Southern African Journal of Anaesthesia and Analgesia 2020; 26(3):116-127
https://doi.org/10.36303/SAJAA.2020.26.3.2428
Open Access article distributed under the terms of the
Creative Commons License [CC BY-NC 3.0]
http://creativecommons.org/licenses/by-nc/3.0

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173
© 2020 The Author(s)
REVIEW ARTICLE

Risk factors and interventions associated with mortality or survival in adult COVID-19 patients admitted to critical care: a systematic review and meta-analysis

EH Taylor,[1] R Hofmeyr,[2] A Torborg,[3,4] C van Tonder,[5] R Boden,[6] E Earle,[7] M Nejthardt,[2] KF Kabambi,[8] M Isaacs,[2] A Usenbo,[8] C Gerber,[2] K van der Spuy,[2] B Mrara,[8] T Ndhlovu,[8] A Chen,[2] J Swanevelder,[2] J Coetzee,[9] BM Biccard[2]

[1] *Nuffield Department of Surgical Sciences, University of Oxford, England*
[2] *Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital, University of Cape Town, South Africa*
[3] *Department of Anaesthesia, University of KwaZulu-Natal, South Africa*
[4] *African Perioperative Outcomes Group, South Africa*
[5] *Department of Anaesthesia, Khayelitsha District Hospital,South Africa*
[6] *University of Cape Town, South Africa*
[7] *Department of Anaesthesia and Intensive Care, Universitas Academic Hospital, University of the Free State, South Africa*
[8] *Department of Anaesthesia, Nelson Mandela Academic Hospital, Walter Sisulu University, South Africa*
[9] *Department of Anaesthesiology, Critical Care, Stellenbosch University and Tygerberg Hospital, South Africa*
Corresponding author, email: *bruce.biccard@uct.ac.za*

Background: Patients with confirmed COVID-19 admitted to intensive care units have a high mortality rate, which appears to be associated with increasing age, male sex, smoking history, hypertension and diabetes mellitus.
Methods: A systematic review to determine risk factors and interventions associated with mortality/survival in adult patients admitted to an intensive care unit (ICU) with confirmed COVID-19/SARS-CoV-2 infection. The protocol was registered with PROSPERO (CRD42020181185).
Results: The search identified 483 abstracts between 1 January and 7 April 2020, of which nine studies were included in the final review. Only one study was of low bias. Advanced age (odds ratio [OR] 11.99, 95% confidence interval [CI] 5.35–18.62) and a history of hypertension were associated with mortality (OR 4.17, 95% CI 2.90–5.99). Sex was not associated with mortality. There was insufficient data to assess the association between other comorbidities, laboratory results or critical care risk indices and mortality. The critical care interventions of mechanical ventilation (OR 6.25, 95% CI 0.75–51.93), prone positioning during ventilation (OR 2.06, 95% CI 0.20–21.72), and extracorporeal membrane oxygenation (ECMO) (OR 8.00, 95% CI 0.69, 92.33) were not associated with mortality. The sample size was insufficient to conclusively determine the association between these interventions and ICU mortality. The need for inotropes or vasopressors was associated with mortality (OR 6.36, 95% CI 1.89–21.36).
Conclusion: The studies provided little granular data to inform risk stratification or prognostication of patients requiring intensive care admission. Larger collaborative research is needed to address this limitation.

Keywords: COVID-19, SARS-CoV-2, critical care, outcomes, mortality, risk factors

Introduction

Initial reports of severe respiratory disease caused by infection with a novel coronavirus emerged from Wuhan, Hubei Province, China, in December 2019. The World Health Organization (WHO) declared this coronavirus disease (COVID-19) a Public Health Emergency of International Concern on 30 January 2020 as case numbers and affected areas rapidly increased. On 11 March 2020, this designation was upgraded to global pandemic, and at the time of writing (10 May 2020) has resulted in more than 4 million confirmed cases and over a quarter of a million deaths worldwide. While the outbreak appears to be under control in some areas of Asia and Europe, case numbers in the Americas are still rapidly increasing, and Africa is notably at an early stage of the pandemic.[1]

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although it is increasingly apparent that asymptomatic and mild infections comprise the majority of cases, existing data suggests that approximately one in five patients will require hospitalisation, and as many as one in 20 may need respiratory support in intensive care.[2] The burden on critical care thus rapidly outstrips available services, even in well-resourced regions. In Africa, where critical care beds are a scarce resource,[3] careful triage will be required. Patients with confirmed COVID-19 admitted to intensive care units have a high mortality rate, which appears to be associated with increasing age, male sex, smoking history, hypertension and diabetes mellitus.[2,4] If we could identify risk factors and/or interventions associated with mortality or survival, it may inform management strategies for countries with limited resources in the early stage of the epidemic, such as most of Africa presently.

The objective of this review was to determine risk factors and interventions associated with mortality/survival in adult COVID-19 patients admitted to an intensive care unit (ICU).

Methods

Protocol and registration

The protocol was registered with PROSPERO (CRD42020181185), and adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[5]

Eligibility criteria

We included studies of adult human patients with confirmed COVID-19/SARS-CoV-2 infection, admitted to intensive care, reporting mortality/survival data. Duplicate studies, reviews, trial registrations, and papers in which the outcomes of interest were not reported were excluded.

Information sources, search and study selection

Searches were conducted using the terms 'coronavirus' OR 'COVID-19' OR 'SARS-CoV-2' OR 'coronavirus 2019 nCoV' AND 'intensive care' OR 'critical care', with allowance for associated MeSH terms. The following databases were accessed: MEDLINE (PubMed), CINAHL (via EBSCOHOST) Scopus (including Embase), Web of Science (all databases), Cochrane Central Register of Controlled Trials, and Proquest. Studies were limited to those published in 2020. The search was limited to studies published between 1 January and 7 April 2020. An example of the search is shown in the Supplementary Table I.

