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Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes—A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation

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Primary Graft Dysfunction Incidence

In the early days of lung transplantation, the incidence of primary graft dysfunction (PGD) was difficult to assess accurately, with a range from 15% to 57%, partly as a result of varying definitions.[1–4] Despite the development of the International Society for Heart and Lung Transplantation (ISHLT) consensus statement defining PGD in 2005, the incidence of PGD in lung transplant recipients still depends on the severity grade and timing of grading for the PGD phenotype being evaluated.

Shortly after the consensus definition of PGD was created, centers around the world began adopting the criteria. The University of Minnesota reported an incidence of PGD grade 3 of 32% in 2006 using the newly developed definition and grading system.[5,6] A report of the outcomes for 1,000 lung transplants performed at Washington University in St. Louis identified an overall PGD incidence of 22.1%.[7] A multicenter prospective cohort study of lung transplant recipients in the United States reported an overall incidence of PGD grade 3 of 30.8% at any point during the first 72 hours of lung transplantation, and grade 3 PGD

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present at 48 or 72 hours after reperfusion had an incidence of 16.8%.[8] Samano et al[9] similarly reported the incidence of PGD grade 3 at a single center in Brazil was 19.8% at 48 hours and 15.4% at 72 hours. In addition, Felten et al,[10] in a study from 6 lung transplant centers in France detailing potential clinical risk factors for PGD in patients with cystic fibrosis, found an incidence of PGD grade 3 at 6 hours after transplant of 34% and a 26% incidence of PGD grade 2.

Taken together, the literature supports incidences of ~30% early after transplant and 15% to 20% for grade 3 PGD present at 48 and 72 hours. The time course of PGD progression and resolution also has an effect on patient survival outcomes, with patients having persistent PGD having the greatest risk of death.[11]

It is important to note that given the lack of research into PGD in the pediatric population, we cannot extrapolate the existing risk factor data in the adult population to patients aged < 18 years. Where available, we have added details on survival implications of potential risk factors in the pediatric population.

Recipient risk factors

The identification of recipient-related risk factors associated with PGD is of great clinical importance. Since the last ISHLT consensus document from 2005, a number of studies have been designed and published, which have extended our knowledge.[8,11–19]

Demographics

Sex and race

Female sex and African American race were identified as PGD risk factors by an unadjusted meta-analysis; however, a large multicenter cohort study did not confirm these findings with multivariable adjustment.[8,16]

Age

Unadjusted analyses showed there was no association of recipient age with PGD risk in a large multicenter cohort study.[8] The data on PGD in the pediatric population is extremely limited. In a study of 344 pediatric lung transplants, PGD was the main indication for post-transplant extracorporeal membrane oxygenation (ECMO) initiation and the leading cause of death among patients requiring ECMO.[20]

Primary diagnosis

The primary diagnosis leading to a lung transplant is an important modifier of the risk of developing PGD. In a systematic review of 10 studies, the incidence of PGD was 11.8% in patients with chronic obstructive pulmonary disease (COPD), 12.4% in cystic fibrosis, 18.0% in patients with idiopathic pulmonary fibrosis (IPF), 50% in sarcoidosis, and 30.3% in patients with idiopathic pulmonary arterial hypertension (IPAH).[16] A meta-analysis and a large multicenter cohort study both found IPF, sarcoidosis, and IPAH were independent predictors of increased PGD, depending on the PGD definition.[8,16] A single-center study similarly showed IPAH was strongly associated with the risk for PGD after adjustment for recipient pulmonary artery systolic pressure (adjusted relative risk, 9.24; 95% confidence interval, 1.75–48.8; $p = 0.009$).[21]

Comorbidities

Pulmonary arterial pressure

Several studies have shown a strong correlation between pulmonary arterial pressures (PAPs) and the risk of PGD. A multicenter cohort study demonstrated an increased risk of PGD of 30% for every increase of 10 mm Hg in the mean PAP, and a meta-analysis showed that the PAP in PGD patients was significantly higher compared with controls.[8,16]

The underlying primary lung disease may also be important when assessing the association of secondary pulmonary hypertension with PGD. In a meta-analysis of 10 studies, secondary pulmonary hypertension did not confer a significantly increased risk of PGD, while others have shown a strong association between higher mean PAP and the risk of PGD among patients with IPF.[8,15,16]

Obesity

A multicenter study of adult lung transplant recipients with COPD or interstitial lung disease found obesity was significantly associated with a more than 2-fold increased risk of any grade 3 PGD within 72 hours of transplant. Plasma levels of leptin, a protein biomarker associated with adiposity, were associated with a greater risk of PGD.[22] systematic review and a large multicenter cohort study confirmed the association of body mass index with PGD.[8,16]

Biologic and genetic

Pre-transplant biologic and genetic risk factors of the recipient are of interest, because these could allow both for risk stratification and hold the promise of pathway-specific interventions and therapies.

Inflammation

In a single-center study of 28 patients, higher baseline levels of interleukin (IL)-10, IL-8, IL-6, and chemokine (C-C motif) ligand 2 before transplant were associated with the subsequent development of ISHLT grade 2 PGD or higher after transplant. This study suggested that the recipient's inflammatory state at the time of transplant may affect early allograft function.[23]

Epithelial injury

A marker of airway epithelial injury, Clara cell secretory protein (CC16), showed an association between both elevated recipient pre-transplant and immediate post-transplant plasma levels with the development of PGD after transplant in non-IPF individuals.[14,18] These studies suggested that markers of airway epithelial injury may be helpful in pre-transplant PGD risk stratification and early identification of PGD.

