Transfusion practice in patients receiving VV ECMO (PROTECMO): a prospective, multicentre, observational study

Gennaro Martucci, Matthieu Schmidt, Cara Agerstrand, Ali Tabatabai, Fabio Tuzzolino, Marco Giani, Raj Ramanan, Giacomo Grasselli, Peter Schellongowski, Jordi Riera, Ali Ait Hssain, Thibault Duburcq, Vojka Gorjup, Gennaro De Pascale, Sarah Buabbas, Whitney D Gannon, Kyeongman Jeon, Brian Trethowan, Vito Fanelli, Juan I Chico, Martin Balik, Lars M Broman, Antonio Pesenti, Alain Combes, Marco V Ranieri, Giuseppe Foti, Hergen Buscher, Kenichi Tanaka, Roberto Lorusso, Antonio Arcadipane, Daniel Brodie*, for the International ECMO Network (ECMONet)*

Summary

Background In patients receiving venovenous (VV) extracorporeal membrane oxygenation (ECMO) packed red blood cell (PRBC) transfusion thresholds are usually higher than in other patients who are critically ill. Available guidelines suggest a restrictive approach, but do not provide specific recommendations on the topic. The main aim of this study was, in a short timeframe, to describe the actual values of haemoglobin and the rate and the thresholds for transfusion of PRBC during VV ECMO.

Methods PROTECMO was a multicentre, prospective, cohort study done in 41 ECMO centres in Europe, North America, Asia, and Australia. Consecutive adult patients with acute respiratory distress syndrome (ARDS) who were receiving VV ECMO were eligible for inclusion. Patients younger than 18 years, those who were not able to provide informed consent when required, and patients with an ECMO stay of less than 24 h were excluded. Our main aim was to monitor the daily haemoglobin concentration and the value at the point of PRBC transfusion, as well as the rate of transfusions. The practice in different centres was stratified by continent location and case volume per year. Adjusted estimates were calculated using marginal structural models with inverse probability weighting, accounting for baseline and time varying confounding.

Findings Between Dec 1, 2018, and Feb 22, 2021, 604 patients were enrolled (431 [71%] men, 173 [29%] women; mean age 50 years [SD 13·6]; and mean haemoglobin concentration at cannulation 10·9 g/dL [2·4]). Over 7944 ECMO days, mean haemoglobin concentration was 9·1 g/dL (1·2), with lower concentrations in North America and high-volume centres. PRBC were transfused on 2432 (31%) of days on ECMO, and 504 (83%) patients received at least one PRBC unit. Overall, mean pretransfusion haemoglobin concentration was 8·1 g/dL (1·1), but varied according to the clinical rationale for transfusion. In a time-dependent Cox model, haemoglobin concentration of less than 7 g/dL was consistently associated with higher risk of death in the intensive care unit compared with other higher haemoglobin concentrations (hazard ratio [HR] 2·99 [95% CI 1·95–4·60]); PRBC transfusion was associated with lower risk of death only when transfused when haemoglobin concentration was less than 7 g/dL (HR 0·15 [0·03–0·74]), although no significant effect in reducing mortality was reported for transfusions for other haemoglobin classes (7·0–7·9 g/dL, 8·0–9·9 g/dL, or higher than 10 g/dL).

Interpretation During VV ECMO, there was no universally accepted threshold for transfusion, but PRBC transfusion was invariably associated with lower mortality only when done with haemoglobin concentration of less than 7 g/dL.

Funding Extracorporeal Life Support Organization.

Introduction

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) has been increasingly used for severe forms of acute respiratory distress syndrome (ARDS), especially during the COVID-19 pandemic.[1] However, uncertainties remain regarding best practice in the management of patients receiving VV ECMO.[2] Among the uncertainties, transfusion practice might be particularly relevant because haemoglobin is crucial in achieving acceptable oxygen delivery (DO_2).[3] Nonetheless, increasing the haemoglobin concentration through transfusion of packed red blood cells (PRBC) has potentially detrimental effects, such as increased rates of infections, transfusion reactions, immunosuppression, inflammation, fluid overload, haemolysis, and potentially death.[4,5]

Haemoglobin thresholds have been established in patients who are critically ill in an attempt to balance the risks of transfusion with the potential benefits of increased DO_2.[6] Current guidelines for patients who are not bleeding who are critically ill support a transfusion protocol based on a haemoglobin concentration threshold of 7 g/dL.[7] Separately, the physiology of DO_2 during ECMO has complicated efforts to standardise a single value as a trigger for transfusions in this setting.[8] The

Lancet Respir Med 2022

Published Online
October 11, 2022
https://doi.org/10.1016/S2213-2600(22)00353-8

See Online/Comment
https://doi.org/10.1016/S2213-2600(22)00367-8

*Contributed equally

Department of Anesthesia and Intensive Care (G Martucci PhD, A Arcadipane MD), **Statistics and Data Management Services** (F Tuzzolino PhD), **Istituto Mediterraneo per i trapianti e Terapie ad alta specializzazione (IRCCS-ISMETT), Palermo, Italy; INSERM 1166, Institute of Cardiometabolism and Nutrition, Sorbonne Université, Paris France** (Prof M Schmidt PhD, Prof A Combes PhD); **Service de Médecine Intensive-Réanimation, Institut de Cardiologie, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Paris, France** (Prof M Schmidt, Prof A Combes); **Department of Medicine and Center for Acute Respiratory Failure, Irving Medical Center, Columbia University, New York, NY, USA** (C Agerstrand MD, Prof D Brodie MD); **School of Medicine, University of Maryland, Baltimore, MD, USA** (A Tabatabai MD); **Ospedale San Gerardo, Università degli Studi Di Milano-Bicocca, Monza, Italy** (M Giani MD, G Foti MD); **Department of Critical Care, University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, PA, USA** (R Ramanan MD); **Department of Anesthesia, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Milan, Italy** (Prof G Grasselli MD, Prof A Pesenti); **Department of Pathophysiology and**

Transplantation, University of Milan, Italy (Prof G Grasselli, Prof A Pesenti MD)**; Department of Medicine I, Intensive Care Unit 13i2, Center of Excellence in Medical Intensive Care, Medical University of Vienna, Vienna, Austria** (P Schellongowski MD)**; Critical Care Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain** (J Riera PhD)**; Shock Organ Dysfunction and Resuscitation, Vall d'Hebron Institut de Recerca, Barcelona, Spain** (J Riera)**; Centro de Investigacion en Red de Enfermedades Respiratorias Instituto de Salud Carlos III, Barcelona, Spain** (J Riera)**; Hamad Medical Corporation, Doha, Qatar** (A A Hssain MD)**; Centre Hospitalier Regional Universitaire Lille, Hôpital Roger Salengro, Lille, France** (T Duburcq MD)**; ECMO Center, Ljubljana, Slovenia** (V Gorjup MD)**; Dipartimento di Scienze dell'Emergenza, Anestesiologiche e della Rianimazione, Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy** (G De Pascale MD)**; Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy** (G De Pascale)**; Kuwait Extracorporeal Life Support Program, Jaber Al-Ahmad Alsabah Hospital, Kuwait City, Kuwait** (S Buabbas MD)**; Department of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA** (W D Gannon MSN)**; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea** (K Jeon MD)**; Meijer Heart Center Butterworth Hospital, Spectrum Health, Grand Rapids, MI, USA** (B Trethowan MD)**; Department of Surgical Sciences, University of Turin, Turin, Italy** (V Fanelli MD)**; Critical Care Department, Alvaro Cunqueiro University Hospital, Vigo, Spain** (J I Chico MD)**; Department of Anesthesiology and Intensive Care, 1st Medical Faculty, General University Hospital, Prague, Czech Republic** (M Balik MD)**; ECMO Centre Karolinska, Karolinska University Hospital,**

