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Review Article

Blood Transfusion Threshold in Patients Receiving Extracorporeal Membrane Oxygenation Support for Cardiac and Respiratory Failure—A Systematic Review and Meta-Analysis

Riccardo Giuseppe Abbasciano, MD[*,1], Hakeem Yusuff, MD[†], Alexander P.J. Vlaar, PhD[‡], Florence Lai, MPhil[*], Gavin James Murphy, MD[*]

[*]*Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Leicester, United Kingdom*

[†]*Department of Anaesthesia and Intensive Care Medicine, Glenfield Hospital, Leicester, United Kingdom*

[‡]*Adult Intensive Care Unit, Academic Medical Centre, Amsterdam, Netherlands*

Objective: To review studies that have evaluated the effects of liberal or restrictive red cell transfusion thresholds on clinical outcomes in patients requiring extracorporeal membrane oxygenation (ECMO) support for cardiac or respiratory failure.

Design: A systematic review and meta-analysis.

Setting and Participants: The study comprised 1,070 patients from observational studies and randomized controlled trials analyzing transfusion policies in venoarterial (VA) and venovenous (VV) ECMO adult populations.

Measurements and Main Results: Eligible studies were identified by searching the Cochrane Central Register of Controlled Trials, Medline, and EMBASE until March 4, 2020, using a combination of subject headings and text words. Risk of bias assessment was performed to assess study quality according to the ROBINS-I tool and the case series studies appraisal checklist. There was high risk of bias in the studies analyzed, and none had methodologic adequacy. Three studies analyzed VA ECMO and VV ECMO patients separately. Five datasets were related exclusively or mostly to VA ECMO. Four were retrospective analyses, and one was conducted as a prospective observational study; the median transfusion threshold reported was 8 g/dL, with a mean mortality of 52%. Eight datasets were related either exclusively or mostly to VV ECMO. Six were retrospective and two were prospective observational studies; the median transfusion threshold was 8 g/dL, and the mean mortality rate was 33%.

Conclusions: The present study did not resolve uncertainty as to transfusion management in ECMO, although several studies (most of them in VV ECMO) demonstrated that a restrictive threshold has acceptable outcomes in single-center cohorts.

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Key Words: blood transfusion; extracorporeal membrane oxygenation; cardiogenic shock; acute respiratory distress syndrome

EXTRACORPOREAL membrane oxygenation (ECMO) is used increasingly in the intensive care unit (ICU) as indications have become wider and outcomes have improved.[1] Bleeding and transfusion requirements with ECMO are higher than in general ICU patients and are associated with increased risk of death and other major adverse outcomes.[2] This has been attributed to bleeding related to cannulation sites or anticoagulation management. Bleeding is more prevalent in venoarterial (VA) ECMO because it requires a higher

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[1]*Address reprint requests to* Riccardo Abbasciano, MD, Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Leicester, LE3 9QP, United Kingdom.

E-mail address: rga8@leicester.ac.uk (R.G. Abbasciano).

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anticoagulation range and arterial cannulation, with reported frequencies ranging from 10% to 61.8%.[3-5] The severity of the underlying condition and prolonged ICU stays also contribute to a high prevalence of anemia requiring transfusion, with reported transfusion rates of up to 100% of patients.[6]

Patient blood management (PBM) refers to the implementation of evidence-based, personalized care bundles of interventions that aim to improve clinical outcomes in patients at increased risk of bleeding and anemia. Uncertainty as to the most effective transfusion strategies in ECMO patients is reflected by variation in care[7] and, therefore, potentially to variation in outcomes in this high-risk patient population. Current guidelines[1] and consensus statements[8] lack specific recommendations for red cell transfusion in ECMO patients as a result of the absence of adequate evidence.

To address this uncertainty, as part of a program to develop the evidence for PBM in ECMO patients, the present study aimed to systematically review existing studies that have evaluated transfusion strategies in ECMO. A secondary aim was to identify important clinical factors and outcomes that would be considered as part of a planned randomized controlled trial (RCT) of liberal versus restrictive transfusion thresholds in this patient cohort.

Methods

Protocol and Registration

A systematic review was performed based on methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1).[9] The study is reported as per the PRISMA statement.[10] The study protocol was registered prospectively and is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135433 and in the Supplementary Appendix.

Eligibility Criteria

For the present study, observational studies and RCTs were included irrespective of blinding, language, publication status, date of publication, and sample size, and transfusion strategies in VA ECMO and VV ECMO adult critically ill patients were evaluated. Studies conducted on pediatric patients were excluded.

Information Sources and Search Methods

Eligible studies were identified by searching the Cochrane Central Register of Controlled Trials (Internet), Medline (Ovid 1946 to present), and EMBASE (Ovid 1974 to present), using a combination of subject headings and text words to identify relevant studies. Part of the search strategy was adapted from the Cochrane review by Carson et al.[11] of trials comparing restrictive versus liberal transfusion thresholds. The following Medline search strategy was adapted as appropriate for other databases:

((*Blood Transfusion/ad, mt, st, td or *Erythrocyte Transfusion/mt, st, td) OR (((transfus* or red cell* or red blood cell* or RBC* or PRBC*) adj5 (trigger* or thresh?old* or target* or restrict* or liberal* or aggressive* or conservative* or prophylactic* or limit* or protocol* or policy or policies or practic* or indicat* or strateg* or regimen* or criteri* or standard* or management or program*)).tw.) OR (((h?emoglobin or h?ematocrit or HB or HCT) adj5 (polic* or practic* or protocol* or trigger* or threshold* or maintain* or indicator* or strateg* or criteri* or standard*)).tw.) OR ((blood adj3 (management or program*)).mp.) OR (((transfus* or red cell* or red blood cell* or RBC* or PRBC*) and (critical* or intensive* or h?emorrhag* or bleed*)).ti.)) AND ((Oxygenators, Membrane/ or Extracorporeal Membrane Oxygenation/) OR (("extracorporeal life support" or "extracorporeal membrane oxygenation" or "ECLS" or "ECMO").ti,ab.))

The last search was run on March 4, 2020. The reference lists of eligible studies and reviews also were examined. Searches were not restricted by language or publication status.

