

Peer review file

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Reviewer A

The authors provided a study about the merging roles of left ventricular assist device therapy as bridge to transplant in Hong Kong. They found an improved waiting list survival in the post-LVAD era driven by the implementation of LVAD service in 2010. In addition, they observed that long-term survival for LVAD recipients as BTT was comparable to survival of heart transplant recipients in Hong Kong.

Despite its limitations, this analysis provides important information to the existing body of evidence. I recommend to consider this manuscript for publication after considering the following suggestions:

Comment 1: Methods, Page 7, Line 105: Please define “obesity” (which BMI?)

Reply 1: In the present cohort, we used the cutoff body mass index $> 25\text{kg/m}^2$ for defining obesity in this Asian Population, however, in order to be more consistent with the international WHO classification, we have changed the term from “obesity” to “overweight”.

Changes in the text: We have modified our text as advised (see page 10, line 122-123).

Comment 2: Table 1: Please define “obesity” (which BMI?)

Reply 2: In the present cohort, we used the cutoff body mass index $> 25\text{kg/m}^2$ for defining obesity in this Asian Population, however, in order to be more consistent with the international WHO classification, we have changed the term from “obesity” to “overweight”.

Changes in the text: We have modified the tables 1-3 and supplementary table 1 as advised (see page 24-31, line 371-384)

Comment 3: Results, Page 9, Line 150: Please change “6.59%” to “6.6%” as one digit after decimal should be enough.

Reply 3: Agreed that one digit after decimal is enough and number is updated. Also, numbers in tables were amended to one decimal place for more consistent presentation.

Changes in the text: We have modified our text as advised (see page 15 line 193, page 14 line 170, line 174, page 16 line 220, line 232-233, page 17 line 235, line 237, line 238, line 242, line 244, page 24-31, line 371-384)

Comment 4: Discussion, Page 15, Line 284: Please change “6.59%” to “6.6%” as on digit after decimal should be enough.

Reply 4: Agreed that one digit after decimal is enough and number is updated.

Changes in the text: We have modified our text as advised (see page 22, line 353)

Comment 5: Results, Page 9, Line 158: How can you have two diagnoses for Re-HTX (cardiac allograft vasculopathy and cardiac allograft dysfunction) if there was only one patient with Re-HTX (Results, Page 10, Line 162: “including one re-transplantation”). Please explain.

Reply 5: The diagnoses “cardiac allograft vasculopathy” and “cardiac allograft dysfunction” were the diagnoses of patients listed for re-heart transplantation among the whole 478 cohort while there was only one re-heart transplantation performed among the 232 heart transplantation performed during the study period. Therefore, there were more than one patient listed for re-heart transplantation but only one patient undergone re-heart transplantation during the whole study period. Amendment was made in the manuscript for more clear presentation.

Changes in the text: We have modified our text as advised (see page 14 line 181-188, page 16 line 218-222)

Comment 6: Figure 3: Please provide the number of patients at risk for each figure.

Reply 6: Number at risk was added to each figure

Changes in the text: We have modified the figure 3 as advised (see page 37 line 399 and page 38 line 400)

Comment 7: Figure 3: Please the unit “months” to “years” for each figure.

Reply 7: The unit “months” was changed to “years” for each figure

Changes in the text: We have modified the figure 3 as advised (see page 37 line 399 and page 38 line 400)

Comment 8: Figure 4: Please provide the number of patients at risk for each figure.

Reply 8: Number at risk was added to each figure

Changes in the text: We have modified the figure 4 as advised (see page 40 line 406 and page 41 line 407)

Comment 9: Figure 4: Please the unit “months” to “years” for each figure.

