Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part V: Predictors and Outcomes

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Primary graft dysfunction (PGD) after lung transplantation results from an acute lung injury developing in the transplanted organ(s) in the immediate post-operative period. There is a wide spectrum of severity from subtle infiltrates on chest X-ray with mild impairment of gas transfer in an asymptomatic patient to a full-blown acute respiratory distress syndrome (ARDS)-like phenomenon manifest by diffuse infiltrates on chest X-ray and severe hypoxemic respiratory failure requiring a high level of critical care support.[1] The cause of PGD is likely multifactorial with brain-death-related donor lung injury, ischemia-reperfusion injury, infection and cardiopulmonary bypass representing some of the possible etiologies.[1] There are many published data on the incidence and outcomes of PGD. However, interpretation of these data is limited by the lack of a widely accepted and concise definition of PGD, which has led to the use of different definitions in each individual study (Table 1). As a result, both the incidence and outcomes of this major early post-operative problem are significantly affected by differing definitions and patient populations included in studies of PGD.

The incidence of PGD in recent studies has varied between 11% and 57%.[2–10] Less stringent definitions will include milder cases, thereby increasing the incidence of PGD, decreasing its impact on outcomes, and interfering with the identification of variables that may be associated with adverse short- and long-term outcomes after severe forms of PGD. Conversely, more stringent definitions that include only the more severe cases of PGD will reduce its incidence, but will increase its apparent impact on clinical outcomes. Therefore, the interpretation of data on outcomes requires caution and consideration of the definition of PGD in individual studies. The topic of definition and classification of PGD is reviewed and a set of uniform definition criteria have been proposed in the accompanying article by Christie and colleagues.

SHORT- AND LONG-TERM OUTCOMES OF PGD

The recognition of outcomes of PGD is essential for determination of the impact of this early post-operative problem on short- and long-term prognosis. PGD remains responsible for significant early morbidity and mortality after lung transplantation.[11] Relevant clinical outcomes of PGD include length of mechanical ventilation (LOV), ICU length of stay (LOS), hospital length of stay (hLOS), mortality, short- and long-term survival, cost, functional status and incidence of bronchiolitis obliterans syndrome (BOS). Most studies have shown that PGD leads to adverse short-term outcomes, including prolonged LOV, ICU LOS, hLOS, increased cost and increased short-term mortality (Table 2).[6–9,12] Conflicting short-term results are generally explained by the differences in the definition of PGD in individual studies and the resultant differences in severity of graft dysfunction in the patient population studied.[3,7–9]

In most studies, long-term survival in patients with severe PGD is also inferior compared with that in patients without PGD (Table 3).[3,5–7,9] Although Kahn et al and Thabut et al did not report a difference in long-term survival between patients with and without PGD, the lack of a difference can be explained in part by the less stringent definitions of PGD in these studies, and by the relatively poor long-term survival rates in patients without PGD in the study by Kahn et al.[7,9] In general, the lower long-term survival rate appears to be secondary to increased early mortality. This was demonstrated in the study by Fisher et al, who found that long-term survival was comparable in patients with and without PGD when early deaths were excluded from their analysis (Figure 1).[6] There is a lack of data on long-term functional outcomes after severe PGD. Christie et al reported a decreased 6-minute walk distance and limited ambulatory status in a small group of survivors of PGD.[3,12]

A possible association between PGD and the future development of BOS has been hypothesized for many years. The recognition that activation of the innate immune response plays an important role in the subsequent orchestration of the adaptive immune response is funda-

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Table 1. Time and Severity Definitions of Primary Graft Dysfunction Used in Prevalence and Outcome Studies

Time from transplantation to onset[3,4,8,9]
24–72 h
Chest radiograph[2–4,7–9,21]
Diffuse pulmonary infiltrates
Chest radiograph score
Measures of oxygenation
Pao_2:Fio_2 ratio: <200–300 mm Hg[3,4,8,9]
Oxygenation index (MAP × Fio_2: Pao_2 ratio)[5]
Others[7]
Exclusion of other causes of graft dysfunction
Hemodynamic measurements: PAOP <12–18 mm Hg[4,7]
Clinical evaluation[2–9]
Lung biopsy
Diffuse alveolar damage[6]

MAP, mean airway pressure; PAOP, pulmonary artery occlusion pressure.

