

Peer Review File

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Reviewer A

Thank you for the opportunity to review the manuscript “Time Since Primary Transplant and Poor Functional Status Predict Survival after Redo Lung Transplant”, which was submitted to the Journal of Thoracic Disease for consideration. Overall this was a nice analysis examining the relationship between time from primary to redo lung transplantation and survival with consideration to etiology of lung allograft failure. The authors demonstrated that there was a significant correlation between the length of time (most remarkably <1 year) between primary and redo lung transplantation and mortality. However, clarification of certain statements within the manuscript would be beneficial.

Line 35-36: “Worse survival after redo lung transplant (LTx) correlates with lower functional status”.

Please clarify this statement.

Reply: We clarified this statement by changing it as follows:

Changes in text: “In a previous study, lower functional status measured by Karnofsky Performance Status (KPS) correlated with worse survival after redo lung transplant.” (See Page 2, line 45-47)

Line 55: “These patients were more likely to require redo lung transplant due to primary graft failure or acute rejection”

Does this include all types of acute rejection (eg. ACR, AMR)?

Reply: This only includes primary graft dysfunction and acute cellular rejection. We have now clarified this in the text.

Changes in text: We clarified this in the text by changing “acute rejection” to “acute cellular rejection.” (See Page 3, line 74)

Line 56-60

Two separate sentences?

Reply: Thank you. We agree that this is best restated in two sentences.

Changes in text: A We changed this to “We categorized redo lung transplant recipients

in two distinct groups. One group has early allograft failure and poor functional status with a very poor prognosis after redo lung transplant. The other group has chronic allograft failure and overall better functional status have relatively better survival after redo lung transplant.” (See Page 3, line 76-80)

Line 86-89

Please clarify this statement.

Is this this study a comparison of:

1. Early allograft failure with poor functional status [to]
2. Chronic allograft failure with good functional status

If so, please clarify this point in lines 89-93 as the comparison is written to compare poor survival to improved functional status.

Reply: Thank you for this suggestion, we see how the current phrasing is unclear. We have changed this as follows:

Changes to text: “However, we hypothesize that early and late lung allograft failure present distinct clinical scenarios correlating with etiology of primary lung allograft failure and functional status before redo LTx. We predict that categorization of redo LTx patients by functional status and time from primary LTx reveals two distinct groups. One group with early allograft failure and poor functional status associated with very poor prognosis after redo LTx. The other group with chronic allograft failure and overall better functional status associated with better survival after redo LTx.” (See Page 6, line 126-133)

Line 103

Prevalence of what?

Reply: This is a great point. The prevalence of redo lung transplant is the answer, and we have now clarified this in the text.

Changes to text: “The SRTR database was used to define the prevalence of redo lung transplant, as well as survival and predictors of survival of patients undergoing redo LTx from 01/01/2005 and 9/1/2019.” (See Page 7, line 171-172)

Line 136-138

This is an excellent data point. Please clarify the time point the LAS score was calculated? Was it calculated prior to the first transplant or the redo transplant?

Reply: Thank you for pointing out this distinction. The LAS was calculated before the redo lung transplant. Changes were made in the text to clarify this.

Changes to text: “The lung allocation score (LAS) prior to redo lung transplant was

higher among patients requiring total assistance (mean 66.55+/-20.72) compared to those requiring some assistance (49.27+/-14.05) or no assistance (54.87+/-18.97) (Table 1, p<0.001).” (See Page 8, line 211-212)

Line 163-164

Please clarify

Reply: Thank you we have re-written this sentence for clarity as follows: “Redo lung transplant patients were divided into three groups according to functional status as determined by KPS. Then the number of redo lung transplants in each group was examined with respect to the time since the primary lung transplant.” (See Page 10, line 242-244)

Line 159-162

This statement has significant clinical implications to help support decision making during time of listing. A discussion of this point in the discussion section would be interesting.

Reply: Thank you for this suggestion. We have added the following paragraph in the discussion that addresses this statement.

