Peer Review File
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Reviewer A

Comment 1: This is an interesting study, demonstrating risk and beneficial factors influencing 20+ years survival after lung transplantation. The aims are clear, very well written and interpreted. The authors should be congratulated for this interesting study.

I have no real comments, as all my possible questions are indeed tackled in the discussion section/limitations of the paper

Reply 1: Thank you for your thoughtful consideration of our work.
Changes in the text: None.

Reviewer B

Comment 1: Overall**:** This is a retrospective analysis of the UNOS database seeking to identify factors positively and negatively associated with 10-year + or 20-year + patient survival following lung transplant. Overall, the analysis is informative as there is relatively little data in this area. The authors identify some interesting factors, like female-female recipient-donor matching, that are associated with greater long-term survival. However, the writing itself could use some improvement to make this a more compelling manuscript.

Abstract: The last sentence in the background section of the abstract is missing the word "transplant" after lung.

Reply 1: We agree with the reviewer and have modified the abstract as advised.
Changes in the text: "transplant" added (Page 2, Paragraph 1).

Comment 2: Introduction: In line 61, where you say "less is known about long-term factors" you should say something like "less is known about factors associated with long-term outcomes"

Reply 2: We agree with the reviewer and have modified the introduction as advised.
Changes in the text: This phrase has been clarified (Page 3, Paragraph 2).

Comment 3: The sentence starting at line 68 is confusing since you say there have been a paucity of significant changes to lung transplant since 1987 then proceed to list out several significant changes. It weakens the argument that you can group all these long-term survivors together rather than having to account to when the transplant was performed as a confounding variable.

Reply 3: We agree that the framing here is confusing. We believe that an inclusion of the major changes is relevant to the reader's understanding of the context of our findings, so we have removed "paucity of significant changes" so as to avoid minimizing these changes.
Changes in the text: Beginning of the sentence has been rewritten (Page 3, Paragraph 3).

Comment 4: Methods: In line 88, you should say multi-organ transplant because I am assuming you mean that you're excluding patients that received heart-lung, lung-kidney, etc. transplant rather than those that received multivisceral transplant.
Reply 4: We did intend to mean exclusion of patients receiving multi-organ transplant. The Methods have been revised accordingly.
Changes in the text: "multivisceral" changed to "multi-organ" (Page 4, Paragraph 3).

Comment 5: In line 107 where you discuss treatment of continuous variables for your Cox regression, it would be helpful to specify which ones were categorized based on the author's discretion. Further, for those variables, was categorization based on the literature in anyway or totally arbitrary?
Reply 5: We agree with the reviewer, and stratification for each continuous variable has been specifically clarified in the Methods. The only variable categorized entirely based on the authors' arbitrary discretion was waitlist time, which we stratified by choosing round number cutoffs close to the mean/median and interquartile range.
Changes in the text: Stratification for each continuous variable has been clarified in the Methods (Page 5, Paragraph 4).

Comment 6: Results: The sentence starting at line 139 is worded confusingly. It would be improved if you worded it something like this: "Importantly, these similarities between cohorts largely extended to post-transplant outcomes, with no significant differences in hospital length of stay, post-transplant complications, or recipient cause of death. However, 20+ year survivors were slightly more likely to have renal failure as a cause of death (7.0% vs. 3.3%, P=.007)."
Reply 6: The reviewer makes a good suggestion. We have revised this sentence accordingly.
Changes in the text: This sentence has been rephrased as per the reviewer's suggestion (Page 7, Paragraph 2).

Comment 7: In the multivariable analysis, I don't think it is helpful to right out every single factor that was significant. I would instead list the ones you think are the most important specifically and then summarize the others. It will aid with the readability of this section.
Reply 7: This is a good suggestion by the reviewer to improve the legibility of the Results. The *Multivariable Analysis* section has been reorganized accordingly, listing out only the most important factors specifically and listing them first.
Changes in the text: The Results have been revised accordingly (Page 7, Paragraph 3; Page 8, Paragraph 1).

Comment 8: For tables 2 and 3, it would be more legible if you included a section head for each variable then indented prior to listing the individual categories within that variable. For example: Age 18-25 25-35 Etc. For tables 2 and 3, it would also be helpful to include the reference category for each of the variables where it is relevant.
Reply 8: These suggestions much improved the tables' readability. Section headings have been inserted for variables with multiple categories, and reference categories have been

clarified for variables that required forcing a reference category on multivariable analysis.
Changes in the text: The Tables have been updated accordingly (Tables 2 and 3).

