Atelectasis in primary graft dysfunction survivors after lung transplantation

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Abstract
Background: Primary graft dysfunction (PGD) is an important contributor to early mortality in lung transplant recipients and is associated with impaired lung function. The radiographic sequelae of PGD on computed tomography (CT) have not been characterized.

Methods: We studied adult double lung transplant recipients from 2010 to 2016 for whom protocol 3-month post-transplant CT scans were available. We assessed CTs for changes including pleural effusions, ground glass opacification, atelectasis, centrilobular nodularity, consolidation, interlobular septal thickening, air trapping and fibrosis, and their relationship to prior post-transplant PGD, future lung function, post-transplant baseline lung allograft dysfunction (BLAD), and chronic lung allograft dysfunction (CLAD).

Results: Of 237 patients studied, 50 (21%) developed grade 3 PGD (PGD3) at 48 or 72 h. PGD3 was associated with increased interlobular septal thickening ($p = 0.0389$) and atelectasis ($p = 0.0001$) at 3 months, but only atelectasis remained associated after correction for multiple testing. Atelectasis severity was associated with lower peak forced expiratory volume in 1 s (FEV1) and increased risk of BLAD ($p = 0.0014$) but not with future CLAD onset ($p = 0.7789$).

Conclusions: Severe PGD was associated with atelectasis on 3-month post-transplant CT in our cohort. Atelectasis on routine CT may be an intermediary identifiable stage between PGD and future poor lung function.

Keywords
atelectasis, lung transplantation, primary graft dysfunction

1 | INTRODUCTION

Primary graft dysfunction (PGD) after lung transplantation is a form of acute lung injury occurring immediately post-operatively and associated with increased mortality.¹ PGD is characterized by hypoxia and radiographic findings of bilateral infiltrates consistent with pulmonary edema. While its imaging features on chest radiography typically resolve around 10 days post-transplant, PGD has been shown to negatively impact recipients in the long term.²⁻⁴ Survival in patients who develop PGD is impaired compared to those who do not and this difference is most distinct in patients who have grade 3 PGD (PGD3), defined as severe reduction in the

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Partial pressure of oxygen (\(\text{PaO}_2\)) to fraction of inspired oxygen (\(\text{FiO}_2\)) ratio of <200 mmHg, at the 48 or 72 h time point.\(^5\) Survivors tend to demonstrate abnormalities in multiple functional domains, most notably in lung function and particularly with respect to either peak forced expiratory volume (FEV\(_1\)) or FEV\(_1\) at one-year post-transplant.\(^5\)–\(^8\) The causes of these abnormalities are not well-established and in particular, there has been little exploration of potential structural or imaging changes in PGD survivors or their prognostic implications.

Protocolized high resolution computed tomography (CT) scans of the lungs can potentially offer greater insight into lung structural and parenchymal abnormalities post-transplant compared with chest radiography, including those associated with PGD.\(^9\) We assessed abnormalities on CT lung scans done routinely at 3-months post-transplant and their association with long-term lung function. We hypothesized that CT abnormalities would be more frequent in PGD survivors and would predict lower lung function at 1 year.

2 | MATERIALS AND METHODS

2.1 | Population

We studied all adult patients who underwent double lung transplant in the University of Alberta Lung Transplant Program from January 2010 to December 2016 for whom 3-month CT chest scans were available. We excluded all single lung, heart-lung, and living lobar lung transplant recipients, as well as patients without sufficient data to grade for PGD post-transplant. Individual consent was waived given the retrospective design and inclusion of deceased patients. The study was approved by the University of Alberta Human Research Ethics Board (Pro00070542).

2.2 | PGD grading

The primary risk factor was the development of grade 3 PGD at 48- or 72-h post-transplant, defined as per the 2016 International Society for Heart and Lung Transplantation (ISHLT) consensus criteria as bilateral lung edema on post-operative chest X-ray according to the interpreting radiologist and \(\text{PaO}_2/\text{FiO}_2\) <200 mmHg.\(^6\) This is accepted as the PGD severity and timing most associated with mortality risk.\(^5\) Patients who were switched to nasal cannula or ventilator oxygen at an \(\text{FiO}_2\) of less than 0.3 were graded at subsequent timepoints as grade 1 PGD if edema is present on chest X-ray and grade 0 PGD if no edema is present. The full ISHLT grading scheme is depicted in Table 1.