Data Collection Process

The search and data extraction followed guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions*. Two authors (R.G.A. and G.J.M.) independently screened the search output to identify records of potentially eligible studies examining the outcomes. After exclusion of studies that were clearly not relevant following a review of study titles and abstracts, the full texts of eligible studies were retrieved and assessed for inclusion. A standardized form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included year and language of publication; country of participant recruitment; year of conduct of the study; study population with inclusion and exclusion criteria; sample size; participant demographics; baseline characteristics (ECMO modality and circuit characteristics, comorbidity, mean hemoglobin value); postoperative course (mortality, ICU length of stay, time on ECMO, transfusion rates, kidney injury, infection, hemorrhagic and thrombotic complications); information for likely sources of heterogeneity; and information for likely sources of bias.

Review authors (R.G.A. and G.J.M.) extracted data independently, and discrepancies were resolved through discussion.

Definitions for Data Extraction

Definitions of comorbidities (chronic kidney disease) and clinical outcomes (acute kidney injury [AKI], infections, thrombotic and hemorrhagic events) were derived from the study authors' description. Hemorrhagic and thrombotic events and daily use of blood components (red blood cells, fresh frozen plasma, and platelets) were as reported. ICU length of stay and time on ECMO were recorded in days.

Risk of Bias and Applicability

For studies that included a comparison of a specified transfusion strategy with a control group, the assessment of methodologic quality was based on the ROBINS-I tool.[12] A response option of Y was considered to refer to the optimal methodologic characteristic; a judgment of N was considered to refer to a less-than-optimal characteristic. An optional field about the predicted direction of bias was present. The "judgment" fields included a description and the justification for the response provided. For case series lacking a proper control group, the tool developed by Moga et al. was used.[13] The domains assessed were study objective, study design, intervention and cointervention, outcome measure, statistical analysis, results, conclusions, and competing interests and sources of support.

Statistical Analysis and Data Synthesis

Descriptive statistics for the included records are presented as mean ± standard deviation or median (interquartile range). The method described by Wan et al.[14] was used to estimate the sample mean and standard deviation when only sample size, median, range, or interquartile range was available. Meta-analysis of studies was performed in the R statistical software, packages *metafor*[15] and *meta,*[16] using a random effects model. Untransformed (raw) means were meta-analyzed for continuous outcomes; the inverse variance method was applied; and the DerSimonian-Laird estimator for tau,[2] Jackson method for confidence interval of tau,[2] and Hartung-Knapp adjustment for random effects model were used. A proportional meta-analysis was conducted for binary outcomes. Subgroup and meta-regression analyses, using a mixed effect model, were performed for moderator exploration (hemoglobin threshold, age, publication year).

An additional narrative synthesis is provided in the Supplementary Material.

Expected Sources of Heterogeneity

The authors of the present review anticipated that likely sources of heterogeneity were study design, concomitant interventions, timing of the intervention, baseline condition, definition of the standard of care, and methodologic quality.

Results

Search Results

A total of 415 abstracts were retrieved from the searches (Fig 1). After removing duplicate entries, 329 articles were screened, and 226 articles were excluded on the basis of title

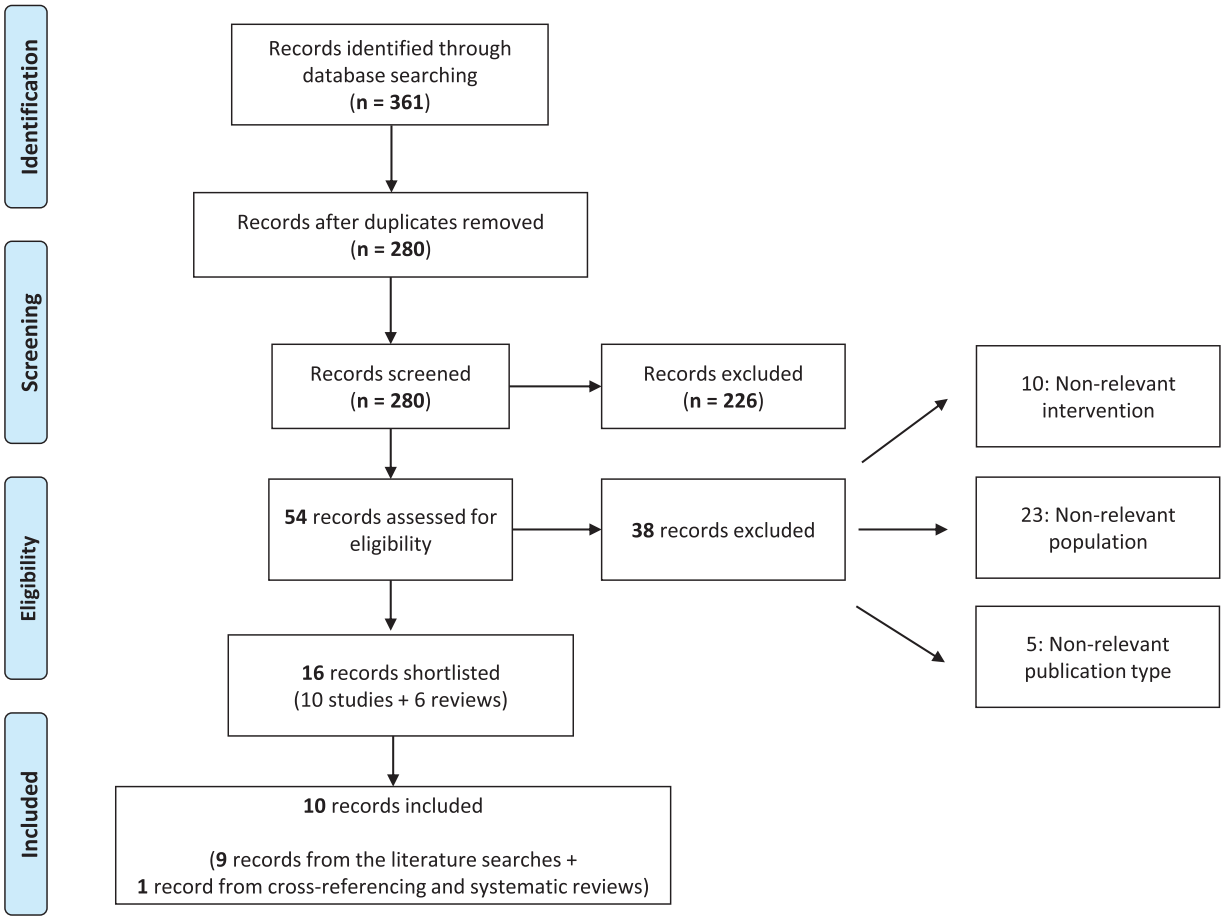

Fig 1. PRISMA flow diagram: Restrictive versus liberal transfusion in extracorporeal membrane oxygenation.

