学位論文

「The impact of uncorrected mild aortic insufficiency at the time of left ventricular assist device implantation（補助人工心臓植え込み時の中等度大動脈弁閉鎖不全症が及ぼす影響に関する研究）」

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

The impact of uncorrected mild aortic insufficiency at the time of left ventricular assist device implantation

（補助人工心臓植え込み時の中等度大動脈弁閉鎖不全症が及ぼす影響に関する研究）

はじめに：

植え込み型補助人工心臓は末期心不全患者に対する標準的治療として定着しつつあり，治療成績も向上している．植え込み型人工心臓はその構造上の問題，血行動態の変化による理由により大動脈弁閉鎖不全症を増悪させると言われている．International Society for Heart & Lung Transplantation のガイドラインでは植え込み時の Moderate 以上の大動脈弁閉鎖不全症に対する合併手術は Class I で推奨されている．しかしながら，補助人工心臓植え込み時の Mild の大動脈弁閉鎖不全症に対する手術適応，術式に関しては定まっていないのが現状である．また，過去の研究では大動脈弁閉鎖不全症の合併は術後の生存率に影響しないとされているが，運動機能や生活の質に対する影響は解明されていない．今回，術前評価 Mild の大動脈弁閉鎖不全症が術後 Moderate 以上の大動脈弁閉鎖不全症の発生，生存率，NYHA classification，入院を要する心不全の発生に及ぼす影響について検討し，補助人工心臓植え込み時の Mild の大動脈弁閉鎖不全症が合併手術の適応となるべきかについて検討した．

方　法：

本研究は Washington University in St. Louis で 2006 年 1 月から 2018 年 3 月の間に補助人工心臓植え込み手術を行った患者 694 人の臨床データを後方視的に解析した．植え込み時に大動脈弁手術を行った患者，データ欠損，右室補助人工心臓の患者合わせて 90 名は除外され，残る 604 名は術前の経胸壁心臓超音波検査をもとに Mild AI と No AI の 2 群に分けられた．さらに，術前の患者背景をもとに 1 : 1 プロペンシティースコアマッチングを行い，術前の心臓超音波検査における大動脈弁閉鎖不全症評価で Mild 101 名（Mild AI group）と Mild 未満 101 名（No AI group）にマッチングした．主要評価項目は術後の Moderate 以上の大動脈弁閉鎖不全症の発生，副次評価項目は術後生存率，Class III 以上の NYHA の発生 ，入院を要する心不全の発生とした．Moderate 以上の大動脈弁閉鎖不全症の発生，NYHA class はプロペンシティースコアマッチング ID をランダムエフェクトとした一般化線型混合モデルにより解析された．術後生存率は Kaplan-Meier 生存曲線により解析された．心不全を原因とする入院の発生率は術後の死亡を競合リスクイベントとした Fine and Gray 法によって解析を行った．

結　果：

主要評価項目である術後の Moderate 以上の大動脈弁閉鎖不全症の発生において，一般化線型混合モデルによる解析では，術前の Mild 大動脈弁閉鎖不全症（Estimate: 2.03, Standard error: 0.36, $p < 0.01$）と補助人工心臓の植え込み期間（Estimate: 0.71, Standard error: 0.12, $p < 0.01$）は術後の Moderate 以上の大動脈弁閉鎖不全症の発生に有意に影響した．副次評価項目の生存率では，Kaplan-Meier 生存曲線による解析で Mild AI group と No AI group の間で有意差は認めなかった（Log-rank; $p = 0.58$）．また，一般化線型混合モデルによる解析で術前の Mild 大動脈弁閉鎖不全症は補助人工心臓植え込み後の NYHA≧Class III の発生と有意に関係した（Estimate: 1.19, Standard error: 0.25, $p < 0.01$）．No AI group と比較して Mild AI group では補助人工心臓植え込み後の入院を要する心不全の累積発生率が有意に高かった（Hazard ratio = 2.62, 95% CI: 1.42-4.69, $p < 0.01$）．補助人工心臓植え込み術前の Mild 大動脈弁閉鎖不全症患者の Subgroup 解析では，多変量解析を行った結果，Destination therapy（Odds ratio = 3.54; 95% CI: 1.46-8.58; $p < 0.01$）と補助人工心臓植え込み期間（OR = 1.51; 95% CI: 1.21-1.88; $p < 0.01$）が術後の Moderate 以上の大動脈弁閉鎖不全症の危険因子であった．

結　論：

補助人工心臓植え込み術前の Mild の大動脈弁閉鎖不全症は補助人工心臓植え込み後の Moderate 以上の大動脈弁閉鎖不全症の発生，NYHA class の悪化，入院を要する心不全の発生と有意に関係した一方で生存率に関する影響は認められなかった．補助人工心臓植え込み時の Mild 大動脈弁閉鎖不全症に対する合併手術は術後の大動脈弁閉鎖不全症の悪化を予防し，心不全症状を抑制する可能性が示唆された．Destination therapy と補助人工心臓植え込み期間は術前に Mild の大動脈弁閉鎖不全症を合併した症例の術後 Moderate 以上の大動脈弁閉鎖不全症の危険因子であり，長期の補助人工心臓サポートが必要な Mild 以上の大動脈弁閉鎖不全症患者においては補助人工心臓植え込み時の大動脈弁手術が考慮されるべきと考えられた．

目次

1. Introduction

Left ventricular assist device (LVAD) implantation has become a bridge to transplantation (BTT) or a destination therapy (DT) for patients with end-stage heart failure, improving the quality of life and survival.[1-3] However, LVAD support has some limitations, including the potential development of aortic insufficiency (AI). In previous studies, 25%–59% of patients with no AI at baseline developed significant post-LVAD AI.[4-8] Risk factors identified for AI progression include a lower frequency of aortic valve opening, aortic root diameter enlargement, longer LVAD support duration, older age, and the use of a continuous-flow pump, especially an axial flow pump.[5-7,9-13] Additionally, an animal study suggested that the outflow graft angle perpendicular to the aorta increased AI grade and recirculation.[14] However, studies have not found a significant association between AI after LVAD implantation and survival. Additionally, the effects of post-LVAD AI on quality of life and physical status have not been fully investigated,[6,8-10] and the relationship between pre-implantation AI severity and the progression of the AI after LVAD implantation remains unclear. The latest International Society for Heart & Lung Transplantation guideline includes a Class I recommendation to consider surgical intervention at the time of LVAD implantation when the AI is moderate or greater.[15] However, there is no consensus on the treatment strategy for patients with mild AI. The purpose of this retrospective study was to investigate the progression of uncorrected mild AI at the time of LVAD implantation and its impact on survival and functional status compared with patients with no AI at baseline.

