RBC Transfusion in Venovenous Extracorporeal Membrane Oxygenation

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RBC Transfusion in Venovenous Extracorporeal Membrane Oxygenation: A Multicenter Cohort Study

OBJECTIVES: In the general critical care patient population, restrictive transfusion regimen of RBCs has been shown to be safe and is yet implemented worldwide. However, in patients on venovenous extracorporeal membrane oxygenation, guidelines suggest liberal thresholds, and a clear overview of RBC transfusion practice is lacking. This study aims to create an overview of RBC transfusion in venovenous extracorporeal membrane oxygenation.

DESIGN: Mixed method approach combining multicenter retrospective study and survey.

SETTING: Sixteen ICUs worldwide.

PATIENTS: Patients receiving venovenous extracorporeal membrane oxygenation between January 2018 and July 2019.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was the proportion receiving RBC, the amount of RBC units given daily and in total. Furthermore, the course of hemoglobin over time during extracorporeal membrane oxygenation was assessed. Demographics, extracorporeal membrane oxygenation characteristics, and patient outcome were collected. Two-hundred eight patients received venovenous extracorporeal membrane oxygenation, 63% male, with an age of 55 years (45–62 yr), mainly for acute respiratory distress syndrome. Extracorporeal membrane oxygenation duration was 9 days (5–14 d). Prior to extracorporeal membrane oxygenation, hemoglobin was 10.8 g/dL (8.9–13.0 g/dL), decreasing to 8.7 g/dL (7.7–9.8 g/dL) during extracorporeal membrane oxygenation. Nadir hemoglobin was lower on days when a transfusion was administered (8.1 g/dL [7.4–9.3 g/dL]). A vast majority of 88% patients received greater than or equal to 1 RBC transfusion, consisting of 1.6 U (1.3–2.3 U) on transfusion days. This high transfusion occurrence rate was also found in nonbleeding patients (81%). Patients with a liberal transfusion threshold (hemoglobin > 9 g/dL) received more RBC in total per transfusion day and extracorporeal membrane oxygenation day. No differences in survival, hemorrhagic and thrombotic complication rates were found between different transfusion thresholds. Also, 28-day mortality was equal in transfused and nontransfused patients.

CONCLUSIONS: Transfusion of RBC has a high occurrence rate in patients on venovenous extracorporeal membrane oxygenation, even in nonbleeding patients. There is a need for future studies to find optimal transfusion thresholds and triggers in patients on extracorporeal membrane oxygenation.

KEY WORDS: extracorporeal membrane oxygenation; mortality; red blood cells; threshold; transfusion

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Venovenous extracorporeal membrane oxygenation (ECMO) is an important supportive therapy in severe respiratory failure (1–3). By securing extracorporeal decarboxylation and oxygenation, venovenous ECMO provides a supportive function in severe respiratory failure, when other

conventional therapies such as (invasive) mechanical ventilation and adjuvant rescue therapies are insufficient (1). However, mortality and complication rates in patients on venovenous ECMO remain high. One possibly contributing factor is anemia, which is frequent in venovenous ECMO. In this population, anemia can be caused by patient- (e.g., comorbidities), disease- (e.g., disseminated intravascular coagulation), and ECMO- (e.g., use of anticoagulation) derived factors.

Currently, the international Extracorporeal Life Support Organization advises, based on expert opinion only, to maintain a hematocrit of over 40%, equivalent to a hemoglobin of 13 g/dL (~8.1 mmol/L) reasoned to secure adequate systemic oxygen delivery (4). This is in sharp contrast with almost all other critically ill patients without ECMO, for which a threshold of 7 g/dL is currently recommended (5). Furthermore, the European Society of Intensive Care Medicine (ESICM) concludes that based on current evidence, no recommendations on the optimal hemoglobin threshold in venovenous ECMO can be made (6). As a consequence, the applied transfusion threshold for RBCs in venovenous ECMO varies but is frequently more liberal than thresholds adopted for other critically ill patients (5, 7). As a result, RBC transfusion during venovenous ECMO is common, with observational studies showing an incidence of 67–100% and 0.3–2 U per (ECMO) day administered (8–15). Although transfusion can be lifesaving, it is also a risk-bearing intervention with substantial risk for morbidity and mortality in the critically ill population (16–18).

Thus far, only observational studies have been performed on RBC transfusion in venovenous ECMO. However, these studies have been limited by single-center design and small sample sizes, which makes extrapolation difficult. Therefore, the aim of this study is to create an overview of RBC transfusion in patients on venovenous ECMO by describing: 1) the proportion of patients receiving RBC, 2) the amount of RBC transfused, 3) the different center's transfusion regimen, and 4) to evaluate RBC transfusion in the absence of bleeding.

