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Prognostic factors associated with mortality among patients receiving venovenous extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis



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Summary

Background Venovenous extracorporeal membrane oxygenation (ECMO) can be considered for patients with COVID-19-associated acute respiratory distress syndrome (ARDS) who continue to deteriorate despite evidence-based therapies and lung-protective ventilation. The Extracorporeal Life Support Organization has emphasised the importance of patient selection; however, to better inform these decisions, a comprehensive and evidence-based understanding of the risk factors associated with poor outcomes is necessary. We aimed to summarise the association between pre-cannulation prognostic factors and risk of mortality in adult patients requiring venovenous ECMO for the treatment of COVID-19.

Methods In this systematic review and meta-analysis, we searched MEDLINE and Embase from Dec 1, 2019, to April 14, 2022, for randomised controlled trials and observational studies involving adult patients who required ECMO for COVID-19-associated ARDS and for whom pre-cannulation prognostic factors associated with in-hospital mortality were evaluated. We conducted separate meta-analyses of unadjusted and adjusted odds ratios (uORs), adjusted hazard ratios (aHRs), and mean differences, and excluded studies if these data could not be extracted. We assessed the risk of bias using the Quality in Prognosis Studies tool and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach. Our protocol was registered with the Open Science Framework registry, osf.io/6gcy2.

Findings Our search identified 2888 studies, of which 42 observational cohort studies involving 17 449 patients were included. Factors that had moderate or high certainty of association with increased mortality included patient factors, such as older age (adjusted hazard ratio [aHR] 2·27 [95% CI 1·63–3·16]), male sex (unadjusted odds ratio [uOR] 1·34 [1·20–1·49]), and chronic lung disease (aHR 1·55 [1·20–2·00]); pre-cannulation disease factors, such as longer duration of symptoms (mean difference 1·51 days [95% CI 0·36–2·65]), longer duration of invasive mechanical ventilation (uOR 1·94 [1·40–2·67]), higher partial pressure of arterial carbon dioxide (mean difference 4·04 mm Hg [1·64–6·44]), and higher driving pressure (aHR 2·36 [1·40–3·97]); and centre factors, such as less previous experience with ECMO (aOR 2·27 [1·28–4·05]).

Interpretation The prognostic factors identified highlight the importance of patient selection, the effect of injurious lung ventilation, and the potential opportunity for greater centralisation and collaboration in the use of ECMO for the treatment of COVID-19-associated ARDS. These factors should be carefully considered as part of a risk stratification framework when evaluating a patient for potential treatment with venovenous ECMO.

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Introduction

COVID-19 is an important cause of acute respiratory distress syndrome (ARDS)^{1,2} and indication for invasive mechanical ventilation. However, despite best practice management, including the use of evidence-based therapies³ and lung-protective ventilation strategies,^{4,5} some patients with COVID-19 will continue to deteriorate. Informed by existing evidence from studies of patients with ARDS unrelated to COVID-19,^{6–9} several

international medical organisations have recommended that venovenous extracorporeal membrane oxygenation (ECMO) is considered for such patients.^{10,11}

A meta-analysis including nearly 1900 patients with COVID-19 who were supported with ECMO during the first year of the pandemic showed that these patients had similar outcomes to those with non-COVID-19-associated ARDS,¹² highlighting the potential effectiveness of ECMO in the treatment of carefully selected patients

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See Online for appendix

Research in context

Evidence before this study

Venovenous extracorporeal membrane oxygenation (ECMO) can be considered for patients with COVID-19-associated acute respiratory distress syndrome (ARDS) who continue to deteriorate despite evidence-based therapies and lung-protective ventilation. The Extracorporeal Life Support Organization has emphasised the importance of prioritising patients who are most likely to benefit from the treatment, requiring a comprehensive and evidence-based understanding of the risk factors associated with poor outcomes; however, to our knowledge, no systematic reviews have summarised the association between important prognostic factors and risk of mortality for this patient population. We searched MEDLINE and Embase from Dec 1, 2019, to April 14, 2022, using clinical content terms including "SARS-CoV-2", "COVID-19", "extracorporeal membrane oxygenation", and "ECMO", and prognostic methodology terms including "predict", "model", "risk", and "mortality". Randomised controlled trials and observational studies were eligible if they included adult patients with confirmed COVID-19 who required ECMO for COVID-associated ARDS and for whom pre-cannulation prognostic factors associated with in-hospital mortality were evaluated. We excluded case reports or case series with fewer than five patients, and studies that did not provide sufficient data to extract or calculate unadjusted odds ratios, adjusted odds ratios, adjusted hazard ratios, or mean differences.