Comment 9: Figure 1 is not really very informative. I would exclude it in favor of just showing the KM curves for specific factors.
Reply 9: This is a good suggestion. The former figure 1 has been replaced with KM curves for the gender-match cohorts, which we thought was more valuable to represent visually.
Changes in the text: The original figure 1 has been excluded in exchange for KM curves for a specific factor (Figure 1).

Comment 10: Discussion: In general, this discussion could be condensed and many of the sentences could be simplified. In line 175, I don't think it is correct to say this paper looked perioperative risk factors specifically since the only one that was really discussed was ischemic time.
Reply 10: The Discussion has been condensed and simplified wherever possible using the feedback from this reviewer and others. The use of the word "perioperative" in the context of this paper's findings has been removed from line 175, along with from the introduction.
Changes in the text: "perioperative" removed (Page 3, Paragraph 2; Page 9, Paragraph 1).

Comment 11: The sentence starting at line 181 is not very clear. I also don't think you have any evidence to say that things like changes to the allocation system and immunosuppression had no impact on any of the variables you used in your regression model.
Reply 11: This sentence has been clarified by removing the claim that the LAS, immunosuppressive agents, and other changes did not impact our statistical model. The main idea of the sentence has been simplified into an expansion of the previous sentence's comment on generalizability and a better transition to the following sentence.
Changes in the text: Sentence starting at line 181 rephrased (Page 9, Paragraph 1).

Comment 12: The sentence at line 200 is an example of one that would be greatly improved with simplification and just saying that patients with COPD/E were less likely to have 20+ year survival.
Reply 12: This sentence has been simplified according to the reviewer's suggestion.
Changes in the text: Sentence starting at line 200 simplified (Page 10, Paragraph 1).

Comment 13: For the sentence at 204, you don't provide any evidence that the improvement in survival for the 20+ year cohort was due to delaying CLAD onset. I would exclude it since you did not look at that specifically.
Reply 13: We agree with the reviewer, and this phrase has been excluded.
Changes in the text: "potentially by delaying CLAD onset has been deleted (Page 10, Paragraph 1).

Reviewer C

Comment 1: Thank you for the opportunity to review the manuscript "20 Year Survival Following Lung Transplantation" which was submitted to the Journal of Thoracic Disease for consideration. Overall this was a well designed analysis examining the outcomes for survivors of lung transplantation comparing those who survived 1-20 years to 20+ years. This well designed retrospective analysis of lung transplant recipients listed in the UNOS database is an important addition to the lung transplantation literature and I believe it will bring further investigation to some important questions of how we decide appropriate candidates while being good stewards of the donor organs. The authors were clear and succinct in their description of the analysis. I look forward to the discussions this paper will bring to the table.

I have one suggestion in regards to the references. Within the Introduction, the first line describes the first successful lung transplantation survivor who lived over 1 year. The cited text is the references for the first human lung transplantation in 1963. Please consider adding the citation of the 1st lung transplant survival >1 year (Patterson, et al. 1988).
Reply 1: We appreciate this suggestion from the reviewer, and the citation has been added.
Changes in the text: Patterson, et al. reference added (Page 3, Paragraph 1).

Reviewer D

Comment 1: The authors have analyzed the UNOS database for long term survivors after lung transplantation. I have the following comments: 1)The authors should be congratulated on a well performed and well written study and manuscript!

2)What % of the recipients were on ECMO support? The table 1, under preiop characteristics lists life support: I am assuming this is intubation and mechanical ventilation?
Reply 1: Thank you for your review of our work. Among our sample size of 6,172, only 3 recipients (0.05%) were on ECMO support prior to transplantation. Because of this, we chose to use the UNOS binary variable encoding life support overall, which does include these ECMO patients but is comprised mostly of patients who were intubated and ventilated.
Changes in the text: None.

Reviewer E

Comment 1: This is an important study looking to better understand predictors of long-term outcomes after transplantation. There are many challenges with this type of study and the authors have done a good job accounting for these aspects in their study. The overall conclusions of this work are not entirely surprising and while some findings are interesting, not clinically translatable as described. However, the findings described by this study would be of interest to the transplant community.

