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ORIGINAL RESEARCH

TRANSFUSION

Transfusion of red blood cells in venoarterial extracorporeal membrane oxygenation: A multicenter retrospective observational cohort study

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Abstract

Background: Evidence-based recommendations for transfusion in patients with venoarterial extracorporeal membrane oxygenation (VA ECMO) are scarce. The current literature is limited to single-center studies with small sample sizes, therefore complicating generalizability. This study aims to create an overview of red blood cell (RBC) transfusion in VA ECMO patients.

Methods: This international mixed-method study combined a survey with a retrospective observational study in 16 centers. The survey inventoried local transfusion guidelines. Additionally, retrospective data of all adult patients with a VA ECMO run >24 h (January 2018 until July 2019) was collected of patient, ECMO, outcome, and daily transfusion parameters. All patients that received VA ECMO for primary cardiac support were included, including

Abbreviations: AKI, acute kidney injury; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; ELSO, Extracorporeal Life Support Organization; GLMM, generalized linear mixed model; Hb, hemoglobin; ICU, intensive care unit; RBC, red blood cells; RRT, renal replacement therapy; TACO, transfusion associated circulatory overload; TRALI, transfusion related acute lung injury; UMC, University Medical Center; VA ECMO, venoarterial extracorporeal membrane oxygenation; VT/VF, ventricular tachycardia/ventricular fibrillation; VV ECMO, venovenous extracorporeal membrane oxygenation; ZI-NB, zero-inflated negative binomial.

For affiliations refer to page 10

surgical (i.e., post-cardiotomy) and non-surgical (i.e., myocardial infarction) indications. The primary outcome was the number of RBC transfusions per day and in total. Univariable logistic regressions and a generalized linear mixed model (GLMM) were performed to assess factors associated with RBC transfusion.

Results: Out of 419 patients, 374 (89%) received one or more RBC transfusions. During a median ECMO run of 5 days (1st–3rd quartile 3–8), patients received a median total of eight RBC units (1st–3rd quartile 3–17). A lower hemoglobin (Hb) prior to ECMO, longer ECMO-run duration, and hemorrhage were associated with RBC transfusion. After correcting for duration and hemorrhage using a GLMM, a different transfusion trend was found among the regimens. No unadjusted differences were found in overall survival between either transfusion status or the different regimens, which remained after adjustment for potential confounders.

Conclusion: RBC transfusion in patients on VA ECMO is very common. The sum of RBC transfusions increases rapidly after ECMO initiation, and is dependent on the Hb threshold applied. This study supports the rationale for prospective studies focusing on indications and thresholds for RBC transfusion.

KEYWORDS

blood management, RBC transfusion, transfusion practices (adult)

1 | BACKGROUND

Venoarterial extracorporeal membrane oxygenation (VA ECMO) is a lifesaving supporting therapy, indicated in potentially reversible cardiac and circulatory failure, refractory to other conventional therapies. Indications range from cardiogenic shock to the increasing implementation as extracorporeal cardiopulmonary resuscitation (ECPR) in refractory cardiac arrest.[1–3] Mortality in VA ECMO is still alarmingly high, varying from 71% in ECPR to 56% in cardiac indications.[4] The high mortality rate can partially be explained by the complexity of the underlying illness, but also by various complications that can occur during ECMO.

A common complication is anemia, resulting from a multifactorial etiology, such as underlying comorbidities, ECMO-induced hemolysis or hemorrhage, that is, due to cannulation (site) related oozing, and maintained by the use of anticoagulant therapy.[5] Although the Extracorporeal Life Support Organization (ELSO) has updated their guidelines in the past decade from an advised minimal hematocrit of 40% to a hemoglobin (Hb) level of 70–90 g/L, scientific ground for these statements is missing.[1,6] Multiple international surveys have shown that current Hb thresholds used in VA ECMO differ highly worldwide, often consisting of liberal thresholds for red blood cell (RBC) transfusion.[7–9] This might explain the large proportion of patients receiving RBC transfusion during VA ECMO, ranging from 82%–100% in previous studies.[10–12] Generalizability of these studies is, however, limited due to single-center designs and small sample sizes.

RBC transfusion can be lifesaving, however, different downsides also should be taken into account. This includes side effects such as transfusion-related immunomodulation, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), high costs, and increasing scarcity of donors.[13–16] Also, in comparable patient populations not supported with ECMO, restrictive thresholds for RBC transfusion were found to be safe, and resulted in shifting rationale in the intensive care unit (ICU).[17,18] Finally, two recent observational venovenous (VV) ECMO cohorts have shown promising results regarding the use of a more restrictive threshold.[19,20] Thus, generating insight into the current global RBC transfusion practices in patients receiving VA ECMO is important.

Therefore, the aim of this study was twofold: (1) to describe transfusion amounts in patients receiving VA ECMO, and (2) to identify factors associated with RBC transfusion. We hypothesize that RBC transfusion in VA ECMO is common, with hemorrhage and a liberal threshold as the most important factors contributing to transfusion.

