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Predicting Primary Graft Dysfunction After Lung Transplantation: Trying to Catch it Early

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Primary graft dysfunction (PGD) remains the leading cause of early morbidity and mortality after lung transplantation and is a significant risk factor for chronic rejection¹⁻³. We have previously demonstrated that transplant clinicians would utilize PGD predictive strategies for evaluating and treating potential transplant recipients⁴. In a recent study, Shah et al developed pretransplant predictive algorithms aimed at identifying, prior to transplant, patients at high risk of PGD based solely on clinical variables⁵. In this issue of *Transplantation*, Pottecher and colleagues significantly add to our understanding of early PGD prediction⁶.

In this single center study of 47 lung transplant recipients, the authors evaluated various physiologic and biologic parameters as potential early, perioperative risk factors for PGD. Extravascular lung water indexed for ideal body weight (EVLWi) measured *at the time of allograft reperfusion* was 1 of the best predictors of grade 3 PGD early after transplant. These findings are highly concordant with previous critical care research. Higher EVLWi was previously shown to have predictive value for death among patients with sepsis as well as acute respiratory distress syndrome (ARDS), disease states with related underlying mechanisms to PGD after lung transplantation⁷.

Additionally, plasma concentration of soluble receptor for advanced glycation end products (sRAGE), similarly measured at the time of allograft reperfusion, predicted the development of PGD by 6 to twenty-four hours post reperfusion. This is consistent with previous literature indicating a strong association of alveolar epithelial cell injury and PGD pathogenesis. Pelaez et al previously demonstrated that lungs that go on to develop PGD have higher donor bronchoalveolar lavage fluid sRAGE levels prior to transplant than those that don't develop PGD⁸. Christie et al previously showed that elevated recipient levels of plasma sRAGE 6 and twenty-four hours after reperfusion were associated with the development of PGD within the first seventy-two hours after transplant⁹. The current paper extends this finding even earlier, indicating that evidence of epithelial injury is evident

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immediately and can be used to identify patients in the operating room at high risk for the development of PGD.

Importantly, Pottecher and colleagues also identified that the $\text{PaO}_2/\text{FiO}_2$ ratio measured early, at the time of allograft reperfusion, also significantly predicted the subsequent development of PGD. While the $\text{PaO}_2/\text{FiO}_2$ ratio at reperfusion is not part of the causal pathway for PGD development and is also a component of the PGD definition used later in the posttransplant time period, early, immediate abnormalities in gas exchange may help identify patients at risk in an easily measured, noninvasive fashion. One of the beauties of prediction is that the relevant parameters identified need not be causal or mechanistic, merely informative.

This study also serves to highlight some of the current glaring limitations we have in clinical lung transplantation. The current manuscript identifies intra-operative sRAGE levels as a very early predictor of developing PGD. Unfortunately, the current utility of such tests is limited by the lack of easy to use rapid tests for potential PGD biomarkers. The development of point-of-care diagnostics are therefore required to enable findings such as this to be clinically useful and evaluated in a prospective manner.

Despite years of research into the clinical, genetic, and molecular risk factors for PGD, the current state of the art treatment is limited to supportive therapy, or interventions extrapolated from ARDS care. The therapeutic interventions available, including C1-esterase inhibitor, are hampered by the lack of randomized clinical trials¹⁰. Despite improving predictive algorithms and risk factor identification and modification, no PGD-specific therapies have been proven effective. As the transplant community further embraces the use of extracorporeal membrane oxygenation as a bridge to lung transplantation and the severity of illness of potential lung transplant recipients increases, the incidence of PGD will likely increase¹¹. The use of early diagnostic and prognostic tools will allow for the more rapid deployment of potential therapies and interventions aimed at PGD therapy, patient stabilization, and, hopefully in the future, preventative therapies.

There are some significant limitations to this study that need to be appreciated. Despite the measurement of EVLWi and sRAGE level concurrent with allograft reperfusion, there is expanding data that the causative injury for PGD likely begins even earlier, in the donor, lessening the predictive utility of these measurements. Additionally, as the authors acknowledge, this study has a very small sample size. Furthermore, while the area under the receiver operating curve for the measured physiologic and biologic parameters was good, the positive predictive values were poor, bringing into question the actual predictive utility of these tests. Future, larger trials are necessary to better assess the validity, generalizability, and true predictive utility of EVLWi and sRAGE level.

New and improved diagnostic and prognostic tests for PGD are clearly needed. The ability to accurately and easily identify a population of lung transplant recipients that are at the highest risk for transplant allows for the implementation of novel clinical trial designs. These include utilizing prognostic enrichment designs aimed at identifying a population most likely to develop the outcome of interest, in this case PGD. The authors rightfully

highlight that pretransplant clinical predictors alone as currently modeled are likely insufficient to identify the patient population at highest risk, with at least two-thirds of all patients being classified as high risk depending on the model utilized⁵. Similarly, biologic and physiologic markers of early lung injury and vascular permeability will be inadequate in isolation for accurate risk prediction. The ideal future PGD predictive algorithm will need to incorporate some combination of donor and recipient clinical, genetic, and protein biomarker parameters, be easily and rapidly quantifiable, and precisely identify the highest risk patients. This will be key to the design of efficient clinical trials, given the relatively small lung transplant population size and the severe morbidity and mortality associated with PGD.

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Abbreviations

PGD	Primary graft dysfunction
EVLWi	Extravascular lung water indexed for ideal body weight
sRAGE	Soluble receptor for advanced glycation end products
ARDS	Acute respiratory distress syndrome

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