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Mandeep R. Mehra, MD, FRCP  
Editor-in-Chief, Journal of Heart and Lung Transplantation

Patricia Uber, PharmD

Scientific Managing Editor, Journal of Heart and Lung Transplantation

October 10, 2017

Dear Dr. Mehra and Reviewers,

Thank you for your careful review of our manuscript entitled   
Incidence of Acute Circulatory Support Prior to Heart Transplantation and Post-Transplant Outcomes (JHLT-D-17-00527), submitted to the Journal of Heart and Lung Transplantation. Your helpful suggestions are much appreciated, and have led to significant improvements in the manuscript. Please find our responses below, outlining edits tracked in the accompanying document.

**Reviewer #1:**

1. The first question that comes to mind is why the Authors used NIS data rather than data from UNOS or the ISHLT Registry which provide more granular and therefore more meaningful data.

**The reviewer makes the important point that the NIS-HCUP database provides different types of data compared to the UNOS registry, and there are limitations to both datasets. TThe NIS has data fields including many diagnoses/comorbidities, complications, costs, hospital and physician characteristics that are not available in the UNOS registry. The NIS has been appropriately used and well received in answering a variety of questions related to LVAD outcomes and incidence (Stretch et al. JACC 2014), transplantation and LVAD costs and outcomes (Mulloy et al. J Thorac Cardiovasc Surg 2012), pre-transplantation risk factors prior to OHT (Mujib et al. Clin Cardiol 2015). he reviewer is correct that the UNOS registry has longer periods of follow-up and allows an examination of long term morbidity, however because our primary question is the short term outcomes of MCS, which should make a difference acutely, we believe that our study avoids the primary limitations of the NIS.**

1. It is stated that the average length of stay after OHT was 17 days. Since the Authors compare the "earlier era" with the "modern era" it would be interesting to know if LOS changed over time.

**The reviewer brings up an interesting question, which is the length of stay after OHT. We previously reported that OHT happens, on average, on day 17 of the hospitalization. We agree it is reasonable and interesting to look at the length of stay after OHT, which we have now added to Table 1 (in aggregate) and Table 2 (broken down by era) and summarized in page 6 paragraph 3. Consistent with the converging trends in mortality between patients needing temporary mechanical circulatory support and patients who did not need mechanical circulatory support prior to transplant, the length of stay after OHT between the two groups converge in the modern era.**

1. What was the duration of ACS before OHT? Did duration of support influence outcomes in one or both eras examined?
2. The statement: "Between 1998 and 2014, the use of acute circulatory support prior to cardiac transplantation increased significantly over time, from 5.9% of transplants from 1998-2006 to 8.2% from 2007-2014 (p <0.001) refers to Figure 3. However, this figure has nothing to do with increase in ACS rates. Figure 3 the Authors provide is instead "Time trend of Stroke Rate by presence of Acute Circulatory Support prior to Transplantation". Are the Authors referring to Figure 3 of a previous draft of the manuscript? This should obviously be corrected or explained.
3. I am not clear on which were the indications for ACS in general and for each type of ACS. In other words, how did the patients selected for ECMO differ from those undergoing IABP implantation? Did the use of one versus another modality of ACS differ over time? This is important because it may contribute to the observed temporal differences in outcomes.   
   More importantly, did morbidity and mortality differ according to the type of ACS that was used?
4. Throughout the manuscript recipients of IABP, ECMO and PVAD are lumped together. I believe they should be analyzed separately. For example, OPTN data has shown that post-transplant one- year mortality was highest for patients transplanted while on ECMO or ACS whereas IABP supported patients achieved one-year mortality comparable to non-MCS transplanted patients (Silvestry SC et al. Journal of Heart Lung Transplant 2015; 34 (5): S179-180).  
   The statement: "The difference in in-hospital mortality decreased for both patients who required acute circulatory support (p < 0.001 for trend), as well as patients who did not require acute circulatory support (p = 0.012 for trend), though the decline in mortality was more pronounced in patients who required acute circulatory support (Figure 1)" is both confusing and redundant, because the authors actually provide the data to which this sentence refers in the paragraph bellow.
5. Subsequently there is a reference to Table 3. This Table is incomplete as it presents the outcomes of patients undergoing OHT between 1998 and 2006, but not those between 2007 and 2014.
6. It is very hard to believe that female gender, diabetes, obesity, hypertension, smoking, chronic kidney disease and ischemic heart disease were "protective" for the increased risk of renal failure and mortality.  What is the meaning and explanation for this finding? These data do not make clinical sense and are contrary to many analyses done using UNOS data or data from the ISHLT data. Is the NIS data granular enough to allow the Authors to make any clinical sense of these findings?

