstract: 250-word limit
- Article (excluding figures, tables, references and abstract): 3000 words
- Tables and figures allowed: 5
- References: limited to 50
- Authors of original papers are requested to provide the following information:
    - A "Take-home message" (two-sentences) which summarizes how the manuscript adds to current knowledge. This will appear in the final published version of the paper.
    - A 140-character Tweet that may appear online via the Intensive Care Medicine website or social media platforms. This Tweet will not form part of the print version of the manuscript.
- The role of authors and contributors must be included

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Chapter 2 Publication-ready manuscript

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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Abstract

Purpose 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 patients with COVID-19 ARDS admitted to the 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), consent was waived for deceased patients and obtained for survivors.

Results Over the 12-month study period 461 patients were admitted to the designated COVID-19 ICU. Of these, 380 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. 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 ICU length of stay of 19.5 days (IQR 9-36). Predictors of mortality after adjusting for confounders 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.

Keywords *Acute respiratory distress syndrome; COVID-19, SARS-COV-2; critically ill; invasive mechanical ventilation; South Africa; Africa; hospital mortality outcomes; low- and middle-income countries.*

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-centre 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 Appendix 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). Consent was obtained for survivors and waived for patients who died.

Data collection

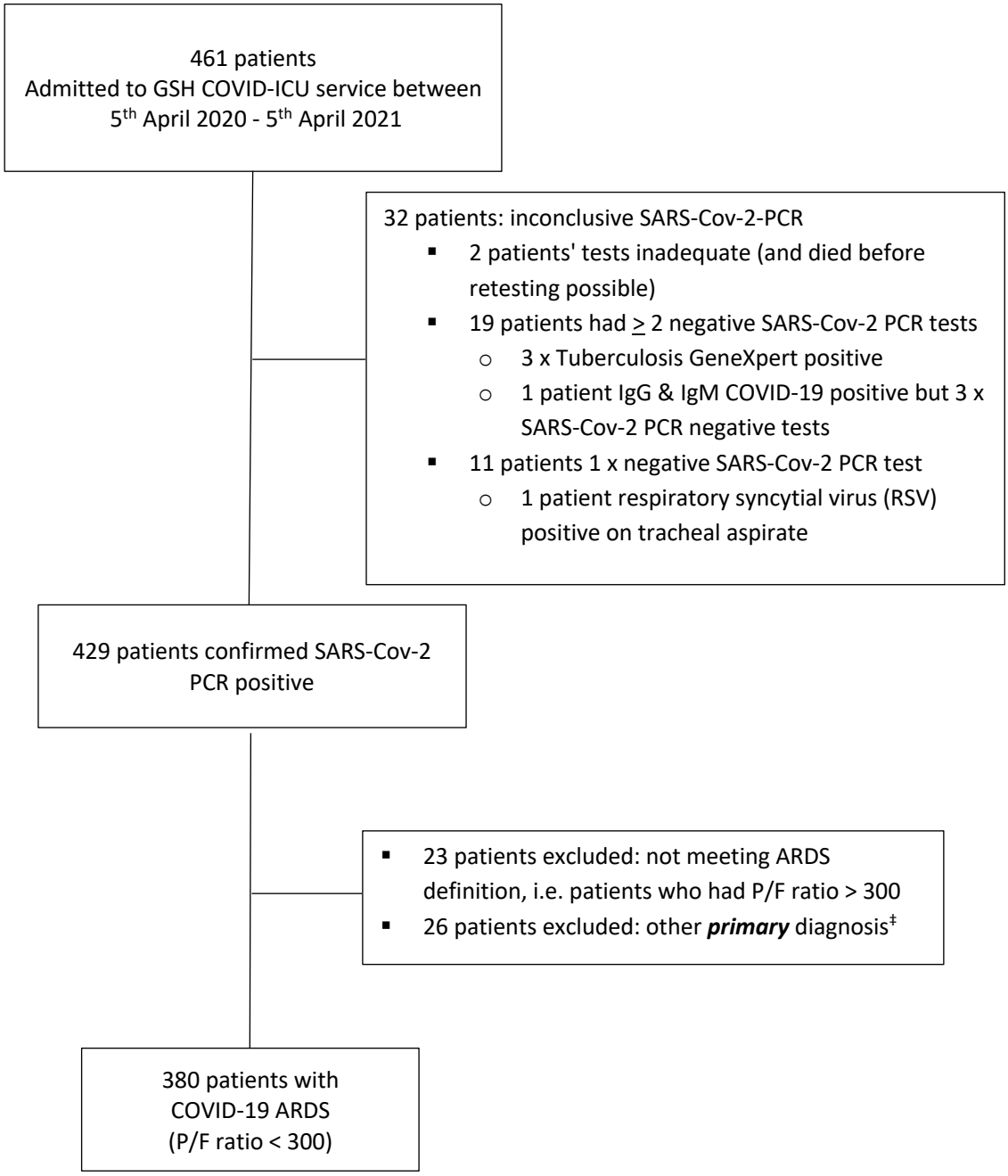
Patient clinical and outcome data were collected prospectively from 5th April 2020 to 5th April 2021. Data were collected on the daily ward round and from the electronic laboratory and radiological systems.