Innate immunity

Innate immune activation is involved in the propagation of ischemia–reperfusion injury responses in transplanted solid organs. In a nested case-control study, plasma level of long pentraxin-3 (PTX3), a secreted innate immune mediator, was associated with PGD among patients with IPF. This study suggested a role for innate immune activation as a pathologic factor associated with PGD in IPF patients.[14] A subsequent study linked genetic variants in *PTX3* to PTX3 plasma protein levels and the risk for PGD in recipients with IPF.[24]

Prostaglandins

A large-scale candidate gene association study found 17 variants were significantly associated with PGD, 4 of which were in the prostaglandin E2 family of genes. Functional evaluation in regulatory T cells identified that a single nucleotide polymorphism in the prostaglandin E2 receptor gene was associated with differential suppressive function of regulatory T cells.[13]

Prediction of PGD risk based on available recipient risk factors

A recent study developed and validated objective estimates of the risk of development of PGD based on readily available clinical variables.[17] Using a multicenter cohort, the study identified abnormal body weight, moderate–severe pulmonary hypertension, and a pre-transplant diagnosis other than COPD or cystic fibrosis could identify a recipient at higher risk for the development of PGD at 48 or 72 hours after transplant.[17]

Donor risk factors

Recent studies have refined our understanding of donor-specific risk factors for PGD. The evidence base has confirmed previous observations, whereas other suspected risk factors have been refuted (Table 1). There is also an expanding body of knowledge on donor management techniques that affect organ availability and recipient outcomes in both the adult and pediatric populations.[25–28]

Table 1 Donor Risk Factors for Primary Graft Dysfunction

Level of evidence	Risk factor
Definite	Cigarette Smoking
Probable	Aspiration
	Chest trauma/pulmonary contusion
	Undersized donor relative to recipient
	Heavy alcohol use
Possible	Age
	Oxygenation
	Chest X-ray abnormalities
	Purulent secretions at bronchoscopy
	Thromboembolism and fat embolism
	Traumatic brain injury
	Shorter time from brain death to cold preservation
	Prolonged mechanical ventilation
	Consequences of brain death and neurologic injury
Unlikely	Gender
	Donor-recipient gender mismatch
	Race
	Positive sputum gram stain

Neurologic injury and brain death

The influence of the mode of brain death on PGD is not clear. An analysis of the United Network of Organ Sharing (UNOS) database found an association with PGD for donor traumatic brain injury.[29] Mode of death was not a risk factor for PGD in a large multicenter cohort study[8] or in large single-center studies.[5,21,30,31] Experimental studies suggest that delaying organ procurement after brain death reduces reperfusion lung injury.[32]

Donation after circulatory death and living-donor lobar transplantation

The use of organs retrieved after circulatory death (DCD) has grown in recent years.[33] A report from Australia of 70 Maastricht category III DCD transplants found an incidence of PGD grade 3 of 8.4%, with 1- and 5-year survival 97% and 90%, respectively,[34] whereas other centers have reported DCD outcomes comparable to donation after brain death (DBD).[35–38] A meta-analysis of 5 studies found no difference in PGD between DCD and DBD (risk ratio, 1.09; 95% confidence interval, 0.68–1.73).[19] In contrast, the investigators in a series of 60 DCD transplants that were matched by propensity score to DBD transplants found a higher incidence of PGD and a trend toward a greater need for extracorporeal life support (ECLS) among recipients of DCD lungs.[39] Data on the effect of using Maastricht category I or II DCD donors on recipient PGD risk is limited to case reports and absent from the ISHLT DCD registry.[40,41]

At the other end of the spectrum from the brain-dead donor is living-donor lobar lung transplantation. Early experience from the University of Southern California

described a mortality rate from PGD of 4%, but the overall incidence of PGD was not reported.[42] In a recent series from Japan, the initial partial pressure of arterial oxygen–to–fraction of inspired oxygen (F_{IO_2}; P/F) ratio of 434 ± 121 among 42 living-donor lobar lung transplant recipients was greater than in a contemporaneous group of 37 cadaveric transplant recipients (303 ± 117).[43] Lobar or reduced-size cadaveric transplants for recipients with small thoracic cavities may be associated with a higher incidence of PGD.[44]

Donor age

Early studies supported that allografts from older donors were prone to PGD. Christie et al[21] found that donor age > 45 years was associated with a nearly 7-fold increased risk of severe PGD, whereas Whitson et al[5] identified a 3% increased risk of PGD per 1-year increase in donor age. Although the risk of longer-term graft failure is higher in allografts from older donors, more recent data suggest the age-related risk of PGD is lower than previously believed and restricted to more extremes of age. A multicenter cohort study found donor age 55 to 64 was not associated with a significantly increased risk of severe PGD after controlling for recipient, surgical, and other donor factors.[45] Other studies have failed to identify an association between donor age and PGD.[46,47] Although donor age < 18 years was previously identified as a risk factor for PGD,[21] more recent studies have failed to confirm this association.[8,45]

Race, gender, and donor-to-recipient total lung capacity ratio

Donor African American race and female gender were identified earlier as risk factors for PGD in a single-center study by Christie et al.[21] However, no association was found for either in a larger UNOS analysis[29] or in the more contemporary and larger multicenter cohort.[8] In the pediatric population, donor-to-recipient gender significantly affected long-term survival, with male-male donor-recipient pairs having improved survival compared with female-female pairs, but no data are available on the effect of gender matching on PGD.[48]

The data regarding donor-recipient gender mismatch are conflicting. In a single-center study, gender mismatch was not associated with PGD.[49] The previously observed effect of gender mismatch on early survival (a potential marker of PGD)[50] has been ascribed by Eberlein et al[51] to transplantation of relatively undersized lungs from female donors to male recipients. A ratio of donor to recipient predicted total lung capacity of > 1.0 was associated with a reduced risk of severe PGD after adjusting for multiple variables, including diagnosis.[52]

Smoking

Donor cigarette smoke exposure is a clear risk factor for PGD.[5,53] Whitson et al[5] found PGD was more common when allografts were obtained from donors with a smoking history, although the association was not significant after multivariate adjustment. More recently, Diamond et al[8] demonstrated donor smoking was associated with PGD after multivariate adjustment. In risk prediction models for PGD, donor smoking increased PGD risk in "high-risk" recipients but not "low-risk."[17]