2. Methods

2-1. Study design and patients

The study protocol was approved by the Institutional Review Board of Washington University in St. Louis (# 201409140). Informed consent was obtained from all of the patients.

We retrospectively reviewed the data for 694 patients enrolled in the Washington University in St. Louis Mechanical Circulatory Support Registry who underwent implantation of continuous-flow LVADs between January 2006 and March 2018. The implanted devices were either HeartMate 2 (Abbott, Abbott Park, IL, USA) or HeartWare (Medtronic, Minneapolis, MN, USA). The study excluded any patients who underwent a concomitant aortic valve procedure at the time of LVAD implantation, received a biventricular assist device, or whose data were incomplete. This resulted in a total of 604 patients being enrolled in the study (Figure 1).

Before the implantation, each patient underwent an assessment of AI severity by transthoracic echocardiography (TTE). This identified mild AI in 111 patients and trace or no AI in 493 patients. As described in a later section, preoperative factors were assessed with propensity scores, and 101 patients with mild AI (Mild AI group) were matched to 101 patients with trace or no AI (No AI group, Figure 1). Follow-up echocardiography parameters, New York Heart Association (NYHA) functional class, readmission rate, and survival were compared between the two groups. The primary endpoint was defined as the progression of AI to moderate or greater after LVAD implantation. The secondary endpoints were NYHA functional class, readmission rate, and survival. A further risk factor analysis for progression to moderate or greater AI was performed for all 111 patients with pre-LVAD mild AI (Table 5).

2-2. Data collection and follow-up

Demographic, echocardiographic, and outcome variables were extracted from electronic medical records and the institutional mechanical circulatory support registry database. The demographic and echocardiographic data were used to characterize the patients prior to LVAD implantation. Operative data, such as cardiopulmonary bypass time and details about other valvular procedures were also obtained.

The pre-LVAD grades of AI, mitral valve regurgitation (MR), and tricuspid valve regurgitation (TR) were obtained from the results of TTE acquired within 30 days before the LVAD implantation. The post-LVAD TTE parameters were collected from all echocardiogram measurements during the follow-up term. These assessments were based on regurgitation jet width in the parasternal short- and long-axis views. According to the recommendations of the American Society of Echocardiography,[16] the scoring was defined as none, trace, mild, moderate or severe. Outcomes including readmission, NYHA classification, and mortality were reviewed for all of the patients. Post-LVAD brain natriuretic peptide (BNP) levels and NYHA functional class were collected at the same time as the echocardiogram measurements. Drop-out and end of study period were regarded as censoring events.

2-3. Propensity score matching

One-to-one propensity score matching was performed using the propensity score matching module of SPSS Statistics version 25 (IBM, Armonk, NY, USA). Propensity scores for the Mild AI and No AI groups were obtained from logistic regression analysis using the following pre-LVAD variables in the propensity model: age, body mass index,

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, ischemia, indication, device implanted, NYHA classification, cardiogenic shock, resuscitation, mitral valve procedure, tricuspid valve procedure, sclerotic aortic valve, left ventricle ejection fraction, tricuspid annular plane systolic excursion (TAPSE), moderate or greater MR, moderate or greater TR, and systemic pulmonary artery pressure. One-to-one matching was performed with a caliper width of 0.1 of the pooled standard deviation of the logit of the propensity score. Standardized differences were compared between two groups before and after propensity score matching, and |standardized difference| $\geq$0.1 was considered statistically significant. It was confirmed that all preoperative factors were well matched between the two groups based on the standardized differences (Tables 1 and 2). The resulting score-matched pairs were used for the outcome analyses. All of the propensity score matching processes were performed with the oversight of a statistician.[17]

2-4. Statistical analysis

SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) were used for the data analysis. The results for quantitative variables are presented as the mean ± standard deviation or median and selected quantiles [25^{th}-75^{th} percentile]; categorical variables are summarized as absolute frequencies and percentages. Continuous variables were compared using Student's *t*-test and the Mann–Whitney *U*-test. Categorical variables were compared using Pearson's χ^2 test, except when the expected frequencies were <5, in which case Fisher's exact test was used. In the propensity score-matched sample, the subjects were pair-matched. Each subject in the Mild AI or No AI groups could have one or more than

one echocardiogram measurements at different time intervals. The serial observations from each subject were correlated. To control for the potential correlation between matched pairs and the correlation of repeated measurements within each subject, we analyzed longitudinal outcome variables such as post-LVAD TTE including progression of moderate or greater AI (primary outcome), MR, TR TAPSE, pulmonary artery pressure, BNP levels and NYHA functional status using the generalized linear mixed effect model. We used logit link ("Binomial distribution") for binary outcomes including moderate or greater AI, MR, TR and III or IV NYHA class, and used identity link ("Gaussian distribution") for continuous outcome variables including TAPSE, systolic pulmonary artery pressure, and BNP level. In the generalized mixed effects model for each outcome variable, we set matched-set id as the random effect term to model the potential correlation between matched subjects within each matching set, and we also modelled the serial correlation of repeated measurements from each study subject using the spatial power variance and covariance structure because of the unequal spacing of time intervals. Pre-LVAD severity and LVAD support duration were included in the generalized mixed effects model as fixed effects.

Incidence of overall readmission and readmission caused by congestive heart failure (CHF) were analyzed by the Fine and Gray sub-distribution hazard method with death after LVAD implant as competing risk and reported as a cumulative incidence curve. For the overall readmission analysis, all first readmissions due to any reasons were counted and plotted on cumulative incidence curves, and second or further readmissions were not included. In the analysis of CHF related readmissions, first CHF related readmissions were plotted and any other causes were not counted. Survival was analyzed by the Kaplan–Meier method, evaluating group comparisons with the stratified

log-rank test. Drop-out and end of study period were regarded as censoring events. In the analysis of short-term outcomes McNemar's test was used for categorical variables, and Wilcoxon signed rank test was used for continuous variables based on the propensity score-matched pair. In the analysis of the risk factors for post-LVAD moderate or greater AI in patients with pre-LVAD mild AI, variables with $p \leq 0.05$ in the univariate analysis and also age and aortic valve non-opening were used in the multivariable analysis. Odds ratios (OR) for progressing to moderate or greater AI were calculated with 95% confidence intervals (CI). *P* values ≤ 0.05 were considered to be statistically significant.