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 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 (Figure 1).

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

Clinical characteristics and outcomes 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. Comorbidities were common with nearly 80% of patients having at least one comorbid 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 ($p<0.001$), (not shown in this table). 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.

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 female 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 (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%).

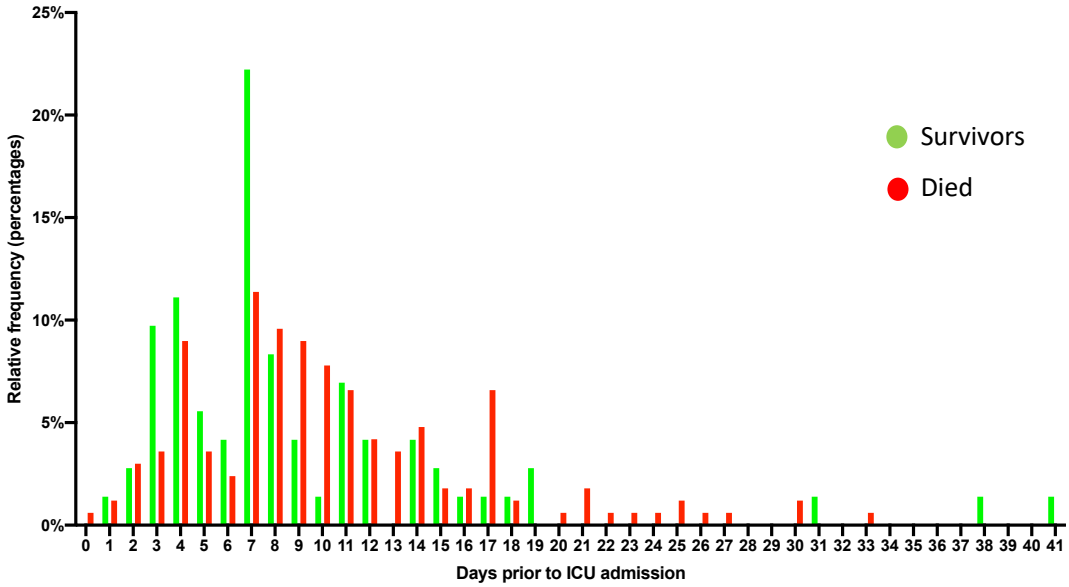


Figure 2: Duration of symptoms prior to ICU admission by survival status

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.

