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Published in:
Journal of Heart and Lung Transplantation

Publication status and date:
Published: 01/02/2024

DOI (link to publisher):
10.1016/j.jhlto.2024.100055

Document Version
Publisher's PDF, also known as Version of record

ELSEVIER

https://www.jhltopen.org/

Effect of rotational thromboelastometry-guided bleeding management in bilateral lung transplantation

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KEYWORDS:
rotational thromboelastometry;
blood transfusion;
lung transplantation;
extracorporeal circulation;
prohemostatic medication

BACKGROUND: Blood transfusion is often necessary during and after lung transplantation surgery. Point-of-care guided bleeding strategies, such as rotational thromboelastometry (ROTEM), can reduce blood transfusion in cardiovascular surgery. This study aimed to assess the effect of ROTEM-guided bleeding management on the need for allogenic blood transfusion, prohemostatic medication, and clinical outcomes in lung transplantation patients.

METHODS: This single-center retrospective cohort study compared patients receiving bilateral lung transplantation between 2010-2014 and 2017-2020. The first cohort was treated with a clinically guided bleeding strategy and the second cohort with a ROTEM-guided bleeding strategy. Multivariable regression analyses were performed to determine the effects on primary outcomes.

RESULTS: A total of 167 (66 clinically guided vs 101 ROTEM-guided) patients were included for analysis. Baseline, intraoperative, and postoperative characteristics were mostly similar, but differed regarding the number of patients with cystic fibrosis, use of cardiopulmonary bypass, and surgical technique. The ROTEM-guided group received significantly less median red blood cells (7 [3; 13] vs 4 [1; 9] units, $p < 0.01$), platelet concentrate (2 [0; 3] vs 0 [0; 2] units, $p = 0.01$), and plasma volume (2,310 [1,320; 3,960] vs 800 [0; 1,600] ml, $p < 0.01$). In multivariable regression analysis, implementation of the ROTEM strategy only remained significantly associated with a decreased use of plasma volume. Cardiopulmonary bypass significantly increased allogenic blood transfusion needs. Moreover, more prothrombin complex concentrate, fibrinogen concentrate, and less tranexamic acid were used in the ROTEM-guided group.

CONCLUSIONS: ROTEM-guided bleeding management reduces plasma transfusion in bilateral lung transplant surgery and cardiopulmonary bypass seems to increase transfusion needs.

JHLT Open 2024;3:100055

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https://doi.org/10.1016/j.jhlto.2024.100055

Background

During and after lung transplant (LTx) surgery, blood transfusion is often necessary. However, blood products are scarce resources and blood transfusion carries risk, such as transfusion-related acute lung injury, primary graft dysfunction (PGD), transfusion-related immunomodulation, and transfusion-associated circulatory overload (TACO).[1-6] PGD is associated with negative short- and long-term patient outcomes. This emphasizes the need to limit blood loss and blood transfusion in patients undergoing LTx.

Point-of-care (POC)-guided bleeding management have shown to reduce blood transfusion in cardiovascular surgery.[7-11] However, studies regarding the effect of POC-guided transfusion strategies during LTx are scarce.[12,13] Nevertheless, limited evidence suggests that POC-guided bleeding management using rotational thromboelastometry (ROTEM) reduces perioperative bleeding and decreases red blood cell (RBC), platelet, and plasma transfusion.[12,13] The limited literature on this topic necessitates further research on the effects of POC management during LTx surgery. Therefore, we conducted a study to evaluate ROTEM-guided transfusion in patients receiving bilateral LTx with and without extracorporeal support.

The objective of this study was to assess whether ROTEM-guided bleeding management reduces allogenic blood transfusion in LTx patients. Secondary objectives were to evaluate its effects on use of prohemostatic agents and clinical outcomes, such as surgical re-exploration due to bleeding, hospital length of stay (LOS), and intensive care unit (ICU) LOS. Furthermore, we aimed to assess the effects of extracorporeal circulation (ECC) using cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) on transfusion need. Our hypothesis was that ROTEM-guided transfusion reduces allogenic blood transfusion in bilateral LTx surgery.

Methods

Study design

This study is a single-center retrospective study conducted in a tertiary university hospital in Rotterdam, the Netherlands (Erasmus Medical Center). The study population consists of 2 cohorts of patients who underwent bilateral LTx surgery in the periods of 2010-2014 and 2017-2020.

The cohort from 2010-2014 (control group) underwent LTx with clinically guided bleeding management. Transfusion was guided based on standard laboratory tests, clinical judgment, and thromboelastography if deemed necessary. No transfusion algorithm was used. In 2015, ROTEM was introduced in the hospital and mid-2016 a transfusion protocol was developed and approved. The second half of 2016 was regarded as the implementation phase of the ROTEM-guided transfusion algorithm. The second cohort (intervention group) of patients underwent LTx surgery between 2017 and 2020 in which the ROTEM-guided transfusion protocol was used. In our center, we do not use plasma exchange (PLEX) for desensitization therapy, as such there was no need to exclude these patients.

The medical ethics committee of the Erasmus Medical Center reviewed this study and decided it was not subject to the Medical Research Involving Human Subjects Act (MEC-2019-0695).

