Review Article



# An oxygen balancing act: a narrative review of red blood cell transfusion in extracorporeal membrane oxygenation

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**Objective:** To review current literature regarding red blood cell (RBC) transfusion thresholds in extracorporeal membrane oxygenation (ECMO).

**Background:** The use of veno-venous and veno-arterial (VA) ECMO as a bridge to cardiopulmonary recovery or organ transplantation has increased in the last decade. Bleeding complications are seen in 30–60% of patients receiving extracorporeal support. Transfusion of blood products while on ECMO occurs frequently for maintenance of the normal hemostatic balance in the setting of bleeding and coagulopathy. RBC transfusion may be indicated in patients for circuit priming, optimizing oxygen carrying capacity, and/or counteracting the effects of bleeding in the setting of anticoagulation and hemolysis due to the circuit. The current Extracorporeal Life Support Organization (ELSO) recommendation is to maintain a hematocrit of >40%. Many centers opt not to utilize a predefined trigger for transfusion and instead, tailor the thresholds based on a patient's clinical status. This is largely due to conflicting retrospective studies within the ECMO population, and the fact that recommendations are extrapolated from studies in the critical care literature, as there are no randomized controlled clinical trials for RBC transfusion thresholds in ECMO. In addition, the potential adverse effects of blood transfusions such as acute kidney injury (AKI), electrolyte imbalances, hypervolemia, and transfusion related lung injury, may outweigh the benefits.

**Methods:** This review evaluated case/brief reports, observation studies, cohort studies, prospective trials, retrospective trials, clinical notes, expert panel reports, review articles, guidelines from international societies, and multiple original articles and references in order to determine if a standard transfusion threshold may be recommended.

**Conclusions:** While ECMO utilization continues to expand worldwide, to date, no prospective studies have investigated the hemoglobin threshold in this population. Therefore, future large multicenter trials are essential to determine optimal monitoring, transfusion goal strategies, and guide future management.

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**Keywords:** Red blood cell transfusion (RBC transfusion); extracorporeal membrane oxygenation (ECMO); hemoglobin level; bleeding; anticoagulation

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## Introduction

Extracorporeal Membrane Oxygenation (ECMO) was originally developed as a closed-circuit adaptation of cardiopulmonary bypass, which involves draining blood from the venous circulation, pumping it through an oxygenator, and returning it to either the venous or arterial circulation (1). When returning blood to the arterial circulation, the configuration is known as veno-arterial (VA) ECMO, and is used primarily for hemodynamic support in the setting of decompensated cardiac failure (1,2). When returning blood to the venous circulation, the configuration is known as veno-venous (VV) ECMO, and is primarily used for respiratory support in the setting of respiratory failure or as a bridge to lung transplantation (1-3). The goal of ECMO support is to allow the rest and recovery of the injured heart and/or lungs, while minimizing harm to other end organ systems by providing adequate oxygenation and perfusion. As a result, ECMO has been utilized as a bridge to improved cardiopulmonary recovery, or to transplantation when recovery is not possible (3).

Since the influenza A H1N1 virus outbreak of 2009, adult ECMO usage has increased substantially (4). The current coronavirus disease-2019 (COVID-19) pandemic has required modified guidelines for ECMO use in adult patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (5). This population introduced an additional level of complexity in patient management due to a higher incidence of coagulopathy and thrombosis associated with COVID-19 infection as compared to non-COVID-19 ECMO patients and the concurrent increased bleeding risk secondary to anticoagulant use to maintain pump integrity (6,7). Reported mortality rates for ECMO remain high, at 30–40% for patients on VV ECMO, and 60–70% for patients on VA ECMO (6). Bleeding complications remain significant, and are seen in 30–60% of patients, with those on VA ECMO being at higher risk than patients on VV ECMO (6). While this difference may in part be attributed to high proportions of post-cardiotomy patients requiring VA ECMO, both patient groups frequently require blood transfusions (3).

Transfusion of blood products such as red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate, and platelets while on ECMO occurs for a variety of reasons. This includes circuit priming, blood loss during cannulation, restoration of oxygen carrying capacity in the setting of chronic anemia, maintenance of the normal hemostatic balance through the correction of coagulopathy, and treatment of hemorrhagic complications (2,3).

When blood comes into contact with the artificial surfaces of the ECMO circuit, the hemostatic balance becomes skewed towards hypercoagulability, necessitating anticoagulant therapy to restore this balance (3). Specifically, factor VIII and von Willebrand factor (VWF) are released from endothelial cells, which creates a prothrombotic state (3,7). Furthermore, free hemoglobin derived from hemolyzed RBC enhances the baseline prothrombotic state that exists in many patients (8).

Most of our knowledge regarding transfusion strategies in ECMO is extrapolated from studies in critically ill patients. One aspect that remains controversial is the threshold for RBC transfusion and the hematocrit goal that needs to be maintained during extracorporeal support. Previous ECMO guidelines have recommended maintenance of a normal hemoglobin level (12–14 g/dL), while current guidelines suggest a goal hematocrit of 40% (3,9). There is moderate variation within the literature regarding the use of hemoglobin or hematocrit as a marker for transfusion requirement. Hemoglobin levels have been used as a surrogate marker for oxygen delivery and as a trigger point for RBC transfusions (1). Studying appropriate markers and triggers for RBC transfusion poses multiple challenges; and thus far there have been no prospective studies evaluating a hemoglobin threshold for RBC transfusion in ECMO patients (3). Lack of randomized controlled trials, lack of large epidemiologic studies, small cohort sizes, multiple confounding variables, and the severity of patient illness limits the types of studies that can be performed and the conclusions that can be

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drawn from the available literature (3,6,10-12).

The aim of this review is to discuss the indications and threshold for RBC transfusions, review the current available literature regarding RBC transfusion in the setting of VV and VA ECMO, and provide some practical management recommendations based on our own institution's extensive ECMO experience.

This literature search process was conducted through PubMed (https://www.ncbi.nlm.nih.gov/pubmed), MEDLINE/OVID, and internet search using the Google Scholar (http://scholar.google.com) on the topics of RBC transfusion, transfusion indication and practices for VA ECMO and VV ECMO, the impact of age of RBC on transfusion, and complications of transfusion. The literature reviewed included case/brief reports, observation studies, cohort studies, prospective trials, retrospective trials, clinical notes, expert panel reports, review articles, guidelines from international societies, and multiple original articles and references from selected articles were also reviewed. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.com/article/view/10.21037/aob-21-29/rc).