Research in context

Evidence before this study

Guidelines for packed red blood cell (PRBC) transfusion in patients who are critically ill suggest a haemoglobin threshold of 7 g/dL, but in the case of venovenous (VV) extracorporeal membrane oxygenation (ECMO) there are few recommendations to guide management. Previously, experts recommended maintaining haemoglobin in the normal range during ECMO to maximise oxygen transport and delivery. This practice has since been questioned due to growing evidence suggesting that transfusion volumes are independently associated with increased mortality, even during ECMO support. As a result, there is considerable uncertainty and variability regarding haemoglobin triggers for PRBC transfusions. We searched PubMed from Jan 1, 2010, to May 5, 2022, with no restriction on the type of study, using the terms "VV ECMO" AND/OR "haemoglobin" AND/OR "PRBC" for studies published in English. 16 studies specifically addressing haemoglobin and triggers for PRBC transfusions during ECMO were identified: two were surveys confirming the wide discrepancy in the ECMO setting compared with other patients who were critically ill, 12 were single-centre retrospective studies highlighting the feasibility of restrictive strategies, one was a meta-analysis, and one was a multicentre study using longitudinal but retrospective data.

Added value of this study

This international, prospective, multicentre observational study discusses the value of haemoglobin concentrations as a trigger for PRBC transfusion and rate of PRBC transfusions during VV ECMO. To the best of our knowledge, this is the largest multicentre study to date, this is the largest multicentre study focused on haemoglobin and transfusion with longitudinal daily data up to 28 days during ECMO. The average haemoglobin value was lower than previously reported, and the factors associated with haemoglobin variation were provided. PRBCs were transfused on 31% of days. The main reason for transfusion was provided, as were the actual triggers used. In a time-dependent analysis, the only cut-off for haemoglobin associated with death was less than 7 g/dL. The effect of PRBC transfusion within different haemoglobin thresholds was investigated by marginal structural models confirming that PRBCs were associated with reduced risk of death only when transfused with haemoglobin concentration lower than 7 g/dL.

Implications of all the available evidence

The findings suggest that PRBC transfusion during ECMO might be beneficial to mortality only when haemoglobin concentration reaches the crucial threshold of 7 g/dL. This conclusion is consistent with modern transfusion guidelines for patients who are critically ill, but is in contrast with historical ECMO practice, which used transfusion as a daily practice to achieve high ECMO blood flow rates and maximise oxygen transport. Despite the large sample size reported in this study, due to multiple potential residual confounders, these results should be confirmed in a prospective interventional study that might specifically address the effect of transfusions only when haemoglobin concentration is lower than 7 g/dL.

previously suggested practice of maintaining haemoglobin within a near-normal range during ECMO (ie, >12 g/dL), regardless of the required transfusion volume, was not supported by clinical data, but relied more on physiological considerations, and it has been challenged by reports of acceptable outcomes with lower haemoglobin transfusion triggers.[9–11] As a result, wide variability between centres has been reported, with haemoglobin thresholds often between 8 g/dL and 10 g/dL; guidelines on ECMO have favoured a restrictive approach, but have not suggested a defined or structured practice because the available data often came from single-centre series, with patients typically enrolled over a number of years.[12] Therefore, a clear-cut framework for interventional trials on this topic is needed.

We aimed to address the uncertainties and describe routine clinical practice for haemoglobin thresholds triggering PRBC transfusions, and to record the number of transfusions in adults receiving VV ECMO.

Methods

Study design and participants

PROTECMO was an international, multicentre, prospective observational study endorsed by the European Society of Intensive Care Medicine and the International ECMO network. PROTECMO was done in 41 ECMO centres in 19 countries in Europe, North America, Asia, and Australia (appendix p 4, 36). Centres applied for participation voluntarily after public announcements of the study.

Consecutive adult patients with ARDS who were receiving VV ECMO were eligible. Patients younger than 18 years, those who were not able to provide informed consent when required, and patients with an ECMO stay of less than 24 h were excluded (appendix p 5). Centres were classified according to the volume of respiratory ECMO activity in the year before enrolment in the study: low volume (one to 11 runs per year), medium volume (12 to 20 runs per year), and high volume (>20 runs per year).[13]

The study was approved by the Institutional Ethics Committee at ISMETT (Palermo, Italy, IRRB/15/17). All participating intensive care units (ICUs) obtained ethics committee approval as per their local regulation. Given the observational nature of the study, written informed consent from each participant or representative was requested according to the rules valid in each centre. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.

Procedures

Patients were enrolled in the database within 48 h from admission to the ICU for ECMO support. The case report form consisted of three sets of data: baseline, daily forms (one form for each day on ECMO and one single form for the first day after ECMO weaning), and outcome. The case report form and definitions are provided in the appendix (pp 6, 18). Patient characteristics were registered at cannulation, and data reported daily for 28 days or fewer, if the ECMO-associated stay in the ICU was shorter. In the daily assessment, haemodynamics, fluid balance, laboratory values (haemoglobin, haematocrit, platelet count, creatinine, fibrinogen, and results for arterial blood gas), and transfusions were recorded. ECMO data were extracorporeal blood flow (Q_{EC}), Q_{EC} rate to estimated cardiac output ratio (Q_{EC}:eCO), revolutions per minute, and sweep gas flow rate. The eCO was estimated by body surface area (Dubois method) × 2·4 L/min. Major adverse events, including bleeding, haemolysis, and circuit change were recorded (appendix p 21). For the first PRBC transfusion of the day, the main clinical rationale according to the principal investigator at each centre, and pre-transfusion and post-transfusion haemoglobin concentration, mixed venous oxygen saturation (SvO_2), arterial oxygen saturation (SaO_2), and Q_{EC} data were recorded. Clinical outcomes recorded were ECMO weaning and mechanical ventilation liberation, and survival in the ICU, hospital, and 6 months after ICU discharge.

Data were collected through an online platform customised on a REDCap server (Vanderbilt University, Nashville, TN, USA). Site investigators were required to answer all the queries in the case report form, with the aim of having no missing data in the baseline and outcome forms. For daily data, investigators were asked to report only data available in daily practice. The quality control of data for completeness and plausibility was done weekly by an automated check for missing data and outliers, and then reported to the local investigator for confirmation or correction. The actual missing data level was 0·5% (appendix p 23).

Statistical analysis

Quantitative variables were reported as mean (SD) or median (IQR); qualitative variables were recorded as percentage and frequency distribution. Differences between continuous variables were analysed by 2-sample *t* test, Wilcoxon-Mann-Whitney test or median test, when appropriate. χ^2 test and Fisher's exact test were used to assess the association between categorical variables. Imputation methods for the minimum amount of missing data are reported in the appendix (p 23).[14]

To assess the effect of variables on the outcome, several generalised estimating equations models were applied. These models were appropriate when there were repeated measures over time on the same patients, with a possible correlation between observations from different timepoints on each patient.

Extended Cox regression models were used to assess recurrent event data of PRBC transfusions, and the Andersen-Gill model was used to model the overall recurrence rate.