Data collection process

Search results from each database were exported to a reference management tool, where duplicates were removed. The titles and abstracts were extracted into two identical spreadsheets. Abstracts were screened independently by two authors based on predefined eligibility criteria. Discrepancies were reviewed and adjudicated by a third independent reviewer, with reference to the full text if required. The full text publications of all eligible studies were independently reviewed by two authors. Data were independently extracted from the included texts into a standardised reporting form by two authors. The extracted data were then compared to ensure accuracy, with adjudication performed by a third or fourth author in cases of discrepancy. Data extraction included review of supplementary material, and attempts were made to acquire relevant data from study authors where it was not presented in the publication.

Data items

Data were extracted regarding sex, age, pre-existing comorbidities, laboratory results, risk indices and critical care interventions for adult patients requiring intensive care. The full list of extracted data for this review is shown in Supplementary Table II.

Outcomes

The primary outcome was mortality/survival in association with sex, age, smoking, pre-existing comorbidities, laboratory results, risk indices and critical care interventions.

Risk of bias (quality) assessment

The methodological quality of included studies was assessed according to a modified Newcastle-Ottawa Quality Assessment Scale for cohort studies (mNOS).[6] The mNOS is presented in Supplementary Table III. The scale is made up of three categories: selection (4 stars), comparability (2 stars) and outcome (3 stars). A maximum of 9 stars can be given for each included study. Studies scoring 7–9 stars are considered high quality, and studies scoring ≤ 6 considered low quality. Each study was independently assessed by two reviewers, and conflicts were resolved by a third reviewer (BB and RH).

Summary measures and synthesis of results

The criterion for data synthesis was a minimum of two studies reporting outcome data. For dichotomous variables, we calculated the pooled odds ratios (OR) and 95% confidence interval (CI) for mortality in ICU patients with COVID-19. Continuous data (i.e. age, and laboratory data), were analysed using the standardised mean difference (SMD). The mean and standard deviation (SD) were used. When a study reported the continuous data as median and interquartile range (IQR), these were converted to mean and SD, using the formula proposed by Wan et al.[7] Between-study heterogeneity was assessed using the X^2 test ($p < 0.10$ indicating presence of heterogeneity, in which case a random-effects model was adopted, otherwise a fixed-effects model was applied) and an I^2 test (to assess the degree of heterogeneity where an I^2 of > 25% indicates heterogeneity requiring a random effects model).

The statistical analyses were conducted using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Individual forest plots were prepared for each risk factor associated with mortality, with the accompanying odds ratio and 95% confidence intervals calculated.

Results

Study selection

The search strategy identified 483 abstracts, which were individually reviewed for inclusion. Two were excluded due to lack of English-language abstract or adequate translation. The full-text publications of 59 articles were reviewed, of which nine studies met inclusion criteria (Figure 1). Data were extracted from these publications and their supplementary material.[4,8-15]

Study characteristics of included studies

The characteristics of the nine included studies are shown in Table I. The majority of the studies presented small cohorts from Wuhan, China with the exception of a study from Seattle, USA,[4] and a large cohort from Lombardy, Italy.[8] The studies were predominantly retrospective cohorts of patients predominantly in their 50s and 60s.