MATERIALS AND METHODS

Study Population

This international mixed methods study was performed in 16 ICUs, in the Netherlands ($n = 9$), Belgium ($n = 3$), Sweden ($n = 1$), Italy ($n = 1$), Croatia ($n = 1$), and Australia ($n = 1$), consisting of a retrospective observational study and survey. The study was approved by the institutional review board of the Amsterdam University Medical Centers (W19_222 Number 19.267), and, thereafter, by local ethical committees. All adult patients who received venovenous ECMO in participating ICUs between January 1, 2018, and July 1, 2019, were included. Exclusion criteria included ECMO solely for extracorporeal Co_2 removal or if the ECMO run duration was less than 12 hours.

Retrospective Data Collection

Patient characteristics prior to ECMO initiation were collected, including demographics, comorbidities, indication for ECMO, and laboratory values within 24 hours prior to initiation of ECMO. Laboratory values focused on hematology (hemoglobin, platelet count), kidney function (creatinine level), and liver function including coagulation variables (aspartate transaminase, alanine transaminase, international normalized ratio, lactate level, activated partial thromboplastin time [aPTT], and prothrombin time [PT]). During ECMO, data on laboratory values (lowest hemoglobin, lowest platelet count, and highest PT and aPTT) and the daily amount of RBC transfusion were collected daily up to a maximum of 28 days of ECMO. Clinical outcome data included complications during ECMO, successful weaning, and survival status. Definitions are presented in the **Additional file: S1** (Definitions, http://links.lww.com/CCM/G927).

Survey

To determine the transfusion practice in the different centers, a survey was developed by the author (S.J.R.) (**Additional file: S2**, Transfusion Questionnaire, http://links.lww.com/CCM/G927). After designing, the survey was evaluated by the authors (M.K., A.P.J.V.). The survey focused on local hemoglobin threshold for RBC transfusion, regional laboratory units, and anticoagulation strategy.

Study Endpoints

The primary endpoint of this study was threefold: the proportion of patients receiving RBC, the daily and total amount of RBC received by patients on venovenous

ECMO. The total transfusion amount was defined as the sum of RBC transfusions (U) received per patient during ECMO (with a maximum of 28 d). The daily transfusion amount was calculated per patient as total transfusion amount divided by the number of days on ECMO (with a maximum of 28 d when data were collected). The daily amount on transfusion day(s) was calculated per patient as total transfusion amount divided by the number of days on which a transfusion was administered. Secondary endpoints were focused on clinical outcomes: complication rate, successful weaning, and 28-day mortality. Furthermore, the hemoglobin course during ECMO was assessed and compared between days with and without transfusion. Last, transfusion amounts and hemoglobin course were assessed between different transfusion threshold. To evaluate protocol adherence, the difference between nadir hemoglobin level on transfusion day and predefined hemoglobin threshold was calculated: "delta hemoglobin." Thus, a negative delta hemoglobin implicated that transfusion was given on days where nadir hemoglobin was below protocol's transfusion threshold, whereas a positive delta hemoglobin reflected that lowest hemoglobin was higher than the transfusion threshold.

Statistical Procedures

Statistical analyses were performed using R with the R Studio interface (version 4.0.3, R Core Team, Vienna, Austria). Normal distributed continuous variables were presented as mean (SD). Non-normal distributed continuous variables were presented as a median (interquartile range). Data were compared using an unpaired *t* test or Mann-Whitney *U* test, depending on the distribution of the data. Categorical variables were presented as percentages and frequencies and analyzed using chi-square test or Fisher exact test. The following groups were compared: 1) transfused versus nontransfused patients, 2) bleeding versus nonbleeding patients, 3) nonbleeding transfused versus nonbleeding nontransfused patients, and 4) survivors versus nonsurvivors. Survival status was defined as being deceased or alive at a minimum of 90 days after ECMO was initiated. Twenty-eight-day survival, defined as being alive at 28 days after ECMO was initiated, was compared between above-described groups using a Log-rank test and a hazard ratio was calculated using the unadjusted Cox regression after checking the assumptions. *p* values of less than 0.05 were considered statistically significant. To compare different transfusion practices, we defined hemoglobin-based RBC transfusion thresholds as restrictive (< 7.5 g/dL), intermediate (7.5–9 g/dL), and liberal (> 9 g/dL) and assigned participating institutions to one of these groups based on the survey (Additional file: S2, Transfusion survey, http://links.lww.com/CCM/G927). Transfusion behavior was compared using a Kruskal-Wallis test and post hoc testing using Dunn test for multiple comparison of groups. Adjusted *p* values (Benjamini-Hochberg method) were considered significant if less than 0.05.