Table 1: 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**	185 (49.5%)	44 (37.9%)	141 (54%)	
▪ **Female**	192 (50.5%)	72 (62.1%)	120 (46%%)	p=0.005
Peripartum	25 (13%)	12 (16.7%)	13 (10.8%)	
Non-peripartum	167 (87%))	60 (83.3%)	107 (89.2%)	**p=0.002**
Comorbidities; n (%)				
▪ **None**	69 (18.3%)	22 (19%)	47 (18%)	p=0.885
▪ **Hypertension**	176 (46.3%)	51 (44%)	125 (47.9%)	p=0.504
▪ **Diabetes Mellitus**	181 (47.6%)	47 (40.5%)	134 (51.3%)	p=0.580
Known DM HbA1c (%) (median, IQR)	9.5 (7.1-11.8)	9.8 (6.8- 12.4)	9.4 (7.3-11.7)	p=0.599
▪ **HIV infected**	40 (10.5%)	9 (7.8%)	31 (11.8%)	p=0.280
CD4 (median, IQR)	258 (166.8-440)	278 (125- 562)	249 (164-452)	p=0.886
▪ **BMI kg/m^2 (median, IQR)**	32 (28-38)	33 (28-38.8)	31 (27.5-38)	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**	299 (79.3%)	89 (76.7%)	210 (80.5%)	p=0.412
▪ **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)	**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)				
▪ **Creatinine (µmol/L)**	85.5 (66-109)	79.5 (60.3-109)	87 (68.5-109)	**p=0.091**
▪ **WCC (x10^9/L)**	9.4 (7.0-14.4)	10.3 (7.5-15.7)	9.5 (7.3-14)	**p=0.133**
▪ **Lymphocyte Count (x10^9/L)**	1.2 (0.9-1.8)	1.37 (1-2)	1.2 (0.9-1.6)	**p=0.092**
▪ **Platelets (x10^9/L)**	248 (188-322)	251 (195-326)	244 (188-321)	**p=0.490**
▪ **CRP (mg/L)**	145 (76-260)	175 (98-258)	161 (86-279)	**p=0.765**
▪ **D-dimer (mg/L)**	0.67 (0.40-2.23)	0.7 (0.47-1.65)	0.76 (0.42-2.43)	**p=0.994**
▪ **HbA1c (%)**	6.8 (6.2-9.7)	6.5 (6-9.3)	6.9 (6.3-10.1)	**p=0.009**
Additional ICU therapy				
▪ **Vasopressor support; n (%)**	244 (64.2%)	44 (37.9%)	197 (75.5%)	**p<0.001**
▪ **Renal Replacement Therapy; n (%)**	57 (15%)	10 (8.6%)	45 (17.2%)	**p<0.001**
▪ **Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO); n (%)**	6 (1.6%)	3 (2.6%)	3 (1.2%)	**p=0.377**
▪ **Tracheostomy; n (%)**	78 (20.5%)	53 (45.7%)	25 (9.6%)	**p<0.001**

*On presentation to hospital

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 (OR:1.79), increasing age (OR:1.04) and higher day 1 SOFA score (OR:1.29) remained significant predictors of mortality.

Table 2: 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	0.951 to 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**

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 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%[11-17]. In these studies, the mortality rates were not consistently reported for the whole cohort or subgroup requiring IMV. 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 majority of patients admitted to our ICU had failed HFNO (79.5%), which 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. 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 comorbidities 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.

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.

Strengths

The data is from a large university and well renowned hospital in South Africa, the data reports on the mortality of patients that were admitted to ICU and due to resource management - could only allow admittance of invasive mechanically ventilated patients to the ICU - this portrays a very unique ICU population and due to the nature of patients admitted to our ICU, higher mortality rates were as expected seen in our cohort.

Limitations

This is a single-centre observational study, and unaccounted confounders may be present, as such results from our hospital-based study may not be representative of other regions in South Africa or the world. Inferences should, therefore, be made with caution. No specified comparisons were made between the first and second waves of the pandemic as experienced in South Africa and may be of value to examine if there were specific confounders influencing mortality differences in the two different waves, e.g. the impact of the new SARS-CoV-2 variant (501.V2) that was identified in South Africa in December 2020.

Data that was not collected as part of this study included: the absence of the description of the vaccinal state of each patient, specific therapeutic interventions such as dexamethasone or antibiotic therapy. The proportion of ventilator acquired pneumonia or any other ICU-related complications were also not commented on as it was not the specific aim of this study but would be very valuable information to look at in future studies.

"Take-home message"

- 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. 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, this could be improved upon by uniformity in defining the context in which critical care is delivered, including invasive mechanical ventilation and the reporting of standardised ICU hospital outcomes.

"Tweet"

The first study reporting on outcome data for COVID-19 ARDS patients admitted to the ICU requiring invasive mechanical ventilation from an LMIC in Africa.

Acknowledgments
We would like to extend our gratitude to all our Intensive Care Unit colleagues at Groote Schuur Hospital who worked so hard to provide excellent care to our patients during this global pandemic. We acknowledge all families affected by COVID-19 and the many who lost loved ones.

Author contributions
CAD, JP assisted with data collection. CAD, RVZS analysed data. All authors had access to the data set, assisted with data review and manuscript preparation, and approved the final manuscript.