with COVID-19. However, this analysis represented only the initial experience with ECMO in the treatment of COVID-19, predominantly during the first wave of the pandemic. Later studies showed an increase in mortality of patients with COVID-19 who were treated with ECMO, possibly due to changes in concomitant treatments (such as corticosteroids, immunomodulators, and non-invasive ventilation), patient selection, and SARS-CoV-2 variants.¹³

A 2022 multicontinental comparative effectiveness study showed that ECMO was associated with a reduction in mortality for some patients with COVID-19.¹⁴ However, the scarcity of ECMO resources during the COVID-19 pandemic¹⁵ and the high associated costs¹⁶ probably affected patient selection in many health-care systems throughout the world.¹⁷ Recognising the intensity of resources required and the potential for major complications associated with ECMO, the Extracorporeal Life Support Organization (ELSO) emphasised the importance of appropriate patient selection—ie, prioritising those most likely to benefit.¹⁰

To better inform appropriate patient selection, a comprehensive and evidence-based understanding of risk factors associated with poor outcomes is necessary. We conducted a systematic review and meta-analysis with the aim of summarising the association between pre-cannulation prognostic factors (including patient factors, disease factors, and centre factors) and the risk of

Added value of this study

This systematic review and meta-analysis summarises the association between several pre-cannulation prognostic factors and the risk of mortality in patients requiring venovenous ECMO for COVID-19. Factors with moderate or high certainty of association with increased mortality included patient factors, such as older age, male sex, and chronic lung disease; pre-cannulation disease factors, such as longer duration of symptoms, longer duration of invasive mechanical ventilation, higher partial pressure of arterial carbon dioxide, and higher driving pressure; and centre factors, such as lower previous ECMO volume. Taken together, these findings provide the framework for evidence-based risk stratification of patients with COVID-19 who require venovenous ECMO.

Implications of all the available evidence

The prognostic factors identified highlight several well established principles of effective ARDS and ECMO care: the importance of patient selection, the effect of injurious lung ventilation, and the potential opportunity for greater centralisation and collaboration in the use of ECMO across centres and regions. We advocate for the careful consideration of these prognostic factors as part of a risk stratification framework when evaluating a patient's potential indication for venovenous ECMO for the treatment of COVID-19.

in-hospital mortality in adult patients receiving venovenous ECMO for acute respiratory failure secondary to COVID-19.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,¹⁸ the Prognosis Research Strategy Group (PROGRESS) recommendations,^{19–22} the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) checklist,²³ and guidelines for meta-analyses of prognostic factor studies.²⁴

An experienced systematic review methodologist (BR) assisted in the development of the search strategy. We searched MEDLINE and Embase from Dec 1, 2019, to April 14, 2022, using clinical content terms combined with terms related to prognostic research, consistent with similar prognostic meta-analyses and recommendations from the PROGRESS group.^{25–28} The full search strategy is included in the appendix (p 2).

We included randomised controlled trials and observational studies published in English that included adult patients (aged ≥ 16 years) with COVID-19 confirmed by PCR, patients requiring any configuration of ECMO for COVID-19-associated ARDS (at least 90% of studies

included venovenous ECMO exclusively), and the evaluation of pre-cannulation prognostic factors associated with in-hospital mortality. We excluded case reports or case series with fewer than five patients, and studies that did not provide sufficient data to extract or calculate unadjusted odds ratios (uORs), adjusted odds ratios (aORs), adjusted hazard ratios (aHRs), or mean differences. ORs and HRs were considered to be adjusted if calculated with confounding adjustment in a multivariable logistic regression (OR) or Cox proportional hazards (HR) model. If these values could not be obtained from the reported data, we contacted the corresponding authors of the studies for clarification.

We screened studies using Covidence (Melbourne, VIC, Australia). We imported titles into Covidence directly from the databases and removed duplicates. Two reviewers (AT and SMF) independently screened the titles and abstracts of all identified studies and resolved disagreements by discussion; no third-party adjudication was necessary. The same two reviewers then independently assessed the full text of the selected studies, and disagreements were resolved by discussion.

