Impact of Baseline Mitral Regurgitation on Postoperative Outcomes After Left Ventricular Assist Device Implantation as Destination Therapy

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ABSTRACT

Background. Currently, there are no guidelines for management of moderate to severe mitral regurgitation (MR) in patients undergoing left ventricular assist device (LVAD) implantation. The present study aimed to investigate the impact of baseline MR on short and midterm survival in patients who had LVAD as destination therapy (DT).

Methods. The DT-LVAD patients were classified into 2 groups based on baseline MR status: $\geq$ moderate MR and $<$ moderate MR. Baseline clinical characteristics and post-LVAD implant adverse events were compared. Unadjusted mortality rates at 30 days, 1 year, and 2 years were analyzed.

Results. Of 91 patients studied, 62 (68%) had $\geq$ moderate MR before LVAD implantation; $\geq$ moderate MR patients had a higher incidence of concomitant pulmonary disease (11% vs 0%; $P = .001$) and $\geq$ moderate tricuspid regurgitation (55% vs 23%, $P = .004$) than $<$ moderate MR patients. Other baseline clinical characteristics were similar in both groups. Post-LVAD adverse events did not differ between the 2 groups. Survival rates at 30 days, 1 year, and 2 years for both groups ($\geq$ moderate MR vs $<$ moderate MR) were 90% vs 100% ($P = .03$), 63% vs 90% ($P = .001$), and 52% vs 83% ($P = .002$), respectively. On multivariable analysis, age, female sex, $\geq$ moderate tricuspid regurgitation, and $\geq$ moderate MR at baseline were found to be independent predictors of overall all-cause mortality. Overall survival was significantly lower in the $\geq$ moderate MR group than the $<$ moderate MR group (log-rank test, $P = .03$).

Conclusion. In DT LVAD patients, $\geq$ moderate MR is common and is associated with worse survival at both short and midterm follow-up.

MITRAL regurgitation (MR) is commonly seen in patients with severe heart failure for whom implantation of left ventricular assist device (LVAD) is considered. Most commonly, MR in these patients is functional MR because of left ventricular dilation and tends to respond to LV remodeling after LVAD insertion [1]. Unlike aortic and tricuspid insufficiency whose post-LVAD pathophysiology is more clearly understood, with MR there is no clinical consensus for the management of MR at the time of LVAD implantation.

Strategies and outcomes for patients with moderate to severe MR undergoing LVAD implantation have been mixed. Some authors have reported improved survival [2] or clinical benefit [3,4] after MV procedures. On the other hand, a few studies have observed greater improved survival in patients with moderate to severe MR than those with less

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MR without MV intervention [5]. Resolution of MR has been reported and this has been associated with remodeling of LV after LVAD implant [6].

Significant MR can contribute to pulmonary arterial pressure increase especially in patients who received LVAD as destination therapy (DT). Clinical course of DT patients with significant MR has not been well documented. Concomitant tricuspid regurgitation (TR) may further complicate pathophysiology, and its relationship with MR is ambiguous. Most studies have reviewed bridge to transplant (BTT) and DT patients as 1 group. However, the clinical benefit of MV procedures may not be apparent in BTT patients because of shorter duration of LVAD support than that of DT patients. Also, the association between baseline MR and survival among DT-LVAD patients has not been reported.

We hypothesized that moderate to severe MR negatively affects survival of DT patients after implantation of LVAD. This study aimed to investigate the impact of baseline MR on short and midterm survival in patients who underwent LVAD implantation as DT.

PATIENTS AND METHODS

Patient Selection

All patients implanted with an LVAD between July 2008 and February 2017 at our center were identified from a prospectively maintained database approved by the Institutional Review Board. Patients who were deemed 1. ineligible for heart transplant by a multidisciplinary heart failure team, and 2. adequate for DT with LVADs were selected. Criteria for determining ineligibility for heart transplant by the heart team included 1. pulmonary hypertension, 2. morbid obesity with body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 35, and 3. comorbidities such as insulin dependent diabetes mellitus with end-organ damage or chronic renal failure. Only patients who had a preoperative transthoracic echocardiogram within at least 3 months before LVAD implantation were included in the study. Those who had a concomitant right ventricular assist device were excluded from the study.

Assessment of Valvular Regurgitation

Preoperatively, all transthoracic echocardiograms were performed by a single echocardiographer who was blinded to patient outcomes. The MR and TR were assessed with qualitative and quantitative echocardiographic parameters, and severity of regurgitation was classified into mild, moderate, and severe according to the American Society of Echocardiography recommendations [7]. Patients were divided into 2 groups based on the severity of MR: $\geq$ moderate MR and $<$ moderate MR.

Device Implantation

The LVAD was implanted via median sternotomy as described elsewhere [8]. All patients in this study were implanted with HeartMate II LVAD (St Jude Medical, St Paul, Minn, United States). No patients underwent aortic, mitral, and tricuspid valve procedure at the time of LVAD implantation.