Declaration of Conflicting Interests
The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
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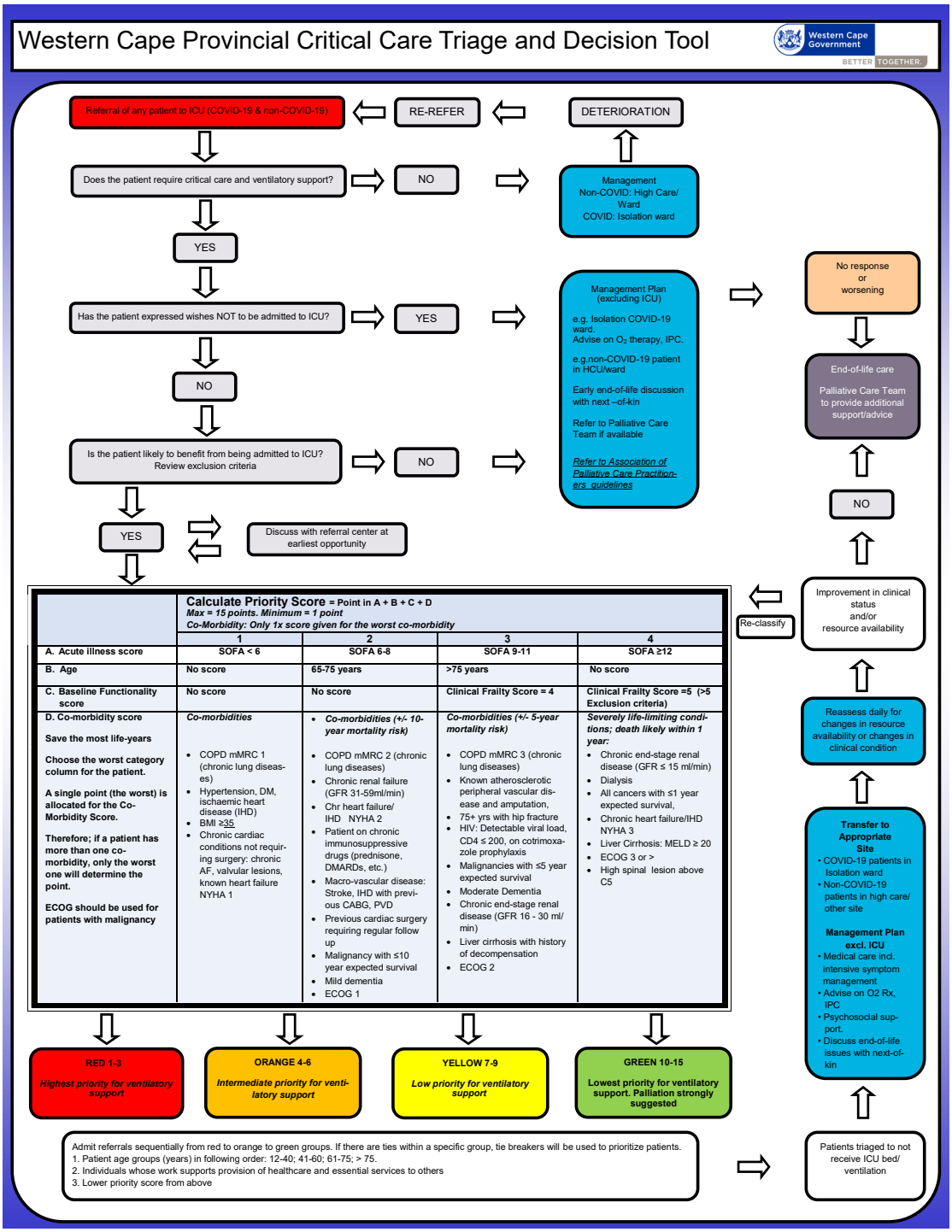
Appendix 1: Western Cape Provincial Critical Care Triage and Decision Tool



Appendix 2: GSH COVID ICU Data Collection Sheet

GSH COVID ICU Data collection sheet:

Patient sticker

Referring hospital / ward: _____

Date of admission to GSH: _____

Date of ICU admission: _____

Admission SOFA: _____ Admission P:F: _____ Pre-ICU O2 Rx: _____

Date of symptom onset: _____ Est BMI / ht / wt: _____

Co-morbidities: _____ RRT during ICU stay: Y / N

HIV status (CD4 / VL / ARVs): _____ Inotropes during ICU stay: Y / N

Covid PCR result: _____ Trachy: Y / N ECMO: Y / N

ICU D/C date: _____ GSH D/C date:_____

Outcome:
- ☐ ICU Death
- ☐ D/C to ward alive
- ☐ D/C to ward for palliation

ADMISSION BLOODS:

