Perioperative Management of Bleeding and Transfusion for Lung Transplantation

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Abstract
Perioperative allogeneic blood product transfusion is common in lung transplantation and has various implications on the short- and long-term outcomes of lung recipients. This review summarizes the effect of transfusion on outcomes including primary graft dysfunction, chronic lung allograft dysfunction, and all-cause mortality. We outline known risk factors for increased transfusion requirement in lung transplantation and present current evidence regarding the effect of hemostatic agents including antifibrinolytics, recombinant factor VII, and prothrombin complex concentrates. Finally, we highlight the roles of point-of-care coagulation testing and goal-directed transfusion strategies in reducing transfusion requirements in lung transplantation.

Keywords
transfusion, lung transplantation, TRALI, TACO, TRIM, primary graft dysfunction, chronic lung allograft dysfunction

Introduction
Allogeneic blood product transfusion is common in the perioperative lung transplant period, though exact rates are poorly reported and vary by institution, patient comorbidities, indication for transplant, and the number of lungs transplanted.1-3 The majority of patients receive at least 3 units of red blood cells (RBCs) in the perioperative period. Liberal blood product transfusion is associated with worse outcomes across a wide range of surgical domains, including general, cardiac, trauma, and liver transplant surgery.4-7

In the lung transplant population, the criteria for the diagnosis of transfusion-related pulmonary complications is difficult to extricate from the diagnosis of primary graft dysfunction (PGD). Transfusion-related adverse events, such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload, pneumonia, sepsis, and prolonged stay in the intensive care unit (ICU) are particularly deleterious for lung transplant recipients when they occur.8 It is challenging to differentiate between PGD and TRALI in the first place, given that the current International Society for Heart and Lung Transplantation definition and grading of PGD does not take into account the number of transfused blood products, and the clinical presentation of these 2 syndromes is quite similar.9

Even though centers routinely administer leukoreduced blood products, the implications for the immunosuppressed lung transplant patient includes the development of transfusion-associated graft-versus-host disease from exposure to donor lymphocytes and the development of human leukocyte antigen (HLA) antibodies, which may influence rates of acute and chronic rejection.8 Preoperative transfusion of red cells and platelets have been associated with the development of HLA antibodies in the recipient, which substantially reduce the ability to match a suitable donor organ. The impact of perioperative transfusions on short- and long-term graft survival is less clear, and it is difficult to identify causality.

There have been numerous diagnostic, surgical, and therapeutic advances since the introduction of lung transplantation that have allowed for the expansion of the donor pool and sustenance of the recipient in anticipation of transplant.10-13 Extracorporeal membrane oxygenation (ECMO) is now used extensively throughout the peritransplant period. Preoperatively, ECMO has been described as a bridge-to-lung transplant. Intraoperatively, the use of veno-venous ECMO is established to support isolated respiratory failure or poorly tolerated one lung ventilation, while veno-arterial ECMO is established as...
an alternative to cardiopulmonary bypass (CPB) either for select patients or a preferred surgical approach in many centers. Postoperatively, patients may be offered ECMO support for PGD. Extracorporeal life support, with implicit cannulae placement, inflammatory response, and anticoagulation, has significant implications on bleeding, coagulopathy, and subsequent risk for transfusion.

Currently, there are few perioperative guidelines to direct transfusion practices in single or bilateral lung transplantation. In this article, we will review the currently available literature, which is mainly single-center, retrospective, or observational trials of limited sample size that identify relationships between short- and long-term outcomes and transfusion in the peritransplant period, risk factors for increased transfusion during lung transplantation, the use of CPB compared with ECMO with regard to transfusion requirement, the use of hemostatic agents including coagulation factor concentrates and antifibrinolics, and goal-directed transfusion and coagulation-monitoring strategies in lung transplantation surgery.