**Reviewer #2:**

The authors have provided the ICD-9 codes in supplement B from which they derived the complications they evaluated in their study.  Although it is clearly indicated for one of the complications, that of post-transplant circulatory support, that this occurred past the day of transplant, no information is provided concerning the other complications and therefore it is unclear to this reviewer whether the authors are able to define whether these complications occurred prior to transplantation or following transplantation.  Indeed, many of these complications could have represented the indications for implantation of the acute circulatory support or could have occurred on the acute circulatory support rather than following transplantation.  The authors need to clarify whether their data analysis was able to define the specific timing of these other listed complications.  
  
It is assumed that patients who had surgically implantable but non-durable mechanical circulatory support, as well as those with implantable durable circulatory support, were included in the patient group that did not receive acute circulatory support, however, this should be completely clarified.  
  
Specific Comments to the Authors:  
  
1.      In line 154, the authors cite Figure 3 as showing an increase in use of acute circulatory support over time, whereas Figure 3 shows the increased risk of stroke over time.  Thus, either a new figure should be provided or the citation removed.  
  
2.      In the text of the manuscript, lines 165-210, the authors describe differences in length of stay and complications between the two different eras in their analyses, whereas Table 2 only shows the data for the cohort between 1998 and 2006.  It would seem appropriate for the authors to expand Table 2 to include the data for the era of 2007-2014 as well and include in the table any statistical differences which were noted between the two eras in the individual parameters analyzed.  
  
3.      The figures are of extremely poor quality and very difficult to read and need to be improved significantly.  
  
4.      Tables 1 and 2 should include an indication of whether there were any statistically significant differences in the patient parameters (For Table 1, this seems to be indicated in lines 160-163 but not included in the table).  
  
5.      Depending on whether indeed the authors are able to define the timing of the complications included in Table 2 (pre-transplant vs. post-transplant), it is possible that the analyses represented in Tables 3, 4 and 5 may need to be redone to reflect only post-transplant complications, which is the message of the manuscript.  
  
  
  
**Reviewer #3:**

Reviewer #3: The authors hypothesize that presence of temporary MCS (tMCS) prior to transplant increases mortality. The authors report a sample from the National Inpatient Sample. The temporary MCS group is defined by ICD-9 codes and their temporal relationship to transplant. The authors perform logistic regression test their hypothesis. The authors find that presence of tMCS. The authors find increasing use of tMCS prior to transplant and an increase in post-transplant mortality associated with tMCS in unadjusted and adjusted analyses. They further describe the frequency of strokes, renal failure and use of tMCS over time. The authors conclude that use of tMCS is increasing and that recent changes to allocation policies could worsen this trend with respect to post-transplant morbidity.  
  
Major:   
1. Please describe further the IRB approval for use of person-level data.

**Thank you for the feedback, this has been added to page 4, paragraph 3.**  
  
2. Confirm the accuracy of determining pre- and post-MCS status based on dates of ICD-9 codes. Are ICD-9 codes in the NIS sufficiently accurate with respect to time to determine pre/post transpalnt status?  
 **Thank you for this important feedback, we believe it is essential to establish the temporal relationship between MCS and OHT as a significant proportion of patients need MCS immediately post OHT. Although the ICD9 code does not specify chronicity, the NIS does specify the date of each procedure (**[**https://www.hcup-us.ahrq.gov/db/vars/prdayn/nisnote.jsp**](https://www.hcup-us.ahrq.gov/db/vars/prdayn/nisnote.jsp)**). In our analysis of pre-OHT MCS, we only included patients who underwent MCS before the date of OHT. This should more explicitly described and we have added a comment to page 5, paragraph 1.**

3. Please comment on why the UNOS was not used. The UNOS registry contains this type of data and may improve the validity of the HCUP approach as similar prevalence of MCS use prior to transplant should be represented in UNOS. The UNOS registry also has longer periods of follow-up, which would allow a better assessment of the long-term effect of morbidity on generating mortality.

