Peer Review File

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Reviewer A

Comment 1: Generally, the design of the study and the very low number of patients does not allow us to draw any conclusions. Therefore, it is even more important to show any kind of data that gives an indication of gaps in the guidelines and this study can indeed do that. That's why I think publication is right and important.

In this study, we are talking about 11 cases in 7 years. Besides the different underlying diseases, the only commonality is anticoagulation with warfarin. Therefore, I think it is appropriate to report the 10 cases under warfarin and call it what it is: a case series.

Reply 1: We have excluded the patient on Enoxaparin and have made the necessary revisions to our manuscript to reflect this change, including the abstract (Lines 33-34 and 41-45), manuscript (Lines 105-107 and 126-170), and Tables 1, 2, and 3.

Comment 2:

Necessary adjustments:

- Changing the title to "Case Series".

Reply 2: We have changed the title as follows: Bleeding and Thrombotic Complications Associated with Anticoagulation Prior to Lung Transplantation: A Case Series. Please see these revisions on Lines 1-2.

Comment 3: Create a table listing all 10 cases and detailing coagulation before reversal, coagulation after reversal, coagulation at start of TPL, coagulation at end of TPL. Under coagulation, all useful and collected parameters can be mentioned (for example INR, platelets, partial thrombin time, factors V and XIII, fibrinogen, Rotem analyses, ACT, hep. ACT, etc.)

Reply 3: Thank you for this comment. We have revised Table 2 in our manuscript to include additional parameters for each patient, such as admission coagulation laboratory values (INR, PTT, Hematocrit, Platelets), post-reversal INR, intraoperative labs at the beginning and end of transplantation, as well as ACT values (when available). Rotem analyses and coagulation factor levels are not usually obtained at our institution. Please see these additions in Table 2 of our manuscript.

Comment 4: One important factor of bleeding frequency was not mentioned: the surgeon. Was it the same in all cases or different surgeons, also the experience level of the team should be mentioned.

Reply 4: Thank you for this important point. We do not believe that surgeon variability played a significant role in the outcomes of our study. All 10 cases in this series had two thoracic surgery attendings scrubbed in during transplantation, all with training and expertise in lung transplantation. Furthermore, the cases shared the same senior thoracic surgeons, each with at least 10 years in practice. We have included this point in our revised manuscript. Please see these additions on Lines 224-226.

Comment 5: Another factor is the time of day. Several large studies have shown the relationship between emergency surgery at night and bleeding frequency as opposed to daytime surgery. This factor should also be included in the study.

Reply 5: Indeed, several studies have demonstrated an association between nighttime surgery and adverse outcomes, including a report published by our own group (PMID 33065051). Thus, we try to delay nighttime surgery to daytime hours whenever possible. In our case series, the majority (8, 80%) of transplants were performed during daytime hours. However, the 2 patients who underwent nighttime transplantation both had inadequate INR reversal and experienced both bleeding and thrombotic complications. We feel it is important to consider delaying transplantation until daytime hours in these patients given the increased monitoring and interventions to achieve adequate INR reversal preoperatively, as well as their increased risk for excessive bleeding intraoperatively. We have included this point in the discussion of our revised manuscript and our proposed perioperative guideline. Additionally, we have included the surgical time of day for each patient in our revised Table 2. Please see these revisions in our Discussion on Lines 204-210 and in Table 2 and Figure 2 of our manuscript.

Comment 6: As a conclusion, the therapy of preoperative anticoagulation in these patients can be shown and a first recommendation based on which an appropriate guideline can be established.

Reply 6: Thank you for this point. Currently, not enough evidence exists to support the use of certain AC agents over others in these patients, but future investigation is warranted in this area. For patients taking warfarin who are called in for lung transplantation, we have created a perioperative guideline for management strategies to ensure prompt reversal and reinitiation. Please see Figure 2 for these additions.

Reviewer B

Comment 1: The patient treated with lovenox prior to lung transplantation did not receive reversal. This may skew data to suggest increase in bleeding complications overall. Should this patient be included in the study group?

Reply 1: We have excluded the patient on Enoxaparin and have made the necessary revisions to our manuscript to reflect this change, including the abstract (Lines 33-34 and 41-45), manuscript (Lines 105-107 and 126-170), and Tables 1, 2, and 3.

Comment 2: Would be interesting to see breakdown of bleeding/thrombosis complications based on type of reversal

Reply 2: We have added details regarding the type and dose of reversal administered to each patient, as well as the subsequent bleeding and thrombotic complications in our revised Table 2. We did note that both patients within our case series who developed fatal thrombotic complications received PCC perioperatively, which we describe in our manuscript on Lines 188-189. Otherwise, we found no notable associations between bleeding/thrombotic complications and type of reversal administered.

Reviewer C

As more complex patients are being listed for lung transplantation, events like this will be found, and a strategy to successfully and adequately manage these patients is needed.

Despite the author's extensive experience with lung transplantation, the problem analyzed is infrequent, even in experienced hands. Hence, an appraisal of their single-center results is important for the transplant professional who may face this critical situation occasionally.

Comment 1: Table 2 can be improved if you add more "columns" with relevant information for the general reader. For example: which patient required CPB or ECMO? Any patients required MCS postoperatively?

Reply 1: We have revised Table 2 in our manuscript to include additional columns with relevant information, including which patients required CPB or ECMO during transplantation. None of the patients in our series required mechanical circulatory support postoperatively. Please see these additions in Table 2 of our manuscript.

Comment 2: Following the same line of thinking, if you have the data, it would be helpful to understand which patients had PGD 3 at 72 h? What is your survival? We understand this is not your main point, but for the reader or the Tx surgeon who faces a dilemma like this, it is important to have an idea about survival. Based on your experience, is it worth performing these transplants? In your experience, was there any combination that was more "critical" concerning outcomes? If the authors believe that our suggestion makes sense, this table can be enriched with valuable information.

