Original Article

Transpulmonary gradient as a predictor for outcomes after lung transplantation

Ernest G. Chan^, Ankitha Madde, Masashi Furukawa, Jenalee N. Coster, John Ryan, James D. Luketich, Pablo G. Sanchez

Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

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Correspondence to: Pablo G. Sanchez, MD, PhD. Associate Professor and Vice Chair, Surgical Director of Lung Transplant and ECMO, Director of Ex vivo Lung Perfusion Director of Lung Transplant Research, Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA, USA. Email: sanchezpg@upmc.edu.

Background: End stage lung disease (ESLD) is commonly associated with pulmonary hypertension (PHTN). In a donor restrictive environment, offering patients single over double lung transplants could increase organ utilization. However, there isn't a clinical consensus on how severe PHTN must be to preclude single lung transplant (SLT) due to poor outcomes. We sought to investigate the predictive value of the transpulmonary gradient (TPG) in SLT in patients with ESLD and PHTN.

Methods: We performed a retrospective analysis of the United Network for Organ Sharing database and identified all patients who underwent lung transplantation (LT) from May 2005 to March 2021. Patients were stratified based on their TPG score above or below 25 mmHg. Primary outcomes include 1-year survival assessed by generalized linear mixed modeling.

Results: Our analysis showed TPG was associated with 1-year survival but this relationship depended on transplant type (P=0.002) with TPG ≥25 being associated with higher mortality in single (P=0.004), but not double LT (P=0.95). This association was maintained when covarying for numerous clinical factors, as well as when excluding deaths within 90 days of LT (P=0.04).

Conclusions: A preoperative TPG >25 was associated with decreased 1-year survival in SLT recipients. The use of preoperative TPG combined with other marks of clinical status can help transplant centers in their decision of offering single vs. double lung transplant in patients with ESLD and PHTN.

Keywords: Lung transplantation (LT); single lung transplantation; transpulmonary gradient (TPG); end stage lung disease (ESLD); pulmonary hypertension (PHTN)

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Introduction

Pulmonary hypertension (PHTN) is a progressive, and potentially fatal disease that has been shown to significantly complicate the disease course of many other chronic lung diseases (CLD) such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) (1-3). In those with more advanced disease, the prevalence of PHTN has been shown to range from 30% to as high as 85% in

^ ORCID: 0000-0001-9849-6371.

a group of patients with ILD, and is strongly associated with an increase in morbidity and mortality (3-6). Though it is known that lung transplantation (LT) remains the only curative treatment strategy for end stage lung disease (ESLD), particularly in the setting of refractory disease despite optimal medical therapy, the choice of procedure (single *vs.* bilateral LT) is still an open debate. For both end stage COPD and ILD, the recent trend favors bilateral lung transplants (BLT) over single lung transplants (SLT), citing improved lung function and superior survival rates as the primary outcomes (7,8). Though a mortality benefit might be apparent, emphasis on BLT has unfortunately led to a significant transplant limitation and outcomes in this group are further hindered by a very high waiting list mortality (12% and 20% for COPD and ILD respectively) (9).

SLT proponents cite the simpler technical nature, shorter duration, and quicker recovery as advantages, and many studies have found equivocal or increased short term survival outcomes when compared to BLT. Meyer *et al.*, one of the first to use UNOS data to study outcomes in SLT *vs.* BLT, found similar 1-month and 1-year survival rates in patients with COPD but reduced 5-year survival, and found better 1-month and 3-year survival rates in patients with ILD (10,11). Likewise, survival outcomes in the International Society for Heart and Lung Transplantation (ISHLT) registry report in 2019 showed similar 1-year survival rates for patients with ILD and COPD however significantly reduced long term survival in SLT *vs.* BLT recipients (12). The equivalent short-term outcomes suggest that SLT should still be considered a viable transplant option, but to provide equivalent long term benefit as well, careful patient selection via disease stratification should be employed to find those with the best chance of survival.