**The reviewer makes the important point that the NIS-HCUP database provides different types of data compared to the UNOS registry. The NIS has data fields including many diagnoses/comorbidities, complications, costs, hospital and physician characteristics that are not available in the UNOS registry. The NIS has been appropriately used and well received in answering a variety of questions related to LVAD outcomes and incidence (Stretch JACC 2014), transplantation and LVAD costs and outcomes (Mulloy et al. J Thorac Cardiovasc Surg 2012), pre-transplantation risk factors prior to OHT (Mujib Clin Cardiol 2015). The reviewer is absolutely correct that the UNOS registry has longer periods of follow-up and allows an examination of long term morbidity, however because our primary question is the short term outcomes of MCS, which should make a difference acutely, we believe that our study avoids the primary limitations of the NIS.**

4. The authors find that mortality with tMCS is declining while the prevalence of use is increasing. If mortality is decreasing with tMCS relative to prior eras and use is increasing, doesn't this indicate a reasonable use of tMCS technology? The authors cannot use their findings to cast suspicion on the new UNOS policy. On the contrary, their findings would support the use tMCS. Notably, the authors carefully use the term "morbidity" in their conclusions, but this circumvents the issue that survival may be improved with judicious tMCS use.

**There have been tremendous advancements in the management and indication for temporary MCS, particularly prior to heart transplantation. We believe this is a driver and a factor for the change in UNOS policy, and we do not mean to cast suspicion on the new policy. We agree with the reviewer that our analysis can be seen to validate UNOS policy change. We see in our analysis the mortality of patients who needed tMCS prior to transplant has improved. We believe this is a timely article to highlight potential reasons why UNOS policy change is reasonable, although with caution since policy changes can influence patient selection. To help clarify our analysis in light of the UNOS changes, we have updated page 8 paragraph 4.**

Minor:  
1. Please report/cite the packages used for analysis for both Python and R.

**Thank you for the feedback, this has been added to page 5, paragraph 2.**   
  
2. Lines 177 and 178 contain relative statistics. Report the absolute reduction in mortality for both groups.   
  
**Thank you, we have made this change to page 6, paragraph 3.**

3. Replace "multivariate" with "multivariable."

**We have made these changes throughout the text.**

4. Provide better descriptions of tables and figures with regard to the period under observation.

5. Improve the resolution of figures.

6. Reduce discussion of baseline characteristics and make better use of sections to highlight analytic findings. For example, temporal trends in tMCS is listed under "Post-transplant outcomes."

While the reasons for decreased utilization of lobectomy for epilepsy are not fully known, we now speculate further on potential contributory factors, such as changing referral patterns, the availability of new medications to trial, financial considerations, and misconceptions related to resective therapy (Discussion p. 14, ¶ 2). The reviewer is correct that our analysis includes all resections for epilepsy, including lobectomy and partial lobectomy of any lobe (now clarified in Discussion p. 14, ¶ 1 ), precluding our ability to track specific resection types. We acknowledge this as a significant limitation of our study (Discussion p. 16, ¶ 3 to p. 17, ¶ 1). We also now address the possibility that increasing use of adjunctive surgical therapies, such as VNS, may contribute to decreased utilization of resection, and that further research will be necessary to delineate this issue (Discussion p. 13, ¶ 3 to p. 14, ¶ 1). We emphasize, however, that VNS rarely results in complete seizure-freedom, and is thus less optimal for those who are good candidates for more definitive surgical resection (Discussion p. 14, ¶ 1).

The reviewer makes an important point that the nature of the NIS database does not allow us to know whether surgery was intended at the time of admission, and we are unable to exclude later re-admission to another hospital for surgery. Thus, reported surgical rates should not be considered reflective of the actual proportion of appropriate candidates who ultimately receive the procedure. We have clarified this limitation in our Discussion (p. 16, ¶ 3). Despite this limitation, our study design does provide a useful mechanism to estimate changes in epilepsy surgery utilization over time, and to compare surgical rates between patient subgroups ( Discussion p. 16, ¶ 3 to p. 17, ¶ 1 ).

We agree with the reviewer that relative risk (RR) analysis is more appropriate in our study than odds ratio (OR). We have re-run all relevant analysis (see Table 1, Table 2) and updated our Methods (p, 9, ¶ 1 ) to reflect this. Please note that our RR values are very similar to the OR values given our large N, and all previously significant results remain statistically significant.

We agree that there are significant limitations to this study, while the major strength of the study lies in our ability to estimate changes in epilepsy surgery utilization over time, and to compare surgical rates between patient subgroups. We hope our updated discussion of the study’s strengths and weaknesses (Discussion p. 16, ¶ 3 to p. 17, ¶ 1) will be helpful to the reader in discerning what can and cannot be inferred from our data.

