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Original Article

Incidence of Massive Transfusion and Overall Transfusion Requirements During Lung Transplantation Over a 25-Year Period

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Objective: To establish the incidence of massive transfusion and overall transfusion requirements during lung transplantation, changes over time, and association with outcome in relation to patient complexity.
Design: Retrospective cohort study.
Setting: University hospital.
Participants: All 514 adult patients who underwent transplantation from 1990 until 2015.
Interventions: None.
Measurements and Main Results: Patient records and transfusion data, divided into 5-year intervals, were analyzed. The incidence of massive transfusion (>10 units of red blood cells [RBCs] in 24 h) was 27% and did not change over time, whereas the median (interquartile range) transfusion requirement in the whole cohort decreased from 8 (5-12) to 3 (0-10) RBCs ($p < 0.001$). In patients transplanted from the intensive care unit, the incidence of massive transfusion increased over time from 25% to 54% ($p = 0.04$) and median transfusion requirements from 4.5 (3-8.5) units to 14.5 (5-26) units of RBCs ($p = 0.03$). Multivariable analysis showed that circulatory support, pulmonary hypertension, re-transplantation, cystic fibrosis, Eisenmenger syndrome, bilateral transplantation, and low body mass index were associated with massive transfusion. Patients with massive transfusion had more primary graft dysfunction grade III at 0, 24, 48, and 72 hours ($p < 0.001$), higher 30-day mortality (13% *v* 4%; $p < 0.001$), and lower 5-year survival (hazard ratio 3.67 [95% confidence interval 1.72-7.85]; $p < 0.001$).

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Conclusion: The incidence of massive transfusion did not change over time, whereas transfusion requirements in the whole cohort decreased. In patients transplanted from the intensive care unit, massive transfusion and transfusion requirements increased. Massive transfusion was associated with poor outcome.

Key Words: lung transplantation; massive transfusion

LUNG TRANSPLANTATION is an established therapy for patients with end-stage lung disease, but remains a high-risk procedure. Substantial blood loss may occur, and this can result in massive transfusion of blood and blood products. The risks of these transfusions are well-known and include an increased risk of infection and transfusion-related acute lung injury (TRALI), which may especially affect lung transplantation recipients. However, there are no data available on the incidence of massive transfusion and its effects on outcome. In addition, little is known about the incidence and quantity of transfusions during lung transplantation and possible changes over time.

It may be expected that the use of blood products decreases as a result of better patient selection, improved team performance and surgical technique, a more restrictive transfusion policy, intraoperative blood salvage, and point-of-care treatment of coagulation disorders. Several studies have reported a decrease in red blood cell (RBC) requirements over time for different surgical procedures, including cardiac surgery.[1,2] On the other hand, more complex patient cases might be accepted for transplantation, with the potential to increase the use of blood products.

The primary objective of this retrospective study was to establish the incidence of massive transfusion and the overall transfusion requirements during lung transplantation. The changes over time and the association with outcome in relation to the patient's underlying condition also were evaluated.

Methods

For this retrospective study, data of all 566 patients who underwent lung transplantation at the University Medical Center Groningen, the Netherlands, from the start of the program in 1990 until January 2015 were used. This period was stratified into 5-year time intervals. The medical ethics committee approved the study and waived patient consent because this was a retrospective study on existing patient data.

Patient characteristics, transfusion records, length of intensive care stay, primary graft dysfunction (PGD), and mortality data were analyzed. For each patient, the number of RBC concentrates, fresh frozen plasma (FFP), and platelets transfused within the first 24 hours were recorded, including the units given during the surgery and in the intensive care unit (ICU). Transfusion of >10 U of RBCs in the first 24 hours was defined as massive transfusion. This definition is widely accepted[3-5] and is proposed in the universal definition of perioperative bleeding in cardiac surgery.[6] In the group of patients with massive transfusion, the incidence of patients requiring more than 20 U of RBCs in the first 24 hours also was recorded.

Primary graft dysfunction was defined as severely reduced oxygenation (if ratio of partial arterial oxygen pressure to fraction of inspired oxygen was less than 200) with evidence of radiographic infiltrates and without other obvious cause.[7] PGD was analyzed at 0, 24, 48, and 72 hours after transplantation.

All transplantations were performed by a dedicated team of surgeons and anesthesiologists. Single lung transplantation was performed through either a right or left dorsolateral thoracotomy. Bilateral transplantations were performed through a clam-shell incision. The decision to use circulatory support (cardiopulmonary bypass [CPB]) or in later periods extracorporeal life support [ECLS]) was made either in advance (eg, Eisenmenger syndrome; severe pulmonary hypertension) or during the surgery in case of severe hemodynamic or respiratory instability. When CPB was used, heparin was given as necessary to maintain an activated clotting time (ACT) of at least 400 seconds. When ECLS was used, an ACT of 150 to 200 seconds was maintained. After the procedure, protamine was titrated to achieve baseline ACT values.