Alcohol

Alcohol use appears to increase PGD risk. Lowery et al[54] categorized donor alcohol use into none, moderate, and heavy. After multivariate adjustment, allografts from donors with heavy use had a 9-fold higher risk of severe PGD compared with those with no use.[54] Trends toward persistent and severe PGD from donors with heavy use were reported by Pelaez et al.[55]

Acquired donor risk factors

Overall, the risk of PGD appears to be higher when allografts from extended criteria donors are used.[56–58] Others have reported no difference in PGD with extended donors.[59,60] Donor P/F ratio was not a significant risk factor for PGD in the Lung Transplant Outcomes Group cohort.[8] Sommer et al[61] reported that matching extended criteria donors with lower-risk recipients resulted in a similar PGD incidence as standard donors matched to higher-risk recipients. Many centers reserve such donors for recipients at otherwise low risk for PGD.[62] A Lung Donor Score has been proposed that incorporates 5 variables—age, smoking history, chest X-ray, secretions at bronchoscopy, and P/F ratio to predict PGD risk—but requires validation in a multicenter study.[63]

Genetic and biologic factors

Early insights into donor biologic risk factors for PGD are emerging. Cantu et al[64] found that donor polymorphisms in the oxidant stress gene *NOX3* were associated with increased risk of PGD. Machuca et al[65] found that lungs that subsequently developed PGD had higher levels of IL-8, macrophage colony stimulating factor, and growth-related oncogene-α compared with lungs that did not develop PGD.

Operative risk factors

Prior cardiothoracic surgery

A single-center study found prior cardiothoracic surgery was not associated with an increased risk of PGD.[66] However, when the incidence of PGD was evaluated according to type of prior procedure, the incidence of PGD was higher in the sub-group with previous pleurodesis (8.7%) than in the group without previous pleurodesis (3.1%). The pleural procedures group also had the highest incidence of re-exploration for bleeding, phrenic nerve injury, and other respiratory complications.

Type of transplant

The data on the association of type of transplant procedure (single vs bilateral) with PGD are mixed. Although transplant type and PGD were not significantly associated in a meta-analysis of 11 studies,[16] a large multicenter cohort study with multivariable adjustment found single lung transplant was an independent risk factor for PGD.[8]

Cardiopulmonary bypass

In a retrospective study of 100 lung transplant recipients over a 2-year period, cardiopulmonary bypass (CPB) use was associated with more severe pulmonary infiltrates and more prolonged intubation than in the group without CPB.[67] A large meta-analysis and a multicenter cohort study both reported CPB as an independent risk factor for the development of PGD.[8,16] Data on the differential effect of intraoperative venoarterial ECMO vs CPB are limited. A single-center study demonstrated no significant difference in the rate of PGD requiring post-transplant circulatory support when intraoperative venoarterial ECMO was compared with CPB.[68]

There remains controversy whether CPB is truly an independent risk factor in the development of PGD. The severity of recipient illness, acute intraoperative alteration in recipient hemodynamics/oxygenation, issues which effect the initiation of CPB, have not undergone investigation and could lead to modification in practice.

Ischemic time

Prolonged ischemic time has been identified as a potential risk factor in multiple previous observational studies.[29] In a multicenter observational trial, the effect of total ischemic time was dependent on the definition of PGD used, with late grade 3 PGD, defined as 48 or 72 hours after transplant, not associated with ischemic time.[8] Although data in the pediatric population are limited, longer ischemic times did not adversely affect survival among children who received an allograft for cystic fibrosis.[69]

Transfusion

A large-volume intraoperative blood product transfusion has been identified as an independent risk factor for the development of PGD.[8,70]

Delayed chest closure

The data on the effect of delayed chest closure are extremely limited, and the relationship between delayed chest closure and PGD is likely confounded by indication due to intraoperative bleeding and large-volume transfusions. A retrospective study of 28 lung transplant recipients revealed higher transfusion requirements, pulmonary artery pressure, use and duration of CPB, lower P/F ratio, and higher incidence of PGD in patients with delayed chest closure.[71] In a single-center study, patients with delayed chest closure had a higher incidence of PGD, post-operative bleeding requiring re-exploration, and 30- and 90-day mortality compared with the primary closure group.[72]

Reperfusion F_{IO_2}

A multicenter cohort study found that increasing reperfusion F_{IO_2} was associated with an independent increased risk of PGD at 48 or 72 hours after reperfusion and that reperfusion at an F_{IO_2} of ≥ 0.4 was associated with an absolute risk increase of 6% compared with a reperfusion F_{IO_2} of < 0.4.[8]

PGD-related outcomes

Before the standard clinical definition of PGD was created in 2005 by the ISHLT consensus report,[73] the data pertaining to PGD and survival were sparse. There were no data on long-term lung function and only 1 study of functional data showing a decreased 6-minute walk distance and limited ambulatory status in a small group of PGD survivors.[74] Other data revealed comparable survival in patients with and without PGD when early mortality was excluded.[75]

Short-term mortality and morbidity

Much of the literature on short-term outcomes of PGD addresses survival and peri-operative morbidity reflected by duration of mechanical ventilation, hospital length of stay, and resource utilization. In addition, a small number of studies have assessed the effect of treatment, including ECLS and retransplantation, inflammatory markers, and humoral and cellular immune responses.

