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Contemporary Trends in PGD Incidence, Outcomes, and Therapies

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Abstract

Background: We sought to describe trends in extracorporeal membrane oxygenation (ECMO) use, and define the impact on PGD incidence and early mortality in lung transplantation.

Methods: Patients were enrolled from August 2011 to June 2018 at 10 transplant centers in the multi-center Lung Transplant Outcomes Group prospective cohort study. PGD was defined as Grade 3 at 48 or 72 hours, based on the 2016 PGD ISHLT guidelines. Logistic regression and survival models were used to contrast between group effects for event (i.e. PGD and Death) and time-to-event (i.e. death, extubation, discharge) outcomes respectively. Both modeling frameworks accommodate the inclusion of potential confounders.

Results: 1,528 subjects were enrolled with a 25.7% incidence of PGD. Annual PGD incidence (14.3% to 38.2%, p=0.0002), median LAS (38.0 to 47.7 p=0.009) and the use of ECMO salvage for PGD (5.7% to 20.9%, p=0.007) increased over the course of the study. PGD was associated with increased 1-year mortality (OR 1.7 [95% C.I. 1.2, 2.3], p=0.0001). Bridging strategies were not associated with increased mortality compared to non-bridged patients (p=0.66); however, salvage ECMO for PGD was significantly associated with increased mortality (OR 1.9 [1.3, 2.7], p=0.0007). Restricted mean survival time comparison at 1-year demonstrated 84.1 days lost in venoarterial salvaged recipients with PGD when compared to those without PGD (ratio 1.3 [1.1, 1.5]) and 27.2 days for venovenous with PGD (ratio 1.1 [1.0, 1.4]).

Conclusion: PGD incidence continues to rise in modern transplant practice paralleled by significant increases in recipient severity of illness. Bridging strategies have increased but did not affect PGD incidence or mortality. PGD remains highly associated with mortality and is increasingly treated with salvage ECMO.

Introduction

Recent trends in lung organ allocation have resulted in transplantation of candidates with increased severity of illness.[1] Reported consequences of these trends include increases in procurement costs, allograft discard rate and ischemic times.[2,3] Impact on short-term mortality has not been observed but increases in length of stay have been noted.[1] It is unknown what effect these changes have had on PGD incidence or longer term mortality. Given the significant effects of PGD on mortality, increased resource utilization, morbidity, and quality of life,[4-9] a better understanding of PGD in the context of changing recipient selection practices is essential.

Concurrently, extracorporeal membrane oxygenation (ECMO) use has increased for both bridging and salvage therapies. The reported effects of each of these strategies on mortality are mixed. Single center accounts of bridging strategies report 1-year post transplant survival ranging from 60 to 100%.[10-22] Registry reports are less favorable with survival significantly reduced in bridged compared to non-bridged patients; [23,24] however, this effect may be lessened with increasing center experience and improved patient selection.[22,24] Not surprisingly, results of ECMO use for salvage after lung transplant are less favorable, with reports of 1-year survival between 40-88%.[25-29]

Our objective in this study is to define the contemporary changes in PGD incidence and outcomes among those with PGD. Our secondary objectives are to clarify the relationship of bridging and salvage therapies with PGD outcomes.

Methods

Study Population

Subjects were selected from the Lung Transplant Outcomes Group (LTOG), a multi-center, prospective cohort study of lung transplant recipients (NCT00457847).[30] We included all adult lung transplant patients enrolled at 10 US transplant centers between August 2011 and June 2018 who consented to participate. Institutional review board approvals were obtained at each center prior to study initiation. For comparisons, data were obtained from the United Network for Organ Sharing (UNOS) through a data use agreement. UNOS Standard Transplant Analysis and Research (STAR) File data were used to demonstrate trends in United States lung transplant practice. All lung transplant recipients in the between 1/1/2012 and 12/31/2021 were included.

Definitions

PGD was graded according to the revised 2016 ISHLT consensus criteria, which is defined by diffuse allograft infiltrates on chest radiograph and Pa_{O_2}/F_{IO_2} ratio.[31] Radiograph assessments were performed by two physicians blinded to clinical status, with adjudication as previously described.[5] Severe primary graft dysfunction (grade 3) was defined by Pa_{O_2}/F_{IO_2} ratio < 200 at any time between 48 and 72 hours after transplant, which has previously demonstrated to have construct validity for long-term outcomes and concurrent lung injury markers.[30] Recipients placed on ECMO post-transplant were considered “ungradable” in cases without diffuse infiltrates while all other recipients on ECMO were considered to have

grade 3 PGD in accordance with the revised 2016 definition. Further references to “PGD” in this manuscript will be considered severe PGD (grade 3) as described above. References to “any PGD” is defined as severe primary graft dysfunction (grade 3) at any time within 72 hours after transplant.

Bridging strategies were defined prospectively by coordinator chart abstraction as cases in which support was initiated prior to transplant, distinct from the time of the transplant operation. Salvage strategies were defined as instances where significant hemodynamic failure or hypoxia post-transplant required initiation of ECMO as a novel therapy distinct from intraoperative support. Criteria for initiation of ECMO salvage were left to the discretion of the individual center clinical teams. In cases where both venovenous (VV) and venoarterial (VA) ECMO were required for either bridging or salvage strategies, VA ECMO was used as the category for analysis.