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Table 1
Baseline Patient Characteristics

Study	Country	Study Type	Reason for ECMO	Transfusion Threshold (g/dL)	Age (y)	VA ECMO	VV ECMO	BMI	CKD	Mean Hb During ECMO (g/dL)
Agerstrand 2015[21]	United States	Retrospective	ARDS	7	33 ± 21	10.6%	89.4%	28 ± 6.9	15.8%	8.3 ± 0.6
Ang 2009[24]	Singapore	Retrospective	Cardiogenic shock	10	46.8 ± 12.7	88%	12%			
Buscher 2017[17] VA	Australia	Retrospective	Cardiogenic shock	8	48 ± 16	100%	0%			
Buscher 2017[17] VV	Australia	Retrospective	ARDS	8	35 ± 13	0%	100%			
Butch 1996[2]	United States	Retrospective	ARDS	14	35	0%	100%			
Cahill 2018[23]	United States	Retrospective	Cardiogenic shock/ cardiomyopathy	8	60.7 ± 12.4	100%	0%			9 ± 3.2
Guimbretiere 2018[18] VA	France	Observational prospective	Cardiogenic shock/ post-cardiotomy	8	54.6 ± 14.1	100%	0%			
Guimbretiere 2018[18] VV	France	Observational prospective	(Indications reported only for VA ECMO)	8	48.2 ± 16.9	0%	100%			
Martucci 2019[19]	Italy	Observational prospective	ARDS	8	42 ± 11	0	100%	29 ± 6		10.3 ± 1
Mazzeffi 2016[3] VA	United States	Retrospective	ARDS /post-cardiotomy/other	10	50 ± 21.1	100%	0%			
Mazzeffi 2016[3] VV	United States	Retrospective	ARDS/post-cardiotomy/other	10	50 ± 21.1	0%	100%			
Swol 2018[22]	Germany	Retrospective	Lung failure, sepsis	8	54	6.2%	93.8%	29.3		
Voelker 2015[20]	Germany	Retrospective	ARDS	7	37.1 ± 15.6	0%	100%	25.2 ± 6.4		8.3 ± 0.5

NOTE. Data are presented as mean ± standard deviation or percentage. Detailed description of indications is available in the description of included studies (Supplementary Material). Cells were left blank if the study authors did not report adequate data to infer a value. Published data for Buscher,[17] Guimbretiere,[18] and Mazzeffi[3] were split into two records based on the ECMO mode.
Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CKD, chronic kidney disease; ECMO, extracorporeal membrane oxygenation; Hb, hemoglobin; VA, venoarterial; VV, venovenous.

and abstracts; a total of 54 relevant publications were retrieved for further assessment. Ten studies [2,3,17-24] analyzing a total of 1,070 participants (see Supplementary Material) met the inclusion criteria and were included in the qualitative analysis. There was no disagreement among the reviewers as to the selection of included studies. The entire process of reference screening and selection is summarized in a PRISMA flow diagram (see Fig 1).

Included Studies

A summary of the characteristics for each of the 10 studies included are reported in Tables 1 and 2 and in the Supplementary Material. The evaluations were divided into two subgroups according to the ECMO mode used. When data about VA ECMO and VV ECMO were provided separately by the study authors, each cohort was considered separately, giving a total of 13 cohort evaluations within the 10 included studies.

Description of VA ECMO Studies

Five analyses were related to VA ECMO[2,3,17,18,24,25] (see Tables 1 and 2 and Supplementary Material). Four studies recorded data exclusively from VA ECMO cohorts, and one study analyzed a mixed population in which VA ECMO was the major modality (88%). Four studies were retrospective analyses, and one was conducted as a prospective observational study. The adopted transfusion threshold was reported in five studies (median 8, range 8-10 g/dL). The median age, reported in four studies, was 52.3 years (range 46.8-60.7). Two studies reported a mean hemoglobin value during ECMO; the median was 8.2 g/dL (range 7.4-9). The predominant indication for VA ECMO therapy was cardiogenic shock.

Only the study by Cahill et al.[23] included a comparison with a control group and was restricted to VA ECMO patients. By introducing a complex protocol including a restrictive transfusion threshold (<8 g/dL) and additional criteria for anticoagulation management, the authors were able to significantly reduce red cell transfusions in their center, going from a mean of 28.1 ± 23.4 per patient in the preprotocol era to 15.3 ± 16.10 ($p = 0.017$) after the introduction of the protocol. Similar results were obtained for fresh frozen plasma units (from 11.0 ± 12.0 to 4.2 ± 5.2; $p = 0.007$) and for platelets (from 6.8 ± 7.4 to 2.5 ± 3.0; $p = 0.006$). The intervention was associated with a significant reduction in mortality (from 70% to 37%, Relative Risk 0.52, 95% confidence interval [CI] 0.31-0.88) and bleeding events (Relative Risk 0.57, 95% CI 0.36-0.89) and a non-statistically significant reduction in the time to weaning from the ECMO circuit (9.5 ± 6.4 *v* 7.4 ± 8.2; $p = 0.275$).