## Indications for RBC transfusion

### *Priming the ECMO circuit*

The ECMO circuit consists of a pump (typically centrifugal in adults), cannulas for drainage and return of blood, a membrane oxygenator for gas exchange, a heat exchanger to keep blood warm, and conduit tubing to connect all aspects of the circuit (3,13). Monitors and ports maintain physiologically acceptable parameters, such as mean arterial line pressure, and monitor gas exchange (3,13). Circuit monitors include pre- and post-oxygenator blood gas sensors, pre- and post-oxygenator pressure sensors, flow meters, and port access for heparin infusions, continuous renal replacement therapy, and venous blood sampling (13). A bridge between pre- and post- oxygenator blood may also be in place, and can be utilized during weaning from ECMO, or for recirculation if the patient is temporarily removed from the system (13).

In adults, the ECMO circuit is primed with an isotonic crystalloid solution similar to extracellular fluid in composition, with or without albumin (3). Infants and smaller patients may require priming with a mix of this solution and RBC or RBC alone (3). In a survey of 121 Extracorporeal Life Support Organization (ELSO) centers, 92% of 119 responding centers indicated RBCs were used in circuit priming, although the study does not delineate clearly whether the centers surveyed were exclusively pediatric ECMO centers or a mix of pediatric and adults centers (14). Unlike platelets and cryoprecipitate which pose an increased clotting risk if introduced rapidly into the ECMO circuit, RBC can be quickly introduced when needed with minimal risk of circuit thrombosis. Current recommendations per ELSO indicate that priming with RBC should be considered in patients who weigh <20 kg, and in adults to minimize the hemodynamic compromise due to the dilutional effect of a crystalloid priming fluid in hemodynamically unstable patients, or those with poor oxygen delivery (3). Another consideration for the use of RBC to prime the ECMO circuit is during circuit exchange to compensate for the blood lost on the circuit being replaced.

### *Maintaining oxygen carrying capacity*

The goal of RBC transfusion is to increase blood oxygen delivery ($DO_2$) to meet the body's oxygen consumption needs (15). $DO_2$ is determined by total arterial oxygen content, and cardiac output (16). Eq. [1]:

$$DO_2 = CaO_2 \times Qt \; mL/\min, \quad CaO_2 = (Hb \times SaO_2 \times 1.34) + (PaO_2 \times 0.23) \; mL/L \qquad [1]$$

($CaO_2$ = arterial oxygen content, $PaO_2$ = partial pressure, $SaO_2$ = saturation, Qt = cadiac output; 1.34 mL is the volume of oxygen carried by 1 g of 100% saturated Hb).

Under normal circumstances, the human body is able to adjust $DO_2$ to compensate for changes in the body's oxygen consumption ($VO_2$). The ratio of $DO_2$ to $VO_2$ is normally maintained at 5:1, allowing consumption to be based on demand rather than supply (1). $VO_2$ becomes supply dependent when the $DO_2$ to $VO_2$ ratio decreases to 2:1 or below (1). The initial response to a decrease in $DO_2$ to $VO_2$ ratio is an increase in oxygen extraction as reflected by the oxygen extraction ratio ($VO_2/DO_2$) (1,15). This ratio is directly correlated with mixed venous oxygen saturation ($mSvO_2$), permitting $mSvO_2$ to be used as a surrogate of the $DO_2$ to $VO_2$ ratio in critically ill patients (1). During ECMO, an $mSvO_2$ of 70% or more may indicate adequate oxygenation (1).

One limitation to consider regarding VV ECMO and $mSvO_2$ is inability of the circuit to capture 100% of the cardiac output. As a result, the oxygen content of the blood not captured by the circuit is dependent on the degree of

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gas exchange in the remaining functional portions of the diseased lung. Where residual lung function is minimal, for example the diffuse alveolar damage and thrombosis in the SARS-CoV-2 infected lung, the poorly oxygenated blood impairs $DO_2$. Therefore, transfusion to a higher hemoglobin or hematocrit goal may increase the absolute oxygen carrying capacity and counteract the shunted blood's effect on $DO_2$. Additionally, recirculation and the shunting of arterial blood back into the venous lumen, commonly during VV ECMO, renders the monitoring of the venous line oxygen saturation no longer reflective of the mixed venous oxygen saturation.

Systemic $DO_2$ can be improved by increasing hemoglobin concentration with RBC transfusion, improving oxygenation, or increasing total ECMO blood flow (1). The theory that increased hemoglobin can increase $DO_2$ in VV ECMO patients was supported by a study by Schmidt *et al.* in acute respiratory distress syndrome (ARDS) patients (16). The authors demonstrated that RBC transfusions improved $DO_2$ and estimated $DO_2/VO_2$ even during reduced blood flow (16). While RBC transfusions in ECMO serve to increase $DO_2$, the above extraction ratios and measurements are not frequently used in clinical practice to determine the need for RBC transfusion (3). Instead, hemoglobin levels have been used as a surrogate marker for oxygen delivery and as a trigger point for RBC transfusions (1).

As adequate oxygen delivery is particularly important in VV ECMO patients with hypoxemia, our institution has adapted a tiered hemoglobin goal based on oxygen saturation in the setting of optimal ECMO flow, with a hemoglobin goal >7 g/dL for oxygen saturations of 88–92%, a hemoglobin goal >8 g/dL for oxygen saturations of 85–88%, and a hemoglobin goal >9 g/dL for oxygen saturations <85%.

Given the well-established increased morbidity and mortality associated with higher RBC transfusion goals in critically ill patients, higher RBC transfusion thresholds to optimize $DO_2$ while on ECMO should be approached with extreme caution (17). RBC transfusion may need to be tailored for the individual patient who has circulatory and respiratory compromise in the setting of optimal ECMO support and mechanical ventilation (17).

### *Treatment of bleeding complications in the setting of anticoagulation*

Bleeding is one of the most common complications in ECMO, occurring at rates of 30–60%, with intracranial hemorrhage being the most dreaded complication because of its short and long term disability and overall cost (3,8). The etiology is suspected to be multifactorial, with contributions from systemic anticoagulation, consumptive coagulopathy, acquired Von Willebrand Syndrome, circuit components leading to hemolysis and thrombocytopenia, surgical interventions, and ongoing critical illness (18). *Table 1* summarizes the following studies related to bleeding and anticoagulation in ECMO.

In a retrospective analysis of 132 VA and VV ECMO patients in a single center over a three year period, where heparin was used as anticoagulation for 84.9% of patients (the remaining patients receiving argatroban, bivalirudin, multiple drugs, or no anticoagulation), serious bleeding events (i.e., a bleed that either required 2 units of RBC due to a hemoglobin decrease of 2 g/dL, new hemodynamic instability, overt bleeding, or required surgical exploration) occurred in 56.1% of patients (6); 54.1% of bleeds occurred in the chest, 24.3% in the gastrointestinal tract, and the fewest number of bleeds occurred in the central nervous system (4.1%) (6). In a larger retrospective study of 418 patients on VA and VV ECMO, there were fewer bleeding events overall (23.2%), but similar rates of thoracic bleeding events (41.2%) (19). Mucus membrane or small bleeding events may be managed with applied pressure or topical hemostatic agents; more significant bleeds typically require more aggressive medical management, surgical management, or both (3).