RESULTS

Patient and ECMO Characteristics

During the study period, 230 patients received venovenous ECMO, of whom 22 were excluded from further analyses (**Additional file: S3**, Flowchart, http://links.lww.com/CCM/G927). Of the remaining 208 patients on venovenous ECMO, 130 (63%) were male and median age was 55 years old (45–62 yr old; **Table 1**). They were slightly overweight with a median body mass index of 25.7 kg/m^2 (22.9–29.5 kg/m^2). Almost two thirds (64%, *n* = 133) had one or more comorbidities stated in the medical history, 44 patients had hypertension (21%), 25 had chronic obstructive pulmonary disease (12%), and 20 diabetes (10%). Severity of illness prior to initiation of ECMO was high, as represented by a Sequential Organ Failure Assessment (SOFA) score of 10 (8–13) and Pao_2/Fio_2 ratio of 68 mm Hg (48–106 mm Hg). Prior to ECMO initiation, hemoglobin was 10.8 g/dL (8.9–13.0 g/dL).

Venovenous ECMO was mostly indicated for acute respiratory distress syndrome (66%; *n* = 137), followed by postsurgery indications (9%; *n* = 18) or bridge to lung transplantation (8%; *n* = 16). A majority of 179 patients (87%) were cannulated percutaneously. The total duration of the initial ECMO run was 9 days (5–14 d).

Transfusion

Table 2 shows that 182 patients (88%) received at least one RBC transfusion during ECMO. A median total amount of 6 U (2–12 U) was transfused per ECMO

TABLE 1.
Demographics and Run Characteristics

Variable	Venovenous ECMO (*n* = 208)	Transfused (*n* = 182)	Nontransfused (*n* = 26)
Age (yr)	55 (45–62)	54[a] (43–61)	60[a] (54–65)
Male	130 (63%)	110 (60%)	20 (77%)
Body mass index, kg/m^2	25.7 (22.9–29.5)	25.7 (22.8–30.3)	26.3 (24.5–28.1)
Medical history: comorbidities			
Cardiovascular disease	65 (32%)	60 (34%)	5 (19%)
Hypertension	44 (21%)	41 (23%)	3 (12%)
Diabetes	20 (10%)	19 (11%)	1 (4%)
Myocardial infarction	14 (7%)	12 (7%)	2 (8%)
Pulmonary disease	75 (36%)	62 (34%)	13 (50%)
Chronic obstructive pulmonary disease	25 (12%)	19 (10%)	6 (23%)
Asthma	18 (9%)	12 (7%)	6 (23%)
Pulmonary hypertension	15 (7%)	13 (7%)	2 (8%)
Chronic kidney disease	13 (7%)	12 (7%)	1 (4%)
Malignancy	20 (10%)	17 (9%)	3 (12%)
Values prior ECMO			
Sequential Organ Failure Assessment	10 (8–13)	10[a] (8–13)	9[a] (7–10)
Pao_2/Fio_2 ratio	68 (48–106)	67 (48–98)	90 (52–148)
Hemoglobin, g/dL	10.8 (8.9–13.0)	10.5[a] (8.7–12.0)	14.4[a] (12.7–16)
Platelets, 10^9/L	229 (137–308)	212[a] (129–296)	312[a] (238–353)
Activated partial thromboplastin time, s	33 (28–37)	34 (29–38)	29 (27–34)
Prothrombin time, s	13.8 (12.0–16.6)	14.3[a] (12.4–17.8)	12.8[a] (11.5–13.8)
Fibrinogen, g/L	5.9 (4.8–8.0)	5.9 (4.7–8.0)	6.1 (5.5–8.1)
Lactate, mmol/L	1.7 (1.2–2.7)	1.6 (1.2–2.8)	1.8 (1.4–2.3)
Creatinine, µmol/L	105 (68–158)	107 (68–168)	85 (65–123)
ECMO indication			
Acute respiratory distress syndrome	137 (66%)	123 (67%)	14 (54%)
Bridge to lung transplantation	16 (8%)	15 (8%)	1 (4%)
Postoperative	18 (9%)	16 (9%)	2 (8%)
Status asthmaticus	14 (7%)	8 (4%)	6 (23%)
Trauma with severe lung contusion	6 (< 3%)	6 (3%)	0 (0%)
Other	11 (5%)	10 (6%)	1 (4%)
Missing	6 (< 3%)	4 (2%)	2 (8%)
ECMO duration (d)	9 (5–14)	9.5[a] (5–15)	5[a] (3–8)
Second run	16 (8%)	16 (9%)	0 (0%)
Percutaneous cannulation	179 (87%)	157 (87%)	22 (85%)

ECMO = extracorporeal membrane oxygenation.

[a]Significant difference $p < 0.05$.

Data presented as *n* (%) for categorical variables and median (first–third quartile) for nonparametric variables.