3. Results

3-1. Demographic and clinical characteristics

Pre-LVAD implantation demographic and clinical characteristics were compared based on the standardized difference between all of the patients with mild AI (n = 111) and all of the patients with trace or no AI (n = 493) (Tables 1 and 2). After propensity score matching, there was no significant difference with |standardized difference| <0.1 between the Mild AI (n = 101) and the No AI (n = 101) groups in any preoperative variable other than pre-LVAD AI grade (Tables 1 and 2).

3-2. Primary outcome: Progression of AI to moderate or greater after LVAD implantation

Forty-four patients (43.6%) in the Mild AI group progressed to moderate or greater AI, while nine patients (8.9%) in the No AI group developed moderate or greater AI with the mean total follow-up period until death or censoring event of 2.3 ± 1.8 and 2.1 ± 1.8

years, respectively (p=0.32). The generalized linear mixed model analyses demonstrated that both pre-LVAD mild AI (p<0.01) and longer LVAD support duration (p<0.01) were significant risk factors for the incidence of post-LVAD moderate or greater AI (Table 4 and Figure 4).

3-3. Secondary outcomes: Survival, NYHA functional class, and readmission rate

The Kaplan–Meier survival analysis indicated that survival was similar in both groups (p=0.58): 74% at 1 year, 64% at 2 years and 59% at 3 years in the Mild AI group, and 71% at 1 year, 69% at 2 years and 63% at 3 years in the No AI group (Figure 2). In the analysis by generalized linear mixed model, mild AI at the time of LVAD implant was also associated with worse NYHA functional status (p<0.01, Table 4). Although the overall readmission rate was similar in both groups (hazard ratio=1.23, 95% CI: 0.91-1.49, p=0.24, Figure 3A), the readmission rate caused by CHF was significantly higher in the Mild AI group (hazard ratio=2.62, 95% CI: 1.42-4.69, p<0.01, Figure 3B).

3-4. Short-term outcomes

For the short-term outcomes the Mild AI group tended to have lower 30-day mortality (Mild AI vs. No AI; 5.9% vs. 10.9%, p=0.14), lower incidence of right ventricular (RV) failure (14.9% vs. 19.8%, p=0.47), stroke (5.0% vs. 10.9%, p=0.18), gastrointestinal bleeding (19.8% vs. 25.7%, p=0.44), and bleeding requiring reoperation (9.9% vs. 13.9%, p=0.52), although there was no significant difference between the two groups. Additionally, there was no significant difference in hospital stay or other complications, such as renal replacement therapy, surgical site infection and sepsis between the two groups (Table 3).

3-5. Post-LVAD echocardiographic parameters and BNP levels

The mean follow-up periods for the serial TTE after LVAD implantation were similar for the Mild AI and No AI groups (0.8 ± 1.3 vs. 0.7 ± 1.1 years, p=0.20). Also, there was no significant difference in time interval (10.9 ± 3.3 vs. 10.7 ± 3.2, p=0.46) and frequency (2.8 ± 1.4 vs. 2.4 ± 1.2 measurements/patient, p=0.06) of echocardiogram measurements between the two groups. Analysis using generalized linear mixed model demonstrated that pre-LVAD mild AI was associated with not only higher incidence of post-LVAD moderate or greater MR (p<0.01) and post-LVAD moderate or greater TR (p<0.01), but also worse TAPSE (p<0.01) and higher systolic PA pressure (p<0.01) after LVAD implantation (Table 4). Furthermore, post-LVAD BNP levels were significantly higher in the Mild AI group (p<0.01) (Table 4). On the other hand, LVAD support duration was not associated with any response variables other than progression of moderate or greater AI (p<0.01), MR (p<0.01) and BNP levels (p<0.01, Table 4).

3-6. Risk factor analysis for the post-LVAD moderate or greater AI in patients with pre-LVAD mild AI

Table 5 summarizes the results of the risk factor analysis for progression of AI to moderate or greater. Overall, 111 patients had mild AI before implantation of the LVAD. Of these, 48 (43.2%) developed moderate or greater AI during the 2.5 year average follow-up period. The univariate analyses identified the following significant predictors: DT (p<0.01), implantation with a HeartMate 2 device (p=0.02), smaller aortic root diameter (p=0.02) and longer LVAD duration (p<0.01). In the multivariable analysis including age, non-opening aortic valve and variables which had $p \leq 0.05$ in the

univariate analysis, DT status (OR=3.54; 95% CI: 1.46-8.58; $p<0.01$) and longer LVAD duration (OR=1.51; 95% CI: 1.21-1.88; $p<0.01$) were significant risk factors for progression to moderate or greater AI for patients with pre-LVAD mild AI.

4. Discussion

The primary finding of this retrospective study of a propensity-matched cohort was that uncorrected mild AI at the time of LVAD implant and LVAD support duration were associated with a significantly higher risk of post-LVAD moderate or greater AI compared to trace or no AI. Previous non-randomized and non-propensity score matched studies reported even worse AI progression in patients without AI at baseline.[4-6] However, there are no clear guidelines regarding the approach for mild AI at baseline with LVAD implantation.[15] Our findings shed light on this condition and suggest the need for further investigation and the development of better treatment strategies to improve the quality of life and reduce readmissions in the long-term management of these patients.

4-1. Survival and functional status

The two propensity score-matched groups in this study, with mild AI and without AI, had similar survival rates. Toda et al.[18] reported that the development of AI within 1 year after LVAD implantation reduced survival in 43 patients with para-corporeal pulsatile devices compared with patients who did not develop AI. Conversely, other studies with implantable continuous-flow LVADs have suggested that post-LVAD moderate or greater AI was not associated with decreased survival.[6-10,13] The results of those studies were consistent with our findings that mild AI before implantation did not

result in worse survival after implantation compared with patients with no or trace AI, even though many of the patients with mild AI experienced deterioration of their condition.