**Reviewer #2:**

1. “On page 7, first line the authors describe the data base they utilized for their analyses. They need to clarify why this data base excluded federal hospitals (some of which are providers of epilepsy surgery services - i.e., Veteran's Hospitals).”

The Nationwide Inpatient Sample includes only hospitals that are members of the American Hospital Association (AHA), and the AHA does not have authorization to collect data from Federal facilities. Consequently, Veterans Hospitals and other Federal institutions (eg., Department of Defense and Indian Health Service) are excluded. We have now clarified this in our Methods (p. 7, ¶ 1), and now acknowledge the exclusion of federal hospital data as a limitation (Discussion p. 17, ¶ 1).

1. “The authors do not speculate as to why there was a 100% increase in hospitalizations for epilepsy during the period under study and speculation would be appropriate.”

While the reasons for significant increase in hospitalizations for epilepsy are not fully known, we now speculate that contributory factors might be increased inpatient referrals to smaller local institutions, increased adjunctive therapies such as VNS, and a continued disease burden (Discussion p. 13, ¶ 3 to p. 14, ¶ 1).

1. “The authors lay out some possible explanations for their findings but seem to hesitate to further elucidate the implications. For example, as we train more epilepsy fellows, many are ending up in general neurology practice with some emphasis in epilepsy. While patients may in fact undergo surgical evaluations, it is less likely that they will receive the same type of evaluation that might occur in a specialized center and as such might not get surgery. Further, while the authors mention newer antiseizure medications, they don't state the obvious that these patients now have more pharmacological possibilities and may in fact never get referred from the generalist or the primary physician because of economic factors (continued trials of new medications and new combinations can go on for years).”

The potential implications of new AEDs and economic considerations on delayed surgical referrals represent important points which we now explain (Discussion p. 14, ¶ 2). To further address the issue of continued trials of new medication, we now emphasize that referral should be pursued after a patient has failed two agents (Abstract, p. 4 ¶ 2; Discussion p. 15, ¶ 2; and Discussion p. 17, ¶ 2). We also place greater emphasis on the unique clinical evaluation and surgical treatment options patients receive at dedicated epilepsy centers which they are less likely to obtain at smaller centers (Discussion p. 15, ¶ 2).

1. “It would be interesting to note if the minority trends were analyzed any further as to geography, teaching hospitals, etc, to see if there were any significant factors that lead to the observed disparity.”

This is an interesting question. In our multivariate statistical model, no significant interactions to explain this trend were observed between patient-level variables (race, payer) and hospital-level variables (hospital size, teaching status, urban vs. non-urban location, or geography). We updated our Methods (p. 8, ¶ 2 to p. 9, ¶ 1) and Results (p. 12, ¶ 2) to reflect this. However, we did find a significant interaction between patient race and insurance payer, as white patients were more likely to have private insurance than non-white individuals (added to Results, p. 12, ¶ 2). Therefore, it is possible that lower rate of surgery among racial minorities is influenced by financial considerations of treating institutions (added to Discussion, p. 16, ¶ 2).

1. “Finally, the color scheme in the supplemental figure is hard to utilize as some of the colors are so close to one another.”

We have changed the color scheme of the supplementary figure (Figure e-1) to yellow/red and have also added distinct borders between the states in order to aid reader comprehension.

**Reviewer #3:**

1. “One of the main findings discussed in the manuscript is the fact that, in the time interval studied, there are LESS admissions of potential epilepsy surgery candidates (focal cases) to high-vol epilepsy centers, and MORE of these admissions to low-vol hospitals which are less likely to perform the surgery and more likely to have worse outcomes. The authors offer only 3 possible reasons for the underutilization of epilepsy surgery, including "the perceived morbidity of surgery, lack of awareness and education, and/or perceived advantages of pharmacological management." It is not clear who they are suggesting is misunderstanding epilepsy surgery, which, as the authors point out, can be safe and very effective. Is it the patients' lack of awareness and education, or that of the treating neurologists? I would ask the same regarding the perceived morbidity of surgery and perceived advantages of pharm tx-- are these misperceptions on the part of the patients or their treating neurologists, and why do they exist? Perhaps they mean both, but it is not clear.”