Study outcomes

The primary outcomes were transfusion of RBCs, platelet concentrate, and plasma volume during surgery up until 7 days after transplantation. Secondary outcomes included percentage of patients transfused with RBC, platelet concentrate and plasma, administration of prothrombin complex concentrate (PCC) (Cofact, Sanquin, Amsterdam, the Netherlands), fibrinogen concentrate (Haemocomplettan P, CSL Behring BV, Breda, the Netherlands), desmopressin (Minrin, Ferring BV, Hoofddorp, the Netherlands), recombinant factor VIIa (rVIIa, NovoSeven; Novo Nordisk BV, Alphen aan den Rijn, the Netherlands), and tranexamic acid (Cyklokapron, Pfizer BV, Capelle aan den IJssel, the Netherlands) during surgery and up until 7 days after transplantation. Furthermore, other outcomes were duration of mechanical ventilation, ICU LOS, hospital LOS, incidence of surgical re-exploration due to bleeding, in-hospital mortality, and 1-year mortality. Lastly, we aimed to assess the effects of CPB or ECMO on transfusion need.

Clinically guided bleeding management and ROTEM-guided bleeding management

Clinically guided bleeding management and the ROTEM-guided bleeding management used in our hospital are described in detail in Karrar et al and included in the supplementary material.[14] Briefly, in the clinically guided bleeding management, blood products were given if deemed necessary by the anesthesiologist. Protamine was administered to antagonize heparin in case of CPB use until activated clotting time was within < 10% difference of baseline. In the ROTEM-guided bleeding management, perioperative blood products were given according to the protocol as described by Görlinger et al and postoperatively as described by Weber et al.[7,15] POC ROTEM testing was performed. Both the clinically guided bleeding management protocol and ROTEM-guided bleeding management protocol are described in detail in the supplement of this study (Figures S1 and S2).

Surgical technique

Recipients were placed in supine position on an inflatable bag under each scapula to lift up the chest (one or both sides as needed). The arms were hanging alongside the chest with elbows in 90 degrees flexion. Either a clamshell or bilateral anterior thoracotomy incision was performed. Over the years, the preference shifted toward the bilateral anterior thoracotomy incision. A clamshell incision was performed in the fourth intercostal space and the sternum was divided, with ligation of the mammary vessels. A bilateral anterior thoracotomy incision was made in the fourth or fifth intercostal space, without sternal division and leaving the mammary vessels intact. If additional access to the thorax was necessary, the surgeon converted to the clamshell incision. Hereafter, pneumonectomy was performed and the donor lungs were implanted sequentially. The lung with the worst function on the preoperative ventilation-perfusion scan was implanted first, with continuous ventilation of the contralateral lung. If needed CPB or ECMO was inserted, either centrally or via the femoral vessels. Over the years, CPB was used more restrictively. After creating the bronchial and vascular anastomoses, methylprednisolone and mannitol were administered and

Table 1 Baseline Characteristics

General characteristics	Clinically guided (n = 67)	ROTEM-guided (n = 101)	p-value
Age, years	55 [42; 60]	58 [51; 62]	0.01
Female, %	34 [50.7]	53 [52.5]	1.00
Body mass index	22.7 [20.0; 26.0]	24.3 [21.0; 28.2]	0.02
Retransplantation, %	1 [1.5]	3 [3.0]	1.00
Previous thoracic surgery, %	5 [7.5]	5 [5.0]	0.52
Admission prior to procedure, %	26 [38.8]	27 [26.7]	0.13
ICU admission prior to procedure, %	9 [13.4]	10 [9.9]	0.63
Diabetes, %	11 [16.4]	13 [12.9]	0.51
Mean pulmonary artery pressure	26 [19; 30]	24 [20; 31]	0.80
ECMO preoperatively, %	6 [9.0]	10 [9.9]	1.00
Veno-venous cannulation, %	4 [66.7]	3 [30.0]	0.44
Veno-arterial cannulation, %	2 [33.3]	7 [70.0]	0.32
Indication for transplantation			
COPD, %	24 [35.8]	38 [37.6]	0.87
Cystic fibrosis or bronchiectasis, %	19 [28.4]	11 [10.9]	< 0.01
Pulmonary fibrosis, %	23 [34.3]	50 [49.5]	0.06
Pulmonary hypertension, %	1 [1.5]	2 [2.0]	1.00
Preoperative anticoagulation			
Acetylsalicylic acid, %	3 [4.5]	8 [7.9]	0.53
P2Y12 antagonists, %	2 [3.0]	1 [1.0]	0.56
Direct oral anticoagulants, %	1 [1.5]	2 [2.0]	1.00
Vitamin K antagonists, %	2 [3.0]	5 [5.0]	0.70
Preoperative laboratory values			
Hemoglobin, mmol/liter	8.4 [6.9; 9.1]	8.4 [7.4; 9.3]	0.37
Platelet count, billion/liter	277 [194; 327]	276 [221; 316]	0.65
International normalized ratio	1.0 [1.0; 1.2]	1.0 [0.9; 1.1]	0.11
Creatinine, µmol/liter	68 [56; 79]	68 [59; 84]	0.30
Fibrinogen, g/liter	4.5 [4.0; 5.3]	3.8 [3.2; 4.6]	< 0.01
Missing, %	6 [9.0]	4 [4.0]	

Abbreviations: COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; ROTEM, rotational thromboelastometry.

