Impact of Primary Graft Failure on Outcomes Following Lung Transplantation*

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Study objectives: **Primary graft failure (PGF) is a severe acute lung injury syndrome that occurs following lung transplantation. We compared the clinical outcomes of patients who developed PGF with those who did not.**

Methods: **We conducted a retrospective cohort study including 255 consecutive lung transplant procedures. PGF was defined as (1) diffuse alveolar opacities developing within 72 h of transplantation, (2) an arterial partial pressure of oxygen/fraction of inspired oxygen (Pao_2/Fio_2) ratio of < 200 beyond 48 h postoperatively, and (3) no other secondary cause of graft dysfunction. PGF was tested for acceptance with 30-day and all-cause hospital mortality rates, overall survival, hospital length of stay (HLOS), duration of mechanical ventilation, and best 6-min walk test (6MWT) distance achieved within 12 months.**

Setting: **Academic medical center.**

Results: **The overall incidence of PGF was 11.8% (95% confidence interval [CI], 7.9 to 15.9%). The all-cause mortality rate at 30 days was 63.3% in patients with PGF and 8.8% in patients without PGF (relative risk [RR], 7.15; 95% CI, 4.34 to 11.80%; $p < 0.001$). A total of 73.3% of patients with PGF died during hospitalization vs 14.2% of patients without PGF (RR, 5.18%; 95% CI, 3.51 to 7.63; $p < 0.001$). The median HLOS in 30-day survivors was 47 days in patients with PGF vs 15 days in those without PGF ($p < 0.001$), and the mean duration of mechanical ventilation was 15 days in patients with PGF vs 1 day in those without PGF ($p < 0.001$). By 12 months, a total of 28.5% of survivors with PGF achieved a normal age-appropriate 6MWT distance vs 71.4% of survivors without PGF at 12 months ($p = 0.014$). The median best 6MWT distance achieved within the first 12 months was 1,196 feet in patients with PGF vs 1,546 feet in those without PGF ($p = 0.009$).**

Conclusions: **PGF has a significant impact on mortality, HLOS, and duration of mechanical ventilation following lung transplantation. Survivors of PGF have a protracted recovery with impaired physical function up to 1 year following transplantation.** ***(CHEST 2005; 127:161–165)***

Key words: acute lung injury; complications; lung transplantation; outcomes; reperfusion injury

Abbreviations: CI = confidence interval; HLOS = hospital length of stay; OR = odds ratio; Pao_2/Fio_2 = arterial partial pressure of oxygen/fraction of inspired oxygen; PGF = primary graft failure; RR = relative risk; 6MWT = 6-min walk test

Primary graft failure (PGF) represents a severe form of ischemia-reperfusion lung injury to the lung allograft occurring in the early posttransplant period.[1,2] The radiographic and histologic features are most similar to those of ARDS.[1,3,4] The incidence of PGF has been reported to be in the range of 12 to 25%, and it has been reported as the leading cause of early death following transplantation.[1,2,5–7] However, some studies[8] have suggested that severe ischemia-reperfusion injury does not adversely impact mortality.

Outside the lung transplant population, survivors

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of severe acute lung injury have impaired functional status and quality of life extending far beyond the initial hospitalization.[9–11] However, the longer term functional outcomes in survivors of PGF have not been systematically studied. The purpose of this study was to test the association of PGF with both short-term and long-term clinical outcomes following lung transplantation.

Materials and Methods

Study Population

A retrospective cohort study was performed including all 255 consecutive lung transplant procedures performed at our institution between October 1991 and July 2000. One heart-lung transplant and two lung-liver transplants were excluded as it was thought that they would not be representative of outcomes in the population at whole. The follow-up period for survival analysis and clinical outcomes extended to July 2002. We chose this time frame to ensure at least 2 years of follow-up time for all subjects. In addition, 250 patients would provide 80% power at an α level of 0.05 to detect a 5% absolute difference in 30-day mortality above an estimated 30-day mortality rate of 8% in the non-PGF group.

Standard Transplant Protocol

Donor selection, graft procurement, immunologic evaluation, surgical technique, postoperative management, and immunosuppression therapy all proceeded according to our standard transplant protocol, which has been previously published.[1,7] Of note, we used antilymphocyte induction therapy in all but 40 of our patients (sequentially between patient 60 and 100) during the time period of study. Other immunosuppression therapy consisted of treatment with cyclosporine, azathioprine, and prednisone, and this was the same in all subjects over the period of the study.