My major concern is regarding focusing on all-cause mortality instead of graft-failure/related mortality. Possible subgroup analyses looking at various recipient COD (i.e., graft vs. non-graft) would be helpful to parse out lung-specific factors. Alternatively, I would suggest propensity score matching (survivors and non-survivors) to better understand which features are predictive.

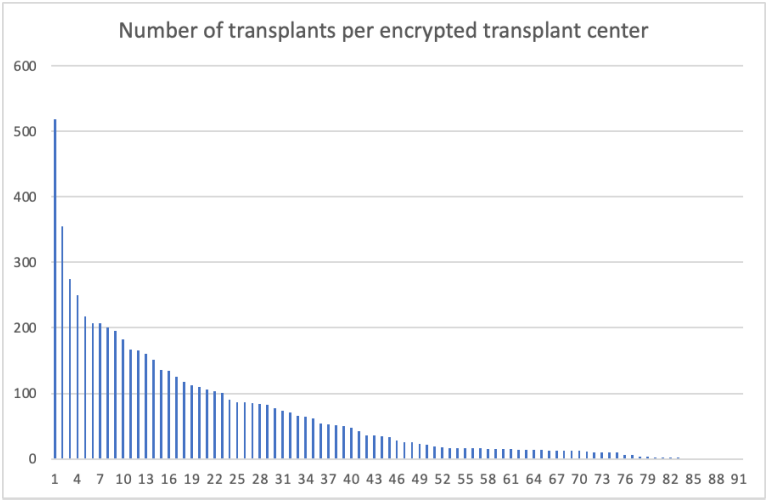
Reply 1: Thank you for your thorough and insightful review of our study. The reviewer makes a good suggestion here about our primary outcomes. To better assess which factors may be lung-specific, we have included two tables in the supplementary material. **Table S4** represents a subgroup analysis replicating our Table 1 for the 1-20-year survivors by cause of death and comparing the graft failure related mortality group to the non-graft group. Interestingly, patients with COD due to a graft cause were more likely to be slightly younger and to have received a bilateral transplant. Because this subgroup analysis exhibited a paucity of significant factors, we also repeated our multivariate models with graft survival, which is a measure by UNOS that incorporates both graft failure and mortality (**Table S3**). Significant factors remained largely the same for graft survival, with HLA mismatch level and donor smoking history becoming significant at 10 years.

Though we considered propensity score matching as you suggested, we ultimately decided that because our outcome of interest would be mortality-related (either all-cause mortality, graft survival, or cause of death), it did not make sense to us to propensity match two groups (20-year survivors and non-survivors) whose delineation was defined by the outcome of interest itself. We did, however, utilize propensity score matching for additional analyses of other factors per your recommendations.

Changes in the text: These analyses have been added to the supplemental materials and cited in the text (Page 6, Paragraph 1).

Comment 2: Can the authors provide any information of participating centers and the degree to which the data is appropriately poolable for this study?

Reply 2: There were 91 participating centers in total. Mean ± SD number of transplants per center = 67.8 ± 87.3. Median [IQR] number of transplants per center = 28 [13-95.5]. Maximum transplants was 518 and minimum was 1. A plot of the number of transplants per center is included below:



As an evaluation of poolability, we forced inclusion of the encrypted center codes as a categorical variable into our Cox regression model to account for inter-center variability. Our most important factors remained significant, including: recipient age, diagnosis of COPD, waitlist time, donor cause of death, donor smoking history, female-to-female gender matching, HLA mismatch, and single lung transplant. Because inter-center variability showed minimal influence on our model, we believe our results remain effectively poolable even with

a smaller sample size than some other UNOS reviews.
Changes in the text: None.

Comment 3: The increased waitlist time and CIT in the 20+ survivors finding is surprising – please provide additional discussion on this topic. Additionally, a propensity matched cohort for severity, BLT, etc. would further clarify these observations.
Reply 3: We have expanded our discussion of both waitlist time and ischemia time. We speculated based on the literature that the significance of ischemia time reflected UNOS's recording an average of the ischemia times for both lungs in double transplants, but we appreciate the reviewer encouraging us to confirm this with our own analysis. Propensity matching for bilateral transplant alone between the 1-20 and 20+ year groups reduced 97.3% of the "bias," or difference, in ischemia time. The Student's T-test measuring differences in ischemia time between these groups became nonsignificant after matching ($P = .858$).