It was difficult to assess the patient's disease severity retrospectively. Currently, the lung allocation score (LAS) is used, but this was only available in the authors' institution from 2014. To measure disease severity the following dichotomous division in patients was used: those who were transplanted from the ICU and those transplanted from elsewhere. In the Netherlands, there is a restrictive admission policy to the ICU. Patients are only admitted in case of severe respiratory or hemodynamic deterioration requiring artificial ventilation, inotropic or vasoactive support, or ECLS. A second measure of disease severity was high urgency (HU) status according to the criteria of Eurotransplant.[8] These criteria were adhered to strictly, and HU status was only granted after external audit.

Transfusion of blood products was based on the Dutch national transfusion protocol. This protocol did not change over time for the intraoperative administration of blood products.[3] Generally, RBCs were transfused when hemoglobin levels were <8.0 g/dL. However, the protocol allowed a transfusion trigger of 9.6 g/dL in patients with severe pulmonary or circulatory impairment. This was at the discretion of the surgical team or the intensivist. FFP was transfused to correct coagulation factor levels based on a prothrombin time 1.5 times normal, and platelet concentrates were given if the platelet count was $<75{,}000 \times 10^9$/L. In case of acute severe bleeding, FFP and platelets were given as necessary to correct primary hemostasis. Coagulation point-of-care testing was available from 2000 onwards (TEG; Haemonetics, Braintree, MA) or RoTEM (TEM International, Basel, Switzerland). Over the years, tranexamic acid (1995), fibrinogen (2010), and recombinant factor VIIa (2011) were introduced. Aprotinin was not used because the authors demonstrated that it only had a small

effect during lung transplantation.[9] Intraoperative cell salvage was used routinely from 1998.

Statistics

The transfusion data did not have a normal distribution. Median values with interquartile ranges are reported, and the Mann-Whitney test was used for comparisons. The primary end point was the incidence of massive transfusion as previously defined. The secondary end points were PGD grade III at any time point (0, 24, 48, and 72 h after surgery); length of ICU stay; 30-day mortality; and 5-year survival. The authors first performed a stepwise logistic analysis to determine which variables would affect these outcomes. For massive transfusion, 5-year periods, sex, age, body mass index (BMI), preoperative hemoglobin level, diagnosis, ECLS preoperatively or postoperatively, HU status, single and bilateral transplantation, preoperative use of mechanical ventilation, use of CPB, and duration of surgery were analyzed. For model selection, an entry p value of 0.10 was used and the variable remained in the model when the p value was < 0.05. The model selection also included all possible 2-way interaction terms, but it always kept the model hierarchical. Except for the survival analysis, the best model was selected based on Akaike's corrected information criterion. For 5-year survival, Cox proportional hazard analysis was used and included ICU stay, hospital length of stay, readmission, and rejection. Collinearity of the variables in the model was investigated with the Pearson correlation coefficient. Model selection was performed with the procedures HPGENSELECT and PHREG from SAS, Version 9.4 (SAS Institute, Cary, NC), and correlations were calculated with the procedure CORR. A p value < 0.05 was considered to be significant.

Results

General Study Population

For the present study, 566 patients who underwent single or bilateral lung transplantation in the authors' institution in the selected time period were identified. Thirty-one children (<18 years old), 16 patients with combined heart-lung transplantation, and 5 patients with a combined lung-liver transplantation were excluded. This resulted in 514 patients. Annually, a mean of 34 transplantations were performed during the last time interval. Patient demographics and preoperative characteristics are shown in Table 1.

Table 1
Patient and Perioperative Characteristics

	All Patients (n = 514)	Massive Transfusion (n = 136)	No massive Transfusion (n = 378)	p Value
General characteristics				
Age	50 [39-57]	44 [31-52]	52 [43-58]	< 0.001
Sex (male), n (%)	259 (50)	70 (51)	189 (50)	0.84
Body mass index	22.3 [19.7-24.8]	20.6 [18.5-24.1]	22.7 [20.3-24.9]	< 0.001
Disease severity				
Transplanted from ICU, n (%)	68 (14)	28 (22)	40 (11)	0.15
Transplanted from location other than ICU, n (%)	446 (86)	108 (78)	338 (89)	< 0.001
High urgency, n (%)	152 (30)	58 (43)	94 (25)	0.01
Preoperative mechanical ventilation, n (%)	27 (5)	15 (11)	12 (3)	< 0.001
Underlying diagnosis				
COPD/α1-antitrypsin deficiency, n (%)	237 (64)	29 (21)	207 (55)	< 0.001
Pulmonary fibrosis, n (%)	90 (17)	17 (12)	73 (19)	< 0.001
Cystic fibrosis, n (%)	91 (18)	39 (29)	52 (14)	0.17
IPAH, n (%)	25 (5)	17 (13)	8 (2)	0.07
Bronchiectasis, n (%)	24 (5)	8 (6)	16 (4)	0.10
Eisenmenger syndrome, n (%)	23 (4)	10 (7)	13 (3)	0.53
Retransplantation, n (%)	15 (3)	11 (8)	4 (1)	0.07
Bronchiolitis obliterans (not retransplantation), n (%)	10 (2)	5 (4)	5 (1)	1.00
Perioperative characteristics				
Red blood cells (U)	4 [1-10]	16 [12-25]	2 [0-5]	< 0.001
Plasma (U)	2 [0-6]	8 [6-16]	0 [0-4]	< 0.001
Platelets (U)	0 [0-1]	10 [5-20]	0 [0-0]	< 0.001
Surgery time (U)	368 [276-473]	509 [407-644]	331 [250-415]	< 0.001
Bypass time (min)	245 [157-334]	307 [224-387]	192 [127-265]	< 0.001
Length of stay in the ICU (d)	6 [3-14]	12.5 [6.5-29]	5 [3-8]	< 0.001
30-day mortality, n (%)	34 (7)	18 (13)	16 (4)	< 0.001
Reexploration, n (%)	88 (17)	78 (58)	10 (3)	< 0.001
ECLS preoperatively/postoperatively, n (%)	32 (6)	23 (17)	9 (2)	< 0.001