In a study of 52 patients implanted with continuous-flow LVADs, Imamura et al.[13] found that post-LVAD AI was associated with lower exercise capacity and higher readmission rates compared with no AI. Similarly, our study showed that the higher incidence of moderate or greater AI in patients with pre-LVAD mild AI was significantly associated with worse NYHA functional class and higher rates of readmission because of CHF. Furthermore, the independent risk factors for the progression of AI were an indication for DT and longer LVAD support (Supplemental data). The recent modification to the organ allocation system in the USA has resulted in a larger proportion of patients receiving LVAD implants as DT.[19] As a result, patients can be expected to continue with the LVAD devices for a longer period, even if they subsequently become eligible for heart transplant. Therefore, a surgical intervention for pre-LVAD mild AI needs to be positively considered, especially for patients who will stay on the LVAD for a long period of time, irrespective of BTT or DT indication, in order to experience better functional status.

4-2. Surgical intervention for pre-LVAD AI

It remains unclear whether concomitant aortic valve procedures for patients with pre-LVAD mild AI are beneficial for their functional status. A large observational study based on INTERMACS data compared the incidence of AI and survival after LVAD implantation between patients who underwent no concomitant aortic valve procedure (n = 5,039) and those who underwent aortic valve closure (n = 125), aortic valve repair

with central suture (n = 95), and aortic valve replacement (n = 85).[20] In this study, aortic valve closure was associated with the highest mortality rates, and aortic valve repair was associated with the highest incidence of AI progression. Fukuhara et al. reported that concomitant aortic valve repair for patients with mild AI pre-LVAD reduced the incidence of moderate or greater AI after the LVAD implantation, although the procedure had no significant impact on survival when compared with the patients with uncorrected mild AI. In this study post-LVAD functional data were not reported.[21] In our study, the data suggested that unrepaired mild AI resulted in significantly worse functional status post LVAD. Considering this result, we now more carefully assess the AI grade and proactively perform concomitant aortic valve central suture (Park stitch) for mild or greater AI. Further analysis is warranted to evaluate the functional and survival benefits of concomitant aortic valve procedure for patients with mild AI at the time of LVAD implant.

4-3. Intervention for post-LVAD AI

In this study, 44% of the Mild AI group patients developed moderate or greater AI, and interestingly, 9% of patients in the No AI group developed "*de novo*" AI during the 2 year follow-up term. Some of these patients who developed severe heart failure underwent either TAVR or surgical aortic valve repair with Park stitch, which resulted in sufficient mid-term outcomes. Some previous case reports also showed excellent outcomes of transcatheter aortic valve replacement (TAVR) for patients with post-LVAD AI.[22, 23] This might be preferred for someone who is a heart transplant candidate to avoid further surgical interventions before complicated heart transplant with LVAD explant surgery, but the decision making process can be complicated for those who are

not adequate candidates for TAVR based on the etiology of AI, aortic annular size and degree of calcification. Further investigations are warranted regarding TAVR versus surgical repair as well as the timing of the intervention for *de novo* AI and worsening significant AI after LVAD implant.

4-4. Effects of AI progression on MR, TR, and RV function

In approximately 2 years of follow-up after LVAD implantation, the patients with mild AI before implantation had significantly worse MR and TR grades and worse RV function with reduced TAPSE than the patients who had no or trace AI. The effects of AI on MR, TR, and RV function after LVAD implantation have not been well investigated. According to the Cowger et al. study of 166 patients implanted with continuous-flow LVADs who had no AI pre-LVAD, there was no significant association between post-LVAD moderate or greater AI and worse MR or RV function.[8] Conversely, our study suggested that mild AI pre-LVAD may lead to worse MR, worse TR, and worse RV function compared to the patients with no AI. It is highly likely that the NYHA functional capacity of the mild AI group was adversely affected by their worse MR, TR, and RV function. Furthermore, it is also possible that echocardiographic evaluation of AI grade may underestimate the degree of AI in LVAD patients compared to non-LVAD patients with significant AI. The AI grade for LVAD patients has been assessed using the traditional method for non-LVAD patients, such as effective regurgitant orifice area or regurgitant jet. For patients with LVAD, AI could occur during a much longer period in a cardiac cycle throughout the diastolic phase or even part of the isovolumetric phase. Precise echocardiographic analyses are desired to

understand the significance of AI and its adverse effect on functional capacity in patients with LVAD.

4-5. Study limitations

This retrospective study has some limitations. First, we used propensity score matching to adjust the patient populations for the groups with pre-LVAD mild AI and pre-LVAD no or trace AI. However, this reduced the number of patients in the study. Second, the study included patients who underwent LVAD surgery performed by multiple surgeons using different surgical strategies. Third, some post-LVAD factors such as medications, arterial pressure, and total aortic flow, which may have affected hemodynamics, were not included in the analysis. Fourth, only patients who were implanted with HeartMate 2 and HeartWare were enrolled in this study, so no conclusions could be made about the possible effects of AI with any other devices. Fifth, the follow-up period is different in each patient because of the retrospective review. As a result, a mixed effect model was necessary to appropriately assess the outcome of each patient group. Additionally, we focused on the freedom from readmission related to CHF rather than severity of CHF with multiple readmissions. Therefore, second or further readmission events with CHF were not collected to run a repeated events model for this study. Finally, no conclusions can be drawn regarding the effects of performing a concomitant aortic valve procedure at the time of LVAD implantation for patients with mild AI, because patients who underwent this procedure were excluded from the study.

5. Conclusions

Uncorrected mild AI at the time of LVAD implantation was associated with a higher risk of progression to moderate or greater AI and worse NYHA functional class and more CHF related readmissions in the mid-term after LVAD implantation compared with no or trace AI. Indication for DT and LVAD support duration were independent risk factors for progression to moderate or greater AI in patients with pre-LVAD mild AI. Concomitant aortic valve procedure may need to be considered for mild or greater AI at the time of LVAD implant to prevent future development of moderate or greater AI and deterioration of functional capacity. Further investigations of the efficacy and safety of surgical treatment for mild AI at the time of LVAD implant are warranted. This may help improve the quality of life in DT and BTT patients with the expected longer LVAD management due to the new US heart allocation system.

6. Compliance with ethical standards

Conflict of interest

The authors declare no conflict of interest.

