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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 titled 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. The detailed and incisive suggestions were 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.

**We appreciate the query regarding the choice of database for this analysis. In short, we used the NIS rather than the UNOS or ISHLT registries because it was better suited than the others to answer our question. 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 contains many data fields that are not available in the ISHLT registry, including diagnoses/comorbidities, complications, costs, and hospital and physician characteristics. Liver disease and in-hospital sepsis are two fields which are 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 regards the short term outcomes of MCS, which should occur acutely, we believe that our study avoids the discontinuity limitations of the NIS.**

**Most 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. Similarly, the UNOS database contains fields regarding IABP or ECMO use at the time of transplantation but no information regarding when this support initiated, nor does it differentiate between percutaneous and permanent VAD support.**

# The NIS has been used to answer a variety of meaningful questions related to in-hospital procedures, including acute circulatory support (Stretch et al. JACC 2014, National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis); cardiac resynchronization therapy (Lindvall et al, Circulation 2016, National Trends in the Use of Cardiac Resynchronization Therapy With or Without Implantable Cardioverter-Defibrillator); and cardiac transplantation and left ventricular assist devices (Mulloy et al. J Thorac Cardiovasc Surg 2013, Orthotopic heart transplant versus left ventricular assist device: A national comparison of cost and survival, and Shah et al. Journal of Cardiac Failure 2016, Impact of Annual Hospital Volume on Outcomes after Left Ventricular Assist Device  (LVAD) Implantation in the Contemporary Era).

# Given the above, we felt most comfortable using the NIS as the database to answer the question regarding the use of acute circulatory support prior to cardiac transplantation and resultant outcomes.

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 occurs, 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 such 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 summarize these results on 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 clearly stated, and the NIS database is unique in allowing us to answer this question. Using the date of procedure from the NIS, we are able to determine the time of initiation of mechanical circulatory support and its temporal relationship to cardiac transplantation. We added this analysis to Table 1 and Table 2 as well as page 6, paragraph 3. In multivariate analysis, we did not find a significant relationship between mortality and duration of support in aggregate or by 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).

**The question of why one type of ACS was used over another is important but difficult to answer, as clinicians use a number of variables to determine which type of ACS to use, including factors such as device availability and institutional preference. In this analysis, we cannot specifically determine the reason why each patient underwent the type of mechanical circulatory support that they did, but we can report differences in baseline characteristics of patients receiving IABP, ECMO, and PVAD (Supplemental Table 6).**

**We sought to explore the use of ACS in aggregate as, given the sample sizes, there was not enough statistical power to perform a meaningful analysis comparing each group. That being said, in our multivariate analysis, there was no significant difference in the incidence of mortality stratified by type of ACS (Table 3) nor in morbidities such as renal failure (Table 4). As requested, we also provide a graphical representation in the use of ACS and type of ACS over time (Figure 1).**

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 was unfortunately cropped off to the right, but we have uploaded 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?

**We appreciate the reviewer’s comment and would like to clarify. The NIS contains diagnoses rather than discrete data regarding parameters such as renal function, serum glucose levels, etc. This makes it difficult to precisely control for those factors in a multivariate analysis. Thus the reviewer’s point is well taken, and though we included those diagnoses in the descriptive analysis of the baseline characteristics of patients who received and did not receive acute circulatory support, they should not be included in the multivariate analysis. Prior multivariate analyses using the NIS have utilized number of comorbid conditions (as we did) rather than focusing on individual diagnoses. We have thus removed the individual diagnoses from the multivariate analysis to avoid confusion and have amended the tables and manuscript accordingly (Tables 3, 4, 5).**

**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. It is essential for this analysis to establish the temporal relationship between complications and OHT as well as circulatory support. Fortunately, the NIS allows us to perform this analysis. 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. Please see Shah et al. "Impact of annual hospital volume on outcomes after left ventricular assist device (LVAD) implantation in the contemporary era." *Journal of cardiac failure* 22.3 (2016): 232-237 for a similar analysis of outcomes after LVAD implantation using the NIS database.**

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.

**Thank you. 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 have 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 was cropped off to the right, and we have uploaded 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. The same type of analysis using the NIS and the same ICD9 codes were used in Shah et al. J Card Fail 2016.**

**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 be more explicit; we have added a comment to page 5, paragraph 1 to clarify.**

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.

**We appreciate the query regarding the choice of database for this analysis. In short, we used the NIS rather than the UNOS or ISHLT registries because it was better suited than the others to answer our question. 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 contains many data fields that are not available in the ISHLT registry, including diagnoses/comorbidities, complications, costs, and hospital and physician characteristics. Liver disease and in-hospital sepsis are two fields which are not reliably available in the ISHLT registry.**

**While the reviewer is correct that the UNOS registry has longer periods of follow-up and allows an examination of long term morbidity, because our primary question regards the short term outcomes of MCS, which should occcur acutely, we believe that our study avoids the discontinuity limitations of the NIS.**

**Most 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 UNOS registry. The UNOS database contains fields regarding IABP or ECMO use at the time of transplantation but no information regarding when this support initiated, nor does it differentiate between percutaneous and permanent VAD support.**

# The NIS has been used to answer a variety of meaningful questions related to in-hospital procedures, including acute circulatory support (Stretch et al. JACC 2014, National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis); cardiac resynchronization therapy (Lindvall et al, Circulation 2016, National Trends in the Use of Cardiac Resynchronization Therapy With or Without Implantable Cardioverter-Defibrillator); and cardiac transplantation and left ventricular assist devices (Mulloy et al. J Thorac Cardiovasc Surg 2013, Orthotopic heart transplant versus left ventricular assist device: A national comparison of cost and survival, and Shah et al. Journal of Cardiac Failure 2016, Impact of Annual Hospital Volume on Outcomes after Left Ventricular Assist Device  (LVAD) Implantation in the Contemporary Era).

# Given the above, we felt most comfortable using the NIS as the database to answer the question regarding the use of acute circulatory support prior to cardiac transplantation and resultant outcomes.

**Because our primary question regards short term outcomes after temporary 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.

**We agree with the reviewer that the reduction in mortality with use of tMCS over time is promising; we only state that that finding should be tempered by an increase in morbidity. Our findings thus both support the new UNOS policy change and provide food for thought about the broader implications of that policy change. We believe this is a timely article to highlight potential reasons why UNOS policy change is reasonable, although with caution since policy changes can also 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.

**Thank you, we have amended the figure and table descriptions to be more specific about the period under observation.**

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