Statistical Analysis:

Summaries of clinical factors were reported with means and standard deviations for continuous measures, and percentages for binary measures. Logistic regression models were used to model development of PGD and mortality. Potential confounders were chosen based on previous work demonstrating significant associations with PGD, and included center as a fixed effect to adjust for center level differences in practice, lung allocation score (LAS), mean pulmonary artery pressure, diagnosis, and age.[5]

In addition to PGD occurrence/prevalence, analysis was focused on the time-course for each of three clinical outcomes: Time to death, time to discharge, and time to extubation. These time-to-event measures may exhibit right-censoring, corresponding to where the event has not occurred in the respective observation window. Classic hazard based time-to-event models are valid only under the proportional hazards (PH) assumption.[32] Additionally, the precision of these models is suspect with low event rates, potentially producing wide confidence intervals for hazard ratios (HR).[32] Hazard ratios might change over time, therefore questioning the utility of a single index covering the entire time course.[33] Hernan (2010) also discusses HR may be characterized by built-in selection bias. Therefore, we used restricted mean survival time (RMST), which provides a summary of the whole survival curve up to a time horizon, in contrast to the survival rate at a specified time.[32,34-36] This time-to-event survival model was formulated by Andersen, Hansen and Klein[37] and implemented using SAS Procedure PROC RMSTREG in the (SAS/STAT 15.1), which incorporates the algorithm (https://uno-san.com/computer_code.html / rmst2_ver003.sas). The algorithm allows for the inclusion of covariates. Models are fitted using estimating equations with pseudovalue regression which facilitates model-based inference and prediction.[37] The main advantage of this approach is that it is directly applicable for performing regression analysis of the restricted mean survival time, where adjustments for potential confounders are needed. Similar to HR in a Cox model, a ratio index to serve as clinical significance indicator representing the percent increase/loss of survival time up through the respective time period can be derived.[32] For time to death, we contrasted groups at 30 days, 1 year and 3 years post-transplant. For length of stay, we contrasted groups at 1-month and 2-months post-transplant. For time to extubation,

we contrasted groups at 1-week, 2-weeks, and 3-weeks post-transplant. To account for the competing risk of death, 28-day ventilator-free days (VFDs) and 28-day hospital-free days (HFDs), composite outcomes that incorporate both mortality and duration of mechanical ventilation or hospital length of stay, were calculated using standardized methodology.[38,39] All analyses adjust for center, LAS, mean pulmonary artery pressure, diagnosis, and age as potential confounding variables. Analyses were performed with SAS/STAT15.1 and STATA v14.2 software (STATA Corp, College Station, TX). For each event, we contrast occurrence and time-to-event between patients who were bridged prior to transplant versus those who were not, patients who were salvaged post-transplant versus those who were not, as well as the impact of combined bridging and salvage strategies. We additionally considered the impact of the type of bridging and type of salvage on occurrence and time-to-event.

Results

Cohort Characteristics

Table 1 presents demographics and clinical measures in our sample of 1528 lung transplant patients. Within this sample, 25.7% developed PGD (43% any PGD), 9.5% of the patients received bridging prior to transplant, and 18.1% received salvage post-transplant. Among this cohort, 59 (4.4%) patients were transplanted after *ex vivo* lung perfusion. If intra-operative support was required to safely perform lung transplant VA ECMO was preferentially used (63%) and remained relatively stable throughout the study period (VA ECMO:2012: 66.7%; 2013: 66.3%; 2014: 57.4%; 2015: 63.1%; 2017: 61.8%; 2018: 62.3%; Cardiopulmonary bypass (CPB) 2012: 33.3%; 2013: 33.7%; 2014: 42.6%; 2015: 36.9%; 2016: 34.5%; 2017: 38.2%; 2018: 37.7%).

Figure 1 presents trends in PGD incidence, LAS, and ECMO use in the LTOG cohort. Over the course of enrollment, there was a significant increase in PGD incidence from 14.3% in 2011 to 38.2% in 2018 (trend p=0.0002). Using the definition of any grade 3 PGD within the first 72 hours, the incidence reflected similar observations with a significant increase from 37.1% to 59.7% (trend p<0.0001). Accordingly, the median LAS increased from 38.0 [34.6, 48.1] to 47.7 [36.0, 66.4] (trend p=0.009) over the same time period. Additionally, increasing LAS was significantly associated with PGD incidence (p<0.0001). The use of ECMO for bridging peaked at 17.4% in 2014 then subsequently decreased to 7.6% in 2018. During the same interval, ECMO salvage increased from 5.7% in 2012 to 20.9% of all transplants in 2018 (trend p=0.007).

Within the US during the same study period in the UNOS cohort, the number of ECMO bridged transplants (defined by the candidate registration form) increased from 1.5% (2012) to 2.7% (2018) which further increased to 7.0% in 2021. The use of ECMO salvage defined by the transplant recipient registration form increased from 1% (2012) to 8% (2018) then 11% in 2021.

The cause of death for recipients is summarized in Table e2 (supplement) for both the LTOG and UNOS STAR file. For both cohorts, the top 3 causes of death as recorded were unknown, pulmonary, and infection in order of frequency.