NOTE. Data are presented as median and interquartile range unless otherwise stated. Percentages are given within each group. The p values refer to massive transfusion versus no massive transfusion. One transfusion bag of platelets consisted of 5 donor units.
Abbreviations: COPD, chronic obstructive pulmonary disease; ECLS, extracorporeal life support; ICU, intensive care unit; IPAH, idiopathic pulmonary arterial hypertension.

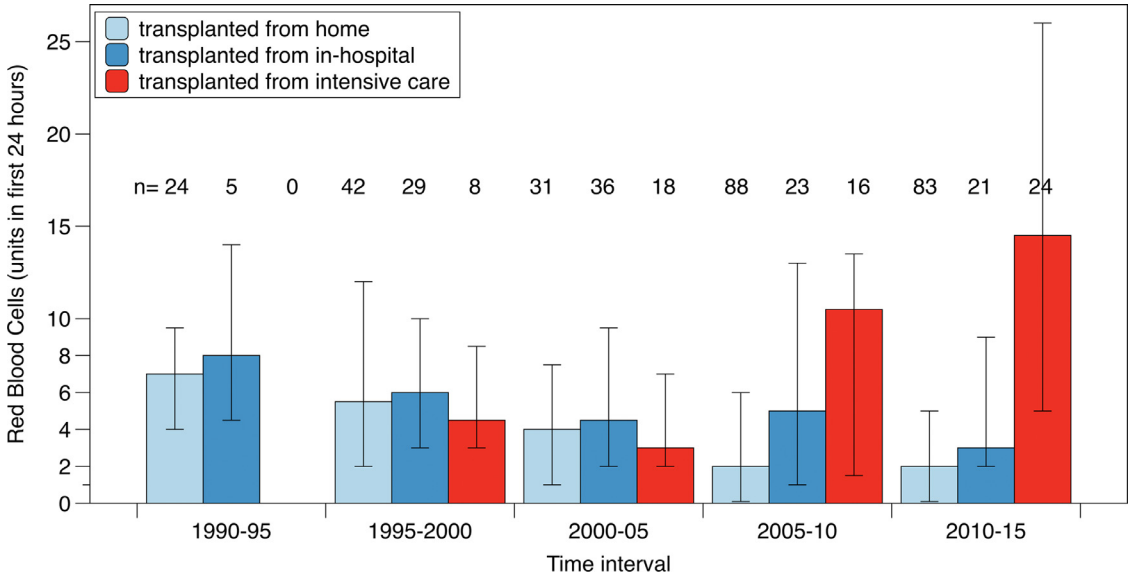

Fig 1. Bar graph of median red blood cell use in the first 24 hours over the years of lung transplantation in patients transplanted from home, from in-hospital, or from the intensive care unit. Data are presented as median with interquartile range. The number of patients in each group and in each period is given above the bars.

Compared with the database of the International Society of Heart and Lung Transplantation, patients with idiopathic pulmonary arterial hypertension (IPAH) and Eisenmenger syndrome were slightly overrepresented.

Patient disease severity also is shown in Figure 1. The percentage of patients transplanted from the ICU remained stable at 14%, except from the first period, when no patients were transplanted from the ICU. Over time an increasing number of patients with HU status were transplanted (from 3% to 43%; $p < 0.001$). From 2000 onwards, 27 patients (5%) were transplanted while receiving mechanical ventilation. In 2005 ECLS was introduced and used in 10 patients as a bridge to transplantation. Overall, 86 (17%) patients underwent surgical reexploration. There was no change in the reexploration rate over time. Reexploration occurred more when massive transfusion was present (see Table 1). Massive transfusion varied between 19% and 33% without trend over time. There was an increase in patients who required >20 RBCs in the last decade. In the last 5-year period these patients comprised 53% of the patients with massive transfusion (Fig 2). Massive transfusions increased over time from 25% to 54% for patients from the ICU ($p = 0.04$), whereas the incidence was 24% in the other patients, without change over time ($p = 0.16$). The postoperative hemoglobin level in the patients with massive transfusion was 9.0 ± 2.1 g/dL and did not change over time ($p = 0.14$). The preoperative and postoperative hemoglobin levels in the whole cohort according to diagnosis are shown in Table 2. There were no significant changes over time. Massive transfusion of RBCs also was accompanied by substantial transfusion of other