While there are no data regarding recommendations of anticoagulation choice or monitoring that may best predict bleeding in ECMO patients, Aubron *et al.* sought to describe bleeding complications and risk factors in this patient population (20). In a retrospective study of VA and VV ECMO patients at two teaching hospital affiliate centers, the authors identified 128 bleeding events using the ELSO definition of a clinical bleed (20). In their study, 60% of ECMO episodes had at least one bleeding event (20). Patients who experienced a bleed were more likely to have had prior surgery (39% to 7%, P<0.001), more likely to have required renal replacement therapy (64% to 35%, P<0.01), and had a higher median SOFA score (11 *vs.* 9, first and third quartiles, P=0.01) (20). Additional factors associated with bleeding included an aPTT ≥70 s on the day prior to the bleed (P<0.01), higher APACHE III score (P=0.01), and ECMO utilized after surgery (P<0.01) (20). The authors concluded that coagulation abnormalities may be a target for future bleeding prevention interventions (20).

While the above study was not able to definitively identify factors that would predict bleeding during ECMO,

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**Table 1** Literature review of bleeding complications in ECMO

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Brogan 2019 | Expert consensus and literature review | | -Frequency of bleeding during ECMO<br>-Management of bleeding during ECMO | Major bleeding occurs in 30–42% of patients on ECMO, 25–63% requiring operative management. Intracranial bleeding occurs in 3–8% of patients | Low |
| Mazzeffi 2016 | Single center retrospective review, 3-year period | N=132 | -Incidence of bleeding events<br>-Incidence of blood product transfusions | -Serious bleeding events: 56.1% of all patients, with 54.1% of bleeds in chest, 24.3% in GI tract, 4.1% in CNS<br>-VA ECMO: median transfusion of 21 RBC<br>-VV ECMO: a median of 15 RBC | Moderate |
| Lamb 2013 | Retrospective single case series, 1 year | N=5 | -Incidence of bleeding events<br>-Incidence of blood product transfusions | Massive bleeding events related to pre or post ECMO chest tube insertion, jejunal arterio-venous malformations, femoral distal limb cannula dislodgement with superficial femoral artery pseudoaneurysm, ventricular rupture at time of cannula insertion | Low |
| Ried 2018 | Single center retrospective | N=418 | -Any bleeding complication, thoracic bleeding complication<br>-Threshold for transfusion 8 g/dL | -Bleeding complications: 97 (23.2%)<br>-Thoracic bleeding: 40 patients (41.2%), diffuse bleeding in 21.6%, cerebral bleeding in 14.4%, GI bleeding in 6.2%<br>-In house mortality: 36.4%, and was significantly higher in patients with bleeding complications (48.5% *vs.* 32.7%, P=0.005) | Moderate |
| Aubron 2016 | Two-center retrospective, 2010–2013 | N=149 : VA ECMO =111, VV ECMO =38 | -Characteristics of patients with and without bleeding events<br>-Frequency of and variables associated with bleeding events | -89 episodes (60%) with at least one bleeding event<br>-Patients who bled more likely to have had surgery (39% *vs.* 7%, P<0.001), have needed RRT (64% *vs.* 35%, P<0.01), higher median SOFA (11 *vs.* 9, P=0.01)<br>-Factors associated with bleeding: aPTT greater than equal to 70 s on day prior (P<0.01), elevated APACHE III score (P<0.01), post-surgical ECMO (P<0.01) | Moderate |

**Table 1** (*continued*)

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**Table 1** (*continued*)

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Lonergan 2017 | Retrospective single center, secondary analysis, 3-year period | N=112 subjects, VA ECMO =48, VV ECMO =64 | Pre-ECMO variables for association with bleeding to develop a multivariable model and an associated risk stratification score | 47.3% of patients experienced coagulopathic bleeding | Moderate |
| | | | | -Fair predictive value characteristics: hypertension, age greater than 65, and ECMO type | |
| | | | | -Characteristics had receiver operator characteristic curve AUC =0.66, superior to HASBLED AUC =0.64 | |
| | | | | -VA ECMO associated with coagulopathic bleeding (P=0.02) | |
| Kurihara 2020 | Single center retrospective, Jan 2015–Feb 2019 | N=74 VV ECMO | -Survival rates | -No difference in overall survival (P=0.58), no circuit thrombosis in either group | Moderate |
| | | | -Bleeding rates | -Standard DVT prophylaxis had lower rates of gastrointestinal bleeding (5.6% *vs.* 28.9% P<0.001), lower rates of blood transfusions (55.5% *vs.* 94.7% P<0.001) | |
| | | | -Thrombosis rates | -No significant difference in incidence of AKI, RRT use, or neurologic dysfunction | |
| | | | Compare patients receiving standard systemic AC compared to DVT prophylaxis AC | | |

ECMO, extracorporeal membrane oxygenation; VA ECMO, venous-arterial extracorporeal membrane oxygenation; VV ECMO, venous-venous extracorporeal membrane oxygenation; GI, gastrointestinal; CNS, central nervous system; RBC, red blood cell; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; aPTT, activated partial thromboplastin time; AKI, acute kidney injury; DVT, deep vein thrombosis; AC, anticoagulation.

Lonergan *et al.* sought to determine which pre-ECMO parameters might be developed into a scoring system to predict individuals at risk for requiring blood transfusion (21). The three factors selected based on optimization of area under the receiver operating characteristic curve from evaluation of multiple factors were presence of hypertension (systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg), patient's age, and ECMO type (VA *vs.* VV), summarized as HAT (hypertension, age, type) (21). Patients were scored in a binary fashion (0 for not present, 1 for present), with a score of 3 being the highest (21). Patients with a score of 0 had a bleeding rate of 30.8%, while patients with a score of 3 had a bleeding rate of 71.4% (21). While this score did have a predictive value for bleeding rate, it did not have an association with total RBC transfusion (21).

The increased bleeding risk in ECMO patients is partially due to systemic anticoagulation (18). However, the need for high levels of systemic anticoagulation for safe administration of ECMO is being re-evaluated. In a retrospective review of 74 patients receiving VV ECMO, a 36-patient cohort receiving low dose standard deep vein thrombosis prophylaxis with heparin was compared to a 38 patient cohort receiving standard systemic anticoagulation (22). The cohort receiving standard deep vein thrombosis prophylaxis did not have higher rates of thrombotic complications or death as compared to their standard of care counterparts (22). Patients not receiving systemic anticoagulation were found to have lower rates of gastrointestinal bleeding (5.6% *vs.* 28.9%, P<0.001), and lower rates of RBC transfusions (55.5% *vs.* 94.7%, P<0.001) (22). While this study demonstrates the feasibility of lower intensity anticoagulation, systemic anticoagulation remains the standard of care in adult ECMO patients until more studies are completed.