Associations with PGD on clinical outcomes

A summary of the effects of PGD is detailed in Table 2. PGD was significantly associated with overall mortality (Odds Ratio (OR) 1.7 [95% C.I. 1.2, 2.3], p=0.001) over the study period. This risk was more apparent with bilateral lung transplants (OR 1.9 [95% C.I. 1.3, 2.7]) compared to single lung transplants (OR 1.2 [0.6, 2.1]). No significant association of mortality with transplant type (p=0.12) or PGD-transplant type interaction (p=0.17) was identified; suggesting transplant type was not associated with PGD and did not change the association of PGD with mortality. Implications of PGD using restricted mean survival time at 30 days demonstrated those with PGD lost 0.8 days of life which at 1 year and at 3 years increased to 26 days and 100 days lost respectively. This translates to 9.8% [95% CI: 5.8, 13.8] attributable risk difference or a relative risk of 2.34 [95% CI 1.65, 3.32] at 1 year.

PGD was significantly associated with prolonged mechanical ventilation (p<0.001). At 1, 2 and 3 weeks, PGD extended the period of required mechanical ventilation by 2.4, 2.7 and 6.2 days, respectively (Figure 2). Similarly, PGD was significantly associated with prolonged length of stay. At 30 and 60 days, PGD necessitated an additional 5.4 and 12 days, respectively (p<0.001). Stratified by transplant type, single lung transplant recipients with PGD required an additional 8.0 and 18.1 days compared to bilateral lung transplant recipients with PGD requiring an additional 5.0 and 11.2 days, respectively.

To account for competing risk of death, ventilator and hospital free days (VFDs and HFDs) were also calculated. Mortality within 28 days was not common (1.6% [95% CI:1.0, 2.4]). Patients with PGD had a median of 6 (95% CI: 4.1, 8.0) less days alive and free of mechanical ventilation (p<0.001). Hospital free days (HFDs) demonstrated similar observations in patients with PGD associated with lower median number of days out of the hospital but the difference was not significant (p=0.56).

Effects of ECMO bridging strategies

A total of 138 candidates were successfully bridged to transplant with ECMO in the LTOG cohort. Use of bridging strategies varied between centers from 3.6% to 42.9%, with individual center cumulative experience varying between 3 and 41 cases over the study period (median 13 [7, 15]. Among those candidates bridged to transplant, 35.8% required mechanical ventilation with the trend demonstrating increasing need over time from 16.7% to 50% (Cochran-Armitage Trend Test, p=0.025). In contrast, the requirement for concurrent ventilation within the UNOS dataset was 58.4% overall with a trend for decreased use of approximately 11% (69.2% to 58.8%).

Table 3 summarizes the associations with ECMO bridging on lung transplant outcomes. Bridging was not significantly associated with PGD in unadjusted analysis (OR 1.5 [0.9, 2.4], p=0.119) or after adjusting for covariates and stratifying for transplant type (OR 1.4 [0.8, 2.5], p=0.147). However, there was a strong association with prolonged post-transplant mechanical ventilator requirement at 1, 2 and 3 weeks in the bridged patients compared to non-bridged patients (p=0.002, p=0.014, p=0.039, respectively). At 3 weeks, on average, bridged recipients required an additional 0.9 ventilator days for single lung transplants and 2 ventilator days for bilateral lung transplants. Similar effects were noted in 30-day

hospital length of stay with single lung transplants requiring an additional 2.5 days and bilateral transplants 2.9 days in the hospital (p=0.0009). Fully adjusted contrasts accounting for competing risk of death in patients bridged to transplant confirmed observations of prolonged need for mechanical ventilation (median of 3 VFDs days; p=0.01) and hospital length of stay (median of 10 HFDs days; p=0.25).

With respect to mortality, no association of bridging ECMO was identified overall (p=0.66) or after stratifying for transplant type and adjusting for confounding (p=0.67, Table 2). Time-to-event analysis at 30 days was also not significantly different between groups (Table 2). Subgroup analysis of bridging type (VV versus VA) demonstrated no association with PGD incidence (p=0.277). Similar observations were noted with respect to mortality, with no significant association at 30 days (p=0.55), 1 year (p=0.40), or 3 years (p=0.16).

Kaplan-Meier analysis of UNOS data on bridging strategies demonstrated significant association with mortality (p=0.01). Contrasts of survival functions between non-bridged and bridged recipients at 30-days (94.4% vs 89.2%), 1-year (84.1% vs 77.2%) and 3-years (67.4% vs 60.0%) were consistently worse for bridged candidates. Stratification by mechanical ventilation status mitigated the association of bridging with mortality (p=0.06). At 30-day, 1-year and 3-years, non-bridged recipients had nominally improved survival (94.5%, 84.3% and 67.5%) compared to those bridged off the vent (89.1%, 79.6% and 61.9%), those not bridged with ECMO but bridged with mechanical ventilation (90.6%, 75.9% and 60.1%) or those bridged with both ECMO and mechanical ventilation (89.2, 75.4, and 28.6%).

Impact of ECMO salvage strategies

275 of 1517 recipients underwent salvage ECMO support after transplantation in the LTOG cohort. Of the 275 recipients requiring salvage 188 patients required intra-operative ECMO use. Table 4 summarizes the associations with salvage on outcomes. Contrary to bridging, ECMO salvage was significantly associated with increased mortality (OR 1.9 [1.3, 2.7], p=0.0007). After adjusting for confounding and stratifying for transplant type, time to event analysis at 30-days and 1 year demonstrated significant reductions in survival (single lung transplant: 1.07 [1.04, 1.11], p=0.0002 and bilateral lung transplant with salvage therapy: 1.16 [1.09, 1.23], p<.0001, respectively). The hazard associated with a salvage strategy was not constant and the effect of salvage on survival became worse over time (Figure 3). By 1-year there were 18.5 and 48.4 days of life lost for single and bilateral lung recipients overall which further increased at 3 years to 56.8 and 146.0 days of life lost respectively.