We believe that misconceptions regarding the potential risks of epilepsy surgery and failure rates of continued medication trials likely both contribute to the underutilization of epilepsy surgery. As an illustrative aside, consider one physician’s response to the 2001 temporal lobectomy trial, in which he promised to “continue to consider this kind of surgery a final, if not desperate, option when all other treatments have failed and my patients are willing to consider possible changes in their personality in order to improve their ‘quality of life’.” (Richards TA, 2002, *N Engl J Med* 346:292-295). We hypothesize that such misconceptions are held by some patients, primary care practitioners, as well as neurologists and neurosurgeons without specialized training in epilepsy. We now state this explicitly in our Discussion (p. 14, ¶ 2). We also now describe other potential reasons for decreasing surgical referrals, including the availability of new AEDs and financial considerations (Dicussion p. 14, ¶ 2). One goal of our manuscript is to promote increased awareness among health-care practitioners regarding these issues. In that regard, we now more clearly define medically-refractory epilepsy as failure of two AEDs (Abstract p. 4, ¶ 2; Introduction p. 5, ¶ 1; Discussion p. 14, ¶ 3; and Discussion p. 17, ¶ 2). We also compare and contrast the mortality and morbidity profiles of epilepsy surgery vs. continued intractable epilepsy (Discussion, p. 14, ¶ 3 to p. 15 ¶ 1).

1. “Only at the very end do the authors encourage early referral to an epilepsy center for surgical evaluation, though they are hinting at it in this "misperceptions" part of the discussion noted above. If they think the problem is that general or non-epilepsy neurologists are caring for these patients locally and not referring to epilepsy centers for surgical eval early enough (or at all), then the recommendation for early referral is sound. They also mention, however, that low-vol and experience has been associated w/ worse outcomes and increased morbidity in general. So perhaps they are also suggesting that epilepsy surgery is a highly specialized area of neurosurgery, best performed by a highly experienced neurosurgeon with expertise in this area (not just the benefits of a multidisciplinary team, etc). Again, they hint at this without actually saying it.”

We believe that early referral to an epilepsy center is important when a patient is diagnosed with medically-refractory epilepsy, defined as failure of two AEDs. We now emphasize this in several instances (Abstract, p. 4 ¶ 2; Discussion p. 15, ¶ 2; and Discussion p. 17, ¶ 2). While one benefit of epilepsy center referral is the multidisciplinary epilepsy team (Discussion, p. 15, ¶ 2), another benefit is indeed the greater expertise of specialized epilepsy neurosurgeons at those centers, as we now specify in the Discussion (p. 15, ¶ 2).

1. “Would consider adding that many high-vol epilepsy centers have a (or a couple) dedicated epilepsy surgeons.”

We appreciate the suggestion, and have added this point to our Discussion (p. 15, ¶ 2).

1. “Haneef et al (#22 under References) pointed to the ambiguity in defining "medically-refractory epilepsy" as part of the lag in referrals for epilepsy surgery, despite class I data on its effectiveness. Since publication of that paper, the ILAE has more clearly defined "medically-refractory" as inefficacy of 2 AEDs. This has only been rolled out to the epilepsy community about 2yrs ago at the AES annual meeting. Would consider adding this point to the manuscript, as now it is the job of epileptologists to educate local neurologists and PCPs about what drug resistance means-- only 2 AED failures.”

This is an important point, and we have now stressed the significance of 2 AED failures throughout the manuscript (Abstract p. 4, ¶ 2; Introduction p. 5, ¶ 1; Discussion p. 14, ¶ 3; and Discussion p. 17, ¶ 2), along with citation of the suggested reference.

1. “With regards to the disparities findings, the authors report that surgery rates were significantly lower in racial minorities and among medicaid and medicare patients, but that procedure rates in white vs minority and private vs public insurance did not reveal significant trends over time. Does this mean that minorities are not being referred to big centers as much as whites, or that even at the low-vol centers, they are not offered (or are not choosing) surgery? Would be helpful to clarify these findings more specifically, and comment on them.”

Please see our response above to Reviewer #2, Comment #4 which addresses this issue.

1. “On page 11, the first sentence in the Discussion section does not make sense as written-- I presume the authors meant to omit the word "increase".”

Thank you, we have corrected this typo (Discussion p. 12, ¶ 3).

1. “The word "underutilized" is sometimes hyphenated, other times not hyphenated throughout the manuscipt. Should be consistent throughout.”

We have made our spelling of “underutilized” consistent throughout the manuscript.

1. “On page 14, the last sentence of the second paragraph does not make sense as written-- the word "the" is used twice but should be omitted both times.”

Thank you, we have fixed this error (Discussion p. 16, ¶ 2).