Sniderman *et al.* compared some of the most commonly used tests for ECMO including activated partial thromboplastin time (aPTT), activated clotting time (ACT),

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anti-Xa level, and thromboelastography (TEG) in the context of heparin anticoagulation, given the infrequent use of bivalirudin or argatroban (23). ACT was found to be unreliable in patients receiving moderate to low dose heparin; therefore ELSO states that heparin monitoring is most commonly done with aPTT and anti-Xa activity (3). When compared with ACT, aPTT demonstrated fewer hemorrhagic complications but increased circuit clotting complications. aPTT also offers the advantage of laboratory standardization and accuracy (2). Anti-Xa values can be utilized as an indirect measure of heparin concentration, as opposed to titration of a coagulation state (2). TEG, while point of care, has no significant data demonstrating an ability to decrease ECMO bleeding complications and is more expensive than aPTT (3). Overall, there are no clear data to guide which test may be the best predictor of clinical outcomes or bleeding events (23).

In our opinion, aPTT is currently the most widely accepted method for titrating heparin anticoagulation in ECMO patients. Therefore, for the management of bleeding complications while on anticoagulation in the setting of extracorporeal support, our institution has adopted the following practice guidelines, with heparin being the systemic anticoagulant administered. The VV ECMO aPTT goal is 45–55 seconds and VA ECMO aPTT goal is 60–80 seconds. These goals were defined, and set based on our institutional experience and have been utilized for over a decade. If a patient experiences a bleeding complication requiring active transfusion or an intervention (interventional radiology or surgical), then either aPTT goals are reduced, or anticoagulation is held until the bleeding complication is addressed. Given the increased risk of thrombotic complications in the ECMO circuit during this situation, particularly when the circuit blood flows are below 3–4 liters per minute, our ECMO perfusionists are vigilant at inspecting the ECMO cannulas and circuit for clot formation.

### *Hemolysis and circuit management*

Hemolysis associated with the ECMO circuit can be an effect of excessive negative pressure generated by the pump causing cavitation or degassing (24). RBC are fractured, leading to anemia and the release of free hemoglobin into the plasma which scavenges endothelial nitric oxide resulting in microvascular vasomotor dysregulation. Hemolysis may also promote thrombosis through enhanced VWF-mediated platelet adhesion (3).

Circuit components contribute to the risk for thrombosis. Therefore, advances in circuit biomaterials may help reduce the need for anticoagulation and subsequently decrease the risk of bleeding for ECMO patients. The proteins most quickly adsorbed onto the ECMO circuit, in decreasing order of rapidity of adsorption, are fibrinogen, factor III, thrombospondin, fibronectin, immunoglobulin E, VWF, albumin, and hemoglobin (23). This sequential adsorption of proteins, including integral components of the coagulation cascade, is known as the Vroman effect (25). Combating this effect by optimizing the biomaterials of the ECMO circuit may in turn lead to decreased bleeding risk and decreased need for blood product transfusion (25). A study on the impact of cannula design found a non-statistically significant reduction in bleeding complications by using a newer cannula coated with albumin and heparin (26). This change in circuit components has not reduced the need for transfusions in ECMO patients, but continues to highlight the need for more research in biomaterials improvement (26).

Circuit components can also be involved in blood conservation strategies and prevention of transfusions. A novel tripartite conservation strategy, proposed by Agerstrand *et al.*, involves autotransfusion of circuit blood in addition to hemoglobin and aPTT reduction goals (11). Eighty percent of circuit blood was autotransfused, preserving RBC mass and reducing the need for additional transfusions in the peri decannulation period. With this strategy, the reported median transfusion rate was less than 10% of historical rates for ECMO (11). In some situations, clinicians have leveraged circuit management to avoid blood product transfusion. In a case report of VV ECMO in a Jehovah Witness patient, the patient was successfully transitioned off VV ECMO by recycling circuit blood during decannulation (27). The team slowly infused 600 mL of saline through the VV ECMO circuit with the pump running at 0 rotations per minute until the blood within the circuit had been replaced completely with saline, and subsequently removed both the venous return and access cannulas (27). At our institution, blood from the circuit is often returned to the patient at the time of decannulation. Priming volumes of a typical adult circuit can be approximately 600–900 mL of blood (10–20% of a normal adult blood volume), and therefore the amount of blood returned to the patient should be tailored based on overall volume status and respiratory and renal function.

While hemolysis is associated with a drop in platelet count and hematocrit, the degree of hemolysis is best quantified using plasma free hemoglobin levels, lactate

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dehydrogenase levels, haptoglobin levels, and the amount of hemoglobinuria. Hemolysis during ECMO is associated with increased morbidity and mortality secondary to the development of pump thrombosis and in severe cases disseminated intravascular coagulation (3). In situations where pump thrombosis occurs, exchange of the oxygenator is usually required.

## Threshold for transfusion

The association between RBC transfusion and increased morbidity and mortality in critically ill patients extends to ECMO patients (11). Prior to the current global health crisis, ELSO recommended a maintenance hematocrit of >40%, to decrease flow while optimizing oxygen delivery, based on expert opinion (3). Furthermore, an observational retrospective single center study of patients undergoing ECMO found a 1.73 relative risk (95% confidence interval: 1.134–2.639) of mortality in patients who had a hematocrit of 31% or greater (28). This study found no statistically significant difference in mortality for patients in their lower hematocrit groups of 25% or less, 26–28%, and 29–31% (28).

The most recent ELSO guidelines for coronavirus patients published in July 2020 suggest a hemoglobin level of 7–8 g/dL be applied during ECMO due to the anticipated shortage of blood products (5). In a consensus document supported by the Canadian Society of Cardiac Surgeons and the Canadian Cardiovascular Critical Care Society, restrictive transfusion strategies with an RBC transfusion threshold of 70–75 g/L is suggested for nonbleeding patients, based on limited evidence from VV-ECMO studies and expert consensus (29). A similar expert consensus document from the European Society of Intensive Care Medicine reviewed current literature regarding blood produce transfusion in ECMO patients, and were not able to make a recommendation between a restrictive 7 g/dL transfusion threshold as opposed to a liberal 9 g/dL transfusion threshold (30).

Many institutions opt not to utilize a pre-defined hemoglobin trigger for RBC transfusion for ECMO patients (9). In the systematic review of existing transfusion guidelines by Abbasciano *et al.*, where transfusion thresholds ranged from 7–14 g/dL, lower transfusion thresholds were associated with lower rates of transfusion, mortality, and acute kidney injury (AKI) (31). However, the authors noted severe publication bias, heterogeneity, and poor study methodology (31). In a more recent systematic review from Hughes et al evaluating 54 studies from 1996–2016, transfusion trigger thresholds ranged from hemoglobin 7–15 g/dL or hematocrit 28–35% (32). Transfusion rates varied from 0.15 to 17.84 units of RBC per day, with VV ECMO patients receiving significantly fewer RBC transfusions compared to VA ECMO patients (1.23 *vs.* 3.86 units per day) (32). Overall, while transfusion threshold targets were heterogenous between institutions, the authors identified a trend of lower transfusion thresholds in studies completed after 2009. The adoption of lower thresholds is attributed to greater familiarity with ECMO and noninferiority studies of lower transfusion thresholds in critically ill non-ECMO patients (32). These aforementioned studies and their quality are evaluated and summarized in *Table 2*.