mental to the hypothesis that acute graft injury can predispose to chronic graft dysfunction in all solid organs.[13] The clinical significance of the "injury response" was first demonstrated in the renal transplant literature when delayed graft function in renal allografts was identified as an independent risk factor for the development of chronic rejection and graft loss in renal transplant recipients.[14] In lung transplantation, PGD represents a major activation of the innate immune response in the allograft. Experimentally, PGD increases MHC Class II expression in the lung, thereby increasing immunogenicity.[15] Furthermore, increased expression of the neutrophil chemokine, interleukin (IL)-8, has been demonstrated in PGD and has been associated with the development of BOS.[16–18] This finding provides additional support for the hypothesis that uncontrolled graft injury can begin with PGD, progress to acute rejection and lymphocytic bronchiolitis, and finally repair and remodeling to produce obliterative bronchiolitis.

In 2002, two large, single-center studies were published which investigated this hypothesis in lung transplant recipients.[5,6] These studies were performed using very different methodologies and reached different conclusions. Although the study by Fiser and colleagues,[5] using uni- and multivariate analyses, revealed a higher incidence of onset of BOS and progressive BOS in patients who had PGD (defined by clinical criteria), Fisher and colleagues[6] reported a lack of association between PGD (defined by acute non-immune graft injury on early histopathologic examination) and the development of BOS when survival analysis was used. Because the larger of the two studies[6] used histologic evidence of diffuse alveolar damage as a marker of PGD and utilized survival analysis rather than uni- or multivariate analysis, it seems to provide a more robust

Table 2. Short-Term Outcomes of Primary Graft Dysfunction

	Kahn et al,[7] 1999	King et al,[8] 2000
Number of patients	99	100
Definition	24 h, infiltrates,[a] hypoxemia (Fio_2 ≥0.3 to keep Pao_2 ≥65 mm Hg), PAOP ≤12 mm Hg, no rejection or infection	48 h, P/F <200, CXR score ≥6[c]
New classification	T24, Grade 1–3	T48, Grade 3
Incidence	57%	22%
LOV	3 (2,7) vs 2 (1,3) days[b] ($p = 0.009$)	393.5 ± 81.6 vs 56.8 ± 12.4 h[d] ($p < 0.001$)
ICU LOS	8 (5,20) vs 6 (5,10) days[b] ($p = 0.03$)	22.2 ± 4.2 vs 10.5 ± 2.1 days[d] ($p < 0.014$)
Hospital LOS	24 (18,39) vs 21 (15,27) days[b] ($p = 0.08$)	48.9 ± 9.9 vs 25.6 ± 2 days[d] ($p < 0.03$)
Cost	—	Total charge ($): 201,120 ± 23,540 vs 124,040 ± 9,260 ($p < 0.006$); Total cost ($): 145,650 ± 16,720 vs 95,630 ± 6,110 ($p < 0.01$)
Mortality	Post-operative: 21.4% vs 18.6% (p = NS)	Hospital: 40.9% vs 11.5% ($p < 0.002$)
Survival	Median: 28 vs 36 months ($p = 0.99$); 30-day: 86% vs 84% (NS)	—

PAOP, pulmonary artery occlusion pressure; P/F, Fio_2: Pao_2 ratio; EHF, early hemodynamic failure; DAD, diffuse alveolar damage; RR, relative risk; HR, hazards ratio; PGD, primary graft dysfunction; LOV, length of mechanical ventilation; LOS, length of stay.

[a]Grade 0–5 based on chest radiograph score. When patients with severe PGD (based on radiographic grade) are considered, LOV (6 vs 2 days), ICU LOS (10 vs 6 days) and hospital LOS (36 vs 20 days) are all significant compared to those without PGD. Such patients fit the more severe definition of PGD with Pao_2:Fio_2 ratio <200 mm Hg.

[b]Data expressed as median (quartiles).

[c]Definition of CXR score not provided.

[d]Data expressed as mean ± SEM.

[e]Data expressed as mean ± SD.

assessment of likely differences in BOS incidence, especially since the risk of BOS increases with time after transplant. However, histologic findings to define PGD may also be subject to problems in the accurate identification of a patient population with this process in that sampling error during biopsy or inability to obtain biopsies from those with more severe degrees of PGD may result in an inability to capture all patients.