Postoperative Follow-up

Data on baseline clinical characteristics, intra- and postoperative outcomes including postimplantation hospitalization and survival were extracted and compared between patient groups. Postoperative complications included device malfunction, thrombosis, major infection, and stroke. Definitions of these adverse events have been published previously [8]. Postoperative follow-up was performed at 1 week, 2 weeks, and monthly postimplantation for the first 3 months then annually afterward. Information of survival was obtained from patients' charts, national death registries, and contact with patients whose information was not found in follow-up charts.

Statistical Analysis

Continuous variables of patients in each group were summarized as mean (standard deviation [SD]) and categorical variables as numbers and percentages. Comparisons of continuous variables were made with the t test, and Pearson χ^2 tests were used to evaluate statistical significance between categorical variables. A univariable Cox regression analysis was performed to identify predictors of overall all-cause mortality. Variables included in the model were all baseline and procedural covariates including patient age, body mass index, race, etiology of heart failure, time to first LVAD implantation, diabetes mellitus, coronary artery disease, previous coronary artery bypass grafting or valve surgery, peripheral artery disease, chronic lung disease, chronic renal failure (glomerular filtration rate $<$ 30 mL/min/1.73 m^2), baseline left ventricular ejection fraction, severity of MR, and TR. Only variables that satisfied an entry criterion of P value less than .05 were used to build a multivariable Cox proportional hazards model. Kaplan-Meier survival curves were used to estimate survival, and the log-rank test was used to compare survival between patient groups. All analysis was 2-tailed and performed using JMP Version 10 (SAS, Cary, NC, United States). A P value less than .05 was considered statistically significant.

RESULTS

Between July 2008 and February 2017, a total of 91 patients (55 [SD, 3] years old) had LVAD implantation as a DT at our institution. The study cohort was predominantly male. On preimplantation echocardiography 68% (n = 62) were found to have moderate to severe MR while only 32% (n = 29) had less than moderate MR.

Table 1 compares baseline demographic data, clinical, and echocardiographic characteristics between patient groups. No significant differences in baseline demographics and clinical characteristics were seen in the 2 groups. Other baseline echocardiographic parameters were comparable between the 2 groups except for baseline TR. A significantly higher incidence of moderate to severe TR was seen in patients with moderate to severe MR (55% vs 23%; P = .004).

Postoperative adverse events after LVAD implantation are shown in Table 2. Overall, postoperative complications were noted in 77% of the patients, 54% were discharged home, and 57% were rehospitalized within 1 year post implant. After a median follow-up of 19 months, unadjusted survival rates were 73% (n = 25) in 1 year and 63%

Table 1. Baseline Demographic and Clinical Characteristics of Study Population

Variable	Overall (n = 91)	≥ Moderate MR (n = 62)	< Moderate MR (n = 29)	*P* Value
Age, mean (SD), y	55 (13)	56 (13)	54 (15)	.58
Sex, No. male (%)	70 (77)	45 (73)	25 (86)	.14
Race				
African American	37 (41)	27 (44)	10 (35)	.41
White	54 (59)	35 (56)	19 (65)	
Primary diagnosis, No. (%)				
ICM	38 (42)	24 (38)	14 (48)	.39
NIDCM	53 (58)	38 (61)	15 (52)	
Diagnosis to implant, time				
<1 mo	4 (4)	3 (5)	1 (4)	
1 mo-1 y	9 (10)	5 (8)	4 (14)	.76
1–2 y	16 (18)	10 (16)	6 (21)	
>2 y	62 (7)	44 (71)	18 (63)	
BMI, mean (SD)	31.3 (6.8)	30.9 (6.8)	32.1 (6.9)	.46
Blood group, No. (%)				
A	35 (38)	28 (45)	7 (24)	
B	20 (22)	13 (21)	7 (24)	.10
AB	2 (2)	2 (3)	0 (0)	
O	34 (37)	19 (34)	15 (52)	
Comorbidity, No. (%)				
Pulmonary HT	7 (8)	3 (5)	4 (13)	.68
Chronic renal failure	5 (7)	2 (3)	3 (10)	.54
COPD	7 (8)	3 (5)	4 (13)	.68
PVD	7 (8)	3 (5)	4 (13)	.15
Previous cardiac surgery, No. (%)				
CABG	16 (18)	11 (18)	5 (17)	.95
AVR	2 (2)	2 (3)	0 (0)	.21
MVR	7 (8)	3 (5)	4 (14)	.15
Baseline Echocardiographic Parameters				
LVEF, No. (%)				
<20	65 (73)	44 (71)	21 (72)	
20–29	21 (24)	15 (24)	6 (21)	.31
30–39	5 (3)	3 (5)	2 (7)	
Aortic regurgitation, No. (%)				
≥ Moderate	7 (8)	5 (8)	2 (7)	
< Moderate	84 (92)	57 (92)	27 (93)	.84
Tricuspid regurgitation, No. (%)				
≥ Moderate	40 (44)	34 (55)	6 (23)	
< Moderate	51 (56)	27 (45)	23 (77)	.004

Abbreviations: AVR, aortic valve replacement; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HT, hypertension; ICM, ischemic cardiomyopathy; IDCM, idiopathic cardiomyopathy; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVR, mitral valve replacement or repair; NIDCM, nonischemic idiopathic cardiomyopathy; PVD, peripheral vascular disease.

