Distinct Phenotypes of Primary Graft Dysfunction After Lung Transplantation

To the Editor:

We read with great interest the article by Shah et al in a recent issue of CHEST (August 2013). Three distinct phenotypes of grade 3 primary graft dysfunction (PGD) were identified by latent class analysis, bringing new insights into the mechanism and treatment of severe PGD. However, a few issues need to be clarified after deeper analysis of the article.

The hypothesis introduced by the authors was that distinct phenotypes of PGD are associated with different prognoses identified by latent class analysis. However, the results may be produced by the evolution of PGD per se and the risk factors for exacerbation of PGD rather than by the distinct phenotypes. By analogy, it is not difficult to recognize that individuals with the same stage of non-small cell lung cancer often have disparate manifestations of the disease and different prognoses. The authors compared different characteristics among classes in the three-class model to identify risk factors for severe PGD. However, if all the factors were included in multivariable logistic regression, independent risk factors for PGD may be discriminated from those presented by the authors (donor age, donor smoking, donor mode of death, cardiopulmonary bypass, intraoperative crystalloids, tidal volume, packed RBC use, pulmonary artery pressure). Previous studies have demonstrated more risk factors, including FIo2 during allograft reperfusion, single lung transplant, recipient BMI indicating overweight or obesity, preoperative sarcoidosis, or pulmonary arterial hypertension and black donors and female donors. PGD was a significant predictor for lung transplant outcomes. Thus, patients could benefit from preventive strategies aimed at reducing reperfusion injury and decreasing the hazardness of risk factors for PGD.

PGD has a reported incidence of between 11% and 57% and accounts for 26% of causes of death within the first 30 days after lung transplant and for 17% within 1 year. Extracorporeal membrane oxygenation (ECMO) provides reliable support for PGD, with acceptable outcomes during the postoperative period. Analysis of the Extracorporeal Life Support Organization registry (January 1987-December 2005) showed that PGD requiring postoperative ECMO support developed in 151 patients, of whom 93 (61.6%) were weaned from ECMO as a result of lung recovery. However, the authors did not provide data on ECMO for all patients with PGD from the 10 participating centers. Such data are important because ECMO can facilitate lung recovery from severe PGD, and ECMO as a confounding factor complicated latent class analysis in the study.

PGD as a form of ischemia/reperfusion injury can present immediately postoperatively and 48 to 72 h later. In the latent class analysis, the authors divided 361 patients with PGD into three classes, with the same morbidity onset time, time zero; however, PGD developed at other time points after 24 h and up to 72 h postoperatively may be omitted. Thus, we argue that PGD developing at different time points should be taken into account when planning the latent class analysis.

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Response

To the Editor:

We thank Dr Mao and colleagues for their insightful comments and the opportunity to clarify a number of points from our work.1 Although we considered inclusion of additional risk variables into the latent class analysis model,1 we chose to use time changes in primary graft dysfunction (PGD) grade only to derive our classes for several reasons. First, we sought to address controversy surrounding PGD phenotypes encompassed within the International Society for Heart & Lung Transplantation definition based on timing of clinical PGD development.2,3 Second, we did not have a large enough sample size to include all known risk factors for PGD in the model and generate stable classes. Third, using grade alone to derive the classes allowed us to demonstrate construct validity of the resultant PGD phenotypes using many of the known clinical risk factors for PGD and mortality.

We have previously published on clinical risk factors in PGD.4 In the current study, we evaluated which of these many risk factors would distinguish between the classes. We agree that recipient BMI, for example, remains an important risk factor for PGD; however, differences in BMI did not help distinguish between those patients who will recover from injury quickly and those with persistent injury. The factors we identified, including volume of blood transfusion and cardiopulmonary bypass use, may be helpful in identifying those who are at risk for graft dysfunction persisting on day 3 as well as identifying potential mechanistic links to the persistent PGD phenotype.

In the Lung Transplant Outcomes Group cohort study, subjects receiving extracorporeal membrane oxygenation (ECMO) for graft dysfunction are classified as having grade 3 PGD. Therefore, we do not believe the use of ECMO in this study created a misclassification bias by making it appear that subjects recovered from PGD when they did not. Additionally, only one subject in this cohort was on ECMO 72 h after transplantation, so we do not think there was significant contribution from the use of ECMO.

Although our analyses generated classes that differed in time of resolution, we did include all subjects with grade 3 PGD at any time. The latent class model best defined classes based on resolution of lung injury, but classes based on development of injury were less apparent. However, had a class of late-onset injury been common, we believe our model would have identified this pattern. We limited our study to PGD within 72 h, as that is the commonly accepted definition,2 although certainly lung injury can occur at later time points.

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N-Acetylcysteine Protection in COPD
An Alternative Mechanism of Action

To the Editor:

We read with interest the study by Tse et al1 in a recent issue of CHEST (July 2013). In their study, 1-year treatment with high-dose N-acetylcysteine (NAC) resulted in improved small airway function and decreased exacerbation frequency in patients with COPD. The authors proposed that the reduction in COPD exacerbations might be related to antioxidant and antiinflammatory effects of NAC, resulting in improved small airway function in COPD. Additionally, they proposed that NAC might reduce exacerbations by inhibiting bacterial adherence to ciliated epithelial cells and by NAC mucolytic effects.

Although we agree with these possibilities, one additional mechanism was not discussed. We propose that a major mechanism of