7. References

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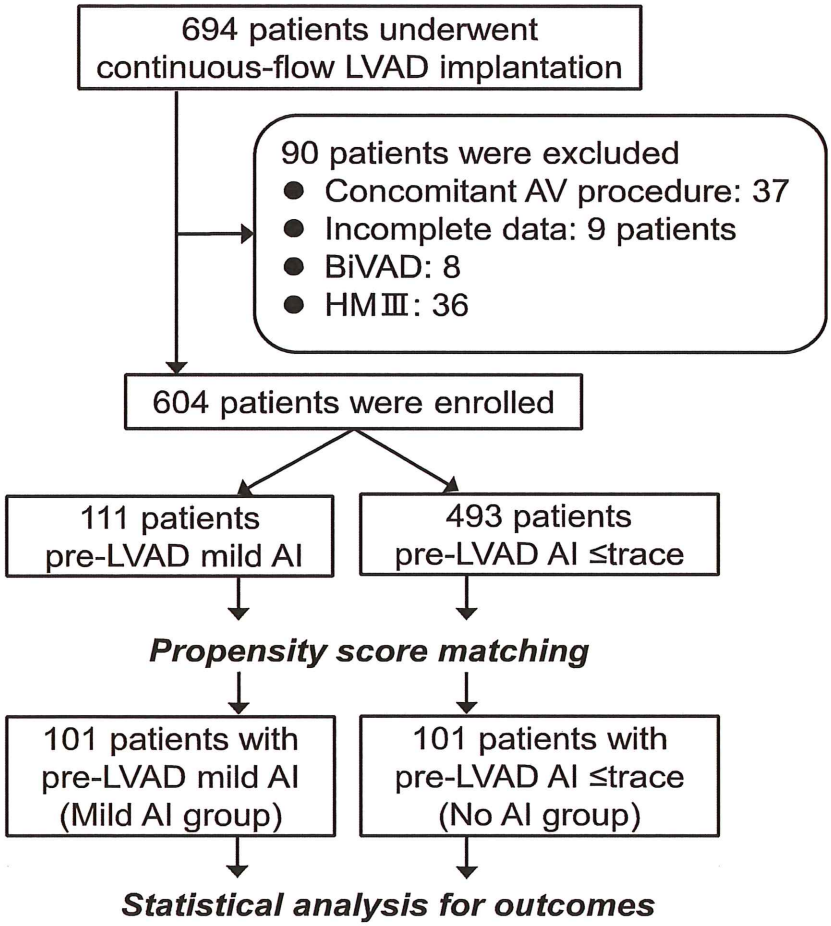
8. Figures

8-1. Figure 1. Patient enrollment.

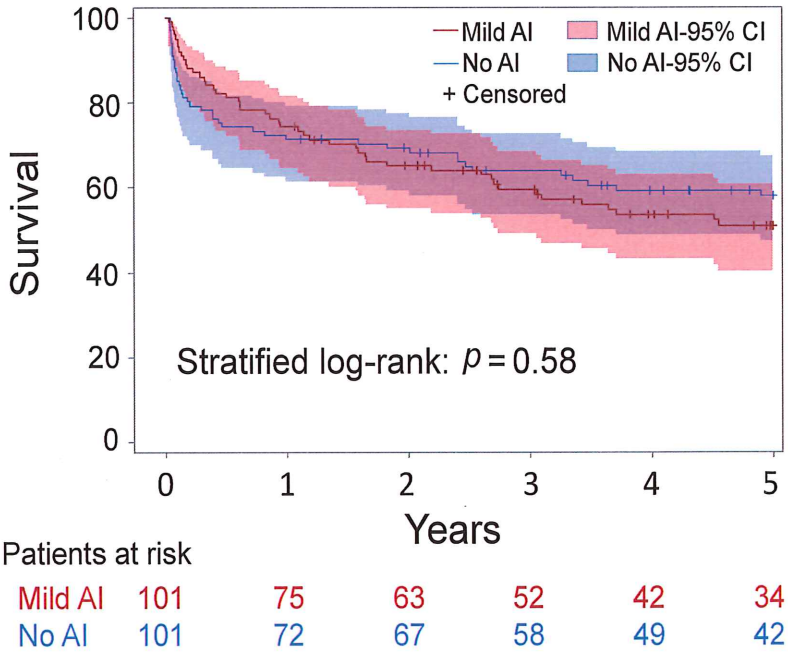
LVAD, left ventricular assist device; HM, HeartMate; AI, aortic insufficiency.



8-2. Figure 2. Kaplan–Meier survival curve for the Mild AI (n = 101) and No AI (n = 101) groups.

The stratified log-rank test was used for estimating survival difference between propensity score matched groups. Drop-out or end of study period were regarded as censoring events. 95% confidence interval bands were shown with the survival curve.

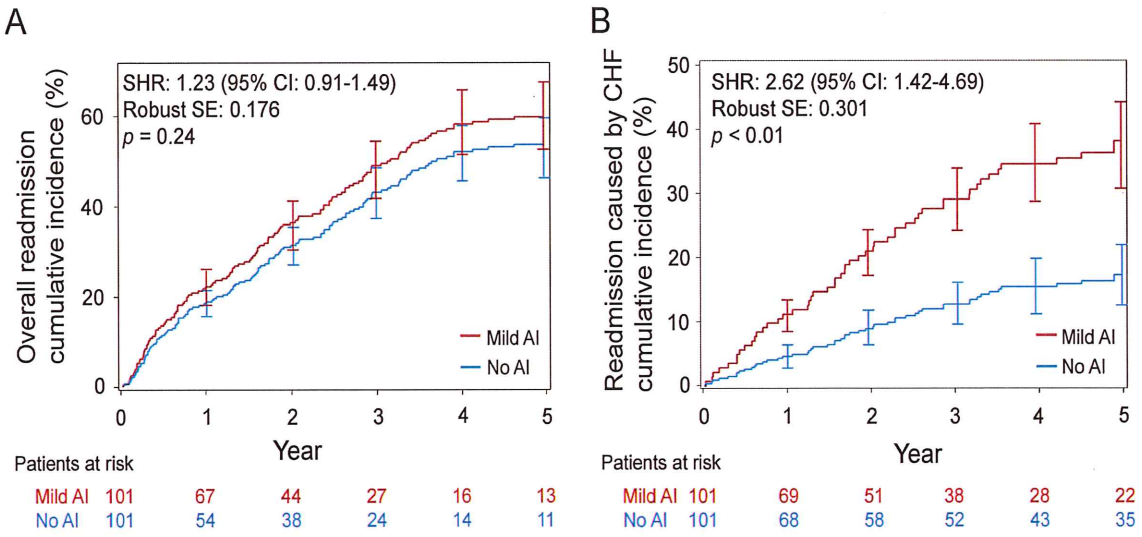
AI, aortic insufficiency; LVAD, left ventricular assist device; CI, confidence interval.