Continuous data are presented as median [IQR], ratios are presented as count [%], missing data are reported as count [%].

deairing was performed before the lung was reperfused. After successful reperfusion of both lungs, chest tubes were inserted, and the incision was closed.

Intraoperative anesthetic management

Anesthetic management was identical in both study groups. Before anesthetic induction, arterial blood gas analysis and POC activated clotting time were measured. Invasive blood pressure monitoring, double lumen endobronchial tube, a 5-lumen central line with continuous venous pressure monitoring, venous catheters and urinary catheter with continuous temperature management were executed and a transesophageal ultrasound was performed. Antibiotic prophylaxis was administered according to local protocol.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS version 26.0 for Mac OS, IBM Corp., Armonk NY). Figures were made in R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). Discrete variables were presented as count (%) and continuous variables as median (interquartile range (IQR)). For determination of normality, distribution of the histograms was inspected, combined with Kolmogorov-Smirnov testing. An unpaired 2-sided Student t-test was utilized in normally distributed data and a Mann-Whitney U test otherwise. For discrete data, Fisher's exact testing was used. Sensitivity analysis was performed to stratify for ECC techniques during surgery for primary outcomes. Multivariable linear regression analyses were executed to correct for confounders to determine the effects of a ROTEM-guided transfusion algorithm on the primary outcomes. Potential confounders consisted of variables that differed significantly at baseline or intraoperatively or were selected based on existing literature. Determining which of those confounders to include in the multivariable analysis was executed per outcome variable. Variables were included in case of a p-value ≤0.1 in the univariable analysis. Normal distribution of residuals was assessed. p-values ≤0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 167 patients were included. Between 2010 and 2014, clinically guided bleeding management was applied in 66 patients (control group) and between 2017 and 2020, the ROTEM-guided bleeding management was applied in

Table 2 Intraoperative and Postoperative Variables

	Clinically guided (n = 66)	ROTEM-guided (n = 101)	p-value
Intraoperative variables			
Ex-vivo lung perfusion	0 [0.0]	12 [11.9]	< 0.01
Clamshell incision, %	66 [100]	28 [27.7]	< 0.01
Duration of surgery, minutes	575 [515; 646]	555 [460; 701]	0.42
Bilateral anterolateral incision, %	0 [0.0]	73 [72.3]	< 0.01
Duration of surgery, minutes	0 [0.0]	517 [452; 601]	NA
Cardiopulmonary bypass, %	40 [60.6]	37 [36.6]	< 0.01
Cardiopulmonary bypass duration, minutes	251 [225; 300]	263 [181; 320]	0.64
ECMO intraoperatively	0 [0.0]	6 [5.9]	0.08
Veno-venous cannulation, %	0 [0.0]	2 [2.0]	0.51
Veno-arterial cannulation, %	0 [0.0]	4 [4.0]	0.15
Ischemia time, minutes			
First lung	251 [225; 300]	273 [240; 308]	0.03
Missing, %	1 [1.5]	6 [5.9]	
Second lung	376 [331; 419]	420 [375; 480]	< 0.01
Missing, %	1 [1.5]	6 [5.9]	
Autologous blood returned, ml	1165 [460; 2,305]	825 [410; 1,570]	0.05
Postoperative laboratory variables			
Hemoglobin, mmol/liter	6.5 [6.0; 8.0]	7.0 [6.3; 8.1]	0.15
International normalized ratio	1.3 [1.2; 1.4]	1.3 [1.2; 1.5]	0.10
Platelet count, billion/liter	109 [82; 159]	134 [107; 221]	< 0.01
Fibrinogen, g/liter	2.3 [1.8; 2.8]	2.4 [1.9; 2.8]	0.49
Missing, %	6 [9.1]	3 [3.0]	
ECMO postoperatively	7 [11.9]	19 [18.8]	0.24
Veno-venous cannulation, %	4 [6.1]	3 [3.0]	0.44
Veno-arterial cannulation, %	3 [4.5]	16 [15.8]	0.09

Abbreviations: ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; ROTEM, rotational thromboelastometry.
Continuous data are presented as median [IQR], ratios are presented as count [%], missing data are reported as count [%].

101 patients (intervention group). Baseline characteristics are presented in Table 1. Overall, most patient characteristics in both groups were comparable. The intervention group had a higher median age (55 years [42; 60] vs 58 years [51; 62]; $p = 0.01$), a higher BMI (22.7 [20.0; 26.0] vs 24.3 [21.0; 28.2], $p = 0.02$), and less cystic fibrosis (CF) as indication for LTx (28% vs 10%, $p < 0.01$). The fibrinogen level was slightly higher in the control group (4.5 [4.0; 5.3] g/liter vs 3.8 [3.2; 4.6] g/liter, $p < 0.01$). No statistically significant differences were found regarding clinical bridging to transplantation on the ward or ICU prior to surgery (39% vs 27%, $p = 0.13$; 13% vs 10%, $p = 0.63$, respectively). Preoperative ECMO rates were similar (9% vs 10%, $p = 1.00$). Additionally, preoperative anticoagulation rates were comparable, alongside hemoglobin, platelet count, and international normalized ratio.