TABLE 2.
RBC Transfusions

Variables	Venovenous ECMO (*n* = 208)	Restrictive Threshold (*n* = 70)	Liberal Threshold (*n* = 64)	*p*
Received RBC, *n* (%)	182 (88)	62 (89)	59 (92)	0.21
Total RBC received, U	6 (2–12)	6 (2–11)	10 (5–17)	< 0.01
RBC per transfusion day, U	1.6 (1.3–2.3)	1.4 (1–2)	1.8 (1.5–2.4)	< 0.01
RBC per day on ECMO, U	0.6 (0.25–1.25)	0.5 (0.3–1.3)	0.9 (0.5–1.5)	0.02
Amount of transfusion days, d	3.0 (1.75–6)	3 (2–6)	5 (2–10)	0.03
Median daily hemoglobin, g/dL	8.7 (7.7–9.8)	8.5 (7.6–9.8)	10.1 (9.7–10.6)	< 0.001
Hemoglobin on transfusion day, g/dL	8.1[a] (7.4–9.3)	8.0[b] (7.3–9.0)	9.9 (9.6–10.4)	< 0.001
Hemoglobin on nontransfusion day, g/dL	9.0[a] (8.1–10.2)	9.0[b] (8.0–10.3)	10.4 (10.1–11.1)	< 0.001
Delta hemoglobin, g/dL	−0.1 (−0.8 to +0.7)	−0.2 (−1.0 to 0.4)	0.9 (0.6–1.4)	< 0.001

ECMO = extracorporeal membrane oxygenation.

[a,b]$p < 0.001$; other differences calculated between restrictive and liberal threshold.

Data presented as *n* (%) for categorical variables and median (first–third quartile) for nonparametric variables. RBC transfusion thresholds defined as: restrictive < 7.5 g/dL and liberal > 9 g/dL. Delta hemoglobin: Difference in hemoglobin on transfusion day minus predefined threshold. Intermediate regimen is not included in this table.

run. On days that transfusion was administered, patients received 1.6 RBC U (1.3–2.3 U). Transfusion of RBC occurred on 3 days in total (1.75–6 d) during their ECMO run, which adds up to a third of all days on ECMO. Per day on ECMO, daily median amount received was 0.6 U (0.25–1.25 U). Interestingly, in case of RBC transfusion, the amount of units transfused per day was the same, with the exception for the first day (**Additional file: S4**, boxplot transfusion amount per day on ECMO, http://links.lww.com/CCM/G927). The same was true for the proportion of patients receiving transfusion, whereas daily a median of 42% (37–47%) was given a RBC transfusion (**Additional file: S5**, bar plot number of patients on ECMO with proportion receiving transfusion, http://links.lww.com/CCM/G927).

Median lowest daily hemoglobin during ECMO was 8.7 g/dL (7.7–9.8 g/dL) and was lower on days when transfusion was administered (transfusion day: 8.1 g/dL [7.4–9.3 g/dL] vs nontransfusion day: 9.0 g/dL [8.1–10.2 g/dL]). On transfusion days, transfusion was given at a median delta hemoglobin of –0.1 g/dL (–0.8 to +0.7 g/dL) below the protocol's predefined threshold, therefore implying protocol adherence. This difference was lower in bleeding patients (delta hemoglobin bleeding: –0.2 g/dL [–0.9 to +0.5 g/dL] vs nonbleeding: 0.0 g/dL [–0.6 to +0.7 g/dL]; $p < 0.001$). In nonbleeding patients, 34% received RBC transfusion despite a nadir hemoglobin of more than 0.5 g/dL higher than the protocol's transfusion threshold.

Transfusion: Regimen

Hemoglobin thresholds for RBC transfusion ranged from 7 to 10 g/dL (**Additional file: S6**, http://links.lww.com/CCM/G927): four centers ($n = 70$) had a restrictive (hemoglobin < 7.5 g/dL), five centers ($n = 64$) a liberal (hemoglobin > 9 g/dL), and seven centers ($n = 74$) an intermediate (hemoglobin 7.5–9 g/dL) threshold. Compared to patients with a restrictive threshold, patients with a liberal transfusion threshold received more RBC units in total, per transfusion day and per day on ECMO (**Fig. 1**; all: $p < 0.05$). Furthermore, in centers with a liberal transfusion threshold, lowest daily recorded hemoglobin was higher on transfusion days as well as nontransfusion days (all: $p < 0.01$). Also, in centers with a liberal regimen, transfusion was administered at a delta hemoglobin level of 0.9 g/dL (0.6–1.4 g/dL) higher than the threshold; on 78% of the times that transfusion was given, nadir hemoglobin level was higher than the protocol's threshold. An overview of the hemoglobin levels and RBC amount per center can be found in the additional materials (**Additional files: S7** and **S8**, http://links.lww.com/CCM/G927).

