Peer Review File

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Reviewer A

The authors describe their retrospective review of deep vein thrombosis following lung transplant and the complications that follow. I think the work is straight forward and interesting, and while not exactly novel worthwhile for publication. I have several comments:

- Most significantly the "Key Findings" is a reference and not related to the findings of the manuscript. Please correct to list your findings for this paper and not a prior reference. As the key findings listed are not supported entirely by your manuscript

Reply

We appreciate the reviewer's insightful comment. We made significant modifications in our manuscript to highlight the unique and important findings in our study that will be impact clinical management of post-lung transplant patients. Currently, there is a lack of lung transplant–specific data on risk stratification of DVT and perioperative management, especially the decision to anticoagulated to prevent pulmonary embolism over risk of postoperative bleeding. This study is the first to identify lung transplant–unique risk factors for VTE and quantify risk of postoperative bleeding associated with anticoagulation vs PE.

We agree that the "Key Findings" section should directly reflect the results of our study rather than prior literature. Accordingly, we have revised the section to highlight the principal findings from our cohort. (Line38-43, 208-220)

- In results, the incidence of DVT is 53.6% but in the abstract and discussion it is listed as 56.5%. Please clarify and correct

Reply

Thank you. 53.6% is correct number. Change was made to the manuscript. (Line18, 209)

- Methods: line 80 makes it seem that all patients included in the review were on preoperative ECMO as a bridge to transplant, but table 1 demonstrates that only 41 patients in the study were on preoperative ECMO. Improving your sentence structure here or separately including inclusion and exclusion criteria in a separate sentence may help clarify.

Reply

We thank the reviewer for pointing out this ambiguity. We agree that our wording may have suggested that all patients were bridged with ECMO. In fact, our study included all 399 adult lung transplant recipients during the study period, of whom 41 were bridged with VV-ECMO. We have revised the *Study Design* section. (Line85-98)

- Results: tables and graphs are appropriate

Reply

We thank the reviewer for this positive comment. We are glad that the tables and figures were found to be appropriate and supportive of the study results.

- Discussion: you have higher rates of DVT compared to prior reports and other studies, would you like to clarify why that is? Do you propose to change your anticoagulation in these patients or not? "a support a risk-adapted thromboprophylaxis strategy: intensified screening and tailored anticoagulation for high-risk patients balanced against bleeding risk" - what are you proposing, did this study change your plans for your transplant patients. Further discussion may be beneficial to help others tailor their strategies or plan their change in outcomes.

Reply

We thank the reviewer for this valuable comment. We agree that our reported incidence of DVT is much higher than prior studies. The main reason for observe difference is a substantial proportion of high-risk recipients in our cohort compared to other studies, such as those bridged with ECMO and those transplanted for COVID/ARDS (listed as others), who may be predisposed to thrombotic complications. Other possible reason is more liberal use of plasmaphoresis (shown to increase DVT) for treatment of mild acute rejection in our institution. We added the reasons in the revised Discussion section. (Line250-257)

Do you propose to change your anticoagulation in these patients or not?

Reply

Our data suggests, although DVT increase risk of PE, the mortality associated with anticoagulation/bleeding was much higher than PE related death in our lung transplant population. In subgroup-analysis of our patient cohorts with PE, patients with lower extremity DVT and higher pre-op platelets were more likely to develop post-operative PE. Therefore, we support a risk-adapted thromboprophylaxis and anticoagulation strategy- tailored anticoagulation for high-risk patients balanced against bleeding risks.

Previously, all the post-lung transplant patients with acute DVT, except those with active GI or surgical site bleeding, received anticoagulation therapy in our institution. Although this study does not mandate a change in anticoagulation protocols, in our institution, we have moved away from anticoagulation therapy in central line related DVTs and some upper extremity DVTs, especially in those who had a difficult operation. However, there are limitations in current study such as lack granularity of the data, modest size of the cohort, and retrospective nature of the study to make a sweeping mandate to change previous protocol. Therefore, our current study highlights the importance of developing a better predictive model to balance bleeding risk vs PE risk, and members in our labs is working to develop artificial intelligent machine learning model to develop individual care. (Line258-265)

Reviewer B

In this manuscript entitled "Risk Factors and Perioperative Complications Associated with Deep Venous Thrombosis and Pulmonary Embolism after Lung Transplantation", the authors assessed the risk factors for the development of DVT and PE. This topic is significant because DVT and PE are associated with the mortality of lung transplant patients.