Intraoperative and postoperative characteristics

Table 2 shows intraoperative and postoperative details. Postoperative hemoglobin, international normalized ratio, and fibrinogen did not differ significantly. Platelet count was higher in the intervention group (109 billion/liter [82; 159] vs 134 billion/liter [107; 221], $p < 0.01$). Postoperative ECMO rates were not significantly different (12% vs 19%, $p = 0.24$). In the control group, all patients underwent a clamshell incision vs 27% in the intervention group ($p < 0.01$). The other patients underwent LTx with the bilateral anterolateral thoracotomy technique. In the control group, no ex-vivo lung perfusion (EVLP) was used, while in the intervention group this was used in 12% of the cases ($p < 0.01$). In case ECC was needed intraoperatively, ECMO was used instead of CPB in 7% of the patients in the intervention group (3% veno-venous ECMO, 4% veno-arterial ECMO), whereas in patients in the control group only CPB was used ($p = 0.08$). CPB was used significantly less in the intervention group (60% vs 37%, $p < 0.01$).

Primary and secondary outcomes

Table 3 shows primary and secondary outcomes. The intervention group received less median RBCs (7 units [3; 13] vs 4 units [1; 9], $p < 0.01$), platelet concentrate (2 units [0; 3] vs 0 unit [0; 2], $p < 0.01$), and plasma volume (2,310 ml [1,320; 3960] vs 800 ml [0; 1,600], $p < 0.01$) (Figure 1). The percentage of patients transfused with RBCs, platelet concentrate, and plasma all decreased significantly.

Multivariable regression analysis of the primary outcomes showed that after adjusting for indication for transplantation, ICU admission prior to surgery, ECMO prior to

Table 3 Primary and Secondary Outcomes

	Clinically guided (n = 66)	ROTEM-guided (n = 101)	p-value
Primary outcomes			
Red blood cells, units	7 [3; 13]	4 [1; 9]	< 0.01
Platelet concentrate, units	2 [0; 3]	0 [0; 2]	< 0.01
Plasma volume, ml	2310 [1320; 3960]	800 [0; 1600]	< 0.01
Secondary outcomes			
Red blood cell transfusion, %	62 [93.9]	74 [73.3]	< 0.01
Platelet concentrate transfusion, %	46 [69.7]	39 [38.6]	< 0.01
Plasma transfusion, %	59 [89.4]	68 [67.3]	< 0.01
PCC, %	4 [6.1]	27 [27.0]	< 0.01
Fibrinogen concentrate, %	11 [16.7]	44 [44.0]	< 0.01
Desmopressin, %	4 [6.1]	1 [1.0]	0.08
rVIIa, %	1 [1.5]	1 [1.5]	1.00
Tranexamic acid, g	4 [2; 5.38]	3.14 [0; 4.50]	< 0.01
Duration of mechanical ventilation, d	2 [1; 7]	2 [1; 6]	0.61
ICU length of stay, d	14 [5; 42]	6 [4; 21]	< 0.01
Hospital length of stay, d	28 [21; 40]	21 [15; 35]	0.02
Surgical re-exploration due to bleeding, %	13 [19.7]	16 [15.8]	0.54
In-hospital mortality, %	6 [9.1]	16 [15.8]	0.25
One year mortality, %	11 [16.7]	21 [20.8]	0.51

Abbreviations: ICU, intensive care unit; IQR, interquartile range; PCC, prothrombin complex concentrate; rVIIa, recombinant factor VIIa; ROTEM, rotational thromboelastometry.

Continuous data are presented as median [IQR] and ratios are presented as count [%].

surgery, CPB use or surgical technique, on average 1293 ml less plasma was used with the ROTEM-guided transfusion strategy (β −12.93 [95%CI −23.72; −2.13], $p = 0.02$) (Table 4). ROTEM-guided transfusion had no significant association with RBC (β 2.39 [95%CI −1.58; 6.37], $p = 0.24$) and platelet concentrate transfusion (β 0.26 [95%CI −1.13; 1.66], $p = 0.71$) after correction for potential confounders. CF as indication for transplantation was