ECMO salvage was significantly associated with prolonged mechanical ventilation at any time point (p<0.0001, Table 3). Salvage strategies increased the number of days on the ventilator by 6.7 and 6.9 days for single and bilateral transplant recipients evaluated at 3 weeks, respectively. Consistent with the increased length of mechanical ventilation, there was also a significant increase in hospital length of stay (p<0.0001). On average, salvage increased length of stay measured at 30 days by 7.9 and 4.4 days for single and bilateral transplant recipients. Similarly, there was a decrease in the VFDs by 8 days (p=0.01) and HFDs by 11 days (p=0.06).

Contrasts between salvage type (VV and VA) demonstrated significant differences in mortality (p=0.0009). This was driven by increased, but different, mortality associations for VV (23.5 ± 4.1%) and VA (36.7 ± 7.6%) compared to no salvage (16.4 ± 2.0%). Effects of salvage type were exaggerated over time with increased days of life lost increasing at later time points. Overall, by 1-year, comparisons between no salvage and VV or VA ECMO demonstrated 27.2 and 84.1 days of life lost, respectively. By 3-years, the days of life lost between no salvage and VV or VA ECMO increased to 90.6 and 219.5 days of life lost. (Figure 3). Transplant type was not significantly associated with mortality (p=0.20).

Center use of ECMO salvage strategies varied between 3.6% to 45.8% with center cumulative experience ranging between 3 to 81 cases over the study period (median 21 [7, 44]. Practice variation provided a unique opportunity to compare effects of treatment strategies (PGD with ECMO salvage versus PGD without ECMO salvage). Among patients who developed PGD, use of ECMO salvage as a treatment strategy was significantly associated with mortality (OR 2.5 [1.4, 4.4], p=0.002). This risk was not associated with transplant type (p=0.97); however, an interaction was identified between transplant type and use of ECMO salvage (p=0.0003) that exaggerated the risk of mortality in bilateral lung transplants (Supplement e2). Comparison of ECMO salvage to no salvage within recipients with PGD demonstrated increasing risk of mortality over time, increased length of mechanical ventilation and increased hospital length of stay (Supplement e2, e3 and e4).

Causes of death after salvage are summarized in Table 5. Among those causes of death within the first 90 days, there was a larger proportion of acute events including organ failure, cerebrovascular and cardiovascular complications and graft failure. This was more pronounced in those subjects salvaged but did not reach significance within the LTOG cohort at any time point (within 90 days p=0.29; between 3-12 months p=0.07; or between 1 and 3 years p=0.90). Over time, these acute causes of death transitioned to more expected chronic complications. Contrasted to causes of death from the UNOS cohort, a similar trend was confirmed (Table 5); however, a statistically significant difference was observed within 90 days of transplant (p<0.001) and between 3-12 months (p=0.001) but not between 1-3 years (p=0.23).

Discussion

We have identified an increasing incidence of PGD and an increasing use of ECMO for salvage for PGD in recent years. These results suggest that PGD remains a significant risk to lung transplant recipients in contemporary practice. Over the same period, ECMO bridging strategies have decreased among the LTOG cohort overall and now more closely reflect the current use of ECMO bridging within the US. This is the first prospective, multicenter cohort study using the ISHLT 2016 consensus PGD definition, which clarified several scenarios where grading was previously ambiguous.[31]

Our study demonstrated an overall PGD incidence of 25.7% and an increasing trend at each year of the study with the final year having a PGD incidence of 38.2% (59.7% for the more inclusive definition of any grade 3 PGD within the first 72 hours). The previously reported incidence of PGD by the Lung Transplant Outcomes Group was 16.8%.[5] This is a

significant increase in a complication that is known to increase risk of death, disability and cost after transplant.[4-8,40-42] This study reconfirmed the strong association with mortality, prolonged need for mechanical ventilation and increased hospital length of stay. Perhaps the most striking effect of PGD is the observation that about a month of life is lost at 1-year and almost 5 months at 3 years compared to recipients who do not develop PGD, highlighting that PGD contributes both to increased early and delayed mortality.

Explanations for the causes of the increased incidence of PGD are speculative but might be related to the increased severity of illness observed among candidates prior to transplant over the course of the study and increasing rate of transplant for patients with combinations of restrictive lung disease, pulmonary hypertension and obesity, all characteristics previously identified as associated with PGD risk.[5] Drivers for transplanting sicker patients may be related to changes in organ allocation, which encourage wider geographic sharing and increased competition for scarce organs. Prior arguments that increasing use of ECMO bridging strategies led to increases in PGD seem less plausible as no association of ECMO bridging with PGD was demonstrated and use of bridging strategies decreased in general over the study period. However, as bridging strategies are tightly correlated with calculation of the LAS and changes to allocation continue to drive increasing use of this therapy in critically ill patients, it is possible our observation is related to allocation. Within the US, the use of bridging strategies has continued to grow comprising about 7% of all recipients in 2021. Among those same recipients, concurrent ventilation decreased by 11% from 69% to 58%. It is unclear if this the increased use of bridging therapies will continue to rise or has reached a new baseline. An alternative explanation is the increased use of extended criteria, donation after cardiac death and *ex vivo* perfused donor strategies. Regardless, further study of allocation policies and donor quality assessment measures and their implications on PGD and mortality will be needed.

