Original Article

Contrasting predictors of severe primary graft dysfunction following transplant for chronic and acute respiratory failure

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Background: Lung transplantation represents a pivotal intervention for individuals grappling with end-stage lung diseases, and the role of lung transplantation in acute respiratory distress syndrome (ARDS) patients has garnered increased attention especially after the coronavirus disease 2019 (COVID-19) pandemic. Multiple studies have demonstrated a high incidence of primary graft dysfunction (PGD) in patients with ARDS compared to contemporaneous controls undergoing transplantation for chronic end-stage lung diseases although underlying mechanisms or risk factors remain unknown. This retrospective study investigates the contrasting risk factors for PGD grade 3 in patients with ARDS and chronic respiratory failure undergoing lung transplantation.

Methods: The study included 293 patients who underwent lung transplantation from January 2018 through June 2023. We performed a multivariate logistic regression analysis using variables from the univariate logistic regression analyses to predict PGD grade 3.

Results: Our findings reveal distinct predictors for PGD grade 3 in the two cohorts. ARDS patients had higher incidence of PGD grade 3 than non-ARDS patients (30.2% *vs.* 9.6%, P<0.001). Multivariate logistic regression analysis showed ischemic time [odds ratio (OR) =0.60; 95% confidence interval (CI): 0.40–0.90; P=0.01] as predictor of PGD grade 3 for non-ARDS patients, and age (OR =0.72; 95% CI: 0.52–0.99; P=0.048), pre-operative albumin (OR <0.01; 95% CI: <0.01–0.74; P=0.042) for ARDS patients. Interestingly, there was no notable difference in post-transplant survival between the two groups.

Conclusions: This study highlights differing risk profiles for severe PGD in ARDS and non-ARDS lung transplant recipients, underscoring the need for tailored approaches in managing these patients. It paves the way for further research to refine strategies aimed at reducing PGD incidence and enhancing transplant outcomes in these distinct populations.

Keywords: Acute respiratory distress syndrome (ARDS); lung transplant; primary graft dysfunction (PGD)

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Introduction

Background

Lung transplantation represents a pivotal intervention for individuals grappling with end-stage lung diseases, offering a renewed chance at life. In the U.S., the field has progressed to performing around 2,500 transplants annually with a steady increase (1). However, primary graft dysfunction (PGD), a form of severe acute lung injury occurring within 72 hours post-transplantation, remains a formidable challenge, often resulting in early morbidity and mortality (2,3). The existing body of research on lung transplantation and PGD has identified several risk factors, such as prolonged ischemic time and the use of intraoperative cardiopulmonary bypass (4-11).

Knowledge gap

However, a significant knowledge gap exists, particularly in the context of acute respiratory distress syndrome (ARDS), a condition with notably high mortality (12). The role of lung transplantation in ARDS management, especially in the wake of the coronavirus disease 2019 (COVID-19) pandemic, has garnered increased attention (13,14), and it is an accepted indication by both the U.S. (Organ Procurement and Transplant Network) and Europe (Eurotransplant) regulatory bodies. However, multiple studies have demonstrated a high incidence of PGD in patients with ARDS compared to contemporaneous controls undergoing transplantation for chronic end-stage lung diseases although underlying mechanisms or risk factors remain unknown (11,15,16). Nevertheless, this disproportionately high incidence of PGD in patients with acute respiratory failure provides a unique opportunity to identify the contrasting clinical risk factors predisposing the two groups of patients which would not only improve our insights into the pathogenesis of PGD but enable better patient selection for transplant.

Objective

Accordingly, this study seeks to bridge this gap by comparing the risk factors for PGD in two distinct patient cohorts: those with ARDS and those with chronic respiratory failures, such as interstitial lung disease and chronic obstructive pulmonary disease. Through a retrospective analysis of lung transplant recipients in these categories, our research aims to illuminate specific risk factors contributing to PGD, thereby enhancing our understanding and management of this critical post-transplant complication.

Highlight box

Key findings

- Lung transplantation represents a pivotal intervention for individuals grappling with end-stage lung diseases, but primary graft dysfunction (PGD) remains an early morbidity and mortality.

What is known and what is new?