2 | STUDY DESIGN AND METHODS

2.1 | Study population

This international study used a mixed methods design, combining a retrospective observational cohort and a survey. It was conducted in 16 ICUs worldwide: one Australian, three Belgian, one Croatian, one Italian, nine Dutch, and one Swedish. The study was approved by the Institutional Review Board of the Amsterdam University Medical Centers, location Academic Medical Center (Amsterdam UMC, AMC: W19_222#19.267), and, thereafter, by local ethical committees. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee, as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was registered at the Netherlands Trial Registry on February 2, 2020 (NL8413). Patients were enrolled if: (i) they were aged ≥18 years, (ii) were admitted to one of the participating ICUs, and (iii) received VA ECMO between January 1, 2018 and July 1, 2019. Patients were excluded if the total time on ECMO was less than 24 h or in case of triple cannulation modes. All patients that received VA-ECMO were included, including both surgical (i.e., post-cardiotomy) and non-surgical (i.e., myocardial infraction) indications for VA ECMO.

2.2 | Data collection

Baseline and ECMO characteristics were collected, including patient demographics, medical history, and ECMO mode and indication. Daily laboratory and transfusion parameters were collected over the first 28 days of ECMO or until ECMO was fully weaned, whatever came first. Complications during ECMO included hemorrhage, thromboembolic events (arterial, venous, or mechanical), acute kidney injury (AKI), and the use of renal replacement therapy (RRT). Successful weaning was defined as alive 48 h after decannulation of ECMO; 28-day mortality as survival status at 28 days after ECMO initiation. The definition for hemorrhage was in line with the definition as stated by the ELSO Registry, and consisted of "*a bleeding that led to either surgical exploration or intervention by an interventional radiologist, or the direct requirement of transfusion of >3 units of RBC or whole blood per day*".[21] All other definitions can be found in Additional File 1.

2.3 | Survey

Additionally, a survey was developed by SJR and evaluated by AV and MK (Additional File 2). This survey focused on providing insight into the local Hb threshold for RBC transfusion, laboratory units, and anticoagulation strategies for patients receiving VA ECMO. Based on the results of this survey, the transfusion thresholds for RBC transfusion were divided into three regimens: restrictive (Hb <7.5 g/dL), intermediate (Hb 7.5–9.0 g/dL), and liberal (Hb >9.0 g/dL).

2.4 | Outcomes

The main outcomes were the occurrence rate of RBC transfusion, number of RBC transfused daily and in total during ECMO. Secondary outcomes included the factors associated with RBC transfusion, Hb course, transfusion regimen, differences in transfusion count among the regimens, protocol adherence, influence of the regimen on transfusion count over time, and patient outcomes (complications and mortality). To evaluate protocol adherence, the difference between lowest (nadir) Hb level on transfusion day and predefined Hb threshold was calculated: "*delta Hb*." Thus, a negative delta Hb implicated that transfusion was given on days where nadir Hb was below the protocol's transfusion threshold (and thus adherence), whereas a positive delta Hb reflected that nadir Hb was higher than the transfusion threshold.

2.5 | Statistical analysis

All statistical analyses were performed with R version 4.0.3.[22] Continuous variables were assessed for normality using Q-Q-plots and reported as mean (± standard deviation [SD]) or median (1^{st}–3^{rd} quartile). Categorical data was presented as frequency (percentage). Missing data was evaluated by using the *naniar* and *visdat* packages for count, correlation, and missingness mechanism. Hereafter, all variables with >50% missing data were excluded (Additional File 3A).

Few factors have been identified in literature as being associated with RBC transfusion in VA ECMO. Therefore, variables of interest were predefined by the main study team, based on clinical expertise (Additional File 3B). To estimate their strength of association with overall transfusion status, complete-case univariable logistic regressions were performed. A multivariable regression was considered beyond the scope of this study.

Variables that were statistically significantly associated with odds of transfusion were used in an exploratory GLMM to estimate the course of daily transfusion count. For the GLMM, missing data was handled using a maximum likelihood estimation. First, distribution of RBC transfusion count was visually inspected and tested using

the Kolmogorov–Smirnov test. Since count data was expected to follow either a Poisson or negative-binominal distribution, two GLMM base models were constructed accordingly. Best model fit was selected based on Akaike Information Criterion (AIC) and residual diagnostics using the *DHARMa* package. Next, the selected base model was tested and corrected for zero-inflation (the number of zeros observed compared with the number of zeros expected). Regimen, duration, the interaction between regimen and duration, and hemorrhage were selected to be added to the best performing base-model. To avoid over-adjustment bias, variables that were expected to share a significant amount of variance were not included in this model: as such hemorrhage was preferred over cannulation site (central vs. peripheral) and type (surgical vs. percutaneous).

Finally, subgroup analyses were performed comparing the main and secondary outcomes between (1) different RBC transfusion regimens and (2) ECPR versus non-ECPR. To do so, either Mann–Whitney *U*, Kruskal–Wallis, or Chi-Square tests were used as appropriate. In case of comparing >2 groups, this was followed by a post-hoc Dunn test and Benjamin-Hoch *p*-value adjustment. All reported tests were two-sided; a $p < .05$ was considered statistically significant. Next to the described adjustments, no further adjustments have been made to reduce the potential for type I error due to multiplicity. Therefore, all findings with regard to secondary outcomes should be considered exploratory and hypothesis-generating.

3 | RESULTS

Between January 1, 2018 and July 1, 2019, 433 patients were entered into the database, of which 14 were excluded for further analysis: 11 patients received triple cannulation modes, and three patients had a run of less than 24 h (Additional File 4). This resulted in 419 VA ECMO patients, of which 107 were ECPR (26%). The majority had a peripheral cannulation site ($N = 356$, 85%), of whom 48% ($N = 165/346$) were cannulated using a surgical method, which was the method of choice in all centrally cannulated patients ($N = 60$). Median ECMO duration was 5 days (1^{st}–3^{rd} quartile 3–8 days), whereafter 38 patients required a second run (9%). Further patient demographics are described in Table 1.