Description of VV ECMO studies

Eight analyses included VV ECMO cohorts[2,3,17-22] (see Tables 1 and 2 and Supplementary Material). Six studies recorded data from a population including exclusively VV ECMO cases, and two studies were conducted in a mixed population in which VV ECMO was the most common modality

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Table 2
Outcomes

Study	Patients	Control	Mortality	Transfusion	ICU LOS (d)	Time on ECMO (d)	AKI	Infection	Bleeding	Thrombosis
Agerstrand 2015[21]	38	No	26.3%	63.2%		9 ± 3.3	31.6%		26.3%	21.1%
Ang 2009[24]	42	No	73.2%			11.0	83.3%	36.8%	64.3%	0.0%
Buscher 2017[17] VA	32	No	31.0%	100.0%						
Buscher 2017[17] VV	16	No	31.0%	75.0%						
Butch 1996[2]	74	No	54.1%			10.9				
Cahill 2018[23]	30	30	63.3%			7.4 ± 8.2			43.3%	
Guimbretiere 2018[18] VA	410	No	43.9%	82.2%		7.4 ± 6.1			59.8%	59.8%
Guimbretiere 2018[18] VV	99	No	40.4%	72.7%		10.5 ± 10.2			34.3%	34.3%
Martucci 2019[19]	82	No	23.2%	92.7%	7 ± 8.4	14 ± 10.4	54.9%	63.4%	41.5%	
Mazzeffi 2016[3] VA	54	No	59.3%			7 ± 6.6			68.5%	16.7%
Mazzeffi 2016[3] VV	64	No	34.4%			7 ± 6.6			39.1%	9.4%
Swol 2018[22]	32	No	34.4%			10.3 ± 12				
Voelker 2015[20]	18	No	38.9%			21.7 ± 30				

NOTE. Data are presented as the mean ± standard deviation or percentage. Outcomes are related to the intervention group (Cahill[23]) or to the groups with lower Hb while on ECMO (Swol[22]). Cells were left blank if study authors did not report adequate data to infer a value. Published data for Buscher,[17] Guimbretiere,[18] and Mazzeffi[3] were split into two records based on the ECMO mode.
Abbreviations: AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; VA, venoarterial; VV, venovenous.

(89.4% and 93.8%). Six studies were retrospective, and two were prospective, observational studies. The adopted transfusion threshold was reported in eight studies (median 8, range 7-14 g/dL). Nine studies reported patients' age with a median age of 42 (range 33-54). Four studies reported a mean hemoglobin value during ECMO with a median of 8.3 (range 8.3-10.3 g/dL). Body mass index was reported in four studies, with the median value of 28.5 (range 25.2-29.3). The predominant indication for VV ECMO therapy was acute respiratory distress syndrome in six studies, lung failure/sepsis in one study, and no indication was provided by the authors in one study.

Risk of Bias in Included Studies

The detailed results and the support for judgment of the ROBINS-I evaluation for the only study with a control arm by Cahill et al.[23] is available in the Supplementary Material. The study was considered to have a high risk of bias, possibly favoring the intervention group. This was because of bias derived from outcome measurement, possible deviations from the intended interventions, and other confounding factors. The mortality and bleeding reduction the authors reported must be mitigated by the observational nature of the study, the lack of risk stratification between the groups, and inadequate information about protocol adherence in the intervention group. None of the included case studies scored using the Moga tool[13] were considered to be methodologically adequate in all the domains. A detailed analysis is provided in the Supplementary Material.

Meta-Analysis

A meta-analysis of the case series was conducted. An overall mortality of 0.42 ([95% CI 0.34-0.49) was identified in the combined populations, with VA patients at a significantly greater risk of death (0.52 [95% CI 0.42-0.61]) than VV patients (0.33 [95% CI 0.25-0.42]). A forest plot for mortality, with the subgroup analyses based on transfusion threshold and ECMO type (VV or VA), is presented in Fig 2. Publication bias was not identified by the Egger's test[26] ($p = 0.8009$), and a funnel plot is presented in Fig 3, although this is of partial applicability to a proportional meta-analysis.

The meta-regression presented in Fig 4 identified a significant, albeit poor, correlation ($p = 0.0297$) between mortality and transfusion threshold (with a greater mortality reported in studies with a higher transfusion threshold), and no significant effect was related to age ($p = 0.5493$) and publication year ($p = 0.0722$). All results were affected by severe heterogeneity.

As shown in the forest plot in Fig 5, a transfusion rate of 86% (95% CI 72%-94%) was identified in the combined populations, and 93% [95% CI 76%-98%] and 79% [95% CI 55%-92%]) of VA and VV patients, respectively, received a transfusion. Publication bias was identified by the Egger's test ($p = 0.0081$).

In the meta-regression analysis (Fig 6), the transfusion rate was not related significantly to the hemoglobin threshold adopted ($p = 0.1137$) and did not depend on age ($p = 0.3942$) or publication year ($p = 0.4268$).

The transfusion threshold was associated with a higher incidence of AKI ($p < 0.0001$) but not with bleeding ($p = 0.1226$) or thrombosis ($p = 0.3256$) (Fig 7). Moreover, weaning time was not significantly related to the transfusion threshold adopted in the meta-regression in Fig 8, although this analysis required pooling together VA and VV ECMO studies ($p = 0.4560$).

Discussion

Main Findings

In this systematic review and meta-analysis (Fig 9), adopting a lower transfusion threshold was associated not only with a lower rate of transfusion but also with lower risks of mortality and AKI. These findings, although statistically significant,