8-3. Figure 3A: Cumulative incidence rate of overall readmission for the Mild AI group (Red, n = 101) and the No AI group (Blue, n =101). **3B**: Cumulative incidence rate of readmission caused by CHF for the Mild AI group (Red, n = 101) and the No AI group (Blue, n =101).

Cumulative incidence curves with 95% confidence interval bars were analyzed by the Fine and Gray sub-distribution hazard method with death as competing risk. For overall readmission analysis, all first readmissions due to any reasons were counted and plotted on cumulative incidence curves, and second or further readmissions were not included. In the analysis of CHF related readmissions, any other causes were not counted but first CHF related readmissions were plotted. Drop-out or end of study period were censored. The robust standard errors were used for estimating the difference in cumulative incidence of readmission between propensity-score matched groups.

AI, aortic insufficiency; CHF, congestive heart failure; SHR, sub-distribution hazard ratio; SE, standard error; CI, confidence interval.



Tables

9-1. Table 1. Comparisons of demographic and clinical characteristics between patients with the Mild AI and No AI groups, before and after propensity score matching

	Before PS matching			After PS matching		
	Mild AI n = 111	No AI n = 493	Standardized differences	Mild AI n = 101	No AI n = 101	Standardized differences
Age, year	59.6 ± 11.4	54.7 ± 12.2	0.415	59.1 ± 11.6	58.8 ± 9.2	0.037
Male, n (%)	78 (70.3)	382 (77.5)	-0.164	71 (70.3)	69 (68.3)	0.043
BMI, kg/m^2	28.6 ± 5.6	29.2 ± 6.7	-0.097	28.8 ± 5.6	29.2 ± 6.3	-0.067
INTERMACS, n (%)						
1	40 (36.0)	160 (32.5)	0.074	38 (37.6)	38 (37.6)	0
2	62 (55.9)	278 (56.3)	-0.008	54 (53.5)	54 (53.5)	0
≥3	9 (8.1)	55 (11.2)	-0.105	9 (8.9)	9 (8.9)	0
Ischemic disease, n (%)	49 (44.1)	206 (41.8)	0.046	47 (46.5)	48 (47.5)	-0.020
Indication, n (%)			-0.060			0.040
BTT	59 (53.2)	277 (56.2)		54 (53.5)	52 (51.5)	
DT	52 (46.8)	216 (43.8)		47 (46.5)	49 (48.5)	
Device, n (%)			-0.073			-0.048
HeartMate 2	83 (74.8)	384 (77.9)		78 (77.2)	80 (79.2)	
HeartWare	28 (25.2)	109 (22.1)		23 (22.8)	21 (20.8)	
Systolic arterial pressure, mmHg	101.4 ± 12.5	102.8 ± 15.4	-0.100	101.5 ± 13.3	100.8 ± 14.1	0.051
Diastolic arterial pressure, mmHg	64.6 ± 9.5	65.9 ± 11.7	-0.122	64.4 ± 9.6	63.7 ± 12.5	0.063
Heart rate, bpm	89.7 ± 16.6	91.5 ± 16.8	-0.153	89.8 ± 16.8	90.5 ± 17.5	-0.041
NYHA, n (%)						

I	0	0	0	0	0	0
II	1 (0.9)	5 (1.0)	-0.010	0	0	0
III	16 (14.4)	54 (11.0)	0.102	14 (13.9)	13 (12.9)	0.029
IV	94 (84.7)	434 (88.0)	-0.096	87 (86.1)	88 (87.1)	-0.029
Cardiogenic shock, n (%)	48 (43.2)	236 (47.9)	-0.094	45 (42.7)	47 (41.6)	0.022
Resuscitation, n (%)	4 (3.6)	15 (3.0)	0.033	4 (4.0)	4 (4.0)	0
Preoperative IABP, n (%)	29 (26.1)	162 (32.9)	-0.150	25 (24.8)	29 (28.7)	-0.088
Preoperative Impella, n (%)	13 (11.7)	51 (10.3)	0.045	11 (10.9)	10 (9.9)	0.032
Preoperative ECMO, n (%)	12 (10.8)	53 (10.8)	0	11 (10.9)	13 (12.9)	-0.062
Arrhythmia, n (%)	57 (51.3)	296 (60.0)	-0.176	55 (54.5)	60 (59.4)	-0.099
Diabetes, n (%)	48 (43.2)	237 (48.1)	-0.098	46 (45.5)	50 (49.5)	-0.080
Dyslipidemia, n (%)	78 (70.3)	371 (75.3)	-0.112	72 (71.3)	76 (75.2)	-0.088
Dialysis, n (%)	3 (2.7)	23 (4.7)	-0.106	3 (3.0)	4 (2.0)	0.064
Hypertension, n (%)	78 (70.3)	369 (74.8)	-0.101	71 (70.3)	75 (74.3)	-0.089
Lung disease, n (%)	48 (43.2)	236 (47.9)	-0.094	44 (43.6)	46 (45.5)	-0.038
Cerebrovascular disease, n (%)	23 (20.7)	80 (16.2)	0.116	22 (21.8)	19 (18.8)	0.075
BNP, pg/ml	1091 [598-1698]	947 [553-1577]	0.116	949 [538-1606]	1075 [637-1758]	-0.087

Continuous variables are presented as mean ± standard deviation and categorical variables as number (%). BNP is presented as median [25th-75th percentile]. AI, aortic insufficiency; LVAD, left ventricular assist device; PS, propensity score; BMI, body mass index; BTT, bridge to transplantation; DT, destination therapy; NYHA, New York Heart Association functional class; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; BNP, brain natriuretic peptide.

