ORIGINAL ARTICLE

Risk factors for early bleeding complications after lung transplantation – a retrospective cohort study

Dieter Adelmann[1,2], Stefan Koch[1], Johannes Menger[1], Philipp Opfermann[1], Peter Jaksch[3], Konrad Hoetzenecker[3], Martin Kurz[4], Mohammed Mouhieddine[1] & Barbara Steinlechner[1]

1 Division of Cardiac Thoracic Vascular Anesthesia and Intensive Care Medicine, Department of Anesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Wien, Austria
2 Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA
3 Division of Thoracic Surgery, Department of Surgery, Medical University of Vienna, Wien, Austria
4 Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Wien, Austria

Correspondence
Dieter Adelmann MD, PhD, Division of Cardiothoracic and Vascular Anesthesia and Intensive Care Medicine, Department of Anesthesia, General Intensive Care and Pain Control, Medical University of Vienna, Währinger Gürtel 18 - 20, 1090 Wien, Austria.
Tel.: +43 (0)1 40400 - 41080;
fax: +43 (0)1 40400 - 41100;
e-mail: dieter.adelmann@ucsf.edu

SUMMARY

Risk factors for early bleeding complications after lung transplantation are not well described. Our aim was to evaluate coagulation test results and the use of extracorporeal membrane oxygenation as risk factors for bleeding after lung transplantation. We analyzed a single-center cohort of bilateral lung transplants between January 2009 and August 2015. Predictors of severe postoperative bleeding (bleeding requiring reoperation within 48 h of transplantation) were assessed using multivariable logistic regression. The effect of bleeding on survival was assessed using a Cox proportional-hazards model. Twenty-nine (4.5%) of 641 patients experienced severe postoperative bleeding. Postoperative fibrinogen levels (OR = 0.99, 95% CI 0.98–0.995, $P = 0.001$; per mg/dl increase) and pre- and postoperative use of extracorporeal membrane oxygenation (OR = 14.41% 95% CI 5.4–40.19, $P < 0.001$ and OR = 4.25, 95% CI 1.0–11.09, $P = 0.002$, respectively) were associated with an increased risk of severe postoperative bleeding. Severe postoperative bleeding was associated with decreased survival within 60 days after transplantation (adjusted HR = 5.73, 95% CI 2.52–13.02, $P < 0.001$). Low postoperative fibrinogen levels, and pre- and postoperative use of extracorporeal membrane oxygenation were risk factors for bleeding after lung transplantation.

Transplant International 2019; 32: 1313–1321

Key words
extracorporeal membrane oxygenation, fibrinogen, lung transplantation, postoperative hemorrhage

Received: 31 March 2019; Revision requested: 19 June 2019; Accepted: 7 August 2019; Published online: 30 August 2019

Introduction

Postoperative bleeding complications can have a significant impact on patient morbidity and mortality [1]. Little is known about risk factors for bleeding complications or the subsequent effect of bleeding complications on patient outcome after lung transplantation. During lung transplantation, intraoperative blood loss and concomitant fluid replacement may lead to dilutional coagulopathy. Coagulation factors, fibrinogen levels, and platelet count can drop below critical levels required for clot formation. In addition, the use of perioperative extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass can impair coagulation through platelet dysfunction and the need for anticoagulation [2].

In cardiovascular surgery [3] and neurosurgery [4], low levels of fibrinogen have been associated with an increased risk of blood loss and/or postoperative bleeding. In trauma patients, low fibrinogen levels have been

doi:10.1111/tri.13491

associated with higher mortality and unfavorable outcomes [5,6].

The use of cardiopulmonary bypass and a history of Eisenmenger syndrome or cystic fibrosis have previously been identified as risk factors for blood loss and transfusion requirements during lung transplantation [7,8]. However, the associations of perioperative fibrinogen concentrations, coagulation parameters (prothrombin time, activated partial thromboplastin time (aPTT), and platelet count), the perioperative use of ECMO, and the incidence of postoperative bleeding complications have not yet been evaluated.

The prespecified, primary objective of this study was to evaluate the association between pre- and postoperative coagulation parameters, the use of perioperative ECMO, and severe postoperative bleeding after lung transplantation. A secondary goal was to assess the impact of postoperative bleeding complications on patient survival after lung transplantation.

Materials and methods

Study design and participants

We performed a retrospective cohort study at a tertiary care university hospital. The study was approved by the institutional review board of the Medical University of Vienna (EK: 1144/2015). Individual patient consent was waived due to the observational nature of the study. All patients who underwent bilateral lung transplantation at the Medical University of Vienna between January 1, 2009 and August 31, 2015 were included. Patients under 18 years of age, patients undergoing single lung transplantation, and patients transplanted using cardiopulmonary bypass were excluded. Patients undergoing multiorgan transplants and transplants with concurrent cardiovascular surgeries were also excluded. No sample size calculation was performed.