3.1 | RBC transfusion

As shown in Table 2, almost nine out of 10 patients received one or more RBC transfusions during VA ECMO ($N = 374$, 89%). On days when an RBC transfusion was administered, patients received a median of 2.5 units (1^{st}–3^{rd} quartile 1.75–4 units). Transfusion was administered on a median of 3 out of 5 days of their ECMO run (1^{st}–3^{rd} quartile 1–5 days transfused out of 3–8 days ECMO-run duration). This summed up to a median total number of eight RBC units administered (1^{st}–3^{rd} quartile 3–17 units).

Univariable logistic regression showed that a lower Hb prior to ECMO initiation, longer ECMO duration, and hemorrhage were associated with receiving one or more RBC transfusions during ECMO (Table 3). Also, compared to myocardial infarction, the odds of being transfused were lower if the indication for VA ECMO was either intoxication or persistent VT/VF. The most evident contributing factor to receive an RBC transfusion was hemorrhage, in which the odds for RBC transfusion were 9.40 times higher (95% confidence interval [95%CI] 3.97–27.70) in bleeding vs. non-bleeding patients. All other nonsignificant variables can be found in Additional File 3C.

3.2 | Hemoglobin course

Median daily Hb during ECMO was 8.7 g/dL (1^{st}–3^{rd} quartile 7.8–9.6 g/dL); daily Hb was significantly lower on days with RBC transfusion compared to days without (8.2 g/dL [1^{st}–3^{rd} quartile 7.5–9.2 g/dL] vs. 9.2 g/dL [1^{st}–3^{rd} quartile 8.4–10.2] g/dL, estimated median difference 0.97 g/dL [95%CI 0.81–1.1], $p < 0.001$). Independent of receiving an RBC transfusion, nadir Hb was the lowest in patients with a restrictive regimen, followed by intermediate, and the highest in patients with a liberal regimen (Table 2, all $p < .001$). Patients with a restrictive regimen mostly received an RBC transfusion when their nadir Hb was −0.1 g/dL lower than the protocol's threshold (1^{st}–3^{rd} quartile −0.7 to +0.4 g/dL). Contrarily, in patients with a liberal regimen, nadir Hb was 0.6 g/dL higher than the protocol's threshold (1^{st}–3^{rd} quartile −0.3 to +1.3 g/dL).

3.3 | Transfusion regimens

Based on the transfusion thresholds stated, 117 patients had a restrictive (four centers), 152 patients a liberal (six centers), and 150 patients an intermediate regimen (six centers, Table 2). The questionnaire's results and a per-center overview of the main and secondary outcomes can be found in Additional File 6A-B. In an unadjusted analysis, no differences were found in total RBC amount, days of transfusion, units per day on ECMO, and per transfusion day among the regimens. Comparing baseline

TABLE 1 Patient demographics.

Variable	VA ECMO ($N = 419$)	Non-transfused ($N = 45$)	Transfused ($N = 374$)	*p-value*
Age, years	57 [47–66]	56 [43–66]	57 [47–66]	.54
BMI, kg/m^2	27.0 [24.3–30.6]	26.3 [24.2–30.5]	27.1 [24.3–30.6]	.54
Female sex	154 (37%)	7 (16%)	147 (39%)	<.01
Medical history				
Asthma/COPD	39 (9%)	5 (11%)	34 (9%)	1.00
Chronic kidney disease	25 (6%)	0 (0%)	25 (7%)	.15
Diabetes	68 (16%)	6 (13%)	62 (17%)	1.00
Hypertension	139 (33%)	12 (27%)	127 (34%)	.82
Myocardial infarction	76 (18%)	6 (13%)	70 (19%)	.77
Pulmonary hypertension	25 (6%)	3 (7%)	22 (6%)	1.00
Values before ECMO				
SOFA-score	11 [8–13]	11 [9–13]	11 [8–13]	.54
Hemoglobin, g/dL	11.6 [9.5–13.5]	13.9 [12.3–16]	11.1 [9.4–13.4]	<.001
Platelet count, 10^9/L	179 [119–253]	218 [159–289]	176 [116–252]	.08
Lactate, mmol/L	5.2 [2.4–10]	3.6 [2.1–10.5]	5.5 [2.4–9.9]	.44
Creatinine, μmol/L	114 [83–157]	112 [83–129]	114 [83–160]	.31
ECMO characteristics				
Duration, days	5 [3–8]	3 [2–5]	5 [3–9]	<.001
Second run indicated	38 (9%)	1 (2%)	37 (10%)	.16
Peripheral cannulation site	356 (86%)	42 (93%)	314 (85%)	.18
Distal femoral cannula	288 (71%)	33 (73%)	255 (70%)	.45
Surgical insertion cannula	227 (56%)	21 (49%)	206 (56%)	.44
ECPR	107 (26%)	14 (31%)	93 (25%)	.60
Indication				.001
Myocardial infarction	117 (28%)	10 (22%)	107 (29%)	.47
Post-cardiotomy	113 (27%)	5 (11%)	108 (29%)	.02
Persistent VT/VF	41 (10%)	10 (22%)	31 (9%)	<.01
Pulmonary embolism	21 (5%)	1 (2%)	20 (5%)	.59
Septic cardiomyopathy	20 (5%)	0 (0%)	20 (5%)	.22
Lung-transplantation[a]	19 (5%)	2 (4%)	17 (5%)	1.00
Myocarditis	15 (4%)	1 (2%)	14 (4%)	.93
Other[b]	73 (18%)	16 (35%)	58 (15%)	.15

Note: Shown as median [1st–3rd quartile] for non-parametric numerical variables and no. (%) for frequency data. All comorbidities in the medical history were listed before the current hospital admission in which the patient was supported with VA ECMO.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; SOFA, sequential organ failure assessment; VT/VF, ventricular tachycardia/ventricular fibrillation.