Transfusion and Primary Graft Dysfunction/Acute Lung Rejection

Primary graft dysfunction\textsuperscript{14} is a form of severe lung injury that occurs in the immediate posttransplant period and is defined by the International Society of Heart and Lung Transplantation as the presence of pulmonary edema and a decreased PaO\textsubscript{2} (partial pressure of oxygen)/FiO\textsubscript{2} (fraction of inspired oxygen) ratio over the first 72 hours after transplantation. The incidence of PGD following transplantation is between 10\% and 30\%, and is the leading cause of early posttransplantation mortality and morbidity including increased ICU stay and prolonged mechanical ventilation.\textsuperscript{15} The pathophysiology of PGD is believed to be multifactorial, associated with ischemia/reperfusion injury, endothelial cell dysfunction, impaired coagulation/fibrinolysis, and alveolar epithelial damage.\textsuperscript{15-17}

Multiple studies have demonstrated that intraoperative large-volume packed RBC (pRBC) transfusion is associated with, and is an independent risk factor for PGD (Figure 1). Between 2002 and 2010, the Lung Transplant Outcomes Group conducted a multicenter, prospective cohort study across 10 US centers with 1225 patients to determine donor, recipient, and perioperative risk factors for the development of PGD.\textsuperscript{18} The prevalence of greater than 1 L RBC transfusion was 34\%, and in adjusted analysis, this was associated with a nearly 2-fold increased risk for the development of grade 3 PGD.

Pretransplant RBC transfusion is also associated with both PGD as well as greater mortality.\textsuperscript{19} A retrospective, propensity-matched US cohort study by Hayes et al\textsuperscript{19} identified pretransplant transfusion as a risk factor for all-cause mortality at 1 year. The incidence of pretransplant transfusion was 34\%, which was associated with an adjusted hazards ratio of 1.18.

The effect of RBC transfusion on long-term graft function and overall mortality, however, is less clear. One retrospective single-center study of 134 patients by Weber et al\textsuperscript{20} found that transfusion of \textgtr 4 U RBCs was associated with increased 1-year mortality, while larger studies by Ong et al\textsuperscript{21,22} found no significant difference in 3- and...
6-month graft function and overall mortality in patients that received large-volume RBC (>3 U) or fresh frozen plasma (FFP; >2 U).

Interestingly, a retrospective review of the United Network of Organ Sharing database by Borders et al\textsuperscript{23} in 2016 found that large-volume pRBC transfusion in the donor prior to lung donation was associated with increased early recipient mortality after transplantation. In this review of a total 16 255 donors, 8835 (54\%) donors had received at least one RBC transfusion prior to organ procurement. Lung transplant recipients with donors who had received massive transfusion, defined as greater than 10 units RBC, had significantly higher 30- and 90-day recipient mortality rates compared with donors who had received sub-massive transfusions. Whether this observed increase in early mortality is secondary to PGD, TRALI, or another process is unclear as the diagnosis of PGD was not controlled for in this study, though PGD is believed to be likely given that it is the leading cause of early posttransplant mortality.\textsuperscript{23}

There are several proposed mechanisms to explain the association between blood product transfusion and subsequent development of PGD. The pathophysiology of PGD appears to be similar to other forms of acute lung injury, and biomarkers that are altered in other pulmonary disease states, acute respiratory distress syndrome, and TRALI are also altered in PGD.\textsuperscript{16,17,24} One biomarker for acute lung injury is the soluble receptor for advanced glycation end products (sRAGE). RAGE is a ubiquitously expressed receptor that binds pro-inflammatory molecules and is abundantly located in alveolar epithelial type 1 cells. sRAGE is released into alveolar and plasma compartments in the setting of acute lung injury and is a measurable factor of alveolar epithelial injury. Between 2003 and 2007, Christie et al\textsuperscript{25} conducted a multicenter, prospective cohort study of 317 lung transplant recipients and found that increased sRAGE in the 6- and 24-hour period following transplantation was associated with the subsequent development of PGD. Increased sRAGE levels were also correlated with RBC transfusion in this study. Stored RBCs express RAGE ligands,\textsuperscript{25} and RBC transfusion has been shown to augment RAGE expression, lung inflammation, and endothelial activation in animal models of RAGE.\textsuperscript{26} This evidence suggests a possible relationship between transfusion and the development of PGD that should be explored in further studies.

Additionally, the strong association between RBC transfusion and PGD suggests that TRALI and transfusion-donor antibody reactions against recipient leukocytes may also contribute to the development of PGD.

While it is difficult to separate large-volume RBC transfusion from the individual donor, recipient, or surgical conditions that necessitated transfusion in the first place, it is clear that RBC transfusion in the peritransplant period is associated with increased short-term morbidity and development of PGD. Efforts should be taken to minimize transfusion in this population when possible and other options should be explored prior to transfusion.