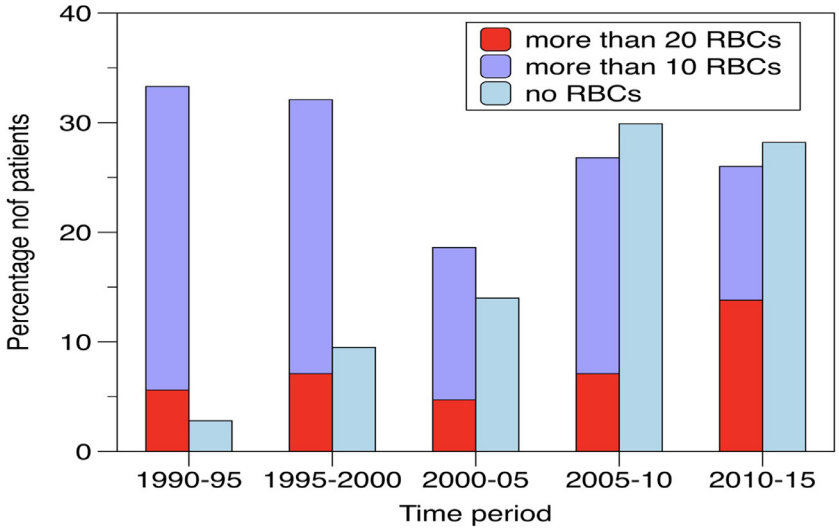

Fig 2. Incidence of massive transfusion (with the subgroup of more than 20 red blood cell in the first 24 h) and lung transplantation without transfusion over the transplantation period.

Table 2
Blood Transfusion Requirements in the First 24 Hours and Preoperative and Postoperative Hemoglobin Levels in Different Diagnosis Groups

Diagnosis:	Hb Preoperatively (mmol/L)	Hb Postoperatively (mmol/L)	RBC (U)	Stratified RBC Units Transfused in Patients, n (%)			
	Mean ± SD	Mean ± SD	Median [IQR]	0 U	1-5 U	5-10 U	10+ U
COPD	7.7 ± 1.2	6.4 ± 1.2	2 [0-6]	76 (32)	89 (38)	42 (18)	30 (13)
Cystic fibrosis	6.9 ± 1.1	6.0 ± 1.4	8 [3-15.5]	9 (10)	23 (25)	20 (22)	39 (43)
Pulmonary fibrosis	7.5 ± 1.3	6.2 ± 1.2	3 [1-8]	19 (21)	38 (42)	16 (18)	17 (19)
IPAH	8.2 ± 1.6	5.8 ± 1.2	13 [8-21]	0 (0)	4 (16)	4 (16)	17 (68)
Eisenmenger syndrome	8.3 ± 1.9	5.9 ± 1.0	8 [2-17]	1 (4)	7 (30)	5 (22)	10 (44)
Bronchiectasis	7.3 ± 1.0	6.2 ± 1.0	5.5 [3-12]	1 (4)	9 (38)	6 (25)	8 (33)
BOS/retransplantation	7.0 ± 1.4	5.6 ± 1.2	11 [3-18.5]	4 (17)	2 (8)	3 (12)	16 (64)

Abbreviations: BOS, bronchiolitis obliterans syndrome; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; RBC, red blood cells; SD, standard deviation.

blood products. The overall use of FFP and platelets concentrates is shown in Table 1. Over time there was a gradual increase in the ratios of FFPs and platelets to RBC transfusions when massive transfusion was present. In the last period, this approached a 1:2 ratio for FFP to RBC. The use of specific coagulation factors, including surgical hemostatic agents, also increased in the last periods. From 2010 onwards, 46 patients received fibrinogen (37 had massive transfusion) and 6 patients received recombinant factor VIIa (all had massive transfusion). Tranexamic acid was used in 131 patients (48 had massive transfusion).

Among the full set of variables used to predict the clinical outcomes, the highest absolute Pearson correlation was 0.45 for the use of CPB and massive transfusion. There was no issue with collinearity among the predictors.

Using multivariable analysis, the factors that predicted massive transfusion were identified. The most important factors were use of circulatory support, specific diagnosis, low BMI, and bilateral transplantation (Table 3). These factors are presented in detail in the following sections.

Circulatory Support

Overall, CPB was used in 50% of the patients and included 62% for patients transplanted from the ICU and 48% for the other patients ($p = 0.04$). The use of CPB decreased from 83% in the first period to 35% in the last period ($p < 0.001$). Massive transfusion occurred in 46% of patients transplanted with CPB, whereas this was the case in only 7% of patients transplanted without CPB ($p < 0.001$). Patients transplanted with CPB had higher intraoperative transfusion requirements than patients transplanted without CPB (median 4 [2-9] *v* 0 [0-2] RBCs). These higher transfusion requirements continued into the immediate postoperative period (median 3 [1-8] *v* 0 [0-1] RBCs). From 2005 onwards, ECLS was used in 32 patients, including preoperatively as a bridge to transplantation (n = 10) and/or in the immediate postoperative period. These patients had a median use of 18 (7-35) RBCs. The majority of them (n = 22 [69%]) required massive transfusion and 13 (40%) of these patients used more than 20 RBCs in the first 24 hours.