Definition of endpoints

Severe postoperative bleeding was defined as bleeding that required surgical revision in the operating room within 48 h after transplantation. Complications at the femoral ECMO cannulation site, usually treated at bedside in the intensive care unit, did not meet the criteria for postoperative bleeding. All operative reports of the revision surgeries were reviewed to classify the source of bleeding as surgical bleeding, diffuse coagulopathy, or both. Data on postoperative follow-up were available for at least 365 days or until date of death (for patients who died within 365 days postoperatively). Mortality data were collected using follow-up data from our post lung transplant clinic and the Austrian national death registry (Statistik Austria, Vienna, Austria).

Variables and data sources

The following patient-related variables were retrieved from our prospective anesthesia database [9]: age, gender, weight, height, underlying lung disease, case duration (time between anesthesia start and anesthesia end), use of ECMO before, during, and/or after surgery, amount of intraoperatively administered crystalloids, colloids, packed red blood cells (PRBCs), fresh frozen plasma, and platelet concentrates, and amount of coagulation factors (prothrombin complex concentrate, fibrinogen concentrate, recombinant activated factor VII), tranexamic acid, and desmopressin given.

Laboratory test results were retrieved from the electronic medical records at four defined time points: the last available results before skin incision (preoperative), the first results after skin closure (postoperative), and 24 and 48 h postoperatively. Coagulation tests included prothrombin time (percent of normal, reference value 80–140%), aPTT (seconds, reference value 27–41 s), and fibrinogen level (Clauss method, mg/dl, reference value 200–400 mg/dl). Complete blood counts were assessed with a Sysmex XE-2100 (TOA Medical Electronics, Kobe, Japan).

Postoperative patient outcome variables (survival, hospital and intensive care unit length of stay, duration of postoperative intubation, and duration of postoperative ECMO therapy) were extracted from the prospective database of the Division of Thoracic Surgery.

Perioperative management

All transplants were performed by one of five senior attending cardiothoracic surgeons. After induction of general anesthesia, patients were intubated using a left-sided double-lumen tube. A balanced crystalloid solution (Elomel-isoton®; Fresenius Kabi, Graz, Austria) was used for fluid maintenance therapy. Additional volume therapy was based on a balanced colloid [hydroxyethyl starch (HES 130/0.4) in an isotonic electrolyte solution (Volulyte®; Fresenius Kabi)] and albumin [Albumin (Human) 5%, CSL Behring GmbH CSL, Vienna, Austria]. Intraoperative fluid therapy was guided by transesophageal echocardiography and changes in preload and afterload. A colloid osmotic pressure >15 mmHg was maintained to avoid interstitial edema.

Transplant International 2019; 32: 1313–1321

A hemoglobin concentration of 10 g/dl or acute massive hemorrhage were defined as triggers for the transfusion of PRBCs. Fibrinogen concentrate and prothrombin complex concentrate were administered to maintain fibrinogen concentrations ≥150 mg/dl and the prothrombin time >70%. Rotational thrombelastometry was only used in selected cases.

Patients on preoperative ECMO were anticoagulated using a continuous infusion of unfractionated heparin (target aPTT between and 55–65 s, held 1–5 h before transplant) or subcutaneous low-molecular heparin (target anti-Xa level: 0.4–0.7 IU/ml, held 12 h before transplant).

All transplants were performed as bilateral sequential transplants, with or without the use of intraoperative ECMO. Our ECMO protocol was reported recently [10]. For intraoperative use, central cannulation was performed using heparin-coated tubing (Medtronic Carmeda BioActive Surface; Medtronic Inc., Minneapolis, MN, USA). A single bolus of 60 IU/kg of intravenous unfractionated heparin was given without subsequent monitoring of the activated clotting time. For postoperative continuation of ECMO, the same circuit was used with arterial and venous cannulation of the femoral artery and vein. Central cannulation was not used for postoperative continuation of ECMO. In the absence of clinically relevant bleeding, anticoagulation with low-molecular heparin was initiated between 6 and 24 h postoperatively (target anti-Xa level: 0.4–0.7 IU/ml).

Statistical analysis

Normally distributed data are reported as mean and standard deviation (SD). Non-normal data are reported as median and interquartile range (IQR). Categorical data are reported as number and percent. The Shapiro–Wilk test was used to test for normal distribution. The independent samples *t*-test was used for normally distributed data. For non-normally distributed data and for categorical data, the Kruskal–Wallis rank sum test and the Chi-square test, respectively, were used.