The preoperative workup of patients with ESLD includes many physiologic parameters to help stratify the severity of disease. Transpulmonary gradient (TPG) is defined as the difference between mean pulmonary arterial pressure (mPAP) and left atrial pressure (Pla), which is usually estimated by mean pulmonary capillary wedge pressure (mPCWP) (13). PHTN due to ESLD is precipitated by alveolar hypoxia leading to pulmonary vasoconstriction and intrinsic vascular remodeling, thus TPG was chosen as it is highly dependent on vascular resistance (14,15). Furthermore, TPG measures are more suitable than the traditional pulmonary artery pressures to characterize PHTN secondary to ESLD due to their independence from factors such as flow, inertia, vascular compliance, and alveolar pressures (16). A TPG value >12–15 is generally associated with a diagnosis of PHTN, and an increase in this value is correlated with an increase in the precapillary stiffness of the pulmonary vasculature indicating a higher severity of lung disease (13). Currently, there is no consensus regarding the use of parameters such as TPG to guide the decision making for the type of LT in patients with ESLD. We predict a TPG greater than 25 mmHg will be associated with poor outcomes following single LT. Therefore, the goal of this study is to investigate the use of TPG as a predictor of outcomes following SLT *vs.* BLT in patients with ESLD. We present the following article in accordance with the STROBE reporting checklist (available at https://shc.amegroups.com/article/view/10.21037/shc-21-22/rc).

Methods

Patients

We performed a retrospective analysis using the United Network of Organ Sharing (UNOS) Standard Analysis and Research (STAR) database based on OPTN data as of March 5, 2021. Adult patients (≥18 years old) who underwent a primary LT between May 4, 2005 and March 3, 2021 were included. Patients undergoing a re-do transplant or multiorgan transplant were excluded, as well as patients with a diagnosis of primary PHTN or suppurative disease (UNOS diagnosis groups "B" and "C"). TPG was calculated by subtracting mPCWP from mPAP at time of transplant. TPG dichotomization was a consensus within the surgical team and based on clinical practice. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of The University of Pittsburgh School of Medicine and individual consent for this retrospective analysis was waived.

Outcomes

The primary outcome was 1-year survival. Secondary outcomes of interest included post-operative length of stay, long term survival (3 and 5 years), and pre-discharge complications including airway dehiscence, stroke, and dialysis. Additional variables that were investigated include patient demographics (age, gender, body mass index, etc.), preoperative kidney function, different types of pulmonary disease, and preoperative pulmonary function.

Statistical analysis

Univariate analyses were performed with Mann-Whitney U

Table 1 Patient characteristics stratified by transpulmonary gradient (TPG) above or below 25 mmHg

Variable	Total cohort (n=22,881)	TPG <25 (n=19,731)	TPG ≥25 (n=3,150)	P
Waitlist time (days), mean (SD)	142.75 (255.0)	146.26 (256.5)	120.72 (244.3)	<0.001
Age (years), mean (SD)	59.65 (9.5)	59.97 (9.4)	57.70 (10.0)	<0.001
Body mass index (kg/m^2), mean (SD)	26.03 (4.3)	26.07 (4.3)	26.62 (4.3)	<0.001
Serum creatinine, mean (SD)	0.87 (0.4)	0.86 (0.41)	0.89 (0.41)	<0.001
Total bilirubin, mean (SD)	0.60 (0.86)	0.50 (0.3)	0.74 (0.9)	<0.001
Lung allocation score, mean (SD)	47.44 (17.7)	45.73 (16.7)	58.08 (34.7)	<0.001
Systolic PAP (mmHg), mean (SD)	41.41 (15.0)	37.33 (9.8)	67.03 (16.1)	<0.001
Diastolic PAP (mmHg), mean (SD)	17.21 (8.4)	15.36 (6.5)	28.82 (9.6)	<0.001
Mean PAP (mmHg), mean (SD)	26.51 (9.9)	23.81 (6.6)	43.46 (10.3)	<0.001
PCWP (mmHg), mean (SD)	10.65 (5.4)	10.72 (5.4)	10.21 (5.7)	<0.001
FEV1 (%), mean (SD)	40.80 (20.6)	39.77 (20.4)	47.27 (20.7)	<0.001
Cardiac output, mean (SD)	5.35 (1.4)	5.39 (1.4)	5.15 (1.6)	<0.001
Male, n (%)	14,191 (62.0)	12,217 (61.9)	1,974 (62.7)	0.42
Diagnosis, n (%)				
Obstructive	7,491 (32.7)	6,980 (35.4)	511 (16.2)	<0.001
Restrictive	15,390 (67.3)	12,751 (64.6)	2,639 (83.8)	
Diabetes, n (%)	3,791 (16.6)	3,168 (16.1)	623 (19.8)	<0.001
Transplant type, n (%)				
Single	7,841 (34.3)	7,312 (37.1)	529 (16.8)	<0.001
Double	15,040 (65.7)	12,419 (62.9)	2,621 (83.2)	
Medical condition, n (%)				
Not hospitalized	18.406 (81.3)	16,266 (83.3)	2,140 (68.5)	<0.001
Hospitalized - Non-ICU	1,962 (8.7)	1,540 (7.9)	422 (13.5)	
ICU	2,276 (10.1)	1,714 (8.8)	562 (18.0)	
Mechanical ventilator bridge, n (%)	1,126 (5.0)	895 (4.6)	231 (7.4)	<0.001
ECMO bridge, n (%)	720 (3.2)	524 (2.7)	196 (6.3)	<0.001