For waitlist time, matching for single lung and the closest surrogate for disease severity we could find in the UNOS database increased the bias / measurable difference in waitlist time between the 1-20 and 20+ year survivors. Thus, we believe our finding on waitlist time, while surprising, is a product of the old allocation method before the Lung Allocation Score. Patients with decreased comorbidity burden or disease severity would be more likely to live to a longer time on the waitlist, resulting in increased survival after transplant for this group. Our discussion has been expanded on this topic, and both sets of propensity score matching have been added to the supplemental materials.
Changes in the text: Propensity matching added in table S2, methods, results, discussion (Page 6, Paragraph 1; Page 8, Paragraph 3; Page 10, Paragraph 3).

Comment 4: Given that they study is limited to 2002 data for practical reasons, the authors should further speculate how more recent changes within lung transplant community would impact their findings. Could the authors look at more recent UNOS data to see the proportion of certain predictive features have changed (i.e., recipient age, sex matching) and speculate what this would mean in terms of suggested 20-year survival? Discussion would help to better understand which conclusions may still apply today and which are likely specific to the cohort studied.
Reply 4: The reviewer makes a good suggestion to further discuss the generalizability of our findings to a contemporary cohort.
Changes in the text: A paragraph comparing the predictive features of our cohort compared to today has been added to the end of the discussion (Page 12, Paragraph 2).

Comment 5: While 1-year censoring and 10-year mortality is important, suggest to include data on 5-year mortality as an additional benchmark/precursor to 20-year survival
Reply 5: The reviewer makes a good suggestion. 5-year mortality conditional to 1-year survival has been included in the supplemental materials, methods, and results.
Changes in the text: 5-year mortality added as table S1 (Page 5, Paragraph 3; Page 8, Paragraph 1).

Comment 6: Please clarify which continuous variables were stratified into categorical variables at the authors' discretion.
Reply 6: Stratification for each continuous variable has been specifically clarified in the Methods. The only variable categorized entirely based on the authors' arbitrary discretion was waitlist time, which we stratified by choosing round number cutoffs close to the mean/median and interquartile range.
Changes in the text: Stratification for each continuous variable has been clarified in the Methods (Page 5, Paragraph 4).

Comment 7: Please clarify whether recipient/donor sex or gender is analyzed and update throughout the manuscript
Reply 7: The variables as encoded in the UNOS database are listed as "gender," so we have updated our language to keep the manuscript consistent.
Changes in the text: All mentions of "sex" have been replaced with "gender" throughout the manuscript to standardize the language (changed throughout).

Comment 8: Findings related to female sex and sex-mismatch are very interesting. Suggest conducting some propensity score matching analysis to better understand this finding.
Reply 8: To solidify our finding on female-to-female gender matching, we conducted a subgroup analysis of female recipients. We propensity score matched two female recipient groups based on male vs female donor. Factors matched for included all factors significant in tables 1-3, plus donor height as a percentage of recipient height to account for size mismatch. Donor cause of death had to be excluded from our propensity score model due to inability to compute. After matching 1:1 without replacement, we repeated our multivariate Cox model with donor : recipient height and recipient cause of death included and assessed the risk associated with donor gender. Female-to-female gender matching exhibited a hazard ratio of 0.85 (0.77-0.94, P=.001) compared to male-to-female gender matching.
Changes in the text: This additional analysis has been added to the supplemental materials, methods, results, and discussion. (Table S2b; Page 6, Paragraph 1; Page 8, Paragraph 3; Page 11, Paragraph 2).

Comment 9: The LAS concerns are important, but adequately addressed in the discussion. Is there any data regarding CLAD (RAS/BOS) and/or FEV1 over time? This would be important information to include in this study.
Reply 9: We agree that both data points would be important outcomes to include in a study like this. Regrettably, UNOS does not currently collect either CLAD or FEV1 as a part of follow-up data over time, though we believe they are planning to include CLAD as an outcome variable soon.
Changes in the text: None.

Reviewer F

Comment 1: Thanks for your thorough review. When reviewing the diagnosis at time of

listing, I didn't see pulmonary hypertension, which along with cystic fibrosis has the best long-term survival. Also wonder if we will do fewer younger patients with CF/PH with improvement in medical therapies over the last 20+ years.
Reply 1: We originally included only the four most represented diagnoses, the reviewer makes a good suggestion to include pulmonary hypertension, which still represents 4.8% of our cohort. Chi-square test indeed revealed increased proportion of patients with pulmonary hypertension living to 20 years; however, diagnosis of pulmonary hypertension was not significant on multivariate Cox regression at 20 or 10 years. Still, the tables, figures, and manuscript have been updated to include pulmonary hypertension.

