The Effect of Primary Graft Dysfunction on Survival after Lung Transplantation

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Rationale: Primary graft dysfunction is a severe acute lung injury syndrome after lung transplantation. Long-term outcomes of subjects with primary graft dysfunction have not been studied. **Objectives:** We sought to test the relationship of primary graft dysfunction with both short- and long-term mortality using a large registry. **Methods:** We used data collected on 5,262 patients in the United Network for Organ Sharing/International Society of Heart and Lung Transplantation registry between 1994 and 2000. We assessed outcomes in all subjects; to assess potential bias from the effects of early mortality, we also evaluated subjects who survived at least 1 year, using Cox proportional hazards models with time-varying covariates. **Main Results:** The overall incidence of primary graft dysfunction was 10.2% (95% confidence intervals [CI], 9.2, 10.9). The incidence did not vary by year over the period of observation ($p = 0.22$). All-cause mortality at 30 days was 42.1% for primary graft dysfunction versus 6.1% in patients without graft dysfunction (relative risk = 6.95; 95% CI, 5.98, 8.08; $p < 0.001$); among subjects who died by 30 days, 43.6% had primary graft dysfunction. Among patients surviving at least 1 year, those who had primary graft dysfunction had significantly worse survival over ensuing years (hazard ratio, 1.35; 95% CI, 1.07, 1.70; $p = 0.011$). Adjustment for clinical variables including bronchiolitis obliterans syndrome did not change this relationship. **Conclusion:** Primary graft dysfunction contributes to nearly half of the short-term mortality after lung transplantation. Survivors of primary graft dysfunction have increased risk of death extending beyond the first post-transplant year.

Keywords: acute lung injury; lung transplantation; outcomes; primary graft dysfunction; reperfusion injury

Primary graft dysfunction (PGD), also known as primary graft failure, is a form of lung allograft ischemia-reperfusion injury (1, 2). Occurring in the first hours to days after transplantation, the clinical course and pathophysiology of the most severe forms are most similar to the acute respiratory distress syndrome (1, 3, 4). With an incidence reported between 10 and 25%, and a high mortality (5), PGD represents the leading cause of early death after transplantation (1, 2, 5–8).

However, the long-term outcomes of PGD have not been

systematically studied because of the low numbers of survivors at single centers (2, 3, 5). In one study, it was suggested that severe ischemia-reperfusion injury increases the risk of chronic rejection and long-term mortality (9); however, others have found no such relationship (3). Furthermore, survivors of severe acute lung injury from a variety of other causes have increased mortality and impaired quality of life extending far beyond the initial hospitalization (10–12). Therefore, survivors of PGD could possibly have an increased risk of long-term mortality because of either chronic rejection or the after-effects of extended critical illness.

The purpose of this study was to test the association of PGD with short- and long-term mortality after lung transplantation using data from the United Network for Organ Sharing/International Society of Heart and Lung Transplantation (UNOS/ISHLT) lung transplant registry.

Some of the results of these studies have been previously reported in the form of an abstract (13).

METHODS

Study Population

We used the combined UNOS/ISHLT Heart and Lung Transplant Registry as our study population (www.unos.org), including all subjects between 1993 and 2000 (14). This data source is the result of a voluntary data entry system by personnel from participating UNOS transplant sites, and includes all transplants at these sites.

Definition of PGD

Beginning in 1993, a field coding “prolonged graft dysfunction during initial hospital stay” was made available for entry. The field was entered as part of the form completed at the time of hospital discharge from the initial transplant, and formed the basis of our definition of PGD. To compare the coded definition of PGD with patients at our institution, we extracted the charts of 188 subjects who underwent lung transplant at our institution between 1994 and 2000 and compared PGD based on detailed chart review with UNOS/ISHLT registry coding of PGD. We defined PGD according to our previously published criteria (1, 8): a $\text{PaO}_2/\text{FiO}_2$ ratio less than 200 beyond 48 hours after transplantation, with evidence of radiographic infiltrates, and absence of secondary causes of allograft dysfunction. An expanded and detailed explanation of our defining criteria is included in an online supplement. In addition, to investigate potential misclassification of this outcome, we cross-referenced those subjects who expired within the first 30 days after transplant and had a cause of death listed as “primary graft failure” with those who died within 30 days and did not have a positive response in the “prolonged graft dysfunction during initial hospital stay” field.

Outcomes

Outcomes studied included mortality at 30 days and 1 year and overall survival during the period of observation as time-to-event analysis. Because of the significant early mortality associated with PGD, we evaluated long-term outcomes among 1-year survivors of PGD to minimize potential biases introduced by competing mortality causes. Furthermore, evaluation of hazard functions among survivors to 1 year

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revealed that the hazard of death among patients with PGD was proportional to those without PGD.