Since the publication of the 2005 guidelines, multiple studies have used the consensus definition to examine the incidence and short-term outcomes of PGD. Prekker et al[6] validated the ISHLT grading system for PGD by retrospectively examining 402 patients who had undergone lung transplantation between 1992 and 2004 at the University of Minnesota. The prevalence of grade 3 PGD declined from 25% at the time of presentation to the intensive care unit (ICU) to 15% at 48 hours after surgery. The 90-day mortality ranged from 7% for grade 1 to 33% for grade 3 PGD at 48 hours.[5] Other investigators have reported similar rates of severe PGD. The 30-day mortality in a retrospective cohort study of 446 lung transplant recipients was 3.5% for PGD grade 1, 6.2% for grade 2, and 24.5% for PGD grade 3 at 24 hours; similarly, 30-day mortality ranged from 5% for grade 1 to 36.4% for grade 3 at 72 hours.[76] In a cohort of 1,000 adult lung transplant recipients at Washington University in St. Louis, PGD developed in 22% of patients, with a significantly higher in-hospital mortality rate compared with those without PGD.[7] A large multicenter, prospective cohort study of 1,255 lung transplant recipients reported unadjusted 90-day mortality was 23% for recipients with severe PGD at 48 or 72 hours compared with 5% for those without.[8]

The resolution of severe PGD over time varies among lung transplant recipients, and persistent PGD may identify lung transplant recipients with worse outcomes.[11,77] In a single-center study, lung transplant recipients with grade 3 PGD at initial presentation to the ICU showed an average 52% increase in their P/F ratio over the next 12 hours, whereas patients with a < 20% increase in P/F ratios during that period had 6.8-times the odds of 90-day mortality.[77] In a different cohort of lung transplant recipients, Shah et al[11] identified distinct phenotypes among patients with severe PGD based on the resolution of their graft dysfunction: patients with severe persistent dysfunction had higher risk of 90-day mortality.

The presence of early graft dysfunction is associated with increased duration of mechanical ventilation, ICU, and hospital length of stay.[3,6,74,77–80] King et al[78,80] reported that reperfusion injury, equivalent to PGD grade ≥ 2 at 48 hours, is also associated with increased resource utilization and hospital costs.

PGD management and short-term outcomes

Assessment of the influence of ventilator management strategies on PGD outcomes has been limited. The 2005 ISHLT Working Group recommended lung protective ventilation (LPV) for PGD patients based on evidence supporting this strategy in acute respiratory distress syndrome (ARDS).[81,82] A single-center study of LPV protocols showed the use of LPV was associated with a reduction in PGD severity at 72 hours but no difference in duration of mechanical ventilation, ICU stay, ICU mortality, or hospital mortality.[83]

ECLS and retransplantation have been used for patients with PGD, although published series to date have not used the consensus definition for PGD. Bermudez et al[84] reported 30-day and 1-year survival in 58 PGD patients receiving ECLS from 1991 to 2006 with 30-day and 1-year survival of 56% and 40%. Hartwig et al[85] reported 30-day and 1-year survival of 82% and 64% for 28 patients receiving ECLS for severe PGD from 2001 to 2009.

Data on outcomes of retransplantation for PGD are limited. A recent assessment of retransplantation reviewed United States outcomes from May 2005 through 2011. Survival at 1 year for 64 patients undergoing retransplantation within 90 days, a group consisting largely of patients with PGD, was 50%. The overall risk for mortality after retransplantation was significantly worse for PGD patients than for those with bronchiolitis obliterans syndrome (BOS).[86] In the 2014 ISHLT Registry, 1-year survival was 39% for retransplantation within 1 month and 54% for retransplantation within 1 month to 1 year after the initial transplantation.[87]

Specific medical therapies for PGD have not been well studied. A recent study evaluated outcomes of 24 patients with PGD grade 3 treated with C1-esterase inhibitor. Compared with a non-randomized cohort of PGD at the same center, the treated patients had a shorter duration of mechanical ventilation; however, 1-year survival in the treated patients was not statistically different from that of untreated patients.[88] Studies reporting the effect of inhaled nitric oxide on short-term outcomes are limited to older case series demonstrating improvement in oxygenation and pulmonary hemodynamics.[89–91]

Alloimmunity after PGD

The inflammatory milieu of PGD and associated release of cytokines, including IL-2 and interferon-γ , may promote upregulation of allograft human leukocyte antigen (HLA) class II antigens, and stimulate cellular and humoral alloimmune responses.

Bharat et al[92] demonstrated upregulation of interferon-γ, IL-1β, IL-2, IL-12, interferon-γ inducible protein-10, and monocyte chemoattractant protein-1 early after transplantation in patients with PGD. PGD of any grade was associated with early increased incidence of alloreactive donor HLA class II–specific cluster of differentiation 4+ T cells and development of de novo HLA class II donor-specific antibodies. In another study of 546 consecutive transplants, PGD grade 2 or 3 at 48 hours after transplant was associated with development of donor-specific antibodies during the initial post-transplant hospitalization.[93]

An association between PGD and acute cellular rejection has not been identified, although limited data evaluating this association exist. A single-center study evaluating 334 consecutive transplants identified patients with PGD graded according to the 2005 ISHLT criteria[73] and found no association of any PGD grade with acute rejection (≥ A2) or lymphocytic bronchiolitis (≥ B2).[94]

In summary, the limited evaluation of immunologic outcomes of PGD suggests a possible relationship between PGD and subsequent humoral alloimmune responses and does not show association with cellular rejection. The role of PGD in triggering or amplifying autoimmune responses has not been evaluated.

Long-term outcomes

Survival data consist of studies reporting outcomes at 1, 2, 3, 5, and/or 10 years after PGD and those reporting outcomes of 90-day or 1-year PGD survivors.

All-cause mortality

There were 6 studies reporting on long-term mortality after PGD using the 2005 ISHLT consensus definitions. Although study designs differed by PGD grades and intervals, all studies demonstrated an association of PGD with increased risk of long-term all-cause mortality. In a study of the UNOS/ISHLT database between 1994 and 2000, all-cause mortality at 1 year was 64.9% in the PGD group (PGD grade 3 beyond 48 hours) vs 20.4% in the non-PGD group.[95] Prekker et al[6] studied a single-center cohort ($n = 402$) and reported that PGD grade 3 in the first 48 hours conferred a significantly reduced long-term survival compared with the group with combined PGD grade 1 and

2. In a study evaluating the construct validity of the ISHLT PGD definition, all-cause mortality was significantly higher in patients with higher grades of PGD.[76] The association of PGD with worse survival was strongest and with better discrimination at 72 hours.[76] Kreisel et al[7] reviewed the outcomes of a single-center cohort (n = 1,000) and reported a significant association of PGD with decreased long-term survival (1-, 5-, and 10-year survival of 72.8%, 43.9%, and 18.7% for the PGD group vs 87.1%, 59.8%, and 35.7% for the no-PGD group, respectively). Finally, Diamond et al[8] showed that grade 3 PGD was associated with a significantly greater risk of 1-year mortality compared with the group without grade 3 PGD.