Table 3
Factors Predictive for Blood Use of >10 Units of RBC

Variable		Odds Ratio	95% CI	p Value
BMI (kg/m^2)	<18	2.46	[1.67-5.20]	0.018
	25-30	1.64	[0.83-3.23]	0.153
Diagnosis	Cystic fibrosis	3.56	[1.81-7.01]	< 0.001
	Pulmonary fibrosis	0.99	[0.44-2.23]	0.977
	IPAH	11.5	[3.63-36.6]	< 0.001
	Eisenmenger syndrome	2.82	[1.00-7.94]	0.049
	Bronchiectasis	1.81	[0.60-5.51]	0.295
	BOS/retransplantation	10.5	[3.51-31.6]	< 0.001
Bilateral *v* unilateral transplantation		3.70	[1.53-8.98]	< 0.001
Circulatory support		8.78	[4.61-16.7]	< 0.001
Preoperative mechanical ventilation without circulatory support		0.49	[0.05-4.99]	0.366
Preoperative mechanical ventilation and circulatory support		7.51	[1.75-32.3]	0.007

NOTE. Diagnosis of chronic obstructive pulmonary disease and normal body mass index were taken as reference category.
Abbreviations: BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CI, confidence interval; IPAH, idiopathic primary pulmonary hypertension.

Median blood use was 23 (9-44) versus 15 (6-26) units when venoarterial (VA) (n = 20) or venovenous ECLS (VV) (n = 12) was used, but this difference was not significant (p = 0.38). There was no difference in blood use when ECLS was used only postoperatively (18 [6-40] RBCs) or patients were transplanted while on ECLS preoperatively (18 [10-30] RBCs; p = 0.91).

Diagnosis

The median and stratified blood use per diagnosis is shown in Table 3. There were no major changes in the diagnoses leading to transplantation during the study. The overall incidence of massive transfusion was 27%. It occurred in 68% of the patients with IPAH, in 62% of the patients with bronchiolitis obliterans syndrome or re-transplantation, and in 43% of the patients with cystic fibrosis. This incidence did not change over time. In patients with chronic obstructive lung disease (COPD), median blood use decreased from 7.5 (3.5-8.5) to 2 (0-4) units over time ($p < 0.001$). Patients with COPD increasingly were transplanted without any transfusion of RBCs (from 0% to 38%; p = 0.001), although the percentage of these patients with HU status also increased (from 0% to 20%; $p < 0.001$).

BMI

The average BMI was 22.4 ± 3.7. This was different across the diagnosis groups ($p < 0.001$)—lowest in patients with cystic fibrosis (19.5 ± 2.5) and highest in patients with pulmonary fibrosis (24.9 ± 3.8). Low BMI occurred not only in patients with cystic fibrosis (35%) but also in patients with bronchiectasis (25%) and patients with bronchiolitis obliterans syndrome/retransplantation (25%). In patients with normal BMI, median blood use was 4 (1-9) RBCs and with a BMI <18 it was 5 (3-17) RBCs with an incidence of massive transfusion of 44%. However, when the BMI was between 25 and 30, the median was only 2 (0-8) RBCs with an incidence of massive transfusion of 22%.

Unilateral and Bilateral Lung Transplantation

Massive transfusion occurred in 11% of patients with unilateral transplantation and in 31% of patients with bilateral transplantation. Patients with unilateral transplantation required fewer RBCs regardless of whether CPB was used (median 1 [0-4] *v* 5 [2-12] RBCs; $p < 0.001$). Fifty percent of patients who underwent unilateral lung transplantation did not require RBCs, whereas this was the case in only 14% of patients who underwent bilateral transplantation (p = 0.001). Unilateral transplantation decreased during the study period from 33% to 16% (p = 0.003).

Outcome

Acute rejection was not more frequent in patients with massive transfusion (45% *v* 40%; p = 0.69). PGD grade III was higher in patients with massive transfusion ($p < 0.001$) (Fig 3).

The overall median ICU stay was 6 (3-14) days. This was 10 (4-29) days for patients transplanted from the ICU and 6 [3-11] days for patients transplanted from elsewhere. Median ICU stay was 3 (3-5) days when transfusion was not necessary compared with 12 (6-29) days in patients with massive transfusion. There was no change in median ICU stay over the years.