If it is true that the recipients with PGD who survive >3 months do not have an increased risk of subsequent BOS, why should this be different in lung transplantation compared with renal transplantation? There are several possible explanations: First, those who survive PGD are likely to have suffered a milder lung injury than those who died in the early postoperative period. As a result, there may not have been a sufficient injury stimulus to increase graft immunogenicity in these recipients. Second, the degree of allograft injury needed to increase the risk of chronic rejection in renal transplantation may not be compatible with survival in lung transplantation. The patient with a dysfunctional renal allograft may be supported with dialysis; thus, severe renal allograft injury has more opportunity to resolve than a comparable degree of injury in a lung allograft.

PREDICTORS/SCORES OF OUTCOMES OF PGD

Although there is more information on the prediction of development of PGD, there are limited data on the prediction of outcomes of PGD once it is present. Certain cellular, molecular, physiologic and clinical variables have been associated with outcomes in PGD in studies that typically included a small number of patients.

Fisher et al reported a significant association between high donor IL-8 concentration in bronchoalveolar lavage fluid and the development of early graft dysfunction and increased early mortality in recipients.[16] de Perrot et al measured various cytokine levels in the peri-operative period and examined the relationship between cytokine levels and allograft function.[17] Lung tissue IL-8 levels at 2 hours after reperfusion correlated negatively with graft oxygenation (Pao_2:Fio_2 ratio) and ICU-free days in the first 30 days, and positively with APACHE score and mean airway pressure at various time-points in the first 24 hours.

Ware et al reported the presence of increased alveolar-capillary barrier permeability by measurement of the pulmonary edema fluid to plasma protein ratio in 6 of their 8 patients with PGD.[19] Although the degree of permeability did not correlate with clinical parameters

Table 2. Continued

Thabut et al,[9] 2002	Fisher et al,[6] 2002	Christie et al.[12] 2004
259	291	255
72 h, diffuse infiltrate, P/F <300 with or without EHF	Histologic evidence of DAD on lung biopsy at 7 days	72 h, diffuse infiltrate, P/F <200 beyond 48 h, continued ventilator dependence beyond Day 5, no other cause
T72, Grade 2	NA	T72, Grade 3
50.6%	19%	11.8%
9.1 ± 1 vs 3.1 ± 0.6 days[e] ($p < 0.001$)	60.8 ± 4.3 vs 32.7 ± 19.5 h[d] ($p = 0.03$)	Median: 15 vs 1 day ($p < 0.001$)
22.7 ± 2 vs 19.7 ± 1.5 days[e] ($p = 0.15$)	—	—
—	—	Median: 47 vs 15 days ($p < 0.001$)
—	—	—
ICU: 29% vs 10.9% ($p < 0.01$)	—	All-cause at 30 days: 63.3% vs 8.8% (RR = 7.15 [4.34–11.80] $p < 0.001$)
—	30-day survival: 62.5% vs 87.5% (HR 0.44 [0.27–0.73]; $p = 0.0001$)	—

Table 3. Long-Term Outcomes of Primary Graft Dysfunction

	Christie et al,[3] 1998	Khan et al,[7] 1999	Thabut et al,[9] 2002
Number of patients	100	99	259
Definition	72 h, diffuse infiltrate, P/F <200 beyond 48 h, continued ventilator dependence beyond Day 5, no other cause	24 h, infiltrates, hypoxemia (Fio_2 ≥0.3 to keep Pao_2 ≥65 mm Hg), PAOP ≤12 mm Hg, no rejection or infection	72 h, diffuse infiltrate, P/F <300 with or without EHF
Incidence	15%	57%	50.6%
Survival	1 y: 40% vs 69% 2 y: 27% vs 66% ($p < 0.005$)	1 y: 68% vs 65% 3 y: 49% vs 48% (p = NS)	Long-term survival not different ($p = 0.2$)
BOS	—	—	—
PFTs	12 months: FEV_1 43 ± 10% vs 55 ± 15% (p = NS)	—	—
6-MWT	6 months: 667 ± 507 vs 1,458 ± 401 ft ($p < 0.005$) 12 months: 883 ± 463 vs 1,513 ± 424 ft ($p < 0.005$)	—	—
Ambulatory status	4 of 6 ambulatory at 6 months; 5 of 6 ambulatory at 12 months; 3 of 6 required supplemental O_2	—	—

PAOP, pulmonary artery occlusion pressure; FEV_1, forced expiratory volume in 1 second; P/F, Pao_2:Fio_2 ratio; EHF, early hemodynamic failure; DAD, diffuse alveolar damage; BOS, bronchiolitis obliterans syndrome; 6-MWT, 6-minute walk test; PGD, primary graft dysfunction.