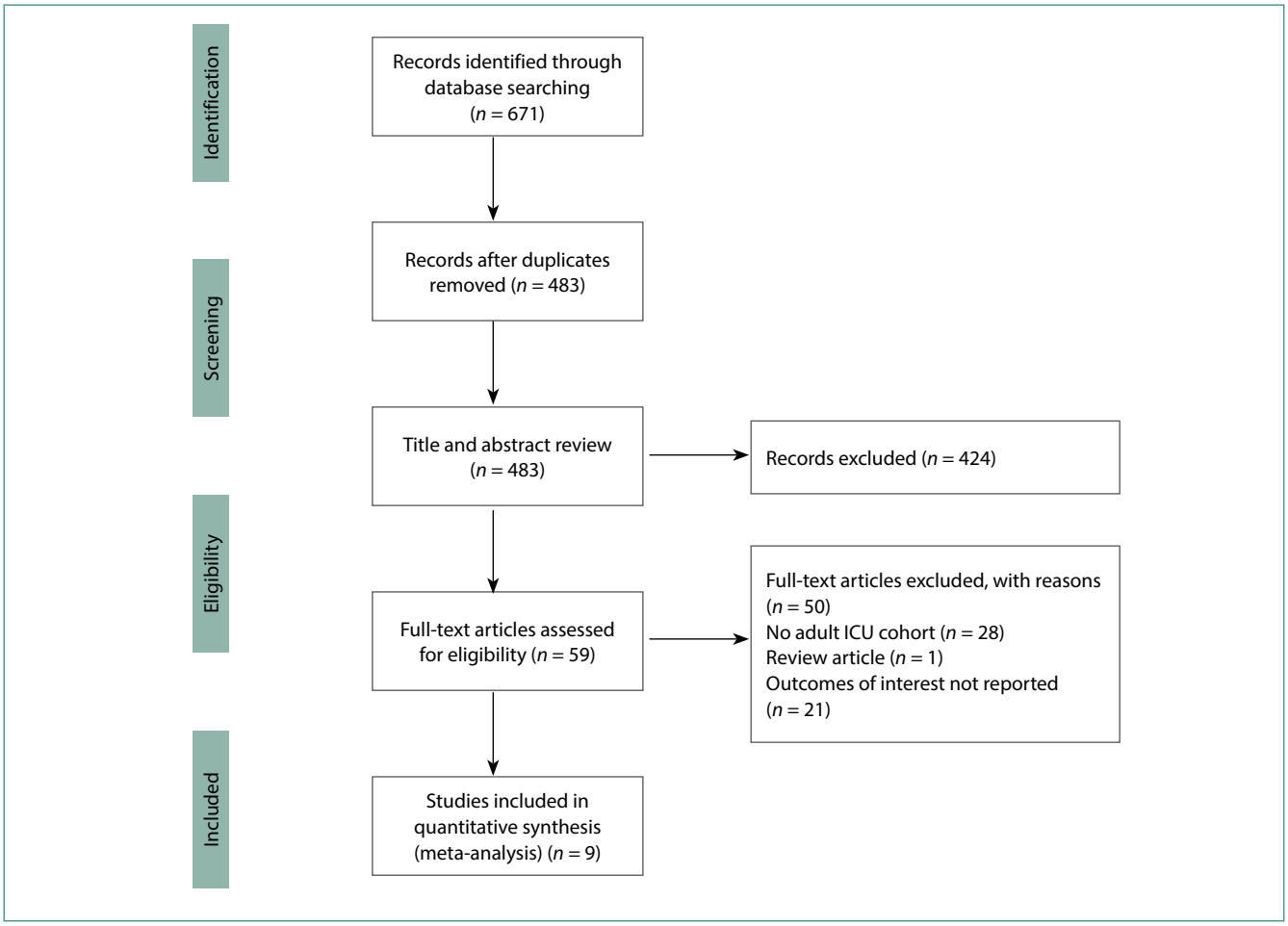


Figure 1: PRISMA flow diagram

Table I: Characteristics of included studies

First author	Region	Cohort size	Age Mean (SD) or Median (IQR)	Cohort type
Bhatraju	USA, Seattle	24	64 (18)	Unclear
Grasselli	Italy, Lombardy	1 591	63 (56–70)	Retrospective
Li	China, Shanghai	8	64 (18)	Retrospective
Ling	China, Hong Kong	8	65 (42–70)	Retrospective
Ma	China, Wuhan	3	63 (7)	Retrospective
Pan	China, Wuhan	12	59 (9)	Retrospective
Ren	China, Wuhan	5	54 (9)	Prospective
Ruan	China, Wuhan	150	Not reported	Retrospective
Yang	China, Wuhan	52	60 (13)	Retrospective

SD – standard deviation, IQR – interquartile range

Risk of bias within studies and across studies

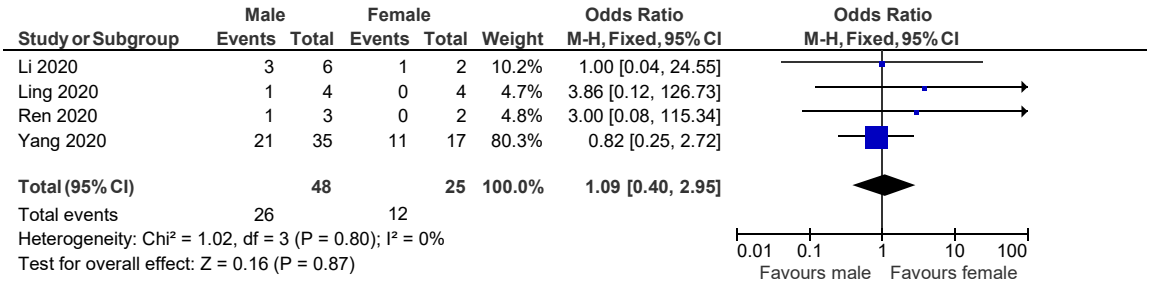
The mNOS assessments for all included studies are listed in Table II. Four studies received the maximum star allocation for 'selection'.[4,8,10,15] Three studies received the maximum star allocation for 'outcome'.[9,10,14] No studies received stars for 'comparability'. Overall, one study was of a high methodological quality with a score of 7 stars.[10] The remaining eight included studies were considered to be of low methodological quality.

Table II: Modified Newcastle Ottawa Quality Assessment Scale Scores

First author, year	Selection (maximum ****)	Comparability (maximum **)	Outcome (maximum ***)
Bhatraju, 2020	****		**
Grasselli, 2020	****		
Li, 2020	*		***
Ling, 2020	****		***
Ma, 2020	**		**
Pan, 2020	***		*
Ren, 2020	**		**
Ruan, 2020	***		***
Yang, 2020	****		**

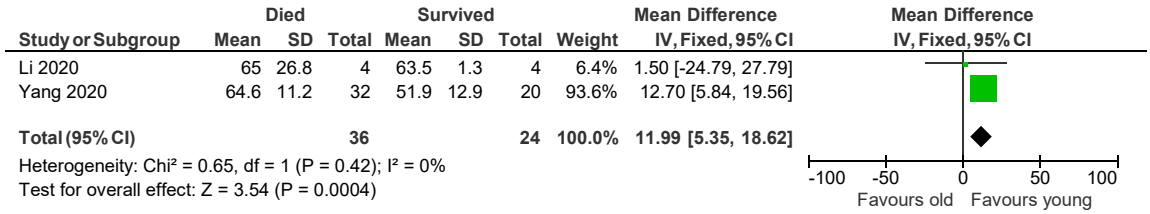
Results of individual studies and synthesis of results

Patient characteristics and comorbidities, and their relationship with patient mortality. There were sufficient data to conduct



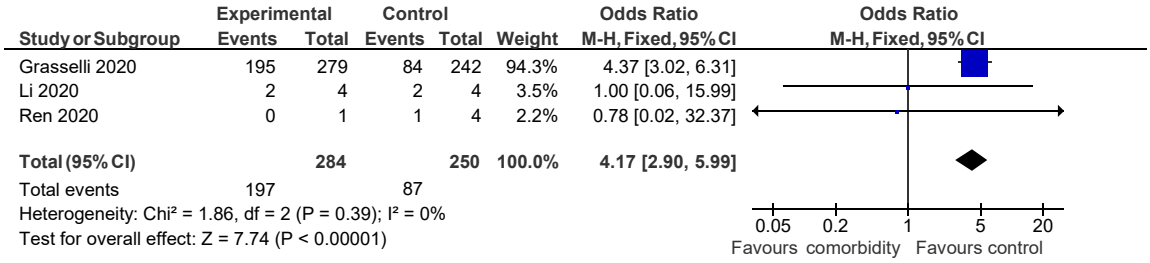
MH – Mantel-Haenszel, CI – confidence interval

Figure 2: Meta-analysis of mortality associated with sex for COVID-19 patients in intensive care