Definition of PGF

The definition of PGF represents an adaptation of the American European Consensus Conference definition of ARDS.[12] Although there is a spectrum of reperfusion injury following lung transplantation,[4,8,13] we chose criteria that select the patients with the most severe form of clinical graft dysfunction, which is most similar to ARDS. To be defined as having PGF, study subjects had to meet all of the following criteria: (1) the presence within 72 h of transplantation of a diffuse alveolar infiltrate involving the lung allograft and, in the case of single-lung transplant, sparing the native lung; (2) a ratio of arterial partial pressure of oxygen/fraction of inspired oxygen (Pao_2/Fio_2) of < 200 persisting beyond the initial 48 h postoperatively; (3) no other secondary cause of graft dysfunction identified, including cardiogenic pulmonary edema (defined as a pulmonary artery occlusion pressure of > 18 cm or the resolution of infiltrates with effective diuresis), pathologic evidence of rejection, pneumonia (as evidenced by the presence of fever, leukocytosis, and purulent secretions with positive cultures on bronchoscopy during the first 3 postoperative days), and pulmonary venous outflow obstruction by clot or kinking (as demonstrated by transesophageal echocardiogram or direct inspection on surgical reexploration or postmortem examination); and, (4) in the event of death prior to day 3, the patient must fulfill the above criteria at the time of death and must demonstrate diffuse alveolar damage as the predominant process on histologic examination of the lung (available on all patients with death within 72 h).

Definition of Outcomes

Study outcomes were all-cause mortality rate at day 30 following transplantation, all-cause hospital mortality rate, overall survival rate, hospital length of stay (HLOS), duration of mechanical ventilation, number of ventilator-free days during the first 30 postoperative days,[14] and 6-min walk test (6MWT) distance within 12 months following transplantation. Due to biases potentially introduced by early death in the postoperative period, HLOS and duration of mechanical ventilation were assessed only among 30-day survivors. To be considered "extubated," subjects needed to be free of mechanical ventilation for 48 h. Reintubation following this 48-h period was not considered part of the duration of mechanical ventilation attributable to PGF, because of the likelihood of other contributing causes. To further evaluate the contribution of PGF to the length of intubation when accounting for the effects of early deaths and reintubation, we calculated the number of 30-day ventilator-free days in all patients.[14]

The 6MWT was performed in a standard fashion.[15] We compared the best distance achieved within the first 12 months of the date of transplantation as a measure of peak function achieved during this time period. A "normal" 6MWT distance was defined as the minimum age-appropriate distance using standard criteria for population norms.[15] Subjects who were alive but unable to perform the test due to physical disability were scored as a zero value. Subjects who were dead were excluded from analysis.

Data Collection and Management

All of the data prior to July 2000 were collected from a review of preexisting medical records. After this time point, the follow-up mortality and 6MWT data were recorded prospectively as part of a prospective cohort study. Data extraction was conducted separately and by persons who were blinded to knowledge of PGF.

Data on mortality outcomes were complete in all subjects. No patients were lost to follow-up during the period of the cohort study. 6MWT data were complete in the survivors who had PGF. However, 6MWT data were not uniformly complete in the group of survivors without PGF. Missing data were mostly due to death within 1 year of lung transplantation and the inability to perform the test due to disability. Of the 214 subjects who were alive at 30 days following transplantation, 194 had performed a 6MWT within the first year. Of the 20 remaining subjects, 16 died prior to completing a test, 2 were alive but too disabled to perform the test, and 1 was performing a home exercise regimen that equated to a normal 6MWT distance. Only one patient was lost to follow-up during the period of observation.

Statistical Analysis

Relative risks (RRs) with 95% confidence intervals (CIs) were calculated as the incidence of outcome (such as 30-day mortality rate) in patients with PGF divided by the incidence of outcome in patients without PGF. Due to the expected skewed distribution of HLOS, duration of mechanical ventilation, and 6MWT distance, these continuous variables were compared using nonparametric methods, using the rank sum test. To assess the potential confounding effects of variables on the relationship of