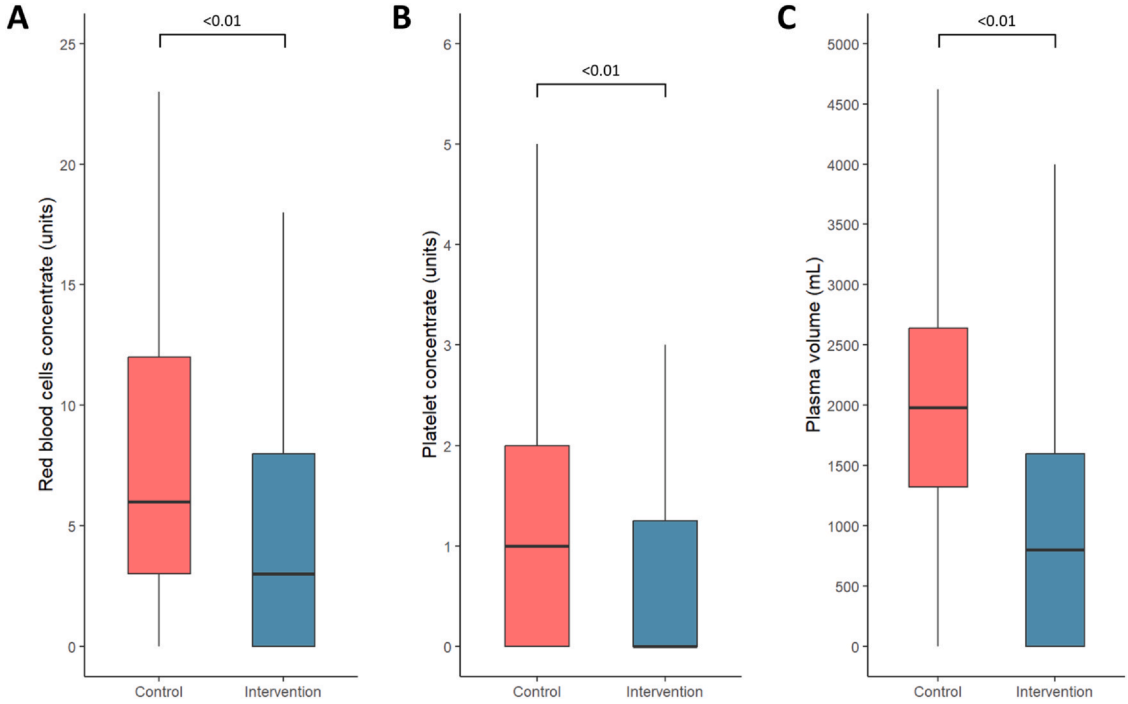

Figure 1 Difference between control and intervention group in transfusion of (**A**) red blood cells concentrate (units); (**B**) platelet concentrate (units); (**C**) plasma volume (ml).

Table 4 Multivariable Regression Analysis

	Beta coefficient	Confidence interval [95%]	*p*-value
Red blood cell transfusion			
ROTEM-guided bleeding management	2.39	−1.58; 6.37	0.24
Cystic fibrosis vs other causes	4.40	0.72; 8.08	0.02
Preoperative hemoglobin	−0.93	−2.14; 0.28	0.13
ECMO prior to surgery	5.04	0.46; 9.63	0.03
ICU admission prior to surgery	−1.12	−8.21; 5.98	0.76
Clamshell vs bilateral anterolateral thoracotomy	2.77	−1.17; 6.70	0.17
Cardiopulmonary bypass during surgery	10.42	7.57; 13.29	< 0.01
Platelet concentrate transfusion			
ROTEM-guided bleeding management	0.26	−1.13; 1.66	0.71
Cystic fibrosis vs other causes	1.44	0.17; 2.71	0.03
Preoperative platelet count (per 10)	−0.05	−0.10; 0.01	0.10
ICU admission prior to surgery	−0.46	−2.67; 1.75	0.68
ECMO prior to surgery	1.03	−0.54; 2.61	0.20
Clamshell vs bilateral anterolateral thoracotomy	−0.07	−1.31; 1.45	0.92
Cardiopulmonary bypass during surgery	2.96	1.96; 3.34	< 0.01
Plasma transfusion (per 100 ml)			
ROTEM-guided bleeding management	−12.93	−23.72; −2.13	0.02
Cystic fibrosis vs other causes	9.37	−0.45; 19.24	0.06
ICU admission prior to surgery	−0.07	−17.10; 17.24	0.99
ECMO prior to surgery	16.47	4.44; 28.48	< 0.01
Clamshell vs bilateral anterolateral thoracotomy	−0.10	−10.64; 10.84	0.99
Cardiopulmonary bypass during surgery	21.52	13.78; 29.24	< 0.01

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; ROTEM, rotational thromboelastometry.
Preoperative thrombocyte count is categorized per 10 units.

associated with increased RBC and platelet concentrate transfusion. Surgical technique and ICU admission prior to surgery were not associated with increased transfusion of allogenic blood products. Supplementary Table B2 shows the outcomes of the regression analyses.

Regarding secondary outcomes, the intervention group received more PCC (6% vs 27%, $p < 0.01$), fibrinogen concentrate (17% vs 44%, $p < 0.01$), and less tranexamic acid (4 g [4; 5.38] vs 3.14 g [0; 4.50], $p < 0.01$). Administration rates of rVIIa and desmopressin were comparable. ICU and hospital LOS were significantly shorter (14 days [5; 42] vs 6 days [4; 21], $p < 0.01$ and 28 days [21; 40] vs 21 days [15; 35], $p = 0.02$, respectively) in the intervention group, while surgical re-exploration due to bleeding (20% vs 16%, $p = 0.54$) and duration of mechanical ventilation were comparable.

Extracorporeal circulation

Sensitivity analyses regarding the effect of ECC use on the primary outcomes are displayed in Supplementary Table B1. Patients who underwent surgery without ECC received significantly less transfusion of all blood products after introduction of ROTEM-guided transfusion (RBCs 3 units [2; 4] vs 1 unit [0; 3], $p < 0.01$; platelet concentrate 0 units [0; 1] vs 0 units [0; 0], $p = 0.01$, plasma volume 1,320 ml [660; 1,980] vs 200 ml [0; 1,000], $p < 0.01$). In patients transplanted using CPB only, there were no significant differences in RBC or platelet concentrate transfusion, but plasma transfusion was significantly lower in the intervention group compared to the control (3,300 ml [2,145; 4,785] vs 1,600 ml [800; 3,200], $p < 0.01$).