Statistical Analysis

Relative risks with 95% confidence intervals (95% CI) were calculated as the incidence of outcome (e.g., 30-day mortality rate) in patients with PGD divided by the incidence of outcome in patients without PGD. Overall survival between subjects with PGD and those without was compared using Kaplan-Meier methods and a log-rank test (15). Cox proportional hazards models were used to estimate a hazard ratio and to test the independence of the association of PGD with mortality when adjusted for the confounding effects of other variables. Because the hazard of death may vary in the post-transplant period, in all cases, the proportionality of hazards assumptions were tested using log-log negative plots (15), and the Schoenfeld residual test in STATA (Stata Corp., College Station, TX). For the multivariable analyses of potential confounding, a logistic regression model was used for evaluating 1-year survival as a dichotomous outcome variable, and a Cox proportional hazards model was used for multivariable analyses of overall survival among 1-year survivors. The following variables were simultaneously entered into the regression models with PGD: calendar year of transplant (to assess the effects of different treatment regimens over time); age, sex, race, and preoperative diagnosis of recipient; age of donor; type of transplant; and development of bronchiolitis obliterans syndrome (BOS). The development of BOS was treated as a time-varying covariate in the Cox model.

All statistical comparisons were performed using STATA version 8.0 (Stata Corp.). This research protocol was approved by the Institutional Review Board of the Office of Regulatory Affairs at the University of Pennsylvania.

RESULTS

A total of 5,262 subjects were available for study. The overall incidence of PGD during the period of observation was 10.2% (95% CI, 9.2, 10.9). As illustrated in Figure 1, the incidence of PGD did not vary by year between 1994 and 2000 (χ^2 test for trend, $p = 0.22$).

In the UNOS/ISHLT registry, of the 305 subjects who died within the first 30 days without the “prolonged graft dysfunction during initial hospital stay” field, only 28 (9.1%) had “primary graft failure” listed as a cause of death. Between January 1, 1994, and January 1, 2000, we performed 188 transplant procedures at the University of Pennsylvania. During this time, 12 subjects were coded as having “prolonged graft dysfunction during initial hospital stay” in the UNOS/ISHLT registry. All 12 of these subjects met our strict criteria for PGD based on our detailed chart review, and all 12 of these subjects had pathologic specimens available that were consistent with diffuse alveolar damage. An additional nine patients met criteria for PGD on chart review but did not receive a code for PGD in the registry. Thus, when comparing the registry definition of PGD to rigorous criteria at our institution, all subjects coded as PGD in the registry had true PGD, but some of the subjects with true PGD were coded

Figure 1. Change in incidence of primary graft dysfunction (PGD) by year of transplant. The χ^2 test for trend p value was 0.22.

as not having PGD in the registry. Using the chart clinical definition of PGD as a gold standard, the positive predictive value of the UNOS/ISHLT registry field at our institution was 100% (12/12; 95% CI, 73.5–100%), and the negative predictive value was 94.6% (158/167; 95% CI, 90.0–97.5%).

All-cause mortality at 30 days was 42.1% for PGD versus 6.1% in patients without (relative risk = 6.95; 95% CI, 5.98–8.08; $p < 0.001$). Of the 509 subjects who died by 30 days, 43.6% had PGD. All-cause mortality at 1 year was 64.9% in PGD versus 20.4% in patients without PGD (relative risk = 3.18; 95% CI, 2.92–3.47; $p < 0.001$). There was a less than 5% change in the point estimate of the relative risk for 1-year mortality when adjusted simultaneously for age, sex, race, and preoperative diagnosis of recipient; age of donor; and type of transplant in a logistic regression model. The overall survival was significantly worse in patients with PGD (log-rank test, $p < 0.001$; Figure 2).

Because the majority of patients who develop PGD die within the first year after lung transplantation, we focused on the population who survived at least 1 year to evaluate differences in longer term outcomes. Evaluation of this population revealed that the hazard functions for mortality were proportional between those with PGD and those without (Schoenfeld residual test of proportional hazards assumption $\chi^2 = 0.18$, $p = 0.67$); thus we could use the Cox proportional hazards model in 1-year survivors. Among patients surviving at least 1 year, those who had PGD had significantly worse survival over subsequent years of observation (hazard ratio = 1.35; 95% CI, 1.07–1.70; $p = 0.011$). These findings are illustrated in Figure 3. When confounding variables, including calendar year of transplant; age, sex, race, and preoperative diagnosis of recipient; age of donor; type of transplant; and development of BOS (as a time-dependent covariate), were simultaneously entered into the multivariable Cox proportional hazards model, PGD remained independently associated with overall mortality (adjusted hazard ratio = 1.38; 95% CI, 1.09–1.74; $p = 0.006$).