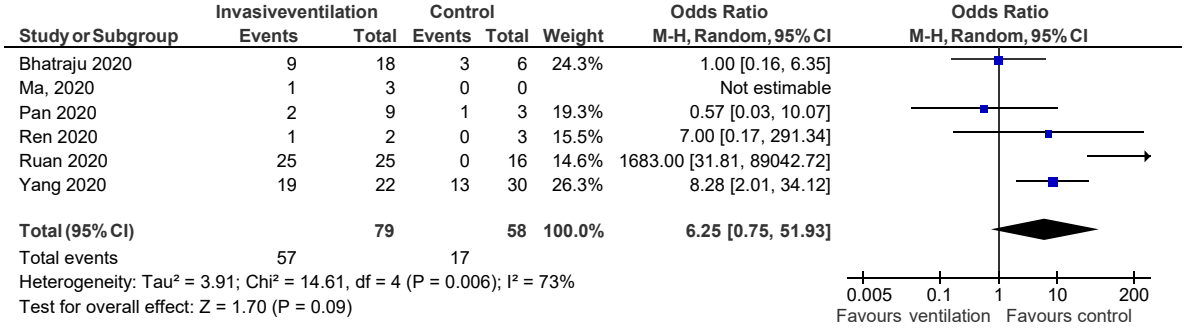
SD – standard deviation, CI – confidence interval

Figure 3: Meta-analysis mortality associated with age for COVID-19 patients in intensive care



MH – Mantel-Haenszel, CI – confidence interval

Figure 4: Meta-analysis of mortality associated with hypertension for COVID-19 patients in intensive care



MH – Mantel-Haenszel, CI – confidence interval

Figure 5: Meta-analysis of the mortality associated with mechanical ventilation for COVID-19 patients in intensive care

a meta-analysis of the association between sex,[9,10,13,15] age,[9,15] hypertension,[8,9,13] cardiovascular, cerebrovascular disease, diabetes and malignancy,[9,15] and intensive care mortality. Sex was not associated with mortality (Figure 2). Advanced age (OR 11.99, 95% CI 5.35–18.62) and a history of hypertension were associated with mortality (OR 4.17, 95% CI 2.90–5.99), Figures 3 and 4 respectively. There was no heterogeneity associated with these estimates.

Data on cardiovascular and cerebrovascular disease, diabetes and malignancy, all had small samples with non-significant results. Outcomes associated with smoking,[15] respiratory[15] and renal disease[9] were only reported by one study, with non-significant results. Usable laboratory investigations were only reported by one study[15] for haemoglobin and platelet count on admission. Neither showed a significant association with mortality. No usable mortality data was available in the reviewed studies for measurements for d-dimer, ferritin, leucocyte, neutrophil or lymphocyte counts. All these results are shown in Supplementary Table IV.

Intensive care risk stratification scores and patient mortality. A single study provided data on intensive care scores and patient mortality (Supplementary Table IV).[15] A lower admission

Sequential Organ Failure Assessment (SOFA) score, and a lower Acute Physiology and Chronic Health Evaluation II (APACHE 2) score on day 1 of intensive care were both associated with increased survival (SMD 2.3, 95% CI 1.2–3.5 and 3.7, 95% CI 1.6–5.7 respectively).

Critical care interventions and patient mortality. Six studies reported mortality data associated with mechanical ventilation.[4,11-15] The mortality of ventilated patients was 57/79 (72%). There was significant heterogeneity associated with the estimate of risk (OR 6.25, 95% CI 0.75–51.93) (Figure 5).

Four studies reporting mortality outcomes associated with prone positioning during mechanical ventilation. Prone positioning was associated with significant heterogeneity, and no difference in outcome (Figure 6).[4,12,14,15] No studies reported on prone positioning in patients not receiving mechanical ventilation.

Five studies reported on mortality associated with extracorporeal membrane oxygenation (ECMO),[11-15] with a reported ECMO mortality of 14/19 (74%). Despite a point estimate towards harm, the relationship between ECMO and increased mortality was non-significant (OR 8.00, 95% CI 0.69–92.33) with significant heterogeneity (Figure 7).

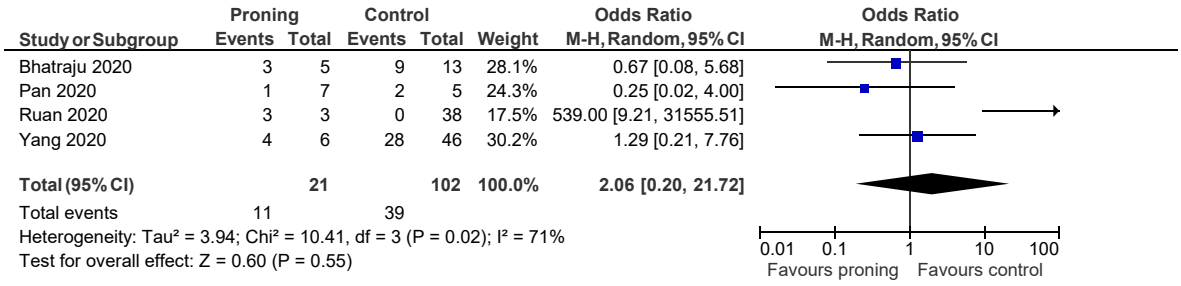
Two of the 12 studies reported mortality associated with inotropes and vasopressors[4,15] which were associated with significantly increased mortality with no heterogeneity (Figure 8) (OR 6.36, 95% CI 1.89–21.36).

Discussion

The principal findings from the available data in this systematic review are that advanced age and hypertension are associated with mortality in adult COVID-19 patients admitted to intensive care. There are currently insufficient data to determine the association between other comorbidities, critical care risk indices, or patient laboratory results and mortality. The intensive care interventions of mechanical ventilation, prone positioning during mechanical ventilation and ECMO were not associated with mortality. The use of (or requirement for) inotrope and/or vasopressor infusions was associated with mortality.