Many single center reports have suggested bridging strategies are safe[10-22] in contrast to registry reports.[23,24] We observed no association of bridging with PGD or mortality among the LTOG cohort; however, prolonged mechanical ventilation and increased hospital length of stay were noted. Given these observations among 10 centers with varying transplant volume and practice, it seems reasonable to conclude that using ECMO bridging strategies in properly selected candidates is a safe and sensible approach for increasing the opportunity for transplant in appropriately selected candidates. However, examination of mortality among bridged patients within the UNOS Starfile demonstrated significantly increased mortality that was mitigated when concurrent ventilation was included as a consideration, highlighting the need to continue to review outcomes in this group to better define suitable candidates for these strategies.

Over the course of the study period, the use of ECMO salvage increased proportionally with PGD. Unsurprisingly, salvage was highly associated with increased mortality. Early effects on mortality were small but became more pronounced with elapsed time after discharge. The findings suggest that the low perioperative mortality (1.5 days of life lost) for ECMO salvage did not translate to similarly low 1- and 3-year mortality (48 and 146 days of life lost) all other things being equal. While patients with PGD salvaged with ECMO can, more often than not, be successfully managed and weaned from ECMO in the short term, it is

clear that detrimental effects are seen in these patients over the long term. Disentangling whether mortality risk was due to severity of PGD within grade 3, recipient severity of illness or the ECMO salvage strategy itself is complicated. Though we demonstrated increased risk among recipients with PGD treated with ECMO salvage compared to those not treated with ECMO, it is likely that those treated with ECMO were sicker, leading to confounding by indication. Analysis of the cause of death among salvaged versus non-salvaged patients demonstrated increased risk for acute events contributing to death including organ failure, graft failure, and cerebrovascular and cardiovascular complications. As time passed, the cause of death more closely resembled frequencies of those not salvaged. Whether this transition to rejection and infection as more prominent cause of death is a result of the tempering of salvage risk or an inability to discern the finer nuance of risk is unclear. Further work will be necessary to better clarify the precise impact of ECMO salvage on PGD specific mortality and implications on long-term survival.

There are limitations to this study. There is the potential for selection bias as not all centers enrolled all potential recipients; however, demographics of those unenrolled are similar to enrolled (Supplement Figure e1). Center effects may confound associations due to significant variability in practice across center. Given this concern, we performed a sensitivity analysis decomposing the effect of interest (i.e. PGD, bridging, or salvage) within and between center with robust variance with pseudo-observations in multivariable analyses for all outcomes to mitigate unmeasured factors.[43] These models yielded similar results to our primary analysis, indicating that center effects alone do not explain the outcome differences. Within this study there is the potential for right censoring due to differences in length of observation; however, sensitivity analysis using 3 cohorts with complete follow-up times on or after January 1, 2018, July 1, 2017 and January 1, 2017 demonstrated no change in significance or directionality of the effects reported. Because the LTOG cohort only enrolls subjects at transplant, no analyses of ECMO bridging efficacy was possible and we are unable to comment on bridging practices more comprehensively. Interaction testing of ECMO bridging strategies and ventilation was not possible due to limited sample size. Detailed reasons for using support, type of support or conversion were not collected in this study, thereby limiting our ability to comment on pre-operative, intra-operative and post-operative decision making with respect to PGD and mortality. Donor factors included in our modeling, previously identified and reported,[5] are not exhaustive and additional donor variables will be needed for better characterization of donor contributions to PGD and mortality in the future. Analysis of *ex vivo* lung perfusion strategies were also not possible given the limited number within this cohort.

In summary, we have demonstrated a dramatic increase in PGD incidence over time in parallel with increasing severity of illness in transplanted recipients. We have shown increases in ECMO bridge to transplant with no negative effect on PGD or mortality. We have identified an increasing use of ECMO salvage for PGD with previously underappreciated increased late mortality. Our findings suggest more work should be invested in PGD risk assessment, therapeutic development, evaluation of ECMO salvage strategies, and implications of changes to allocation strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

PGD	Primary Graft Dysfunction
ISHLT	International Society of Heart and Lung Transplantation
ECMO	Extracorporeal Membrane Oxygenation
LAS	Lung Allocation Score
LTOG	Lung Transplant Outcomes Group
VV	Venovenous
VA	Venoarterial
RMST	Restricted Mean Survival Time
HFDs	Hospital-Free days
VFDs	Ventilator-free days