BMI, body mass index; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; FEV1, forced expiratory volume in one minute; HTN, hypertension.

tests for continuous variables, and chi squares for categorical data. Relationships between TPG and one-year survival were modeled using generalized linear mixed models with a binomial distribution and logit link (17). TPG and transplant type were entered as fixed effects, transplant center as a random effect, and survival as a binarized outcome. Covariates included recipient age, donor sex, diagnosis group, body mass index, transplant type (single or double), LAS at the time of transplant, ischemic time lung allocation score (LAS), transplant type, total bilirubin, medical condition at time of transplant (home, hospitalized, or hospitalized-ICU), ventilator status at time of match, and ECMO status at time of match. Univariable analyses were performed using SPSS (v. 27, IBM Corp., Armonk, NY, USA) and Kaplan-Meier and multivariable analyses were performed using R (v. 4.0.3) with packages "survival" and "GLMMAdaptive". A P<0.05 was considered statistically significant.

Results

A total of 22,881 patients underwent LT between May 2005

Table 2 Donor characteristics stratified by recipient TPG above or below 25 mmHg

Variable	Total cohort	TPG <25	TPG ≥25	P
Age (years), mean (SD)	35.19 (14.1)	35.18 (14.1)	35.20 (13.9)	0.76
Body Mass Index (kg/m^2), mean (SD)	26.29 (5.5)	25.39 (5.5)	26.47 (5.9)	0.35
pO_2, mean (SD)	381.37 (143.3)	418.0 (143.2)	383.06 (143.6)	0.48
pCO_2, mean (SD)	37.18 (6.7)	37.22 (6.8)	36.92 (6.4)	0.09
LV ejection fraction, mean (SD)	58.14 (11.7)	58.14 (11.7)	58.14 (11.8)	0.70
Ischemic time (hours), mean (SD)	5.29 (2.0)	5.24 (2.0)	5.60 (1.9)	<0.001
Male, n (%)	13,934 (60.9)	12,165 (61.7)	1,769 (56.2)	<0.001
History of HTN, n (%)	5,455 (23.8)	4,729 (24.0)	726 (23.0)	0.53
History of diabetes, n (%)	1,730 (7.6)	1,506 (7.6)	224 (7.1)	0.17
CDC high risk, n (%)	4,148 (18.1)	3,594 (18.2)	554 (17.6)	0.41

TPG, transpulmonary gradient; LV, left ventricle; HTN, hypertension; CDC, Centers for Disease Control.

and March 2021 who met inclusion and exclusion criteria. *Table 1* details the recipient characteristics. Patients with TPG ≥25 mmHg had a shorter waitlist time (P<0.001), younger age (P<0.001), higher BMI (P<0.001), higher serum creatinine (P<0.001) and bilirubin (P<0.001), and higher LAS (P<0.001). Patients with TPG ≥25 mmHg also had higher systolic (P<0.001), diastolic (P<0.001), and mean PAP (P<0.001) and FEV1 (P<0.001), and were more likely to have received bilateral LT over single LT (P<0.0001). Patients with PGD ≥25 mmHg were more likely to have a diagnosis of restrictive disease (P<0.001), were more likely to be hospitalized at time of transplant (P<0.001) and were more likely to be on mechanical ventilation or ECMO as a bridge to transplant (P<0.001).

Donor characteristics

Donor information is displayed in *Table 2*. There were no differences between TPG groups in donor age (P=0.76), BMI (P=0.35), and cardiac ejection fraction (P=0.70). However, patients with TPG ≥25 mmHg were more likely to receive donor lungs from a female donor (P<0.001) and receive lungs with longer ischemic times (P<0.001).

Post-operative outcomes

Table 3 summarizes post-operative and survival outcomes. Following surgery, patients with TPG ≥25 had longer length of stay (P<0.0001), increased incidence of airway dehiscence (P=0.02), and were more likely to receive postoperative dialysis (P<0.001). There was no difference in the incidence of post-operative stroke between TPG groups (P=0.46). Patients with TPG ≥25 mmHg had a lower one-year survival (P<0.001) (*Figure 1*). However, this difference was eliminated at three-year (P=0.43) and 5-years (P=0.61) post-transplant.