Univariate Cox regression models were applied to assess the risk of death in the ICU within 28 days. The multiple analysis was done using the variables with a significant parameter in the univariate analysis. Highly correlated variables were removed by multiple analyses to avoid multicollinearity. Because the number of variables was large, a stepwise selection was done to identify the subset of variables that gave the lowest –2 log L value. As an exploratory analysis, Cox extended models with Heaviside functions were used to assess how the hazard ratio (HR) for death in the ICU at 28 days changed over the first 4 weeks.[15] When Heaviside functions are used, Cox models provide four separate HRs, one for each time interval (4 weeks) of follow-up. p values for the models based on Heaviside functions are reported as nominal results.

To measure the effect of PRBC transfusions within different haemoglobin cutoffs, we used marginal structural Cox proportional hazards models with inverse probability weighting. The probability of receiving PRBC transfusion was weighted by adjusting for baseline factors (age, sex, body-mass index, haemoglobin concentration, and sequential organ failure assessment [SOFA] score) and time-varying confounding factors (fluid balance, urine output, Q_{EC}, SaO_2, pH, bleeding, and transfusion on the day before the considered transfusion event; appendix p 33). Furthermore, we identified a data-driven threshold repeating the models with 0·1 g/dL increase in the haemoglobin threshold until reaching the highest value of haemoglobin when PRBC transfusion was still associated with reduction in mortality.

p values less than 0·05 were considered statistically significant. Statistical analyses were done using SAS (version 9.4). More information on our statistical analysis is reported in the appendix (p 29). The trial is registered on ClinicalTrials.gov, NCT03815773.

Role of the funding source

The PROTECMO project received a Research Grant from the Extracorporeal Life Support Organization (ELSO). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 1, 2018, and Feb 22, 2021, 604 patients (431 [71%] men, 173 [29%] women; mean age 50 years [SD 13·6]) with ARDS supported by VV ECMO were enrolled. Baseline data are reported in table 1 and in the appendix (p 42–45). COVID-19 was the principal risk factor for ARDS, followed by viral pneumonia of other

Stockholm, Sweden (L M Broman PhD); **Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden** (L M Broman); **Alma Mater Studiorum, University of Bologna, Bologna, Italy** (Prof M V Ranieri MD); **Department of Intensive Care Medicine, St Vincent's Hospital, Sydney, NSW, Australia** (H Buscher MD); **The University of Oklahoma Health Sciences Center, University of Oklahoma, Oklahoma City, OK, USA** (Prof K Tanaka MD); **Cardiothoracic Surgery Department, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands** (Prof R Lorusso MD)

Corresponding to Dr Gennaro Martucci, Department of Anesthesia and Intensive Care, Istituto Mediterraneo per i trapianti e Terapie ad alta specializzazione (IRCCS-ISMETT), Palermo 90133, Italy
gmartucci@ismett.edu

See **Online** for appendix

	All patients (n=604)	Patients who did not receive PRBC transfusion (n=100)	Patients who received PRBC transfusion (n=504)	p value
Age, years	49·9 (13·6)	49·1 (14·5)	50·1 (13·4)	0·46
Sex				
Male	431 (71%)	80 (80%)	351 (70%)	0·036
Female	173 (29%)	20 (20%)	153 (30%)	0·036
Height, cm	171 (10)	173 (8)	170 (10)	0·017
Body-mass index, kg/m^2	28·8 (25·2–34·5)	30·1 (25·6–39·2)	28·6 (25·2–33·6)	0·0062
SAPS 2	41 (31–56)	42 (30–55)	40 (31–56)	0·18
SOFA score at cannulation	10 (7–12)	10 (7–12)	10 (7–12)	0·50
PRESERVE score	3 (2–5)	3 (1–5)	4 (2–5)	0·088
RESP score	2 (0–4)	3 (1–5)	2 (0–4)	0·0004
P/F ratio	70 (59–93)	74 (60–97)	70 (59–93)	0·24
Pre-ECMO hospital stay, days	5·4 (2.0–10·7)	3 (1–6·6)	6·1 (2·2–11·4)	<0·0001
Pre-ECMO ICU stay, days	3·1 (1–7)	1·7 (0·6–4·4)	3·7 (1·1–7·7)	<0·0001
Pre-ECMO mechanical ventilation, days	2·3 (0·7–5·7)	1·3 (0·4–3·9)	2·8 (0·8–6·2)	0·0006
Haemoglobin at cannulation, g/dL	10·7 (9·3–12·3)	12 (10·5–13·5)	10·4 (9·2–12)	<0·0001
Platelets, × 10^3/µL	205 (135–289)	187 (152–278)	205 (127–292)	0·33
Cause of ARDS				0·043
Bacterial pneumonia	103 (17%)	11 (11%)	92 (18%)	..
Viral pneumonia	115 (19%)	29 (29%)	86 (17%)	..
COVID-19	218 (36%)	28 (28%)	190 (38%)	..
Aspiration pneumonia	27 (4%)	7 (7%)	20 (4%)	..
Trauma or burns	25 (4%)	5 (5%)	20 (4%)	..
Pancreatitis	8 (1%)	0	8 (2%)	..
Graft failure after lung transplant	31 (5%)	4 (4%)	27 (5%)	..
Other acute respiratory diagnosis	60 (10%)	12 (12%)	48 (10%)	..
Non-respiratory and chronic respiratory	17 (3%)	4 (4%)	13 (3%)	..
Surgical procedure in the last 7 days	85 (14%)	15 (15%)	70 (14%)	0·77
Pregnancy or puerperium	7/173 (4%)	1/173 (1%)	6/173 (3%)	0·82
Configuration				0·38
Femoro-jugular	390 (65%)	71 (71%)	319 (63%)	..
Femoro-femoral	152 (25%)	23 (23%)	129 (26%)	..
Double lumen cannula	33 (5%)	5 (5%)	28 (6%)	..
Jugular-femoral	23 (4%)	0	23 (5%)	..
Femoro-jugular-femoral	5 (1%)	1 (1%)	4 (1%)	..
Subclavian-femoral	1 (<1%)	0	1 (<1%)	..

Data are n (%), mean (SD), or median (IQR). ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. P/F ratio=PaO_2/FiO_2 ratio. PRESERVE=PRedicting dEath for SEvere ARDS on VV-ECMO. RESP=Respiratory ECMO Survival Prediction. SAPS 2=Simplified Acute Physiology Score 2. SOFA=Sequential Organ Failure Assessment.

Table 1: **Baseline characteristics**

	Longitudinal daily data and outcomes (n=604)
Daily data	
Days on ECMO	7944
Urine output, mL	2199 (648 to 3090)
CRRT, days (%)	2474/7944 (31%)
Fluid balance, mL	170 (–327 to 689)
Cardiovascular SOFA	1·3 (0·6 to 2)
Haemoglobin, g/dL	9 (8·3 to 9·9)
Pre-transfusion haemoglobin, g/dL	7·9 (7·2 to 9)
Platelets, x1000 micro/L	146 (94 to 194)
Q_{EC}, L/min	4·1 (3·6 to 4·6)
Q_{EC}:eCO, %	86 (75 to 97)
Total PRBC during ECMO, mL	1432 (398 to 3050)
PRBC per day in ECMO, mL	115 (48 to 223)
Bleeding	
All cases (days with bleeding/total days on ECMO)	1157/7944 (15%)
Type 1* (days with type 1/total days with bleeding)	699/1157 (61%)
Type 2† (days with type 2/total days with bleeding)	347/1157 (30%)
Type 3‡ (days with type 3/total days with bleeding)	86/1157 (7%)
Type 4§ (days with type 4/total days with bleeding)	16/1157 (1%)
Circuit change	211 (3%)
Major haemolysis	152 (2%)
Outcomes	
ECMO duration, days	10·9 (5·9 to 20·0)
Successfully weaned off ECMO	406/604 (67%)
ICU discharge alive	359/604 (59%)
ICU length of stay, days	26·4 (15·7 to 43·7)
Hospital discharge alive	351/604 (58%)
Hospital length of stay, days	37·9 (22·7 to 59·0)
6-month survival	336 (56%)

