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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[5]; 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 al[1] 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