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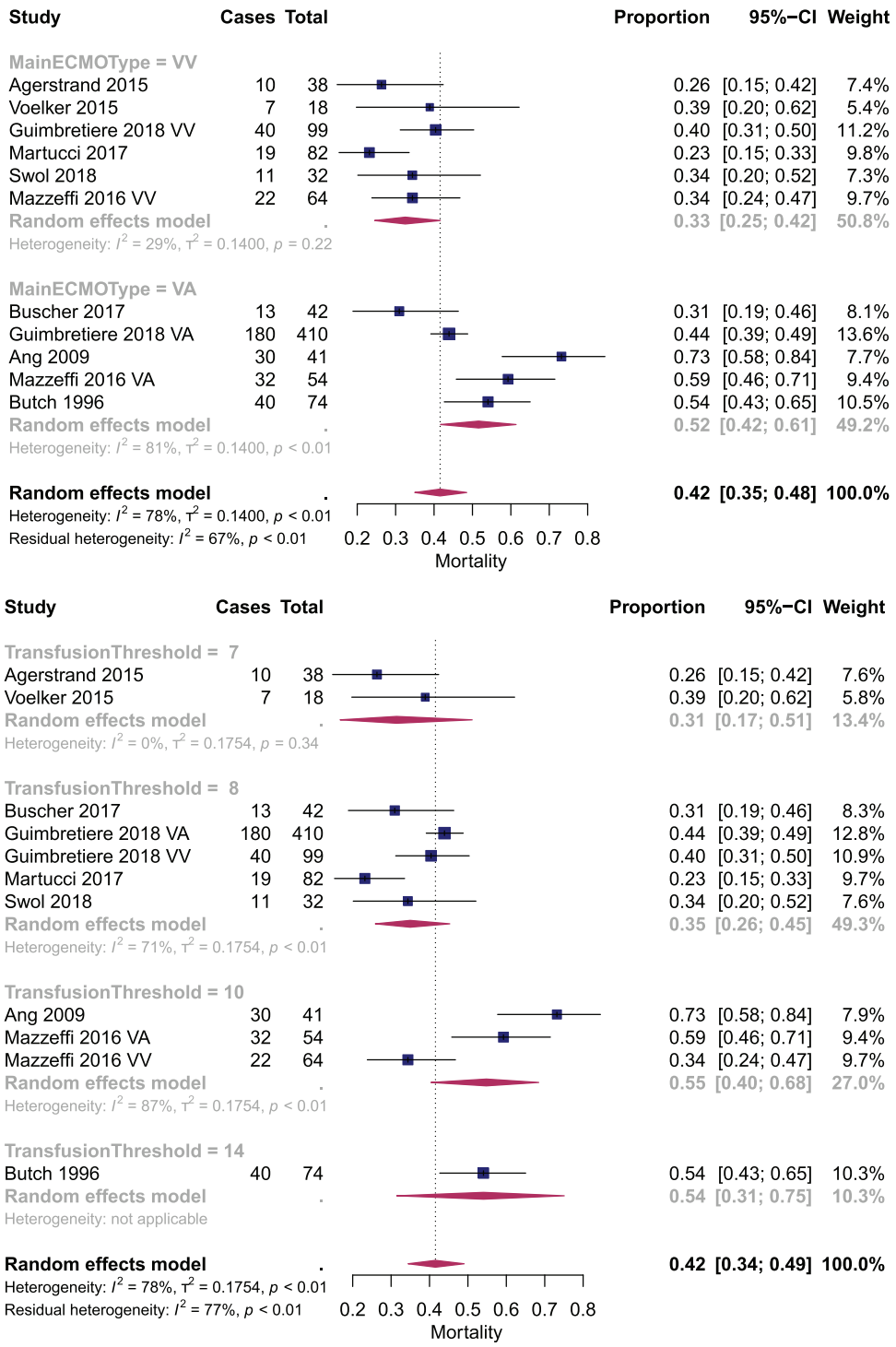

Fig 2. Mortality forest plot. CI, confidence interval; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

were affected by an extremely high level of uncertainty, due principally to publication bias, poor methodologic quality of the studies included, and moderate-to-severe heterogeneity.

Clinical Importance

This systematic review has characterized a knowledge gap with respect to evidence-based transfusion management for patients undergoing ECMO; no high-quality evidence was identified to guide transfusion decisions. The most recent Extracorporeal Life Support Organization guidelines[1] suggest, in the absence of evidence, maintaining the hematocrit >40% in order to optimize oxygen delivery while allowing the lowest reasonable blood flow. A hematocrit of 40% translates to a hemoglobin threshold of >13 g/dL. The range of transfusion thresholds reported in published series identified in the searches were in the range of 7-to-10 g/dL. This was closer to what is currently recommended for critically ill patients[8,27]

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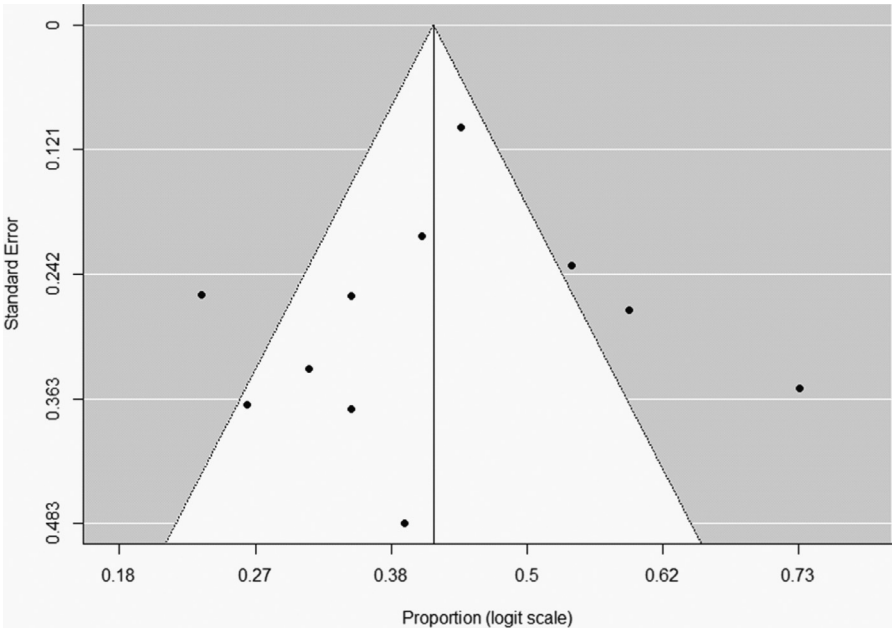

Fig 3. Funnel plot for studies reporting mortality.