WCC _____ CRP _____ LYMPHS _____

D-DIMER _____ PLTS _____ HbA1C: _____

CREAT _____ 24-HR ICU CREAT _____

Patient sticker

Referring hospital / ward: _____

Date of admission to GSH: _____

Date of ICU admission: _____

Admission SOFA: _____ Admission P:F: _____ Pre-ICU O2 Rx: _____

Date of symptom onset: _____ Est BMI / ht / wt: _____

Co-morbidities: _____ RRT during ICU stay: Y / N

HIV status (CD4 / VL / ARVs): _____ Inotropes during ICU stay: Y / N

Covid PCR result: _____ Trachy: Y / N ECMO: Y / N

ICU D/C date: _____ GSH D/C date:_____

Outcome:
- ☐ ICU Death
- ☐ D/C to ward alive
- ☐ D/C to ward for palliation

ADMISSION BLOODS:

WCC _____ CRP _____ LYMPHS _____

D-DIMER _____ PLTS _____ HbA1C: _____

CREAT _____ 24-HR ICU CREAT _____

Appendix 3: Departmental Research Committee Approval

UNIVERSITY OF CAPE TOWN

Department of Surgery
Departmental Research Committee
Dr Timothy Pennel
D24 Office, Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 3430
Email: **tim.pennel@uct.ac.za**

23 Jun 2020

Dr C Arnold-Day

Department of Surgery
University of Cape Town

Dear Dr Arnold-Day

RE: Project 2020/089

PROJECT TITLE: A Single-Centre, Retrospective, Cohort Study On The Mortality Outcomes For Patients With Covid-19 Admitted To The Intensive Care Units Of Groote Schuur Hospital, Western Cape, South Africa

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

DR TIMOTHY PENNEL
CHAIR: SURGICAL DRC

DR MARITZ LAUBSCHER
CHAIR: PROTOCOL REVIEW COMMITTEE

Appendix 4: Human Research Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 July 2020

HREC REF: 362/2020

Dr J Piercy
Division of Critical Care
c/o Mrs Ingrid Wilson, C27-14 ICU NGSH
Email: jenna.piercy@uct.a.za
Student: arnchr002@myuct.ac.za

Dear Dr Piercy

PROJECT TITLE: A SINGLE-CENTRE REVIEW STUDY ON THE MORTALITY OUTCOMES FOR PATIENTS WITH COVID-19 ADMITTED TO THE INTENSIVE CARE UNITS OF GROOTE SCHUUR HOSPITAL, WESTERN CAPE, SOUTH AFRICA (MPHIL STUDENT DR CHRISTAL ARNOLD-DAY) SUB-STUDY 205/2020

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 July 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Christal Arnold-Day will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Appendix 5: Groote Schuur Hospital Institutional Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: Bernadette.Eick@westerncape.gov.za

Dr Jenna Piercy
DIVISION OF CRITICAL CARE

E-mail: jenna.piercy@uct.ac.za / arnchr002@myuct.ac.za

Dear Dr Piercy,

RESEARCH PROJECT: A Single-Centre Review Study On The Mortality Outcomes For Patients With COVID-19 Admitted To The Intensive Care Units Of Groote Schuur Hospital, Western Cape, South Africa (Phil Dr Christel Arnold-Day)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 July 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 24 July 2020

C.C. Mr. L. Naidoo, Dr S. Peter, Professor I. Joubert

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Appendix 6: Instructions for Authors: Intensive Care Medicine

Intensive Care Medicine: Instructions for Authors

Contents

Instructions for Authors

General

All papers providing pre-clinical data (experimental, animal, in-vitro, bench studies or studies without patients) should be submitted to ICM Experimental ICM Experimental/.

It is necessary for you to upload the appropriate EQUATOR checklist for your study. Please find the appropriate checklist at EQUATOR Network.

All manuscripts undergo review. An initial check is conducted soon after submission to ensure that all manuscripts comply with the guidelines outlined in the Instructions for Authors. A pre-evaluation is then performed by the Editor-in-Chief and one or more Editors to determine which papers are sent for external peer review. Papers not sent out for review will be immediately rejected.

If you have been invited to revise and resubmit your paper, you should follow instructions provided by the editor in their decision email. You will be expected to provide a document where changes from the previous version can be tracked.