As regards severe postoperative bleeding, for univariable analysis, logistic regression models were used to assess the association between the following parameters pre- and postoperative coagulation test results (aPTT, prothrombin time, fibrinogen level, and platelet count), use of ECMO (preoperative, intraoperative, and postoperative), gender, etiology of lung disease, retransplantation, and the number of packed red blood cells transfused.

Two multivariable logistic regression models were used to identify the predictors of severe postoperative bleeding. The first "preoperative" model included variables known prior to transplantation: preoperative coagulation test results (aPTT, prothrombin time, fibrinogen level, and platelet count) and preoperative need for ECMO. The second "postoperative" model included the following predefined variables: pre- and postoperative coagulation test results and use of ECMO (preoperatively, intraoperatively, and postoperatively). Twenty-three cases (3.6%; 1 with and 22 without severe postoperative bleeding) were excluded from both models due to missing laboratory values. Pearson correlation coefficients were used to determine collinearity between coagulation test results. No strong correlation (maximum coefficient 0.63) was found and no variables were excluded for collinearity. Stepwise variable selection with the Akaike information criterion was used to select the final "postoperative" model. The same three variables were identified as significant both before and after stepwise variable selection. The Hosmer–Lemeshow test for goodness of fit was used to evaluate model calibration. Akaike information criterion and the area under the receiver operating characteristics (AUROC) are reported to assess model performance for both multivariable models.

There were significant associations between Etiology of Lung Disease and pre-, intra-, and postoperative use of ECMO (Chi-squared test for each time point of ECMO use, $P < 0.001$) and female gender and postoperative use of ECMO (Chi-squared test, $P < 0.001$). To avoid multicollinearity, both etiology of lung disease and gender were not added as additional variables in the multivariable logistic regression model. Only variables prespecified in the initial analysis plan were used in the multivariable model.

Patient survival: Survival at 30 days and 1 year was compared between the two groups using the Kaplan–Meier log-rank test. A Kaplan–Meier survival curve was used to visualize 1-year survival.

The association between severe postoperative bleeding and 1-year survival was evaluated using a stratified Cox proportional hazards model adjusted for pulmonary hypertension as the indication for transplant, recipient age, and retransplantation. Severe postoperative bleeding and retransplantation did not meet the assumption of proportional hazards over time as evaluated by smoothed scaled Schoenfeld residual plots and the Grambsch–Therneau test. After visual inspection of the Schoenfeld residual plots for severe postoperative bleeding, the dataset was divided into two periods: early (the first 60 days after transplantation) and late (61 days to 1 year after transplantation). Both variables met the assumptions for proportional hazards after stratification for the two periods.

$P < 0.05$ (two-sided) was considered statistically significant. No correction for multiple comparisons was performed. Data were analyzed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The R-packages *MASS* [11] and *survival* [12] were used for variable selection and survival analysis, respectively.

Results

We performed 675 lung transplants in adult recipients during the study period. Twenty-five patients received single lung transplants and were excluded. Nine transplants were excluded due to intraoperative use of cardiopulmonary bypass. The remaining 641 patients were included in this study.

Twenty-nine patients (4.5%) required surgical revision due to bleeding within 48 h after transplantation. Median time between the end of the transplant and revision was 15 h (IQR 10, 20). The cause of bleeding was as follows: surgical bleeding in 9 (31%), diffuse coagulopathy in 15 (52%), and both in 5 (17%) cases. No patient on postoperative ECMO received heparin prior to reoperation for bleeding.

Patient characteristics and perioperative parameters, including fluid balance, transfusion requirements, and intraoperative laboratory results, are shown in Table 1. The time course of perioperative fibrinogen levels in patients with and without bleeding complications is shown in Fig. 1. Patient outcomes, including duration of mechanical ventilation, intensive care unit and hospital length of stay, and survival are shown in Table 2.

Severe postoperative bleeding

In the univariable analysis, the use of ECMO (pre-, intra-, and postoperatively) was associated with increased odds of severe postoperative bleeding (Tables 2 and S1). The results of the univariable analysis of predictors for severe postoperative bleeding are given in the Table S1.

In the "preoperative" multivariable logistic regression model, the need for preoperative ECMO was associated with increased odds of severe postoperative bleeding (Table 3).

In the "postoperative" multivariable logistic regression model, lower postoperative fibrinogen levels and the use of preoperative and postoperative ECMO were independently associated with increased odds of severe postoperative bleeding (Table 4). The intraoperative use of ECMO was not associated with severe postoperative bleeding.