Reply 9: The unit “months” was changed to “years” for each figure

Changes in the text: We have modified the figure 4 as advised (see page 40 line 406 and page 41 line 407)

Reviewer B

The authors presented a manuscript with the title: “Emerging Roles of Left Ventricular Assist Device Therapy as Bridge to Transplant in an Asian City with Scarce Heart Transplant Donor”. The original article aimed to assess the impact of implementation of LVAD therapy on heart transplant (HTx) service in Hong Kong (HK). The LVAD program was started in 2010 in HK and patients who had been put on HTx waiting list since the start of HTx program in HK from 1992 to 2020 were included for analysis. Survival on HTx waiting list between pre-LVAD era 1992-2009 and post-LVAD era 2010-2020 were analyzed. In the pre-LVAD era (n=178), the 1-, 2- and 3-year survival on waiting list were 82.3%, 61.7% and 43.0% and improved in the post-LVAD era (n=300) to 85.7%, 81.8% and 78% (p=0.003). Time-dependent multivariate analysis revealed that LVAD support was independently associated with significant reduction of waiting list mortality (OR 0.21, CI: 0.10-0.44, p<0.001). There was no significant difference when comparing survival after LVAD as BTT and survival after HTx (76.1% vs 72% at 8 years respectively, p=0.732). The authors concluded: Waiting list survival improved in the post-LVAD era driven by the implementation of LVAD service. Long-term survival for LVAD recipients as BTT were comparable to heart transplant recipients in HK.

Comment 1: The study is interesting, certainly an enrichment for the journal and I congratulate to the improvements. However, the manuscript has several drawbacks that hamper immediate publication:

Overall, the English language needs improvement. The manuscript is in some sections difficult to understand.

Abstract: acceptable, but the result section needs workup. It needs to be stated more clearly.

Reply 2: Thank you for the suggestion and amendment has been made for the result section in the Abstract for more clear presentation.

Changes in the text: We have modified the result session in the abstract as advised (see page 3-4 line 40-51)

Comment 2: Introduction: acceptable

Methods: This section of the manuscript should be better prepared. It should have subtitles (e.g. "Patient population", "Data attributes" or "Statistical analysis"). A clear guideline is needed.

Reply 2: Thank you for the suggestion and subtitles were added to the method session.

Changes in the text: We have added subtitles for the method session as advised (see page 10 line 108, page 10 line 115, page 11 line 140)

Comment 3: The type of study should be stated and described better at the beginning of the methods section, here retrospective analysis.

Reply 3: Thank you for the suggestion and the type of study were added to the beginning of the method session

Changes in the text: We have added the type of study to the beginning of the method session (see page 10 line 109)

Comment 4: The ethical approval statement should be written in the first paragraph of this section or should be a separate paragraph at the end of the methods section. Was patient consent waived or obtained?

Reply 4: Thank you for the suggestions and the section of ethical approval statement were added at the end of method section. Individual consent for this retrospective analysis was waived.

Changes in the text: We have modified our text as advised (see page 11 line 160-164)

Comment 5: Following statements missing, e.g.: “The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013)”.

Reply 5: Thank you for the suggestion and the statement was added to the ethical statement section.

Changes in the text: We have added the statement to the ethical statement section as advised (see page 11 line 161-162)

Comment 6: In the period from 1992 to 2020, the heart failure therapy (e.g. medication) of the patients has certainly changed. This may have an impact on survival on the waiting list and on overall survival. It should therefore be taken into account in the multivariate analysis or at least reported as a limitation.

Reply 6: Thank you and agreed there were significant changes in heart failure therapies from 1992 to 2020 which may have impact on waiting list survival. Although we have data on device therapy including ICD and CRT use, unfortunately we don't have data on anti-heart failure medications due to difficulty to retrospectively retrieve these data especially for patients > 15 years ago and thus this was reported as a limitation as suggested.

Changes in the text: We have modified the text as advised (see page 22 line 356-358)

Comment 7: Results: Needs as well a somewhat more clear line. In line 210 - 212 the comparison with the ISHLT results should be placed in the discussion section.