[a]Lung transplantation combines if indicated for bridge to LTx or post-LTx.

[b]Other includes accidental hypothermia with arrest, per-partum cardiomyopathy, postoperative graft dysfunction, intoxication, other.

characteristics among the regimens showed significant differences in body mass index, incidence of hypertension, SOFA-score, and cannulation site (Additional File 7). No association was found between these covariates and RBC transfusion, except for cannulation site. Notably, a potentially effect modifying difference in the proportion of hemorrhagic complications was present among the regimens, whereas hemorrhage ranged from 43% in the liberal to 56% in the restrictive group ($p = .08$, Table 2). Corrected for this proportional difference in hemorrhagic complications among the regimens, the estimated total RBC ranged from 11.5 units (95%CI 9.5–14) for a restrictive, 11.2 (95% CI 9.4–13.3) for intermediate, and 12.7 (95%CI 10.7–15) for a liberal regimen ($p = .056$).

TABLE 2 Unadjusted transfusion parameters and patient outcomes stratified by regimen.

Variable	Total ($n = 419$)	Liberal threshold ($n = 152$)	Intermediate threshold ($n = 150$)	Restrictive threshold ($n = 117$)	Adjusted p-value
RBC occurrence rate, no. (%)	374 (89%)	139 (91%)	132 (88%)	103 (88%)	.55
Days of transfusion	3 (1–5)	3 (2–5)	3 (1–5)	3 (1–5)	.20
RBC, total	8 (3–17)	8 (4–17)	9 (2–18)	8 (3–17)	.76
RBC, per day on ECMO	1.6 (0.7–3)	1.7 (0.8–2.8)	1.5 (0.7–3.0)	1.5 (0.5–3.0)	.71
RBC, per transfusion day	2.5 (1.75–4)	2.4 (1.7–3.5)	2.5 (1.9–3.7)	2.9 (1.7–4.9)	.39
Hb, daily	8.7 (7.8–9.6)	9.4 (8.4–10.2)	8.7 (7.9–9.5)	7.7 (7.1–8.6)	res-int***, res-lib***, int-lib***
Hb on transfusion day†	8.2 (7.5–9.2)	9.1 (8.2–9.9)	8.2 (7.7–8.9)	7.3 (6.8–7.8)	res-int***, res-lib***, int-lib***
Hb on non-transfusion day†	9.2 (8.4–10.2)	9.7 (8.9–10.8)	9.2 (8.6–10)	8.4 (7.7–9.5)	res-int***, res-lib***, int-lib***
Difference in Hb before and after ECMO initiation	1.9 (0.5–4.2)	1.6 (0.0–3.5)	2.3 (0.8–4.7)	2.0 (0.6–4.3)	int-lib*
Delta Hb	0.1–0.7 to +0.7	0.6–0.3 to +1.3	−0.2 –0.9 to +0.3	−0.1 –0.7 to +0.4	res-lib***, int-lib***
Outcome Variables					
Acute kidney injury	242 (58%)	87 (58%)	74 (49%)	81 (69%)	int-res**
Renal replacement therapy	154 (37%)	66 (43%)	39 (26%)	49 (42%)	int-res*, int-lib**
Hemorrhage	207 (49%)	65 (43%)	76 (51%)	66 (56%)	.08
Thrombotic event					
Arterial	63 (15%)	21 (14%)	14 (9%)	28 (24%)	int-res**, res-lib*
Venous	23 (5%)	13 (9%)	2 (1%)	8 (7%)	int-lib*
Mechanic	44 (11%)	20 (13%)	11 (7%)	13 (11%)	.25
Successful weaning	257 (61%)	90 (59%)	93 (62%)	74 (63%)	.78
28-day mortality	188 (45%)	63 (41%)	73 (49%)	52 (44%)	.45
Overall survival	210 (50%)	80 (53%)	74 (49%)	56 (48%)	.72
Referred to another center while still on ECMO	24 (6%)	19 (13%)	2 (1%)	3 (3%)	int-lib**, res-lib***

Note: Shown as median [1st–3rd quartile] for non-parametric numerical variables and no. (%) for frequency data.

Abbreviations: ECMO, extracorporeal membrane oxygenation; Hb, hemoglobin; int, intermediate (Hb 7.5–9 g/dL); lib, liberal (Hb >9 g/dL); res, restrictive (Hb <7.5 g/dL); RBC, red blood cells. RBC, units; hemoglobin, g/dL.

*$p < .05$; **$p < .01$; ***$p < .001$.†Significant difference ($p < .001$) in all groups (total, restrictive, liberal, intermediate) between Hb on transfusion-day and Hb on non-transfusion day.

TABLE 3 Factors associated with red blood cells transfusion, univariable regression.