Causes of death in 1-year survivors are listed in Table 1. In general, 1-year survivors of PGD died of the same causes as those with no PGD, because there was no significant association of PGD with any particular cause of death.

DISCUSSION

Using a large lung transplant registry, our results confirm that PGD is a major contributing factor to early mortality. In addition,

Figure 2. Overall survival in patients with PGD and those without. The analysis time is years. The hatch marks represent censored patients, and the number at risk at the start of a specified interval appears along the x axis.

TABLE 1. CAUSE OF DEATH IN SURVIVORS TO 1 YEAR AFTER TRANSPLANT

Cause of Death	N	Odds Ratio (95% CI)	p Value
Unknown	139	Referent	Referent
Other graft failure, including acute rejection	55	0.91 (0.17–4.69)	0.913
Chronic rejection or bronchiolitis	356	1.84 (0.73–4.65)	0.195
Bacterial infection, other	78	1.28 (0.34–4.70)	0.712
Pneumonia	109	0.43 (0.08–2.18)	0.309
Fungal infection	71	1.36 (0.37–5.04)	0.637
Other infection	24	0.95 (0.10–8.39)	0.969
Cardiovascular	46	2.25 (0.60–8.45)	0.228
Other respiratory failure	179	1.07 (0.36–3.17)	0.900
Cerebrovascular event	17	1.47 (0.16–13.2)	0.729
Hemorrhage	13	1.91 (0.20–17.5)	0.565
Malignancy	103	0.66 (0.16–2.74)	0.577
Organ failure, other	72	0.38 (0.04–3.20)	0.371
Multiple organ failure	73	0.98 (0.23–4.03)	0.972
Other	84	0.28 (0.03–2.35)	0.240

Definition of abbreviation: CI = confidence interval.

The odds ratio represents the odds of a particular cause of death category for subjects who had primary graft dysfunction (PGD) relative to those without PGD, with "unknown" as the referent category. "N" denotes the total number of deaths in a given cause of death category among those subjects who survived past 1 year after transplant.

tion, a key finding of our study is that subjects who survive to 1 year after PGD continue to have a higher risk of mortality over the next 4 years. These findings illustrate the importance of PGD to short- and long-term outcomes, and suggest that further research is needed to evaluate the reasons for the observed impact of PGD on longer term mortality.

The relationship of PGD with mortality among 1-year survivors is striking, with a relative 35% increase in the risk of mortality over the next 4 years. Although the etiology of this finding is uncertain, plausible explanations include the influence of an episode of prolonged critical illness in survivors of PGD, as well as the potential for increased immunogenicity of the allograft after earlier severe lung injury. Because data on potential factors related to prolonged critical illness are not completely available in the registry (e.g., length of stay in the hospital or intensive care unit), we could not explore their influence on our results. However, in a single center, we have previously reported that survivors of PGD have worse pulmonary function and functional exercise capacity at 1 year (1, 5). Furthermore, nontransplant subjects who survive acute respiratory distress syndrome or sep-

sis have greater mortality after hospital discharge (11, 16, 17), and survivors of acute respiratory distress syndrome have an increased risk of prolonged disability because of neuropathy, myopathy, malnutrition, and deconditioning (12). Thus, our findings may be attributable to the lingering effects after prolonged critical illness and the inability to withstand another illness.

Alternately, the relationship of PGD with impaired longer term survival may be from the effects of increased incidence of acute and/or chronic rejection. Although there was no statistically significant increase in any individual cause of death, the point estimate for the odds ratio for chronic rejection among patients with PGD was greater than 1. We were unable to detect this potential difference in chronic rejection as a cause of death between our subjects with PGD and those without, perhaps because of the following reasons: the relatively small numbers of subjects with chronic rejection listed as a cause of death, misclassification of causes of death, or effects of patients with chronic rejection being listed as dying of other causes. In separate analyses, when we adjusted for the diagnosis of BOS in the multivariable mortality models, it did not diminish the association of PGD with mortality. Thus, although PGD may potentially have a relationship with BOS (18), we saw no evidence of BOS accounting for the increased long-term mortality associated with PGD in our models. However, these findings should be interpreted with caution, given that the diagnosis of BOS may be underreported in the ISHLT registry (19).