Data analysis

Two investigators (AT and SMF) extracted the following variables: author information, year of publication, study design, study dates, eligibility criteria, prognostic factors available before cannulation for ECMO, and mortality as defined by study authors. Prognostic factors included patient factors, such as age, sex, pre-existing comorbidities, and obesity (as defined by study authors); disease factors, such as the duration of invasive mechanical ventilation before ECMO or the duration of symptoms (as defined by study authors), and physiological markers of oxygenation and ventilation, such as the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air ($\text{PaO}_2/\text{FiO}_2$) or respiratory system compliance; and centre factors, such as more previous experience (higher-volume centres) or less previous experience (lower-volume centres) with ECMO (as defined by study authors). For each prognostic factor, two investigators (AT and SMF) independently collected or calculated ORs and HRs for mortality. For mean differences, means and corresponding SDs were collected or estimated from medians and IQRs using Wan's method.²⁹ In the event of overlapping patient cohorts, we preferentially included data from the larger patient cohort. We extracted data using a modified CHARMS checklist for prognostic factors.²³

Two reviewers (AT and SMF) independently assessed the risk of bias in the included studies using the Quality in Prognosis Studies tool.³⁰ Disagreements were resolved by consensus following discussion. Specific domains were judged to be at low, moderate, or high risk of bias. Funnel plots were constructed for analyses with at least ten included studies to evaluate for publication bias.

We extracted or calculated uORs, aORs, aHRs, and mean differences on the basis of available data and mortality as defined by the study authors. Specifically, the primary outcome of interest was in-hospital mortality, and alternative definitions are addressed in the sensitivity analysis. We conducted meta-analyses of uORs, aORs, aHRs, and mean differences separately using the random-effects method³¹ and the Review Manager software (version 5.3; Cochrane, Copenhagen, Denmark). In accordance with Cochrane guidance, given the high event rate for mortality in this review, we pooled aOR and aHR in separate analyses.³² We present results as pooled uORs, aORs, aHRs, and mean differences with 95% CIs. We assessed statistical heterogeneity using the I^2 statistic, the χ^2 test for homogeneity, and visual inspection of the forest plots.

An investigator (BR) with expertise in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology assessed overall certainty in pooled estimates using the GRADE approach for the meta-analyses of prognostic studies.³³ All assessments were reviewed with the whole author group, discussed, and approved with unanimous consent. The overall certainties in estimates were categorised into one of four levels: high, moderate, low, or very low. Consistent with GRADE guidance for prognostic studies, observational data start as high-certainty evidence, but certainty can be downgraded as a result of concern for the precision, consistency, risk of bias, directness, or publication bias. A GRADE evidence profile was created with the GRADEpro Guideline Development Tool. If multiple analyses were available for the same prognostic factor, including those based on different categorisation thresholds and those with or without confounding adjustment, we highlighted results from the analysis with the highest certainty. Consistent with GRADE recommendations, high certainty was described as was associated, moderate certainty was described as was probably associated, low certainty was described as may have been associated, and very low certainty was described as uncertain.³⁴

We conducted two pre-specified sensitivity analyses (appendix p 34–35). In the first analysis, we excluded studies evaluating intensive care unit (ICU) mortality or 28-day mortality,^{35–39} rather than the intended primary outcome of in-hospital mortality. In the second analysis, we excluded adjusted analyses from studies with a potential risk of bias due to poor adherence to best practice methodological guidelines for prediction model development.^{35–37,39–46} We considered the use of metaregression to further explore subgroups of interest, but did not have a sample size of ten or more studies per adjusted variable, as recommended by Cochrane guidance.⁴⁷ For the unadjusted analyses, we decided not to use study-level metaregression because it was unlikely to further benefit the analysis.

Our protocol was registered with the Open Science Framework registry, osf.io/6gcy2.

For more on the GRADEpro Guideline Development Tool see <https://grade.pro>

Role of the funding source

There was no funding source for this study.

Results

Of 2888 studies identified (figure), we selected 123 for full-text review. We included 42 observational cohort studies^{13,35–46,48–75} involving 17 449 patients (table 1), predominantly from North America or Europe. We did not identify any randomised controlled trials that met our eligibility criteria. In-hospital mortality was most commonly reported (54% across all included studies).

Using the Quality in Prognosis Studies tool for the evaluation of prognostic studies,³⁰ most studies were judged to be at low risk of bias in the domains of study participation, study attrition, prognostic factor measurement, and outcome measurement. Some studies were judged to be at moderate or high risk of bias for outcome measurement if only ICU mortality or 28-day mortality was reported.^{35–39} Studies were judged to be at some risk of bias for confounding adjustment and for statistical analysis and reporting if they did not account for clinically important confounders using either logistic regression or Cox proportional hazards models.^{15,39,44,46,48–66} Studies reporting adjusted analyses were judged to be at some risk of bias for statistical analysis^{35–37,40–46} if they did

not adhere to methodological standards set by the PROGRESS guidelines,^{19–22} in particular with regards to a priori selection of clinically important confounders and consideration of an appropriate sample size to minimise potential overfitting.^{28,76} The composition and methodological quality of individual prediction models for each study and funnel plots used to evaluate for publication bias among variables that were assessed in at least ten studies are included in the appendix (p 36–41). Forest plots for each prognostic factor and GRADE certainty assessments and rationale are included in the appendix (p 26–31).

