

Peer Review File

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Reviewer A

Comment 1: It is a well written manuscript that provides data regarding the impact of TPG on lung transplant outcomes. TPG a measurable value and clinicians may monitor its possible change in response to treatment. In my opinion this manuscript provides clinicians an extra tool to decide how to list a patient.

I would encourage you to continue this line of research.

Reply 1: Thank you for these comments.

Reviewer B

In this study, Chan et al. investigated the association between transpulmonary gradient (TPG) and outcomes after single and double lung transplantation. Unadjusted analysis showed that $TPG \geq 25$ was associated with decreased survival at 1 year but not at 3 or 5 years in the overall group. Interestingly, further analyses revealed that this association was only significant in the single lung transplant cohort, and survival beyond 90-day did not seem to be impacted by high TPG. It was an important study performed by an outstanding research team, and the manuscript was well written. However, I have several comments for the authors.

Comment 1. Were patients with UNOS group B diagnosis (eg. Primary pulmonary hypertension) also included in the analysis? With potentially both primary and secondary pulmonary hypertension patients included in the high TPG cohort, I'm wondering if the results may be confounded by the outcomes from idiopathic/primary pulmonary hypertension patients (oftentimes worse outcomes than COPD/IPF patients and have different etiology from secondary PAH). Though multivariable model can alleviate this bias somewhat, the collinearity between iPAH and TPG can be hard to address.

Reply 1: We thank the reviewer for this insight. In the original manuscript, patients with UNOS diagnosis group B were not excluded from the sample. After consideration of the impact that these patients may have on the results, we have opted to exclude these patients from the dataset. The revised manuscript presents results in all patients with the exception of UNOS group B. We are pleased to report that exclusion of these patients did not affect the overall results of the study, suggesting that the effects were not due to a confounding of diagnosis grouping.

Comment 2. For the TPG cutoff at 25, it seems to be very reasonable but I'm curious whether the authors have tried using methods such as restricted cubic splines to find

out a statistical cutpoint? It may be interesting to see if an identifiable turning point exists for the relationship between TPG and short-term survival and I think the manuscript could be significantly strengthened by this. This can just be an addition to the current results.

Reply 2: We thank the reviewer for the suggestion and agree that a quantitatively derived cut point would be more optimal. Our initial cut point was based off clinical experience, and in response to this suggestion we performed an ROC analysis to examine if TPG had an optimal cut point for detecting 1-year mortality. The ROC analysis found that a threshold of 26.15 mmHg was the optimal threshold for discriminating survival probabilities at one-year post transplant.

Comment 3. Authors thoughtfully and appropriately used mix-effect model to take the bias of transplant center into account. In the multivariable models, critical variables such as LAS and ischemic time were included, but some other potentially important variables available in the UNOS database such as if the patient was in ICU/hospitalized, on ventilation, or on ECMO were not incorporated in the model. Given the large sample size I think it would be reasonable to have those covariables included in the model unless authors have specific considerations.

Reply 3: We thank the reviewer for the suggestion and have incorporated hospital status, ventilator status and ECMO bridge at time of transplant as additional covariates in the multivariable models.

Comment 4. I think adding a Kaplan-Meier figure showing the 1-year survival difference between high vs. low TPG groups would likely be very helpful especially for the readers to visualize the significant survival difference within the first 90 days.

Reply 4: We thank the reviewer for the suggestion and have added a KM figure of 1-year survival in the postoperative outcomes subsection of the results section.

Overall I think this is an excellent manuscript answering an important question in an era of organ shortage. I would like to congratulate the authors for this strong piece of work.