Changes to text: “We found that redo lung transplant candidates requiring total assistance had significantly fewer days on the waitlist, consistent with the higher LAS values in this group. Also, redo lung transplant recipients who required total assistance also had a shorter time interval between the initial LTx and redo LTx compared to the other two groups. While salvage redo lung transplant for recipients with a high LAS and very poor functional status is certainly a readily available option, these redo lung recipients may not benefit from lung transplant to the same degree as primary lung transplant recipients with a similar LAS.” (See Page 13, line 325-333)

In summary, this is an interesting paper, however several issues need to be addressed and the manuscript needs to be revised for consideration for publication.

Reviewer B

The authors describe in their manuscript the relationship of time since primary lung transplantation and function status as predictors of survival after redo transplants. I have the following comments:

- 1) Provide the actual mortality in each of the 3 groups in Table 1
- 2) No lab values that reflect nutritional status are provided in table 1. Are these available in the SRTR database? for eg. albumin, pre albumin?

3)Table 4: has a missing 'n' value

Reply: Thank you for these suggestions. We have provided a separate table with mortality estimated for the three groups according to functional status. No lab values for albumin are provided because the SRTR database only has data for pre-transplant albumin for 57% of lung transplant recipients (it was apparently not required after 2015), and no data is recorded for pre-albumin in SRTR. We enlarged the textbox to show the N=22 for the Primary or Secondary LTx en-bloc or right lobar group.

Changes to text: The textbox to show the N=22 for the Primary or Secondary LTx en-bloc or right lobar group. (See Page 26, table 4)

Reviewer C

The authors demonstrated, using the national transplant data, that early mortality after retransplant was significantly associated with low physical status performance and short-term period from first lung transplantation. I have some comments as follows:

Comment: What is novelty of this study? According to a previous report from the registry of the International Society for Heart and Lung Transplantation (ISHLT), recipient illness of increased severity, including ICU hospitalization and requirement of mechanical ventilatory support at the time of transplantation, and retransplantation were significantly associated with mortality during first post-transplant.

Reply: Thank you for this question. The novelty of this study is that while the previous report only focused on the above stated factors (primarily functional status before redo lung transplant), we have found that this correlates with a clinical scenario of salvage lung transplant in patients with primary lung allograft failure or acute rejection and very poor functional status in the early time period after the first lung transplant. This is associated with very poor outcome after redo lung transplant. On the other hand, in patient who have chronic rejection and a higher functional status, typically more than one year post primary lung transplant, outcomes of redo lung transplant are much better. This is the novelty of the study, and this is outlined in the introduction, demonstrated in the results, and reviewed in the discussion.

Changes made to text: none. Please see above. This is proposed in the introduction, demonstrated in the results section, and analyzed extensively in the discussion section since it is the main point of the study.

Comment: I cannot understand the difference between the sentences in Results of Abstract (line 50-54): “Redo lung transplant survival was worse in the KPS 10-40% group....” and “Mortality was significantly higher for patients who underwent redo

lung transplant within one year of.....”.

Author response: This is an instance where two inter-related variables, lower KPS score and less time between primary and redo lung transplant, were both associated with decreased survival after redo lung transplant. This is mentioned succinctly in the abstract and expanded upon in more depth in the Results and Discussion.

Changes to text: none.

Comment: Please correct the word “primary” to “redo” (line178): if the primary LTx was done in the first year after the primary LTx (Figure 2D, $p<0.001$).

Author response: Thank you for noticing this error. It is now corrected.

Changes to text: the word “primary” is changed to “redo.” (See Page 10, line 261)

Comment: Why did the authors use quartiles to analyze the impact of time between transplants on survival on Figure 3? I think it is better to divide two groups ‘0-1 years’ and ‘>1year’ as shown in other analyses.

Reply: The use of quartiles was chosen in order to have balanced groups. The finding is still clear and relevant.

Changes in text: none.

Comment: I suggest that the authors should talk with a statistician for analyses in this study, especially for multivariable analysis in Table 3.

Reply: All statistical analyses were performed by a biostatistician who is the second author, Scott Jackson.

Reviewer D

Well performed study, despite the inherent limitations of a retrospective SRTR database analysis, with interesting findings relevant to the field. Methodology and Statistical analyses are OK.