In the multivariable analysis, CPB use during surgery had a significant effect on RBC, platelet concentrate, and plasma transfusion. ECMO during surgery did not have a significant association with any of the primary outcomes (Supplementary Table B2). When corrected for other factors, red blood cell transfusion was increased by 5.04 units (β 5.04 [95%CI 0.46; 9.63], $p = 0.03$) and plasma transfusion by 1,674 ml (β 16.47 [95%CI 4.44; 28.48], $p < 0.01$) in patients receiving ECMO prior to surgery compared to patients who did not.

Discussion

To improve perioperative care for LTx surgery patients, the effects of ROTEM-guided bleeding management on blood product transfusion and patient outcomes were investigated. Following introduction of ROTEM-guided bleeding management, there was a significant decrease in transfusion of RBCs, platelet concentrate, and plasma. After adjustment for confounders, the effect on plasma transfusion persisted. At the same time, the implementation of ROTEM-guided transfusion increased the rate of administration of PCC and fibrinogen concentrate. Hospital and ICU LOS decreased significantly, while duration of mechanical ventilation and

rates of surgical re-exploration and mortality were similar in both groups.

After the introduction of ROTEM-guided bleeding management, less blood products were needed. This is in concordance with 2 prior studies on this topic.[12,13] Durila et al found in their RCT that perioperative blood loss was decreased and that there was a lower perioperative need for RBCs and fresh frozen plasma in patients in whom the ROTEM-guided strategy was used compared to a clinically guided strategy.[12] Plasma transfusion was avoided, if possible, in the ROTEM group. In another retrospective cohort study by Smith et al, significantly less patients received RBCs, fresh frozen plasma, and platelet transfusion when ROTEM was introduced.[13] However, these studies did not perform multivariable regression analysis of the primary outcomes. In our study, after adjusting for confounders, such as use of CBP, indication for transplantation, and surgical technique, ROTEM-guided transfusion was solely associated with decreased plasma transfusion in our study. Overall, ROTEM-guided transfusion seems an effective tool to reduce plasma transfusion. This is relevant, as minimizing plasma transfusion reduces the incidence of transfusion-associated circulatory overload and right ventricular failure.[16-20]

This study distinguishes itself from other studies by including patients transfused with CPB in the study cohort. In the multivariable regression analysis, CPB use was associated with increased RBC, platelet concentrate, and plasma transfusion, whereas intraoperative ECMO use was not significantly associated with any of the primary outcomes. This corroborates findings from others, even though some only investigated or found significant differences in RBC transfusion.[21,22] In another study by Durila et al in which either intraoperative ECMO or no ECC was used, ECMO patients needed more RBC transfusion, but not platelet transfusion.[12] Two recent meta-analyses demonstrated that the use of intraoperative ECMO instead of CPB can be associated with a lower rate of PGD, bleeding, renal failure requiring dialysis, and tracheostomy, along with fewer intraoperative transfusions, shorter intubation time, ICU LOS, and hospital LOS.[23,24] Also, in other recent studies, CPB assistance was related with higher mortality, more RBC transfusion, and more PGD.[25,26] On the contrary, in a propensity-matched analysis comparing intraoperative VA-ECMO to CPB in bilateral LTx, Chan et al showed that patients with VA-ECMO needed more intraoperative blood products, while there was a significantly lower postoperative transfusion need.[27] This contrasts our results, as we found that CPB was associated with increased use of blood products, but intraoperative ECMO was not. A difference to this study is the propensity-matched analysis they performed, using 5 variables that were expected to impact their primary outcomes. These variables were age, lung allocation score, history of thoracic surgery, and RV dilation and dysfunction. These are not fully in concordance with our study, because these variables were either not significant in our univariable regression analysis or the data were not present. Taking available literature and our analysis into account, CPB seems to impact transfusion as well as clinical outcomes negatively and intraoperative VA-ECMO should be considered when feasible in patients when ECC is necessary.

After stratification, the ROTEM-guided strategy reduced transfusion of all blood products in patients without ECC. However, in patients who underwent LTx with CPB, ROTEM-guided transfusion only significantly reduced plasma transfusion. This may indicate that ROTEM-guided transfusion can be more effective in reducing blood product transfusion in patients transplanted without the use of ECC.

Over time, novel insights and surgeon's preferences have altered the surgical approach during LTx, which led to several intraoperative differences between the 2 cohorts. Whereas the clamshell incision was routinely used in the first cohort, this has gradually shifted to a less invasive bilateral anterior thoracotomy approach. The thoracotomy incision was associated with less blood loss and reduced need for blood or platelet transfusion, shorter duration of mechanical ventilation duration, and shorter ICU LOS in prior studies.[28-34] Because in our intervention group the majority (72%) of patients received a bilateral thoracotomy incision instead of clamshell, it is possible that the difference in outcomes is in part attributable to this difference in surgical approach. However, the surgical approach was not significantly associated with transfusion requirement in our multivariable regression analysis. The distribution of indications for LTx has changed over time, which may in part explain the reduction in blood product transfusion in our later cohort. The proportion of patients transplanted for CF decreased, largely owing to novel CFTR therapy.[35] Pulmonary fibrosis became the most important indication for LTx in the later cohort. CF as indication for LTx was associated with increased RBC and platelet transfusion after correction for confounders. Furthermore, higher baseline fibrinogen levels in the clinically guided group could be attributed to higher incidence of CF. Similarly, Cernak et al found that LTx for CF was often associated with massive transfusion requirement.[21]