Daily data median (IQR), number of days (%), n (%). All bleeding cases indicates the number of days of bleeding and their proportion in the whole dataset; for types of bleeding, the crude number and the percentage of the total amount of bleeding cases are reported. Major haemolysis was defined as a free haemoglobin concentration of more than 50 g/dL or a diagnosis of haemolysis prompting the change of the circuit. CRRT=continuous renal replacement therapy. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. PRBC=packed red blood cells. Q_{EC}=extracorporeal blood flow. Q_{EC}:eCO=extracorporeal blood flow rate to estimated cardiac output ratio. SOFA=Sequential Organ Failure Assessment. *Any overt bleeding that requires heparin infusion rate reduction or PRBC transfusion (provided haemoglobin concentration decrease was associated with bleeding). †Any overt bleeding that requires heparin infusion rate reduction and transfusion of PRBC or non-surgical procedure to stop bleeding (provided haemoglobin concentration decrease was associated with bleeding). ‡Any life-threatening bleeding that required PRBC transfusion or surgical intervention for control of bleeding or both, or ECMO discontinuation. §Any fatal bleeding.

Table 2: **Summary of longitudinal daily data and outcomes**

causes and bacterial pneumonia (table 1). Mean haemoglobin concentration at cannulation was 10·9 g/dL (2·4) and was significantly lower in high-volume centres (appendix p 46).

Longitudinal data were collected for 7944 days on ECMO (table 2; appendix p 48). The mean haemoglobin concentration during ECMO was 9·1 g/dL (SD 1·2); higher values were reported in the first 7 days (mean haemoglobin was 9·3 g/dL [SD 1·5]), but progressively decreased despite the different quartiles of haemoglobin at baseline (figure 1A, B). To explore the baseline and daily variables associated with variations in haemoglobin, we created

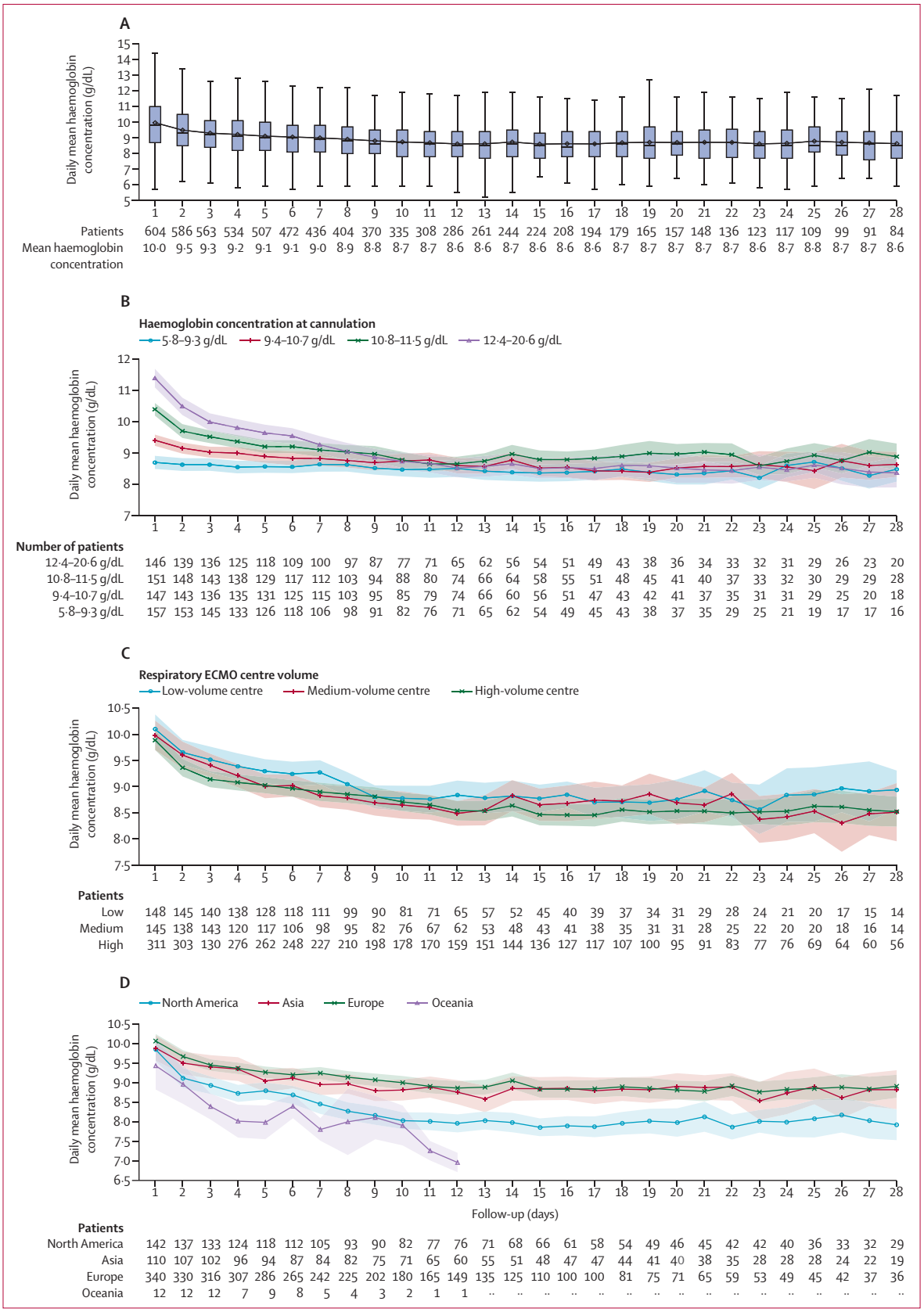

Figure 1: **Variation in haemoglobin concentration over 28-day follow-up**
(A) Box plot of dynamics for mean haemoglobin values. (B) Change in mean haemoglobin concentration according to initial quartiles of haemoglobin concentration. Data are mean daily values of haemoglobin; shaded areas are 95% CI. (C) Change in mean haemoglobin concentration over time according to the caseload of the ECMO centre in the cohort. Data are mean daily values of haemoglobin; shaded areas are 95% CI. (D) Change in mean haemoglobin concentration over time according to the continent where the patient was treated. Data are mean daily values of haemoglobin; shaded areas are 95% CI. Oceania was reported as description but was excluded from the final analysis due to the low number of patients and because no patients completed the 28-day follow-up. ECMO: extracorporeal membrane oxygenation.