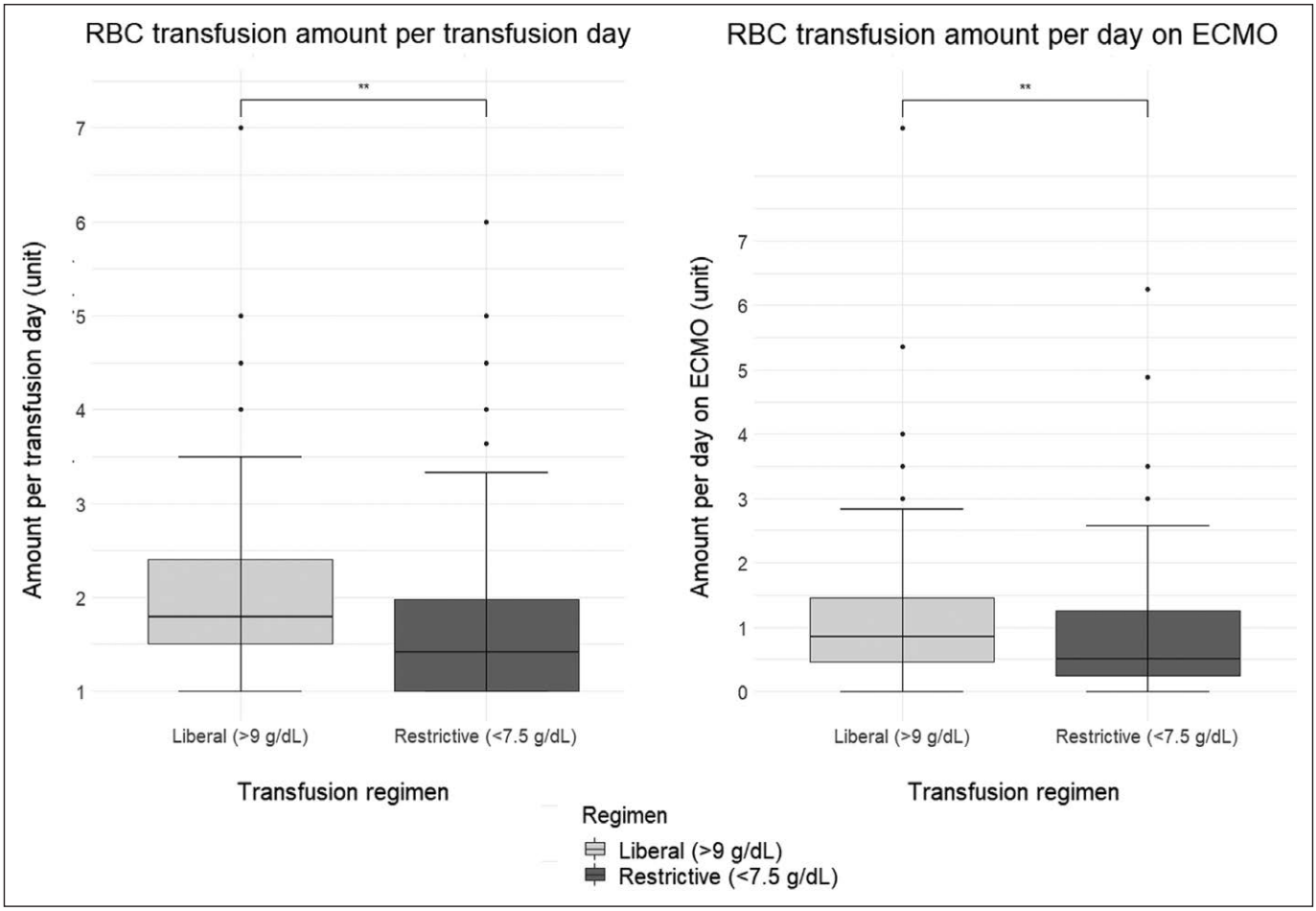

Figure 1. RBC transfusion amount per transfusion day and per day on extracorporeal membrane oxygenation (ECMO). *$p < 0.05$, **$p < 0.01$. Subgroups defined as liberal (> 9 g/dL, $n = 64$), restrictive (< 7.5 g/dL, $n = 70$), and intermediate (7.5–9 g/dL, $n = 74$) thresholds. Intermediate group is not included in this figure.