Using a radiographic definition and grading instead of the ISHLT consensus definition, Burton et al[96] described the outcomes of PGD in 181 single lung transplant recipients, with an overall PGD incidence of 63% and a significant reduction in 3-year survival in the PGD group. The presence and extent of allograft infiltration, but not P/F ratio, correlated with survival. Of note, the interobserver and intraobserver agreement for radiographic infiltration and severity grading was low in this study.

All-cause mortality adjusting for early deaths

To assess longer-term survival without the influence of early mortality after PGD, some investigators evaluated the outcomes of patients who survived the first 90 days or the first year after lung transplantation. Prekker et al[6] found that the cohort with grade 3 PGD demonstrated significantly worse long-term survival. Similarly, in a study of 90-day survivors (n = 374), Whitson et al[97] noted significantly worse 5-year and 10-year survival in patients with grade 3 PGD. Daud et al[94] identified an increased risk of death in patients who developed grade 3 PGD and survived 90 days in univariate models. After adjusting for potential confounding variables, Prekker et al[6] showed a decrease in all-cause mortality among patients without PGD, whereas after multivariable analysis adjusting for BOS and single lung transplantation, PGD was not found to be an independent risk factor for mortality in a study by Daud et al.[94] One study that examined patients surviving 1 year after transplant found patients with PGD had significantly worse longer-term survival than those without, even after adjustment for other clinical variables.[95]

Functional outcomes

Only one single-center study evaluated the functional outcomes after PGD. At 12 months after transplant, significantly fewer PGD survivors achieved a normal age-appropriate 6-minute walk distance compared with survivors without PGD, and the median best walk distance among PGD survivors was significantly lower than among survivors without PGD.[74]

PGD and chronic lung allograft dysfunction

In most of the studies reported, PGD is associated with the development of the BOS phenotype of chronic lung allograft dysfunction (CLAD). No studies have investigated the association of PGD and restrictive CLAD. Seven studies, 6 using the 2005 PGD consensus definition, examined the association between PGD and the BOS phenotype of CLAD. Similar to the long-term mortality studies, study methodology varied with regard to chosen PGD grades and the times used as predictors.

Prekker et al[6] studied the pulmonary function tests of bilateral lung transplant recipients who developed grade 3 PGD in the first 48 hours and found a significantly lower mean forced expiratory volume in 1 second (FEV_1) value at 1 year compared with those with lower grades, although the difference was not sustained at 2 years. In a study of 374 lung transplant recipients surviving > 90 days after transplant, bilateral lung transplant recipients with grade 3 PGD demonstrated significantly lower mean FEV_1 and decreased freedom from BOS compared with those with lower PGD grades.[97] FEV_1 decreased significantly as PGD grade increased in bilateral lung transplant recipients at all time points. In this study, pulmonary function and freedom from BOS for single lung transplant recipients were not associated with PGD grade.

Two studies from Washington University in St. Louis, published in 2007 and 2008, reported the association of early (at the start of reperfusion of the transplanted lung) and late-onset (24–72 hours) PGD with the development of BOS.[94,98] There was a direct relationship between increasing severity of PGD and relative risk of BOS, and in multivariable analysis, the increased risk of BOS with all PGD grades was independent of acute rejection, lymphocytic bronchitis, and community-acquired respiratory viral infections. Late PGD was also a significant risk factor for BOS development and progression, independent of acute rejection, lymphocytic bronchitis, and respiratory viral infections, with increasing PGD grade associated with increasing BOS risk.[98] In a third study from the surgical group at Washington University in St. Louis, Kreisel et al[7] reported the outcomes of 1,000 lung transplant recipients. Although the PGD definition used in their study was not supplied in the Methods section, freedom from BOS at 1, 5, and 10 years was lower in patients who had PGD than in those without PGD.

Using a different definition of PGD, Burton et al[96] reported FEV_1 and BOS grades in their 181 recipients of single lung transplantation. The peak FEV_1 achieved was significantly lower in patients with PGD (defined by radiographic infiltrate) compared with those without PGD; peak forced vital capacity values were similar in both groups. There was a significant linear trend between the presence and severity of radiographic infiltrates and the decline in peak FEV_1 value. The freedom from BOS in 3-month survivors was similar in patients with and without PGD. The latter finding contradicts findings of all other studies that describe an association between PGD and

increased risk of BOS and can likely be explained by the different definition of PGD used in that study.

Quality of life, cognition, and other patient outcomes

Few data regarding long-term prognosis after PGD are available beyond graft and patient survival. Patient-important outcomes, such as quality of life, occurrence of post-traumatic stress disorder or anxiety/depression, or cognitive dysfunction after PGD are particularly sparse. Cohen et al[99] performed a small study of 42 patients, of whom 10 developed grade 3 PGD within the first 72 hours, and found that PGD was not associated with cognitive impairment. The effect of ARDS on psychologic and quality of life outcomes has been reported in the non-transplant literature.[100,101] Given that lung transplant patients with PGD have a similar experience compared with that of patients with ARDS (intubated, sedated, decreased ambulation, etc.), similar associations should likely be investigated.

Disclosure statement

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Supplementary data

A list of the International Society for Heart and Lung Transplantation Primary Graft Dysfunction Working Group Members can be found in the online version of this article at www.jhltonline.org.