Multivariable analyses

Generalized mixed-effects analyses were conducted to examine the relationship between TPG, transplant type (single or double) and one-year survival. In a multivariable analysis, TPG category (P<0.001) was significantly associated with one-year survival, but this relationship was qualified with a significant transplant type by TPG interaction (P<0.001) indicating that the relationship between TPG and survival differed by transplant type (*Table 4*). To probe the interaction, the data were stratified by transplant type. In single LT recipients, TPG ≥25 remained a significant predictor of one-year survival (P=0.004), but this relationship was not present for double LT recipients (P=0.95). Regardless of transplant type, older age, being in the ICU, or on a ventilator at time of match were associated with increased risk of one-year mortality. In single-lung recipients, being hospitalized (non-ICU) was associated with increased risk of one-year mortality (*Table 4*). Double lung recipients with a restrictive lung disease (relative to obstructive) as well as those with longer ischemic times were at increased risk of one-year mortality (*Table 4*).

Within single LT, 479 (5.6%) died within 90 days of

Table 3 Postoperative outcomes

Variable	Total cohort	TPG <25	TPG ≥25	P
Length of stay, mean (SD)	25.97 (31.5)	25.30 (30.7)	30.13 (36.2)	<0.001
Pre-discharge, n (%)				
Airway dehiscence	355 (1.6)	290 (1.5)	65 (2.1)	0.02
Dialysis	1,487 (6.6)	1,164 (6.0)	323 (10.4)	<0.001
Stroke	524 (2.3)	446 (2.3)	78 (2.5)	0.46
Survival, % (95% CI)				
1-year	86.5 (86.1–86.9)	87.2 (86.7–87.7)	85.1 (83.8–86.3)	<0.001
3-year	69.4 (68.8–70.1)	69.9 (68.9–70.4)	69.9 (68.1–71.7)	0.43
5-year	55.5 (54.8–56.3)	55.7 (54.9–56.6)	56.1 (54.1–58.3)	0.61

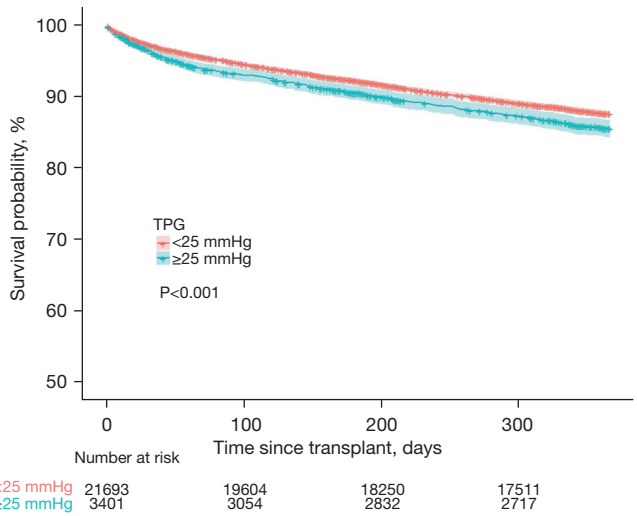

Figure 1 Patients with TPG ≥25 mmHg had a lower one-year survival (P<0.001).

transplant. To examine the relationship between TPG and one-year survival, but excluding deaths related to surgical complications, we repeated the multivariable analysis, but excluded patients who died within the 90-day post-transplant period. In this analysis, TPG ≥25 mmHg remained a significant predictor of one-year survival (*Table 5*). Older age, having higher bilirubin levels, being in the ICU or hospitalized at time of match were additional significant predictors of one-year mortality.

Discussion

Although overall waitlist mortality has decreased for most diagnoses of ESLD since the implementation of the LAS system, waitlist mortality in patients is still high, especially those with restricted listing preferences (9,18). In a recent study by Anderson *et al.* looking at 14,000 patients with COPD or ILD, they found nearly 25% of patients listed for BLT were not transplanted due to death and other outcomes. Furthermore, their adjusted analyses identified a decreased risk of death as well as comparable 1-year and 5-year graft survival rates for unrestricted *vs.* restricted listings, showing the utility of allowing patients to undergo SLT whenever possible (9).