Transfused Versus Nontransfused

As shown in Table 1, transfused patients were younger (54 yr old [43–61 yr old] vs 60 yr old [54–65 yr old]), had a higher SOFA score prior to ECMO (10 [8–13] vs 9 [7–10]), and a longer ECMO run (9.5 d [5–15 d] vs 5 d [3–8 d]; all $p < 0.05$). Furthermore, prior to ECMO initiation, transfused patients had a lower hemoglobin level (10.5 g/dL [8.7–12.0 g/dL] vs 14.4 g/dL [12.7–16 g/dL]; $p < 0.001$) and platelet count prior to ECMO (212 $\times 10^9$/L [129–296 $\times 10^9$/L] vs 312 $\times 10^9$/L [238–353 $\times 10^9$/L]). The same trend was found when comparing nontransfused patients with patients receiving a total amount of 6–12 or greater than 12 U (**Additional file: S9**, http://links.lww.com/CCM/G927). Of the 81 patients (39%) suffering a hemorrhagic complication, 98% received RBC (**Additional file: S10**, http://links.lww.com/CCM/G927). However, in nonbleeding patients, transfusion rate was still remarkably high with 81% ($n = 102$) receiving RBC during ECMO (**Additional file: S11**, http://links.lww.com/CCM/G927). In **Figure 2**, transfusion days are compared with nontransfusion days with respect to the lowest daily hemoglobin value. In the first week, the lowest hemoglobin level was significantly lower on the days a patient received a transfusion. After day 12, this significant difference disappears (**Additional file: S12**, http://links.lww.com/CCM/G927).

Clinical Outcome

During ECMO, 148 patients (71%) suffered from one or more complications during ECMO, of which acute kidney injury (48%; $n = 100$), a new infection (44%; $n = 92$), or hemorrhage (39%; $n = 81$) were most frequent (**Table 3**). A majority of 69% was successfully weaned ($n = 144$), of whom 16 died after a median of 11 days after decannulation (6–25 d). A total of 150 patients (72%) were still alive 28 days after ECMO was initiated,