With regards to trends: between 2015-2019, cystic fibrosis only represented 9.7% of transplants (versus 13.7% in our study period), while pulmonary hypertension represented 2.6% (versus 4.8% in our study period). While we cannot comment on trends in the proportion of all CF/PH patients who go on to receive transplants, these statistics demonstrate that the overall proportion of transplants represented by these two diagnoses has decreased, likely due to improvements in medical therapies, as you say.
Changes in the text: Diagnosis updated to include pulmonary hypertension (Tables 1-3, Figure 4, Page 6 Paragraphs 2 & 3).

Comment 2: I would also be interested in seeing more information regarding female donor to female recipient, and if this would warrant an adjustment to the Lung Allocation Score.
Reply 2: Because the LAS is calculated using recipient factors alone to then assign allocation priority for donor matching, it is unlikely that our findings on female-to-female matching would warrant an alteration to the LAS. We still consider this to be an important finding and have expanded our analysis using propensity score matching at another reviewer's request.
Changes in the text: Propensity score matching for female recipients is included in the supplemental materials, results, and discussion (table S2; Page 6, paragraph 1; Page 8, Paragraph 3; Page 11, Paragraph 2).

Comment 3: As the lung transplant community moves towards older patients with ILD (and more single lungs in the NE USA, i would expect longer-term survival to decline. Your study may be applicable to a small subgroup of patients, but important for these younger patients to have hope for a longer survival than what the registry data suggests. thank you
Reply 3: The reviewer makes a very important point here about preserving hope for patients. Part of our intentions with this analysis was to inform patients that long-term survival is indeed possible with any diagnosis, and we believe our data particularly gives those younger patients hope given that they fare the best. We also agree that an increase in single lung transplants will reduce long-term survival, and we hope that our long-term results conditional to short-term survival will emphasize the lasting consequences of a single lung.
Changes in the text: None.

Reviewer G

Comment 1: The authors are to be congratulated on this poignant and instructive study on

factors associated with long term (20+ year) survival of lung transplant recipients in the UNOS database. Despite the limitations inherent in a study which spans 2 decades, the authors have made several novel observations regarding factors associated with long term survival. I recommend acceptance based on the purpose, methods and results of the study which are all fairly clear. One might quibble with the statistical methods of the study where all patients from surviving 1-20 years postoperatively were group together and compared to the few surviving 20+ years, but the findings are still relevant and informative. It is not a surprise that there are very few 20+ year survivors with IPF who received a single lung at age 60 (maybe none?), and a previous study discussed by the authors examined these types of scenarios with respect to single versus double lung transplant. The authors appropriately mention this in the discussion.
Reply 1: Thank you for your thoughtful critique of our work. We found your suggestions with regards to the style of the discussion to be incredibly useful for improving the strength of the manuscript, and we hope you find the changes amenable.
Changes in the text: See Comment 2.

Comment 2: The main criticism pertains to the syntax, phrasing and style of the discussion section. While the Background, Methods, and Results are written in clear, formal, and objective scientific writing style, the Discussion section has a jocular and casual tone with multiple syntax errors. This needs to be re-written before the manuscript can be accepted for publication. Each paragraph should have a brief introductory sentence introducing the topic of the paragraph, followed by a series or supportive statement. Then a conclusion statement should summarize the argument of the paragraph. There are currently some run-no sentences that are very difficult to comprehend. For example, in lines 177-181, the authors state: "Examining early UNOS entries may be scrutinized due to the changes in LTx since 1987—bilateral LTx (1988), bronchial anastomosis (1990), tacrolimus (1994), LAS (2005), DCD (2012), and EVLP. The main alteration here limiting our results' generalizability to a contemporary cohort is the LAS, which initiated allocation based on estimated urgency and utility rather than waitlist time." These are very confusing sentences. I would re-write this along these lines: "Significant changes in LTX have occurred since 1987, and these changes must be considered when utilizing the UNOS database. Relevant changes since 1987 include bilateral LTx (1988), the technique of bronchial anastomosis (1990), treatment with tacrolimus (1994), allocation using the LAS (2005), utilization of DCD donors (2012), and use of EVLP. Possibly the most significant change that limits the generalizability of our results to a contemporary cohort is the LAS, which initiated allocation based on estimated urgency and utility rather than waitlist time." Lines 181-184 and lines 187-190 and lines 200-202 are also confusing. Lines 181-184 is a spectacularly confusing run-on sentence. The lungs (line 188) and results (line 180) are not sovereign entities that possess anything in scientific writing (lung's and result's). "Immunologic specifics" is a strange, vague term that I am not familiar with. Line 224-227: "While universal bilateral LTx would unfortunately reduce the number of available organs for waitlisted patients, our analysis demonstrates that a double lung yields a superior individual longevity that is particularly evident in the long-term." This phrasing is redundant--of course superior individual longevity is particularly evident in the long-term." Line 256: "But be it histocompatibility antigens, " is a dependent