Reply 7: Thank you for the suggestion and the comparison with ISHLT results were amended to discussion section

Changes in the text: We have modified our text as advised (see page 20 line 310-314)

Comment 8: Discussion: acceptable

Literature: acceptable

Figures acceptable

Tables: acceptable, even some prefer a different presentation of data and standard deviation.

Reply 8: Thank you very much for your kind comments.

Reviewer C

Comment: Nicely written study, which aimed to assess the impact of implementation of LVAD therapy on heart transplant (HTx) service in Hong Kong. Waiting list survival improved in the post-LVAD era driven by the implementation of LVAD service. Long-term survival for LVAD recipients as BTT were comparable to heart transplant recipients in HK.

Reply: Thank you very much for your kind comments.

Reviewer D

The authors described improved heart transplant waiting list survival in Honk Kong in the post-LVAD era.

This is well described the role of LVAD as BTT has changed because of donor shortage and improved outcome in patients with LVAD.

I have the following remarks:

Comment 1: In the present study, pre-LVAD era covers 1992-1999. With advance in immunosuppression and perioperative care, post-transplant survival improved over the last three decades. Today, prognosis of heart failure patients is markedly better than those in 20 years ago, as well. Outcome should be analyzed between 2000-2009 and 2010-2020.

Reply 1: Thank you for your comments and fully agreed that treatment and prognosis of heart failure patients significantly evolved over the last three decades. However, we decided to cover 1992-1999 cohort for the following reasons. First, we have tried to compare the waitlist survival among the cohort 1992-1999 and 2000-2009 and found similar waitlist mortality ~20% per year for the two cohort as shown in figure 3(b). This is in consistent with the fact that there were limited therapeutic options for patients with end stage heart failure other than heart transplant in that era and clinical outcome remained similarly dismal between 1992-1999 and 2000-2009. Second, there were 52, 126 and 300 listing episodes for 1992-1999, 2000-2009 and 2010-2020 respectively. Therefore, the cohort 1992-1999 significantly contributed about one-third of the whole

pre-LVAD era cohort. Third, we believe by including the whole Hong Kong service cohort since its beginning can minimize potential selection bias using an arbitrary cutoff time for the pre-LVAD era cohort. Therefore, we sincerely hope you would allow us to keep including 1992-1999 for the pre-LVAD cohort for analysis.

Changes in the text: None

Comment 2: Many similar studies reported cardiac transplant outcome for LVAD patients and outcome on LVAD support as BTT were satisfactory. In addition, donor shortage is major problem in many countries. Consequently, as authors mentioned in discussion, revision of allocation system in the United States were performed. What is unique about the authors' study?

Reply 2: Thank you for your comments and fully agreed that it is well known that short term outcome of LVAD as BTT has better 1-year survival at 68-86% when compared to other patients on heart transplant waiting list especially those who were inotropic dependent which carried 50% 1-year mortality. However, medium-term survival as reported in the INTERMACS registry were still modest at 70% and 49% at 2-year and 4-year which were still inferior to 80.7% and 75.3% 2-year and 4-year survival after heart transplantation as reported by the ISHLT. Even in the latest MOMENTUM study (N Engl J Med. 2019 Apr 25;380(17):1618-1627) which showed the most favorable event-free survival of 84% and 74.7% at 1-year and 2-year respectively for patient supported on latest generation of fully magnetically levitated LVAD, which seems approaching 84.0% and 80.7% survival at 1-year and 2-year post heart transplantation as reported by ISHLT, thus the outcome of patients supported on LVAD as BTT was not regarded as comparable to heart transplantation due to lack of long-term real world data. Our study is unique in demonstrating in a city with good heart transplantation outcome comparable to ISHLT results, patients supported with LVAD as BTT in a real-world setting has comparable long-term survival up to about eight years to those patients received heart transplantation (76.1% vs 72% at 8 years respectively, $p=0.732$) (Figure 4(d)).

Changes in the text: We have modified our text as advised (see page 21-22 line 346-350)

Minor comment

Comment 3: "Impella" is a tradename and should be properly referenced the first time it appears in the manuscript: (Abiomed, Danvers, Massachusetts).