**Transfusion and All-Cause Mortality/Chronic Lung Rejection**

Lung transplantation is associated with the shortest survival among solid organ transplantation, with a median survival of only 5.8 years.\textsuperscript{27} Long-term survival after lung transplantation is restricted by chronic lung allograft dysfunction and progressive airflow decline. Chronic rejection is an immune-mediated process that is believed to have both an acute cellular rejection or T-cell mediated component as well as an antibody-mediated or B-cell-mediated component. Serum HLA antibody levels are used as a marker of possible antibody-mediated rejection, and patients with donor-specific HLA antibodies have a higher risk of developing bronchiolitis obliterans syndrome (BOS) and worse posttransplant survival.\textsuperscript{28,29}

Developing de novo HLA antibodies is known to negatively affect lung transplant outcomes, particularly with regard to increasing the risk of chronic lung allograft dysfunction. In 2013, Snyder et al\textsuperscript{28} conducted a single-center, prospective observational study of 441 patients with 10-year follow-up to test the association between serum HLA and long-term patient outcomes including BOS and mortality. HLA antibodies were detected in 32\% of patients and associated with increased risk for BOS and mortality (hazards ratio [HR] = 1.5, HR = 2.4 for donor-specific antibodies). Platelet transfusion within 30 days of lung transplantation was identified in the adjusted analysis as a positive risk factor for the development of HLA antibodies. Recently, Islam et al\textsuperscript{29} demonstrated an association between platelet transfusion in the posttransplant period and the development of de novo donor-specific HLA antibodies. In many medical centers, transfused platelets are frequently ABO-non identical.\textsuperscript{30} The role this may play in the formation of HLA antibodies in the lung transplantation population is not clear, though this may be a risk factor to investigate further.

Platelet transfusion has been repeatedly identified as an independent risk factor for increased short- and long-term mortalities following lung transplantation (Figure 1), a signal also present in patients undergoing cardiac surgery and liver transplantation.\textsuperscript{21,31,32} A retrospective single-center study by Ong et al\textsuperscript{21} of 311 bilateral lung transplant recipients found no difference in 1-year mortality based on the amount of RBC or FFP transfused, and a HR of 2.3 for 1-year mortality in patients who had received greater than 1 unit of platelets intraoperatively. Zalunardo et al\textsuperscript{33} also noted increased in-hospital mortality in the immediate posttransplant period in patients who had received...
platelets. Notably, this association was independent of the intraoperative use of cardiopulmonary bypass as well as the total heparin dose administered.

In addition to activating the coagulation system, platelets influence the recruitment and binding of leukocytes to vascular sites of inflammation, and platelet activation results in the release of vasoactive and inflammatory mediators. A prospective cohort study by Sternberg et al in 2008 found that soluble CD40-ligand and soluble p-selectin, both markers of platelet activation, were significantly elevated in off-bypass lung transplantation compared with nontransplant thoracotomy. This suggests that platelet activation is involved in early inflammatory processes in the lung allograft following ischemia and reperfusion. Additionally, among all blood products platelets have the greatest potential for bacterial or viral contamination, which may also contribute to early morbidity or mortality in immunosuppressed recipients.

The effect of other blood components including RBC, FFP, and cryoprecipitate on chronic lung rejection is not clear. A majority of the studies described above have not demonstrated a correlation between RBC or FFP and 1-year mortality, and one study by Mason et al suggests that chronic lung rejection may actually be attenuated by chronic RBC transfusion. In a retrospective review of 342 patients who underwent primary lung transplantation, increased RBC transfusion was associated with lower histologic grade of rejection on surveillance biopsies at serial time points over a 1-year period. Similarly, decreased chronic rejection rates have previously been associated with RBC transfusion in the context of renal and liver transplantation and this has been attributed to transfusion-related immunomodulation.

Across other solid-organ transplant populations, the impact of transfusion-related immunomodulation is complex and unclear, as allogeneic blood products can either induce alloimmunization or tolerance through leukocyte-mediated processes. Modern immunosuppressive medications and the standardized practice of using leukocyte-reduced blood products in transplant patients have likely greatly reduced any beneficial effects of transfusion in immune tolerance. In medical patients receiving repeated blood transfusions, HLA alloimmunization is well known. The humoral response to RBCs and subsequent HLA alloimmunization is linked to RBC presentation of class I antigen. Contamination by leukocytes and platelets, and certain RBC antigens serving as “look alike” antigens to particular class I HLA antibodies. We do not routinely screen patients for RBC alloimmunization posttransfusion; their role in solid organ transplant outcomes is unknown. If there is an association between perioperative RBC transfusion and de novo anti-HLA antibodies after lung transplantation, more frequent immune surveillance and suppression may be warranted.