Major comments: none

Minor comments:

- P6, line 105: August 30th should be 31th

Reply: Thank you for this correction.

Change to text: August 30th is changed to 31st. (See Page 7, line 175)

- P9, line 174: IN patients who required ...
- P9, line 177: However, IN patients requiring

Reply: Thank you for suggestion regarding syntax.

Change to text: “However, in patients requiring...” (See Page 10, line 245, 249)

- P9, line 192: chronic rejection: its shist mainly the CLAD phenotype of BOS (likely), or RAS (less likely)?, please add and comment, if possible.

Reply: The determination and classification of chronic rejection is made by the reporting center and may include both BOS and RAS definitions of chronic lung allograft dysfunction. These types are not distinguished in the SRTR database.

Changes to text: none.

- P11, line 236: please change: The authors used propensity score ...

Reply: Thank you for this suggestion.

Changes to text: “They used propensity score...” has been changed to “The authors used propensity score...”(See Page 13, line 336)

Reviewer E

Abstract

Background: I would say - Low functional status at the time of redo lung transplant correlates with worse survival. The functional status comes first.

Reply: Thank you. We have made this change.

Changes to text: “In previous studies, lower functional status measured by Karnofsky Performance Status (KPS) correlated with worse survival after redo lung transplant.” (See Page 2, line 45-47)

Results: Mortality was significantly higher for patients who underwent redo lung transplant within one year of primary transplant when KPS was 10- 40% (p<0.001),

these patients were more likely to require redo lung transplant due to primary graft failure or acute rejection.

Shouldn't this be 2 sentences?

Reply: Thank you. We agree that this is best restated in two sentences.

Changes in text: "Mortality was significantly higher for patients who underwent redo lung transplant within one year of primary transplant when KPS was 10-40% ($p < 0.001$). These patients were more likely to require redo lung transplant due to primary graft failure or acute cellular rejection." (See Page 3, line 71-72)

Conclusion: Awkward 1st sentence. Functional status and time from transplant are good predictors of outcome?

Reply: We can see how this sentence is unclear.

Changes to text: "Functional status and time from primary lung transplant are strong predictors of outcome after redo lung transplant. We categorized redo lung transplant recipients in two distinct groups. One group has early allograft failure and poor functional status with a very poor prognosis after redo lung transplant. The other group has chronic allograft failure and overall better functional status have relatively better survival after redo lung transplant." (See Page 3, line 75-80)

Put the 1-year survival for the salvage redo and primary allograft failure or acute rejection rather than dismal prognosis.

Reply: We agree with this clarification.

Changes to text: "Salvage redo lung transplant for primary allograft failure or acute rejection is associated with low one year survival." (See Page 3-4, line 80, 94-95)

Intro:

Lines 68-70 – Awkward sentence. Of course early and late graft failure lead to M&M, what's your point?

Reply: We agree that this was somewhat awkward and we changed "or" to "and" for optimal syntax. The point of the sentence is to bring the purpose of the study into focus. While many other clinical events such as surgical complications and infections also lead to significant morbidity and mortality after lung transplant, the present study focuses on complications leading to early or late lung allograft failure that might be treated with redo lung transplant.

Changes to text: “However, early graft failure due to primary graft dysfunction [3] or acute cellular rejection [4] and late graft failure due to chronic lung allograft dysfunction [5] both lead to significant morbidity and mortality after LTx.” (See Page 5, line 105-108)

Your paper is very similar to the paper reference #6.

Reply: The present study uses reference #6 as a starting point, but our study delves further into the clinical scenario surrounding the categorization of functional status. The recognition of time between the primary and redo lung transplant, as well as the etiology of failure of the primary lung allograft as predictors of outcome after redo lung transplant was not discussed in reference #6 or any other previous publication in the medical literature.

Changes to text: none.

However, we hypothesize that early and late lung allograft failure present distinct clinical scenarios correlating with etiology of primary lung allograft failure, functional status before redo LTx, and directed toward disparate clinical trajectories.

This is a really convoluted sentence. What are you trying to say?