Reply 3: Thank you for the suggestion and proper reference has been added to the manuscript.

Changes in the text: We have modified our text as advised (see page 11 line 129)

Reviewer E

The reviewed manuscript reports the effect of LVAD availability on outcomes for patients listed for heart transplantation in a region with extremely low donor organ availability. Short- and mid-term mortality significantly improved, without a demonstrable effect on post-transplant outcomes. These results highlight the important role of durable left ventricular support in comprehensive management of end-stage heart failure patients. While uptake of durable LVAD in Asian countries has lagged significantly behind Europe and North America (Sivathasan et al, J Heart Lung Transplant 2020; 39(11): 1195-1198), these results suggest that patients managed in heart failure programs in Asian countries could benefit greatly from expanded access/utilization.

The results and implications of this manuscript would be of great interest to the readership and a meaningful contribution to the literature. However, I do have suggested modifications to give a fuller picture of how LVAD availability has changed management at the author's center.

Comment 1. Additional information is necessary regarding the indications leading to LVAD implantation and patient clinical condition at time of implantation. The authors have an admirably complete dataset of patient conditions at transplant listing, but comparably little information if provided on LVAD implantation.

a. Utilizing variables describing clinical condition at LVAD implantation as a covariate instead of, or in addition to, 'time to LVAD' in multivariable analysis might be more appropriate. 'Time to LVAD' is likely to be highly inversely correlated at early time points with the variables describing HF severity at listing (cardiogenic shock, ECMO/Impella, Invasive MV), which could confound analysis.

Reply 1a: Thank you for your comments and suggestions. Fully concur about the need to illustrate the characteristics of patients with LVAD vs those without LVAD as well

as the clinical status at the time of LVAD implant as reflected by their INTERMACS Profiles as well as the need for inotropic support, IABP, ECMO or Impella use. Therefore, we have added Table 2 to provide this important additional information as well as modified our text. When analyzing survival on waiting list, as reviewer correctly pointed out that not all patients have LVAD implantation done at baseline at the time of heart transplant listing. Time to LVAD is likely inversely related to the severity of clinical state at the time of listing and some patients might be stable at the time of listing but subsequently deteriorated months to years later while on waiting list requiring LVAD support. As a result, LVAD status cannot be used as a simple baseline categorical characteristics for survival analysis and time-dependent analysis utilizing the variable “time-to-LVAD” is more appropriate to account for the time-varying LVAD status. Also, we have adjusted other significant factors at baseline that might potentially confound the effect of LVAD on waiting list survival such as cardiogenic shock and VA-ECMO in multivariate analysis to minimize confounding effects of these factors as pointed out by reviewer. We have seriously considered the suggestion to use clinical conditions at LVAD implantation as covariates, but we noticed that these conditions occurred at different time points while the patients were on heart transplant waiting list and thus it would be difficult to define comparable time point in the cohort without LVAD for comparison on the clinical status after transplant listing. In addition, it might not be statistically appropriate to compare clinical status at the time of LVAD implantation, which might occur months to years after listing, to the baseline characteristics in the cohort without LVAD for waiting list survival analysis. Therefore, sincerely hope that reviewer would accept our current analysis approach which aimed to address the impact of LVAD as a time-dependent factor on waiting list survival together with the effort to minimize potential confounding effect of baseline severity status and characteristics by using time-dependent multivariate Cox-regression model.

Changes in the text: We have modified the text and added table 2 as advised (see page 15-16 line 204-216, page 27-28 line 377-379)

b. Related to this, the length of time between initial heart transplant listing and LVAD implantation should be reported.

Reply 1b: Thank you for the suggestion and the mean time from listing to LVAD support as well as the range were added.

Changes in the text: We have modified the text and added data in table 2 as advised (see page 16 line 215-216, page 27-28 line 377-379)

Comment 2: Table 1 would be better utilized as a comparison of patient characteristics between the 'before LVAD' and 'after LVAD' eras, rather than reporting results of multiple imputation. Reporting of multiple imputation results is appreciated, however, and could still be included as supplementary material.