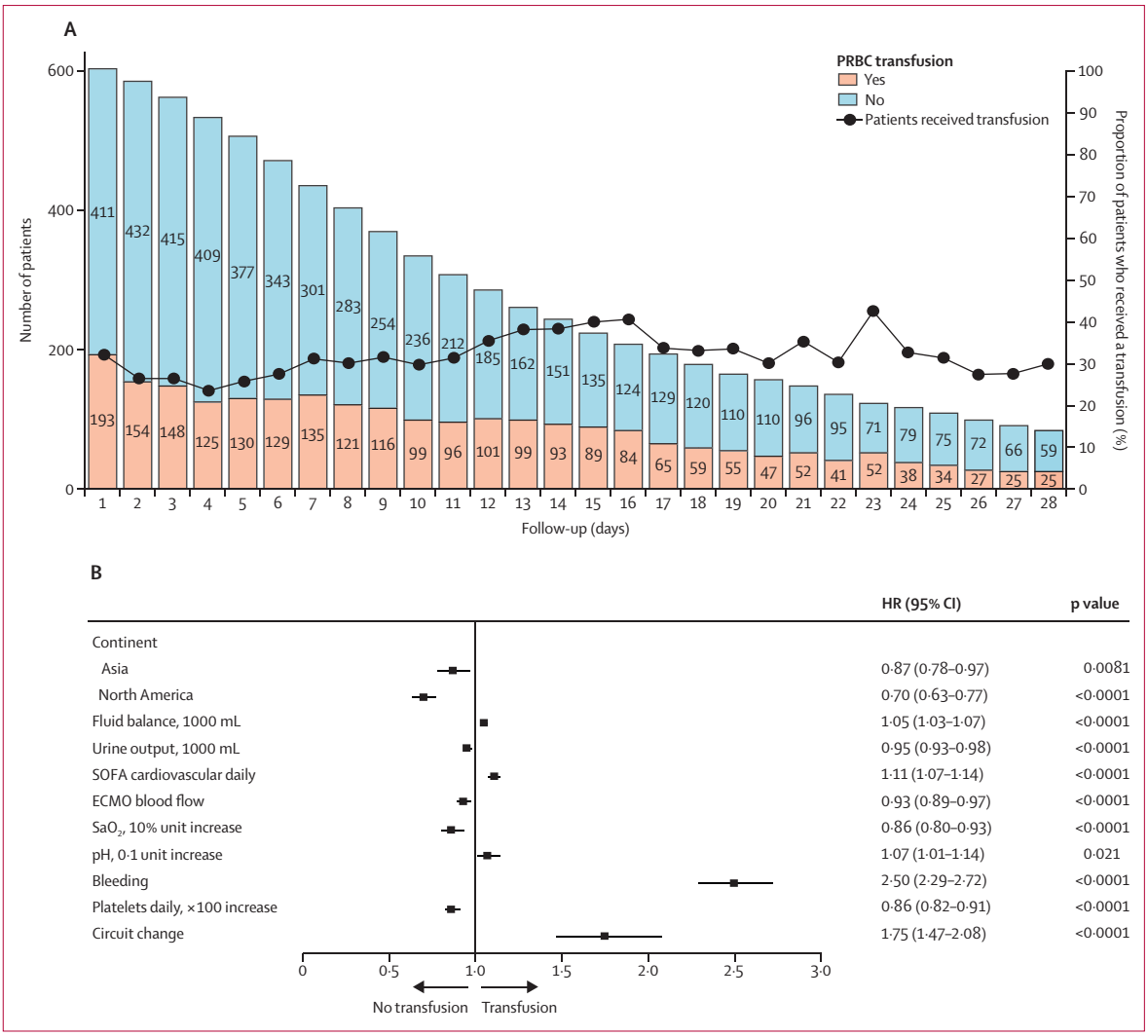

Figure 2: **Proportion of patients receiving PRBC transfusion (A) and factors independently associated with PRBC transfusion recurrence (B)**
The forest plot of factors independently associated with PRBC transfusion recurrence during the ECMO stay was developed with stepwise multiple analysis. ECMO=extracorporeal membrane oxygenation. HR=hazard ratio. PRBC=packed red blood cells. SaO_2=arterial oxygen saturation. SOFA=sequential organ failure assessment. *Asia and North America were compared with Europe; no data for Oceania are reported.

univariate generalised estimating equations models (appendix p 49). Lower haemoglobin concentrations were reported in high-volume centres compared with low-volume centres (average haemoglobin concentration difference –0·26 g/dL, p=0·022; figure 1C), and in North America compared with Europe (difference –0·66 g/dL, p<0·0001; figure 1D). In a multiple analysis, only ECMO treatment in European centres (average haemoglobin difference compared with other continents 0·73 g/dL, p<0·0001) and use of vasopressors (average haemoglobin difference compared with days without vasopressors 0·26 g/dL, p=0·0005) remained independently associated with variation in haemoglobin concentration higher than 0·1 g/dL (appendix p 51).

PRBC transfusions were done on 2432 (31%) of 7944 study days. On average, patients received a median of 115 mL (IQR 48–223) of PRBC per day during ECMO. The rate of patients transfused daily remained stable even with longer runs (figure 2A). The median amount of PRBC transfused on days when a transfusion occurred was 425 mL (350–556); 504 (83%) of 604 patients received at least one unit of PRBC and were transfused on a median of 31% of days (15–37). 100 (17%) patients completed the ECMO run without any PRBC transfusion, with a median ECMO duration of 5·7 days (3·4–9·8), significantly shorter than patients who received transfusions. Patient transfused had a higher body surface area, had a longer hospital stay before ECMO cannulation, and higher Respiratory ECMO Survival Prediction score (appendix p 52).

The principal reasons for PRBC transfusion were low haemoglobin (1521 [63%] of 2432 transfusions), bleeding

	Overall effect during follow-up	p value	Heavyside functions			
			Week 1	Week 2	Week 3	Week 4
Univariate Cox model for 28-day ICU mortality*						
Haemoglobin, g/dL	0·87 (0·78–0·98)†	0·016	0·96 (0·82–1·12)	0·82 (0·66–1·02)	0·88 (0·68–1·13)	0·68 (0·47–0·97)†
Haemoglobin strata (reference 8–10 g/dL)						
Haemoglobin concentration <7 g/dL	3·15 (2·01–4·93)†	<0·0001	3·64 (1·61–8·24)†	2·44 (1·08–5·52)†	3·03 (1·22–7·54)†	16·51 (3·99–68·31)†
Haemoglobin concentration 7–8 g/dL	1·29 (0·91–1·84)	0·16	1·21 (0·62–2·39)	0·87 (0·44–1·73)	1·51 (0·77–2·96)	2·77 (0·89–8·64)
Haemoglobin concentration ≥10 g/dL	0·93 (0·64–1·40)	0·77	1·04 (0·61–1·81)	0·89 (0·41–1·92)	0·60 (0·18–2·01)	1·22 (0·30–4·94)
Cut-off 7 g/dL						
Haemoglobin concentration <7 g/dL vs ≥7 g/dL	2·99 (1·95–4·60)	<0·0001	3·49 (1·59–7·65)†	2·56 (1·16–5·65)†	2·82 (1·19–6·70)†	11·98 (3·18–45·12)†
Multiple Cox model for ICU 28-day mortality‡						
Time-fixed variable						
RESP score	0·91 (0·88–0·95)	<0·0001	0·91 (0·86–0·96)†	0·90 (0·84–0·96)†	0·96 (0·87–1·05)	0·87 (0·78–0·97)†
Time-dependent variables						
Fluid balance, 1000 mL increase	1·18 (1·11–1·25)	<0·0001	1·13 (1·04–1·23)†	1·24 (1·07–1·43)†	1·21 (1·02–1·42)†	1·23 (1·05–1·45)†
Q_{EC}:eCO, 10% increase	0·91 (0·84–0·97)	0·0078	0·84 (0·74–0·96)†	0·93 (0·81–1·06)	0·97 (0·84–1·13)	0·91 (0·73–1·14)
Cardiovascular SOFA	1·19 (1·06–1·32)	0·0020	1·24 (1·04–1·49)†	1·04 (0·85–1·26)	1·28 (1·02–1·61)	1·01 (0·71–1·45)
Haemolysis	2·19 (1·19–4·02)	0·012	1·38 (0·42–4·53)	2·32 (0·85–6·37)	3·88 (1·08–13·88)†	3·06 (0·40–23·56)
Platelets, ×100 increase	0·68 (0·55–0·84)	0·0003	0·75 (0·54–1·03)	0·52 (0·33–0·82)†	0·74 (0·51–1·07)†	0·72 (0·37–1·42)
pH, 0·1 increase	0·59 (0·51–0·68)	<0·0001	0·74 (0·60–0·91)†	0·49 (0·33–0·72)†	0·47 (0·31–0·70)†	0·53 (0·36–0·78)†
Lactate concentration, 1 mmol/L increase	1·06 (1·03–1·09)	<0·0001	1·15 (1·10–1·21)†	1·04 (0·99–1·08)	0·99 (0·90–1·08)	1·08 (0·99–1·17)