Reply: This is a valid criticism and the sentence has been rephrased similar to the suggestion but the reviewer.

Changes to text: “However, we hypothesize that early and late lung allograft failure present distinct clinical scenarios correlating with etiology of primary lung allograft failure and functional status before redo LTx. We predict that categorization of redo LTx patients by functional status and time from primary LTx reveals two distinct groups. One group with early allograft failure and poor functional status associated with very poor prognosis after redo LTx. The other group with chronic allograft failure and overall better functional status associated with better survival after redo LTx.” (See Page 6, line 126-133)

Couldn't you just categorize them by time? Early allograft failure vs chronic rejection? Functional status probably poor in the first and variable in the second – my hypothesis.

Reply: We did also categorize the groups according to time from the primary lung transplant and these findings are portrayed in Figure 3. The hypothesis of early allograft failure versus chronic rejection predicting outcome after redo lung transplant is worth investigating but beyond the scope of the present study.]

Changes to text: None

Figures:

#1: nice illustration showing time and number of redo txs.

#2A: I realize there are very few 80-100% but that survival line looks similar to the 10-40% survival. Was is really sig different between the 2?

Reply: For the difference in the estimated survival curves between these two groups, $p < 0.001$, consistent with a statistically significant difference.

Changes to text: none.

2D: Time 0 represents what? Peri-op mortality? What do the two numbers at the bottom mean? # at risk and # surviving? What is the exact 1 year survival? Can you include the numbers for 1 year?

Reply: Time 0 is the time of redo lung transplant. The number at the bottom are at risk (below) and surviving (above) at each time point. The exact one year survival for each group is provided in a separate table.

Changes to text: none.

Figure 3: Interesting

Figure 4: How do you have primary non-function after 1 year? Is this just database labeling error? Same thing for acute rejection. Same thing for chronic rejection before 1 year.

Reply: It is conceivable to have a patient who has primary non-function and remains ventilator dependent for over 1 year after primary lung transplant. It is impossible to know if this is a database labelling error without contacting the transplant center and reviewing each case individually. This is a limitation of the SRTR database. Similarly, chronic rejection could conceivably occur near the end of the first year after the primary lung transplant. Whether this is a database labelling error or a misdiagnosis by the transplant center team is impossible to discern without reviewing the individual cases. This also is a limitation of the SRTR database.

Changes to text: none.

From figure 1, I thought a larger proportion of redo transplants were done within the first year. Only 200 out of 700?

Reply: Looking at Figure 1, one bar corresponds to a three-month period, and adding up the number of redo lung transplants in the first 4 bars for each KPS group, the total is about 200. Nearly 80 redo lung transplants were performed in the first 3 months after primary lung transplant in the patients with the lowest functional status.

Changes to text: none.

Figure 5: Are they all statistically different from each other? Acute rejection and primary non-function cross twice.

Reply: "We performed BH-adjusted pairwise comparisons of survival following re-transplant based on cause of first lung transplant failure. We found no difference between chronic and acute rejection ($p=0.083$) or between primary non-function and acute rejection ($p=0.465$). Survival for the chronic rejection group was significantly better than those whose first lung failed due to primary non-function ($p<0.001$)."

Changes to text: none

Figure 6: Interesting

Reply: We agree that this is interesting.

Changes to text: none.

Discussion:

Lines 222 – 231: How can you say the primary allograft failure or acute rejection was the more common situation? 200/700 were done in the first year. This is a good theory but your data doesn't support it because Figure 4 doesn't make any sense.

Reply: We agree that this statement in the discussion is unclear, and we have rephrased it to clarify the point illustrated by Figure 4. The figure demonstrates objective data obtained from the SRTR database, and whether or not the reviewer believes that the data "makes sense," it does in fact exist. As authors, we have offered our interpretation of the objective.