- Research articles must meet the following criteria:
- The manuscript presents the results of primary scientific research.
- The results have not been published in full elsewhere.
- Analyses are performed to a high technical standard and are described in full in the manuscript.
- Conclusions are presented in a clear and concise manner and are supported by the data.
- Manuscripts must be written English using standard scientific terms.
- The research meets all applicable ethical standards.
- The article adheres to appropriate reporting guidelines and community standards for full data disclosure.
- All conflicts of interest should be clearly stated in the manuscript.
- According to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, designation as an author must satisfy three conditions. The author must have:
    - Contributed substantially to the conception and design of the study, the acquisition of data, or the analysis and interpretation of the data.
    - Drafted or provided critical revision of the article.
    - Provided final approval of the version submitted for publication.

- Authors of original papers and reviews are requested to provide the following information:
    - A "Take-home message" (two-sentences) which summarizes how the manuscript adds to current knowledge. This will appear in the final published version of the paper.
    - A 140-character Tweet that may appear online via the Intensive Care Medicine website or social media platforms. This Tweet will not form part of the print version of the manuscript.

- The role of authors and contributors has recently been clarified by the ICMJE

Types of Papers

ICM is not accepting papers providing pre-clinical data (experimental, animal, in-vitro, bench studies or studies without patients). These manuscripts should be submitted to ICM Experimental

Original Papers

Research articles must meet the following criteria:

- The manuscript presents the results of primary scientific research
- The results have not been published in full elsewhere
- Analyses are performed to a high technical standard and are described in full in the manuscript
- Conclusions are presented in a clear and concise manner and are supported by the data
- Manuscripts must be written in English using standard scientific terms
- The research meets all applicable ethical standards
- The article adheres to appropriate reporting guidelines and community standards for full data disclosure. In general papers of studies that have been pre-registered or have a pre-published or approved protocol and analysis plan are prioritized
- All conflicts of interest should be clearly stated in the manuscript

- It is mandatory to upload the appropriate EQUATOR checklist for your study. Please find the appropriate checklist at EQUATOR Network
- According to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, designation as an author must satisfy three conditions. Each author must have:
    - Contributed substantially to the conception and design of the study, the acquisition of data, or the analysis and interpretation of the data
    - Drafted or provided critical revision of the article
    - Provided final approval of the version submitted for publication
- A statement detailing the role of each author in the study should be reported in an appropriate Authorship statement section of the manuscript in compliance with the ICMJE recommendations.
- At the Editor's discretion, authors may be asked to reduce the number of authors in the byline, whenever appropriate. The authors may add a study group name as an author in the byline and list the study group members in an appropriate footnote in the first page of the manuscript in order to have their names entered in PubMed as Collaborators.
- In addition to the abovementioned statements an Authorship and Conflict of Interest form should be completed, signed by each author and uploaded with the manuscript. The form can be downloaded here.
- A 250-word abstract and 3-5 keywords are required

Original papers must not exceed 3,000 words and should include no more than 5 illustrations and tables.

- Up to 50 references are permitted. If a higher number of references is needed, explain the reasons during the submission processes.
- When reporting the results of a randomized controlled trial, author(s) should use the CONSORT statement as a guide in preparing the manuscript.
- If the authors consider that their manuscript needs to be longer than 3,000 words or contain more figures or tables, the reasons for this should be justified in the cover letter to the Editor-in-Chief.
- Supplementary information can be published in electronic supplements without limitation.
- The journal considers only pre-registered trials. A statement should be reported in the manuscript.
- The journal does not consider single centre retrospective studies
- IRB/ethical committee approval and patient informed consent statements should be reported in the manuscript in the Materials and Methods section or in a separate section at the end of the manuscript

Authors of original papers and reviews are requested to provide the following information:

- A "Take-home message" (two sentences) which summarizes how the manuscript adds to current knowledge. This will appear in the final published version of the paper.
- A 140-character Tweet that may appear online via the Intensive Care Medicine website or social media platforms. This Tweet will not form part of the print version of the manuscript

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission
Please follow the hyperlink “Submit manuscript” on the right and upload all of your manuscript files following the instructions given on the screen.
Please ensure you provide all relevant editable source files. Failing to submit these source files might cause unnecessary delays in the review and production process.

Title Page
Please make sure your title page contains the following information.

Title
The title should be concise and informative.