Dependent variable	OR	Lower limit	Upper limit	Significance
Hb prior (g/dL)	1.32	1.15	1.54	<.001
Duration (days)	1.17	1.06	1.33	.01
Indication (ref: Myocardial infarction)	(ref)	(ref)	(ref)	(ref)
Intoxication	0.19	0.05	0.80	.05
Persistent VT/VF	0.29	0.11	0.77	.05
Hemorrhage (ref: no)	9.40	3.97	27.70	<.001

Note: Outcome variable defined as whether the patient received one or more RBC transfusions during their support with ECMO, resulting in $N = 374$ who did versus $N = 45$ who did not receive RBC transfusion. Reference = not transfused. Stated in odds ratios with 95% confidence interval. Hb prior = numerical, with 1 g/dL decrease resulting in corresponding OR (CI). All nonsignificant variables can be found in Additional File 3C.

To investigate the differences in daily transfusion count, a GLMM was built. Distribution tests showed a negative binomial (NB) distribution, and model fit improved after correcting for zero-inflation (ZI). Best-model-fit was found using a ZI-NB GLMM with random intercepts for patients and accounting for hemorrhage, duration, regimen applied, and interaction between time and regimen. Independent of regimen and hemorrhage, the total count of RBC transfusions decreased over time with a ratio of 0.97 (95%CI 0.94–0.99). Figure 1 shows the transfusion count over time, stratified by regimen, and whether the patient suffered a hemorrhagic complication. The predicted RBC count at day 0 is comparable among patients regardless of their regimen. However, patients with a restrictive regimen had a statistically significant difference in slope when compared to intermediate and liberal regimen ($p < .001$). This resulted in a significantly lower estimated RBC count for restrictive patients respectively at day 10 for hemorrhagic, and at day 12 in non-hemorrhagic patients (Table 4).

3.4 | Patient outcomes

In total, 349 patients (83%) suffered from one or more complications, mostly AKI ($N = 242$, 58%), hemorrhage ($N = 207$, 49%), or RRT ($N = 154$, 37%). RRT was more common in patients who had received an RBC transfusion (both $p < .001$; Additional File 8). A total of 257 patients (61%) were successfully weaned, after which 47 patients died, resulting in an overall survival of 210 patients (50%). No unadjusted differences were found in successful weaning and overall survival between either transfusion status or the different regimens, which remained after adjustment for potential confounders. While being transfused was not associated with mortality, hemorrhage did result in an increased odds of mortality (OR 1.17 [95%CI 1.07–1.29]).

3.5 | Extracorporeal cardiopulmonary resuscitation

A total of 107 patients received ECMO as part of ECPR. Compared to the non-ECPR population, this subgroup had a shorter ECMO duration (4 days [1st–3rd quartile 2–6 days] vs. 5 [1st-3rd quartile 3–9 days], $p < .001$; Additional File 9A). Similar transfusion rates and amounts were found, whereas Hb was higher during ECMO independent of whether a transfusion was administered (Additional File 9B).

4 | DISCUSSION

This study aimed to create an overview of RBC transfusion practices in patients receiving VA ECMO. We report the following relevant findings. First, a large majority of the patients received RBC transfusions during VA ECMO, adding up to a high total amount during their ECMO run. Second, different Hb thresholds are applied among the centers, and despite worse protocol adherence in patients with a liberal regimen, no unadjusted differences were found in the frequency and amounts of RBC transfused. Third, hemorrhage is the most important independent factor in receiving RBC during VA ECMO. Fourth, the amount of daily administered RBC is the highest in the first days of ECMO, and decreases over time. After correcting for a difference in the occurrence of hemorrhage among the transfusion regimens, a difference is found in the predicted RBC count per day, wherein a restrictive regimen shows a faster decrease in RBC administered.

In the general critically ill population in the ICU, the occurrence rate of RBC transfusion has been described as around 26%.[23] This occurrence rate is strikingly lower than the almost 90% in our study population receiving VA ECMO. Although previous studies describe a higher total sum of RBC transfused during ECMO, the amount