Table 1. Baseline patient characteristics

	All patients
Baseline characteristics	
Number of patients	641
Postoperative bleeding*	29 (4.5%)
Age, years	50 (34–58)
Gender, female	309 (48.2%)
Weight, kg	61 (51–73)
Height, cm	169 (163–176)
Retransplantation	37 (5.8%)
Preoperative ECMO	53 (8.3%)
Etiology of lung disease	
Chronic obstructive pulmonary disease	191 (29.8%)
Pulmonary fibrosis	161 (25.1%)
Cystic fibrosis	120 (18.7%)
Primary pulmonary hypertension	38 (5.9%)
Alpha 1-antitrypsin deficiency	29 (4.5%)
Bronchiectasis	14 (2.2%)
Other	88 (13.7%)
Perioperative parameters	
Case duration	382 (339–435)
Intraoperative ECMO use	487 (76.0%)
Intraoperative fluids	
Crystalloids, ml	1500 (1000–2250)
Colloids, ml	0 (0–250)
Packed red blood cells, units	4 (2–6)
Fresh frozen plasma, units	10 (7–13)
Platelet concentrates, units	0 (0–0)
Urine, ml	400 (250–605)
Coagulation factors administered	
PCC given	82 (12.8%)
PCC dose, IU†	1500 (1000–2000)
Fibrinogen concentrate given	134 (20.9%)
Fibrinogen concentrate dose, g†	3 (2–4)
Activated factor VII given	4 (0.6%)
Desmopressin given	19 (3.0%)
Tranexamic acid given	36 (5.6%)
Intraoperative laboratory results	
Lactate, maximum	2.80 (2.20–3.70)
Glucose, maximum	181 (163–201)
Hemoglobin, minimum	9.00 (8.20–9.95)
Base Excess, minimum	−2.00 (−4.10 to 1.00)

ECMO, extracorporeal membrane oxygenation.

Data are presented as median (IQR) or *n* (%).

*Postoperative bleeding complication was defined as reoperation for bleeding within 48 h of transplantation.

†Median dose if given.

Patient survival

Survival at 30 days and 1 year was lower in patients with postoperative bleeding (Table 2). A Kaplan–Meier survival curve for 1-year survival is shown in Fig. 2.

Transplant International 2019; 32: 1313–1321

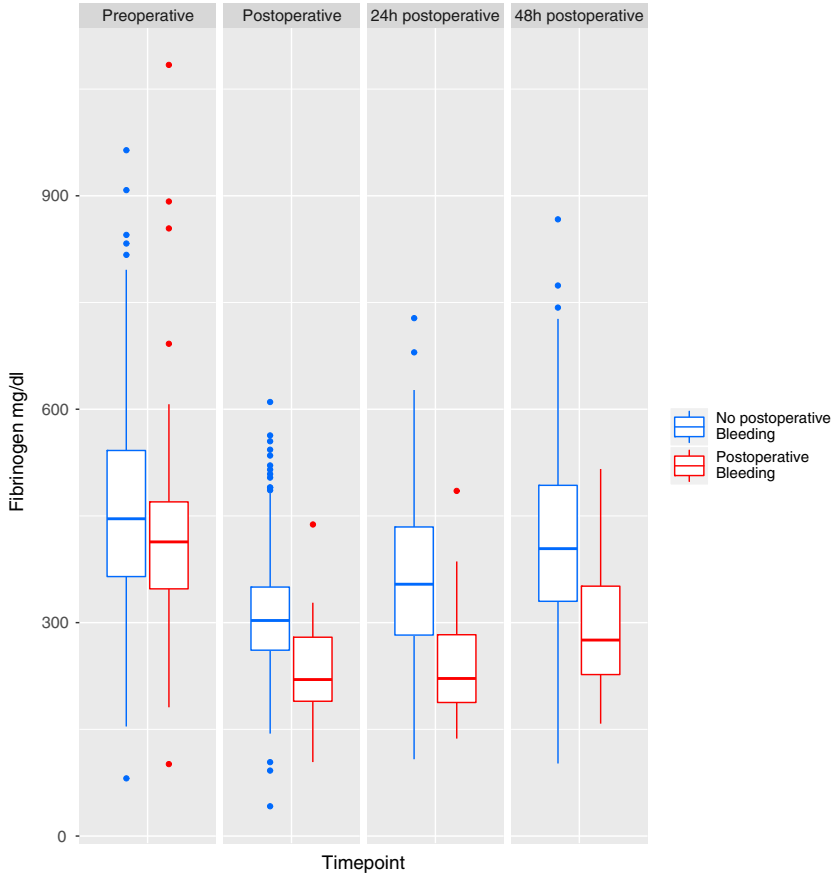

Figure 1 Time course of perioperative fibrinogen concentrations. Box plots show fibrinogen concentrations at four time points: preoperatively, postoperatively (the first results after skin closure), and 24 and 48 h postoperatively.