clause, and starting a sentence with a dependent clause it is not acceptable in formal writing. Basically, I am not an editor or an English major, but you need to either figure this out or have an editor help you re-write it. As it stands, the discussion undermines the valuable substance of the paper. The points are valid and interesting, but it has to be re-written in a formal, scientific style.
Reply 2: The reviewer raises multiple valid concerns regarding the discussion. Each location where a word, line, or sentence was specifically referenced as confusing, redundant, or inappropriate has been altered accordingly. The discussion as a whole was then reorganized into a more logical paragraph structure. Many sentences were re-worded to make the language and style more straightforward. Run-ons and sentences that begin with lengthy dependent clauses were rephrased wherever possible.
Changes in the text: The discussion has been revised in its entirety.

Comment 3: On an immunologic note, it is unexpected that the combination of female donor to male recipient has the worst long term survival because the Y chromosome antigens are on the male recipient. A female recipient might have alloreactivity against Y chromosome antigens on a male donor, but a male recipient (XY) would not be expected to have alloreactivity against female (XX) antigens.
Reply 3: We have expanded our analysis of gender matching. To clarify, female-to-male did not have the worst survival. By Kaplan-Meier analysis, it appears that female-to-female exhibits the best survival, while male-to-female exhibits the worst, while male recipients regardless of donor gender exhibited intermediate survival. This finding was clarified via propensity score matching followed by multivariable Cox regression including adjustment for estimated organ size. Our matched, adjusted analysis exhibited HR=0.85 for female-to-female compared to male-to-female. Thus, we believe this finding to be real and significant in the long term. As you indicate, a potential explanation for this finding is the alloreactivity of a female to Y chromosome antigens on an XY male donor.
Changes in the text: Change to Figure 1, addition of Table S2b, and additional discussion (Page 11, Paragraph 2).

Reviewer H

Comment 1: A novelty of this study is that the authors analyzed the protective factors for 20-year survival after lung transplantation, using the UNOS data. I have major comments as follows: Comment: This study cohort was transplanted between 1987 and 2002, which was too old, and the results were not so surprising and were consistent with the previous report on associated factors on 5- and 10-year survival.
Reply 1: Thank you for your review of our work. We agree that our results are largely consistent with previous studies, though we believe that censoring for 1-year mortality and extending analysis through two decades effectively isolates specific long-term factors in a unique way. Though the cohort was necessarily transplanted between 1987 and 2002 given our methods, we concede this as a limitation in the discussion.
Changes in the text: None.

Comment 2: Comment: The authors can assess the protective factors associated with longer survival. However, I am not sure whether they could assess risk factors associated with decreased 20-year survival, because 20-year survival seems to be enough longer survival after lung transplantation. This statistical analysis should be checked by a statistician.
Reply 2: We understand the reviewer's point that 20-year survival seems to be long enough after transplantation that risk may not be assessable. Our statistical analysis and its interpretation have been verified by all co-authors, and we believe it is valid. Just as a protective factor indicates increased likelihood of surviving to 20 years, a risk factor would be associated with decreased likelihood of surviving to 20 years. Additionally, because Cox regression evaluates time to event, with the event here being death prior to 20 years, our risk factors represent both increased likelihood and faster occurrence of death prior to 20 years.
Changes in the text: None.

Comment 3: Comment: Please simplify the Table 2 and 3.
Reply 3: Tables 2 and 3 have been simplified to the best of our ability by removing factors that were nonsignificant on univariable analysis that went unmentioned in the body of the manuscript. They have otherwise been made more legible per another reviewer's recommendation to add section headings to variables with multiple categories.
Changes in the text: Tables simplified as much as possible, while also incorporating feedback from other reviewers (Tables 2 and 3).