- Known risk factors of PGD are prolonged ischemic time and the use of intraoperative cardiopulmonary bypass. The role of lung transplantation in acute respiratory distress syndrome (ARDS) management, especially in the wake of the coronavirus disease 2019 pandemic, has garnered increased attention.
- Multiple studies have demonstrated a high incidence of PGD in patients with ARDS compared to traditional lung transplant patients. However, the risk of PGD in patients with ARDS has not been investigated.

What is the implication, and what should change now?

- This study highlights differing risk profiles for severe PGD in ARDS and non-ARDS lung transplant recipients, underscoring the need for tailored approaches in managing these patients. It paves the way for further research to refine strategies aimed at reducing PGD incidence and enhancing transplant outcomes in these distinct populations.

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Northwestern University (Nos. STU00207250 and STU00213616). The need for patient consent for data collection was waived by the institutional review board because this was a retrospective study. Patient data were collected retrospectively using electronic medical records that were stored in a lung transplant database at the Northwestern University Medical Center in Chicago, Illinois, USA. Consecutive adult patients who underwent lung transplantation at our institution from January 2018 to June 2023 were included. From the study, patients with multiorgan transplants and re-lung transplant were excluded. Data on patient demographics, comorbidities, donor characteristics, preoperative laboratory values, intraoperative, and postoperative outcomes were collected. ARDS patients were defined as listed diagnosis for lung transplant.

Definition of ARDS and indication and management of extracorporeal membrane oxygenation (ECMO)

ARDS was defined by accordance with the American-European Consensus Conference (AECC) (12,17). Intubated patients were managed by our multidisciplinary team led by critical care pulmonologists in the medical intensive care unit (ICU) in accordance with ARDSnet guidelines. Patients who developed respiratory failure were considered for ECMO if they fail to achieve satisfactory gas exchange (PaO_2 >55 mmHg, oxygen saturations >88%, pH >7.2, with plateau pressures less than 35) despite lung protective mechanical ventilation and recruitment maneuvers with neuromuscular blockade as well as prone ventilation, based on the Extracorporeal Life Support Organization (ELSO; www.elso.org). The decision to cannulate was made by a multidisciplinary ECMO team including pulmonologists, thoracic surgeons, ECMO specialists, and intensivists, using a multidisciplinary teleconference line. Different cannulation strategies [internal jugular vein-femoral vein cannulation or ProtekDuo® cannulation (CardiacAssist Inc., Pittsburgh, PA, USA)] were used. The venovenous extracorporeal membrane oxygenation (VV-ECMO) circuit included Quadrox iD adult (7.0) oxygenator (MAQUET Holding B.V. & Co. KG, Germany) and Rotaflow pump (MAQUET Holding B.V. & Co. KG). Patients did not receive continuous anticoagulation unless there was clinical and/or radiological evidence of a thrombotic complication including deep vein thrombosis (DVT), pulmonary embolism (PE), arterial thrombosis, etc. that warranted its use consistent with our prior reports (18-20). Patient received unfractionated heparin (5,000 U given subcutaneously every 8 hours) for deep venous thrombosis prophylaxis. To avoid thrombotic complications in ECMO circuit, flow was maintained at least 3.0–3.5 L/min consistent with our recent reports demonstrating the feasibility of using VV-ECMO without anticoagulation (18-20). Transfusion thresholds included: platelets <50,000/mL, hemoglobin <7 g/dL, or hemodynamic instability in the setting of active blood loss.

Immunosuppression management

Induction

- Methylprednisolone 1,000 mg via intravenous at intraoperatively;
- Basiliximab 20 mg at intraoperatively and postoperative day (POD) 4.

Maintenance immunosuppression

- Prednisone 0.5 mg/kg p.o. daily from POD 1. Maximum dose = prednisone 40 mg daily. 0.5 mg/kg daily for 1 month, then taper by 5 mg every 2 weeks down to 5 mg/day as a maintenance dose.
- Mycophenolate mofetil 1,000 mg b.i.d. from POD 1.
- Tacrolimus start POD 1. Goal target levels 8–12 within first year post-transplant; then target 8–10 thereafter.