Reply 2: Thank you for these comments. None of the patients in our study developed PGD 3 at 72 hours. Excluding the 2 patients who suffered early mortality due to thrombotic complications (patients 7 and 10 in Table 2), the posttransplant survival for all other patients exceeded 1 year.

Furthermore, the overall survival in these patients appears comparable to the general population after lung transplantation (see our added survival curve in Figure 1). Therefore, we believe it is worth performing these transplants and that favorable outcomes are feasible. However, posttransplant outcomes are highly dependent on adequate reversal of coagulopathy as well as proper re-initiation of anticoagulation. We have included these points in our revised manuscript. Please see these additions on Lines 144-146, as well as the added survival data in Table 2 and the survival curve in Figure 1.

Comment 3: In addition, if possible, you could link Table 3 to your Table 2 for the reader to understand the complications and their relations to the transplant demographics. Is a Tx under these conditions performed with CPB be more associated with thrombotic events, and if yes, which type? This is an example of a "line of events" that the authors can capitulate on, built on their expertise, and are essential for the reader.

Reply 3: We have revised Table 2 in our manuscript to include additional information for each patient to help give adequate context for the outcomes in each case. These details include which patients developed thrombotic events and required CPB or ECMO during transplantation. We did not appreciate an association between CPB and thrombotic events. Please see these additions in Table 2 of our manuscript.

Comment 4: As a suggestion, a survival curve could also be done if the authors judge appropriately for the reader to have a graphical idea of what happens to each patient. You have only 11 patients, so we suggest you explore this small population to give as many details as possible to the reader.

Reply 4: Thank you for this suggestion. We have added a survival curve, as well as revisions to describe the survival findings in our study. Please see these additions on Lines 144-146, as well as the added survival data in Table 2 and the added survival curve in Figure 1.

Comment 5: It would help the reader to understand, for example, among the 11 patients, the complications related (and the mortalities) were more common in the past? Or in recent years?

Reply 5: We have expanded Table 2 to describe the complications for each patient, as well as the year of their transplant. Overall, the distribution of cases were fairly consistent over time, with at least one patient who underwent transplantation each year between 2014 and 2020. We did not appreciate a significant difference in the rate of complications in recent years compared to those prior. Please see these additions on Lines 131-132 and in Table 2 of our manuscript.

Comment 6: In the author's experience, thrombotic complications were the ones associated with mortality, and interestingly, intracardiac thrombosis and acute mesenteric ischemia were the main issues here. Building on this information, can the authors recommend a strategy for managing these patients in greater detail?

Reply 6: Thank you for this comment. We have expanded our discussion to describe possible management strategies for these patients. Please see these revisions on Lines 173-181 and 192-210 as well as our added perioperative guideline in Figure 2.

Comment 7: Line 220: it would be interesting to hear from the authors what would be their suggestion for early resumption of AC therapy post tx.

Reply 7: Given the high risk of thrombotic complications observed, and their associated mortality within our series, we suggest resumption of AC therapy as early as clinically appropriate – preferably within 72 hours after chest closure. The reason for this being that patients rarely die from bleeding in this context – but we have observed a true risk of fatal thrombotic complications, and these patients are highly susceptible if therapeutic AC is not promptly restarted postoperatively. Notably, none of the patients in our case series had therapeutic AC restarted within 7 days after transplantation, and most did not have therapeutic AC prescribed at hospital discharge. We feel this is an important factor in overall mortality in these patients. We have added these points to our manuscript. Please see these revisions on Lines 173-181, Lines 192-210, as well as Figures 1 and 2.

Comment 8: Line 232: "presence of antiplatelet agents preoperatively," "cirrhosis or ESLD" are variables that, if identified among the 11 patients, could be added to a hypothetical table 2 based on our recommendations.

Reply 8: While these factors are important considerations, they were not present in any of the patients in our study. We have therefore removed this statement from our discussion. We have further expanded on considerations for managing these patients perioperatively, and have added potential management strategies. Please see these revisions on Lines 192-210 and Figure 2.

Comment 9: Finally, we believe the authors can be more assertive in their recommendations. As they mentioned, this is likely the most extensive series of patients under these specific conditions. Hence, based on what they learned, can the authors extrapolate potential strategies to, for example, indicate Tx in these patients, or how to manage intraoperatively, which surveillance strategy, AC strategy, and if any specific recommendations for complex issues like cardiac thrombosis, mesenteric ischemia are needed?

Reply 9: Thank you for this comment. We agree that the learning points gained from this small, yet valuable, cohort of patients should be applied to management strategies to minimize risks in the future. Thus, we have outlined considerations for preoperative, intraoperative, and postoperative management strategies in our discussion and an additional figure. Please see these additions on Lines 192-210 and Figure 2.

Comment 10: The authors reference list is incomplete. There is a large DVT study recently analyzed in lung transplantation which should be referenced. References 14 and 15 are fine, but incomplete.

Reply 10: We have added additional references which demonstrate the incidence and risk factors for DVT in lung transplant recipients. Please see these additions on Lines 71-79 and added references 1-2, 5, 7, and 10-12.

Reviewer D

This article, submitted by Ruben Nava and G. Alexander Patterson's Group at The Washington University School of Medicine in St. Louis Missouri addresses bleeding and thrombotic complications encountered in a cohort of their lung transplant patients who were anticoagulated prior to lung transplantation. I found no grammatical or spelling errors. The manuscript adheres to the JTD editorial and length requirements. The patients studied represent essentially all indications for lung transplant except Covid-19 lung complications. This is a single center, retrospective cohort study which received institutional approval. I have no questions for the Authors as the Methods, Results and Conclusions are clear and well described.