The majority of the current literature supports preferred use of BLT over SLT for secondary PHTN as it has been shown to be associated with a better long-term survival (19). However, one limitation of many of these studies is the lack of quantifying severity of disease. Huerd *et al.* reported outcomes after SLT for moderate PHTN defined as mPAP 30–40 mmHg and found overall successful outcomes in early and late allograft function with acceptable long term overall survival (20). Fitton *et al.* also found survival to be equivalent with mild/moderate PHTN (*vs.* severe PHTN) in both SLT and BLT, concluding that SLT is an acceptable transplantation option (21). Finally, a recent 2019 study which looked at PHTN stratified by mPAP (<40 *vs.* ≥40 mmHg) also found those who underwent SLT with mPAP <40 mmHg to have a higher long-term survival compared to those with mPAP ≥40 mmHg, further offering evidence that SLT in mild/moderate PHTN is acceptable (22).

Our current study similarly looked at the outcome and survival differences between SLT and BLT in the setting of secondary PHTN when stratifying by disease

Table 4 Multivariable mixed-effects models: relationship between TPG above or below 25 mmHg and one-year survival based on type of lung transplant

	Estimate	Std.Err	O.R.	95% CI	P
All lung transplant recipients					
TPG ≥25 mmHg	0.41	0.12	1.50	1.19–1.91	0.001
Age (years)	0.02	0.00	1.02	1.02–1.03	<0.001
Diagnosis – Restrictive[a]	0.18	0.06	1.20	1.08–1.34	0.001
Body mass index (kg/m^2)	0.01	0.01	1.01	0.99–1.02	0.32
Ischemic time (hours)	0.08	0.01	1.09	1.06–1.11	<0.001
Lung allocation score	0.00	0.00	1.00	1.00–1.00	0.66
Transplant type (double)	–0.08	0.06	0.92	0.83–1.03	0.15
Bilirubin	0.14	0.03	1.15	1.09–1.21	<0.001
Hospitalized – ICU[b]	0.67	0.10	1.95	1.61–2.37	<0.001
Hospitalized – Non-ICU[b]	0.26	0.08	1.29	1.10–1.52	0.002
Ventilator at match	0.31	0.10	1.36	1.12–1.65	0.002
ECMO at match	–0.04	0.12	0.96	0.75–1.22	0.73
Donor sex (male)	–0.08	0.04	0.92	0.85–1.00	0.06
TPG transplant type	–0.42	0.14	0.66	0.50–0.86	0.002
Intercept	–4.05	0.24			
Single lung transplant recipients					
TPG ≥25 mmHg	0.36	0.12	1.43	1.12–1.82	0.004
Age (years)	0.02	0.01	1.02	1.01–1.03	<0.001
Diagnosis – Restrictive[a]	0.04	0.09	1.04	0.87–1.26	0.64
Body mass index (kg/m^2)	0.00	0.01	1.00	0.98–1.02	0.99
Ischemic time (hours)	0.04	0.02	1.04	1.00–1.09	0.06
Lung allocation score	0.00	0.00	1.00	1.00–1.01	0.18
Bilirubin	0.09	0.03	1.10	1.03–1.17	0.005
Hospitalized – ICU[b]	0.89	0.18	2.43	1.72–3.44	<0.001
Hospitalized – Non-ICU[b]	0.46	0.13	1.58	1.21–2.06	0.001
Ventilator at match	0.45	0.20	1.57	1.06–2.34	0.02
ECMO at match	0.29	0.30	1.34	0.75–2.39	0.32
Donor sex (male)	0.04	0.07	1.04	0.90–1.20	0.60
Intercept	-3.81	0.43			

Table 4 (*continued*)

Table 4 (*continued*)

	Estimate	Std.Err	OR	95% CI	P
Double lung transplant recipients					
TPG ≥25 mmHg	0.00	0.07	1.00	0.87–1.14	0.95
Age (years)	0.03	0.00	1.03	1.02–1.03	<0.001
Diagnosis – Restrictive[a]	0.26	0.07	1.29	1.13–1.48	<0.001
Body mass index (kg/m^2)	0.01	0.01	1.01	1.00–1.02	0.20
Ischemic time (hours)	0.10	0.01	1.10	1.07–1.13	<0.001
Lung allocation score	0.00	0.00	1.00	0.99–1.00	0.60
Bilirubin	0.17	0.03	1.19	1.12–1.27	<0.001
Hospitalized – ICU[b]	0.58	0.12	1.79	1.42–2.26	<0.001
Hospitalized – Non-ICU[b]	0.10	0.11	1.11	0.90–1.36	0.34
Ventilator at match	0.28	0.11	1.33	1.06–1.66	0.01
ECMO at match	–0.07	0.14	0.93	0.71–1.22	0.61
Donor sex (male)	–0.16	0.05	0.85	0.77–0.95	0.004
Intercept	–4.29	0.27			

[a], reference group: obstructive lung disease; [b], reference group: non-hospitalized. TPG, transpulmonary gradient, HTN, hypertension.