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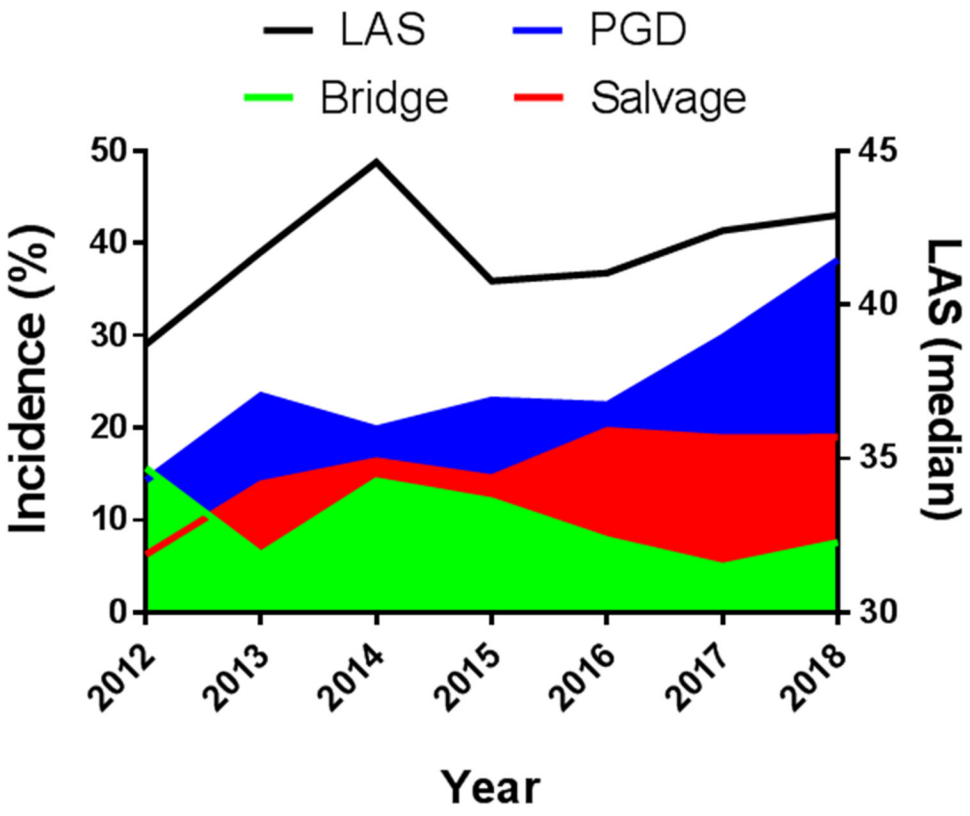

Figure 1. Recipient LAS, PGD incidence and ECMO bridging and salvage strategies over time

Note: 2018 data only includes transplants performed before July.

The single case in 2011 was moved to 2012.

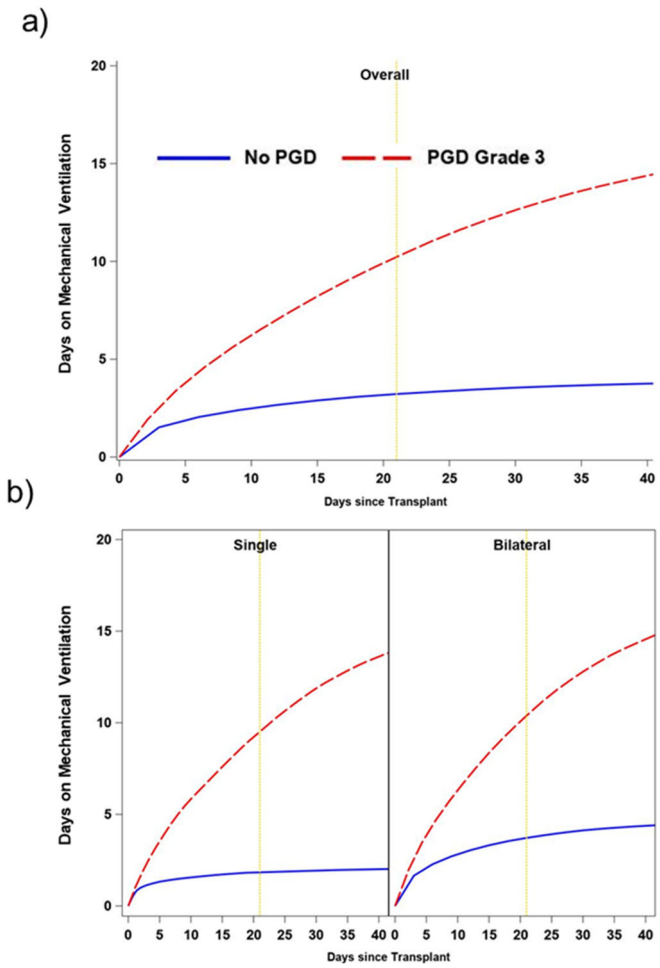

Figure 2. Effects of PGD on length of mechanical ventilation over time

Yellow bar signifies 21 days after lung transplant when a majority of US transplant recipients have been discharged from the hospital.