Patients who required reoperation for bleeding within 48 h had a higher hazard ratio for death in the early postoperative period (within 60 days after transplantation) in both the unadjusted and adjusted survival analysis [hazard ratio 4.94 (95% CI 2.19–11.11, $P < 0.001$) and 5.73 (95% CI 2.52–13.02, $P < 0.001$), respectively], but not in the late period (between 61 days and 1 year after transplantation).

Discussion

In this study, low fibrinogen levels at the end of surgery and the preoperative and postoperative use of ECMO were associated with increased odds of postoperative bleeding requiring surgical intervention after lung transplantation. Patients who required surgery for postoperative bleeding had a lower 30-day and 1-year survival rate than patients who did not.

In previous studies, low postoperative fibrinogen levels were associated with bleeding complications in patients undergoing both cardiac and noncardiac surgery [4,13]. Our study shows similar results in patients undergoing lung transplantation.

Low postoperative fibrinogen levels could be seen a surrogate for intraoperative coagulopathy, rather than a risk factor in itself: patients who developed postoperative bleeding complications required a significantly higher amount of intraoperative blood products and coagulation factors. Coagulopathy was identified as a contributory cause to postoperative bleeding in 69% of reoperations.

There are no randomized controlled trials evaluating the use of hemostatic interventions during lung transplantation. Only a few randomized trials have evaluated the use of fibrinogen concentrate in cardiothoracic surgery. In a single-center pilot study, there was a significant reduction in transfusions and postoperative bleeding in cardiac surgery with fibrinogen supplementation, but these results could not be reproduced in larger study [14,15]. Similarly, fibrinogen concentrate reduced transfusions during aortic surgery in a single-center study [16], but the results could not be reproduced in a subsequent multicenter study [17].

In one study, the introduction of point-of-care coagulation testing was associated with decreased blood product utilization during lung transplantation [18]. In our cohort, coagulation therapy was guided by standard

Table 2. Patient outcomes

	No postoperative bleeding	Postoperative bleeding*	*P*
Postoperative ECMO	144 (23.5%)	20 (69.0%)	<0.001
Duration of postoperative ECMO, days	2 (1–3)	3 (1–3)	0.76
Days until extubation, days	2 (1–4)	10 (2–27)	<0.001
Length of intensive care unit stay, days	7 (5–18)	25 (12–30)	<0.001
Length of hospital stay, days	23 (18–39)	42 (29–62)	0.001
Patient survival			
30-day survival	591 (96.6%)	23 (79.3%)	<0.001
1-year survival	517 (84.5%)	18 (62.1%)	0.004

ECMO, extracorporeal membrane oxygenation.

Data are presented as median (IQR) or *n* (%).

*Postoperative bleeding complication was defined as reoperation for bleeding within 48 h of transplantation.

Table 3. Multiple binary logistic regression model for bleeding complications within 48 h* (risk factors known at the beginning of surgery)

Variable	Odds ratio	95% Confidence interval (lower–upper)	Coefficient	*P*
(Intercept)	0.04	0.002–0.79	−3.33	0.030
Preoperative prothrombin time per %	1.00	0.985–1.024	0.00	0.662
Preoperative fibrinogen per mg/dl	1.00	0.997–1.002	0.00	0.809
Preoperative aPPT per second	0.98	0.936–1.018	−0.02	0.393
Preoperative Platelet Count, per G/L	1.00	0.995–1.004	0.00	0.978
Preoperative ECMO	23.97	7.614–80.681	3.18	<0.001
Hosmer–Lemeshow goodness-of-fit test				0.915
Akaike information criterion: 197				
Area under the receiver operating characteristics (AUROC): 0.73				

aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation.

*Postoperative bleeding complication was defined as reoperation for bleeding within 48 h of transplantation.

Table 4. Multiple binary logistic regression model for bleeding complications within 48 h* (risk factors known at the end of surgery)

Variable	Odds ratio	95% Confidence interval (lower–upper)	Coefficient	*P*
(Intercept)	0.16	0.007–4.123	−1.86	0.249
Preoperative prothrombin time per %	1.02	0.997–1.037	0.02	0.101
Postoperative fibrinogen per mg/dl	0.99	0.981–0.995	−0.01	0.001
Postoperative aPPT per second	0.98	0.947–1.005	−0.02	0.241
Preoperative ECMO	14.41	5.438–40.19	2.67	<0.001
Postoperative ECMO	4.25	1.703–11.093	1.45	0.002
Hosmer–Lemeshow goodness-of-fit test				0.711
Akaike information criterion: 173				
Area under the receiver operating characteristics (AUROC): 0.86				

aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation.

Final model after stepwise variable selection.

*Postoperative bleeding complication was defined as reoperation for bleeding within 48 h of transplantation.