Definition of complications

PGD

Patients with no evidence of pulmonary edema on chest X-ray (CXR) were considered grade 0. The absence of invasive mechanical ventilation was graded according to the PaO_2/FiO_2 ratio using methods similar to those used for mechanical ventilation. If PaO_2 was not available for calculation of the PaO_2/FiO_2 ratio, then an oxygen saturation/FiO_2 ratio was used. Grade 1: PaO_2/FiO_2 ratio >300; grade 2: PaO_2/FiO_2 ratio is 200–300; grade 3: PaO_2/FiO_2 ratio <200. The lowest PaO_2/FiO_2 ratio, within 72 hours of lung transplantation, was used. The use of ECMO for bilateral pulmonary edema on CXR images was classified as grade 3. Continuous use of ECMO without pulmonary edema on CXR imaging was excluded (21).

Acute kidney injury (AKI)

AKI was defined using the risk, failure, loss of kidney function, and the end-stage kidney disease classification (22).

Statistical analysis

Recipient and donor characteristics, preoperative laboratory values, and intra- and post-operative outcomes were compared between ARDS patients and non-ARDS patients. The Mann-Whitney *U* test or Student *t*-test was used to compare independent, continuous variables between the groups. The Chi-squared test was used to compare categorical variables, which were reported as numbers and percentages. The Kaplan-Meier test was used to estimate survival, while the Wilcoxon signed-rank test was performed to compare survival between the groups. Univariate logistic regression analyses were utilized to assess the ability of recipient and donor characteristics, and other intra-operative outcomes to predict PGD grade 3. We then

performed a multivariate logistic regression analysis using variables from the univariate logistic regression analyses with a P value <0.5 (6,10,20,23-26). Statistical significance was set at P<0.05. EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), and a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), were used to perform all of the analyses (27).

Results

Study cohort and transplant outcomes of ARDS and non-ARDS patients

This study included 301 patients who underwent lung transplantations during the study period. Of these, 5 patients underwent multi-organ transplantations and 3 patients underwent re-transplant were excluded. Consequently, a total of 293 patients were included in this study. We first compared the recipient's characteristics between ARDS and non-ARDS patients. Age was found to be higher in the recipients in the non-ARDS patients compared to the ARDS patients (59.8±11.9 *vs.* 50.3±11.2 years, P<0.001). The ARDS patients had lower prevalence of smoking history (20.9% *vs.* 52.4%, P<0.001), pre-transplant ECMO use (65.1% *vs.* 3.6%, P<0.001), pre-transplant blood transfusion within 4 weeks (58.1% *vs.* 3.2%, P<0.001), shorter wait list days {17 [7–43] *vs.* 9 [5–20] days, P<0.001}, lower hemoglobin (g/dL), platelet ($\times10^3$/mm^3), creatinine (mg/dL), and albumin (g/dL) levels (8.7±1.8 *vs.* 12.0±2.4 g/dL, P<0.001; 217.8±115.8 *vs.* 250.3±90.9 $\times10^3$/mm^3, P=0.04; 0.60±0.23 *vs.* 0.81±0.23 mg/dL, P<0.001; 3.6±0.6 *vs.* 3.9±0.5 g/dL, P<0.001; respectively) and higher sodium (mEg/L) and BUN (mg/dL) (141.0±4.1 *vs.* 139.5±3.3 mEq/L, P<0.01; 20.2±12.5 *vs.* 16.0±6.4 mg/dL, P<0.001; respectively). Additionally, there were no significant differences in donor characteristics between the two groups (*Table 1*).

We then determined whether there were differences in transplant outcomes between the two groups. The operative time and ischemic time were longer in the ARDS group [8.7 (7.7–9.7) *vs.* 5.8 (5.0–7.5) hours, P<0.001; 5.8 (5.2–6.1) *vs.* 4.9 (4.0–5.8) hours, P<0.001]. The use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) during lung transplantation were also higher in the ARDS group (97.7% *vs.* 57.2%, P<0.001). Intra-operatively, ARDS patients had significantly more blood product transfusions, including packed red blood cells (pRBC) {7 [3–14] *vs.* 0 [0–2] units, P<0.001}, fresh frozen plasma (FFP) {2 [0–6] *vs.* 0 [0–0] units, P<0.001}, and platelets {1 [0–3] *vs.* 0 [0–0] units, P<0.001}. Post-operatively, ARDS patients were more likely to require VV-ECMO (46.5% *vs.* 8.0%, P<0.001), and