9-2. Table 2. Comparisons of preoperative echocardiography, cardiac catheterization, and operative data between the Mild AI and No AI groups, before and after propensity score matching

	Before PS matching			After PS matching		
	Mild AI n = 111	No AI n = 493	Standardized differences	Mild AI n = 101	No AI n = 101	Standardized differences
Preoperative echocardiography						
Aortic root diameter, mm	32.5 ± 3.6	31.8 ± 3.8	0.189	32.5 ± 3.7	32.2 ± 3.5	0.083
Sclerotic aortic valve, n (%)	48 (43.2)	123 (24.9)	0.394	40 (39.6)	36 (37.6)	0.041
LAD, mm	48.9 ± 7.5	49.0 ± 8.0	-0.013	48.8 ± 7.6	49.2 ± 7.4	-0.053
LVEDD, mm	68.7 ± 8.9	68.5 ± 10.5	0.021	68.9 ± 9.0	69.0 ± 11.4	-0.010
LVDs, mm	61.7 ± 10.0	61.3 ± 11.6	0.037	61.8 ± 10.1	61.7 ± 11.9	0.009
RVEDD, mm	42.8 ± 9.2	42.5 ± 9.3	0.032	42.6 ± 9.3	42.5 ± 9.5	0.011
LVEF, %	18.0 ± 7.0	18.5 ± 8.1	-0.066	18.1 ± 7.2	18.4 ± 8.5	-0.038
MR ≥mod, n (%)	67 (60.4)	256 (51.9)	0.172	62 (61.4)	60 (59.4)	0.041
TR ≥mod, n (%)	32 (28.8)	172 (34.9)	-0.131	29 (28.7)	32 (31.7)	-0.065
TAPSE, mm	14.1 ± 5.3	13.9 ± 5.5	0.037	14.2 ± 5.2	14.1 ± 5.6	0.019
Systolic PA pressure, mmHg	52.1 ± 15.0	48.8 ± 12.1	0.242	51.1 ± 14.8	51.4 ± 11.5	-0.025
Cardiac catheterization						
RA pressure, mmHg	14.0 ± 6.8	14.9 ± 7.0	-0.130	13.9 ± 6.7	14.5 ± 7.3	-0.086
Mean PA pressure, mmHg	40.0 ± 10.0	40.3 ± 9.7	-0.037	39.6 ± 10.2	39.8 ± 9.4	-0.020
Wedge pressure, mmHg	26.6 ± 8.1	27.5 ± 8.4	-0.109	26.6 ± 8.2	27.2 ± 8.7	-0.071
PVR, Wood units	4.2 ± 2.2	3.9 ± 2.4	0.130	4.1 ± 2.1	3.9 ± 2.0	0.098
CI, l/min/m^2	1.8 ± 0.5	1.8 ± 0.5	0	1.8 ± 0.5	1.8 ± 0.4	0

Operative data						
Surgical approach, n (%)						
Full sternotomy	100 (90.1)	464 (94.1)	-0.149	93 (92.1)	94 (93.1)	-0.038
Partial sternotomy	6 (5.4)	17 (3.4)	0.098	4 (3.0)	4 (3.0)	0
Left thoracotomy	5 (4.5)	12 (2.4)	0.115	4 (2.0)	3 (1.0)	0.054
CPB time, min	77.8 ± 37.1	76.4 ± 39.6.	0.053	76.9 ± 34.9	76.0 ± 37.9	0.025
MV procedure, n (%)	1 (0.9)	13 (2.6)	-0.130	1 (1.0)	1 (1.0)	0
TV procedure, n (%)	14 (12.6)	66 (13.4)	-0.024	13 (12.9)	13 (12.9)	0

Continuous variables are shown as mean ± standard deviation and categorical variables are shown as number (%). AI, aortic insufficiency; LVAD, left ventricular assist device; PS, propensity score; AV, aortic valve; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; RVEDD, right ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; ≥mod, moderate or greater; TR, tricuspid valve regurgitation; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery; RA, right atrium; PVR, pulmonary vascular resistance; CO, cardiac output; CI, cardiac index; CPB, cardio-pulmonary bypass; MV, mitral valve; TV, tricuspid valve.

9-3. Table 3. Short-term outcomes for the Mild AI and No AI groups

	Mild AI, n = 101	No AI, n = 101	*p*-value
Hospital stay, days	27.3 ± 20.8	26.8 ± 22.2	0.87
Complications within 30 days, n (%)			
Mortality	6 (5.9)	11 (10.9)	0.14
RV failure	15 (14.9)	20 (19.8)	0.47
Unplanned RVAD	10 (9.9)	7 (6.9)	0.58
Inotropic use over 2 weeks after LVAD	5 (5.0)	13 (12.9)	0.10
Stroke	5 (5.0)	11 (10.9)	0.18
Renal replacement therapy	9 (8.9)	11 (10.9)	0.69
GI bleeding	20 (19.8)	26 (25.7)	0.44
Bleeding requiring reoperation	10 (9.9)	14 (13.9)	0.52
Surgical site infection	6 (5.9)	6 (5.9)	0.99
Sepsis	11 (10.9)	11 (10.9)	0.99

McNemar's test was used for categorical variables, and Wilcoxon signed rank test was used for continuous variables in propensity-score matched pair. Continuous variables are shown as mean ± standard deviation and categorical variables are shown as number (%). AI, aortic insufficiency; RVAD, right ventricular assist device; GI, gastrointestinal.

9-4. Table 4. The generalized linear mixed effect model analysis of pre-LVAD mild AI on post-LVAD echocardiogram parameters, BNP and NYHA functional status

	Estimate	SE	*p*-value
Post-LVAD AI ≥mod			
Mild AI	2.03	0.36	<0.01
LVAD support duration	0.71	0.12	<0.01
Post-LVAD MR ≥mod			
Mild AI	0.95	0.26	<0.01
LVAD support duration	0.51	0.11	<0.01
Post-LVAD TR ≥mod			
Mild AI	0.74	0.23	<0.01
LVAD support duration	0.09	0.09	0.33
Post-LVAD TAPSE			
Mild AI	-3.08	0.54	<0.01
LVAD support duration	-0.30	0.20	0.14
Post-LVAD systolic PA pressure			
Mild AI	5.94	0.84	<0.01
LVAD support duration	0.06	0.31	0.85
Post-LVAD BNP			
Mild AI	364.27	76.03	<0.01
LVAD support duration	87.36	28.31	<0.01
Post-LVAD NYHA ≥Class III			
Mild AI	1.19	0.25	<0.01
LVAD support duration	0.13	0.09	0.13

The generalized linear mixed model included all post-LVAD echocardiogram, BNP and

NYHA data with sample size of 281 in the Mild AI group and 241 in the No AI group. BNP and NYHA were collected at the same time as the echocardiogram measurements. LVAD, left ventricular assist device; BNP, brain natriuretic peptide; AI, aortic insufficiency; SE, standard error; ≥mod, moderate or greater; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery; NYHA, New York Heart Association functional class.