Transplant International 2019; 32: 1313–1321

laboratory parameters, with the additional use of thrombelastometry in selected cases. Fresh frozen plasma was used as the primary fluid for both resuscitation and replacement of coagulation factors. In addition, >50% of patients with subsequent bleeding complications received fibrinogen concentrate and/or prothrombin complex concentrate.

In our cohort, the intraoperative use of ECMO was not associated with an increased risk of postoperative bleeding. Our current findings further support the safe use of intraoperative ECMO during lung transplantation.

In the univariable analysis, both the use of postoperative ECMO and a diagnosis of primary pulmonary hypertension were associated with an increased risk of postoperative bleeding. At our center, postoperative ECMO is used to reduce transpulmonary blood flow to prevent volume overflow to the newly implanted lungs in patients with pulmonary hypertension. Despite the increased risk of postoperative bleeding associated with postoperative ECMO, our group has recently shown that intraoperative ECMO support and prophylactic ECMO prolongation into the early postoperative period result in superior outcomes in recipients with pulmonary hypertension or questionable graft function compared to recipients without ECMO support [10].

The use of preoperative and postoperative ECMO was associated with increased odds of bleeding in the multivariable model. Compared to intraoperative ECMO support, patients who require preoperative and postoperative ECMO are exposed to an extracorporeal circuit and artificial surface for a longer period of time. Acquired von Willebrand syndrome can develop within 24 h after ECMO implantation and may explain, at least in part, the increased risk of bleeding in patients requiring preoperative and postoperative ECMO [19,20]. It is unclear to what extent acquired von Willebrand syndrome or any residual heparin effect contributed to bleeding in our patients on ECMO. Acquired von Willebrand syndrome cannot be identified by routine coagulation tests. Intraoperative heparin administration may also increase the risk of postoperative bleeding. In our cohort, aPTT prolongation, as a surrogate for a prolonged heparin effect, was not associated with an increased risk of postoperative bleeding.

Preoperative fibrinogen levels were not predictive of postoperative bleeding. A recent meta-analysis of four studies evaluated the value of preoperative fibrinogen concentrations on postoperative bleeding and could only show a weak predictive effect (AUC 0.60) [21].

Patient survival was significantly lower in patients with bleeding complications than in patients without bleeding. Similar associations between both intraoperative transfusion requirements and bleeding complications after lung transplantation and postoperative morality have been reported. Intraoperative transfusion of more than four units of PRBCs was associated with an increased risk for overall mortality [HR 4.7 (CI 1.7–13.3)] [22]; postoperative hemothorax, defined clinically by chest-tube output or need for thoracentesis, was

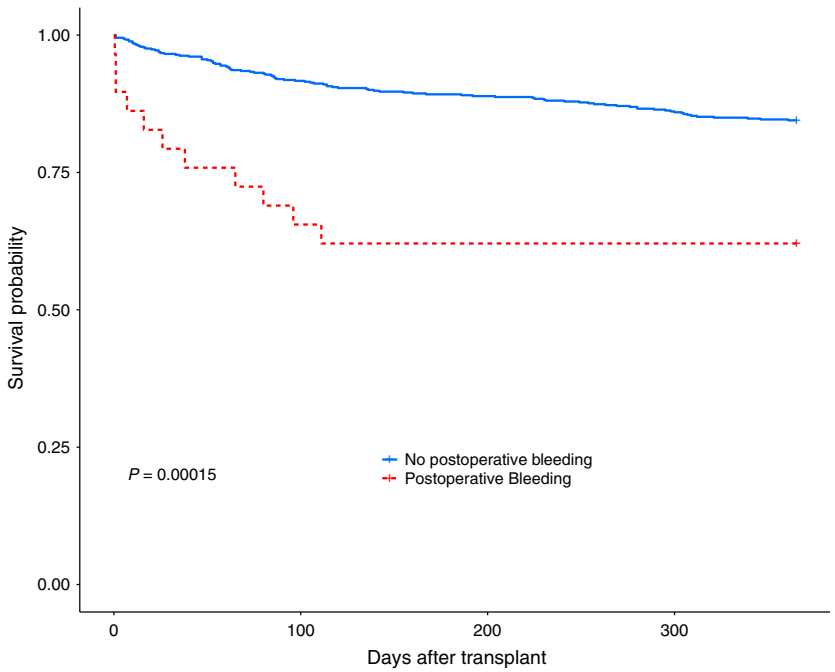

Figure 2 Kaplan–Meier survival curves showing 1-year survival after lung transplantation based on postoperative bleeding.

associated with an increased risk for in-hospital mortality [OR 4.13 (CI 1.21–14.14)] [23]. In another study of 132 lung transplant recipients, the development of postoperative hemothorax, defined by chest-tube output and radiographic findings, was also associated with decreased short-term survival. Most of the cases of hemothorax in that study developed more than 5 days after surgery, after the initiation of anticoagulation [24].