Cardiovascular SOFA=cardiovascular dysfunction item of the Sequential Organ Failure Assessment score; ICU=intensive care unit. Q_{EC}:eCO=extracorporeal blood flow rate to estimated cardiac output ratio. RESP=respiratory ECMO survival prediction. *Data are hazard ratio (95% CI) for ICU mortality according to haemoglobin as continuous variable, different strata, and binary cutoffs. †p value less than 0·05, when p value is not reported. ‡Data are hazard ratio (95% CI) for ICU mortality for variables that remained significant in the multiple model.

Table 3: **Univariate and multiple Cox model with time-fixed and time-dependent covariates for ICU mortality**

(560 [23%] transfusions), haemodynamic impairment (210 [9%] transfusions), and low ECMO blood flow rate (73 [3%] transfusions); 68 (3%) patients had PRBC transfusion for other reasons. Overall, mean pre-transfusion haemoglobin concentration was 8·1 g/dL (SD 1·1), but it varied according to the clinical rationale for transfusion (appendix p 54). The transfusion trigger showed wide variability between the same haemoglobin concentration classes (<7 g/dL, 7–8 g/dL, 8–10 g/dL, or >10 g/dL; appendix p 54). In days when haemoglobin concentration was less than 7 g/dL, PRBC transfusions were given on 230 (71%) of 325 days. Whereas on days when the haemoglobin concentration was more than 10 g/dL, PRBC transfusions were given on 375 (21%) of 1760 days. This variability was evident within patients and centres, and higher haemoglobin thresholds were increasingly used with older patients, in patients with kidney failure developed during ECMO (lower urine output or use of continuous renal replacement therapy), and in those with reduced Q_{EC}:eCO (appendix p 55).

The clinical factors associated with the occurrence of PRBC transfusions during ECMO were assessed by bivariate models for recurrent events (adjusted for daily haemoglobin concentration; appendix p 56) and a stepwise multiple analysis. Variables independently associated with an increased recurrence rate of PRBC transfusions were positive fluid balance, higher cardiovascular item of the SOFA score, higher pH, bleeding, and ECMO circuit change (figure 2B).

359 (59%) of 604 patients survived to discharge from the ICU, and 351 (58%) were alive at hospital discharge (table 2). The haemoglobin concentration at cannulation was similar between people who were discharged from the ICU (11·1 g/dL [SD 2·4]) and those who died while in the ICU (10·8 g/dL [SD 2·4]; p=0·23). Patients in different quartiles of haemoglobin at cannulation showed no significant difference in ICU outcomes (appendix p 47).

In a time-dependent Cox model, higher haemoglobin concentration was associated with a reduced probability of death in the ICU across the 28-day follow-up (HR 0·87 [95% CI 0·78–0·98]; table 3). However, when assessed by each week during the 28 days, this association was not consistent over time. By contrast, considering haemoglobin concentration by strata, a daily haemoglobin concentration of less than 7 g/dL was the only consistent threshold as a risk factor for death (2·99 [1·95–4·60]). In

Figure 3: **Effect of PRBC transfusion on risk of death at different haemoglobin concentrations**
HR (95% CI) calculated with marginal structural Cox proportional hazards models to adjust for baseline and daily covariates. HR=hazard ratio. PRBC=packed red blood cells.

a multiple Cox model with time-fixed and time-dependent covariates, haemoglobin and PRBC transfusions were excluded in the stepwise selection process and were not significant even when forced into the models. Increased fluid balance, cardiovascular SOFA, lactate concentration, and major haemolysis were associated with higher risk of death (table 3). Therefore, a higher Respiratory ECMO Survival Prediction score, increased Q_{EC}:eCO, a higher number of platelets, and higher pH were retained as associated with an increased chance of ICU survival. However, when the associations for each of the 4 weeks were assessed, the increase in fluid balance and reduction in pH were the only two variables consistently associated with death.

The effect of PRBC transfusions within different haemoglobin strata on mortality was verified with marginal structural Cox proportional hazards models to adjust for baseline and daily covariates: PRBC transfusions reduced the risk of death only when done when haemoglobin concentration was less than 7 g/dL (HR 0·15 [95% CI 0·03–0·74]; p=0·019; figure 3; appendix p 61). This effect was also confirmed by applying this method to the multiple model (0·09 [0·02–0·42]; p=0·0025; appendix p 61). Following these analyses, the highest haemoglobin concentration used as a trigger for PRBC transfusion that was associated with a reduction in the risk of death was 7·2 g/dL, in both the time-dependent Cox model (0·38 [0·17–0·83]) and the marginal structural Cox proportional hazards model (0·23 [0·06–0·87]; appendix p 62).

Discussion

Our study on patients receiving VV ECMO for ARDS has five key findings. First, haemoglobin concentrations were maintained at a lower level than traditionally recommended; second the haemoglobin concentration threshold for transfusion varied considerably across centres and clinical conditions; third PRBC were transfused on 31% of ECMO days; fourth, PRBC was consistently associated with survival only when done when haemoglobin concentrations were less than 7 g/dL; and finally a more positive fluid balance, at each timepoint of follow-up, was independently associated with increased transfusion rate and risk of death.

Until 2021, the ELSO guidelines recommended maintaining haematocrit at more than 40%.[16] By contrast, several randomised trials in patients who are critically ill have shown that the lower thresholds for transfusion reduced the patients' exposure to allogenic PRBC, with improved or similar outcomes compared with higher thresholds.[17–19] Given the scarcity of evidence-based data, a strict haemoglobin trigger would still be difficult to compare in ECMO versus another strategy considered to be standard practice.[20,21] The terms restrictive and liberal might not readily be implemented in this setting because deviation from protocols are common and statistical significance can be reached with very low haemoglobin concentration differences (often in the range of 0·1 g/dL).[7,21,22] In addition, the longitudinal differences in haemoglobin concentration seen in our data were relatively minor from a clinical perspective (in the range of 0·1 g/dL to 0·7 g/dL). Therefore, these changes would be considered clinically relevant, and consequently result in a change in clinical practice, only when a haemoglobin concentration is near the set threshold for transfusion. Nonetheless, restrictive transfusion strategies are being increasingly implemented during ECMO. These restrictive transfusion strategies are extrapolated from data in patients not receiving ECMO and who are in an ICU, and are based on expert advice or institutional experience.[10] Of note, the two main randomised trials of ECMO for respiratory failure protocolised haemoglobin quite differently (12–14 g/dL *vs* 8–10 g/dL).[23] However, the results of a survey, published in 2019, showed that the haemoglobin concentration trigger is typically higher in patients receiving VV ECMO than in other patients who are critically ill: 9·1 g/dL (SD 1·8).[12] This discrepancy between triggers was confirmed by our data, suggesting that although there is increasing tolerance of greater degrees of anaemia during ECMO, there is no universal agreement on transfusion thresholds, and, in the same patients, different triggers might be applied according to the clinical picture and the preference of the attending specialist. Transfusion is still reliant on clinician behaviour, and small differences in haemoglobin concentration can be affected by the response of the clinicians at the bedside, who might turn to transfusions or other, probably more complex, strategies to stabilise the clinical picture, accepting a higher degree of anaemia. The different behaviour is probably represented by the tendency to accept lower haemoglobin concentration thresholds in higher volume centres compared with low volume centres, and by centres located in North America that probably follow a stricter application of guidelines for patients who are critically ill or that are facing shortages and higher costs for PRBC.[24] Moreover, our data also provides evidence for rationales other than haemoglobin concentration for PRBC transfusion. As expected, an increased daily cardiovascular dysfunction in the SOFA score played a role