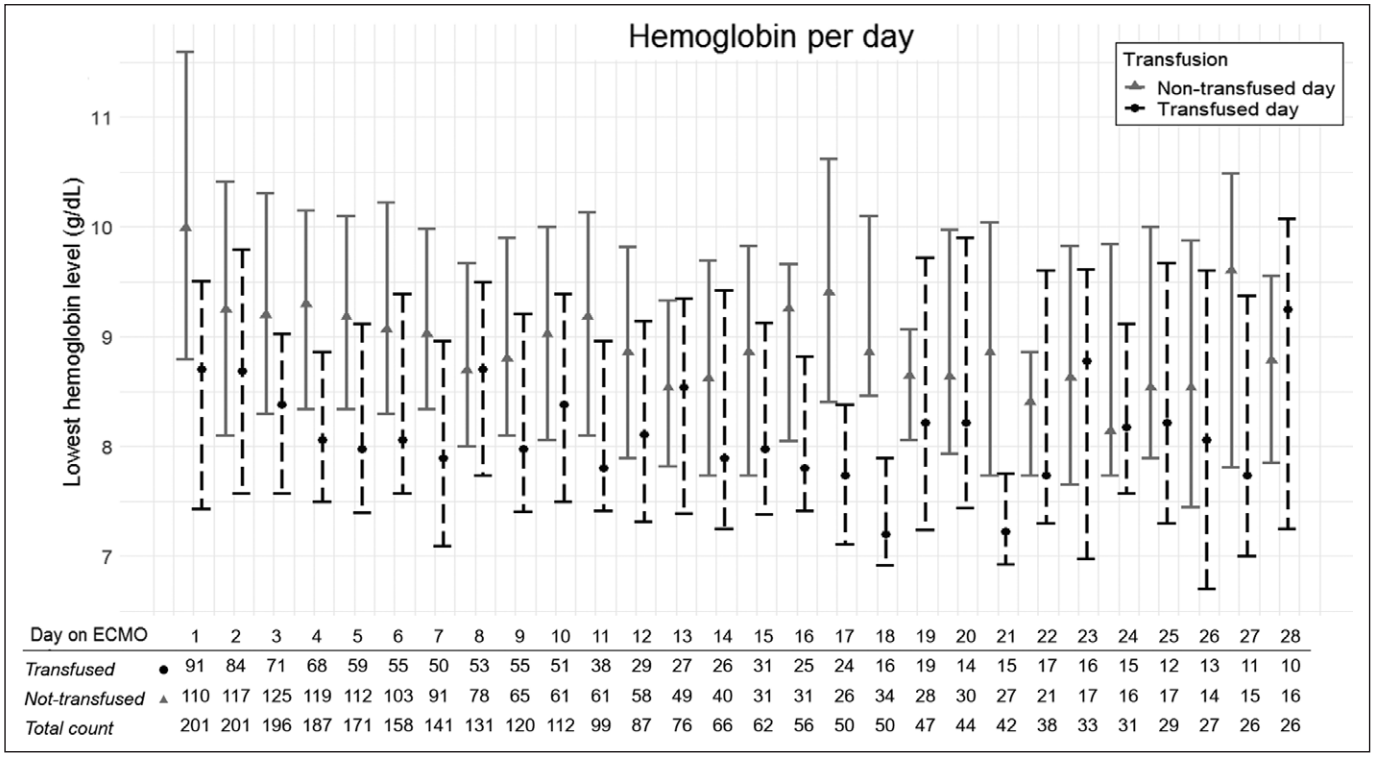

Figure 2. Daily hemoglobin level on extracorporeal membrane oxygenation (ECMO). Daily lowest hemoglobin level (g/dL) in patients on ECMO, divided by if transfusion was or was not administered. In the table below, the amount of patients still on ECMO for whom a hemoglobin value was known is shown.

of which 21 (10%) were still on ECMO. Of those patients still on ECMO, 10 were successfully weaned. No differences were found in complication rate between survivors and nonsurvivors, with the exception of mechanical thrombosis (14 survivors [11%] vs 21 nonsurvivors [26%]). Prior ECMO, during transfusion and nontransfusion days, and overall during ECMO, lowest daily hemoglobin was equal between survivors and nonsurvivors (**Additional files: S13** and **S14**, http://links.lww.com/CCM/G927). There was no difference in 28-day mortality between the transfused and nontransfused patients overall (unadjusted hazard ratio, 0.83; 0.4–1.7; $p = 0.60$). Last, no differences in survival, hemorrhagic and thrombotic complication rates were found between the different transfusion thresholds applied (**Additional file: S15**, http://links.lww.com/CCM/G927).

DISCUSSION

We present the first international multicenter data (16 centers) on transfusion of RBC in patients on venovenous ECMO. The main finding of our study is that transfusion of RBC in patients on venovenous ECMO is very common, with almost nine out of 10 patients receiving RBC during venovenous ECMO, and the amounts received during ECMO are considerably high. Furthermore, this frequency and amount of RBC transfusion are also found in the absence of bleeding. Last, variance in center's thresholds is high, although no differences were found in complication rate and survival between the regimen.

The incidence and amount of RBC received by patients on venovenous ECMO are remarkably high in comparison with the general ICU population. It has been described that during ICU admission, approximately one third of the patients in the ICU receive a RBC transfusion (19). One explanation for this difference could be the relatively liberal thresholds used in ECMO patients. In line with our findings, international surveys and guidelines describe a liberal RBC transfusion threshold applied in venovenous ECMO (4, 5, 7). However, those current recommendations regarding the optimal transfusion threshold are solely based on expert opinion. An existing hypothesis states that in respiratory failure, decreased oxygen diffusion and thereby decreased uptake can be expected, resulting in tissue hypoxia (20). By providing a larger hemoglobin buffer, it is assumed that the oxygen

TABLE 3.
Patient Outcomes and Complication Rate

Variable	Venovenous ECMO (*n* = 208)	Transfused (*n* = 182)	Nontransfused (*n* = 26)
Complications during ECMO			
Hemorrhage	81 (39%)	79[a] (44%)	2[a] (8%)
Arterial thrombosis	5 (2%)	5 (3%)	0 (0%)
Stroke	1 (< 1%)	1 (< 1%)	0 (0%)
Leg ischemia	3 (1%)	3 (2%)	0 (0%)
Other	1 (< 1%)	1 (< 1%)	0 (0%)
Venous thrombosis	15 (8%)	12 (7%)	3 (12%)
Lower extremity	6 (3%)	4 (2%)	2 (8%)
Upper extremity	4 (2%)	3 (2%)	1 (2%)
Other	6 (3%)	5 (4%)	1 (4%)
Mechanical thrombosis	35 (17%)	33 (2%)	2 (8%)
Cannula	8 (4%)	8 (4%)	0 (0%)
Pump	7 (4%)	6 (3%)	1 (4%)
Oxygenator	22 (11%)	21 (12%)	1 (4%)
Other	1 (< 1%)	1 (1%)	0 (0%)
Infection	92 (44%)	87[a] (48%)	5[a] (19%)
Acute kidney injury	100 (48%)	93[a] (51%)	7[a] (27%)
Renal replacement therapy	89 (43%)	87[a] (48%)	2[a] (8%)
ECMO outcome			
Successful weaning	144 (69%)	126 (69%)	18 (69%)
28-d mortality	58 (28%)	50 (27%)	8 (31%)
28-d mortality, hazard ratio	0.83		(0.4–1.7)

ECMO = extracorporeal membrane oxygenation.
[a]Differences significant with $p < 0.05$.
Data presented as *n* (%) for categorical variables and median (first–third quartile) for nonparametric variables.