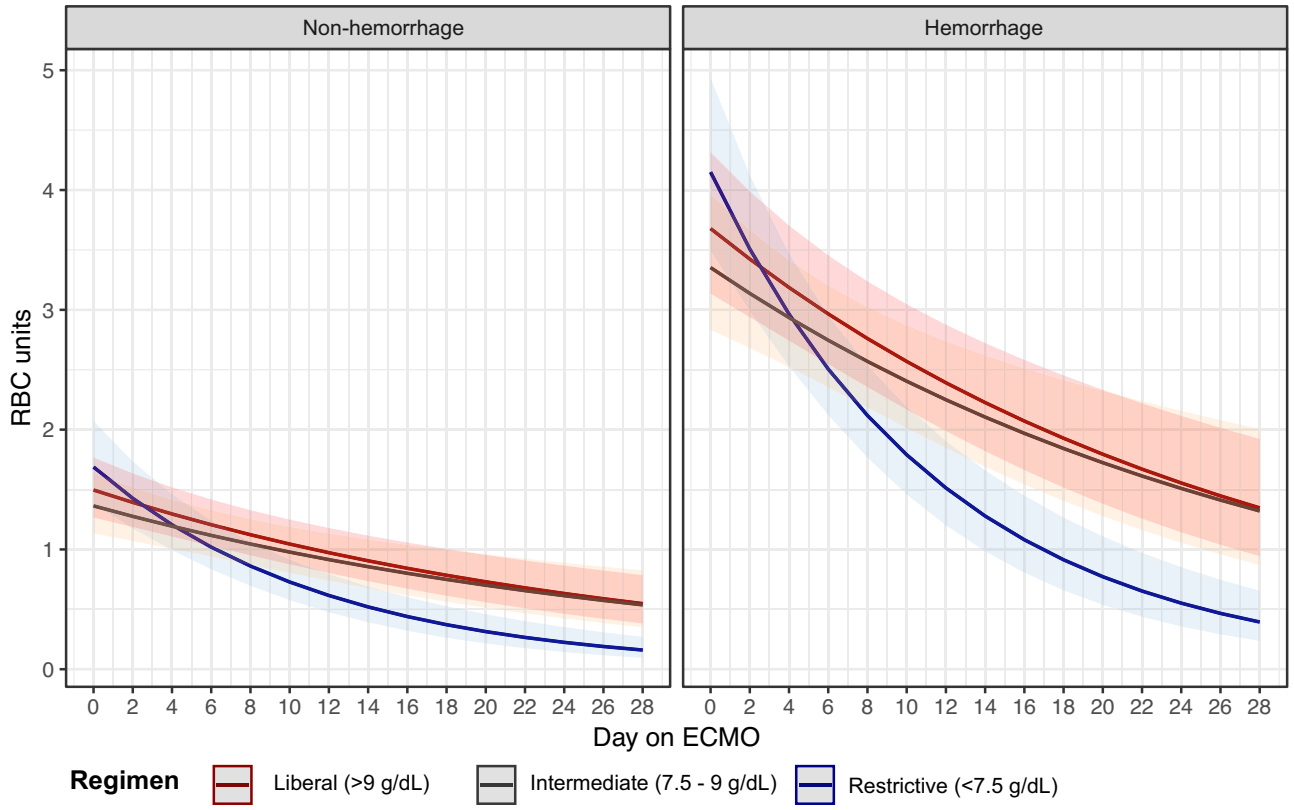

FIGURE 1 Predicted amount of red blood cells transfused, stratified by hemorrhage. RBC, red blood cell; hemorrhage defined according to ELSO Registry definitions. Subgroups defined as liberal (Hb >9 g/dL, $N = 152$), intermediate (Hb 7.5–9.0 g/dL, $N = 150$), and restrictive (Hb >7 g/dL, $N = 117$) Hb trigger for RBC transfusion. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Predicted red blood cells amount, resulting from zero-inflated negative binomial generalized linear mixed model.

	Liberal (>9 g/dL)		Intermediate (7.5–9 g/dL)		Restrictive (<7.5 g/dL)	
	Estimated count	**(95% CI)**	**Estimated count**	**(95% CI)**	**Estimated count**	**(95% CI)**
Non-hemorrhage						
Day 0	1.50	(1.27–1.77)	1.36	(1.13–1.64)	1.69	(1.38–2.07)
Day 7	1.16	(0.99–1.37)	1.08	(0.90–1.29)	0.94	(0.76–1.15)
Day 10	1.05	(0.87–1.25)	0.98	(0.80–1.19)	0.73	(0.58–0.92)
Day 12	0.97	(0.80–1.18)	0.91	(0.74–1.13)	0.62	(0.48–0.79)
Day 14	0.91	(0.73–1.12)	0.86	(0.68–1.08)	0.52	(0.39–0.69)
Day 21	0.70	(0.53–0.93)	0.68	(0.49–0.94)	0.29	(0.19–0.43)
Day 28	0.55	(0.38–0.79)	0.54	(0.35–0.83)	0.16	(0.10–0.27)
Hemorrhage						
Day 0	3.68	(3.14–4.32)	3.35	(2.83–3.97)	4.15	(3.49–4.94)
Day 7	2.86	(2.45–3.34)	2.66	(2.27–3.11)	2.30	(1.94–2.74)
Day 10	2.57	(2.17–3.05)	2.40	(2.01–2.87)	1.79	(1.46–2.16)
Day 12	2.39	(1.99–2.88)	2.25	(1.85–2.74)	1.51	(1.20–1.91)
Day 14	2.23	(1.82–2.72)	2.10	(1.69–2.62)	1.28	(0.99–1.66)
Day 21	1.73	(1.32–2.28)	1.67	(1.22–2.28)	0.71	(0.49–1.04)
Day 28	1.35	(0.94–1.92)	1.32	(0.87–2.01)	0.39	(0.24–0.66)

Note: Predicted RBC amount (estimated daily count) after correction for hemorrhage, duration, transfusion regimen, and interaction term between duration and transfusion regimen.

Abbreviations: CI, confidence interval; GLMM, generalized linear mixed model; RBC, red blood cell; ZINB, zero-inflated negative binomial.

remains remarkably high.[24,25] This high sum of RBC in patients receiving VA ECMO versus the general ICU population can be explained by different factors, including the high variance in Hb threshold applied, the higher incidence of AKI and hemorrhage (among others due to the use of systemic anticoagulation), and possibly the "wish to act" in this severely ill patient population.