The summary of findings is presented in table 2. Of the patient factors, older age, as defined by the study authors (five studies;^{13,38,45,70,71} aHR 2.27 [95% CI 1.63–3.16]; high certainty), was associated with increased mortality. Studies most commonly differentiated between older and younger age at between 50 years and 59 years,^{38,44,49,61,62,67–69} although age thresholds between 40 years and 49 years,⁴³ 60 years and 69 years,^{13,52,70–72} and over 70 years were also used.⁴⁵ Similarly, when the effect of age was measured in 10-year increments in eight studies,^{35,40–42,44,60,69,73} older age remained associated with mortality (aOR 1.19 [95% CI 1.11–1.27]). Of the 26 studies^{36,37,39,40,46–56,58,60,62–68,71,74} that included sex as a prognostic factor, male sex was found to be probably associated with increased mortality (uOR 1.34 [95% CI 1.20–1.49]; moderate certainty) and of the three studies^{13,35,71} that included lung disease as a prognostic factor, chronic lung disease was found to be probably associated with increased mortality (aHR 1.55 [95% CI 1.20–2.00]; moderate certainty). In the 14 studies^{35,41,49,51,54,55,61,62,66–68,72–74} that included obesity as a prognostic factor, obesity may have

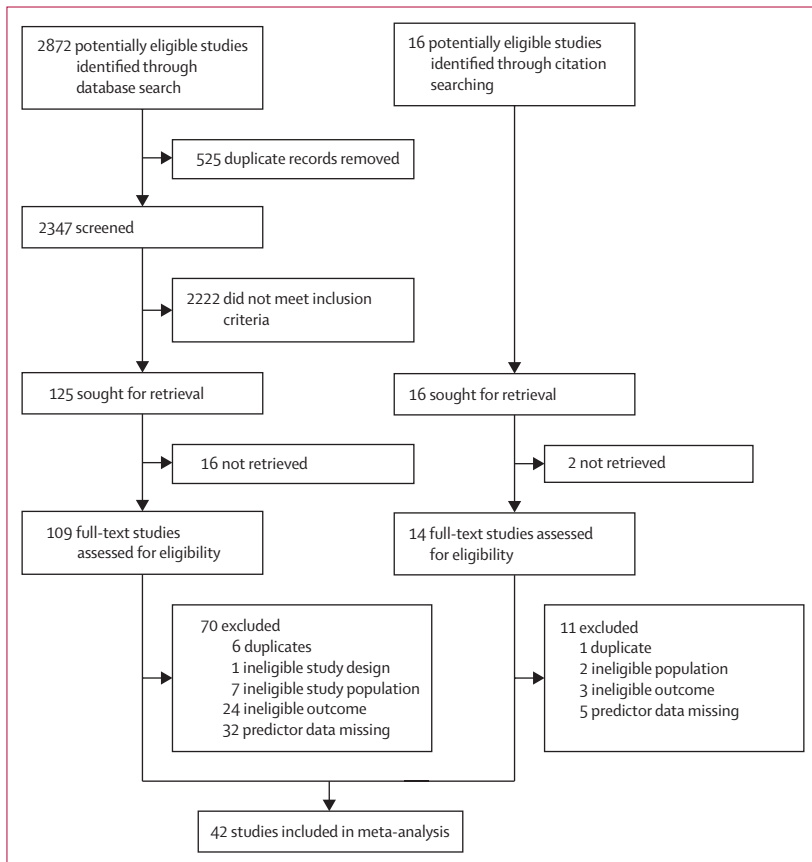


Figure: Study selection

Studies	
Location	
North America	16 (38%)
Europe	15 (36%)
Asia	4 (10%)
South America	1 (2%)
Multicontinental	6 (14%)
Design	
Retrospective cohort	38 (91%)
Prospective cohort	4 (10%)
Patient population	
Overall sample size of meta-analysis, n	17 449
Median sample size (IQR)	83 (41–294)
Overall mortality, %	54%
Median mortality, % (IQR)	47% (41–56%)
Measure of mortality	
In-hospital	28 (67%)
28-day or intensive care unit	5 (12%)
60-day	5 (12%)
90-day	4 (10%)
Data are n (%), unless otherwise stated.	