In ECMO, as in general critical care, experts have argued that relying exclusively on hemoglobin triggers without taking into account other patient factors may be too simplistic (12,15). An expert panel review in 2018 highlighted the lack of evidence for a specific hemoglobin trigger, and advised transfusion decisions be based on the patient's cardiorespiratory state or oxygen delivery rather than a strict hemoglobin or hematocrit level (23). An additional confounding element in VV ECMO is the "inherent hypoxemia" driven by the circuit providing fully oxygenated blood that mixes with deoxygenated venous return blood (2). Additionally, patients on VA ECMO have a higher frequency of bleeding events as compared to their counterparts on VV ECMO (31). Due to these differences in complications and in physiology, a delineation between transfusion practices in VA ECMO and VV ECMO should be considered (31).

### *RBC transfusion in VA ECMO*

A review of prospectively collected data at Rennes University Hospital sought to elucidate the impact of different factors on transfusion practices in VA ECMO and VV ECMO (10). VA ECMO patients received a higher rate of FFP (60.5% *vs.* 31.8%, P<0.001) and platelets (61.7% *vs.* 34.1%, P<0.001), but had no significant difference in RBC transfusion (83.2% *vs.* 80.9%, P=0.601) (10). Further subgroup analysis of patients undergoing VA ECMO found that post-cardiotomy and post heart transplantation patients required more transfusions overall, including RBC transfusions (respectively 92.2% and 94.4%, compared to others 76.3%, P<0.001) (10). Another study of retrospective data collected from a single ECMO center studied the rate of RBC transfusion in patients on VA ECMO and VV ECMO with a general hemoglobin trigger of 8 g/L (33). Patients on VA ECMO received on average 2.04 RBC units

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**Table 2** Literature review of RBC transfusion in ECMO

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Brogan 2019 | Expert consensus and literature review | | | Maintenance hematocrit of >40% | Low |
| Shekar 2020 | Expert consensus | | | Hemoglobin transfusion threshold of 7–8 g/dL | Low |
| Singh 2020 | Expert consensus and multi-center survey | 17 centers | Blood product transfusion policies and practices in ECMO | Hemoglobin RBC transfusion threshold of 70–75 g/L in nonbleeding patients | Moderate |
| Vlaar 2020 | Expert consensus | 13 experts | Blood product transfusion practices in critically ill adults | Not enough high quality evidence to make a recommendation of low (7 g/dL) *vs.* high (9 g/dL) transfusion threshold | Low |
| Abbasciano 2020 | Literature meta-analysis | 10 studies | Red blood cell transfusion thresholds in ECMO, important clinical factors and outcomes for future RCTs | -Transfusion thresholds range from 7–14 g/dL<br>-Lower transfusion thresholds associated with fewer transfusions, lower mortality rates, lower rates of AKI | Moderate |
| Hughes 2021 | Literature meta-analysis | 54 studies | Red blood cell transfusion practices in ECMO | -Transfusion thresholds range from 7 to 15 g/dL<br>-Lower transfusion rates were associated with VV ECMO patients as compared to VA ECMO patients | Moderate |
| Swol 2018 | Retrospective single center | 81 | Hematocrit level association with mortality in trauma and non-trauma patients undergoing ECMO | -Hematocrit >31% associated with increased relative risk for mortality<br>-No significant differences in relative risk of mortality for lower hematocrit groups | Moderate |
| Martucci 2019 | Multi-center survey | 447 | Red blood cell transfusion practices in VV ECMO | -54.4% did not use predefined hemoglobin trigger<br>-VV ECMO patients had a statistically significant higher hemoglobin trigger for red blood cell transfusion than in other critically ill patients | Moderate |
| Angerstrand 2015 | Retrospective single center | 38 | Transfusion requirements, bleeding complications, clinical outcomes | Number of transfusions found to be associated with higher ICU and hospital death | Moderate |

RBC, red blood cell; ECMO, extracorporeal membrane oxygenation; RCT, randomized controlled trial; AKI, acute kidney injury; VA ECMO, venous-arterial extracorporeal membrane oxygenation; VV ECMO, venous-venous extracorporeal membrane oxygenation; ICU, intensive care unit.

per day compared to patients on VV ECMO who received on average 0.7 RBC units per day (P=0.016), consistent with prior studies where patients on VA ECMO required higher rates of RBC transfusion (33). Overall, the authors argued that their RBC transfusion rates were lower than prior studies such as Ang et al, which retrospectively studied rates of transfusion in VA and VV ECMO for a hemoglobin transfusion trigger of 10 g/dL (33,34).

A 2018 study evaluated VA ECMO patients before and after establishing a restrictive transfusion protocol (35). Researchers compared 30 patients before and 30 patients after implementation of a transfusion protocol that guided RBC, platelet, FFP, and cryoprecipitate transfusion, as well as antithrombin III and protamine administration (35).

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**Table 3** Literature review of RBC transfusion in VA ECMO

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Guimbetiere 2019 | Single center, prospective data collection, 2005–2016 | N=509 patients<br>-VA ECMO =410 (81%)<br>-VV ECMO =99 (19%) | Primary outcome: describe clinical results of transfusions. Secondary outcomes: assess effects of indications of transfusion requirements | VA ECMO patients:<br>-Higher lactate (7.3±5.4 *vs.* 7±3.1, P<0.001)<br>-Higher rate of FFP (60.5% *vs.* 31.8%, P<0.001)—higher platelet transfusions (61.7% *vs.* 34.1%, P<0.001)<br>-No significant difference in RBC transfusion (83.2% *vs.* 80.9%, P=0.601)<br>-VA ECMO patients post cardiomyotomy or post heart transplant required more transfusions than others within the group (92.2% and 94.4% *vs.* 76.3% P<0.001) | High |
| Buscher 2017 | Single center retrospective data review, 18 months | N=42 patients: -VA ECMO =32, -VV ECMO =16, Hemoglobin trigger =8 g/dL | ECMO duration, hemorrhagic complications incidence and type, survival | -VA ECMO =2.04 RBC units per day<br>-VV ECMO =0.7 RBC units per day, P=0.016<br>-49% of all transfused blood products were RBC | Moderate |
| Cahill 2018 | Single center retrospective data analysis | N=60: VA ECMO, pre-intervention =30, post-intervention =30 | ECMO duration, survival, blood transfusion rates, clinical outcomes | Pre intervention:<br>-More bleeding events (23 pre-protocol *vs.* 13 post-protocol, P=0.008)<br>-Higher mean total RBC transfusion (28.1±23.4 pre-protocol *vs.* 15.3±16.1 post-protocol, P=0.017)<br>Post intervention:<br>-Higher rates of reoperation (57% pre-protocol *vs.* 83% post-protocol P=0.024)<br>-ECMO survival (33% pre-protocol *vs.* 63% post-protocol, P=0.022)<br>-30-day survival (30% pre-protocol *vs.* 63% post-protocol, P=0.024) | Moderate |

RBC, red blood cell; VA ECMO, venous-arterial extracorporeal membrane oxygenation; VV ECMO, veno-venous extracorporeal membrane oxygenation; FFP, fresh frozen plasma; ECMO, extracorporeal membrane oxygenation.

