

To World Journal of Cardiology Review Committee:

We thank you for considering our paper, "Optimal timing of same-admission orthotopic heart transplantation after left ventricular assist device implantation," for publication in your journal. We appreciate the insightful comments and have accordingly made changes to our manuscript. We have enumerated each major point from the reviewers in red parenthesis () and address these points in red font below. We believe our manuscript is stronger because of these changes and should be ready for publication.

**Reviewer: 02474355**

Ouyang et al. from the Stanford University School of Medicine and the Division of Adult Cardiac Surgery, Department of Cardiothoracic Surgery aimed at describing the impact of timing of same-admission orthotopic heart transplantation (OHT) after the implantation of left ventricular assist devices (LVAD) on in-hospital mortality and post-transplant length of stay. They used data from the Nationwide Inpatient Sample (NIS) from 1998 to 2011 and identified patients 18 years of age or older who underwent implantation of a LVAD and for whom the procedure date was available. They calculated in-hospital mortality for those patients who underwent OHT during the same hospitalization as a function of time from LVAD to OHT, adjusting for age, sex, race, household income, and number of comorbid diagnoses. There were 2200 patients who underwent implantation of a LVAD in this cohort: 164 (7.5%) patients also underwent OHT during the same hospitalization, which occurred on average 32 days (IQR 7.75 - 66 days) after LVAD implantation. Of patients who underwent OHT, patients who underwent transplantation within 7 days of LVAD implantation ('early') experienced increased in-hospital mortality (26.8% vs. 12.2%,  $p = 0.0483$ ) compared to patients who underwent transplant after 8 days ('late'). Cofactors and length of stay post-op were not contributors. Thus, delayed timing of OHT after LVAD implantation did not correlate with longer hospital stays post-transplant and might be a preferred option. This is a well written contribution, exploring a clinically important differential option. (1) I believe the Authors should explicitly point to this in their conclusions. The Authors nicely point out that "For patients who receive an LVAD for bridge to transplant therapy (BTT), the optimal timing of post-LVAD OHT is controversial. The need for clinical stability and time to recover from major surgery is counterbalanced by the risk of LVAD complications and the formation of adhesions and scarring, particularly when OHT is considered early after LVAD implantation.". This might be the rationale in support of their results and the comment that delayed OHT after LVAD during the same hospitalization should be a preferred option with no increased hospital stay, might indeed be taken as a measure to control for CHF mortality.

We thank reviewer #02474355 for his/her thoughtful evaluation and commendation of our manuscript. We have taken heed to the reviewer's suggestion in (1) and replaced the first line of the concluding paragraph with the following statement:

“In conclusion, our analysis suggests that delayed same-admission OHT after LVAD implantation decreases mortality risk without increasing post-transplant length of stay, and, therefore, may be the preferred option in such a clinical setting.”

**Reviewer: 03650337**

Very interesting and clinically relevant question with novel use of the NIS database. Overall well written with interesting findings.

We thank reviewer #03650337 for his/her time and positive assessment of our manuscript.

**Reviewer: 00608305**

Dear Author, It is an interesting retrospective study based on data from Nationwide Inpatient Sample analyzing early vs late (8 days or more) heart transplantation which occurred during the same hospitalization. This an interesting and important topic which was analyzed on smaller samples.. Studies baed on database records are naturally have numerous limitations. Most of them were stated by the Authors. Nevertheless the results seems interesting for all which face the decision of appropriate timing of OHT in pts with implanted LVAD. The two samples seems well matched and comparable. My main critical remarks are (1) 1. I am not sure if pts pulsatile and continuous LVAD were analyzed together. If so in GLM multivariate analysis an additional parameter ( pulsatile or continuous LVAD should be included as an independent variable . or state why it was not included). This can change the overall results substantially. Maybe an analysis of both periods (early with predominant pulsatile and late with continuous flow devices ) should be done separately. Due to huge differences in mortality the results and significance of variable can differ. (2) 2. Please state wheteher BIVAD supported pts were excluded from analyses (BIVAD from the beginning or BIVAD as right ventricular support added later before OHT due to right ventricular failure). (3) 3. In table 3 was stated that all pairwise comparisons were not statistically significant. It seems that the difference in sepsis and maybe acute respiratory failure were indeed significant . Please check it once more. Sincerely yours

We thank reviewer 00608305 for his/her careful review and critique of our manuscript. We have responded to each of your comments below:

(1) In our study, pulsatile (1998-2005 LVADs; n = 102) and continuous LVADs (2006-2011 LVADs; n = 62) were mostly analyzed together. Analysis of early versus late OHT post-LVAD implantation in the pulsatile era and continuous era reveals similar trends as the grouped data. However, due to the small sample size of same-admission OHT post-LVAD, pairwise comparison of early versus late OHT within the pulsatile and continuous era subgroups does not achieve statistical significance. Therefore, for completion, we have now added this data to our Table 2 and justified its withstanding significance in the text under “Results”, subsection “Timing of Post-LVAD Orthotopic Heart Transplant”, as follows:

“The reduced mortality trend with delayed OHT post-LVAD was observed in both the pulsatile-flow (13.8% vs. 36.4%;  $p = 0.081$ ) and continuous-flow eras (9.3% vs. 15.8%;  $p = 0.672$ ), although due to small sample numbers in each subgroup, the differences were not statistically significant (Table 2).”

Furthermore, as the reviewer suggested, LVAD era is a parameter in our current GLM multivariate model (Table 4). The pulsatile-flow era is defined as years

1998-2005, while the continuous-flow era is defined as years 2006-2011. Our GLM model shows that LVAD era is not sufficient to explain the variance in mortality observed in our dataset ( $p = 0.113$ ). However, the timing of OHT post-LVAD does explain a significant proportion of the variance in mortality observed in our dataset ( $p = 0.004$ ).

- (2) BIVAD supported patients were not excluded from this study. We identified 4 patients with the ICD-9 code 3752 for BIVADs in our entire cohort of 2200 LVAD patients. The ICD-9 code for LVAD, 3766, specifically excludes BIVAD implantations, so we do not anticipate any more than the 4 we have identified to have undergone BIVAD implantation during admission.
- (3) As per the reviewer's suggestion, we have recalculated the p-value for the pairwise comparison of sepsis and acute respiratory failure between early OHT and late OHT groups by chi-squared test. The two-tailed p-value for sepsis rate between early and late OHT is  $p = 0.252$  and for acute respiratory failure is  $p = 0.427$ .