**Reviewer #4:**

1. “Discharge coded data do not allow for a chronological or causal association regarding lobectomy and diagnosis of refractory localized epilepsy (ie., epilepsy could have followed, not preceded lobectomy, or the lobectomy could have been performed for a reason other than epilepsy). However, if the admission diagnosis was coded as refractory localized epilepsy, and there was a new code of lobectomy at discharge, the association is stronger (although still not definitive). Were diagnoses only included if they were in the primary position, ie., if they were the most likely cause of admission? If not, discuss the implications of including patients where a different diagnosis was the cause of admission. In what percentage was epilepsy coded in the primary position?”

Localized refractory epilepsy was the primary diagnosis in 95.6% of the hospitalizations returned by our query, and was a secondary diagnosis in the remainder of admissions (now stated in our Results p. 9, ¶ 2). As an aside, for the majority of hospitalizations in which localized refractory epilepsy was a secondary diagnosis, the primary diagnosis typically related to a lesion which may cause focal epilepsy (eg., brain tumor). However, we agree that a causal relationship cannot be definitively ascertained, and now acknowledge in our limitation section that cases of lobectomy preceding epilepsy cannot be excluded (Discussion p. 17, ¶ 1).

1. “Are there other changes in coding practices that could account for the findings? Selective resections have increased in popularity in the last decade, these are not lobectomies. How are they coded? The same applies to corticectomies or more limited resections, how are they coded?”

These are important questions, as resective procedures for epilepsy also include partial lobectomy, selective amygdalohippocampectomy, and targeted corticectomy. While some of these procedures have different codes under the International Classification of Diseases (ICD) system, they are lumped together under a single code in the NIS database (01.53), and are thus all captured in our study. This is now clarified in our Discussion (p. 14, ¶ 1). The NIS allows us to trend the totality of resective procedures for epilepsy, but it does not allow us to trend various subtypes of resections. To emphasize this, we now specify that our study examines both lobectomies and partial lobectomies together throughout the text. Finally, neither the NIS diagnosis codes nor procedure codes utilized in this study have changed during the duration of this study, 1990-2008.

1. “Table 3 is repetious, data are presented in text in the results. Omit this table or instead present a table with the entire multivariate model (ie., all variables included in the model and their corresponding odds ratios).”

We appreciate the suggestion, and have eliminated Table 3, as these data are contained in the text of the Results (p. 12, ¶ 2).

1. “The authors may wish to incorporate in their discussion a recent single institution analysis (Neurology 75 (8):699-704, 2010) demonstrating a lack of increase in epilepsy surgery following the published guidelines, and an accompanying editorial (Neurology 75 (8):678-679, 2010) exploring some of the causes for this phenomenon.”

We have incorporated these relevant references in the Discussion, and appreciate the suggestion (Discussion, p. 13, ¶ 1; and Discussion p. 13 ¶ 2 to p. 14 ¶ 1).

**Editor comments:**

1. “Omit the Background in the Abstract. Provide a 1 sentence Objective.”

Thank you, we have made this change to the Abstract (p. 3, ¶ 1).

1. “Shorten the Introduction to 250 words.”

We have shortened the Introduction accordingly.

1. “In a subsection within your Methods labeled “Standard Protocol Approvals, Registrations, and Patient Consents”, please state that you: 1. Received approval from an ethical standards committee on human experimentation (institutional or regional) for any experiments using human subjects; 2. Received written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research), if applicable.”

No human subjects or identifiable patient data were used in this study. We have now added the requested section to the Methods stating this (p. 6, bottom).

1. You have established a specific ‘p’ value as being “significant” in the article. For this reason, you do not need to use ‘significant’ with regard to the p value in subsequent mentions because it is redundant.  For example, “the presence of a lesion on the spinal cord was moderately significant (p=0.02).” could be re-written as : “the presence of a lesion on the spinal cord was moderate (p=0.02).”

We have made these changes throughout the text.

1. “Delete the word “conclusion” or “summary” from your discussion.

We have done this.

1. “Your web data are not labeled correctly. Please see the instructions in your author area at [http://submit.neurology.org](http://submit.neurology.org/). Place the e-legend on the same page as the e-figure.”

Thank you, we have made this change.

1. “In our initial review, it appears that the study may require compliance with the STROBE statement guidelines. Please provide this checklist.”

We have completed this checklist and uploaded it as Supplemental/Additional File.

We hope you will look favorably on our revisions, and consider the manuscript now suitable for publication in Journal of Heart and Lung Transplantation.

Sincerely,

David Ouyang, Gunsagar Gulati, Richard Ha, and Dipanjan Banerjee