Changes to text: "In the first year after primary LTx, the most common indication for redo LTx was primary allograft failure, and these patients were more likely to have low functional status, to remain hospitalized until redo LTx, and to require mechanical ventilation or bridging with ECMO. These patients had significantly higher early postoperative mortality after redo LTx. Patients who underwent redo LTx greater than one year after the primary LTx were more likely to be discharged after the primary LTx, have chronic rejection, and only require some assistance prior to redo LTx. This latter scenario was associated with better survival, albeit lower survival than after primary LTx." (See Page 12, line 317-325)

Lines 238-240: I don't understand this sentence. "redo LTx recipients would reflect the propensity matching in that study are exceedingly rare"

Reply: We agree this was phrased in a confusing manner, and the sentence has been re-phrased.

Changes to text: “However, the present study suggests that in the past decade, redo LTx recipients greater than a year out from primary LTx with chronic rejection reflecting the propensity matched population in by Shuhauber *et al.* are exceedingly rare. In recent years, the vast majority of redo LTx have required some or total assistance.” (See Page 13, line 337-340)

I agree that redo lung transplants do worse despite what a propensity score may say.

Line 245: what common rule?

Reply: This is a misnomer. It is actually the OPTN Final Rule. The National Organ Transplant Act ("NOTA") created the OPTN and gave the initial guidance regarding the development of organ allocation policies. The Secretary of HHS promulgated regulations for the operation of the OPTN, which operationalized the requirements contained in NOTA ("OPTN Final Rule"). The OPTN Final Rule contains the regulatory requirements for the OPTN.

Changes to text: “This assessment should include the time from primary LTx, cause of lung allograft failure, and functional status in redo LTx candidates in accordance with the fundamental ethical principles of utility and justice pertaining to the OPTN Final Rule (reference).” (See Page 14, line 363-366)

Reference: <https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethical-principles-in-the-allocation-of-human-organs/>

Line 263-265: reference 6 looked at this and found more total assist preop led to more postop.

Reply: Yes, this was published previously by Kilic *et al.*, and we have added to the discussion in the present study.

Changes to text: “However, most patients who undergo redo LTx occur in the early period after primary lung transplant require total assistance before the redo LTx and still require total assistance preoperatively. (See Page 14, line 368-371)

Lines 281-283: debatable. A >50% mortality rate for a hugely resource intensive operation is not a good outcome.

Reply: We agree, and we believe that the present study demonstrates this point.

Change to text: none.

Conclusion: Was your hypothesis met or disproved?

Reply: We hypothesized that early and late lung allograft failure present distinct clinical scenarios correlating with etiology of primary lung allograft failure and functional status before redo LTx. We predicted that categorization of redo LTx patients by functional status and time from primary LTx would reveal two distinct groups of lung graft failure with disparate clinical trajectories after redo LTx. One group with early allograft failure and poor functional status has a very poor prognosis after redo LTx, and the other group with chronic allograft failure and overall better functional status has better survival after redo LTx. We believe that the present study confirms this hypothesis.

Changes to text: We removed the following sentences from the conclusion: “This study examined a national cohort to investigate the impact of preoperative functional status on outcomes of redo LTx recipients. The data suggest that several patient specific characteristics, including preoperative KPS score, time since primary LTx, and etiology of allograft failure after the primary LTx are strong predictors of early mortality after redo LTx. Redo LTx within one year of primary LTx carries significantly increased risk of death, especially with lower functional status.”

We replaced this sentence with: “We confirmed our hypothesis that early and late lung allograft failure present distinct clinical scenarios correlating with etiology of primary lung allograft failure and functional status before redo LTx. We found that categorization of redo LTx patients by functional status and time from primary LTx reveals two distinct groups of lung graft failure with disparate clinical trajectories after redo LTx. One group with early allograft failure and poor functional status has a very poor prognosis after redo LTx, and the other group with chronic allograft failure and overall better functional status has better survival after redo LTx. (See Page 16, line 425-432)

Etiology of failure seems to split between chronic and acute which relates to timing of failure.

Put the 1-year survival rate for the worse group. Would suggest maybe we shouldn't re-transplant that group.

Reply: We agree with these statements and this would be suitable for an editorial commenting on the present study.