References

1. Haydock DA, Trulock EP, Kaiser LR, Knight SR, Pasque MK, Cooper JD. Management of dysfunction in the transplanted lung: experience with 7 clinical cases. Washington University Lung Transplant Group. Ann Thorac Surg 1992;53:635-41.
2. Sleiman C, Mal H, Fournier M, et al. Pulmonary reimplantation response in single-lung transplantation. Eur Respir J 1995;8:5-9.
3. Khan SU, Salloum J, O'Donovan PB, et al. Acute pulmonary edema after lung transplantation: the pulmonary reimplantation response. Chest 1999;116:187-94.
4. Christie JD, Bavaria JE, Palevsky HI, et al. Primary graft failure following lung transplantation. Chest 1998;114:51-60.
5. Whitson BA, Nath DS, Johnson AC, et al. Risk factors for primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 2006;131:73-80.
6. Prekker ME, Nath DS, Walker AR, et al. Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2006;25:371-8.
7. Kreisel D, Krupnick AS, Puri V, et al. Short- and long-term outcomes of 1000 adult lung transplant recipients at a single center. J Thorac Cardiovasc Surg 2011;141:215-22.
8. Diamond JM, Lee JC, Kawut SM, et al. Lung Transplant Outcomes Group. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
9. Samano MN, Fernandes LM, Baranauskas JC, et al. Risk factors and survival impact of primary graft dysfunction after lung transplantation in a single institution. Transplant Proc 2012;44:2462-8.
10. Felten ML, Sinaceur M, Treilhaud M, et al. Factors associated with early graft dysfunction in cystic fibrosis patients receiving primary bilateral lung transplantation. Eur J Cardiothorac Surg 2012;41:686-90.
11. Shah RJ, Diamond JM, Cantu E, et al. Latent class analysis identifies distinct phenotypes of primary graft dysfunction after lung transplantation. Chest 2013;144:616-22.
12. Barr ML, Kawut SM, Whelan TP, et al. Report of the ISHLT working group on primary lung graft dysfunction part IV: recipient-related risk factors and markers. J Heart Lung Transplant 2005;24:1468-82.
13. Diamond JM, Akimova T, Kazi A, et al. Genetic variation in the prostaglandin e2 pathway is associated with primary graft dysfunction. Am J Respir Crit Care Med 2014;189:567-75.
14. Diamond JM, Kawut SM, Lederer DJ, et al. Elevated plasma Clara cell secretory protein concentration is associated with high-grade primary graft dysfunction. Am J Transplant 2011;11:561-7.
15. Fang A, Studer S, Kawut SM, et al. Elevated pulmonary artery pressure is a risk factor for primary graft dysfunction following lung transplantation for idiopathic pulmonary fibrosis. Chest 2011;139:782-7.
16. Liu Y, Liu Y, Su L, Jiang SJ. Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. PloS One 2014;9:e92773.
17. Shah RJ, Diamond JM, Cantu E, et al. Objective estimates improve risk stratification for primary graft dysfunction after lung transplantation. Am J Transplant 2015;15:2188-96.
18. Shah RJ, Wickersham N, Lederer DJ, et al. Preoperative plasma club (Clara) cell secretory protein levels are associated with primary graft dysfunction after lung transplantation. Am J Transplant 2014;14:446-52.
19. Krutsinger D, Reed RM, Blevins A, et al. Lung transplantation from donation after cardiocirculatory death: a systematic review and meta-analysis. J Heart Lung Transplant 2015;34:675-84.
20. Puri V, Epstein D, Raithel SC, et al. Extracorporeal membrane oxygenation in pediatric lung transplantation. J Thorac Cardiovasc Surg 2010;140:427-32.
21. Christie JD, Kotloff RM, Pochettino A, et al. Clinical risk factors for primary graft failure following lung transplantation. Chest 2003;124:1232-41.
22. Lederer DJ, Kawut SM, Wickersham N, et al. Lung Transplant Outcomes Group. Obesity and primary graft dysfunction after lung transplantation: the Lung Transplant Outcomes Group obesity study. Am J Respir Crit Care Med 2011;184:1055-61.
23. Allen JG, Lee MT, Weiss ES, Arnaoutakis GJ, Shah AS, Detrick B. Preoperative recipient cytokine levels are associated with early lung allograft dysfunction. Ann Thorac Surg 2012;93:1843-9.
24. Diamond JM, Meyer NJ, Feng R, et al. Lung Transplant Outcomes Group. Variation in PTX3 is associated with primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2012;186:546-52.
25. Mallory GB Jr, Schecter MG, Elidemir O. Management of the pediatric organ donor to optimize lung donation. Pediatr Pulmonol 2009;44:536-46.
26. Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA 2010;304:2620-7.
27. Minambres E, Coll E, Duerto J, et al. Effect of an intensive lung donor-management protocol on lung transplantation outcomes. J Heart Lung Transplant 2014;33:178-84.