A hypothesis to transfuse liberally in VA ECMO holds that in those patients receiving VA ECMO, tissue hypoxemia can develop as a result of reduced cardiac output due to cardiac failure. By providing a larger Hb buffer, the resulting decreased oxygen delivery (DO_2) can possibly be compensated. However, this does not take into account that VA ECMO blood flow leads to a fixed cardiac output, and thus maintenance of the DO_2. Evidence to either confirm or refute this hypothesis is lacking. Although an RBC transfusion can be lifesaving, it is also a possible risk-bearing intervention with substantial risk for transfusion-related sequelae, and therefore unnecessary transfusions should be avoided, especially in this critically ill population. In similar patient populations not on ECMO, several studies have shown that maintaining a restrictive transfusion threshold is non-inferior, including in septic shock, cardiac surgery, and even acute myocardial infarction.[17,18,26] Recent observational studies performed in VV ECMO confirmed the safe use of a restrictive regimen; however, randomized trials have yet to confirm this result.[19,20] In our study, no differences were found among the regimens with regard to mortality. However, the unadjusted rate of multiple complications, such as AKI, was the lowest in the intermediate regimen. Although this can be the result of a center-specific effect, this warrants future attention.

Surprisingly, in unadjusted analyses, no differences were found in the daily and total amount of transfusions among the regimens. This contrasts our previous findings in patients receiving VV ECMO, in which patients with a liberal threshold received transfusion at a higher amount and rate.[20] However, when comparing VA ECMO with VV ECMO patients, multiple differences exist. First, in VA ECMO, cannulation is more often performed surgically, as an important indication is post-cardiotomy. Second, the total duration of support is shorter in VA ECMO. As such, the differences in transfusion behavior may be a result of different indications to transfuse (i.e., non-ECMO related post-surgical hemorrhage in VA ECMO compared to "improving weaning" in a later stage on VV ECMO). Both hemorrhage and ECMO duration matter when assessing the transfusion behavior among the regimen. For example, our results show that in bleeding patients with a restrictive regimen, the predicted number of RBC units transfused is higher in the first days. However, this is followed by a rapid decrease in the predicted daily number of RBC units. This emphasizes the importance of hemorrhage as one of the main complications during ECMO.

The hemorrhage rate we found is relatively high when compared to previous studies resulting from the ELSO registry.[27] This can possibly be explained by a difference in patient selection. For example, a relatively large part of our study group was cannulated surgically, which is known to be associated with a higher risk of hemorrhage. Not only is hemorrhage strongly associated with receiving RBC transfusions, we also confirm its association with mortality. Therefore, identifying the causes and preventing hemorrhage should be the main focus. Different factors have been identified to contribute to hemorrhaging, ranging from severity of disease, development of ECMO-associated coagulopathy, and anticoagulation targets applied.[28–30] Further evaluating the optimal anticoagulation monitoring, type, and targets is thus essential to decrease this risk of hemorrhage.

To our knowledge, our study is one of the largest multicenter studies performed on this topic in an international collaboration. It creates a complete overview by reporting both RBC transfusions, Hb course, and thresholds applied, thereby adding important information on the topic of transfusion behavior in VA ECMO. However, some limitations have to be acknowledged. First, a retrospective study design brings along different limitations, including unmeasured confounding and the fact that conclusions regarding causality cannot be drawn. Second, neither the exact time of transfusion and corresponding laboratory values, nor indications for transfusion or alternative reasons or physiological triggers than Hb were collected. Third, we were limited to the information available in electronic patient records, therefore not being able to record both severity of hemorrhages as well as transfusion-related complications such as TRALI and TACO.

5 | CONCLUSIONS

Transfusion of RBC in patients receiving VA ECMO is very common, as well in frequency, daily and total number of RBC transfused. Hemorrhage plays an important role in the probability of being transfused. Transfusion behavior among different regimens differs, but does not influence patient outcomes. Future studies should focus on indications and thresholds for RBC transfusion in a prospective manner.

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CONFLICT OF INTEREST STATEMENT

LMB is a member of the Medical Advisory Boards of Eurosets Srl., Medolla, Italy, and Xenios AG, Heilbronn, Germany. In addition, LMB is a Medical Advisory Board Member of HemoCue AB, Ängelholm, Sweden. FST is a member of the Medical Advisory Boards of Eurosets Srl., Medolla, Italy, and Xenios AG, Heilbronn, Germany. RL is consultant to Medtronic, Getinge and LivaNova, and member of the Medical Advisory Board of Eurosets, Hemocue, and Xenios. DdRM has received personal fees from Getinge. DWD is involved in institutional research consultancy to Getinge - Maquet Critical Care AB, Solna, Sweden; institutional research cooperation with Sonion BV, Hoofddorp, the Netherlands; and consultancy to HBOX Therapies GmbH, Aachen, Germany; all fees and financial compensation paid to the University of Twente, no personal fees received. All other authors have not reported any disclosures or conflict of interest.

DATA AVAILABILITY STATEMENT

After publication, encrypted data can be requested by contacting the corresponding author. Reasonable data request will be taken into consideration. Additional, related documents can be requested separately.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of the Amsterdam University Medical Centers (Amsterdam UMC: W19_222#19.267), and, thereafter, by local Ethics Committees. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee, as well as with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

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, location Academic Medical Center (Amsterdam UMC, AMC; W20_199#20.230), and, if applicable by national law, thereafter, by local Ethics Committees.

CONSENT TO PARTICIPATE

Due to the retrospective nature of the analysis, in accordance with article 9 paragraph 2 sub j 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.