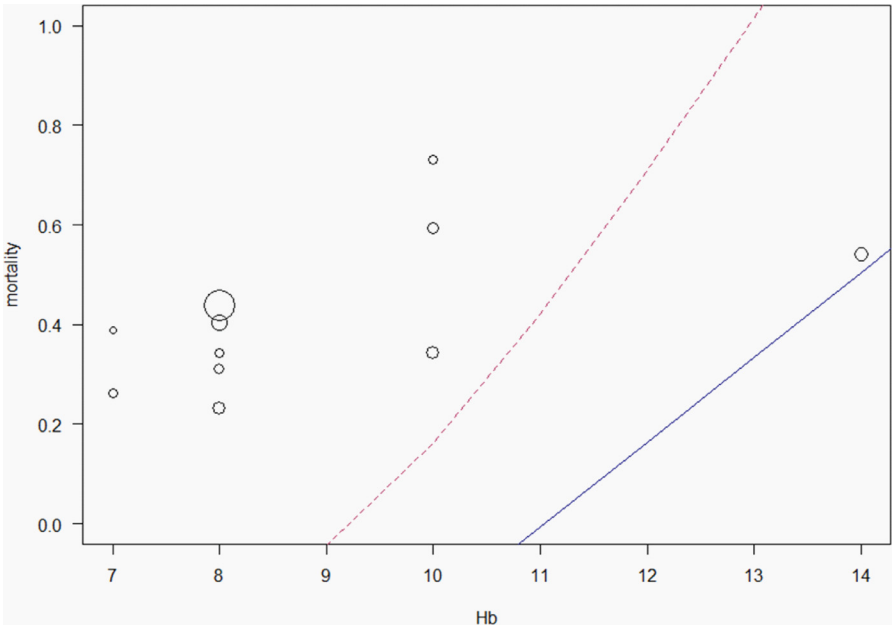

Fig 4. Meta-regression analysis between mortality and transfusion threshold. Hb, hemoglobin.

based on RCTs.[28-30] Although the range of transfusion thresholds identified in the present review probably reflected contemporary practice, it is clear that a wide range of values currently is being adopted as a trigger, similarly to what is shown in the report by Esper et al.,[7] in which approximately 70% of the respondents adopted a hemoglobin value between 7 g/dL and 11 g/dL.

The cohorts identified in the searches were heterogeneous, and this was reflected by different ranges for transfusion thresholds, transfusion rates, and outcomes among studies. Transfusion requirements were greater in patients requiring VA ECMO compared with VV ECMO. This may have been attributable to the higher percentage of patients with bleeding complications associated with surgical procedures and anticoagulation for the circuit and not to prespecified transfusion thresholds. For example, Buscher et al.[17] reported a restrictive threshold of 8 g/dL, with a reported transfusion of red blood cells in 100% of patients. This suggested that the transfusion threshold applied may only be important when part of a wider care bundle of PBM interventions. The underlying pathologic conditions of patients requiring VA ECMO, principally cardiogenic shock with or without cardiotomy, may add another important confounding factor to the transfusion management. In addition, physicians may aim for higher hemoglobin

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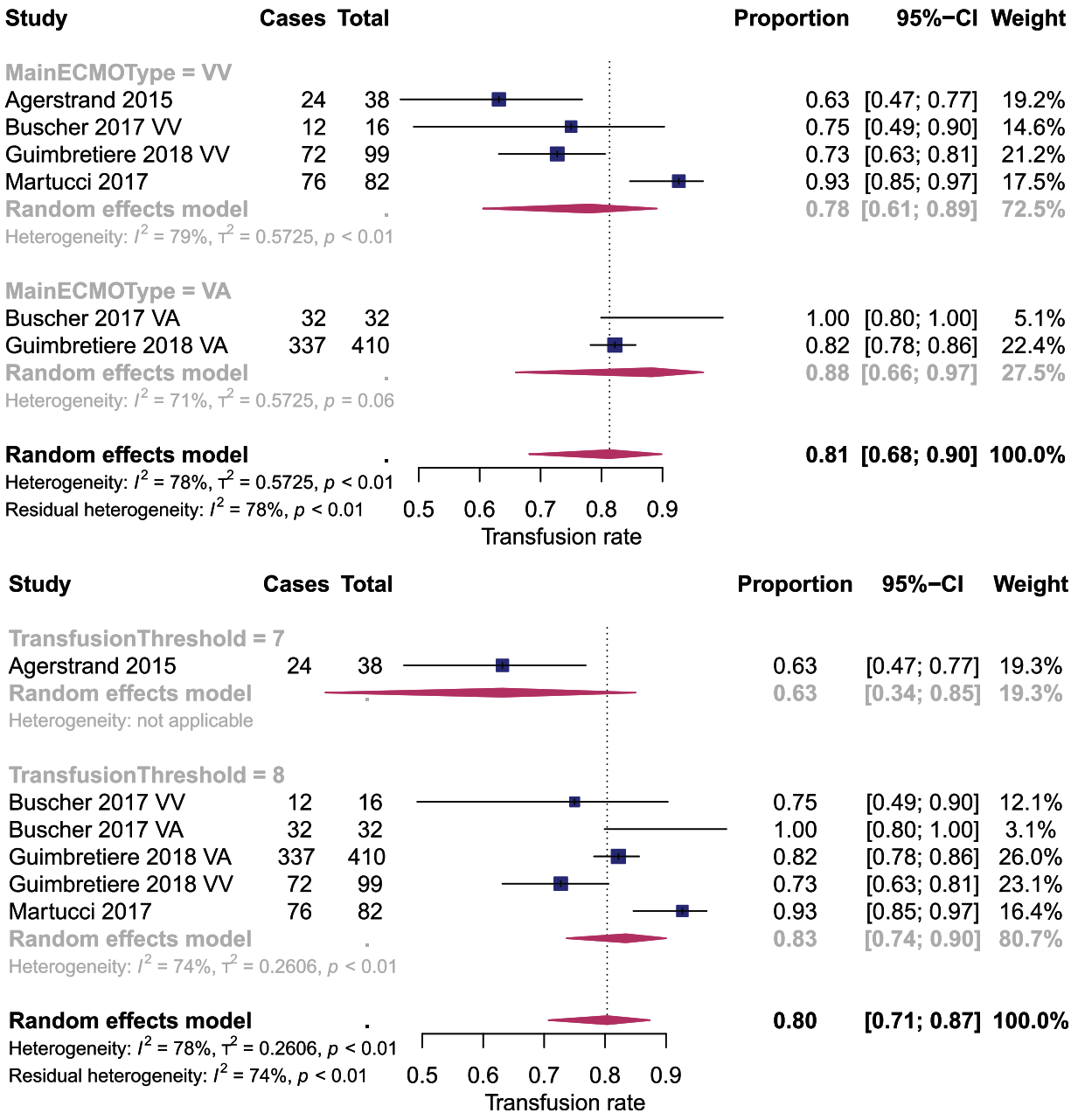