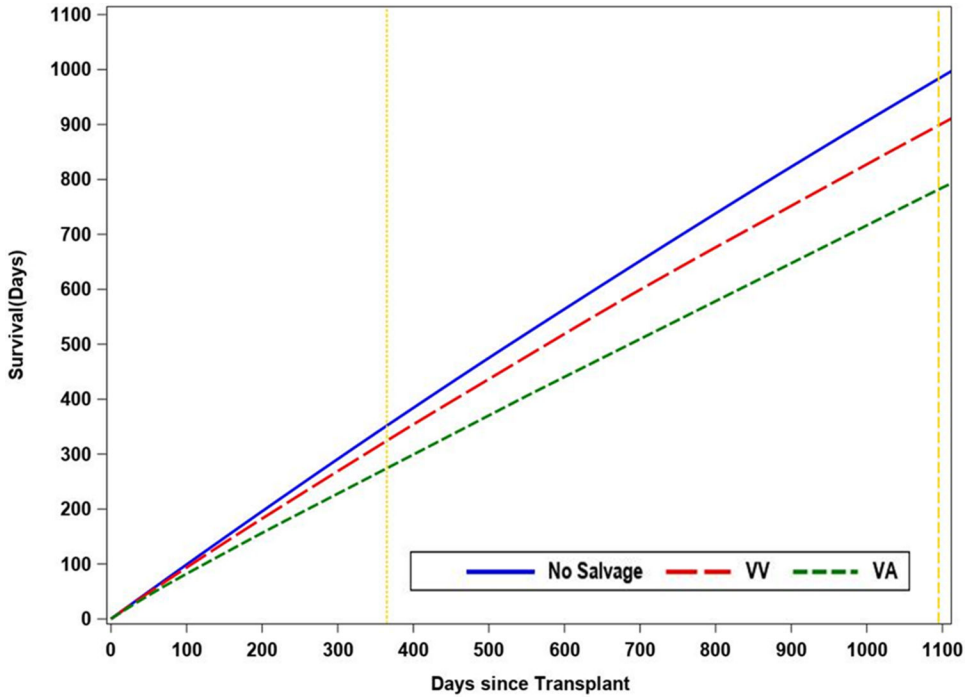

Figure 3. Association of salvage ECMO strategy with mortality

Restricted mean survival time analysis of salvage by ECMO type. Stratification was not performed because transplant type (single versus bilateral) was not associated with mortality (p=0.20). Solid line (Blue) represents no salvage, dashed line (Red) VV ECMO salvage, and dotted line (Green) VA ECMO salvage, respectively. Yellow bars set at 1 year (365 days) and 3 years (1095 days) after transplant.

Table 1.

Demographics

	All Subjects (n=1528)	No PGD (n=1111)	PGD (n=383)
Recipient Factors			
LAS	48.5 ± 17.9	46.7 ± 17.2	53.4 ± 18.9
Age	55.9 ± 13.3	56.6 ± 13.3	54.1 ± 13.3
Male	58.6	60.3	55.1
BMI	25.1 ± 4.4	24.8 ± 4.3	25.9 ± 4.5
Race			
White	85	87	78.9
African American	7.6	6.4	11.2
Latino/Hispanic	4.7	4.0	7.1
Other	4.5	3.3	7.6
Diagnosis			
COPD	22.9	26.6	13.4
IPF	52.2	50.2	57.9
CF	14.9	16.4	10.7
PAH	4	2	9.4
Other	6	4.9	8.6
PAP (mmHg)	29.1 ± 13.2	28.2 ± 12.2	31.7 ± 15.2
RAP/CVP (mmHg)	13.5 ± 8.0	13.3 ± 8.1	14.1 ± 7.7
Class I PRA ≥10%	43.7	42.7	46.8
Class II PRA ≥10%	32.5	29.8	39
Bridge	9.5	7.6	12.9
Salvage	18.1	9.8	40.2
Bridge + Salvage	4.2	2.4	8.3
Operative Factors			
Single Transplant	24.4	26.3	17.8
Intraoperative CPB/ECMO	37	31.6	52
Ischemic time (min)	291.6 ± 114.6	288.2 ± 112.8	299.9 ± 119.7
Any Nitric Oxide	50.8	51.8	48
Any PRBC	69.9	65.6	82.1
Donor Factors			
Age	36.1 ± 13.9	35.6 ± 13.8	37.8 ± 14.2
Male	59.2	59.6	58.5
PAO2 (mmHg)	485.2 ± 73.2	486.8 ± 72.8	482.7 ± 72.8
Smoking History	45.2	44.6	47.9

Continuous variables shown as mean ± S.D. Categorical variables as percentages. Abbreviations: LAS, Lung Allocation Score; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; IPF, Idiopathic Pulmonary Fibrosis; CF, Cystic Fibrosis; PAH, Pulmonary Arterial Hypertension; PAP, Pulmonary Artery Pressure; RAP, Right Atrial Pressure; CVP, Central Venous Pressure; PRA, Panel Reactive Antibodies; CPB, Cardiopulmonary Bypass; ECMO, Extracorporeal Membrane Oxygenation; PRBC, Packed Red Blood Cells; PAO_2, Partial Pressure of Oxygen. * Note: 34 recipients did not have chest radiographs for evaluation of PGD status on days 2-3 precluding assessment. PGD is defined by PaO_2/FIO_2 ratio < 200 at any time between 48 and 72 hours after transplant. No PGD is defined as all recipients not meeting PGD definition.

Table 2.

Effects of PGD

	Length of mechanical ventilation (days ± S.E.)		Hospital length of stay (days ± S.E.)		Mortality (% ± S.E.)	
Overall		p<0.001		p<0.001		p=0.001
No PGD	3.0 ± 0.3		17.9 ± 0.3		17.0 ± 2.1	
PGD	9.3 ± 4.7		23.2 ± 0.5		25.4 ± 3.3	
Adjusted		p<0.001		p<0.001		p=0.03
Single No PGD	2.1 ± 0.4		15.9 ± 0.5		21.6 ± 3.5	
Single PGD	9.2 ± 1.0		23.9 ± 0.9		24.2 ± 5.7	
Bilateral No PGD	3.8 ± 0.3		19.6 ± 0.3		13.5 ± 1.8	
Bilateral PGD	9.8 ± 0.5		24.6 ± 0.5		22.8 ± 3.1	

Depicted are the means and medians of each outcome by PGD status overall and stratified by transplant type. Abbreviations: PGD, Primary graft Dysfunction; S.E., Standard Error.

Table 3.