Bleeding events were defined as bleeding greater than 300 mL/hour, more than 150 mL/hour for three hours, or at the discretion of the clinical team, and RBC transfusion was only indicated in cases of bleeding with a hemoglobin <8 g/dL (35). Patients in the pre-intervention group had more bleeding events than those in the post-intervention group (23 *vs.* 13 events, P=0.008) (35). Furthermore, total RBC transfusion was decreased by 45.4% post-protocol (mean 28.1±23.4 pre-protocol compared to 15.3±16.1 post-protocol, P=0.017) (35). While post-intervention patients were found to have higher rates of reoperation (pre-protocol 57% *vs.* post-protocol 83%, P=0.024), they also had higher rates of ECMO survival (pre-protocol 33% *vs.* post-protocol 63%, P=0.022) and 30-day survival (pre-protocol 30% *vs.* post-protocol 63%, P=0.024) (35). These studies and their quality of evidence are summarized in *Table 3*.

### *RBC transfusion in VV ECMO*

A retrospective study of 18 ARDS patients on VV ECMO by

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Voelker *et al.* used a hemoglobin level of 7.0 g/dL to trigger RBC transfusion and maintained hemoglobin between 7.0 to 9.0 g/dL (36). The volume of RBC transfusion was lower in survivors than non-survivors (0.96 *vs.* 1.97 units/day, P=0.07) (36). The overall survival rate of 61.1% is consistent with ELSO registry survival; however, compared to survivors, non-survivors had statistically significantly higher Sequential Organ Failure Assessment scores on the first day (7.9±4.8 *vs.* 13.0±3.2, P=0.03) and full ECMO period (9.8±3.4 *vs.* 14.7±4.7 days, P=0.02), and statistically higher Simplified Acute Physiology Scores for the full ECMO period (40.2±12.6 *vs.* 55.9±15.9, P=0.03) (36). This reflects the more clinically severe nature of non-survivors, which may have factored into their higher volume of blood transfusion. More studies would be needed to confirm this hypothesis (36).

A retrospective study of 38 ECMO patients (34 on VV ECMO) in 2015 by Agerstrand *et al.* utilized a restrictive transfusion trigger of hemoglobin <7.0 g/dL, with low dose anticoagulation (aPTT goal of 40–60 seconds) and autotransfusion (11). Overall, 24 patients (63.2%) required RBC transfusion. A median of 1 unit (0.11 units/day) of RBC was transfused per patient over the course of their ECMO treatment (11). Clinically apparent bleeding occurred in 26.5% of patients with 2 severe bleeding complications, however a trend of decreasing hemoglobin over time was noted in their subjects (11). The median preoxygenator saturation of 74.5% indicated that oxygen delivery was sufficient despite the low hemoglobin level (11). A survival rate of 28 patients (73.7%) to hospital discharge suggests the conservative transfusion protocol did not have a negative effect on survival, although increased number of transfusions was associated with higher mortality (11).

An 82-patient prospective observational cohort study performed by Martucci *et al.* aimed to elucidate factors that might be associated with higher RBC transfusion needs. Their ECMO treatment protocol targeted an aPTT (40–50 seconds) and hematocrit (24–30%), lower than in previous literature (12). They also utilized a composite style RBC transfusion trigger consisting of hemoglobin with $SvO_2$, urine output, lactate, and need for vasopressors (12). In addition to traditional aPTT monitoring, antithrombin III was evaluated daily and repleted, and platelets were transfused for a goal between [40–50]×$10^9$/L per L (12). In an analysis of patients treated with the above protocol, patients who had a lower pre-ECMO hematocrit required more RBC transfusions (P=0.02), at a relation of 5 mL/d increase in RBC transfusion for every 1 point reduction in pre-ECMO hematocrit or every 10×$10^9$/L platelet reduction, 3 mL/d for every one point reduction of antithrombin III (12). AKI individually was associated with a 50 mL/d increase in RBC transfusion (12). Patients who required more RBC transfusions had a lower 90-day survival compared to those who required less transfusions (62.7% *vs.* 89.9%, P<0.01) (12). The aforementioned studies and their quality of evidence are summarized in *Table 4*.

Given the mixed results in the existing literature and lack of large ECMO specific randomized control trials that better delineate the acceptable hemoglobin threshold for those on VV and VA ECMO, our institution has adopted the following transfusion thresholds based on clinical experience at our high-volume center: Patients will receive a RBC transfusion while on VA ECMO for a hemoglobin <8 g/dL and for patients on VV ECMO for a hemoglobin <7 g/dL in the absence of bleeding or circulatory compromise.

## Adverse effects of blood transfusions

While transfusions are frequently used in ECMO patients, they can have negative consequences and may increase mortality. In a review of adult ECMO patients in Taiwan, RBC transfusion was shown to be significantly associated with mortality (Adult OR =8.65, 95% CI: 3.56–22.50, P<0.0001) (37). Even after adjustment for confounding variables, RBC transfusion was associated with thrombotic events (Adult OR 1.01, 95% CI: 1.00–1.02, P=0.007) (37). Patients on ECMO may have concurrent renal complications, and in an assessment of factors associated with transfusion requirements, patients with AKI stage 3 had an association with an increased need for transfusion (12).

Blood transfusion in critically ill patients has been systematically shown to have multiple adverse effects, which can be divided into infectious and non-infectious serious hazards of transfusion (38). In a nationwide cohort study in Taiwan by Chen *et al.*, complications from transfusion included coagulopathy, electrolyte and acid-base imbalance, hypothermia, transfusion-related acute lung injury (TRALI), infection, and AKI. TRALI accounted for 37% of transfusion related mortality (39).