The overall 30-day mortality rate was 7%. This was 12% for patients transplanted from the ICU and 5% for patients who were transplanted from elsewhere. There were no major changes over time. The 30-day mortality increased to 14% in patients with massive transfusion and in the subgroup of patients with transfusion >20 RBCs to 25%. The final multivariate model for 30-day mortality is shown in Table 4. Massive transfusion and circulatory support were not only independent risk factors for 30-day mortality but also for 5-year survival. The hazard ratios (with 95% confidence interval) were 3.67 (1.72-7.85; $p < 0.001$) for massive transfusion and 4.34 (1.64-11.5; p = 0.003) for circulatory support. This association between survival and massive transfusion

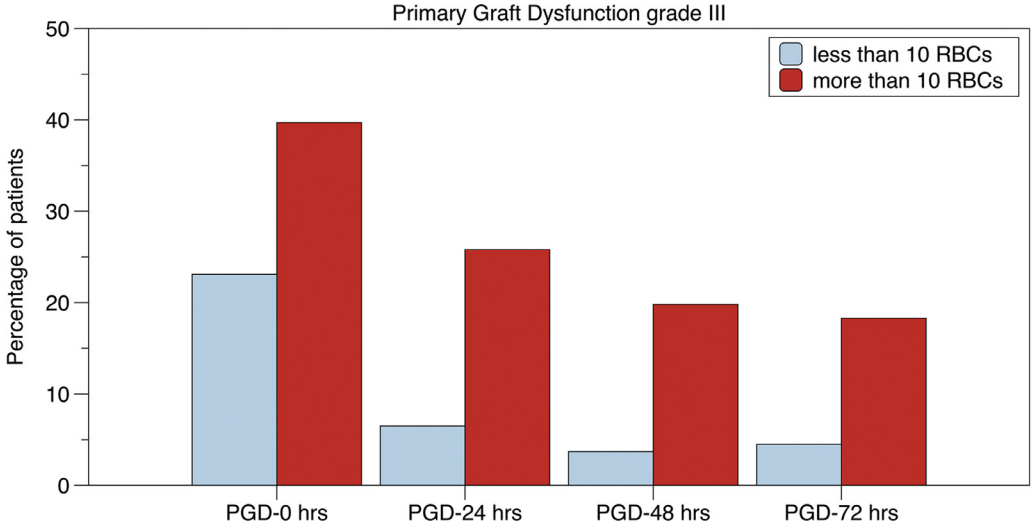

Fig 3. Incidence of primary graft dysfunction grade III at different time points after lung transplantation with and without massive transfusions.

Table 4
Factors Predictive for 30-Day Mortality

Variable	Odds Ratio	95% CI	p Value
Sex (male v female)	2.14	[0.95-4.79]	0.066
Transfusion >10 U	2.48	[1.08-5.73]	0.033
Circulatory support	8.91	[2.74-29.0]	< 0.001
Duration of surgery without circulatory support	0.99	[0.98-1.00]	0.174
Duration of surgery with circulatory support	0.97	[0.95-0.99]	< 0.001

Abbreviation: CI, confidence interval.

remained significant after exclusion of patients who died within the first year after transplantation.

Discussion

Over 25 years of lung transplantation, the incidence of massive transfusion did not change despite an overall gradual decrease in RBC use. Massive transfusion occurred in 27% of the patients in the present study, with a substantial increase in median RBC use in these patients over time. The incidence of massive transfusion was significantly greater in patients transplanted from the ICU compared with other patients. Because the authors' transfusion protocol remained unchanged and postoperative hemoglobin levels were not different over time, the most likely explanation for this is a greater blood loss. Unfortunately, the authors could not differentiate this blood loss between predominant vascular or hemostatic problems.

The gradual decrease in RBC use in the whole cohort over time was caused by an increasing number of patients who were transplanted without any transfusion. This occurred in more than one-third of the patients in the last time period, mainly patients with COPD. Despite an increasing percentage of HU patients in the COPD group over time, the use of CPB decreased. This most likely was due to increased experience and improved team performance.

Patient disease severity and complexity were difficult to establish retrospectively. The LAS was introduced in the last year of the study and retrospective analysis was not possible. The authors instead decided to differentiate patients transplanted from the ICU and the other patients. The HU status of the patient also was used and demonstrated an increase over time. An LAS score applied to these factors appeared to accurately predict survival.[10]

CPB use decreased over time. In the last time period, CPB was used in 35% of the cases, which is similar to what other centers have reported.[11,12] In the literature the transfusion requirements in transplantations with CPB varied between a mean of 4 RBCs in the first 24 hours and a mean of 12 RBCs intraoperatively.[11,12] In a study with standard use of CPB, a median of 3 RBCs in the first 24 hours was reported.[13] The present study's data show higher transfusion requirements when CPB was used, which continued into the postoperative period. Unfortunately, the authors could not differentiate between predominant vascular or hemostatic problems. It might be that the conditions of the present study's patients transplanted with CPB were more complex; however, coagulation problems due to extracorporeal circulation may have played a role. From 2014 onwards CPB was replaced with ECLS during the surgery, if this was possible. Several studies have demonstrated that ECLS during surgery was at least equal in outcome to CPB.[14-18] Preoperative use of ECLS as a bridge to transplantation or postoperative ECLS as prolonged cardiopulmonary support into the postoperative period was associated with massive transfusion in almost 70% of the patients. These are the most complex patients and, in addition to the necessary anticoagulation treatment, they also frequently experience the deleterious effects of ECLS on platelet function and hemostatic factors. VA-ECLS is associated with more blood use than VV-ECLS.[19] In the present study, no difference in blood use in patients who underwent VA-ECLS or VV-ECLS was found, but there was a small group of patients and blood use was recorded only in the first 24 hours.