Effects of Bridging Strategy

	PGD (% ± S.E.)		Length of mechanical ventilation (days ± S.E.)		Length of hospital stav (days ± S.E.)		Mortality (% ± S.E.)	
Overall		p= 0.12		p= 0.02		p<0.0001		p=0.66
No Bridging	25.7 ± 2.6		4.7 ± 0.4		19.1 ± 0.4		19.4 ± 2.2	
Bridging	33.9 ± 5.8		6.4 ± 0.7		21.8 ± 0.7		17.5 ± 4.1	
Adjusted		p= 0.15		p= 0.04		p= 0.0009		p=0.67
Single No Bridging	22.8 ± 3.5		3.8 ± 0.5		17.5 ± 0.5		22.9 ± 3.5	
Single Bridging	32.4 ± 10.7		4.7 ± 1.1		20.0 ± 1.4		20.3 ± 8.2	
Bilateral No Bridging	28.7 ± 2.5		5.6 ± 3.6		20.9 ± 0.3		16.4 ± 1.9	
Bilateral Bridging	35.8 ± 6.5		7.6 ± 8.5		23.8 ± 0.8		14.8 ± 4.1	
Strategy Type		p=0.28		p=0.05		p<0.0001		p=0.39
No Bridging	25.7 ± 2.6		4.7 ± 0.4		19.1 ± 0.4		19.5 ± 2.2	
Venovenous	35.2 ± 6.9		6.7 ± 1.0		22.1 ± 0.8		13.5 ± 4.5	
Venoarterial	31.6 ± 8.4		6.1 ± 1.0		21.3 ± 1.0		23.2 ± 6.8	

Depicted are the means and medians of each outcome by bridging status overall, stratified by transplant type and adjusted by bridging status and type. Abbreviations: PGD, Primary graft Dysfunction; S.E., Standard Error.

Table 4.

Effects of Salvage Strategy

	Length of mechanical ventilation {days ± S.E.)		Length of hospital stay (days ± S.E.)		Mortality (% ± S.E.)	
Overall		p<.0001		p<.0001		p= 0.0007
No Salvage	3.5 ± 0.3		18.4 ± 0.3		17.0 ± 2.1	
Salvage	10.3 ± 0.5		23.3 ± 0.5		27.8 ± 3.9	
Adjusted		p<.0001		p<.0001		p=0.10 *
Single No Salvage	2.4 ± 0.4		16.1 ± 0.1		22.0 ± 3.5	
Single Salvage	4.5 ± 0.3		20.4 ± 0.3		18.4 ± 5.4	
Bilateral No Salvage	9.2 ± 1.1		24.0 ± 0.9		13.6 ± 1.7	
Bilateral Salvage	11.4 ± 0.6		24.8 ± 0.5		28.6 ± 4.1	
Strategy Type		p<.0001		p<.0001		p=0.0009
No Salvage	3.4 ± 0.3		18.3 ± 0.3		16.4 ± 2.0	
Venovenous	10.4 ± 0.6		23.6 ± 0.6		23.5 ± 4.1	
Venoarterial	10.1 ± 1.1		23.1 ± 0.9		36.7 ± 7.6	

Depicted are the means and medians of each outcome by salvage status overall, stratified by transplant type and adjusted by bridging status and type. Abbreviations: PGD, Primary graft Dysfunction; S.E., Standard Error. Ventilator and hospital free days were calculated using a 28-day time horizon as previously reported.[38,39]

* Significant interaction noted between transplant type and salvage ECMO (p=0.004) which mitigated salvage strategy significance.

Table 5.

Causes of death with and without ECMO salvage after lung transplant

	0-90 Days		3-12 Months		1-3 Years	
LTOG	**No Salvage**	**Salvage**	**No Salvage**	**Salvage**	**No Salvage**	**Salvage**
Unknown	0.0	11.1	16.4	0.0	57.7	56.3
Pulmonary	13.0	7.4	23.9	12.5	18.6	25.0
Infection	21.7	14.8	26.9	25.0	11.2	15.6
Hemorrhage	4.4	3.7	1.5	0.0	5.1	0.0
Organ Failure	13.0	14.8	4.5	25.0	2.9	3.1
Cardiovascular	26.1	14.8	9.0	0.0	2.2	0.0
Cerebrovascular	13.0	14.8	4.5	0.0	1.0	0.0
Other	4.4	0.0	1.5	0.0	0.6	0.0
Graft Failure	0.0	18.5	0.0	12.5	0.3	0.0
Gastrointestinal	0.0	0.0	3.0	0.0	0.3	0.0
Drug Related	4.4	0.0	1.5	0.0	0.0	0.0
UNOS						
Unknown	10.1	10.9	14.0	5.4	65.0	68.3
Pulmonary	17.0	10.9	26.9	16.2	18.2	15.6
Infection	17.6	16.7	27.8	31.1	6.3	8.8
Cardiovascular	17.9	13.8	8.0	10.8	2.3	2.4
Organ Failure	11.3	22.4	9.0	13.5	2.3	2.0
Cerebrovascular	10.4	7.5	3.8	8.1	0.8	0.5
Hemorrhage	6.3	4.6	1.7	4.1	0.4	0.0
Other	0.3	0.0	0.3	0.0	0.3	0.0
Gastrointestinal	3.1	0.0	1.0	0.0	0.2	0.0
Graft Failure	2.8	12.6	1.2	5.4	0.2	0.5
Drug Related	0.9	0.0	0.2	0.0	0.1	0.0
Hospice	0.0	0.0	0.2	2.7	0.0	0.5
Natural Causes	0.0	0.0	0.0	0.0	0.0	0.0

Depicted are percentages among each group.