Table 1 Patient characteristics by ARDS

Variables	ARDS group (n=43)	Non-ARDS group (n=250)	P value
Recipient factors			
Age (years)	50.3±11.2	59.8±11.9	<0.001
Female, n (%)	19 (44.2)	104 (41.6)	0.74
Body mass index (kg/m^2)	26.1±4.2	25.8±4.6	0.70
Body surface area (m^2)	1.9±0.2	1.9±0.2	0.71
Smoking history, n (%)	9 (20.9)	131 (52.4)	<0.001
Hypertension, n (%)	19 (44.2)	130 (52.0)	0.41
Diabetes, n (%)	15 (34.9)	75 (30.0)	0.59
Pre-transplant ECMO use, n (%)	28 (65.1)	9 (3.6)	<0.001
Bilateral lung transplant, n (%)	43 (100.0)	141 (56.4)	<0.001
Lung allocation score	82.0±14.6	50.6±15.7	<0.001
On the waiting list (days)	9 [5–20]	17 [7–43]	0.01
Pre-transplant blood transfusion within 4 weeks, n (%)	25 (58.1)	8 (3.2)	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variables	ARDS group (n=43)	Non-ARDS group (n=250)	P value
Etiology of lung failure, n (%)			
Interstitial lung disease	0 (0.0)	109 (43.6)	–
ARDS	43 (100.0)	0 (0.0)	–
COPD	0 (0.0)	55 (22.0)	–
Pulmonary artery hypertension	0 (0.0)	27 (10.8)	–
Other	0 (0.0)	59 (23.6)	–
Laboratory values			
Hemoglobin (g/dL)	8.7±1.8	12.0±2.4	<0.001
WBC ($\times10^3/mm^3$)	9.8±4.1	9.9±3.9	0.87
Platelets ($\times10^3/mm^3$)	217.8±115.8	250.3±90.9	0.04
Sodium (mEq/L)	141.0±4.1	139.5±3.3	<0.01
BUN (mg/dL)	20.2±12.5	16.0±6.4	<0.001
Creatinine (mg/dL)	0.60±0.23	0.81±0.23	<0.001
AST (U/L)	25.7±16.2	27.3±20.4	0.63
ALT (U/L)	20.5±13.3	20.5±17.4	0.98
Albumin (g/dL)	3.6±0.6	3.9±0.5	<0.001
Total bilirubin (mg/dL)	0.7±1.0	0.7±0.5	0.33
INR	1.2±0.2	1.1±0.2	0.07
PRA, n (%)	22 (51.2)	98 (39.2)	0.18
Arterial blood gas			
pH	7.40±0.07	7.37±0.07	0.05
$PaCO_2$ (mmHg)	50.0±12.7	49.1±11.0	0.62
PaO_2 (mmHg)	207.8±105.2	278.3±108.9	<0.001
Donor			
Age (years)	30.9±11.8	33.4±11.9	0.20
Female, n (%)	16 (37.2)	76 (30.4)	0.38
Cause of death, n (%)			
Head trauma	20 (46.5)	94 (37.6)	0.31
Anoxia	17 (39.5)	94 (37.6)	0.87
Other	6 (14.0)	62 (24.8)	0.17

Continuous data are shown as means ± standard deviation for age and laboratory data, and as medians and interquartile ranges [Q1–Q3]. Etiology of lung failure other: sarcoidosis, hypersensitivity pneumonitis, cystic fibrosis, bronchiectasis, obliterative bronchiolitis, bronchoalveolar carcinoma, primary ciliary dyskinesia. ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; PRA, panel reactive antibodies.