[a]When early deaths within 30 days were excluded, no difference was found for survival of those with and without DAD (HR 0.69 [0.37–1.30]; $p = 0.2$).

(A-a gradient, severity of infiltrates, LOV, ICU LOS), the preservation of net alveolar epithelial fluid clearance was associated with better clinical outcomes. Four of 6 patients with intact transport had good results, with rapid resolution of infiltrates and hypoxemia. In contrast, 2 patients with no net fluid transport had prolonged hypoxemia and infiltrates with a trend toward longer ICU stay and LOV. These data suggest that the preservation of alveolar epithelial transport capacity is critical for timely resolution of the inflammatory edema in acute lung injury, and the rate of fluid transport may be an important prognostic indicator in PGD.

The prediction of outcomes of PGD using clinical variables has recently been reported by Thabut et al,[9] who retrospectively studied 259 lung transplant recipients. One hundred thirty-one (50.6%) patients had PGD, which was defined as radiographic infiltrates developing over 72 hours along with a Pao_2:Fio_2 ratio <300 in the absence of other identifiable causes. The authors also evaluated the association between PGD and early hemodynamic failure (EHF) and graded the severity of EHF based on vasopressor requirements. They noted a 29% ICU mortality rate among those who developed PGD and 10.9% for those who did not. In addition, they tested multiple variables in a univariate analysis and found that 5 variables were associated with ICU mortality: ischemic time; severe EHF; bilateral lung transplantation; Pao_2:Fio_2 ratio; and age. These variables were entered into a multivariate logistic regression, and 4 variables were found to be independent predictors of ICU mortality: age; ischemic time; Pao_2:Fio_2 ratio; and severe EHF. The coefficient for each variable was multiplied by a factor of 10, and all the variables were added to derive an ischemia-reperfusion injury severity score (IRISS). The group used 67% of their cohort to develop this model and IRISS; they then validated the model and score using the other 33% of the cohort, with good results. An IRISS point-scale system was provided, and a probability of ICU mortality was determined from this score (Figure 2). It is important to note that the objective of the study was not to develop a scoring system to predict an individual patient's probability of mortality, but rather to develop a system that would allow for better assessment of severity of PGD and would ensure comparability between groups in the studies of PGD.

Using a similar approach, Sekine et al retrospectively analyzed donor, recipient, operative factors and immediate post-operative physiologic parameters in 122 lung transplant recipients to identify risk factors for 30-day mortality and prolonged ICU LOS.[20] They found that the use of marginal donors, cardiopulmonary bypass, recipient body mass index (BMI) >25 kg/m^2 and recipient diagnosis of a pulmonary hypertensive disorder were significant risk factors for 30-day mortality and prolonged ICU stay. On multivariate analysis, recipient BMI >25 kg/m^2 and certain physiologic post-operative parameters, including APACHE II score, systolic pulmonary artery pressure, Pao_2:Fio_2 ratio and oxygenation

Table 3. Continued

Fiser et al,[5] 2002	Fisher et al,[6] 2002	Christie et al,[12] 2004
115	291	255
24 h, infiltrates, at least moderate dysfunction (oxygenation index = MAP × Fio_2:Pao_2 >7)	Histologic evidence of DAD on lung biopsy at 7 days	72 h, diffuse infiltrate, P/F <200 beyond 48 h, continued ventilator dependence beyond Day 5, no other cause
20%	19%	11.8%
—	Long-term survival not different[a]	—
Uni-variate: increased risk of BOS onset ($p = 0.017$) and progressive BOS ($p = 0.011$); Multi-variate: PGD an independent predictor of BOS development and progression ($p = 0.017$)	Incidence of BOS with and without DAD: 46% vs 59% ($p = 0.22$); median time to BOS with and without DAD: 953 vs 665 days ($p = 0.48$)	—
—	—	
—	—	Median best within first 12 months: 1,196 ft (range 600–1,223 ft) vs 1,546 ft (100–2,645 ft) ($p = 0.009$)
—	—	28.5% vs 71.4% of ambulatory survivors achieved a normal age-appropriate 6-MWT distance