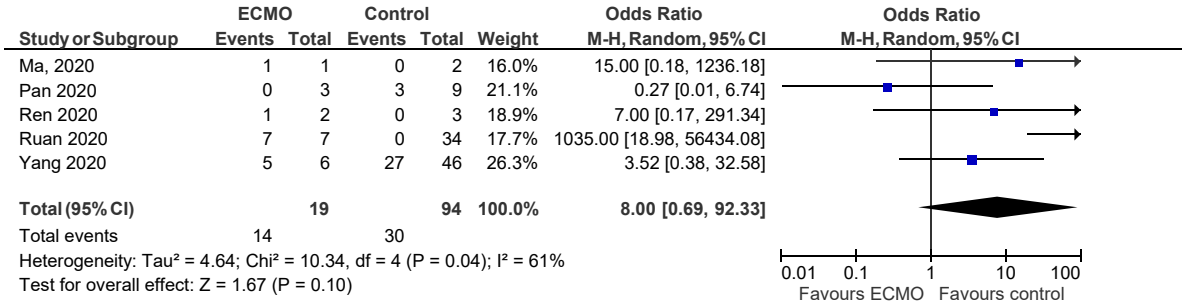
Strengths and weaknesses of this review

The strengths of this review are that it was conducted with robust systematic review methodology on nearly all the published literature of intensive care patients with COVID-19 (two articles with an inadequate translation did not allow evaluation for inclusion). All abstracts, studies, data and quality assessments



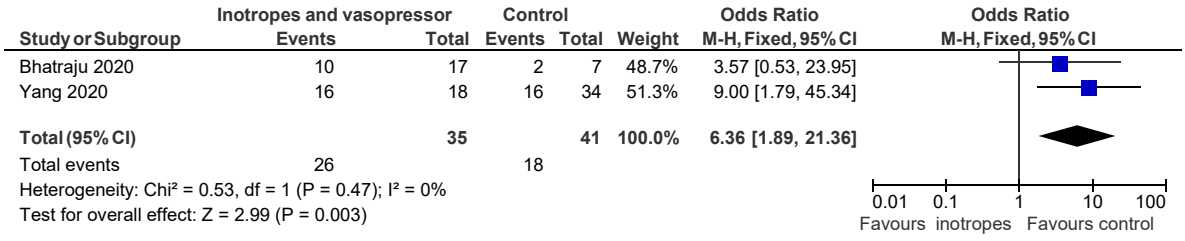
MH – Mantel-Haenszel, CI – confidence interval

Figure 6: Meta-analysis of the mortality associated with prone ventilation for COVID-19 patients in intensive care



MH – Mantel-Haenszel, CI – confidence interval

Figure 7: Meta-analysis of the mortality associated with ECMO for COVID-19 patients in intensive care



MH – Mantel-Haenszel, CI – confidence interval

Figure 8: Meta-analysis of the mortality associated with inotropes and vasopressors for COVID-19 patients in intensive care

were performed independently by two authors and adjudicated in cases of discrepancy.

The weaknesses of this review are that all of the studies, barring one, were of a high-bias, and the total sample size is small. The small sample size means that we were unable to provide estimates of risk for most common comorbidities, risk indices and laboratory test values in COVID-19 patients requiring ICU. Of 59 articles selected for full-text review, only nine provided data for extraction. Of the studies excluded, many documented patient factors, investigations and interventions, but did not discriminate between groups when providing mortality numbers. Thus, due to the paucity of specific outcomes data, only nine studies could be included in the meta-analysis, and data were limited to one or two studies for many variables of interest. Several requests to obtain raw data sets were declined based on regulations pertaining to data sharing, particularly for studies coming out of China. Finally, the majority of studies were small case series or cohorts.

The majority of data which allowed meta-analyses were of interventions in intensive care. The point estimates for mechanical ventilation, prone positioning during mechanical ventilation and ECMO were all towards harm. The sample size for prone positioning was too small for the reported control and intervention event rates, and the sample sizes for mechanical ventilation and ECMO were numerically adequate, but due to the high heterogeneity were too small to definitively address the question.

The need for inotropes and/or vasopressors was associated with mortality, with no heterogeneity for this estimate. Although these findings are strongly suggestive of mortality associated with the use of inotropes and/or vasopressors, all the data were from observational studies, and therefore do not imply causality. It is likely that the need for this intervention reflects the severity of the COVID-19 infection.

Strengths and weaknesses in relation to other studies

The increased mortality with increasing age has been well described in studies of COVID-19 patients,[2] and it is therefore unsurprising that this is borne out in the ICU cohorts. Although advanced age and frailty contribute to mortality in a wide spectrum of diseases, the near absence of severe illness in paediatric patients and dramatic increase in mortality in the elderly for COVID-19 does suggest a mechanistic relationship. Some theories regarding the link to cardiovascular disease, but in particular hypertension may inform this discussion. Our meta-analysis strengthens the evidence linking hypertension (rather than cardiovascular disease in general) to COVID-19 severity and ICU mortality. COVID-19 patients who are hypertensive are more likely to require intensive care admission.[16] Our review now suggests that they are also more likely to die following intensive care admission. The data was insufficient to determine the impact of the treatment and stage of hypertension on mortality in ICU. The role of affinity of the virus for ACE-2 receptors in contributing to this mortality is however far more inconclusive.[17-19]

It would be unsurprising to find an association between interventions such as mechanical ventilation, prone ventilation, ECMO, renal replacement therapy and other intensive care organ support strategies and mortality, as patients must be critically ill and in organ failure to require the instigation thereof. However, the paucity of available outcomes data does not allow meaningful assessment of the risk associated with these interventions. The reported clinical success of prone patient management[20] is not reflected in our data. This may reflect the limited data but may also be related to the fact that all prone positioned cases in this meta-analysis were of mechanically ventilated patients, rather than self-prone positioning in spontaneously breathing patients.

Implications for clinicians and future research

There has been a tremendous number of rapid publications associated with COVID-19, and this is reflected in the nearly 500 publications we identified within the first four months of 2020 which had the terms 'COVID-19' and 'intensive care'. Yet, the amount of clinically useful data is minimal. We would contest that the quality of the rapid publications is generally poor in this field, and it is currently of little use to busy clinicians. Importantly, these publications are fundamentally useless for the following reasons: i) publications are often in print before the very patients they document have progressed to discharge or demised, which results in an outcome assessment bias; ii) the nature of the reporting is superficial with little to no useful supplementary data; and iii) the granular data are unavailable or there is an unwillingness to share these data. Rapid publication and sharing of information during a developing global public health emergency is essential for the accelerated problem-solving offered by the global medical *gestalt*. However, the data need to be sufficiently granular to inform decision-making. This systematic review finds that the facade of many publications is not well supported by a foundation of analysable data.