Table 1: Characteristics of included studies

	uOR analysis			aOR analysis			aHR analysis			Mean difference analysis			GRADE certainty
	Studies, n	Patients, n	uOR (95% CI)	Studies, n	Patients, n	aOR (95% CI)	Studies, n	Patients, n	aHR (95% CI)	Studies, n	Patients, n	Mean difference (95% CI)	
Patient factors													
Older age	11 ^{45-48,49,52,55,61,62,68,69,72}	6275	2.51 (2.07 to 3.03)	4 ^{43,44,67,68}	1137	2.09 (1.22 to 3.59)	5 ^{13,38,45,70,71}	5607	2.27 (1.63 to 3.16)	High
Male sex	26 ^{5,37,39,40,46-51,58,60,64,66,67,68,71,74}	7947	1.34 (1.20 to 1.49)	4 ^{42,44,67}	887	1.42 (0.98 to 2.05)	3 ^{14,42,72,73}	5669	1.06 (0.96 to 1.16)	Moderate
Chronic lung disease	19 ^{33,37,39,40,46,49,50,52,55,60,62,64,66,68,71,74}	9387	1.08 (0.92 to 1.26)	3 ^{35,44,44}	431	2.50 (1.09 to 5.74)	3 ^{13,35,71}	5103	1.55 (1.20 to 2.00)	Moderate
Obesity	14 ^{33,41,48,51,54,55,61,62,64,66,67,74}	5408	0.84 (0.72 to 0.97)	2 ^{43,44}	330	0.67 (0.36 to 1.27)	2 ^{7,74}	275	0.94 (0.75 to 1.19)	Low
Immunocompromised	5 ^{35,46,50,68,71}	666	2.34 (1.19 to 4.61)	1 ⁷³	1985	4.35 (2.46 to 7.69)	1 ³	4812	1.06 (0.83 to 1.35)	Low
Pre-cannulation disease factors													
Higher driving pressure	2 ^{35,74}	244	2.36 (1.40 to 3.97)	High
Longer symptom duration	8 ^{27,45,56,58,63,65,69,71}	463	-1.51 days (-2.65 to -0.36)	Moderate
Higher PaCO ₂	2 ^{38,74}	244	3.18 (1.41 to 7.15)	16 ^{3,37,40,41,43,46,49,51,53,54,58,60,64,71,72,74}	1929	-4.04 mm Hg (-6.44 to -1.64)	Moderate
Longer IMV duration	6 ^{35,36,45,53,57}	1482	1.94 (1.40 to 2.67)	3 ^{45,67,73}	455	1.11 (0.65 to 1.92)	1 ⁴⁵	127	1.66 (1.00 to 2.75)	20 ^{35,39,40,43,45,53,54,56,58,60,63,65,69,71,74}	3897	-1.15 days (-1.85 to -0.46)	Moderate
Lower PaO ₂ /FIO ₂ ratio	2 ^{38,71}	349	1.28 (1.12 to 1.46)	20 ^{35,37,38,41,43,49,51,53,55,58,60,63,65,69,71,74}	4189	1.52 (-1.16 to 4.20)	Low
Higher plateau pressure	12 ^{35,38,40,41,43,48,54,58,65,72,74}	1738	-0.71 cm H ₂ O (-1.15 to -0.06)	Low
Need for renal replacement therapy	7 ^{9,31,54,60,65,72,73}	1145	3.18 (1.41 to 7.17)	Low
Lower positive end expiratory pressure	16 ^{27,40,46,49,51,54,58,60,63,66,68,71,74}	3750	-0.05 cm H ₂ O (-0.37 to 0.26)	No effect (low)
Higher tidal volume	9 ^{35,38,40,41,53,54,71,72,74}	1304	0.03 mL/kg (-0.09 to 0.15)	No effect (low)
Lower compliance	10 ^{38,41,43,53,64,66,63,65,71,74}	1149	1.55 (-0.12 to 3.21)	Very low
Higher peak pressure	5 ^{27,48,51,64,73}	2235	1.20 (-1.51 to 3.90) cm H ₂ O	Very low
Bacterial co-infection	2 ^{40,73}	2059	0.58 (0.13 to 2.57)	2 ^{13,70}	5131	1.03 (0.88 to 1.20)	Moderate
Pre-ECMO proning	2 ^{67,73}	2490	0.97 (0.58 to 1.63)	2 ^{44,75}	667	1.18 (0.86 to 1.61)	Low
Centre factors													
Lower volume	2 ^{43,48}	609	2.27 (1.28 to 4.05)	3 ^{13,70,75}	5526	1.57 (1.11 to 2.20)	Moderate

uOR=unadjusted odds ratio, aOR=adjusted odds ratio, aHR=adjusted hazard ratio, GRADE=Grading of Recommendations Assessment, Development and Evaluation, PaCO₂=partial pressure of arterial carbon dioxide, IMV=inverse mechanical ventilation, PaO₂=partial pressure of arterial oxygen, FIO₂=fractional concentration of oxygen in inspired air, ECMO=extracorporeal membrane oxygenation.