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REFERENCES

1. ELSO. General Guidelines for all ECLS Cases. ELSO Guidel [Internet]. (August):1–26. 2017 https://www.elso.org/Resources/Guidelines.aspx
2. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single Centre, open-label, randomised controlled trial. Lancet. 2020;396(10265):1807–16.
3. Belohlavek J, Smalcova J, Rob D, Franek O, Smid O, Pokorna M, et al. Effect of intra-arrest transport, extracorporeal cardiopulmonary resuscitation, and immediate invasive assessment and treatment on functional neurologic outcome in refractory out-of-hospital cardiac Arrest. J Am Med Assoc. 2022;327(8):737–47.
4. ELSO. ECLS Registry Report Centers by year. 2020;2020(c):1–37. 2020.
5. Murphy DA, Hockings LE, Andrews RK, Aubron C, Gardiner EE, Pellegrino VA, et al. Extracorporeal membrane oxygenation-hemostatic complications. Transfus Med Rev. 2015;29(2):90–101. https://doi.org/10.1016/j.tmrv.2014.12.001
6. McMichael ABV, Ryerson LM, Ratano D, Fan E, Faraoni D, Annich GM. 2021 ELSO adult and pediatric anticoagulation guidelines. ASAIO J. 2022;68(3):303–10.
7. Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, 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. De Bruin S, Scheeren TWL, Bakker J, Van Bruggen R, Vlaar APJ, Antonelli M, et al. Transfusion practice in the non-bleeding critically ill: an international online survey-the TRACE survey. Crit Care. 2019;23(1):1–8.
9. Esper SA, Welsby IJ, Subramaniam K, John Wallisch W, Levy JH, Waters JH, et al. Adult extracorporeal membrane oxygenation: an international survey of transfusion and anticoagulation techniques. Vox Sang. 2017;112(5):443–52.
10. Guimbretiere G, Anselmi A, Roisne A, Lelong B, Corbineau H, Langanay T, et al. Prognostic impact of blood transfusion in VA and VV ECMO. Perfusion. 2018;34:1–8.
11. Buscher H, Vukomanovic A, Benzimra M, Okada K, Nair P. Blood and anticoagulation Management in Extracorporeal Membrane Oxygenation for surgical and nonsurgical patients: a single-center retrospective review. J Cardiothorac Vasc Anesth. 2017;31(3):869–75.
12. Abbasciano RG, Yusuff H, Vlaar A, 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. 2020;35:1202. https://doi.org/10.1053/j.jvca.2020.08.068
13. Bosboom JJ, Klanderman RB, Migdady Y, Bolhuis B, Veelo DP, Geerts BF, et al. Transfusion-associated circulatory overload: a clinical perspective. Transfus Med Rev. 2019;33(2):69–77.
14. Semple JW, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. Blood. 2019;133(17):1840–53.
15. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet. 2013 [cited 2019 Sep 12];382(9896):984–94. https://www.sciencedirect.com/science/article/pii/S0140673612621977?via%3Dihub
16. Remy KE, Hall MW, Cholette J, Juffermans NP, Nicol K, Doctor A, et al. Mechanisms of red blood cell transfusion-related immunomodulation. Transfusion. 2018;58:804–15.
17. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, 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. J Am Med Assoc. 2021;325(6):552–60.
18. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or Liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377(22):2133–44.
19. Martucci G, Schmidt M, Agerstrand C, Tabatabai A, Tuzzolino F, Giani M, et al. Transfusion practice in patients receiving VV ECMO (PROTECMO): a prospective, multicentre, observational study. Lancet Respir Med. 2022;2600(22):1–11.
20. Raasveld SJ, Karami M, van den Bergh WM, Lansink-Hartgring AO, van der Velde F, Maas JJ, et al. RBC transfusion in Venovenous extracorporeal membrane oxygenation: a multicenter cohort study. Crit Care Med. 2022;50(2):224–34.
21. Extracorporeal Life Support Organization (ELSO) ELSO Registry Data Definitions. 1–12. 2018.
22. Team RC. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2022.
23. Vincent JL, Jaschinski U, Wittebole X, Lefrant JY, Jakob SM, Almekhlafi GA, et al. Worldwide audit of blood transfusion practice in critically ill patients. Crit Care. 2018;22(1):1–9.
24. Aubron C, Cheng AC, Pilcher D, Leong T, Magrin G, Cooper DJ, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: a 5-year cohort study. Crit Care. 2013;17(2):R73.

25. Mazzeffi M, Greenwood J, Tanaka K, Menaker J, Rector R, Herr D, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECLS Working Group on thrombosis and hemostasis. In: Annals of Thoracic Surgery. Elsevier USA, p. 682–689. 2016.
26. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371(15):1381–91.
27. Willers A, Swol J, Buscher H, McQuilten Z, van Kuijk SMJ, Ten Cate H, et al. Longitudinal trends in bleeding complications on extracorporeal life support over the past two decades-extracorporeal life support organization registry analysis. Crit Care Med. 2022;50(6):e569–80.
28. Aubron C, DePuydt J, Belon F, Bailey M, Schmidt M, Sheldrake J, et al. Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation. Ann Intensive Care. 2016;6(1):97.
29. Granja T, Hohenstein K, Schüssel P, Fischer C, Prüfer T, Schibilsky D, et al. Multi-modal characterization of the coagulopathy associated with extracorporeal membrane oxygenation. Crit Care Med. 2020;48(5):E400–8.
30. Oude Lansink-Hartgring A, de Vries AJ, Droogh JM, van den Bergh WM. Hemorrhagic complications during extracorporeal membrane oxygenation—the role of anticoagulation and platelets. J Crit Care. 2019;54:239–43. https://doi.org/10.1016/j.jcrc.2019.09.013

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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