Reviewer I

Comment 1: Page 3, Line 68: The advances (LAS, tacrolimus, etc) listed are significant changes in lung transplant and lung transplant management. I don't think this negates all of the findings of the manuscript, but it does make it difficult to 1) generalize the findings across 20 years and 2) generalize findings to current state.

Discussion: Given LAS was implemented in 2005, all patients in this cohort were transplanted based on the time accrual system rather than urgency based - that greatly changes the applicability to current cohort of lung transplant recipients given substrate at time of transplant. The numbers of lung transplants are also now much higher and there has been significant evolution of the field and specialty. Lung transplant programs, practice patterns, and protocols have evolved significantly since this era.

Discussion, 185: long term survival does lag behind other SOT but is improving.
Reply 1: The reviewer makes an important point. This sentence has been altered to emphasize the continuous strides made in long-term lung transplant survival. Additionally, the concerns about generalizability are valid, and we have emphasized this limitation in the discussion.
Changes in the text: Sentence rephrased (Page 9, Paragraph 1; Page 12, Paragraph 4).

Comment 2: Discussion, 224: perhaps superior individual longevity but not necessarily overall life years gained.

Reply 2: This is another important point. This sentence has been rephrased to consider how unilateral transplants may increase total life-years gained depending on regional supply.
Changes in the text: Sentence rephrased (Page 10, Paragraph 2).

Comment 3: Overall, I think the findings of this manuscript are important and worth reporting. I think caution needs to be taken in the generalizability of the findings to the current era of lung transplant patients given above. The tone of the manuscript could be adjusted to reflect this while still reporting these important findings.
Reply 3: We have adjusted the tone of the manuscript where appropriate, particularly in the discussion, with the assistance of multiple reviewers' suggestions. The limited generalizability of our findings has been emphasized in the limitations section as well.
Changes in the text: Limitations clarified (Page 12, Paragraph 4).

Reviewer J

Comment 1: The authors present a very novel, useful, and interesting retrospective data analysis looking at 20-year survival. while some of the findings are "obvious" this review is still very useful and puts on paper the data that one suspects. can the authors speculate on

1) was the longer time on waitlist association with improved survival the result of test for "hardiness"

Reply 1: Thank you for your insightful review of our findings. This very well may be the case. Prior to the implementation of the Lung Allocation Score, lungs were allocated nearly entirely based on time spent on waitlist (so long as allografts were geographically available and ABO compatible).

We believe the portion of our cohort with shorter waitlist time likely represents a general cross-section of the transplant population during our study time, including patients with a variety of comorbidities and acuity of illness; however, the portion with longer waitlist time can only be comprised of those who could survive a certain amount of time without transplant. For instance, a less "hardy" patient—by nature of worse comorbid illness, perhaps—who could only survive a year without transplant could only appear in our cohort with a shorter waitlist time, making the longer waitlist group appear better by comparison. Though we have attempted to control for certain comorbidities as they were encoded in the UNOS database at that time, many go unaccounted for, and we believe that the longer waitlist time bearing out as significant may be a manifestation of this limitation.
Changes in the text: No specific changes, though this finding is addressed in the discussion.

Comment 2: 2) is it possible to see if COPD death (and shorter cohort of long-term survival) was the result of other comorbidities secondary to smoking
Reply 2: While we cannot with absolute certainty attribute the cause of death among the COPD cohort to other smoking comorbidities, the effect of these comorbidities can be estimated. Among 2,692 recipients with COPD, 160 (5.9%) had cause of death attributed to a smoking comorbidity (stroke, myocardial infarction, cardiac arrest, atherosclerosis, coronary artery disease, aortic aneurysm, other cardiac causes, diabetes), which was slightly elevated

from the non-COPD cohort (4.7%, Chi-square *P*=.038). Thus, recipients with COPD, and therefore likely smoking history, have slightly elevated likelihood of death due to other comorbidities secondary to smoking; however, these causes altogether comprise a small portion of the causes of death, both in the COPD cohort and overall.
Changes in the text: None.

Comment 3: 3) any chance to see if the long term your CF patients who survived over 20 years were the non-diabetic cohort?? otherwise great review of UNOS data base
Reply 3: Among the 843 patients with cystic fibrosis included in our study, 644 (76.4%) had diabetes, and there was no statistically significant difference in the prevalence of diabetes between the 20+ year survivors versus the 1-20 year survivors (Chi-square *P* =.622).
Changes in the text: None.