What is preferably needed is fewer, high quality studies. We hope and recommend that future publications will include (even if only in supplemental material) detailed mortality data for outcomes of interest, and/or that researchers in the field of COVID-19 and other pandemics can be encouraged and permitted to share their de-identified data in near-real-time, to allow for meaningful individual patient data meta-analyses which can inform clinical care.

The current data does not allow for any risk stratification or prognostication of patients requiring intensive care admission. Larger collaborative research is needed to address this limitation. We are currently in the process of conducting such research (African COVID-19 Critical Care Outcomes Study [ACCCOS], ClinicalTrials.gov NCT04367207).

In conclusion, advanced age and hypertension are associated with increased mortality in patients with COVID-19 requiring intensive care. The severity of ICU admission score and use of inotropes or vasopressors are associated with increased mortality, as would be expected in patients with more severe disease. The current data are of a low quality and more robust prospective observational work is needed to inform prognostication for COVID-19 patients requiring intensive care.

Conflict of interest

The authors do not have any conflicts of interest.

Funding

Local Departmental resources.

Availability of data and materials

All reviewed abstracts and articles are available online, and the dataset is available from the corresponding author.

Author's contributions

Screening, extraction of articles and data extraction was performed by all authors. The first draft of the manuscript was written by RH, ET and BB. The manuscript was critically reviewed by all authors.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

ORCID

EH Taylor https://orcid.org/0000-0002-8462-6582
R Hofmeyr https://orcid.org/0000-0002-9990-7459
A Torborg https://orcid.org/0000-0002-1584-0112
C van Tonder https://orcid.org/0000-0002-8223-1579
R Boden https://orcid.org/0000-0002-8650-161X
E Earle https://orcid.org/0000-0001-5757-808X
M Nejthardt https://orcid.org/0000-0002-8997-7242
KF Kabambi https://orcid.org/0000-0003-3166-016X
M Isaacs https://orcid.org/0000-0001-5365-2190
A Usenbo https://orcid.org/0000-0002-6366-5945
C Gerber https://orcid.org/0000-0003-0377-0337
K van der Spuy https://orcid.org/0000-0002-9159-7855
B Mrara https://orcid.org/0000-0002-2130-1756
T Ndhlovu https://orcid.org/0000-0001-6581-4425
A Chen https://orcid.org/0000-0001-7508-7188
J Swanevelder https://orcid.org/0000-0001-6986-4470
J Coetzee https://orcid.org/0000-0002-9925-7767
BM Biccard http://orcid.org/0000-0001-5872-8369

References

1. Coronavirus Resource Center [cited 10 May 2020]. Available from: https://coronavirus.jhu.edu/map.html.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. [published Online First: 2020/03/15]. https://doi.org/10.1016/S0140-6736(20)30566-3.
3. Houreld K, Lewis D, McNeill R, Granados S. Virus exposes gaping holes in Africa's health systems: Reuters; 2020 [cited 10 May 2020]. Available from: https://graphics.reuters.com/HEALTH-CORONAVIRUS/AFRICA/yzdpxoqbdvx/.
4. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle Region - case series. N Engl J Med. 2020;382:2012-22. [published Online First: 2020/04/01]. https://doi.org/10.1056/NEJMoa2004500.
5. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. [published Online First: 2009/07/23]. https://doi.org/10.1136/bmj.b2535.
6. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [22 April 2014]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
7. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodo.l 2014;14:135. [published Online First: 2014/12/20]. https://doi.org/10.1186/1471-2288-14-135.
8. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-1581. [published Online First: 2020/04/07]. https://doi.org/10.1001/jama.2020.5394.
9. Li X, Guo Z, Li B, et al. Extracorporeal membrane yxygenation for coronavirus disease 2019 in Shanghai, China. ASAIO Journal. 2020;66(5):475-81. [published Online First: 2020/04/04]. https://doi.org/10.1097/MAT.0000000000001172.
10. Ling L, So C, Shum HP, et al. Critically ill patients with COVID-19 in Hong Kong: a multicentre retrospective observational cohort study. Crit Care Resusc. 2020 [published Online First: 2020/04/06].
11. Ma J, Xia P, Zhou Y, et al. Potential effect of blood purification therapy in reducing cytokine storm as a late complication of critically ill COVID-19. Clin Immunol. 2020;214:108408. [published Online First: 2020/04/05].https://doi.org/10.1016/j.clim.2020.108408.
12. Pan C, Chen L, Lu C, et al. Lung recruitability in SARS-CoV-2-associated acute respiratory distress syndrome: a single-center, observational study. Am J Respir Crit Care Med. 2020. [published Online First: 2020/03/24]. https://doi.org/10.1164/rccm.202003-0527LE.
13. Ren LL, Wang YM, Wu ZQ, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chinese Medical Journal. 2020;133(9):1015-24. [published Online First: 2020/02/01]. https://doi.org/10.1097/CM9.0000000000000722.
14. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-48. [published Online First: 2020/03/04]. https://doi.org/10.1007/s00134-020-05991-x.
15. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475-81. [published Online First: 2020/02/28]. https://doi.org/10.1016/S2213-2600(20)30079-5.
16. Roncon L, Zuin M, Zuliani G, Rigatelli G. Patients with arterial hypertension and COVID-19 are at higher risk of ICU admission. Br J Anaesth. 2020. [published Online First: 2020/05/10]. https://doi.org/10.1016/j.bja.2020.04.056.
17. Mehra MR, Desai SS, Kuy S, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. 2020. [published Online First: 2020/05/02]. https://doi.org/10.1056/NEJMoa2007621.
18. Mancia G, Rea F, Ludergnani M, et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med. 2020. [published Online First: 2020/05/02]. https://doi.org/10.1056/NEJMoa2006923.
19. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med. 2020. [published Online First: 2020/05/01]. https://doi.org/10.1056/NEJMoa2008975.
20. Ghelichkhani P, Esmaeili M. Prone position in management of COVID-19 patients; a commentary. Arch Acad Emerg Med. 2020;8(1):e48. [published Online First: 2020/04/21].