Both the definition of bleeding complications and the observation time for the development of such complications vary widely among studies. We chose our endpoint for the following reasons: Returning to the operating room is a clear definition that leaves little room for interobserver variability. By limiting the observation time to 48 h, we focused on bleeding complications in the immediate postoperative period when anticoagulation had not yet been established.

The bleeding rate of 4.5% in our cohort is low, compared to studies using definition based on chest tube output or imaging (13–15%) [22,23]. This might be in part due to the more stringent definition of our endpoint. In addition, use of ECMO rather than cardiopulmonary bypass might also have contributed to a lower incidence of bleeding. Lung transplantation using cardiopulmonary bypass has been associated with an increased risk of bleeding when compared to ECMO [25,26].

In patients undergoing cardiac surgery, the need for reoperation for bleeding accounts for a relative risk of death of 2.56 (95% CI 1.46–4.50) [27]. A smaller study of 224 patients undergoing lung transplantation did not show an increased mortality risk for patients undergoing reoperation. In that study, reoperation mostly occurred in the late postoperative period with a mean time between transplant and reoperation of 16 days [28].

The aim of our study was to assess intraoperative predictors that may directly contribute to the risk of early postoperative bleeding. To our knowledge, our study is the largest cohort to report a negative effect of bleeding complications on mortality for bleeding after lung transplantation. Postoperative bleeding requiring early reoperation may be considered a "second hit" after the initial surgery. In our cohort, patients requiring reoperation had a longer duration of mechanical ventilation, intensive care unit, and hospital stay. Similar results have been reported for patients undergoing coronary artery bypass grafting, where reoperation is associated with an increased risk of sepsis, pneumonia, and death [1].

Some important limitations of this study have to be considered. We present data from a single, but high-volume, transplant center with all of its known limitations. In our cohort, there was a low incidence of bleeding events, leading to an imbalanced dataset. This resulted in a low event to predictor ratio in our model. We therefore only included predictors prespecified in our analysis plan in the multivariable model. The use of ECMO was not equally distributed when grouped based on recipient disease. We did not include recipient disease in our model due to multicollinearity. Due to the observational nature of this study, the association of low fibrinogen concentrations, pre- and postoperative use of ECMO, and the need for reoperation cannot imply causality. We cannot exclude that recipient disease, not the need for pre- and postoperative ECMO, had a causal effect on postoperative bleeding. Point-of-care viscoelastic tests were only used in select patients. Platelet function tests were not used; thus, ECMO-induced platelet dysfunction was not detected. Our dataset did not include postoperative drain output. The differentiation between coagulopathy and surgical bleeding was done retrospectively and must therefore be interpreted with caution.

We excluded single lung transplants and transplants using cardiopulmonary bypass. Single lung transplantation is only rarely performed (3.7%), and patients have a unique risk profile. Intraoperative ECMO has replaced cardiopulmonary bypass during lung transplantation at our center over 10 years ago. Cardiopulmonary bypass is reserved for highly complex cases such as concomitant cardiac surgery or retransplantation after single lung transplantation [10].

In conclusion, this study identified potential risk factors for postoperative bleeding after lung transplantation. Low perioperative fibrinogen levels and the pre- and postoperative use of ECMO were associated with increased odds of bleeding. Patients requiring reoperation for bleeding after lung transplantation had an increased risk of death within 1 year after transplantation.

Authorship

All authors have contributed significantly to the content of the article. DA, SK and BS: drafted the study protocol and obtained Institutional Review Board approval. DA, SK, JM, PJ, KH, MH and MM: collected patients' data. MM: set up and maintained the study database. DA: performed the statistical analysis. DA, SK, PO, KH and BS: prepared the manuscript.

Funding

The study was solely funded by departmental funds (Department of Anesthesia, General Intensive Care

and Pain Control, Medical University of Vienna, Austria).

Conflict of interest

The authors declare no conflict of interest relating to any companies or relevant entities pertinent to the paper.

SUPPORTING INFORMATION

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

Table S1. Summary table of univariate logistic regression models for predictors of bleeding complications within 48 h.