Hospital and ICU LOS decreased significantly over time. Although many factors are of influence, reduction of fluid overload due to less plasma transfusion may have played a role in this improvement, as fluid overload is associated with increased LOS.[36]

Because of prohemostatic medication use in the ROTEM-guided bleeding management, administration of fibrinogen concentrates, and PCC increased significantly. This raises concern on possible adverse outcomes, such as thromboembolic events. Although current literature is inconclusive regarding this topic in transplantation surgery, in high-risk cardiac surgery there seems to be no increased risk of thromboembolic events when PCC is administered with guidance of thromboelastometry.[37,38] However, due to insufficient literature, the consensus statement on PCC use states caution is necessary, especially in patients with high thromboembolic risk.[39]

Lastly, another difference that occurred between the groups was use of EVLP. This technique was introduced after implementation the ROTEM-guided bleeding management. However, EVLP is unlikely to influence transfusion requirements. Regardless of the COVID-19 pandemic, there were no blood shortages at our institution.

Strengths and limitations

To our knowledge, this study is the largest cohort study evaluating the effects of ROTEM-guided bleeding management in patients undergoing bilateral LTx to date. The wide spectrum of patient characteristics, intraoperative and surgical techniques increase the generalizability of this study.

The retrospective nature of this study forms a limitation, especially as over time patients and procedures may have been subject to change. The heterogeneity between groups poses a potential source of bias. However, this has been addressed using multivariable linear regression models to adjust for potential confounders for the primary endpoints and sensitivity analyses, but should be kept in mind, especially when interpreting the unadjusted estimates. Additional confounding through unreported variables is always a possibility, however the most important known factors have been accounted for and protocols have largely remained the same over time. Furthermore, our recently published study on ROTEM-guided bleeding management in proximal aortic surgery with deep hypothermic circulatory arrest shows a clinically significant decrease in transfusion needs, especially plasma transfusion. This underlines our hypothesis that implementation of an ROTEM-guided hemostasis strategy reduces transfusion needs in our institution, even when taking the heterogeneity into account. Moreover, it is possible that the study was underpowered for some characteristics and outcomes. Also, no data were available on effect of an ROTEM-guided transfusion strategy on PGD and thromboembolic events.

Conclusion

This study is the largest retrospective study to date to assess the effects of ROTEM-guided bleeding management on blood transfusion in LTx patients with and without intraoperative ECC. After adjusting for potential confounders, ROTEM-guided bleeding management was associated with reduced plasma transfusion. CPB seems to negatively affect blood transfusion need, urging development of an optimal ECC strategy for this group of patients. Additionally, ICU and hospital LOS were shorter in the ROTEM-guided group. Overall, the findings in this study show that adequate coagulation in patients undergoing LTx surgery is a complex process. Multiple factors play a role, and more research is needed to minimalize use of blood products and improve patient outcomes. Furthermore, safety of prohemostatic agents in LTx needs to be determined.

CRediT authorship contribution statement

All authors contributed to the study design and by writing and critically revising the manuscript. The first and second authors contributed to gathering and analyzing data, as well.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

We would like to thank Ted Reniers, MD, for his help in data extraction.

The authors declare no financial conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100055.

References

1. Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Intensive Care Med 2004;30:51-61.
2. Elmaleh Y, De Tymowski C, Zappella N, et al. Blood transfusion of the donor is associated with stage 3 primary graft dysfunction after lung transplantation. Clin Transplant 2021;35:e14407.
3. Ognjen G, Rimki R, Jeffrey LW, et al. Transfusion-related acute lung injury in the critically Ill. Am J Respir Crit Care Med 2007;176:886-91.
4. Popovsky MA. Transfusion-associated circulatory overload: the plot thickens. Transfusion 2009;49:2-4.
5. Surgenor SD, Kramer RS, Olmstead EM, et al. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg 2009;108:1741-6.
6. Weber D, Cottini SR, Locher P, et al. Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. Perioper Med 2013;2:20.
7. Görlinger K, Shore-Lesserson L, Dirkmann D, Hanke AA, Rahe-Meyer N, Tanaka KA. Management of hemorrhage in cardiothoracic surgery. J Cardiothorac Vasc Anesth 2013;27(Suppl 4):S20-34.
8. Bolliger D, Tanaka KA. Roles of thrombelastography and thromboelastometry for patient blood management in cardiac surgery. Transf Med Rev 2013;27:213-20.
9. Deppe A-C, Weber C, Zimmermann J, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: a meta-analysis of 8332 patients. J Surg Res 2016;203:424-33.
10. Li C, Zhao Q, Yang K, Jiang L, Yu J. Thromboelastography or rotational thromboelastometry for bleeding management in adults undergoing cardiac surgery: a systematic review with meta-analysis and trial sequential analysis. J Thorac Dis 2019;11:1170-81.
11. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev 2016.
12. Durila M, Vajter J, Garaj M, et al. Rotational thromboelastometry reduces blood loss and blood product usage after lung transplantation. J Heart Lung Transplant 2021;40:631-41.
13. 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;31:426-33.
14. Karrar S, Reniers T, Filius A, et al. Rotational thromboelastometry-guided transfusion protocol to reduce allogeneic blood transfusion in proximal aortic surgery with deep hypothermic circulatory arrest. J Cardiothorac Vasc Anesth 2022;36:1029-39.
15. Weber Christian F, Görlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology 2012;117:531-47.