Supplementary material

Risk factors and interventions associated with mortality or survival in adult COVID-19 patients admitted to critical care: a systematic review and meta-analysis

Elliott H Taylor, Ross Hofmeyr, Alexandra Torborg, Charmé van Tonder, Regan Boden, Etienne Earle, Marcin Nejthardt, Kasandji Freddy Kabambi, Mariam Isaacs, Anthony Usenbo, Carmen Gerber, Karen van der Spuy, Busisiwe Mrara, Tamuka Ndhlovu, Aaron Chen, Justiaan Swanevelder, Johan Coetzee, Bruce M Biccard

Supplementary Table I: Example of search strategy for this review

PubMed	MESH	KEYWORDS	
	Betacoronavirus [MH] OR Coronavirus [MH] OR "Coronavirus Infections"[MH] OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]	Betacoronavirus OR Betacoronaviruses Corona Virus OR Corona Viruses OR Coronavirus OR Coronaviruses OR Coronovirus OR Coronoviruses Coronavirus Infection OR Coronavirus Infections Corona Infection OR Corona Infections OR COVID OR COVID19 OR COVID-19 OR CoV OR CoV2 OR HCoV-19 OR nCoV OR 2019nCoV OR Severe Acute Respiratory Syndrome CoV OR severe acute respiratory syndrome coronavirus 2 OR SARS CoV 2 OR SARS-CoV-2 OR SARSCoV OR SARS-CoV OR SARS2	((((("Betacoronavirus"[Mesh] OR (("betacoronavirus"[MeSH Terms] OR "betacoronavirus"[All Fields]) OR ("betacoronavirus"[MeSH Terms] OR "betacoronavirus"[All Fields] OR "betacoronaviruses"[All Fields]))) OR ("Coronavirus"[Mesh] OR ((Corona[All Fields] AND ("viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields])) OR (Corona[All Fields] AND ("virology"[Subheading] OR "virology"[All Fields] OR "viruses"[All Fields] OR "viruses"[MeSH Terms])) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR Coronovirus[All Fields] OR Coronoviruses[All Fields]))) OR ("Coronavirus Infections"[Mesh] OR (("coronavirus infections"[MeSH Terms] OR ("coronavirus"[All Fields] AND "infections"[All Fields]) OR "coronavirus infections"[All Fields] OR ("coronavirus"[All Fields] AND "infection"[All Fields]) OR "coronavirus infection"[All Fields]) OR (("coronavirus infections"[MeSH Terms] OR ("coronavirus"[All Fields] AND "infections"[All Fields]) OR "coronavirus infections"[All Fields]) AND Corona[All Fields] AND ("infections"[MeSH Terms] OR "infections"[All Fields] OR "infection"[All Fields])) OR (Corona[All Fields] AND ("infections"[MeSH Terms] OR "infections"[All Fields])))))) OR ("COVID-19"[Supplementary Concept] OR (COVID[All Fields] OR ("COVID-19"[Supplementary Concept] OR "COVID-19"[All Fields] OR "covid19"[All Fields]) OR ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT])))) OR CoV[All Fields] OR CoV2[All Fields] OR HCoV-19[All Fields] OR nCoV[All Fields] OR 2019nCoV[All Fields])))) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR (((("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]) AND CoV[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR SARSCoV[All Fields] OR ("sars virus"[MeSH Terms] OR ("sars"[All Fields] AND "virus"[All Fields]) OR "sars virus"[All Fields] OR ("sars"[All Fields] AND "cov"[All Fields]) OR "sars cov"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars2"[All Fields]))))
	"Critical Care"[Mesh]	critical care OR Intensive care	(("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields]) OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields])) OR "Critical Care"[Mesh]

COVID AND CRITICAL CARE			(((((("Betacoronavirus"[Mesh] OR (("betacoronavirus"[MeSH Terms] OR "betacoronavirus"[All Fields]) OR ("betacoronavirus"[MeSH Terms] OR "betacoronavirus"[All Fields] OR "betacoronaviruses"[All Fields])))) OR ("Coronavirus"[Mesh] OR ((Corona[All Fields] AND ("viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields])) OR (Corona[All Fields] AND ("virology"[Subheading] OR "virology"[All Fields] OR "viruses"[All Fields] OR "viruses"[MeSH Terms])) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR Coronovirus[All Fields] OR Coronoviruses[All Fields])))) OR ("Coronavirus Infections"[Mesh] OR (("coronavirus infections"[MeSH Terms] OR ("coronavirus"[All Fields] AND "infections"[All Fields]) OR "coronavirus infections"[All Fields] OR ("coronavirus"[All Fields] AND "infection"[All Fields]) OR "coronavirus infection"[All Fields]) OR (("coronavirus infections"[MeSH Terms] OR ("coronavirus"[All Fields] AND "infections"[All Fields]) OR "coronavirus infections"[All Fields]) AND Corona[All Fields] AND ("infections"[MeSH Terms] OR "infections"[All Fields] OR "infection"[All Fields])) OR (Corona[All Fields] AND ("infections"[MeSH Terms] OR "infections"[All Fields])))))) OR ("COVID-19"[Supplementary Concept] OR (COVID[All Fields] OR ("COVID-19"[Supplementary Concept] OR "COVID-19"[All Fields] OR "covid19"[All Fields]) OR ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) OR CoV[All Fields] OR CoV2[All Fields] OR HCoV-19[All Fields] OR nCoV[All Fields] OR 2019nCoV[All Fields])))) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR ((("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]) AND CoV[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR SARSCoV[All Fields] OR ("sars virus"[MeSH Terms] OR ("sars"[All Fields] AND "virus"[All Fields]) OR "sars virus"[All Fields] OR ("sars"[All Fields] AND "cov"[All Fields]) OR "sars cov"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars2"[All Fields])))) AND ((("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields]) OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields])) OR "Critical Care"[Mesh])