Table 2 Intra- and post-operative outcomes of lung transplant recipients by ARDS

Variables	ARDS group (n=43)	Non-ARDS group (n=250)	P value
Intra-operative outcomes			
Operative time (hours)	8.7 [7.7–9.7]	5.8 [5.0–7.5]	<0.001
Intra-op blood transfusion			
pRBC (units)	7 [3–14]	0 [0–2]	<0.001
FFP (units)	2 [0–6]	0 [0–0]	<0.001
Plt (units)	1 [0–3]	0 [0–0]	<0.001
Ischemic time (hours)	5.8 [5.2–6.1]	4.9 [4.0–5.8]	<0.001
Veno-arterial ECMO use, n (%)	42 (97.7)	143 (57.2)	<0.001
Post-operative outcomes			
Acute kidney injury, n (%)	26 (60.5)	99 (39.6)	0.01
Dialysis, n (%)	4 (9.3)	13 (5.2)	0.29
Stroke, n (%)	0 (0.0)	6 (2.4)	0.60
Bowel ischemia, n (%)	0 (0.0)	4 (1.6)	>0.99
Digital ischemia, n (%)	1 (2.3)	5 (2.0)	>0.99
PGD (any grade), n (%)	28 (65.1)	100 (40.0)	<0.01
PGD (grade 3), n (%)	13 (30.2)	24 (9.6)	<0.001
Post-transplant ECMO support, n (%)	20 (46.5)	20 (8.0)	<0.001
Intensive care unit stay (days)	20 [12–30]	7 [5–13]	<0.001
Post-transplant ventilator (days)	7 [2–18]	2 [1–3]	<0.001
Hospital stay (days)	29 [18–39]	16 [11–28]	<0.001

Continuous data are shown as medians and interquartile ranges [Q1–Q3]. ARDS, acute respiratory distress syndrome; pRBC, packed red blood cells; FFP, fresh frozen plasma; Plt, platelets; ECMO, extracorporeal membrane oxygenation; PGD, primary graft dysfunction.

had longer ICU admissions {20 [12–30] *vs.* 7 [5–13] days, P<0.001}, post-transplant ventilator requirements {7 [2–18] *vs.* 2 [1–3] days, P<0.001}, and overall hospital stays {29 [18–39] *vs.* 16 [11–28] days, P<0.001}. ARDS patients also had significantly higher incidences of post-operative PGD grade 3 (30.2% *vs.* 9.6%, P<0.001) and AKI (60.5% *vs.* 39.6%, P=0.01) (*Table 2*). Moreover, there was no difference in the post-transplant survival rate during the two periods (P=0.11, *Figure 1*).

Predictors of PGD grade 3: ARDS and non-ARDS patients

Predictors of PGD grade 3: non-ARDS patients

Univariate logistic regression analysis of donor and recipient characteristics, and intra-operative outcomes, revealed chronic kidney disease (CKD) history [odds ratio (OR) =4.69; 95% confidence interval (CI): 1.62–13.6; P=0.004], pre-transplant ECMO support (OR =8.84; 95% CI: 2.20–35.6; P=0.002), lung allocation score (OR =1.03; 95% CI: 1.01–1.05; P=0.02), pre-transplant blood transfusion within 4 weeks (OR =19.6; 95% CI: 4.34–88.2; P<0.001), pre-operative albumin (OR =0.36; 95% CI: 0.16–0.79; P=0.01), pre-operative total bilirubin (OR =2.16; 95% CI: 1.19–3.94; P=0.01), intra-operative pRBC transfusion (OR =1.15; 95% CI: 1.03–1.29; P=0.01), intra-operative platelets transfusion (OR =1.51; 95% CI: 1.11–2.06; P=0.009), and ischemic time (OR =0.67; 95% CI: 0.49–0.93; P=0.02) as predictive of PGD grade 3 development (*Table 3*). On subsequent multivariate logistic regression analysis, ischemic time (OR =0.60; 95% CI: 0.40–0.90; P=0.01) remained predictive (*Table 4*).