Alternatively, PGD may increase risk of acute allograft rejection (18). Unfortunately, incidence, severity, or number of acute rejection episodes were not recorded in our data source, making it a potential uncontrolled confounding variable, although there was no increase in the report of acute rejection as a cause of death among 1-year survivors of PGD.

We found a 30-day mortality rate of 42%, with a relative mortality risk of nearly 7, and a 1-year mortality rate of 64.9% among patients with PGD, with a relative mortality risk of more than 3. These findings are consistent with reported mortality rates and relative risks in single-center studies for the most severe forms of PGD, including our own (1, 2, 5). In addition, a recent ISHLT registry report describes PGD as accounting for greater than 30% of mortality in the first 30 days, according to listed cause of death (14, 19). Our results differ from those reported by the ISHLT registry because we include subjects with PGD as a diagnosis who had a primary cause of death other than

Figure 3. Overall survival in patients who survived at least 1 year. The analysis time is years. The log-rank p value for the comparison of PGD to those without PGD is 0.014.

PGD (e.g., multiorgan failure). Thus, in addition to those whose direct cause of death was PGD, we captured those with PGD who died of other causes.

The consistent finding of the strong influence of PGD on short-term mortality reinforces the notion that further research into the prevention and early treatment of PGD is warranted (20). In addition, the relationship of PGD with mortality in the first year has important implications for organ allocation systems, which are based on 1-year mortality (21). In the United States, plans for organ allocation rely heavily on the influence of recipient variables (e.g., diagnosis) on 1-year mortality. Given that PGD is a major contributor to 1-year mortality, and that donor factors seem to be important to risk of PGD (8), careful evaluation of the relationship between donor and recipient variables in mitigating PGD risk is warranted in future investigations.

Our study has several sources of potential error. The most important of these relates to the definition of PGD in the registry and the potential for exposure misclassification. The field “prolonged graft dysfunction during initial hospitalization” was part of a data entry form that had to be completed at the time of discharge. There were no specific instructions for filling out this field. Lung injury after lung transplantation is a spectrum, and the definition in the current study appears to represent the most severe forms, as evidenced by the relatively low incidence, as well as the findings in our population, where all subjects had a $\text{PaO}_2/\text{FiO}_2$ ratio less than 200 beyond 48 hours. Inclusion of only the most severe forms of PGD in our outcome definition would have the greatest effect on our findings of increased short-term mortality, whereas milder forms of PGD may not have such a profound impact on mortality. In addition, there may have been differential misclassification based on vital status at the time of hospital discharge, potentially because of data entry personnel being aware of vital status at the time of entering this field, perhaps being more likely to code dead subjects as having PGD. Although this effect may possibly have led to an inflated estimate of the impact of PGD on early mortality, it should not have affected the relationship of PGD with long-term mortality among 1-year survivors, because the field was entered long before the 1-year mark. Nonetheless, our early mortality rates are consistent with published rates from single centers; thus, if inflation of association with mortality was present, it likely was minimal.

Exposure misclassification may also have resulted from the lack of clear criteria for “prolonged graft dysfunction” among centers, or from inclusion of other causes of early graft dysfunction unrelated to ischemia reperfusion injury in this field. However, investigation of the coded field definition when compared with a rigorous definition at our center revealed that no subjects who had other causes of graft dysfunction (e.g., later pneumonia) had been coded as having PGD. In addition, in the registry, the “prolonged graft dysfunction during hospitalization” field itself missed less than 10% of people who died within the first 30 days with PGD listed as the cause of death. Thus, there was consistency of PGD reporting in two different fields within the registry. Furthermore, given that the incidence in our study is comparable to, and not greater than, more detailed cohort studies using a stringent definition of the most severe form of PGD (1, 2, 5), we believe that there were not a large number of “later” causes of prolonged graft dysfunction (e.g., from pneumonia occurring 2 weeks postoperatively) mixed in with our case definition. Misclassification of subjects with PGD into the “non-PGD group” should bias results toward the null. Therefore, it is extremely unlikely that the finding of association of PGD with long-term mortality is because of a false-positive association. Nonetheless, we believe that efforts to refine and standardize

this definition in the registry and other future studies should continue.

In conclusion, we have determined that, among patients who survive at least 1 year after PGD, there is a persistent increased risk of mortality. The underlying mechanisms explaining this finding remain uncertain. Furthermore, we illustrate that PGD is associated with a high early mortality risk, and is a major cause of early death after lung transplantation. These results highlight the importance of PGD to outcomes after lung transplantation, and reinforce the importance of efforts aimed at its prevention and understanding the risk factors for the observed increase in long-term mortality among PGD survivors.

Conflict of Interest Statement: J.D.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; V.N.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.E.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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