in deciding whether to proceed with transfusion, as did bleeding and circuit change, suggesting that transfusion might be intended to stabilise the clinical picture in some patients, whereas transfusion should be considered only when the other causes of general impairment are addressed.

Following the association between haemoglobin concentration thresholds and death, a meta-analysis, published in 2021, reported a correlation between higher transfusion thresholds and increased risk of death during VV ECMO.[25] Regarding physiology, the principal reason to recommend transfusions in cases of anaemia is to directly increase the DO_2, even though anaemia can be tolerated in a goal-oriented VV ECMO approach.[26,27] A Cochrane review on transfusion thresholds suggests that there is no additional risk of death when haemoglobin is between 7 g/dL and 8 g/dL compared with higher concentrations.[6] During ECMO, the optimal transfusion threshold might vary from day to day in the same patient according to the degree of support needed, and this is confirmed by our data. Despite the variability of the transfusion threshold, the use of the lower threshold for PRBC transfusion remained strongly associated with better survival, prompting the hypothesis that in patients receiving VV ECMO, haemoglobin targets and PRBC transfusion might be managed similarly to other patients who are critically ill, at least when the Q_{EC} is able to fulfil the metabolic needs (according to the clinical evolution, it might vary from the total theoretical Q_{EC} to a lesser degree of support). In the evaluation of the adequate Q_{EC} the degree of recirculation has a specific role, which should always be addressed as soon as possible once it is evident because it decreases the efficiency of ECMO oxygen delivery. The effectiveness of transfusions in case of very low haemoglobin values is also a reasonable and intuitive concept that is founded on patient blood management: both in acute and chronic anaemia. Transfusions are lifesaving only when haemoglobin concentration drops to a level that is crucial for DO_2 or coagulation. This concept seems to be also confirmed by our data; however, historically (either for the higher rate of bleeding or because of the need for intravascular volume to assure blood flow) the administration of PRBC has been applied as a frequent tool to stabilise patients receiving ECMO.

As an additional finding, we confirmed that an increase in daily fluid balance, at any stage of support, affected clinical outcomes. The negative effect of positive fluid balance has been reported to start from day 3 after ECMO cannulation, and in different settings of critical care.[28,29] Increase in daily fluid balance is probably explained by the preload dependency of Q_{EC} without frequent fluid administration. A low red blood cell mass might expose the patient to the risk of inconsistent blood flow rates, with consequent low DO_2. The setting of a daily real-time target for oxygenation was proposed to avoid unnecessarily high blood flow rates and, consequently, to allow for a reduction in the administration of fluids and PRBC.[30] In this setting, the role of transfusion becomes a last resort that is done only when haemoglobin concentration is less than 7 g/dL.

One major strength of the study is that, to the best of our knowledge, PROTECMO is the largest prospective study collecting longitudinal data on haemoglobin concentrations and thresholds, PRBC transfusions, clinical characteristics, and outcomes. In addition, the timeframe of the study was short, avoiding the inherent biases that occur with changes in practice, personnel, and technology over time. To summarise the potential effect of the study, there are two main findings: the evaluation through the robust approach of marginal structural models to estimate the effectiveness of transfusions with different targets and some insights for a potentially confirmatory randomised trial on transfusion in the ECMO setting. As a practical result, we might conclude that applying a haemoglobin threshold of less than 7 g/dL is feasible and ethical on most ECMO days. When patients have a haemoglobin concentration between 7 g/dL and 8 g/dL transfusions of PRBC should be considered, only if deemed necessary after other relevant interventions have been done for patient optimisation, with a goal of avoiding a positive fluid balance. With a future randomised trial in mind, we provide the most frequent haemoglobin trigger in ECMO: 8 g/dL; consequently, a potential restrictive protocol (with a haemoglobin concentration transfusion threshold of <7 g/dL) could be compared with the 8 g/dL threshold that we can consider as the standard practice. Moreover, the restrictive protocol should also provide regulations to increase the haemoglobin threshold when the daily fluid balance increases, when the ECMO blood flow rate is reduced, when there is acidosis despite support, and when vasopressors are in place.

This study has also several limitations. First, the effect of haemoglobin and PRBC transfusion on clinical outcomes might be confounded by other strategies unreported in the study. Second, many variables were collected, and this might increase the risk of type 1 error. Third, the longitudinal data, for feasibility reasons, were limited to the first 28 days of follow-up, and outcomes of interest might have occurred after this period. This limitation is balanced by most patients having a short duration of ECMO, and the main outcomes are determined within the first weeks on ECMO, whereas the number of potential confounding factors are considerable, with a prolonged ICU stay. Moreover, for some of the variables (such as the diagnosis of haemolysis or the clinical rationale for administering PRBC) included in a feasible dataset, were left to the clinical investigator's judgement, and were not standardised by variable definitions. Yet this pragmatic compromise still reflects real-world practice. Finally, we did not have access to the clinical data directly at each centre, and we relied on local principal investigators for data collection and quality. Although there were challenges due to staff

and resource crises during the COVID-19 pandemic, the quality of data collection was assured by the participation of centres that consistently completed and revised data in the appropriate timeframe.

In conclusion, during VV ECMO for ARDS there was no universally accepted trigger for transfusion, although the threshold appears to be lower than in previous recommendations. Transfusion of PRBC was consistently associated with lower mortality when done when haemoglobin concentrations were less than 7 g/dL. However, residual confounding exists, and these associations should be confirmed in a prospective interventional trial.

Contributors

All authors had access to the underlying data. GM, AA, MS, DB, and FT verified the underlying data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. GM, AA, DB, and FT were responsible for the decision to submit the manuscript. AA, DB, GG, GM, MS, and KT conceived and designed the study. GM, MG, AT, MS, CA, VF, JIC, RR, PS, GDP, MB, AAH, JR, SB, and TD curated the data. FT did the formal analyses. DB, MS, KT, PS, GG, GF, JR, and FT designed the methods. GM, DB, MS, HB, RL, MVR, KT, GG, and AA wrote the original draft. CA, AT, MG, LMB, AAH, JR, SB, TD, VG, WDG, BT, AC, and AP reviewed and edited the manuscript. GM and AA acquired the funding. CA, MB, GDP, SB, and KJ were the project administrators and managed resources. DB supervised the project. All the authors have read and approved the final text.