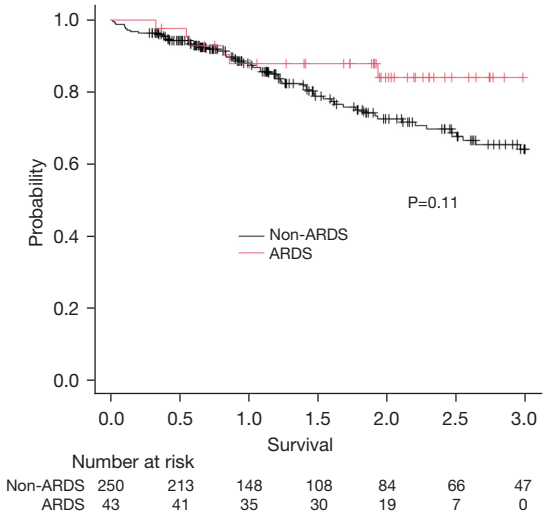

Figure 1 Kaplan-Meier analysis of overall survival after lung transplantation. Comparison of survival rates ARDS and non-ARDS patients. ARDS, acute respiratory distress syndrome.

Predictors of PGD grade 3: ARDS patients

Univariate logistic regression analysis of donor and recipient characteristics, and intra-operative outcomes, revealed age (OR =0.91; 95% CI: 0.85–0.98; P=0.008), bilateral lung transplant (OR =0.43; 95% CI: 0.23–0.83; P=0.01), pre-transplant blood transfusion within 4 weeks (OR =6.29; 95% CI: 1.18–33.3; P=0.03), pre-operative albumin (OR =0.26; 95% CI: 0.07–0.93; P=0.04), intra-operative pRBC transfusion (OR =1.17; 95% CI: 1.04–1.31; P=0.006), intra-operative FFP transfusion (OR =1.20; 95% CI: 1.04–1.38; P=0.01), and intra-operative platelets transfusion (OR =1.46; 95% CI: 1.06–2.01; P=0.02) as predictive of PGD grade 3 development (*Table 5*). On subsequent multivariate logistic regression analysis, age (OR =0.72; 95% CI: 0.52–0.99; P=0.048), pre-operative albumin (OR <0.01; 95% CI: <0.01–0.74; P=0.042) remained predictive (*Table 6*). The receiver operating characteristic (ROC) curve analysis showed that 46 was the cut-off value [area under the curve (AUC) =0.771] for the risk of PGD grade 3 in the ARDS patients (*Figure 2*).

Discussion

PGD represents a significant challenge in lung transplantation, markedly impacting early morbidity and mortality (2,3). Our study sheds light on the contrasting risk factors for PGD in patients with ARDS and those with chronic respiratory failure. This distinction is critical, as PGD is an umbrella term encompassing complex pathophysiological mechanisms in lung grafts, influenced by both the recipient's pre-existing condition and the transplantation process itself.

In patients with ARDS, we identified age and pre-operative albumin levels as significant predictors of PGD. ARDS, a rapidly progressive lung disease, often necessitates lung transplantation as a last resort due to its high mortality rate (12). The pre-transplant condition of these patients, characterized by heightened inflammation and compromised nutritional status reflected in albumin levels, plays a pivotal role in their susceptibility to PGD. In contrast, ischemic time stands out as a critical factor in patients with chronic respiratory failure. This aligns with the understanding that prolonged ischemic time exacerbates ischemia-reperfusion injury, a primary trigger for PGD.

Interestingly, studies have highlighted other risk factors, including donor smoking history, FiO_2 during allograft reperfusion, and the recipient's body mass index, as significant contributors to PGD development (4,28,29). Moreover, specific recipient-related factors, such as female gender, African American race, idiopathic pulmonary fibrosis, and sarcoidosis, have been associated with increased PGD risk (30,31). These findings point towards a multifactorial nature of PGD, where both donor and recipient characteristics, along with procedural variables, interplay to influence the outcome.

Comparing the outcomes of lung transplantation in ARDS *vs.* chronic lung diseases, the literature suggests that while lung transplantation remains controversial for

Table 3 Univariate logistic regression analysis to predict PGD grade 3 in non-ARDS group (n=250)