Reply 2: Thank you for the suggestion and Table 1 has been modified to illustrate the data for the whole cohort after imputation, before LVAD era as well as after LVAD era. The original table 1 was changed to supplementary table 1 as suggested.

Changes in the text: We have modified our text, changed original table 1 to supplementary table 1 as well as modified table 1 as advised (see page 15 line 195-204, page 24-26 line 371-376, page 31 line 384)

Comment 3: Number at risk should be included on the x-axis of kaplan-meier curves. This is especially important when comparing different eras, as more recent patients are likely to have shorter follow-up time on average.

Reply 3: Thank you for the suggestion and number at risk was added to the X-axis of figure 3 and figure 4 for better illustration.

Changes in the text: We have modified figure 3 and figure 4 as advised (see page 37-38 line 399-400, page 40-41 line 406-407)

Comment 4: Testing for proportional hazards should be performed prior to using log-rank tests to compare K-M curves. If non-proportional hazards are present, alternate statistical comparison is required.

Reply 4: Thank you for your suggestion. We have tested and fulfilled the proportional hazards assumption and the method section was updated accordingly.

Changes in the text: We have modified our text as advised (see page 11 line 147-150)

Minor comments:

Comment 1: Table 1 appears to have a typo for Cardiac Output in 'After Imputation' column, as value changed from 3.06 to 2.02 after imputation. If this is actually the result, imputation is likely unstable and requires correction.

Reply 1: Thank you for sporting the typo error and value should be 3.02 after imputation. Also, data in table were adjusted to 1 place after decimal for more consistent presentation.

Changes in the text: We have modified the table value as advised (see page 24-26 line 372-376, page 31 line 383-384)

Comment 2: The manuscript may benefit from review from grammar review. Grammar errors are minor, but frequent.

Reply 2: Thank you for your suggestions and we have reviewed the grammar of the manuscript and make necessary amendments.

Changes in the text: We have modified our text as advised (see page 8 line 87-89, line 92-93, line 102-103, page 10 line 125, page 11 line 130, page 12 line 154, line 156, page 14 line 170, line 172, line 176-177, page 16 line 224, line 227, line 231-234, page 17 line 236, line 241, line 243, line 250-252, line 256, page 18 line 269-270, line 274-276, page 19 line 280, line 286, line 290, page 20 line 305, line 317, line 321-322, page 21 line 325-328, line 334-336, line 338-341, page 22 line 351, line 353, line 355, page 23 line 366, line 368-369.)

Reviewer F

Comment: The authors described that heart transplant (HTx) waiting list survival improved in the post-LVAD era driven by the use of LVAD support and that long-term survival of patients received LVAD as BTT was comparable to survival of heart transplant recipients up to about eight years in Hog Kong. This paper may have information worthy to know in terms of regional registry in Hong Kong.

However, this paper analyzed only patient survival after LVAD implantation and HTx. To conclude their summary, more data about adverse events or cause of death during waiting for HTx will be needed to understand why LVAD may improve waiting list patient outcome.

Reply: Thank you very much for your comments and we admitted that more detailed data on cause of death such as death related to cardiovascular cause, death related to heart failure, death due to arrhythmia, or death due to other causes were lacking due to difficulty in retrospectively retrieve these granular data in a retrospective study across

a time span of nearly 30 years. We have thus acknowledged this as a limitation in the discussion session. However, all cause mortality, which has been used in the present study, has been commonly used as a hard clinical end point and widely adopted in many cardiovascular studies as well as adopted as the primary outcome measure in the ISHLT post heart transplant survival analysis. Therefore, despite the presence of limitation, we would sincerely hope that reviewer could still consider our manuscript for publication. Changes in the text: We have acknowledged the limitation in the discussion session as advised (page 22 line 359-361)