2.3 | Chest computed tomography abnormalities

The primary outcome was the presence of abnormalities on routine CT of the chest as noted by the study’s interpreting radiologist – all sub-specialists in thoracic radiology – including pleural effusion, ground glass opacification (GGO), centrilobular nodularity (CLN), interlobular septal thickening (ILS), atelectasis, consolidation, fibrosis, and air trapping. Grading of radiographic abnormalities was done according to the number of involved lobes for each of consolidation, atelectasis, CLN, GGO, and ILS. Air trapping and fibrosis were graded as present or absent, and pleural effusions were graded and ranked as none, trace, small, medium or large as well as bilateral or unilateral.

2.4 | Allograft microbiology on routine 3-month bronchoscopy

We assessed microbiology on bronchoalveolar lavage on 3-month bronchoscopy. Findings were refined to a list of clinically relevant organisms based on consensus between a lung transplant physician and a transplant infectious disease physician. Both were blinded to all other patient data including PGD status and long-term lung function.

2.5 | Long term lung function

We reviewed FEV\(_1\) values over all recorded post-transplant measurements. We analyzed long-term lung function both continuously as well as in terms of the presence or absence of baseline lung allograft dysfunction (BLAD), defined as failure to achieve an FEV\(_1\) and forced vital capacity (>80% predicted on two consecutive occasions >3 weeks apart.\(^1\) We designated chronic lung allograft dysfunction (CLAD) as decline in FEV\(_1\) to <80% of established baseline in liters, as well as grades and phenotypes in accordance with the 2019 ISHLT consensus statement. Our CLAD analysis described below focused on the time to onset of CLAD grade 1 or higher.\(^1\)

2.6 | Statistics

We compared continuous variables using t-tests or Wilcoxon rank sum tests depending on normality, and binary or categorical variables using Fisher’s exact tests or Pearson chi-square tests. Ranked ordinal variables were compared via Cochran Armitage
We applied Bonferroni correction for multiple testing on the eight CT-abnormality outcomes of interest, resulting in a p-value significance threshold of \( p = 0.00625 \) for the primary outcomes of interest. Although conservative, this was justified by the high sensitivity of Cochrane Armitage trend testing. To account for potential confounders in baseline characteristics, we ran adjusted ordinal regression models for the association between PGD3 and atelectasis rank. In our secondary analysis, we used a multivariable linear regression to model the impact of radiographic abnormalities on 1-year FEV1, controlling for history of grade 3 PGD. We also used logistic and proportional hazards regression modelling to measure the association between atelectasis and the presence of BLAD or future risk of death-censored grade 1 CLAD onset, respectively. All analyses were performed on JMP version 12 software (SAS Institute, Inc).

### Results

#### Baseline characteristics

A total of 316 patients underwent transplant during the indicated timeframe, 23 of whom were excluded on the basis of non-double lung transplant, 14 for death prior to three months and 42 for missing data (n = 3 insufficient data to grade for PGD, n = 39 no 3-month CT), for a final cohort of 237 patients (Figure 1). Baseline characteristics and post-operative outcomes are summarized in Tables 2 and 3. 50 patients (21%) developed grade 3 PGD at 48 or 72 h. Patients who developed grade 3 PGD had higher body mass indices (BMI) at the time of transplant (27 vs. 25, \( p = 0.0150 \)) and were more likely to have received a non-Caucasian donor. PGD3 patients had more complex post-transplant courses with longer ventilation times as well as intensive care unit and hospital lengths of stay. Other baseline characteristics were similar.

#### Radiographic abnormalities on 3-month CT scans

Sample images of the noted abnormalities are provided in Figure 2. The extent of CT abnormalities stratified by PGD3 status is illustrated in Figure 3 and summarized in Supplementary Table S1. Grade 3 PGD was associated with more frequent and/or widely distributed interlobular septal thickening (\( p = 0.0389 \)) and atelectasis (\( p < 0.0001 \)) at three months. Increasing PGD grades (0-3) correlated with increasing frequency and severity of atelectasis (Figure 4, \( p = 0.0003 \)). Fibrosis was also increased in PGD3 survivors, but there were very few cases. There was no notable difference in the presence or extent of pleural effusion, consolidation, centrilobular nodularity, ground glass opacification, and air trapping. After Bonferroni correction for multiple testing, only atelectasis remained significantly associated with a history of severe PGD.