Variables	OR	95% CI	P value
Recipient factors			
Age	0.98	0.95–1.02	0.33
Female	1.46	0.63–3.38	0.38
Body mass index	0.99	0.90–1.08	0.77
Body surface area	0.77	0.14–4.22	0.76
Smoking history	0.90	0.39–2.09	0.81
Hypertension	0.76	0.33–1.77	0.53
Diabetes	0.96	0.38–2.41	0.93
CKD	4.69	1.62–13.6	0.004
Pre-transplant ECMO use	8.84	2.20–35.6	0.002
Bilateral lung transplant	1.09	0.47–2.56	0.84
Lung allocation score	1.03	1.01–1.05	0.02
Pre-transplant blood transfusion within 4 weeks	19.6	4.34–88.2	<0.001
Laboratory			
Hemoglobin	0.91	0.76–1.09	0.33
WBC	0.97	0.86–1.09	0.60
Platelets	1.00	0.99–1.00	0.32
Sodium	1.07	0.95–1.21	0.24
BUN	1.04	0.99–1.10	0.16
Creatinine	0.98	0.83–1.15	0.81
AST	1.01	1.00–1.03	0.16
ALT	1.00	0.97–1.02	0.77
Albumin	0.36	0.16–0.79	0.01
Total bilirubin	2.16	1.19–3.94	0.01
INR	3.32	0.86–12.8	0.08
PRA	1.96	0.84–4.57	0.12
Donor			
Age	1.00	0.97–1.04	0.83
Female	2.10	0.89–4.92	0.09
Intra-operative outcomes			
Operative time	0.99	0.97–1.02	0.64
Intra-op blood transfusion			
pRBC	1.15	1.03–1.29	0.01
FFP	1.22	1.00–1.49	0.05
Plt	1.51	1.11–2.06	0.009
Ischemic time	0.67	0.49–0.93	0.02
Veno-arterial ECMO use	1.93	0.77–4.83	0.16

PGD, primary graft dysfunction; ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; ECMO, extracorporeal membrane oxygenation; WBC, white blood cell; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; PRA, panel reactive antibodies; pRBC, packed red blood cells; FFP, fresh frozen plasma; Plt, platelets.

Table 4 Multivariate logistic regression analysis to predict PGD grade 3 in non-ARDS group (n=250)

Variables	OR	95% CI	P value
Recipient factors			
CKD	3.13	0.88–11.1	0.08
Pre-transplant ECMO use	0.31	0.01–9.09	0.50
Lung allocation score	1.00	0.97–1.03	0.86
Pre-transplant blood transfusion within 4 weeks	12.2	0.76–197	0.08
Laboratory			
Albumin	0.58	0.22–1.50	0.26
Total bilirubin	1.42	0.60–3.33	0.43
Intra-operative outcomes			
Intra-op blood transfusion			
pRBC	1.16	0.97–1.37	0.10
Ischemic time	0.60	0.40–0.90	0.01

PGD, primary graft dysfunction; ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; ECMO, extracorporeal membrane oxygenation; pRBC, packed red blood cells.

ARDS due to the acute nature of the disease, selected patients can achieve acceptable survival rates, comparable to those with chronic conditions (11,14). This is particularly noteworthy given the high survival rate in ARDS patients despite the severity of their pre-transplant condition and the complexities involved in their management, including prolonged ICU stays and the frequent need for ECMO support (11).

Our study comes with limitations. Firstly, we studied patients at a single center, at Northwestern Memorial Hospital, which may limit the generalizability of our conclusions. Also, the number of patients studied were small, which may reduce statistical power. Furthermore, since these results are based on the experiences of a small cohort in a single large institution, differences in patient referral patterns, ECMO management standards, and eligibility criteria cannot be generalized and must be considered. Second, ARDS patients included a very wide variety of diagnoses such as severe bacterial pneumonia, COVID-19 infection, and others which could impact the statistical analysis results.

Conclusions

Our study emphasizes the need for a nuanced understanding of PGD risk factors in different patient populations. It advocates for personalized approaches in preoperative assessment and perioperative care, considering the unique challenges posed by each patient's underlying lung condition. The identification of specific risk profiles paves the way for tailored strategies aimed at minimizing PGD risk, ultimately improving lung transplant outcomes. Future research should delve deeper into the underlying mechanisms of these risk factors, exploring novel biomarkers and therapeutic interventions to further enhance patient care in lung transplantation.