Table 5 Multivariable mixed-effects model: relationship between TPG above or below 25 mmHg and one-year survival in single-lung recipients excluding patients who died within 90 days of transplant

	Estimate	Std.Err	OR	95% CI	P
TPG ≥25 mmHg	0.31	0.15	1.36	1.01–1.84	0.04
Age (years)	0.03	0.01	1.03	1.02–1.05	<0.001
Diagnosis – Restrictive[a]	0.02	0.12	1.03	0.81–1.29	0.83
Body mass index (kg/m^2)	0.00	0.01	1.00	0.98–1.02	0.97
Ischemic time (hours)	0.05	0.03	1.05	0.99–1.11	0.10
Lung allocation score	0.01	0.00	1.01	1.00–1.01	0.05
Bilirubin	0.06	0.03	1.06	1.01–1.12	0.03
Hospitalized – ICU[b]	0.551	0.23	1.73	1.10–2.73	0.02
Hospitalized – Non-ICU[b]	0.49	0.16	1.63	1.18–2.24	0.003
Ventilator at match	0.27	0.26	1.31	0.78–2.19	0.31
ECMO at match	0.59	0.35	1.80	0.90–3.60	0.10
Donor sex (male)	0.06	0.09	1.06	0.89–1.27	0.53
Intercept	–5.06	0.55	0.01		

[a], reference group: obstructive lung disease; [b], reference group: non-hospitalized. TPG, transpulmonary gradient, HTN, hypertension.

severity defined by TPG. When analyzing patients undergoing SLT, we found patients with more severe PHTN defined as a TPG ≥25 mmHg were associated with a longer postoperative course and higher postoperative complications, such as airway dehiscence, dialysis and stroke. On multivariable analysis, age, LAS at transplant, ischemic time, transplant type, and TPG ≥25 mmHg were all independent predictors of 1-year survival, however when separating by the type of transplant, TPG ≥25 mmHg was independently associated with reduced survival only in SLT recipients.

Furthermore, TPG ≥25 mmHg was found to be independently associated with an increased hazard of 1-year mortality in SLT. The association remained significant even after excluding patients who died within 90 days of transplant. However, differences in survival were eliminated at longer follow-up times (3+ years). These results may indicate that complications associated with severe PHTN and LT may occur in the early postoperative period. With proper postoperative care, once patients are ushered out of this early window of increased morbidity and mortality, long term outcomes may not be compromised. Ultimately, additional studies are needed to further elicit the relationship between TPG and outcomes following SLT in patients with PHTN.

There are a number of limitations that should be highlighted. First, this is a retrospective study and therefore the results are subjected to reporter and recall bias. Second, this is an analysis of a nationally collected dataset and therefore the results of our study are reliant on the quality of its data. Therefore, though it contains extensive patient-level data on LT in the past couple decades, it is also subject to its limitations including but not restricted to data entry errors, and missing data. Specifically, some important results which are not included in the database but would provide additional insight into the current topic are postoperative quality of life measures, allograft function, rates of rejection, and donor lung hemodynamic measures. Furthermore, our use of the TPG values were limited as well. Nonetheless, this is a high-powered study as one of the first to evaluate the role of TPG in predicting post-transplant mortality, and thus still provides valuable results.

In conclusion, elevated TPG is a significant predictor of decreased post-transplant long-term survival in SLT recipients but not BLT recipients. This may indicate that efforts in minimizing the severity of PHTN can be associated with better outcomes after SLT, and specifically promotes the use of TPG as a prognostic factor in predicting SLT post-transplant mortality rates.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://shc.amegroups.com/article/view/10.21037/shc-21-22/rc

Peer Review File: Available at https://shc.amegroups.com/article/view/10.21037/shc-21-22/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://shc.amegroups.com/article/view/10.21037/shc-21-22/coif). PGS serves as an unpaid editorial board member of *Shanghai Chest* from June 2021 to May 2023. The other 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 institutional review board of The University of Pittsburgh School of Medicine and individual consent for this retrospective analysis was waived.

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