**Risk Factors for Increased Transfusion Requirement in Lung Transplantation**

There are multiple risk factors for perioperative hemorrhage in lung transplant, including the indication for transplant, certain patient and procedural characteristics, preexisting or acquired coagulopathies, and extent of surgical trauma (Figure 2). In the lung transplantation population, additional considerations include the indication for transplant, chronic inflammatory or infectious processes, prior thoracotomy or sternotomy, and additional medical comorbidities such as severe pulmonary hypertension. Chronic anemia is common both before and after lung transplantation, and recipients remain at an increased risk for RBC transfusion long after the perioperative period. Mason et al list many possible contributing factors to chronic anemia in lung transplant recipients, including repetitive blood sampling, anemia of chronic disease, steroid-induced gastritis, iron deficiency, viral infections, and the myelosuppressive effects of immunosuppressive medications.

A bilateral, as compared with a single, lung transplant procedure is associated with an increased risk of intraoperative hemorrhage and need for allogeneic blood product transfusion in lung transplantation. Wang et al found that bilateral lung transplants are associated with an approximately 5-fold increase in RBC and FFP transfusion requirement compared with single-lung transplants, likely due to the increased surgical complexity and use of CPB or ECMO. Certain indications for lung transplant and preexisting pulmonary conditions are also associated with greater intraoperative blood loss and transfusion requirement during lung transplant. In particular, pleural adhesions, whether iatrogenic from prior surgery or pleurodesis are associated with increased blood loss. Other lung conditions such as lymphangioleiomyomatosis, bronchiectasis, and cystic fibrosis are associated with increased bleeding. Patients with cystic fibrosis and evidence of dominant inflammatory/infectious disease or pleural thickening on high-resolution computed tomography especially have a high transfusion requirement. Wang et al found that patients with a history of Eisenmenger’s syndrome also had a much higher transfusion requirement, possibly due to a combination of pulmonary hypertension, collaterals, and significant scarring from prior procedures.

In cardiac surgery there is a well-accepted relationship between increased blood loss, systemic anticoagulation, and CPB, with the amount of blood products transfused is correlated to total time on bypass. This relationship holds true for use of CPB in lung transplant procedures. CPB causes coagulopathy through multiple mechanisms, including dilution, heparinization, as well as activation of
clotting factors and degranulation of platelets, thrombin generation, and stimulation of fibrinolysis in the bypass circuit.

ECMO is used in lung transplantation as a bridge-to-transplant, hemodynamic support intraoperatively, and as a therapy for refractory hypoxemia or circulatory support in the postoperative period. Notably, on CPB blood may be directly salvaged and returned to the bypass circuit, while on VA ECMO, salvaged blood is hemoconcentrated prior to return to the patient. Bleeding is a common complication associated with ECMO, and blood contact with the ECMO circuit affects the coagulation cascade, platelet function, and fibrinolysis leading to coagulopathy. ECMO also requires heparinization, though targeted activated clotting times are typically not as high as in CPB. When compared with CPB, the impact of ECMO on transfusion requirement in lung transplantation is unclear and there is heterogeneity of the overall benefit in multiple studies. 

A recent meta-analysis of 7 retrospective observational studies compares ECMO versus CPB in a total of 785 lung transplant recipients, and showed a lower rate of bleeding and intraoperative transfusion in ECMO patients. Other benefits of ECMO compared with CPB include reduced rates of PGD, renal failure requiring dialysis, tracheostomy, and shorter hospital stay. A similar meta-analysis by Hoechter et al in 2017 also showed a tendency toward a benefit of ECMO in reducing the intraoperative amount of RBC, FFP, and platelets transfused, but these differences did not reach statistical significance. To date there have been no randomized studies or large, multicenter trials comparing the benefits of ECMO versus CPB with regard to transfusion requirement in lung transplantation.

### Use of Coagulation Factors and Antifibrinolitics: Aprotinin, Tranexamic Acid, Prothrombin Complex Concentrates, Recombinant Activated Factor VII

Antifibrinolytic agents include the serine protease inhibitor aprotinin and lysine analogs such as aminocaproic acid and tranexamic acid. These agents have been shown to reduce allogeneic blood product transfusion requirement in cardiac surgery, as well as overall blood loss and chest tube drainage. In the 2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines antifibrinolitics are strongly recommended as part of a blood conservation approach (Class 1, Level A recommendation), and many institutions support the use of antifibrinolitics for a wide range of procedures.