Fig 5. Transfusion rate forest plot. CI, confidence interval; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

transfusion thresholds in VA ECMO, despite determining cardiac output by flow in the ECMO circuit, because they may believe it is important to have a buffer in these patients to cope with a reduced cardiac output for weaning. On the other hand, it could be reasoned that there are many patients in the ICU with a lower cardiac output than the one VA-ECMO generates (4-5 L/min), and liberal transfusion strategies are not applied routinely in these patients. Restrictive practice in arguably similar settings, such as cardiac surgery, is supported by large trials; however, these do not constitute a support for evidence-based judgment in ECMO.[29,30] In the setting of VV ECMO, physicians also may argue that oxygen delivery is hampered as a result of a lower arterial oxygen content because of the underlying indications for VV ECMO, and a higher hemoglobin level therefore should be targeted to have some safety buffer when weaning is considered. However, in patients with acute respiratory distress syndrome in the absence of VV ECMO support, as well as in other more peculiar clinical settings, a restrictive transfusion policy of 7 g/dL was associated with acceptable results.[31-33]

Limitations

The present review had several limitations. No proper randomized trial could be identified, and a single observational analysis included a control group. All the identified studies had significant methodologic limitations. However, the present review has identified important considerations that should be

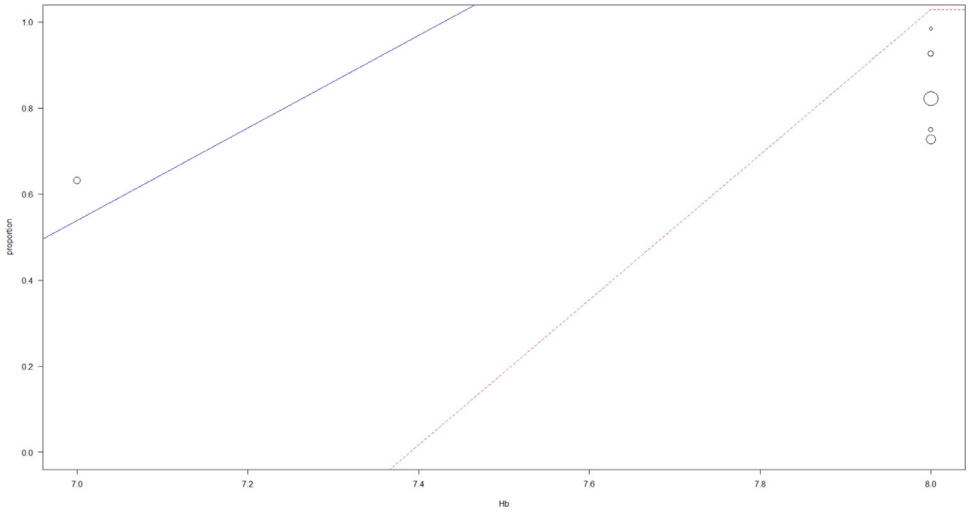

Fig 6. Meta-regression analysis between transfusion rate and transfusion threshold. Hb, hemoglobin.

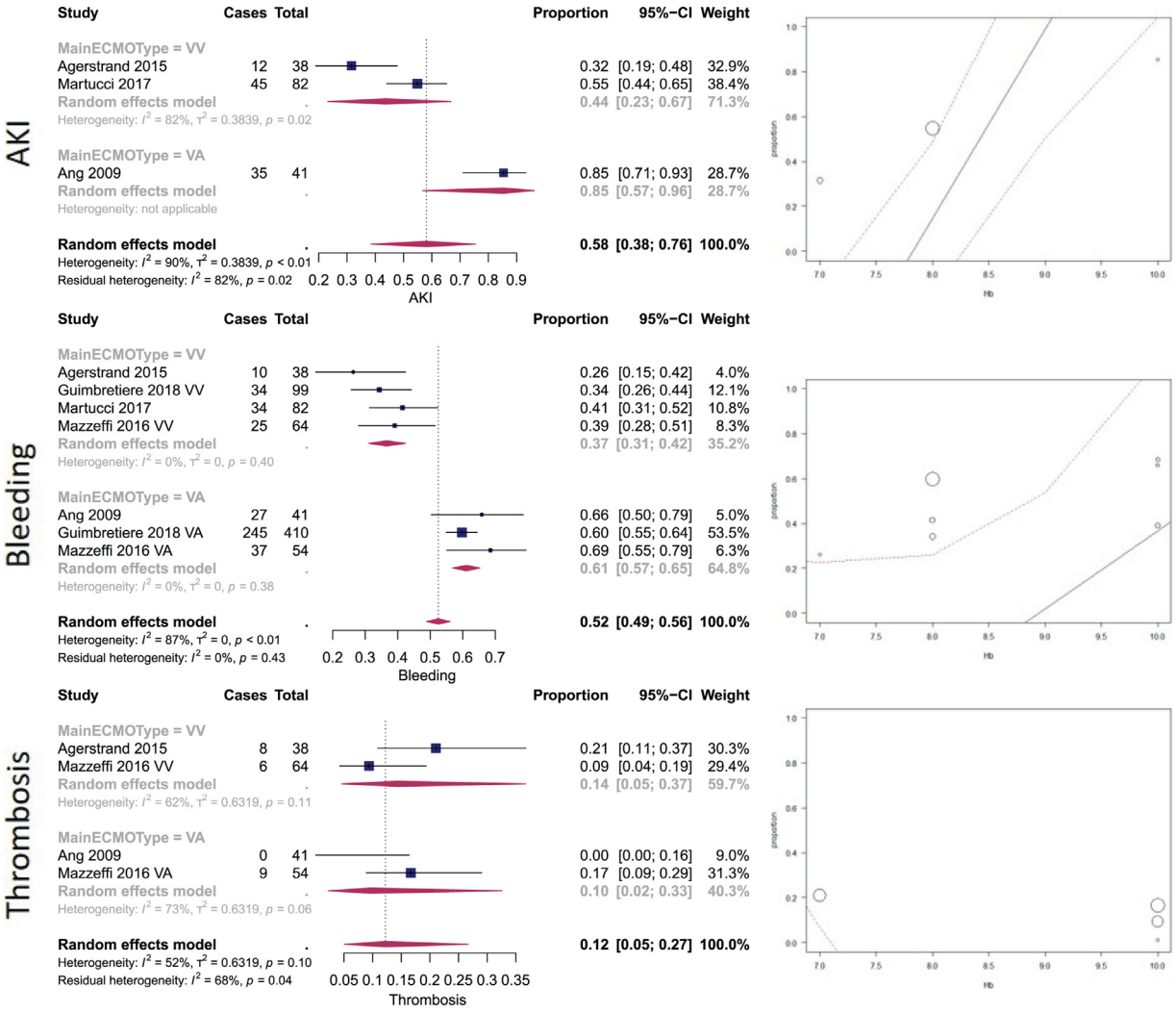

Fig 7. Meta-analysis results of dichotomous secondary clinical outcomes. AKI, acute kidney injury; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