9-5. Table 5. Univariate and multivariable analyses for risk factors for developing moderate or greater AI in patients with pre-LVAD mild AI (n = 111)

	Univariate analysis			Multivariable analysis		
	Post-LVAD ≥Mod AI n = 48	Post-LVAD ≤Mild AI n = 63	*p*-value	Odds ratio	95% CI	*p*-value
Age, year	60.5 ± 10.6	58.8 ± 12.0	0.44	1.02	0.97-1.06	0.48
Male, n (%)	33 (68.8)	45 (71.4)	0.76			
BMI, kg/m^2	28.9 ± 5.5	28.4 ± 5.8	0.62			
INTERMACS, n (%)			0.68			
1	18 (37.5)	22 (34.9)				
2	26 (54.2)	36 (57.1)				
≥3	4 (8.3)	5 (8.0)				
Ischemic disease, n (%)	22 (45.8)	27 (42.9)	0.75			
Indication, n (%)			<0.01	3.54	1.46-8.58	<0.01
BTT	17 (35.4)	42 (66.7)				
DT	31 (64.6)	21 (33.3)				
Device, n (%)			0.02	0.70	0.28-2.14	0.53
HeartMate 2	41 (85.4)	42 (66.7)				
HeartWare	7 (14.6)	21 (33.3)				
Systolic arterial pressure, mmHg	101.0 ± 14.1	101.6 ± 11.2	0.79			
Diastolic arterial pressure, mmHg	63.9 ± 8.6	65.1 ± 10.1	0.50			
Heart rate, bpm	87.3 ± 16.4	91.6 ± 16.7	0.18			
NYHA, n (%)			0.21			

I	0	0				
II	1 (2.2)	0				
III	4 (8.7)	12 (20.0)				
IV	43 (89.1)	51 (80.0)				
Cardiogenic shock, n (%)	22 (45.8)	26 (41.3)	0.63			
Resuscitation, n (%)	3 (6.3)	1 (1.6)	0.19			
Preoperative IABP, n (%)	15 (31.3)	14 (22.2)	0.28			
Preoperative Impella, n (%)	4 (8.3)	9 (14.3)	0.33			
Preoperative ECMO, n (%)	4 (8.3)	8 (12.7)	0.46			
Arrhythmia, n (%)	23 (47.9)	34 (54.0)	0.53			
Diabetes, n (%)	19 (39.6)	29 (46.0)	0.50			
Dyslipidemia, n (%)	33 (68.8)	45 (71.4)	0.76			
Dialysis, n (%)	0	3 (4.8)	0.13			
Hypertension, n (%)	33 (68.8)	45 (71.4)	0.76			
Lung disease, n (%)	21 (43.8)	27 (42.9)	0.93			
Cerebrovascular disease, n (%)	14 (29.3)	9 (14.3)	0.06			
BNP, pg/ml	1192 [572.5-1833.8]	1028.0 [616.0-1503.0]	0.91			
Preoperative echocardiography						
Aortic root diameter, mm	31.5 ± 3.8	33.2 ± 3.5	0.02	1.07	0.94-1.22	0.30
Sclerotic aortic valve, n (%)	18 (37.5)	30 (47.6)	0.29			
LAD, mm	49.5 ± 8.1	48.4 ± 7.1	0.45			
LVEDD, mm	70.2 ± 8.5	67.6 ± 9.1	0.12			
LVDs, mm	63.3 ± 9.9	60.5 ± 10.0	0.14			

RVEDD, mm	43.1 ± 8.4	42.6 ± 9.8	0.79			
LVEF, %	19.2 ± 7.1	17.0 ± 6.9	0.10			
MR ≥mod, n (%)	32 (66.7)	35 (57.1)	0.24			
TR ≥mod, n (%)	13 (27.1)	19 (30.2)	0.72			
TAPSE, mm	14.7 ± 4.9	13.6 ± 5.5	0.29			
Systolic PA pressure, mmHg	52.2 ± 15.4	52.1 ± 14.7	0.97			
Cardiac catheterization						
RA pressure, mmHg	13.1 ± 7.2	14.7 ± 6.4	0.29			
Mean PA pressure, mmHg	38.7 ± 11.3	40.5 ± 8.9	0.39			
Wedge pressure, mmHg	26.0 ± 8.4	27.0 ± 7.8	0.54			
PVR, Wood units	4.2 ± 2.3	4.3 ± 2.1	0.90			
CI, l/min/m^2	1.7 ± 0.4	1.8 ± 0.5	0.24			
Operative data						
Surgical approach, n (%)			0.29			
Full sternotomy	43 (89.6)	57 (90.5)				
Partial sternotomy	4 (8.3)	2 (3.2)				
Left thoracotomy	1 (2.1)	4 (6.3)				
LVAD pump speed, rpm						
HeartMate 2	9228.2 ± 395.5	9185.7 ± 736.7	0.75			
HeartWare	2795.6 ± 138.1	2662.1 ± 200.9	0.09			
LVAD duration, years	3.6 ± 2.1	1.7 ± 1.8	<0.01	1.51	1.21-1.88	<0.01
Aortic valve non-opening, n (%)	25 (52.1)	30 (47.6)	0.64	1.25	0.75-1.84	0.55

Continuous variables are presented as mean ± standard deviation and categorical variables as number (%). BNP is presented as median and 25th - 75th quantile. AI, aortic

insufficiency; LVAD, left ventricular assist device; ≥mod, moderate or greater; ≤mild, mild or less; 95% CI, 95% confidence interval; BMI, body mass index; BTT, bridge to transplantation; DT, destination therapy; NYHA, New York Heart Association functional class; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; BNP, brain natriuretic peptide; AV, aortic valve; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; RVEDD, right ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; mod, moderate; TR, tricuspid valve regurgitation; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery; RA, right atrium; PVR, pulmonary vascular resistance; CI, cardiac index; CPB, cardio-pulmonary bypass.