COVID AND CRITICAL CARE AND 01/01/2020-07/04/2020			(((((("Betacoronavirus"[Mesh] OR (("betacoronavirus"[MeSH Terms] OR "betacoronavirus"[All Fields]) OR ("betacoronavirus"[MeSH Terms] OR "betacoronavirus"[All Fields] OR "betacoronaviruses"[All Fields]))) OR ("Coronavirus"[Mesh] OR ((Corona[All Fields] AND ("viruses"[MeSH Terms] OR "viruses"[All Fields] OR "virus"[All Fields])) OR (Corona[All Fields] AND ("virology"[Subheading] OR "virology"[All Fields] OR "viruses"[All Fields] OR "viruses"[MeSH Terms])) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR Coronovirus[All Fields] OR Coronoviruses[All Fields]))) OR ("Coronavirus Infections"[Mesh] OR (("coronavirus infections"[MeSH Terms] OR ("coronavirus"[All Fields] AND "infections"[All Fields]) OR "coronavirus infections"[All Fields] OR ("coronavirus"[All Fields] AND "infection"[All Fields]) OR "coronavirus infection"[All Fields]) OR (("coronavirus infections"[MeSH Terms] OR ("coronavirus"[All Fields] AND "infections"[All Fields]) OR "coronavirus infections"[All Fields]) AND Corona[All Fields] AND ("infections"[MeSH Terms] OR "infections"[All Fields] OR "infection"[All Fields])) OR (Corona[All Fields] AND ("infections"[MeSH Terms] OR "infections"[All Fields])))))) OR ("COVID-19"[Supplementary Concept] OR (COVID[All Fields] OR ("COVID-19"[Supplementary Concept] OR "COVID-19"[All Fields] OR "covid19"[All Fields]) OR ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) OR CoV[All Fields] OR CoV2[All Fields] OR HCoV-19[All Fields] OR nCoV[All Fields] OR 2019nCoV[All Fields]))) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR ((("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]) AND CoV[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) OR SARSCoV[All Fields] OR ("sars virus"[MeSH Terms] OR ("sars"[All Fields] AND "virus"[All Fields]) OR "sars virus"[All Fields] OR ("sars"[All Fields] AND "cov"[All Fields]) OR "sars cov"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars2"[All Fields])))) AND ((("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields]) OR ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields]) OR "intensive care"[All Fields])) OR "Critical Care"[Mesh]) AND ("2020/01/01"[PDAT] : "2020/04/07"[PDAT])

Supplementary Table II: The full list of extracted data for this review

Risk factors:	ICU Scores	Laboratory investigations	Interventions
Sex	SOFA	D-Dimer	Prone position
Age	APACHE	Ferritin	Ventilation
Hypertension		Platelets	ECMO
CVS disease		Haemoglobin	FiO2
Smoking		Leucocyte count	PEEP
Respiratory disease		Neutrophil count	Inotropes
Diabetes		Lymphocyte count	Anticoagulation
Renal disease			
Malignancy/Cancer			
Cerebrovascular disease			

ICU – Intensive Care Unit, SOFA – Sequential Organ Failure Assessment, APACHE 2 – Acute Physiology and Chronic Health Evaluation II, CVS – cardiovascular system, ECMO – extracorporeal membrane oxygenation, FiO2 – fraction of inspired oxygen, PEEP – positive and expiratory pressure.

Supplementary Table III: Modified Newcastle Ottawa Quality Assessment Scale

Category	Criteria
Selection	**1. Representativeness of the exposed cohort:** a) all COVID-19 positive patients in the named intensive care unit during the study period were included in the cohort★ b) a random selection of COVID-19 positive patients in the named intensive care unit during the study period were included in the cohort★ c) a non-random selection of COVID-19 positive patients within the named intensive care unit during the study period were included in the cohort. d) no description of how the cohort was selected **2. Selection of the non-exposed cohort:** a) drawn from the same COVID-19 positive intensive care unit cohort as the exposed cohort ★ b) drawn from a different COVID-19 intensive care unit cohort as the exposed cohort c) no description of how the non-exposed cohort was selected **3. Ascertainment of exposure:** a) secure record (eg hospital medical records) ★ b) reported by intensive care practitioners ★ c) written self report d) no description **4. Demonstration that outcome of interest was not present at start of study** a) yes ★ b) no
Comparability	**1. Comparability of cohorts on the basis of the design or analysis:** a) study controls for comorbidity risk factors (e.g. logistic regression model, case control) ★ b) study controls for interventions in intensive care (e.g. logistic regression, case control) ★
Outcome	**1. Assessment of outcome:** a) independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (medical records, etc.)★ b) record linkage (e.g. identified through ICD codes on database records) ★ c) self-report (i.e. no reference to original medical records to confirm the outcome) d) no description. **2. Was follow-up long enough for outcomes to occur:** a) yes (until intensive care discharge, or at least 30 days follow up in intensive care) ★ b) no **3. Adequacy of follow up of cohorts:** a) complete follow up - all subjects accounted for ★ b) subjects lost to follow up unlikely to introduce bias – small number lost (>95 % follow up, or description provided of those lost) ★ c) follow up rate ≤95% and no description of those lost d) no statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Supplementary Table IV: Comorbidities, laboratory results, intensive care risk indices and associated mortality in patients with COVID-19 admitted to ICU

Comorbidity or intervention	Studies (*n*)	Participants (*n*)	Statistical method	Effect estimate (95% confidence interval)
Cardiovascular disease	2	60	Odds ratio	1.33 (0.26, 6.75)
Respiratory disease	1	52	Odds ratio	0.60 (0.08, 4.64)
Smoking	1	52	Odds ratio	0.11 (0.01, 2.50)
Malignancy	2	60	Odds ratio	1.35 (0.17, 10.90)
Cerebrovascular disease	2	60	Odds ratio	5.27 (0.77, 35.90)
Renal disease	1	8	Odds ratio	0.26 (0.01, 8.52)
Diabetes	2	60	Odds ratio	1.59 (0.39, 6.41)
APACHE 2 on day 1	1	52	Mean difference	3.67 (1.62, 5.72)
SOFA score on admission	1	52	Mean difference	2.33 (1.20, 3.46)
Haemoglobin count	1	52	Mean difference	2.00 (-8.02, 12.02)
Platelet count	1	52	Mean difference	27.00 (-12.09, 66.09)

SOFA – Sequential Organ Failure Assessment, APACHE – Acute Physiology and Chronic Health Evaluation