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**FIGURE 1** Study cohort

**FIGURE 3** Extent of CT abnormalities stratified by PGD3 status. Grade 3 PGD was associated with more frequent and/or widely distributed interlobular septal thickening (\( p = 0.0389 \)) and atelectasis (\( p < 0.0001 \)) at three months. Increasing PGD grades (0-3) correlated with increasing frequency and severity of atelectasis (Figure 4, \( p = 0.0003 \)). Fibrosis was also increased in PGD3 survivors, but there were very few cases. There was no notable difference in the presence or extent of pleural effusion, consolidation, centrilobular nodularity, ground glass opacification, and air trapping. After Bonferroni correction for multiple testing, only atelectasis remained significantly associated with a history of severe PGD.
associated with atelectasis ($p = 0.0297$) in a multivariable ordinal regression model, adjusted for all observed baseline discrepancies (recipient gender, BMI, pulmonary diagnosis, bridging status, donor ethnicity and donor-recipient pTLC ratio). Finally, to ensure atelectasis on 3-month CT scan was not an artifact of post-transplant weight gain during this time period and extrinsic
compression, we analyzed the relationship between the 3-month post-transplant BMI and atelectasis and found no BMI differences related to atelectasis severity \( (p = .324) \).

We considered whether post-transplant chest interventions – such as chest tube insertion or surgical decortication – could be associated with post-transplant atelectasis. A total of 12 patients required post-transplant chest intervention, 11 chest tube insertions and one video-assisted decortication. Of these 12, 11 (92%) were patients with some degree of atelectasis, reflecting 10% of the overall cohort of patients with atelectasis \( (n = 125) \) and consistent with the above observed association between atelectasis and post-transplant pleural effusions.

Ideally, we could assess whether these findings persisted over time, however our center does not perform protocol CT scans aside from at the 3-month time point. We were however able to assess a subset of 58 of the 125 (46%) patients who had atelectasis on 3-month CT scan who went on to undergo a subsequent CT done for other indications at 1-year post-transplant or beyond. Among these, 50 (86%) had atelectasis again noted, improved in 24, stable in 22, and progressed in 12 patients.

### 3.4 Atelectasis and microbiology on 3-month bronchoscopy

The presence of a clinically relevant bacteria (Supplementary Table S4) or fungi on 3-month protocol bronchoscopy done concurrently with CT chest was not more common in PGD3 survivors.
The presence of an organism on 3-month protocol bronchoscopy did not differ by the presence or severity of any of the radiographic abnormalities (data not shown).

### 3.5 | Atelectasis and future lung function

Recipient post-operative outcomes stratified by atelectasis are depicted in Supplementary Table S5. Peak post-transplant FEV1 was lower in patients with atelectasis on 3-month CT in a lobe-dependent fashion (Figure 5). Atelectasis was strongly associated with peak FEV1 percent predicted in an unadjusted linear regression model ($p = .0007$) and after adjustment for PGD3 status ($p = .0066$). Atelectasis was similarly associated with the risk of baseline lung allograft dysfunction both unadjusted ($p = .0014$) and adjusted for PGD3 status ($p = .0069$) (Figure 6). Of note in the latter model, PGD3 was no longer associated with baseline lung allograft dysfunction. Atelectasis was not associated with the risk of future death-censored grade 1 CLAD onset, either unadjusted ($p = .7789$) or adjusted for PGD3 status ($p = .7971$). Atelectasis on 3-month CT scan was also not associated with highest CLAD grade achieved over the follow up period ($p = .3717$, Supplementary Figure S1).

### 4 | DISCUSSION

Our findings indicate atelectasis at 3-months post-lung transplant is more frequent and more severe in PGD3 survivors. These CT changes may help identify patients at risk for baseline lung allograft dysfunction, which is associated with poorer survival after lung transplant.

Atelectasis is the regional collapse of alveolated lung tissue and associated volume loss. It can result from one or a combination of compression, airway obstruction, respiratory muscle weakness and increased alveolar surface tension as a consequence of deficient surfactant action.\(^{13}\) Surfactant deficiency has previously been demonstrated in a study of lung transplant biopsies, where up to 34% of the total cells in the samples underwent apoptosis following graft reperfusion in vitro.\(^{14}\) The majority of these apoptotic cells were surfactant-producing alveolar type II pneumocytes. Another study found significant biochemical alterations in the surfactant of lung transplant recipients both in the short- and long-term that correlated with decreased surfactant function.\(^{15}\) Impaired surfactant function is thought to be a key mechanism of lung dysfunction in acute respiratory distress syndrome, which has similar pathophysiology to PGD.\(^{16}\) Bronchoscopic instillation of exogenous surfactant has been...
effective for improving oxygenation in both acute respiratory distress syndrome and severe PGD though it remains experimental.\textsuperscript{17,18} It is possible that the apoptotic response and subsequent surfactant dysfunction may be especially pronounced with severe PGD, such that recovery is incomplete at 3-months post-transplant, resulting in the persistence of atelectasis.