To the authors' knowledge this is the first study with a focus on the incidence of massive transfusion during lung transplantation. Several studies have addressed strategies to reduce blood transfusion, such as use of aprotinin or recombinant factor VIIa.[20,21] These approaches underline that perioperative blood loss and transfusion requirements are real problems, but surprisingly few studies address blood transfusion requirements during lung transplantation. Most have a small number of patients and date from the early period of lung transplantation.[22,23]

Only 2 studies reviewed blood transfusions in a comparable patient population over a longer period.[11,13] In the first study, only mean RBC use was reported, and blood transfusion amounts had a Poisson distribution.[24] Age, bilateral transplantations, use of CPB, or transplantation for Eisenmenger syndrome and cystic fibrosis were reported to be predictors for the need of additional blood products, and changes in blood use over the years were not observed.[11] In the present analysis, blood use changed over the years and age did not appear to be a predictive factor for massive transfusion, although patients with massive transfusion generally were younger. In the second study, CPB was used in all transplantations and a median of 3 RBCs (range 0-40) was used.[13] The incidence of massive transfusion was not reported, but the range of RBCs suggests that massive transfusion did occur. The dichotomous analysis in the second study showed that RBC transfusion had no effect on 1- and 10-year mortality. The present study found that massive transfusion reduced 5-year survival, which is explained by the higher cut-off value (10 RBCs). The present study's findings are supported by another study in which intraoperative transfusion of more than 4 RBCs was an independent predictor of mortality.[12]

In the present study, patients with IPAH, retransplantation, cystic fibrosis, and Eisenmenger syndrome were at the highest risk for massive transfusion among different pulmonary pathologies. The authors suppose that these patients are, due to their underlying pathology and progress during conservative and supportive therapy, accepted for transplantation in a more severe stage of their disease. This results in more technically challenging surgeries, which are accompanied with more bleeding. In addition, in most of these patients the use of circulatory support was

inevitable, and ECLS was increasingly used in the preoperative or postoperative period.

Little is known about the influence of BMI on perioperative blood use. The influence of BMI on mortality was demonstrated in a recent meta-analysis that showed that patients who are either underweight or obese have a higher risk of post-transplantation mortality than recipients with a normal BMI.[25] Interestingly, the present study found that mildly obese patients had the lowest transfusion requirement. This could be a reflection of better overall condition. A low BMI may reflect sicker patients because, for example, patients with cystic fibrosis not only had the lowest BMI, but also the lowest preoperative hemoglobin levels. However, the selection of BMI in the prediction model was not caused by any form of collinearity, which supports the study's finding that a low BMI was an independent factor for massive transfusion.

Bilateral transplantation has been reported as a risk factor for increased transfusion requirements.[11,22,23] However, currently there is agreement that lungs should be transplanted bilaterally when possible because of better long-term survival.[26] This puts unilateral transplantation and its effects on massive transfusion in a different perspective.

Massive transfusions are accompanied by the transfusion of FFPs and platelet concentrates. The ratio of RBC to FFP and platelets gradually shifted over time in favor of plasma and platelets in accordance with current massive transfusion protocols.[3]

Early mortality data vary between 7.5% and 8.9%.[12,27] The present study's 30-day mortality rate was 7% and remained stable over the period studied. Massive transfusion predicted a higher 30-day mortality and lower 5-year survival. The effects on these outcome parameters are likely a combination of massive bleeding, with associated hemodynamic instability and the resulting transfusion of blood products. Massive transfusion could not only be an epiphenomenon of patient complexity, but as shown in cardiac surgery, as a single entity strongly associated with in-hospital mortality.[28] Even if transfusion itself could have a proregulatory effect on long-term rejection, this is very unlikely in the case of massive transfusion.[29]

A limitation of the present analysis is that the use of intraoperative cell salvage was not accounted for because the quantity of the processed blood was not reliably reported. However, cell salvage did not reduce the incidence of massive transfusions, which was the focus of the study. In addition, the effect of hemostatic drugs on the transfusion rate could not be differentiated. Paradoxically, use of these drugs was associated with a higher incidence of massive transfusion because these drugs were used preferentially in bleeding patients. Intraoperative blood loss is notoriously difficult to measure and transfusions of RBCs are frequently used as surrogate for bleeding.[28,30] The postoperative hemoglobin levels in our study support this practice. Finally, the significant associations obtained from the present analysis are specific to the study's patient population and cannot be generalized to other patient populations. The authors therefore recommend future studies in other lung transplantation populations to confirm the present study's findings. This could be helpful to compare immediate perioperative results among centers.

In conclusion, the incidence of massive transfusion did not change over time, whereas transfusion requirements in the whole cohort decreased. In patients transplanted from the ICU and in HU patients, median RBC use increased significantly. These results may reflect the underlying condition of the patient and may improve with interventions such as increased intraoperative use of ECLS or treatment of severe aortopulmonary collaterals with catheterization techniques. Massive transfusion should be matter of concern because of the association with increased PGD and 30-day mortality rates and reduced 5-year survival.