delivery will be preserved and the incidence of hypoxia will be reduced. However, this has not been demonstrated in clinical studies thus far. The present study raises the question if transfusion thresholds should be reconsidered in patients on ECMO. Thus far, no prospective or interventional studies have been performed examining the effects of implementing a more restrictive guideline regarding transfusion thresholds in patients on ECMO. However, in similar patient populations, such as septic shock, a restrictive transfusion threshold has been proven noninferior to liberal thresholds in large randomized controlled trials (RCTs) (21). In addition, even in previously considered "risk groups," such as cardiac surgery and acute myocardial infarction, a restrictive regimen is safe (22, 23).

During the past decades, it has become clear that transfusion carries a substantial risk for morbidity and mortality. Examples are transfusion-related acute lung injury, transfusion-associated circulatory overload, allergic reactions, alloimmunization, transfusion-related infections, and immunomodulation (17, 24). This population on venovenous ECMO might be extremely vulnerable to develop transfusion-related complications due to the presence of several risk factors including longer mechanical ventilation duration, previous exposure to high peak pressures, and other ICU-related complications such as hypervolemia (25). Therefore, it might be extra important that unnecessary transfusion of blood in patients on venovenous ECMO is avoided. Beside the risk associated with transfusion exposure, blood products

are also expensive, adding costs to the growing national healthcare expenses. Last, blood products are becoming more and more scarce, so indications for transfusion should be informed by high-quality data where possible.

Another reason for the high frequency and amount of RBC transfused in patients on venovenous ECMO may be the high occurrence rate of hemorrhage, possibly associated with the use of anticoagulation. In our study, almost all bleeding patients required transfusion. More noteworthy, however, also in nonbleeding patients, still four out of five patients received RBC. Therefore, hemorrhage itself may be an insufficient explanation for the high incidence and amount of RBC transfused, and other indications for RBC transfusion should be identified. Potential explanations include circuit-related hemolysis or gradual, undocumented ooze from cannulation.

This study has several strengths. First, to our knowledge, this is the first multicenter and international retrospective study regarding transfusion of RBC in patients on ECMO. Second, a mixed method approach was used to combine observational data with center-specific protocols. Third, it gives a complete overview by not only reporting on RBC transfusion but also the daily hemoglobin and including the threshold applied. Some limitations should however be recognized. A major limitation is that the chronology between transfusion time and corresponding laboratory values cannot be ascertained; therefore, the direct effect of transfusion could not be evaluated. Furthermore, the indications for transfusion were not recorded. Last, despite being a large international multicenter study, the sample size is still relatively small due to the specific patient population. Therefore, no multivariate model for the relation between transfusion and outcome could be performed.

Determining the optimal transfusion thresholds in patients on ECMO is an important topic for future research. This was recently underlined by the members of the ESICM, concluding in their clinical practice guideline that no recommendation on transfusion thresholds for patients on ECMO could be made due to the lack of solid evidence (6). Generating randomized control trial data comparing liberal and restrictive transfusion thresholds of hemoglobin (for RBC transfusion) in both venovenous and venoarterial ECMO is a priority.

CONCLUSIONS

The occurrence rate of RBC transfusion in patients on venovenous ECMO is very high, even in the absence of bleeding. Although transfusion practice was usually liberal, this high variation in thresholds reflects the lack of evidence. No differences in survival, hemorrhagic and thrombotic complication rates were found between the different transfusion thresholds applied. Our data support the conduct of additional clinical RCTs to determine indications for and optimal transfusion thresholds in this patient population.

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Drs. Raasveld, Karami, Henriques, and Vlaar had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Raasveld, Karami, van den Bergh, and Vlaar were involved in concept and design. Drs. Raasveld, Karami, van den Bergh, de Bruin, and Vlaar were involved in statistical analysis. Drs. Henriques, van den Bergh, and Vlaar were involved in supervision. All authors were involved in acquisition, analysis, or interpretation of data; drafting of the article; and critical revision of the article for important intellectual content.

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This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board of the Amsterdam University Medical Centers (W19_222 Number 19.267), and, thereafter, from local Ethics Committees.

Due to the retrospective nature of the analysis, in accordance with article 9 paragraph 2 sub j General Data Protection Regulation (GDPR) jo. article 24 Dutch GDPR Implementation Act, and/or any additional data protection laws in its country, informed consent of Data subjects is not required. It has been determined that requesting explicit permission from patients for this data processing is impossible or requires a disproportionate effort. Patients were not actively contacted for follow-up on survival status, other than stated in the electronic patient record.

After publication, encrypted data can be requested by contacting the corresponding author. Reasonable data request will be taken in consideration.

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