Table 5 Univariate logistic regression analysis to predict PGD grade 3 in ARDS group (n=43)

Variables	OR	95% CI	P value
Recipient factors			
Age	0.91	0.85–0.98	0.008
Female	1.75	0.47–6.50	0.40
Body mass index	0.93	0.79–1.10	0.39
Body surface area	0.13	0.01–4.42	0.25
Smoking history	1.20	0.25–5.77	0.82
Hypertension	0.71	0.19–2.69	0.62
Diabetes	0.77	0.19–3.09	0.71
Pre-transplant ECMO use	<0.01	0–inf	0.99
Bilateral lung transplant	0.43	0.23–0.83	0.01
Lung allocation score	1.05	0.98–1.12	0.20
Pre-transplant blood transfusion within 4 weeks	6.29	1.18–33.3	0.03
Laboratory			
Hemoglobin	0.74	0.48–1.14	0.17
WBC	1.09	0.93–1.28	0.28
Platelets	0.99	0.98–1.00	0.09
Sodium	0.99	0.84–1.17	0.93
BUN	1.01	0.96–1.06	0.76
Creatinine	14.5	0.70–302	0.08
AST	1.05	1.00–1.10	0.05
ALT	1.04	0.99–1.10	0.12
Albumin	0.26	0.07–0.93	0.04
Total bilirubin	1.88	0.65–5.42	0.25
INR	7.60	0.11–505	0.34
PRA	1.83	0.49–6.90	0.37
Donor			
Age	1.01	0.95–1.06	0.82
Female	0.67	0.17–2.67	0.57
Intra-operative outcomes			
Operative time	1.29	0.81–2.04	0.29
Intra-op blood transfusion			
pRBC	1.17	1.04–1.31	0.006
FFP	1.20	1.04–1.38	0.01
Plt	1.46	1.06–2.01	0.02
Ischemic time	1.60	0.80–3.22	0.19
Veno-arterial ECMO use	<0.01	0–inf	0.99

PGD, primary graft dysfunction; ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; WBC, white blood cell; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; PRA, panel reactive antibodies; pRBC, packed red blood cells; FFP, fresh frozen plasma; Plt, platelets; inf, infinity.

Table 6 Multivariate logistic regression analysis to predict PGD grade 3 in ARDS group (n=43)

Variables	OR	95% CI	P value
Recipient factors			
Age	0.72	0.52–0.99	0.048
Pre-transplant blood transfusion within 4 weeks	201	0.0005–82400000	0.42
Laboratory			
AST	1.46	0.93–2.29	0.10
Albumin	0.00028	0.00000011–0.74	0.042
Intra-operative outcomes			
Intra-op blood transfusion			
pRBC	2.71	0.82–9.02	0.10
FFP	0.91	0.40–2.07	0.82
Plt	0.22	0.023–2.06	0.18

PGD, primary graft dysfunction; ARDS, acute respiratory distress syndrome; OR, odds ratio; CI, confidence interval; AST, aspartate aminotransferase; pRBC, packed red blood cells; FFP, fresh frozen plasma; Plt, platelets.

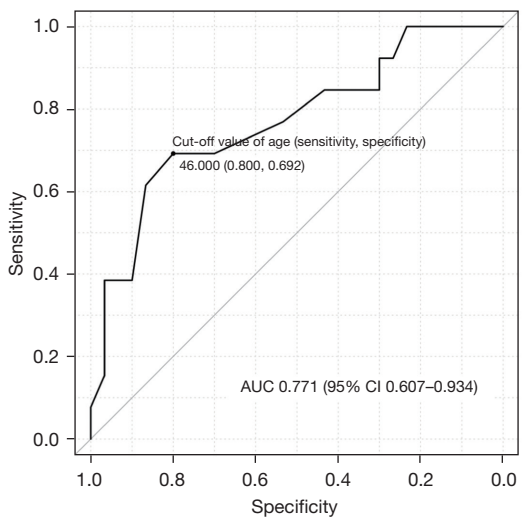

Figure 2 Receiver operating characteristic curve of age cut off for predictor of primary graft dysfunction. AUC, area under the curve; CI, confidence interval.

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Footnote

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-100/dss

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-100/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Northwestern University (Nos. STU00207250 and STU00213616). The need for patient consent for data collection was waived by the institutional review board because this was a retrospective study.

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