Prior to its removal from the market for concerns over stroke, renal failure, and mortality, several studies...
examined the effect of aprotinin on blood transfusion requirement in bilateral lung transplant procedures. Balsara et al. examination of a total of 215 patients in a single center over a 6-year period and found a statistically significant decrease in PRBC, FFP, and total blood products transfused in a subgroup analysis of their patients with COPD who had received aprotinin compared with those who did not. Notably, this study did not find a significant difference in transfusion requirement in their whole group analysis. Similarly, Herrington et al. conducted a single-center prospective randomized study of aprotinin on PGD, and also found a trend toward decreased transfusion requirement that did not reach statistical significance. This study was stopped early due to published concerns of renal toxicity caused by aprotinin.

There are few studies that specifically investigate the influence of tranexamic acid or aminocaproic acid on transfusion requirement in lung transplantation, though these agents have been previously studied in the orthopedic, cardiac, and liver transplant surgery populations and have an established association with decreased blood loss and decreased PRBC transfusion. Furthermore, their side effect profile at the clinical doses used for these procedures is generally favorable. In a proposed targeted bleeding management plan, Smith et al. encourages the use of tranexamic acid for all lung transplantation on CPB; whether these agents are beneficial in lung transplantation off of CPB warrants further investigation.

Recombinant Activated Factor VII

Recombinant activated factor VII (Novoseven; rFVIIa) is a vitamin K–dependent glycoprotein that has a structurally similar amino sequence as plasma-derived factor VII, and is activated. It is a dose-dependent, potent hemostatic agent and is used for numerous off-label indications such as massive hemorrhage in the setting of surgery, trauma, or liver disease. Administration of rFVIIa is associated with an increased risk of arterial thromboembolic events such as stroke and myocardial infarction and should only be administered after consideration of these potential adverse effects. Administration of this drug to patients on mechanical circulatory support should be avoided wherever possible, due to risk of pump thrombosis.

A small, single-center retrospective study by Bhaskar et al. examined patients undergoing lung transplantation between 2005 and 2011 who received rFVIIa for uncontrolled bleeding following reversal of heparin in the operating room or for postoperative bleeding in the ICU. Administration of rFVIIa was associated with a significant decrease in overall blood loss and transfusion of all blood product components. Important, none of the patients in this small cohort was on mechanical circulatory support at the time of administration of rFVIIa, the 1-year survival for this group was 95%, and there were no mortalities attributed to use of rFVIIa.

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) are hemostatic agents that are derived from pooled plasma and 4-factor PCCs contain vitamin K–dependent clotting factors II, VII, IX, and X that are not activated. PCCs were originally developed for the treatment of hemophilia B, and both 3-factor PCC (II, IX, X) and 4-factor PCC (II, VII, IX, X) are commercially available. Four-factor PCC use has expanded to include the urgent reversal of warfarin, and has shown to be efficacious in heart transplantation. PCCs have several advantages over FFP; it has a shortened time to correction of a supratherapeutic INR, there is no risk of transfusion reactions such as TRALI, and PCCs are small-volume agents, which allow for faster administration and a decreased fluid load. Again, extreme caution must be taken with administration of these drugs while the patient is on mechanical circulatory support, as the risk of clotting and thromboembolism of the circuit may outweigh the benefit.

The use of both 3-factor and 4-factor PCC has been studied in the management of severe perioperative bleeding as well as for coagulopathy in the context of orthotopic liver transplant; however, there is only limited evidence to support their use in these settings. PCCs are associated with thrombotic complications including venous thromboembolism, disseminated intravascular coagulation, and myocardial infarction. To date there are no studies that specifically investigate the use of PCC in lung transplantation; however, it has been incorporated into several goal-directed transfusion algorithms, which are discussed in the following section.

Transfusion Strategies/Coagulation Monitoring

Targeted blood management approaches in lung transplant include the use of point-of-care coagulation testing (POCCT) such as rotational thromboelastometry (ROTEM), goal-based transfusion criteria, the use of blood-conserving medications such as antifibrinolytics, and blood scavenging systems to minimize blood loss. A concerted effort to avoid the use of intraoperative CPB or ECMO and subsequent heparinization when possible is also important to minimize acquired-coagulopathy and subsequent blood loss during the procedure.