28. Munshi L, Keshavjee S, Cypel M. Donor management and lung preservation for lung transplantation. Lancet Respir Med 2013;1:318-28.
29. Kuntz CL, Hadjiliadis D, Ahya VN, et al. Risk factors for early primary graft dysfunction after lung transplantation: a registry study. Clin Transplant 2009;23:819-30.
30. Ciccone AM, Stewart KC, Meyers BF, et al. Does donor cause of death affect the outcome of lung transplantation? J Thorac Cardiovasc Surg 2002;123:429-34.
31. Wauters S, Verleden GM, Belmans A, et al. Donor cause of brain death and related time intervals: does it affect outcome after lung transplantation? Eur J Cardiothorac Surg 2011;39:e68-76.
32. Avlonitis VS, Wigfield CH, Golledge HD, Kirby JA, Dark JH. Early hemodynamic injury during donor brain death determines the severity of primary graft dysfunction after lung transplantation. Am J Transplant 2007;7:83-90.
33. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. Br J Anaesth 2012;108(Suppl 1):i108-21.
34. Levvey BJ, Harkess M, Hopkins P, et al. Excellent clinical outcomes from a national donation-after-determination-of-cardiac-death lung transplant collaborative. Am J Transplant 2012;12:2406-13.
35. De Oliveira NC, Osaki S, Maloney JD, et al. Lung transplantation with donation after cardiac death donors: long-term follow-up in a single center. J Thorac Cardiovasc Surg 2010;139:1306-15.
36. De Vleeschauwer SI, Wauters S, Dupont LJ, et al. Medium-term outcome after lung transplantation is comparable between brain-dead and cardiac-dead donors. J Heart Lung Transplant 2011;30:975-81.
37. Mason DP, Brown CR, Murthy SC, et al. Growing single-center experience with lung transplantation using donation after cardiac death. Ann Thorac Surg 2012;94:406-11.
38. Levvey BJ, Whitford HM, Williams TJ, et al. Donation after circulatory determination of death lung transplantation for pulmonary arterial hypertension: passing the toughest test. Am J Transplant 2015;15:3208-14.
39. Sabashnikov A, Patil NP, Popov AF, et al. Long-term results after lung transplantation using organs from circulatory death donors: a propensity score-matched analysis. Eur J Cardiothorac Surg 2016;49:46-53.
40. Cypel M, Levvey B, Van Raemdonck D, et al. International Society for Heart and Lung Transplantation. International Society for Heart and Lung Transplantation donation after circulatory death registry report. J Heart Lung Transplant 2015;34:1278-82.
41. Erasmus ME, van Raemdonck D, Akhtar MZ, et al. DCD lung donation: donor criteria, procedural criteria, pulmonary graft function validation, and preservation. Transpl Int 2016;29:790-7.
42. Starnes VA, Bowdish ME, Woo MS, et al. A decade of living lobar lung transplantation: recipient outcomes. J Thorac Cardiovasc Surg 2004;127:114-22.
43. Date H, Sato M, Aoyama A, et al. Living-donor lobar lung transplantation provides similar survival to cadaveric lung transplantation even for very ill patients. Eur J Cardiothorac Surg 2015;47:967-72.
44. Stanzi A, Decaluwe H, Coosemans W, et al. Lobar lung transplantation from deceased donors: a valid option for small-sized patients with cystic fibrosis. Transplant Proc 2014;46:3154-9.
45. Baldwin MR, Peterson ER, Easthausen I, et al. Donor age and early graft failure after lung transplantation: a cohort study. Am J Transplant 2013;13:2685-95.
46. Lopez I, Zapata R, Sole J, et al. Early and mid-term results of lung transplantation with donors 60 years and older. Interact Cardiovasc Thorac Surg 2015;20:47-53.
47. Shigemura N, Horai T, Bhama JK, et al. Lung transplantation with lungs from older donors: recipient and surgical factors affect outcomes. Transplantation 2014;98:903-8.
48. Goldfarb SB, Levvey BJ, Edwards LB, et al. International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: nineteenth pediatric lung and heart-lung transplantation report-2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant 2016;35:1196-205.
49. Alvarez A, Moreno P, Illana J, et al. Influence of donor-recipient gender mismatch on graft function and survival following lung transplantation. Interact Cardiovasc Thorac Surg 2013;16:426-35.
50. Sato M, Gutierrez C, Kaneda H, Liu M, Waddell TK, Keshavjee S. The effect of gender combinations on outcome in human lung transplantation: the International Society of Heart and Lung Transplantation registry experience. J Heart Lung Transplant 2006;25:634-7.
51. Eberlein M, Reed RM, Maidaa M, et al. Donor-recipient size matching and survival after lung transplantation. A cohort study. Ann Am Thorac Soc 2013;10:418-25.
52. Eberlein M, Reed RM, Bolukbas S, et al. Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. J Heart Lung Transplant 2015;34:233-40.
53. Oto T, Griffiths AP, Levvey B, et al. A donor history of smoking affects early but not late outcome in lung transplantation. Transplantation 2004;78:599-606.
54. Lowery EM, Kuhlmann EA, Mahoney EL, Dilling DF, Kliethermes SA, Kovacs EJ. Heavy alcohol use in lung donors increases the risk for primary graft dysfunction. Alcohol Clin Exp Res 2014;38:2853-61.
55. Pelaez A, Mitchell PO, Shah NS, et al. The role of donor chronic alcohol abuse in the development of primary graft dysfunction in lung transplant recipients. Am J Med Sci 2015;349:117-23.
56. Botha P, Trivedi D, Weir CJ, et al. Extended donor criteria in lung transplantation: Impact on organ allocation. J Thorac Cardiovasc Surg 2006;131:1154-60.
57. Somers J, Ruttens D, Verleden SE, et al. A decade of extended-criteria lung donors in a single center: was it justified? Transpl Int 2015;28:170-9.
58. Zych B, Garcia SD, Sabashnikov A, De RF, et al. Lung transplantation from donors outside standard acceptability criteria—are they really marginal? Transpl Int 2014;27:1183-91.
59. Alvarez A, Moreno P, Espinosa D, et al. Assessment of lungs for transplantation: a stepwise analysis of 476 donors. Eur J Cardiothorac Surg 2010;37:432-9.
60. Moreno P, Alvarez A, Santos F, et al. Extended recipients but not extended donors are associated with poor outcomes following lung transplantation. Eur J Cardiothorac Surg 2014;45:1040-7.
61. Sommer W, Kuhn C, Tudorache I, et al. Extended criteria donor lungs and clinical outcome: results of an alternative allocation algorithm. J Heart Lung Transplant 2013;32:1065-72.
62. Schiavon M, Falcoz PE, Santelmo N, Massard G. Does the use of extended criteria donors influence early and long-term results of lung transplantation? Interact Cardiovasc Thorac Surg 2012;14:183-7.
63. Oto T, Levvey BJ, Whitford H, et al. Feasibility and utility of a lung donor score: correlation with early post-transplant outcomes. Ann Thorac Surg 2007;83:257-63.
64. Cantu E, Shah RJ, Lin W, et al. Oxidant stress regulatory genetic variation in recipients and donors contributes to risk of primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 2015;149:596-602.
65. Machuca TN, Cypel M, Yeung JC, et al. Protein expression profiling predicts graft performance in clinical ex vivo lung perfusion. Ann Surg 2015;261:591-7.
66. Shigemura N, Bhama J, Gries CJ, et al. Lung transplantation in patients with prior cardiothoracic surgical procedures. Am J Transplant 2012;12:1249-55.
67. Aeba R, Griffith BP, Kormos RL, et al. Effect of cardiopulmonary bypass on early graft dysfunction in clinical lung transplantation. Ann Thorac Surg 1994;57:715-22.
68. Bermudez CA, Shiose A, Esper SA, et al. Outcomes of intraoperative venoarterial extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation. Ann Thorac Surg 2014;98:1936-42: discussion 1942-3.
69. Hayes D Jr, Tumin D, Kopp BT, Tobias JD, Sheikh SI, Kirkby SE. Influence of graft ischemic time on survival in children with cystic fibrosis after lung transplantation. Pediatr Pulmonol 2016;51:908-13.
70. Lee J. Clinical risk factors for the development of primary graft dysfunction. J Heart Lung Transplant 2008;27:A396.