Table 2: Prognostic factors associated with mortality

been associated with decreased mortality (uOR 0.84 [0.72–0.97]), although this finding was based on low-certainty evidence with a serious risk of bias and imprecision. Obesity was most commonly defined^{143,44,49,54,61,66,68,72,73} as a BMI of at least 30 kg/m², although it was also defined as at least 40 kg/m² in one study,⁷¹ and was not explicitly defined in others.^{35,51,55,62,67,74} In the five studies^{35,46,50,68,71} that included immunocompromised status as a prognostic factor, immunocompromised status might have been associated with increased mortality (uOR 2.34 [1.19–4.61]; low certainty), but this finding was also limited by a high risk of bias and imprecision.

Two studies^{38,74} included pre-cannulation disease factors, and showed that higher driving pressure was associated with increased mortality (aHR 2.36 [95% CI 1.40 to 3.97]; high certainty). Higher driving pressure was defined as greater than 16 cm H₂O in both studies that examined this variable.^{38,74} Eight studies^{37,42,56,58,63,65,69,71} included symptom duration before cannulation as a prognostic factor, and showed that longer symptom duration was probably associated with increased mortality (mean difference 1.51 days [95% CI 0.36 to 2.65]; moderate certainty). 16 studies^{35,37,40,41,43,46,49,51,53,54,58,60,64,71,72,74} included partial pressure of arterial carbon dioxide (PaCO₂) as a prognostic factor, and showed that higher PaCO₂ was probably associated with increased mortality (mean difference 4.04 mm Hg [95% CI 1.64 to 6.44]; moderate certainty). Six studies^{35,36,45,57,59,72} assessed duration of invasive mechanical ventilation before cannulation and showed that longer duration of ventilation was probably associated with increased mortality (uOR 1.94 [95% CI 1.40 to 2.67]; moderate certainty). However, adjusted analyses showed wide variation in effect sizes, suggesting increased risk when categories of longer duration were used but not when duration was assessed as a linear, per-day variable. Studies most commonly defined shorter duration as less than 7 days and longer duration as 7 days or more,^{35,36,45,57,72,73} although 6 days,⁶⁷ 4 days,⁵⁹ and 2.5 days⁴³ were also used as predefined thresholds. Two studies^{13,70} included bacterial co-infection as a prognostic factor, and showed that co-infection probably had no effect on mortality (aHR 1.03 [0.88 to 1.22]; moderate certainty). Analysis of studies that included physiological markers of oxygenation and ventilation as prognostic factors (PaO₂/FiO₂ [n=20 studies^{35,37,38,41,43,49,51,53–55,58,60,63–65,69,71–74}], plateau airway pressure [n=12 studies^{35,38,40,41,43,49,54,58,65,71,72,74}], and pre-cannulation renal replacement therapy [n=seven studies^{49,51,54,60,65,71,72}]) showed that a lower PaO₂/FiO₂ (mean difference 1.52 [95% CI –1.16 to 4.20 points]; low certainty), higher plateau airway pressure (mean difference 0.71 cm H₂O [95% CI 0.26 to 1.15]; low certainty), and need for pre-cannulation renal replacement therapy (uOR 3.18 [95% CI 1.41 to 7.17]; low probability) might have been associated with increased mortality, although these data were limited by high risk of bias, imprecision, and unclear clinical significance. Two studies^{67,73} showed that proning before ECMO might

have had no effect on mortality (aOR 0.97 [0.58 to 1.63]; low certainty), although these data were limited by very serious imprecision. 16 studies^{37,40,46,49,51,54,58,60,63–65,68,71–74} that included positive end-expiratory pressure and nine studies^{35,38,40,41,53,54,71,72,74} that included tidal volume showed that these factors might have had no effect on mortality (mean difference in positive end-expiratory pressure 0.05 cm H₂O [95% CI –0.37 to 0.26]; low certainty; mean difference in tidal volume 0.03 mL/kg [95% CI –0.09 to 0.15]; low certainty), although the findings were limited by high risk of bias and imprecision. Ten studies^{38,41,43,53,54,60,63,65,71,74} included respiratory system compliance and five studies^{37,49,51,64,73} included peak airway pressure, and showed that the effect of these prognostic factors on survival was uncertain (mean difference in respiratory system compliance 1.55 cm H₂O [95% CI –0.12 to 3.21]; very low certainty; mean difference in peak airway pressure 1.20 cm H₂O [–1.51 to 3.90]; very low certainty).