REFERENCES

1. Mehta RH, Sheng S, O'Brien SM, *et al.* Reoperation for bleeding in patients undergoing coronary artery bypass surgery: incidence, risk factors, time trends, and outcomes. *Circ Cardiovasc Qual Outcomes* 2009; **2**: 583.
2. Tauber H, Streif W, Fritz J, *et al.* Predicting transfusion requirements during extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth* 2016; **30**: 692.
3. Waldén K, Jeppsson A, Nasic S, Backlund E, Karlsson M. Low preoperative fibrinogen plasma concentration is associated with excessive bleeding after cardiac operations. *Ann Thorac Surg* 2014; **97**: 1199.
4. Adelmann D, Klaus D, Illievich U, *et al.* Fibrinogen but not factor XIII deficiency is associated with bleeding after craniotomy. *Br J Anaesth* 2014; **113**: 628.
5. Hagemo JS, Stanworth S, Juffermans NP, *et al.* Prevalence, predictors and outcome of hypofibrinogenaemia in trauma: a multicentre observational study. *Crit Care* 2014; **18**: R52.
6. Rourke C, Curry N, Khan S, *et al.* Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012; **10**: 1342.
7. Hoechter DJ, von Dossow V, Winter H, *et al.* The munich lung transplant group: intraoperative extracorporeal circulation in lung transplantation. *Thorac Cardiovasc Surg* 2015; **63**: 706.
8. Triulzi D, Griffith B. Blood usage in lung transplantation. *Transfusion* 1998; **38**: 12.
9. Bernardi M, Schmidlin D, Schiferer A, *et al.* Impact of preoperative serum creatinine on short- and long-term mortality after cardiac surgery: a cohort study. *Br J Anaesth* 2015; **114**: 53.
10. Hoetzenecker K, Schwarz S, Muckenhuber M, *et al.* Intraoperative ECMO and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. *J Thorac Cardiovasc Surg* 2018; **155**: 2193.
11. Venables WN, Ripley BD. *Modern Applied Statistics with S*, 4th edn. New York, NY: Springer, 2002.
12. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer Science & Business Media, 2013.
13. Carling MS, Jeppsson A, Wessberg P, Henriksson A, Baghaei F, Brisby H. Preoperative fibrinogen plasma concentration is associated with perioperative bleeding and transfusion requirements in scoliosis surgery. *Spine* 2011; **36**: 549.
14. Karlsson M, Ternström L, Hyllner M, *et al.* Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost* 2009; **102**: 137.
15. Jeppsson A, Waldén K, Roman-Emanuel C, Thimour-Bergström L, Karlsson M. Preoperative supplementation with fibrinogen concentrate in cardiac surgery: a randomized controlled study. *Br J Anaesth* 2016; **116**: 208.
16. Rahe-Meyer N, Solomon C, Hanke A, *et al.* Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology* 2013; **118**: 40.
17. Rahe-Meyer N, Levy J, Mazer C, *et al.* Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. *Br J Anaesth* 2016; **117**: 41.
18. Smith I, Pearse BL, Faulke DJ, *et al.* Targeted bleeding management reduces the requirements for blood component therapy in lung transplant recipients. *J Cardiothorac Vasc Anesth* 2017; **31**: 426.
19. Malfertheiner M, Pimenta L, von Bahr V, *et al.* Acquired von Willebrand syndrome in respiratory extracorporeal life support: a systematic review of the literature. *Crit Care Resusc* 2017; **19**: 45.
20. Kalbhenn J, Schmidt R, Nakamura L, Schelling J, Rosenfelder S, Zieger B. Early diagnosis of acquired von Willebrand Syndrome (AVWS) is elementary for clinical practice in patients treated with ECMO therapy. *J Atheroscler Thromb* 2015; **22**: 265.
21. Ranucci M, Jeppsson A, Baryshnikova E. Pre-operative fibrinogen supplementation in cardiac surgery patients: an evaluation of different trigger values. *Acta Anaesthesiol Scand* 2015; **59**: 427.
22. Weber D, Cottini SR, Locher P, *et al.* Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. *Perioper Med (Lond)* 2013; **2**: 20.
23. Ferrer J, Roldan J, Roman A, *et al.* Acute and chronic pleural complications in lung transplantation. *J Heart Lung Transplant* 2003; **22**: 1217.
24. Hong A, King CS, Brown WA, *et al.* Hemothorax following lung transplantation: incidence, risk factors, and effect on morbidity and mortality. *Multidiscip Respir Med* 2016; **11**: 40.
25. Ius F, Natanov R, Salman J, *et al.* Extracorporeal membrane oxygenation as a bridge to lung transplantation may not impact overall mortality risk after transplantation: results from a 7-year single-centre experience. *Eur J Cardiothorac Surg* 2018; **54**: 334.
26. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Zacharoulis D. Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: a meta-analysis. *Gen Thorac Cardiovasc Surg* 2018; **66**: 38.
27. Biancari F, Mikkola R, Heikkinen J, Lahtinen J, Airaksinen JK, Juvonen T. Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2011; **41**: 50.
28. Paradela M, González D, Parente I, *et al.* Surgical risk factors associated with lung transplantation. *Transplant Proc* 2009; **41**: 2218.