Changes to text: none

Reviewer F

1. The biggest caveat to the study is not inclusion of KPS scores, as functional status

carries with it a lot of observer bias

Reply: Use of KPS scores is a limitation of the study. This has been added to the limitations portion of the manuscript.

Changes to text: “Another limitation to the study is the use of KPS scores that are subject to inherent observer bias.”

Changes to text: none.

2. This study carries over the earlier published study with a data time period before this (LAS scores carry more weightage as well), thus more relevant in current day and time of transplantation with evolving services including ECMO as a bridge to transplantation, many missing variables including SRTR data can skew the study results

Reply: We agree that the present study provides updated relevant data regarding the practice of redo LTx.

Changes to text: none.

3. The authors overall have done justice to correcting as many statistical points a possible

Reply: Thank you, we have meticulously addressed all of the concerns with the statistical analysis.

Changes to text: none.

4. Authors have been able clearly state and follow the hypothesis of the manuscript Impactful in lung allocation matching the demand supply ratio for lungs

Reply: Thank you, we had a clearly stated hypothesis, and the findings support that hypothesis.

Changes to text: none.

Reviewer G

This is a well done study on an important subject matter in lung transplantation. It demonstrates that redo lung transplantation in patients with short survival interval since primary lung transplant and poor functional status predicts poor survival after

redo lung transplant. Although their results seem somewhat predictable to some of us, it seems the concept is not completely accepted in general practice. As their data would suggest, there remains a significant number of redo transplants being performed under these unfavorable circumstances. It would be interesting to get a better idea whether this practice is improving over time. I would suggest one additional data demonstration: The authors do a nice job demonstrating redo trends over the years based on KPS scores in figure 6. It would be helpful if they would show a similar graph demonstrating the trends over the study period (2005-2019) showing the variable of time since primary transplant (<1 yr vs >1r) or perhaps even the variables of indication for redo (PGD, acute rejection, chronic rejection, other) vs year within the study period. This would give an idea of whether our practices are improving in terms of redo recipient selection. Overall, I think this is an important contribution to the literature on the subject of redo lung transplantation.

Reply: Thank you, these are important points. We have addressed these points by adding two additional figures (Figure 7 and 8).

Changes to text: Figure legends 7 and 8 (See page 20, line 554-563). Figure 7 and 8 were added at the end of manuscript and as separate files.

Reviewer H

The authors are trying to investigate the outcomes for redo transplant in this study, focusing on timing and functional status. However, there are multiple issues in this study.

In terms of the functional status, in the group with KPS 10-40%, 40% of patients have been on mechanical ventilation and 17.3% on ECMO. This population generally has the worst outcome whether redo or not. I think that functional status is just one surrogate marker for these situations, ventilator or ECMO dependence. In this study, it is not clear if the functional status is a strong independent factor regardless of ventilator/ECMO status, and the negative effect of the functional status is applied just for redo patients.

Reply: Thank you, that is an interesting point of discussion. The present study built on previous work examining functional status and outcomes after redo lung transplant. We found that the time since primary lung transplant and the indication for redo LTx are strong predictors of survival after redo lung transplant. We did note an association of worse functional status with mechanical ventilation and ECMO, but we did not examine mechanical ventilation and ECMO as independent predictors of outcomes after redo LTx. The present study cannot exhaustively examine every single possible predictor of survival after redo LTx. Perhaps, a separate study could examine the

relationship of mechanical ventilation and ECMO with outcomes after redo LTx.

Changes to text: none.

Moreover, the early vs late redo transplant outcome has already been studied and published by the other groups. It is not sure that there are any novel findings in this study to answer clinical questions to improve transplant outcomes in the current practice.

Reply: The relationship between time from primary lung transplant to redo lung transplant has not been published recently.

Changes to text: none.

There are multiple periods from primary transplant where the authors classified patients into: 6months, 9 months, 1 year, 24 months... Are there any premises to split the periods in those multiple different ways? The different cutoff line in each table makes the message from this study incoherent.

Reply: This comment was addressed by a previous reviewer. The decision to examine survival in the time periods in Figure 3 was made in order to divide the groups evenly. The basic point is the same but this allows for sounds statistical analysis.

Changes to text: none.