There are other potential explanations for atelectasis after lung transplant. An oversized donor may lead to atelectasis through extrinsic compression. However, were this a strong driver of atelectasis in our study, we would have expected a relationship between donor-recipient height ratio and atelectasis, which was not observed (Supplementary Table S2). We also addressed this via models adjusted for pTLC ratio and did not note a change in the PGD-atelectasis association. Adjustment for other baseline differences associated with either atelectasis or PGD – including recipient BMI, sex, pulmonary diagnosis, bridging therapy and donor ethnicity

\textbf{FIGURE 5} Peak FEV1 in liters stratified by atelectasis severity

\textbf{FIGURE 6} Proportion of patients with baseline lung allograft dysfunction by history of atelectasis of 3-month CT
did not alter the strength of the relationship between PGD3 and post-transplant atelectasis. Another possibility is post-transplant diaphragmatic dysfunction, which can occur as the result of phrenic nerve trauma.19 This could produce passive atelectasis through incomplete expansion of the chest, but we reviewed post-transplant clinically indicated diaphragm investigations – ultrasonography or fluoroscopy – and did not observe a discrepancy between patients with atelectasis or severe PGD and those without (Table 3 and Supplementary Table S5). Despite this, these were not routine investigations, so this remains a potential contributor. Finally, the presence of atelectasis was strongly associated with presence and extent of pleural effusions after transplant in our study. Our study cannot clarify whether the effusions are an atelectasis cause or effect, or rather simply an associated phenomenon that tends to occur with atelectasis. However, were pleural effusions the primary driver of the atelectasis findings, we would expect to have observed a PGD-pleural effusion association, which we did not. We suspect based on this that the effusions may be reactive to the atelectasis but disentangling these would require a dedicated study with a different design.

We further addressed the possibility that allograft microbiology could produce confounding imaging changes on CT scans and even that PGD3 itself could increase the risk of subsequent bacterial or fungal colonization or infection. If PGD were to produce permanent structural abnormalities in the lung, microbial defense could be impaired.20,21 We were surprised to observe no such association, even with a refined list of clinically relevant organisms (Supplementary Table S4). This may suggest PGD’s effects on microbial defense of the transplanted lungs noted in prior studies – for example, impairments in mucociliary function – may not persist.22 It also suggests that imaging changes on routine post-transplant imaging are not consistently accounted for by infection.

The associations between severe PGD, atelectasis and baseline lung allograft dysfunction are notable. Baseline lung allograft dysfunction is a physiologic entity after lung transplantation where lung function fails to reach population-referent normal thresholds. In our study, CT evidence of atelectasis at three months was associated with a reduced peak FEV1 and increased risk of BLAD, even when adjusting for a prior severe PGD, and more widespread atelectasis was associated with greater risk of BLAD in a stepwise fashion (Figure 6). This suggests that post-PGD atelectasis may serve as an identifiable early marker of risk by highlighting patients who are less likely to normalize their lung function. The lack of association with CLAD onset or increased CLAD grade may suggest that these same patients are not at increased risk for progressive lung function loss. The findings also raise the question as to whether interventions at this early stage – intensive ongoing physiotherapy, incentive spirometry and even potentially exogenous surfactant at the time of PGD or otherwise – could modify this finding or long-term lung function in general. These questions await a dedicated study of this group.

Our study has limitations. The single-center design may introduce center-specific effects and, as with all single center studies, would benefit from validation in a second cohort. Second, the retrospective design resulted in some cases with missing data which could not be analyzed. Third, CT abnormalities would ideally be scored in terms of percentage of involved lung tissue, however many of these abnormalities (including atelectasis) lack a formal method for doing this, so ordinal lobe involvement was used as a surrogate. Finally, clinical interpretation of chest CT has demonstrated interobserver variability, resulting in an intrinsic error rate.23 At our institution, radiologists reporting post-lung transplant CT scans are experienced subspecialists in thoracic radiology, which mitigates this to some degree. Also, this type of error would likely weaken associations rather than produce false positives, so it is unlikely the robust atelectasis association is the result of this.

We have demonstrated a relationship between severe primary graft dysfunction, atelectasis on 3-month post-transplant CT imaging, and poor post-transplant lung function. This suggests atelectasis may be an identifiable intermediary marker of poor future lung function in PGD survivors. The pathophysiologic of these changes warrants further investigation.

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CONFLICTS OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose. This study was presented in poster form at the annual meeting of the International Society for Heart and Lung Transplantation, held virtually in April 2020.

AUTHORS CONTRIBUTION

DJJ participated in research design, collected data, contributed to the analysis, helped prepare and finalize the manuscript. JA, JW, AK, AH, RV, JN, DL, KD helped formulate the study and prepare the final version of the manuscript. KH designed the study, conducted the main analyses, and prepared then finalized the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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