The effects of added fluid volume from blood transfusion were evaluated in a study of ECMO patients from three tertiary care hospitals (40). Patients were divided into quartiles based on cumulative fluid balance during their ECMO course, analyzed based on their original need for ECMO (cardiovascular *vs.* non-cardiovascular), and were evaluated for overall survival (40). Patients with non-

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**Table 4** Literature review of RBC transfusion in VV ECMO

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Voelker 2015 | Single center retrospective | N=18 VV ECMO | -Hospital mortality | -Survival=61.1%, consistent with the ELSO registry | Moderate |
| | | | -Time on ECMO | -Volume of RBC transfusion lower in survivors than nonsurvivors (0.96 *vs.* 1.97 units/day, P=0.07) | |
| | | | -Hemoglobin and hematocrit | Nonsurvivors likely had more severe illness: | |
| | | | -RBC received | -A trend for higher lactate (1.8±1 *vs.* 3.5±2.6, P=0.07) | |
| | | | -Lactate | -Higher SOFA scores on first day (7.9 ±4.8 *vs.* 13.0±3.2, P=0.03) | |
| | | | -Mortality on patients | -Longer time on ECMO (9.8±3.4 *vs.* 14.7±4.7 days, P=0.02) | |
| | | | | -Higher SAPS scores for the full ECMO period (40.2±12.6 *vs.* 55.9±15.9, P=0.03) | |
| | | | Transfusion trigger of 7 g/dL or were triggered by physiologic transfusion requirements for a goal hemoglobin between 7 and 9 | | |
| Martucci 2019 | Single center prospective observational cohort, 2006-2015 | N=82 VV ECMO | -Describe transfusion protocol | -Lower pre ECMO hematocrit associated with higher needs for RBC transfusion (P=0.02) | High |
| | | | -Identify factors associated with increased transfusions | -Patients who required more transfusions had a lower 90-day survival (62.7% *vs.* 89.9%, P<0.01) | |
| | | | -Define effects on short term mortality | -AKI was also associated with a 50 mL/d increase in RBC transfusion | |
| Angerstrand 2015 | Retrospective single center chart review study Jan 2010–Dec 2012 | N=38 patients: VV ECMO =34, VA ECMO =4 | Primary outcome: ECMO transfusion requirements, survival, neurologic and renal function, bleeding complications | -RBC transfusions to 63.2% patients (24 patients) | Moderate |
| | | | Hemoglobin trigger <7 g/dL | -Median transfused was 1 unit PRBCs over the entire duration of ECMO | |
| | | | | -Clinically apparent bleeding occurred in 10 patients (26.3%) | |
| | | | | -28 (73.7%) of patients survived to hospital discharge | |

RBC, red blood cell; VV ECMO, venous-venous extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score; AKI, acute kidney injury.

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cardiovascular disease with a cumulative fluid balance greater than 194.7 mL/kg (quartile 4) were found to have significantly lower rates of survival (P<0.047) than patients in the first quartile with a cumulative fluid balance of –3.9 mL/kg (40). Similarly patients with cardiovascular disease and a cumulative fluid balance greater than 109.7 and 222.9 mL/kg were also found to have significantly lower rates of survival (P<0.001) than those in the first and second quartile with a cumulative balance of –4.8 and 38.2 mL/kg, respectively (40).

A second study examining blood transfusion complications across ECMO found that massive blood transfusions augmented negative outcomes such as coagulopathy, electrolyte/acid-base imbalances, hypothermia, TRALI, AKI, and infection due to the dilutional effect of transfusion on white blood cells (39). Patients who received massive blood transfusions, defined as ten or more units of RBC within the one month period of initiation of ECMO, overall after propensity score matching had worse primary outcomes including longer length of stays in the hospital (24.8±18.8 *vs.* 20.5±18.8, P<0.001) and intensive care unit (ICU) (18.5±17.6 *vs.* 12.3±15.3, P<0.001), more ventilator days (16.8±17.1 *vs.* 10.8±15.0, P<0.001), more ECMO days (4.7±4.1 *vs.* 2.5±2.6 P<0.001), and more frequent AKI (1,108 *vs.* 644 patients, P<0.001) (39). The above studies and their quality of evidence are evaluated and summarized in *Table 5*.

## Impact of age of RBCS

Length of RBC storage can have a significant impact on transfusion associated outcomes. As transfusions in ECMO are to support $DO_2$, alterations in blood product viability and effective delivery of oxygen to tissues have suggested a detrimental clinical effect of storage on RBC efficacy (41). This collection of deleterious physical and biochemical changes is occasionally referred to as "the storage lesion" (38). RBCs undergo physical transformation during storage, deforming into echinocytes at day 14, and ultimately permanently losing their biconcave shape as spheroechinocytes at day 42 of storage (41). This morphological change limits their ability to navigate the microcirculation and impairs their ability to deliver oxygen (41).

On the biochemical level, prolonged RBC storage leads to loss of total adenine nucleotide pool, loss of membrane phospholipid vesiculation, and lipid peroxidation of the cell membrane; these effects contribute to impaired RBC deformability (41). Furthermore, storage of RBCs has been shown to decrease 2,3-diphosphoglycerate, a critical modulator that allows RBCs to adequately deliver oxygen to tissues. Pooled RBCs have been found to have increased neutrophil activation, as well as an increased proinflammatory cytokine accumulation that, in conjunction with these white blood cell factors, may contribute to transfusion related immunomodulation (11,42). These deleterious effects on the RBCs may impair cellular $DO_2$, reducing the desired effects of transfusion in ECMO patients.

While rat models have demonstrated that stored RBCs had impaired ability to oxygenate tissue when transfused (43), no studies have addressed this effect in humans. Initial observational studies demonstrated an association between RBC age and an increased risk of infection, thromboembolic events, multiorgan failure, ventilator time, ICU, and hospital length of stay and mortality. The majority of those studies were limited by bias and confounding (3). Therefore, several large randomized controlled studies have been conducted to address the clinical ramifications of RBC storage in critically ill patients requiring transfusions. The following studies are summarized and evaluated for quality in *Table 6*.

The Age of Blood Evaluation (ABLE) study evaluated the impact of fresh RBC (those stored for 8 days or fewer) transfused to critically ill patients, and found no significant benefit to transfusing fresh RBC with regards to hospital and ICU length of stay, multiple organ dysfunction score (MODS) and mortality (44).

Red Cell Storage Duration Study (RECESS) evaluated the impact of short term (10 days or less) versus long term (21 days or more) storage of RBCs on MODS for individuals undergoing complex cardiac surgery (45). This study found no significant difference in their primary outcome or mortality between patients who received RBCs stored for a shorter *vs.* longer period (45). The authors acknowledged that this study did not isolate and address RBCs at the end of their storage life (35–42 days or more), and therefore these conclusions may not extend to those blood products (45).