However, several concerns arise regarding this study. I believe that a substantial revision would be required before publication.

Major comments

1. In the study design, you mention that "Adult patients who underwent lung transplantation with preoperative VV-ECMO were included," yet the table shows that only about 10% of patients received VV-ECMO. Since preoperative VV-ECMO itself can be a cause of VDT, if all patients indeed received ECMO, the title should clearly indicate that the study focuses on patients with preoperative ECMO. If not all patients received it, the inclusion criteria should be revised accordingly.

Reply

We thank the reviewer for this helpful comment and agree that our initial wording was misleading. In the original version, the phrasing "patients who underwent lung transplantation with preoperative VV-ECMO were included" unintentionally implied that all patients received ECMO support. In fact, our study included all consecutive adult lung transplant recipients during the study period (n = 399), of whom 41 (approximately 10%) were bridged with VV-ECMO. We have revised the *Study Design* section to clarify the inclusion and exclusion criteria, and the text now reads:

"Adult patients who underwent lung transplantation at our institution between January 2018 and May 2024 were included. Multiorgan transplant recipients and re-transplant recipients were excluded from the study."

This revision removes ambiguity and ensures the inclusion criteria are consistent with the data presented in Table 1.(Line85-98)

2. What protocol was used to detect DVT? Was an ultrasound performed routinely or only when symptoms appeared? If it were performed routinely, the protocol should be clearly described. If it were only conducted when symptoms appeared, wouldn't there be a significant risk of missing cases, especially in sedated patients?

Reply

We thank the reviewer for this important comment. At our institution, all patients receive postoperative prophylaxis with subcutaneous unfractionated heparin (5,000 units three times daily). Duplex ultrasound or other imaging studies are not performed routinely but are obtained when patients develop clinical symptoms suggestive of venous thrombosis. We agree with the reviewer that this approach carries a risk of under-detection, particularly in sedated or critically ill patients. We have revised the *Methods* section to clearly describe this protocol and acknowledged the potential for underestimation of asymptomatic DVT in the *Discussion* as a limitation of our study. (Line136-141, 226-228)

3. The occurrence of DVT is strongly influenced by preoperative ADL and respiratory status. Therefore, it would be necessary to include data such as the preoperative P/F ratio and the duration of ECMO support.

Reply

We thank the reviewer for this insightful comment. Unfortunately, detailed data on preoperative ADL, P/F ratio, and duration of preoperative ECMO support were not consistently available in our dataset and therefore could not be included in this analysis. We agree that these factors may significantly influence the risk of DVT, and we have added this point to the *Discussion* as a limitation of our study. (Line228-232)

4. It remains unclear why renal impairment was more frequently observed in patients who developed hemothorax or hematoma. Given that renal dysfunction is a common and critical complication following lung transplantation, if the authors suggest a potential association between hemothorax and renal impairment, a discussion supported by relevant literature would be warranted.

Reply

We thank the reviewer for this insightful comment. As shown in Table 3, patients who developed hemothorax or hematoma had higher rates of acute kidney injury and dialysis. We did not have sufficient data to establish a causal relationship between bleeding complications and renal impairment. However, several mechanisms may underlie this association. First, significant hemorrhage often requires blood product transfusion and re-operation, which can lead to hemodynamic instability and hypoperfusion of the kidneys. Second, patients with bleeding complications frequently required prolonged ICU stay and postoperative ECMO support, both of which are recognized risk factors for renal dysfunction. Prior reports have also highlighted the bidirectional relationship between postoperative bleeding and acute kidney injury in thoracic and surgery populations. We have added this discussion point and cited relevant literature in the revised *Discussion*. (Line273-287)

5. Why was the proportion of PE not attributed to DVT relatively high? Is it possibly related to factors such as the donor lung or issues with vascular anastomosis?