Declaration of interests

DB reports research support from ALung Technologies; being on the medical advisory boards for Abiomed, Xenios, Medtronic, Inspira, and Cellenkos; is the President-Elect of the Extracorporeal Life Support Organization (ELSO) and the Chair of the Executive Committee of the International ECMO Network (ECMONet). LMB is on the Medical Advisory Boards of Eurosets, and Xenios. AC reports grants and personal fees from MAQUET, Xenios, and Baxter. GG reports payment for lectures from Getinge, Draeger Medical, Pfizer, MSD, Fisher & Paykel, Biotest, and research grants from Fisher & Paykel and MSD, all outside of the submitted work. RL is consultant for Medtronic, LivaNova, Getinge, and Abiomed; is a member of the medical advisory board for Eurosets and Xenios, all honoraria for research support are paid to their institutions. RL reports honoraria from Baxter for educational talks. PS reports speaker's honoraria from Getinge, and his institution received a Horizon 2020 Fast track Innovation Grant by the European Commission (NCT04115709). MS reports lecture fees from Getinge, Drager, and Xenios, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Individual patient data reported in this Article will be shared after deidentification, beginning 6 months and ending 2 years after publication to researchers who provide a methodologically sound proposal, and after approval by the steering committee. Proposals should be addressed to the corresponding author.

Acknowledgments

The PROTECMO project received a Research Grant from the ELSO. This study was endorsed by the European Society of Intensive Care Medicine (ESICM) and ECMONet. We thank Jordi Mancebo, for his support during the endorsement, and ISMETT's Language Services Department for help in editing the manuscript. We thank the PROTECMO study group collaborators for their work. Europe: Matteo Brioni, Luca Montini, Linda Bosa, Pierfrancesco Curcio, Eugenio Garofalo, Luis Martin-Villen, Raquel Garcìa-Álvarez, Marta Lopez Sanchez, Nuno Principe, Violeta Chica Saez, Vanesa Gomez, Joaquin Colomina-Climent, Andres F Pacheco, Julien Goutay, Konstanty Szułdrzyński, Philipp Eller, Elisabeth Lobmeyr, Silvia Mariani, Pavel Suk, Michal Maly, Jakob Forestier, Monica Rizzo, and Marco Barbara. North America: Tyler Holsworth, Alexis Serra, Yiorgos A Cavayas, Jay Menaker, Samuel Galvagno, Todd W Rice, E Wilson Grandin, Jose Nunez, Collette Cheplic, and Ryan Rivosecchi. Asia: Young-Jae Cho, Ming Chit Kwan, Hend Sallam, Joy A Villanueva, Jeffrey Aliudin, Kota Hoshino, Yoshitaka Hara, Kollengode Ramanathan, and Graeme Maclaren. Australia: Hergen Buscher.

References

1 Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021; **398:** 1230–38.

2 Combes A, Brodie D, Chen YS, et al. The ICM research agenda on extracorporeal life support. *Intensive Care Med* 2017; **43:** 1306–18.

3 Spinelli E, Bartlett RH. Anemia and transfusion in critical care: physiology and management. *J Intensive Care Med* 2016; **31:** 295–306.

4 Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA* 2014; **311:** 1317–26.

5 Smith A, Hardison D, Bridges B, Pietsch J. Red blood cell transfusion volume and mortality among patients receiving extracorporeal membrane oxygenation. *Perfusion* 2013; **28:** 54–60.

6 Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database Syst Rev* 2021; **12:** CD002042.

7 Vlaar AP, Oczkowski S, de Bruin S, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 2020; **46:** 673–96.

8 Spinelli E, Bartlett RH. Relationship between hemoglobin concentration and extracorporeal blood flow as determinants of oxygen delivery during venovenous extracorporeal membrane oxygenation: a mathematical model. *ASAIO J* 2014; **60:** 688–93.

9 Mazzeffi M, Greenwood J, Tanaka K, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECLS Working Group on thrombosis and hemostasis. *Ann Thorac Surg* 2016; **101:** 682–89.

10 Agerstrand CL, Burkart KM, Abrams DC, Bacchetta MD, Brodie D. Blood conservation in extracorporeal membrane oxygenation for acute respiratory distress syndrome. *Ann Thorac Surg* 2015; **99:** 590–95.

11 Martucci G, Panarello G, Occhipinti G, et al. Anticoagulation and transfusions management in veno-venous extracorporeal membrane oxygenation for acute respiratory distress syndrome: assessment of factors associated with transfusion requirements and mortality. *J Intensive Care Med* 2019; **34:** 630–39.

12 Martucci G, Grasselli G, Tanaka K, et al. Hemoglobin trigger and approach to red blood cell transfusions during veno-venous extracorporeal membrane oxygenation: the international TRAIN-ECMO survey. *Perfusion* 2019; **34** (suppl)**:** 39–48.

13 Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015; **191:** 894–901.

14 Molenberghs G, Kenward M. Missing Data in Clinical Studies. John Wiley & Sons: Chichester, 2007.

15 Kleinbaum DG, Klein M. Survival analysis: a self-learning text. Springer: New York, NY, 2012.

16 Tonna JE, Abrams D, Brodie D, et al. Management of adult patients supported with venovenous extracorporeal membrane oxygenation (VV ECMO): Guideline from the Extracorporeal Life Support Organization (ELSO). *ASAIO J* 2021; **67:** 601–10.

17 Hébert PC, Martin C, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999 **340:** 409–17.

18 Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014; **371:** 1381–91.

19 Mazer CD, Whitlock RP, Fergusson DA, et al. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. *N Engl J Med* 2018; **379:** 1224–33.

20 Hunsicker O, Materne L, Bünger V, et al. Lower versus higher hemoglobin threshold for transfusion in ARDS patients with and without ECMO. *Crit Care* 2020; **24:** 697.

21 Raasveld SJ, Karami M, van den Bergh WM, et al. RBC Transfusion in venovenous extracorporeal membrane oxygenation: a multicenter cohort study. *Crit Care Med* 2022; **50:** 224–34.

22 Vlaar APJ, Dionne JC, de Bruin S, et al. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med* 2021; **47:** 1368–92.

23 Combes A, Peek GJ, Hajage D, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. *Intensive Care Med* 2020; **46:** 2048–57.

24 Owyang CG, Donnat C, Brodie D, et al. Similarities in extracorporeal membrane oxygenation management across intensive care unit types in the United States: an analysis of the Extracorporeal Life Support Organization Registry. *Artif Organs* 2022; **46:** 1369–81.

25 Abbasciano RG, Yusuff H, Vlaar APJ, Lai F, Murphy GJ. Blood transfusion threshold in patients receiving extracorporeal membrane oxygenation support for cardiac and respiratory failure-a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth* 2021; **35:** 1192–202.

26 Munshi L, Kiss A, Cypel M, Keshavjee S, Ferguson ND, Fan E. Oxygen thresholds and mortality during extracorporeal life support in adult patients. *Crit Care Med* 2017; **45:** 1997–2005.

27 Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: The REALITY randomized clinical trial. *JAMA* 2021; **325:** 552–60.

28 Schmidt M, Bailey M, Kelly J, et al. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. *Intensive Care Med* 2014; **40:** 1256–66.

29 Zhang L, Xu F, Li S, et al. Influence of fluid balance on the prognosis of patients with sepsis. *BMC Anesthesiol* 2021; **21:** 269.

30 Shekar K, Buscher H, Brodie D. Protocol-driven daily optimisation of venovenous extracorporeal membrane oxygenation blood flows: an alternate paradigm? *J Thorac Dis* 2020; **12:** 6854–60.