The TRANFUSE trial compared the effect of the transfusion of the freshest available blood (11.8±5.3 days) to that of the oldest available blood (22.4±7.5 days), with the oldest blood available approximately 42 days old in a large patient population across hospitals in Australia, Finland, Ireland, New Zealand and Saudi Arabia (46). The authors found no difference in 90-day mortality among both groups, although those who were transfused with newer

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**Table 5** Literature review of complications associated with RBC transfusion in ECMO

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Martucci 2019 | Single center prospective observational cohort, 2006–2015 | N=82 VV ECMO | -Describe transfusion protocol<br>-Identify factors associated with increased transfusions<br>-Define effects on short term mortality | AKI stage three was associated with a 50 mL/d increase in RBC transfusion | High |
| Qin 2020 | Single center retrospective 2009–2016 | N=217: 88 adult, 57 pediatric, 72 neonates | Evaluate for association between blood product administration and adverse outcomes | RBC transfusion associated with mortality (adult OR =8.65, 95% CI: 3.56–22.50, P<0.0001) and thrombotic events (OR 1.01, 95% CI: 1.00–1.02, P=0.007) | Moderate |
| Chen 2020 | Nationwide retrospective cohort study, 2000–2013 | N=2,757 patients | Evaluate in-hospital complications, mortality, all cause mortality, ESRD, respiratory failure, in patients who did and did not receive massive blood transfusions | Patients who had MBTs:<br>-More in-hospital days (24.8±18.8 *vs.* 20.5±18.8, P<0.001)<br>-More ICU days (18.5±17.6 *vs.* 12.3±15.3, P<0.001)<br>-More ventilator days (16.8±17.1 *vs.* 10.8±15.0, P<0.001)<br>-More days on ECMO support (4.7±4.1 *vs.* 2.5±2.6 P<0.001)<br>-More frequent AKI (1,108 *vs.* 644 patients, P<0.001) | Moderate |
| Kim 2018 | Multicenter (3) retrospective cohort study, 2005–2016 | N=723 | Association between cumulative fluid balance and outcomes (mortality) in patients on ECMO, stratified by those requiring ECMO for cardiovascular *vs.* non-cardiovascular causes | Non-cardiovascular cause for ECMO:<br>-Cumulative fluid balance greater than 194.7 mL/kg (quartile 4) had significantly lower rates of survival (P<0.047) than patients with cumulative fluid balance of –3.9 mL/kg (quartile 1)<br>Cardiovascular cause for ECMO:<br>-Cumulative fluid balance greater than 109.7 mL/kg (quartile 3) and 222.9 mL/kg (quartile 4) had lower rates of survival (P<0.001) than those with a fluid balance of –4.8 mL/kg (quartile 1) and 38.2 mL/kg (quartile 2) | Moderate |

RBC, red blood cell; ECMO, Extracorporeal Membrane Oxygenation; VV ECMO, venous-venous extracorporeal membrane oxygenation; ECMO, extracorporeal membrane oxygenation; MBT, massive blood transfusion; ICU, intensive care unit; ESRD, end stage renal disease; AKI, acute kidney injury.

blood experienced more febrile non-hemolytic transfusion reactions (46).

The INFORM trial, randomly assigned patients who required a RBC transfusion to receive type A or O blood that had been stored for the shortest duration (mean storage 13±7.6 days) or the longest duration (mean storage 23.6±8.9 days) in a 1:2 ratio (47). There was no significant difference in the rate of death among the two groups (47).

Finally, a meta-analysis of studies evaluating the clinical impact of storage length on RBC in critically ill patients found no benefit to transfusion of fresher blood, and no significant impact of RBC storage time on mortality (48).

Theoretically, while it might be advantageous to administer newer RBCs for improved oxygen delivery, no

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**Table 6** Literature review of impact of age of RBC on clinical outcomes in RBC transfusion

| Author/year | Study type | Number of subjects | Outcomes evaluated | Results and conclusion | Quality of evidence |
|---|---|---|---|---|---|
| Lacroix 2015 (ABLE) | Multicenter randomized controlled trial | N=2,430 critically ill patients: fresh blood (8 days) =1,211, standard issue =1,219 | Primary outcome: 90-day mortality | No statistically significant benefit to transfusing fresh RBC (8 days or fewer) compared to standard | |
| | | | Secondary outcomes: | Deaths at 90 days | High |
| | | | -Major illnesses | -36.9% in fresh blood group | |
| | | | -Duration of respiratory, hemodynamic, or renal support | -34.1% in standard | |
| | | | -Length of stay in hospital | | |
| | | | -Transfusion reactions | | |
| Steiner 2015 (RECESS) | Multicenter randomized controlled trial, 2010–2014 | N=1,098 | Primary outcome: change in Multiple Organ Dysfunction Score from preop to highest composite score through day 7 or death or discharge in patients undergoing complex surgery | -No statistically significant difference in 7-day mortality between short term (2.8%) *vs.* long term (2.0%), P=0.43 | High |
| | | | -Short term storage (median of 7 days) | -No statistically significant difference in 28-day mortality between short term 4.4% *vs.* longer term 5.3%, P=0.57 | |
| | | | -Longer term storage (median of 28 days) | | |
| Cooper 2017 (TRANSFUSE) | International multicenter randomized controlled trial | N=4,919: short term storage =2,457, long term storage =2,462 | Primary outcome: 90-day mortality | No statistically significant difference in 90-day mortality between short term storage 610 (24.8%), and long-term storage 594 (24.1%), P=0.57 | High |
| Heddle 2016 (INFORM) | International multicenter randomized controlled trial | N=20,858: short term storage (mean storage 13±7.6) N=6,936, long term storage (mean storage 23.6±8.9 days) N=13,922 | Primary outcome: in hospital mortality estimated by means of logistic regression after adjustments in general hospital population, patients type A or type O blood | Short term group: 634 deaths (9.1%) *vs.* long term group: 1213 (8.7%) deaths, P=0.34. Not statistically significant | high |
| Rygard 2018 | Meta-analysis | N=7 randomized controlled clinical trials including adult ICU patients (N=18,283 ICU patients) | Outcome assessed: impact of storage length on RBC in critically ill patients | No significant benefit to transfusion of fresher blood, no significant impact of RBC storage time on mortality | Low |

RBC, red blood cell; ICU, intensive care unit.

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such difference has been elucidated in clinical practice. Additionally, whether a facility receives newer or older blood is dependent on allocation policies within the region and allocating newer blood to ECMO patients may not be feasible.

## Conclusions

ECMO as an adaptation of cardiopulmonary bypass has served to support patients during cardiopulmonary failure, as a bridge to improved mechanical ventilation or circulatory support, or as a bridge to transplantation. RBC transfusion in ECMO is indicated for circuit priming, blood loss during cannulation, significant bleeding events, and restoration of oxygen carrying capacity. ELSO currently recommends maintaining a hematocrit of >40% based on expert recommendations; given the lack of prospective multicenter studies and the inherent limitations of the currently available literature. As a result, many centers opt to not utilize such a predefined trigger for transfusion and instead, tailor the thresholds based on a patient's clinical status. Blood transfusion is not without risk; patients on ECMO have been shown to develop AKI, electrolyte imbalances, and transfusion related lung injury as a result of RBC transfusion. Therefore, any RBC transfusion should be considered with the patient's unique physiology and oxygen requirements in mind.

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