Author information
The name(s) of the author(s)
The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
A clear indication and an active e-mail address of the corresponding author
If available, the 16-digit ORCID of the author(s)
If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Abstract
Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Purpose (stating the main purposes and research question)
- Methods
- Results
- Conclusion

Keywords
Please provide 4 to 6 keywords which can be used for indexing purposes.

Declarations
All manuscripts must contain the following sections under the heading 'Declarations'.
If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.
To be used for all articles, including articles with biological applications

Funding (information that explains whether and by whom the research was supported)

Conflicts of interest/Competing interests (include appropriate disclosures)
Availability of data and material (data transparency)

Code availability (software application or custom code)

Authors' contributions (optional: please review the submission guidelines from the journal whether statements are mandatory)

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

Ethics approval (include appropriate approvals or waivers)

Consent to participate (include appropriate statements)

Consent for publication (include appropriate statements)

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

Please note:

- An abstract is not required for Editorials, Short articles such as 'Focus on, Less is More in Intensive Care, Understanding the Disease, etc.'
- For details, or to submit an outline of your manuscript, please contact the Intensive Care Medicine Managing Editor at intensivecaremedicine@unimib.it

Text Formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.
Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Zotero

If you use Zotero, the ICM styling template can be found here.

Scientific style

Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:
1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list
The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. "https://doi.org/abc").

- Journal article
  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8
  Ideally, the names of all authors should be provided, but the usage of "et al" in long author lists will also be accepted:
  Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI
  Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

- Book
  South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter
  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document
  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation
  Trent JW (1975) Experimental acute renal failure. Dissertation, University of California
  Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see
  ISSN.org LTWA
  If you are unsure, please use the full journal title.

Please note:
References are not necessary for the following sections: Correspondences, Imaging, and From the inside.

Tables
All tables are to be numbered using Arabic numerals.
Tables should always be cited in text in consecutive numerical order.
For each table, please supply a table caption (title) explaining the components of the table.
Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

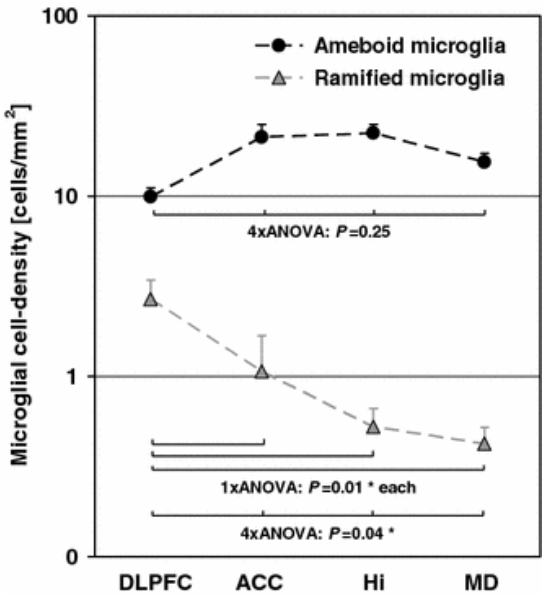
Tables for ICM publication should be prepared taking into account the current style of the journal. Tables that do not exceed the A4 width of a page (portrait format) are preferred. Decimals should be limited to two digits, unless data require to specify up to the third or fourth decimal digit (e.g. 0.0004). Unnecessary decimals should be avoided (e.g. 4.00 should be 4).

Artwork and Illustrations Guidelines

Electronic Figure Submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



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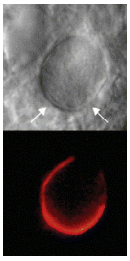

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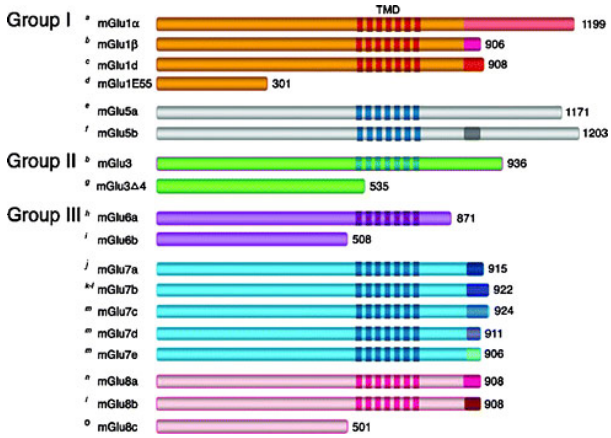

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