POCCT-based transfusion strategies have been successful in reducing overall blood loss and transfusion requirement in cardiac surgery on CPB, and this approach may be beneficial in lung transplants performed on CPB, as well. Karkouti et al. conducted a large, multicenter
stepped-wedge cluster randomized trial on the effects of a transfusion algorithm on medical and surgical patients across 12 medical centers and demonstrated an overall reduction in number of RBC and platelet transfusion as well as a reduction in overall blood loss. The algorithm incorporated the use of ROTEM and platelet-aggregometry assays after rewarming and discontinuation of CPB, as well as accurate blood loss measurements. Of note, the time point that triggers providers to check these tests, rewarming, typically does not occur in lung transplantation because patients are intentionally kept warm. Notably, this algorithm did not specify a strict hemoglobin-goal for RBC transfusion, nor did it encourage the use of antifibrinolytics or cell-savage. Furthermore, while the study encouraged providers to follow this transfusion algorithm, it did not enforce utilization. These decisions were made deliberately to allow for a more pragmatic approach that allowed for flexibility of individual and hospital-specific practices.

To date there has only been one study of the use of POCCT-based transfusion strategies in bilateral lung transplantation.69 Smith et al conducted a single-center, retrospective study comparing 47 bilateral lung transplant procedures that were performed at the usual standard of care to a group of 46 bilateral lung transplant procedures which were performed after the introduction of POCCT and a goal-directed transfusion algorithm. This algorithm included antifibrinolytic use, and goal-directed therapy based on ROTEM + platelet aggregometry assays as well as hemoglobin, temperature, pH, and calcium. All the lung transplant procedures in this study were conducted on CPB, and patients who required preoperative or postoperative extracorporeal support were excluded. The implementation of this transfusion strategy was associated with a significant decrease in the number of patients requiring allogeneic blood products, including pRBC, FFP, and platelets. A cost-analysis was also performed, which demonstrated an overall reduction of cost after the introduction of this strategy.

In certain high-risk populations there may be additional interventions that can be employed to avoid transfusion altogether.68 In a matched case-control study, Partovi et al describe the approach taken for a transfusion-free single-lung transplant in 2 Jehovah’s Witness (JW) recipients who were unable to receive allogeneic blood products. The blood-conserving strategies that were employed included optimizing preoperative hemoglobin levels through the use of erythropoietin injections and B12/iron supplementation, avoiding the intraoperative use of CPB/ECMO, and utilizing cell-scavenging throughout the procedure. Postoperative strategies included limiting blood draws, encouraging early oxygen and intravenous fluid resuscitation, and avoiding antiplatelet/anticoagulation medications. When these 2 cases were compared with a matched control group of 10 non-JW single-lung transplant recipients, the JW group was found to have increased postoperative hemoglobin levels and decreased postoperative creatinine levels, without any adverse events noted.

There is currently a lack of investigation of the efficacy of POCCT or goal-directed transfusion strategies in reducing transfusion requirements in lung transplantation performed off CPB. A randomized control study would be especially beneficial in this population in order to determine if these algorithms should be used to guide transfusion practices.

**Conclusion**

Allogeneic blood product transfusion, specifically large-volume RBC transfusion and platelet transfusion, is associated with PGD and mortality in lung transplant recipients in multiple studies. It is possible that large-volume transfusion is a marker of disease severity and increased overall risk. Although the associations between transfusion and poorer outcomes are clear, attributing worsened outcomes to transfusion is impossible with a retrospective and observational study design, in the setting of institutional and provider variability. The need to transfuse is intertwined with a difficult lung transplant procedure, the use of mechanical circulatory support, and need for systemic anticoagulation, and difficult recovery. The majority of available data comes from single-center cohort studies, some of which precede the ECMO era. While there is strong evidence linking platelets and PGD through the biomarker sRAGE, the mechanism of how large volume-RBCs directly cause increased mortality, short- or long-term graft function is unclear.

There are a number of additional risk factors associated with increased perioperative hemorrhage and subsequent transfusion requirement in the lung-transplant population; these factors should be acknowledged by providers and efforts should be taken to minimize blood loss where possible. The use of antifibrinolytics, coagulation factors, and POCCT/goal-directed transfusion strategies may help reduce allogeneic blood product usage. Future investigations should help clarify the overall benefit of these interventions. Larger, multicenter studies are needed to better describe the current practice patterns of transusing allogeneic blood products, better characterize the risks associated with peritransplant transfusion, and understand how each blood component may influence short- and long-term outcomes.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

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