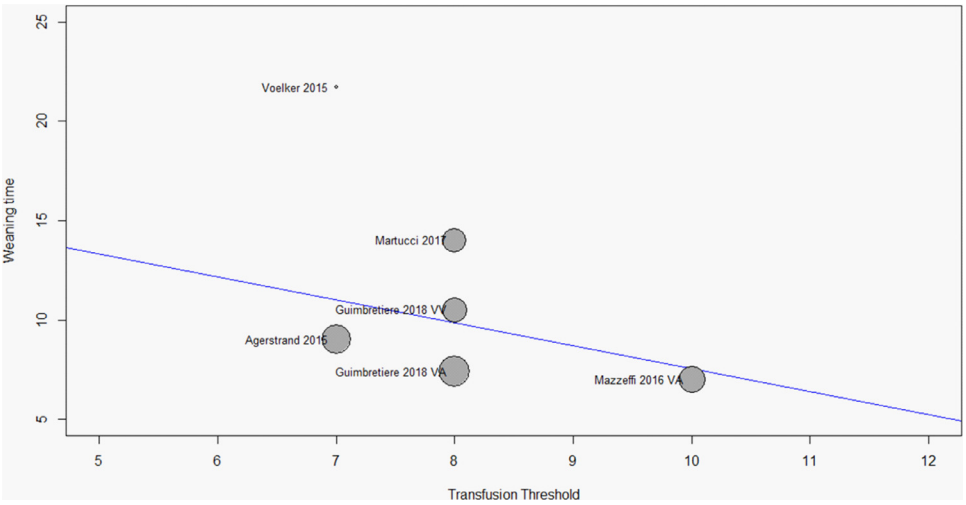

Fig 8. Meta-regression analysis between transfusion threshold and weaning time.

Indication	Transfusion threshold	Mortality	Time to wean		Study	Transfusion Rate
ARDS	7	26.31%	9.0	9 ± 3.33	(Agerstrand 2015)	63.16%
		38.89%	21.7	21.7 ± 30	(Voelker 2015)	(no data)
	8	30.95%	(no data)		(Buscher 2017 VV)	75.00%
		23.17%	14.0	14 ± 10.37	(Martucci 2017)	100.00%
		40.40%	10.5	10.5 ± 10.2	(Guimbretiere 2018 VV)	72.73%
		34.38%	10.3	10.3 ± 12	(Swol 2018)	(no data)
	10	34.38%	7.0	7 ± 6.6	(Mazzeffi 2016 VV)	(no data)
Cardiogenic Shock	8	30.95%	(no data)		(Buscher 2017 VA)	100.00%
		70.00%	7.4	7.4 ± 8.2	(Cahill 2018)	(no data)
		43.90%	7.4	7.4 ± 6.1	(Guimbretiere 2018 VA)	82.20%
	10	73.17%	11.0	11.00	(Ang 2009)	(no data)
		59.26%	7.0	7 ± 6.6	(Mazzeffi 2016 VA)	(no data)

Fig 9. Transfusion threshold and outcomes. Data presented as mean ± standard deviation or percentage. Outcomes are related to the intervention group (Cahill 2018[23]) or to the 2 groups with lower Hb while on ECMO (Swol 2018[22]). Cells were left blank if the study authors did not report adequate data to infer a value. ARDS, acute respiratory distress syndrome; VA, venoarterial; VV, venovenous.

incorporated into the design of a trial investigating transfusion thresholds in ECMO. First, separate RCTs are required for both VV and VA ECMO because the populations represent distinct patient groups with different underlying problems. On the basis of the ranges reported in the present review, a potential randomization strategy could be 7 g/dL versus 10 g/dL in VV ECMO and 8 g/dL versus 10 g/dL in VA ECMO. Even though managing individualized clinical cases could benefit from considering other factors besides hematocrit, alternative transfusion triggers lack the necessary evidence to be reasonably used as the indication for transfusion in such a trial.[27] Second, trial designs should specify whether randomization should be stratified by ECMO indication. Third, consideration should be given as to whether other aspects of PBM, including bleeding treatment algorithms, anticoagulation, or the use of antifibrinolytics, should be protocolized or recorded. Evidence of similar treatment rates in observational analyses despite apparently similar hemoglobin transfusion thresholds suggested that compliance with allocated thresholds and indications for transfusion outside of hemoglobin parameters also should be recorded. PBM interventions should be protocolized to minimize unmeasured confounding. Fourth, trials should be focused on effectiveness outcomes of importance to patients. Another consideration is whether in the era of precision medicine, hemoglobin levels are appropriate indicators of the need for transfusion.[34] Alternatives, such as measures of oxygen supply dependence (mixed venous oxygen levels, serum lactate concentrations) or tissue oxygenation (using near-infrared spectroscopy), have been suggested as potential adjuncts to hemoglobin, although none is supported by RCT evidence.[35] In contrast, hemoglobin levels are measured accurately and routinely and guide almost all transfusion decisions in critical care.[36] It, therefore, is intuitive that a pragmatic trial would consider hemoglobin as the transfusion indicator in the absence of evidence of better alternatives.

Conclusion

There is uncertainty as to optimal transfusion management in ECMO patients. The present systematic review of studies that evaluated transfusion management in ECMO patients did not resolve this uncertainty, and the quality of evidence was

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very low. A range of transfusion thresholds was reported in cohorts in whom clinical outcomes were acceptable. This is evidence of equipoise and justifies an RCT of different transfusion thresholds in ECMO patients.

Conflict of Interest

No potential competing interest is reported by the authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2020.08.068.

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