Two studies^{43,68} that included centre volume showed that lower patient volume (or less experienced) was probably associated with increased mortality (aOR 2.27 [95% CI 1.28–4.05]; moderate certainty). The threshold for classification varied between studies, with centres being defined as high volume (or more experienced) if they had treated at least 30 patients with venovenous ECMO,^{13,68} had treated 30 or more⁷⁰ or 50 or more⁷⁵ patients with venoarterial or venovenous ECMO, or if they had established ECMO services before January, 2020.⁴³

We conducted two pre-specified sensitivity analyses (appendix p 34, 35). In the first analysis, we excluded studies evaluating ICU mortality or 28-day mortality.^{35–39} In the second analysis, we excluded adjusted analyses from studies with moderate or higher risk of bias in the domains of confounding adjustment or statistical analysis. Specifically, bias in these studies was associated with poor adherence to methodological guidelines for the development of prediction models.^{35–37,39–46} In this sensitivity analysis, the results from unadjusted analyses or mean difference analyses remained unchanged. In both sensitivity analyses, no meaningful effect on the overall results or conclusion was observed.

Discussion

In this systematic review and meta-analysis, we investigated the prognostic association between several pre-cannulation factors and in-hospital mortality for patients who received venovenous ECMO for COVID-19. Factors with moderate or high certainty of association with increased mortality included patient factors, such as older age, male sex, and chronic lung disease; pre-cannulation disease factors, such as longer duration of symptoms, longer duration of invasive mechanical ventilation, higher PaCO₂, and higher driving pressure; and centre factors, such as less previous experience with ECMO.

The prognostic factors identified highlight several well established principles of effective ARDS and ECMO

care: the importance of patient selection, the effect of pre-ECMO injurious lung ventilation on prognosis, and the potential benefit of greater centralisation in the use of ECMO across centres and regions.⁷⁷ ECMO is highly invasive and is associated with a high risk of adverse events, including vascular injury, infection, major bleeding, and worsening systemic inflammation,⁷⁸ many of which could be amplified in the context of COVID-19-associated ARDS.³⁸ Acknowledging the associated risks, the high demand on resources, and the scarcity of ECMO, ELSO advocated for the importance of patient selection, in particular for the prioritisation of younger patients with fewer comorbidities.^{10,79} This guidance is supported by our findings, in which we have shown, with moderate or high certainty, that older age and chronic lung disease are important patient-specific prognostic factors.

Of the pre-cannulation disease factors, we showed with moderate or high certainty that higher driving pressure, longer symptom duration before cannulation, longer duration of invasive mechanical ventilation before cannulation, and higher PaCO₂ are associated with increased mortality. We also showed with moderate certainty that bacterial co-infection is probably not associated with a difference in mortality. These findings suggest the effect of injurious lung ventilation and indicate that the severity of pre-cannulation acute lung injury is a major determinant of outcome. Despite well established, evidence-based principles for lung protective ventilation,⁴⁵ wide variation in the management of ARDS across hospitals continues in practice, with up to half of patients not receiving care consistent with guideline recommendations during the first year of the COVID-19 pandemic.⁸⁰ The identification of driving pressure as an important prognostic factor, based on high-certainty evidence, is consistent with existing evidence showing that this ventilation variable is strongly associated with mortality in patients with ARDS.^{81,82} Additionally, we found that a longer duration of invasive mechanical ventilation (most commonly defined by a 7-day threshold) and a higher PaCO₂ are poor prognostic signs. However, the potentially synergistic interaction between protracted and injurious lung ventilation could not be elucidated within the scope of this review. Only one study⁷⁴ adjusted for both driving pressure and the duration of mechanical ventilation, and suggested a small increased risk of mortality per additional day of ventilation before cannulation. Specific to COVID-19, we showed with moderate certainty that longer duration of symptoms before ECMO cannulation was probably associated with increased mortality, further highlighting the importance of efficient referral pathways and early intervention.⁷