Reply

We appreciate the reviewer's important comment. As noted, only a subset of PE cases in our cohort could be directly attributed to documented DVT. Several factors may explain this finding. First, our institutional practice does not include routine duplex surveillance, so some lower extremity or pelvic DVTs may have gone undetected, particularly in sedated or critically ill patients. Thus, the true proportion of PE attributable to DVT may be underestimated. Second, embolic events after lung transplantation may also arise from in-situ pulmonary artery thrombosis, possibly related to donor lung factors, ischemia-reperfusion injury, or technical aspects of vascular anastomosis, which have been described in prior literature. Finally, hypercoagulability inherent to the perioperative transplant setting may contribute to de novo thrombus formation within the pulmonary circulation. We have revised the *Discussion* to clarify these points and to highlight that PE in lung transplant recipients may not always originate from systemic venous thrombosis. (Line288-300)

6. The manuscript presents a mixture of acute-phase and chronic-phase data, making it difficult to interpret. Although the survival curves suggest a follow-up period exceeding five years post-transplantation, no information is provided regarding chronic complications such as CLAD or postoperative infections. Consequently, it remains unclear which factors are contributing to survival outcomes. Focusing the analysis on acute-phase data alone may enhance the clarity and coherence of the study.

Reply

We thank the reviewer for this insightful comment. We agree that our study primarily focuses on acute perioperative complications (DVT, PE, and bleeding events) and does not include long-term outcomes such as CLAD, infection, or chronic graft failure, which are important determinants of survival after lung transplantation. Unfortunately, these long-term data were not consistently available for all patients in our cohort at the time of analysis, and our study design was not intended to evaluate chronic complications. We have clarified in the Methods and Discussion that our analysis is restricted to acute-phase outcomes. In addition, we have revised the Limitations section to explicitly acknowledge the absence of chronic-phase complications as a limitation. (Line95-98, 233-241)

7. If patients with DVT who did not develop pulmonary embolism (PE) still exhibited poor prognoses, factors such as acute kidney injury (AKI) or postoperative bleeding may have contributed to the observed mortality. Clarifying these associations would be a valuable addition to the study. Therefore, conducting a multivariate analysis to assess risk factors for mortality within the DVT group is recommended.

Reply

We appreciate the reviewer's thoughtful suggestion. In response, we conducted a multivariate Cox regression analysis restricted to patients with DVT (n=214) to identify risk factors for mortality. As shown in the newly added Supplemental Table 1, postoperative hemothorax/hematoma was independently associated with increased mortality (OR 2.24, 95% CI 1.32–3.81, p=0.003). In contrast, PE was not significantly associated with survival (OR 1.12, 95% CI 0.62–1.99, p=0.72). AKI and PGD grade 3 demonstrated trends toward worse outcomes but did not reach statistical significance. These findings suggest that mortality in DVT patients is largely driven by postoperative bleeding complications and overall clinical severity rather than by PE itself. We have incorporated these results into the Results and Discussion sections of the revised manuscript. (Line177-183, 301-307)

Minor comments

1. The abbreviation “pre-Txplt” is not defined in the table, which may impede comprehension. It is recommended to either explain the abbreviation or revise it for clarity.

Reply

We thank the reviewer for pointing this out. We agree that “pre-Txplt” may be unclear. We have revised the table to replace “pre-Txplt ECMO” with “Pre-transplant ECMO”. (Table1,2,3,5)

2. It would be important to include data on the use of antithrombotic agents before surgery, as this may influence the risk of thrombotic or bleeding complications.

Reply

We thank the reviewer for this important comment. Unfortunately, detailed information on the use of antithrombotic agents prior to surgery was not consistently available in our dataset and therefore could not be included in this analysis. We agree that preoperative antithrombotic therapy may significantly influence both thrombotic and bleeding risks, and we have added this point as a limitation in the revised *Discussion*. (Line238-241)