index trend, were identified as risk factors for 30-day mortality. A recipient BMI >25 kg/m^2, use of cardiopulmonary bypass, APACHE II score, and oxygenation index trend were risk factors associated with prolonged ICU stay. Furthermore, they developed a scoring system, referred to as the risk quantification for lung transplantation (RQLT), to predict outcomes and found that the RQLT correlated very well with early post-transplantation outcomes. It is of interest to note that both of the aforementioned articles sought to predict outcomes after transplantation and to develop a scoring system that would objectively quantify the severity of early graft dysfunction and predict early outcomes, although they found relatively different results. Clearly, further studies are necessary to corroborate the results of these studies. Ideally, future studies should be prospective, multicenter trials that include a large number of patients, in which a proportion of the cohort can be used to develop a model and the remainder used for its validation.

In summary, severe PGD leads to adverse short-term outcomes. The relationship with long-term outcomes, including BOS, is not well defined. A uniform definition of the spectrum of PGD as well as a definition of outcomes will allow for an accurate assessment of the impact of this problem after lung transplantation. A reliable prediction

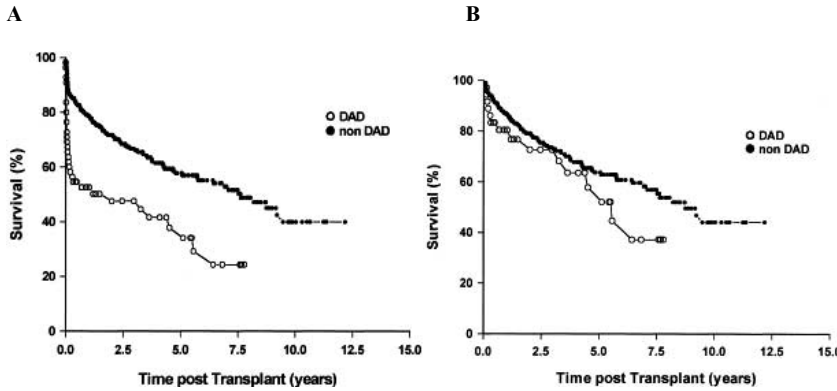

Figure 1. Survival in patients with primary graft dysfunction. (A) Kaplan-Meier survival curves in patients with and without diffuse alveolar damage (DAD). Hazards ratio 0.44 (0.27 to 0.73); $p = 0.001$, chi-square test. (B) Kaplan-Meier survival curves in patients with and without DAD surviving at least 30 days after lung transplantation. Hazards ratio 0.69 (0.37 to 1.30); $p = 0.25$, chi-square test. (Modified from Fisher et al. J Heart Lung Transplant 2002;21:1206–12, with permission.[6])

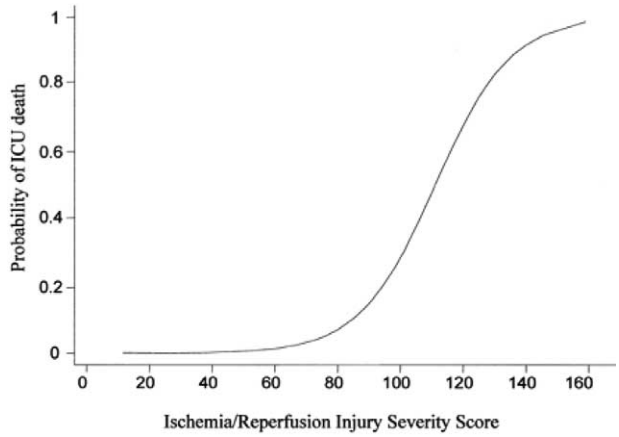

Figure 2. The relationship between ischemia-reperfusion injury severity score and probability of ICU mortality. (Modified from from Thabut et al. Chest 2002;121:1876–82, with permission.[9])

model for outcomes of PGD could then be developed and validated across multiple lung transplant centers. More work is needed in this area to collect short- and long-term outcome data across multiple lung transplant centers, focusing on functional outcomes as well as survival and risk of chronic graft dysfunction.

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