16. Bolton-Maggs PH, Cohen H. Serious hazards of transfusion (SHOT) haemovigilance and progress is improving transfusion safety. Br J Haematol 2013;163:303-14.
17. Clifford L, Jia Q, Subramanian A, Yadav H, Schroeder DR, Kor DJ. Risk factors and clinical outcomes associated with perioperative transfusion-associated circulatory overload. Anesthesiology 2017;126: 409-18.
18. Desborough M, Sandu R, Brunskill SJ, et al. Fresh frozen plasma for cardiovascular surgery. Cochrane Database Syst Rev 2015;2015 :CD007614.
19. Refaai MA, Goldstein JN, Lee ML, Durn BL, Milling Jr. TJ, Sarode R. Increased risk of volume overload with plasma compared with four-factor prothrombin complex concentrate for urgent vitamin K antagonist reversal. Transfusion 2015;55:2722-9.
20. Sarode R, Milling Jr. TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43.
21. Cernak V, Oude Lansink-Hartgring A, van den Heuvel ER, et al. Incidence of massive transfusion and overall transfusion requirements during lung transplantation over a 25-year period. J Cardiothorac Vascu Anesth 2019;33:2478-86.
22. Wang Y, Kurichi JE, Blumenthal NP, et al. Multiple variables affecting blood usage in lung transplantation. J Heart Lung Transplant 2006;25:533-8.
23. Hoechter DJ, Shen Y-M, Kammerer T, et al. Extracorporeal circulation during lung transplantation procedures: a meta-analysis. ASAIO J 2017;63:551-61.
24. 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;66:38-47.
25. Loor G, Huddleston S, Hartwig M, et al. Effect of mode of intraoperative support on primary graft dysfunction after lung transplant. J Thorac Cardiovasc Surg 2022;164:1351-61.
26. Ruszel N, Kiełbowski K, Piotrowska M, et al. Central, peripheral ECMO or CPB? Comparsion between circulatory support methods used during lung transplantation. J Cardiothorac Surg 2021;16:341.
27. Chan EG, Hyzny EJ, Furukawa M, et al. Intraoperative support for primary bilateral lung transplantation: a propensity matched analysis. Ann Thorac Surg 2022;115:743-9.
28. Bittner HB, Lehmann S, Binner C, Garbade J, Barten M, Mohr FW. Sternum sparing thoracotomy incisions in lung transplantation surgery: a superior technique to the clamshell approach. Innovations (Phila) 2011;6:116-21.
29. Giménez-Milà M, Videla S, Pallarés N, et al. Impact of surgical technique and analgesia on clinical outcomes after lung transplantation: a STROBE-compliant cohort study. Medicine (Baltimore) 2020;99:e22427.
30. Marczin N, Popov AF, Zych B, et al. Outcomes of minimally invasive lung transplantation in a single centre: the routine approach for the future or do we still need clamshell incision? Interact Cardiovasc Thorac Surg 2016;22:537-45.
31. Meyers BF, Sundaresan RS, Guthrie T, Cooper JD, Patterson GA. Bilateral sequential lung transplantation without sternal division eliminates posttransplantation sternal complications. J Thorac Cardiovasc Surg 1999;117:358-64.
32. Palleschi A, Lomauro A, Privitera E, et al. Clamshell vs bilateral anterolateral thoracotomy for double lung transplantation: impact on vital capacity. Eur Respir J 2020;56(Suppl 64):1941.
33. Taghavi S, Bîrsan T, Seitelberger R, et al. Initial experience with two sequential anterolateral thoracotomies for bilateral lung transplantation. Ann Thorac Surg 1999;67:1440-3.
34. Venuta F, Rendina EA, De Giacomo T, et al. Bilateral sequential lung transplantation without sternal division. Eur J Cardio-Thorac Surg 2003;23:894-7.
35. Pierre-Régis B, Isabelle D, Raphaël C, et al. Rapid improvement after starting elexacaftor–tezacaftor–ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. Am J Respir Crit Care Med 2021;204:64-73.
36. Magee G, Zbrozek A. Fluid overload is associated with increases in length of stay and hospital costs: pooled analysis of data from more than 600 US hospitals. Clinicoecon Outcomes Res 2013;5:289-96.
37. Li JY, Gong J, Zhu F, et al. Fibrinogen concentrate in cardiovascular surgery: a meta-analysis of randomized controlled trials. Anesth Analg 2018;127:612-21.
38. Roman M, Biancari F, Ahmed AB, et al. Prothrombin complex concentrate in cardiac surgery: a systematic review and meta-analysis. Ann Thorac Surg 2019;107:1275-83.
39. Erdoes G, Koster A, Ortmann E, et al. A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. Anaesthesia 2021;76:381-92.