71. Force SD, Miller DL, Pelaez A, et al. Outcomes of delayed chest closure after bilateral lung transplantation. Ann Thorac Surg 2006;81:2020-4: discussion 2024-5.
72. Shigemura N, Orhan Y, Bhama JK, et al. Delayed chest closure after lung transplantation: techniques, outcomes, and strategies. J Heart Lung Transplant 2014;33:741-8.
73. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2005;24:1454-9.
74. Christie JD, Sager JS, Kimmel SE, et al. Impact of primary graft failure on outcomes following lung transplantation. Chest 2005;127: 161-5.
75. Fisher AJ, Wardle J, Dark JH, Corris PA. Non-immune acute graft injury after lung transplantation and the risk of subsequent bronchiolitis obliterans syndrome (BOS). J Heart Lung Transplant 2002;21:1206-12.
76. Christie JD, Bellamy S, Ware LB, et al. Construct validity of the definition of primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2010;29:1231-9.
77. Prekker ME, Herrington CS, Hertz MI, Radosevich DM, Dahlberg PS. Early trends in PaO(2)/fraction of inspired oxygen ratio predict outcome in lung transplant recipients with severe primary graft dysfunction. Chest 2007;132:991-7.
78. King RC, Binns OA, Rodriguez F, et al. Reperfusion injury significantly impacts clinical outcome after pulmonary transplantation. Ann Thorac Surg 2000;69:1681-5.
79. Thabut G, Vinatier I, Stern JB, et al. Primary graft failure following lung transplantation: predictive factors of mortality. Chest 2002;121: 1876-82.
80. Arcasoy SM, Fisher A, Hachem RR, Scavuzzo M, Ware LB; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part V: predictors and outcomes. J Heart Lung Transplant 2005;24:1483-8.
81. Shargall Y, Guenther G, Ahya VN, Ardehali A, Singhal A, Keshavjee S; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part VI: treatment. J Heart Lung Transplant 2005;24: 1489-500.
82. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
83. Currey J, Pilcher DV, Davies A, et al. Implementation of a management guideline aimed at minimizing the severity of primary graft dysfunction after lung transplant. J Thorac Cardiovasc Surg 2010;139:154-61.
84. Bermudez CA, Adusumilli PS, McCurry KR, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: long-term survival. Ann Thorac Surg 2009;87:854-60.
85. Hartwig MG, Walczak R, Lin SS, Davis RD. Improved survival but marginal allograft function in patients treated with extracorporeal membrane oxygenation after lung transplantation. Ann Thorac Surg 2012;93:366-71.
86. Osho AA, Castleberry AW, Snyder LD, et al. Differential outcomes with early and late repeat transplantation in the era of the lung allocation score. Ann Thorac Surg 2014;98:1914-20: discussion 1920-1.
87. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report-2014; focus theme: retransplantation. J Heart Lung Transplant 2014;33:1009-24.
88. Sommer W, Tudorache I, Kuhn C, et al. C1-esterase-inhibitor for primary graft dysfunction in lung transplantation. Transplantation 2014;97:1185-91.
89. Adatia I, Wessel DL. Therapeutic use of inhaled nitric oxide. Curr Opin Pediatr 1994;6:583-90.
90. Date H, Triantafillou AN, Trulock EP, Pohl MS, Cooper JD, Patterson GA. Inhaled nitric oxide reduces human lung allograft dysfunction. J Thorac Cardiovasc Surg 1996;111:913-9.
91. Macdonald P, Mundy J, Rogers P, et al. Successful treatment of life-threatening acute reperfusion injury after lung transplantation with inhaled nitric oxide. J Thorac Cardiovasc Surg 1995;110: 861-3.
92. Bharat A, Kuo E, Steward N, et al. Immunological link between primary graft dysfunction and chronic lung allograft rejection. Ann Thorac Surg 2008;86:189-95: discussion 196-7.
93. Ius F, Sommer W, Tudorache I, Kuhn C, et al. Early donor-specific antibodies in lung transplantation: risk factors and impact on survival. J Heart Lung Transplant 2014;33:1255-63.
94. Daud SA, Yusen RD, Meyers BF, et al. Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2007;175:507-13.
95. Christie JD, Kotloff RM, Ahya VN, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med 2005;171:1312-6.
96. Burton CM, Iversen M, Milman N, et al. Outcome of lung transplanted patients with primary graft dysfunction. Eur J Cardiothorac Surg 2007;31:75-82.
97. Whitson BA, Prekker ME, Herrington CS, et al. Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant 2007;26:1004-11.
98. Huang HJ, Yusen RD, Meyers BF, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant 2008;8:2454-62.
99. Cohen DG, Christie JD, Anderson BJ, et al. Cognitive function, mental health, and health-related quality of life after lung transplantation. Ann Am Thorac Soc 2014;11:522-30.
100. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. Psychosom Med 2008;70: 512-9.
101. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. Gen Hosp Psychiatry 2001;23:90-6.