However, the median RBC use in the whole patient cohort decreased over time, which, in the authors' opinion, reflects progress made over the study period.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

References

1 Nuttal GA, Stehling LC, Beighley CM, et al. Current transfusion practices of members of the American Society of Anesthesiologists: A survey. Anesthesiology 2003;12:1433–43.
2 Geissler RG, Rotering H, Buddendick H, et al. Utilization of blood components in cardiac surgery: A single-center retrospective analysis with regard to diagnosis-related procedures. Transfus Med Hemother 2015;42:75–82.
3 Dutch Society of Anesthesiologists. Blood transfusion guideline. Available at: https://www.anesthesiologie.nl/uploads/files/KD_RL_Bloedtransfusiebeleid_2011.pdf. Accessed March 12, 2017.
4 American Society of Anesthesiologists Committee on Blood Management. Massive transfusion protocol (MTP) for hemorrhagic shock. Available at: https://www.asahq.org/~/media/sites/asahq/files/public/resources/asa%20committees/mtp%20for%20asa%20transfusion%20committee%20final.pdf?la=en. Accessed February 7, 2019.
5 Pham HP, Shaz BH. Update on massive transfusion. BJA 2013;111(S1):i71–82.
6 Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg 2014;147:1458–63.
7 Christie JD, Bavaria JE, Palevsky HI, et al. Primary graft failure following lung transplantation. Chest 1998;114:51–60.
8 Eurotransplant. Eurotransplant manual. Chapter 6: ET Thoracic Allocation System (EThAS). Available at: https://www.eurotransplant.org/cms/mediaobject.php?file=Chapter6_Thoracic8.pdf. Accessed February 7, 2019.
9 Gu YJ, de Haan J, Brenken UP, et al. Clotting and fibrinolytic disturbance during lung transplantation: Effect of low-dose aprotinin. Groningen Lung Transplant Group. J Thorac Cardiovasc Surg 1996;112:599–606.
10 Smits JM, Nossent GD, de Vries E, et al. Evaluation of the lung allocation score in highly urgent and urgent lung transplant candidates in Eurotransplant. J Heart Lung Transplant 2011;30:22–8.
11 Wang Y, Kurichi JE, Blumenthal NP, et al. Multiple variables affecting blood usage in lung transplantation. J Heart Lung Transplant 2006;25:533–8.
12 Weber D, Cottini SR, Locher P, et al. Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. Perioperative Med 2013;2:20.
13 Ong LP, Sachdeva A, Ramesh BC, et al. Lung transplant with cardiopulmonary bypass: Impact of blood transfusion on rejection, function, and late mortality. Ann Thorac Surg 2016;101:512–9.
14 Machuca NT, Collaud S, Mercier O, et al. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2015;149:1152–7.

15 Ko WJ, Chen YS, Lee YC. Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations. Artif Organs 2001;25:607–12.
16 Ius F, Kuehn CH, Tudorache I, et al. Lung transplantation on cardiopulmonary support: Venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass. J Thorac Cardiovasc Surg 2012;144:1510–6.
17 Aigner C, Wisser W, Taghavi S, et al. Institutional experience with extracorporeal membrane oxygenation in lung transplantation. Eur J Cardiothorac Surg 2007;31:468–73.
18 Biscotti M, Yang J, Sonett J, Bachetta M. Comparison of extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2014;148:2410–65.
19 Aubron C, Cheng AC, Pilcher D, et al. Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: A 5-year cohort study. Crit Care 2013;17:R73.
20 Cooper JD. Use of aprotinin in lung transplantation. Perfusion 1993;8:43–6.
21 Bhaskar B, Zeigenfuss M, Choudary J, et al. Use of recombinant activated factor VII for refractory after lung transplant bleeding as an effective strategy to restrict blood transfusion and associated complications. Transfusion 2013;53:798–804.
22 Griffith BP, Hardesty RL, Armitage JM, et al. A decade of lung transplantation. Ann Surg 1993;218:310–8.
23 Triluzi GJ, Griffith BP. Blood usage in lung transplantation. Transfusion 2001;38:12–5.
24 Pereira A, Sanz C, Attance R. Statistics to describe blood usage. Transfusion 1998;38:1119–20.
25 Upala S, Panichsillapakit T, Wijarnpreecha K, et al. Underweight and obesity increase the risk of mortality after lung transplantation: A systematic review and meta-analysis. Transpl Int 2016;29:285–96.
26 Puri V, Patterson GA, Meyers BF. Single versus bilateral transplantation: Do guidelines exist? Thorac Surg Clin 2015;25:47–54.
27 Yusen RD, Edwards BL, Kucheryavaya AY, et al. The Registry of International Society for Heart and Lung Transplantation report – 2015. J Heart Lung Transplant 2015;34:1264–77.
28 Karkouti K, Wijeysundera DN, Yau TM, et al. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004;44:1453–62.
29 Mason DP, Little SG, Nowicki ER, et al. Temporal pattern of transfusion and its relation to rejection after lung transplantation. J Heart Lung Transplant 2009;28:558–63.
30 Brecher ME, Monk T, Goodnough LT. A standardized method for calculating blood loss. Transfusion 1997;37:1070–4.