We showed with moderate certainty that lower case volume at medical centres is an important determinant of mortality risk. These findings are consistent with the well established association between higher case volume and better outcomes across a wide range of procedures and

disease conditions,⁸³ and particularly for ECMO,⁸⁴ including in the setting of COVID-19.¹³ Specific to ARDS, a large nationwide cohort study⁸⁵ in the USA found that higher hospital case volumes were associated with lower ARDS mortality at both the individual and hospital level. The identification of a case volume benchmark is not within the scope of this review; rather we aimed to emphasise the importance of the relationship between volume and outcome in principle. Additionally, we note that the discrepancy in ARDS and ECMO outcomes in different centres suggests that a meaningful opportunity exists to improve the coordination between centres, in addition to the optimisation and distribution of resources.^{13,77,86} Similar to other regionalised care models that have been used successfully for coronary revascularisation, complex cancer surgery, and major vascular procedures,⁸³ the concentration of resources at specialised, high-volume ECMO centres in a hub-and-spoke model could offer a greater degree of efficiency and effectiveness.⁷⁷

Appropriate use of ECMO should begin with well established clinical practice guidelines and incorporate more nuanced prognostic enrichment principles to develop an individualised harm–benefit profile for each patient.⁸⁶ An improved understanding of individualised prognostication not only has meaningful implications for bedside care, but could also offer important insight for the enrolment and conduct of clinical trials.⁸⁷ The fundamental basis of accurate prognostication begins with a comprehensive and evidence-based understanding of potentially important clinical factors,²¹ which are summarised in this review. However, we emphasise that although evidence-based prognostication is an important consideration for patient selection, it should not be solely responsible for identifying appropriate candidates for ECMO. Specifically, this review does not address how patients with high expected risk of mortality on ECMO would have fared without it and, as such, we are unable to make definitive recommendations regarding patient selection. Ultimately, ECMO has the largest effect when it is most likely to change an individual patient's risk of mortality, even if overall mortality on ECMO remains high.

This review was strengthened by a comprehensive search, adherence to recommendations for the meta-analysis of prognostic studies,²⁴ and use of the GRADE approach to assess the certainty in the estimates and contextualise results.³³ The face validity, consistency, precision, and generally robust effect sizes for the prognostic factors we identified justify their inclusion in any risk stratification framework. However, this review also has limitations. The prognostic factors identified reflect their importance for patients who ultimately received ECMO, rather than for all patients who are potentially eligible for ECMO. As such, despite our best efforts to specifically evaluate pre-cannulation factors and emphasise confounding adjustment, the potential for residual confounding and selection bias remains.

Importantly, few studies provided appropriate adjustment for extrapulmonary organ failure, which could have affected patient selection and outcomes. We are also limited by variability in practice and quality of the prognostic modelling methodology used by the included studies, many of which did not adhere to prognostic guideline recommendations^{21,22,28,88} and were therefore prone to overfitting.^{22,28} Additionally, a scarcity of well established prognostic factors contributed to few studies prespecifying clinically important variables,^{21,22,88} and models therefore differed in terms of outcome definition, variable definition, categorisation thresholds, and composition. These limitations resulted in a GRADE certainty downgrade for risk of bias for confounding adjustment and statistical analysis.^{23,30}

We took a pragmatic approach to the inclusion of studies and grouping of variables, allowing for use of the definitions in the included studies to maximise data yield and utility. However, the appropriate interpretation of results is supported by confirmation after clinically important sensitivity analyses and characterisation of certainty using GRADE methodology.³³

Contributors

AT, SMF, BR, EF, and DB conceived the idea. AT and SMF curated the data and did the investigation and formal analysis. BR, EF, and DB provided supervision. AT wrote the initial draft. All authors participated in methodology, data interpretation and the reviewing and editing of the manuscript. AT and SMF accessed and verified the data. AT, DB and EF were responsible for the decision to submit the manuscript.

Declaration of interests

RPB is Chair of the Extracorporeal Life Support Organization (ELSO) registry. GM serves on the Board of Directors for ELSO. KR reports honoraria from Baxter and Faeseniuss, outside of the submitted work. LJB reports research support from Medtronic and Draeger, and honoraria from Fisher Paykel, outside of the submitted work. NDF reports consulting fees from Baxter and Xenios, outside of the submitted work. ASS reports consulting fees from Baxter and Xenios, outside of the submitted work. He is the Chair of the Scientific Committee of the International ECMO Network (ECMONet). EF reports personal fees from Alung Technologies, Aerogen, Baxter, Boehringer-Ingelheim, GE Healthcare, Inspira, and Vasomune, outside of the submitted work. He is the Chair of the Data Committee of ECMONet. DB reports research support from Alung Technologies, outside of the submitted work. He has been on medical advisory boards for Abiomed, Xenios, Medtronic, LivaNova, Inspira, and Cellenkos, and is the President-Elect of ELSO and the Chair of the Executive Committee of ECMONet. All other authors declare no competing interests.

Data sharing

This manuscript makes use of publicly available data from the included studies and their supplementary information files; therefore, no original data are available for sharing.

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