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

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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 ISHLT registry, and there are limitations to both datasets. . 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). The NIS has data fields including many diagnoses/comorbidities, complications, costs, hospital and physician characteristics that are not available in the ISHLT registry. Liver disease and in-hospital sepsis are two fields which not reliably available in the ISHLT registry. While the reviewer is correct that the ISHLT registry has longer periods of follow-up and allows an examination of long term morbidity, because our primary question is the short term outcomes of MCS, which should make a difference acutely, we believe that our study avoids the discontinuity limitations of the NIS.Many of the complications we assess are short term complications which require the granularity of the NIS to provide procedure dates and timing to assess the temporal relationship that is not available in the ISHLT registry.**

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. 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. We agree it is reasonable and interesting to look at the length of stay after OHT, which we have added to Table 1 (in aggregate) and Table 2 (broken down by era) and summarized in page 6 paragraph 3.**

1. What was the duration of ACS before OHT? Did duration of support influence outcomes in one or both eras examined?

**Thank you for this interesting question. We believe this deserves to be more clearly fleshed out in our analysis. Using the date of procedure from the NIS, we are able to determine the time of initiation of mechanical circulatory support and are able to determine the earliest date of MCS and the temporal relationship with transplantation. We added this analysis to Table 1 and Table 2 as well as page 6, paragraph 3. On multivariate analysis, we did not find a significant relationship with mortality and duration of support in aggregate or in either era.**

1. 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 to8.2% 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.

**Thank you for bringing this to our attention. This was a mislabeling error. We have produced higher quality figures and have revised the figure references in the manuscript.**

1. 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? 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).

**Given the variation in the amount of circulatory support provided by each modality as well as the limitations and benefits for each modality, it makes sense that there are different indications for each type of ACS. In addition to that, factors such as availability and institutional habits also influence the decision for type of ACS. In this analysis, we cannot specifically determine the reason why each patient underwent the type of mechanical circulatory support that they did. The thing in common is that all these patients would be prioritized for transplantation under the framework, and we sought to explore this relationship in aggregate. Unfortunately, there was not enough statistical power given the limited sample size to do in-depth analysis for each group individually. That said, in our multivariate analysis, there was no significant difference in mortality by type of ACS (Table 3) as well as morbidities such as renal failure (Table 4).**   
**Need to address more in-depth.**

1. 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.

**Thank you for the feedback, we have clarified this and edited page 7 paragraph 1.**

1. 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.

**Table 3 refers to the multivariable model for predictors of mortality. This includes all patients in our cohort, inclusive of patients between 1998 and 2014. Table 2 might have been cropped off to the right, but we will upload the newest version that includes all patients.**

1. 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?

**Need to address more in-depth.**

**Reviewer #2:**

1. 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.

**Thank you for this important feedback, we believe it is essential to establish the temporal relationship between complications and OHT as well as circulatory support. For diagnoses such as renal failure and respiratory failure requiring procedural intervention (hemodialysis and intubation), the procedure date was used to identify post OHT complications. Gun, can you add in where you got the ICD9 codes and the citation.**

2. 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.

**In our study, the patient population was identified by ICD9 codes, specifically 37.61, 37.68, 39.61 for IABP, TandemHeart, Impella, and both central and peripheral ECMO. We clarified this in our revisions on page 3 paragraph 5 and page 5 paragraph 1.**

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.

**Thank you for bringing this to our attention. This was a mislabeling error. We have produced higher quality figures and have revised the figure references in the manuscript.**

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.

**Thank you for the feedback. Table 2 might have been cropped off to the right, but we will upload the newest version that includes all patients.**

3.      The figures are of extremely poor quality and very difficult to read and need to be improved significantly.

**Thank you for bringing this to our attention. We have produced higher quality figures and have revised the figure references in the manuscript. Please see the new attached figures. We have increased the font, improved the labeling, and colors of the figures.**

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).

**Thank you, Tables 1 and 2 were edited to add p-values and the manuscript was edited to avoid repetition of reported data (page 6, paragraph 2).**   
  
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.

**Thank you for this important feedback, we believe it is essential to establish the temporal relationship between complications and OHT as well as circulatory support. For diagnoses such as renal failure and respiratory failure requiring procedural intervention (hemodialysis and intubation), the procedure date was used to identify post OHT complications. Gun, can you add in where you got the ICD9 codes and the citation.**

**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.

**Not sure about this comment, please let me know if there is something I can help change**

5. Improve the resolution of figures.

**Thank you for bringing this to our attention. This was a mislabeling error. We have produced higher quality figures and have revised the figure references in the manuscript.**

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."

**Thank you for the feedback, we have edited the results section to better reflect areas of interest in our analysis. We have also added additional section headers to clarify the text.**

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