(n = 34) in 2 years for the entire population. Figure 1 compares Kaplan-Meier survival curves between both patient groups. Survival was significantly worse in the moderate to severe MR group than the ≤ moderate MR group (log-rank test, $P = .03$).

Analysis of mortality based on the severity of MR and TR is shown in Figure 2. Patients were divided into 4 subgroups: ≥ moderate MR and < moderate TR, ≥ moderate (MR + TR), < moderate (MR + TR), and < moderate MR and ≥ moderate TR. At both 1 and 2 years post implantation, survival was noted to be lowest in the ≥ moderate (MR + TR) subgroup ($P = .004$ and .04, respectively).

Findings from the univariable and multivariable Cox proportional hazards models are shown in Table 3. Preoperative factors that were associated with mortality at a univariate level were age older than 60 years, female sex, rhythm other than sinus, ≥ moderate MR, and ≥ moderate TR. On multivariate analysis, age older than 60 years, female sex, ≥ moderate MR and ≥ moderate TR were found to be independently associated with all-cause mortality.

DISCUSSION

In the present study we demonstrated that moderate to severe MR is common and a significant risk factor for increased mortality in patients undergoing LVAD implantation as DT. Furthermore, patients with ≥ moderate MR at baseline had a higher incidence of concomitant ≥ moderate TR, which

Table 2. Postoperative Outcomes and Unadjusted Mortality Rates at 1 and 2 Years Post-LVAD Implantation

Postoperative Event, No. (%)	Overall (n = 91)	≥ Moderate MR (n = 62)	< Moderate MR (n = 29)	*P* Value
Complications overall	70 (77)	49 (79)	21 (72)	.49
Device malfunction and thrombosis	47 (52)	36 (58)	11 (38)	.07
Major infection	50 (55)	35 (56)	15 (52)	.67
Stroke	24 (26)	12 (19)	12 (41)	.03
Discharge location				
Home	49 (54)	30 (48)	19 (66)	
Other than home	44 (48)	32 (52)	12 (41)	.66
Rehospitalization	52 (57)	33 (53)	19 (66)	.27
Overall all-cause mortality				
1 y	25 (27)	23 (37)	2 (7)	.001
2 y	34 (37)	29 (47)	5 (17)	.005

Abbreviations: LVAD, left ventricular assist device; MR, mitral regurgitation.

translated into worse survival than patients who had < moderate MR and < moderate TR.

Management of moderate to severe MR in patients who are undergoing LVAD implantation is not clear. Several studies reviewed outcomes to identify the risk and benefit of MV procedure for this patient group; however, outcomes have been mixed. In theory, MR is expected to improve after LVAD insertion because of LV unloading and remodeling by the device, and concomitant MV procedure has been deemed unnecessary by some authors. Stulak et al reported improved survival in patients with severe preoperative MR and discussed lack of value of addressing significant MR at the time of LVAD implantation [5]. Goodwin et al observed significant resolution of MR across the cohort regardless of the severity of MR, and there was no survival difference with uncorrected MR [6].

There were a few studies that reviewed efficacy of mitral valve (MV) procedure in patients undergoing LVAD implantation. In a study with the Interagency Registry for Mechanically Assisted Circulatory Support database, concomitant MV procedures were not associated with increased survival overall [9]. Fukuhara et al reported that concurrent MV repair appeared to be efficacious in controlling MR after device implant, and repaired patients developed less frequent late right heart failure. There was no significant difference in survival between repaired and nonrepaired patients at 2 years [2].

Although current consensus appears to be leaning toward no intervention for MR, there was worse survival in DT patients with moderate to severe MR in our study. Along with MR, TR is also commonly seen in patients undergoing LVAD implantation [2,5,9,10]. Moderate to severe TR was observed in 44% of our cohort. Tricuspid regurgitation is associated with pulmonary hypertension and right ventricular dysfunction. We speculate concomitant TR is a sign of decreased right ventricular function; thus, patients with moderate MR plus moderate TR have the worst survival because of right ventricular failure. A few studies reviewed the relationship of MR and TR in patients undergoing LVAD implant. Stulak et al demonstrated that preoperative findings of less MR and worse TR (suggestive of right ventricle > left ventricle dysfunction) portend worse survival. It is possible that the moderate to severe MR group in our cohort had worse survival since 55% of them had severe TR compared with 23% in the less than moderate MR group ($P = .004$). Also, unloading by LVAD may be insufficient to counteract MR. In a previous report, 20% of LVAD patients continued to have significant MR despite device support, and significant residual MR post-LVAD implantation has been associated with persistent

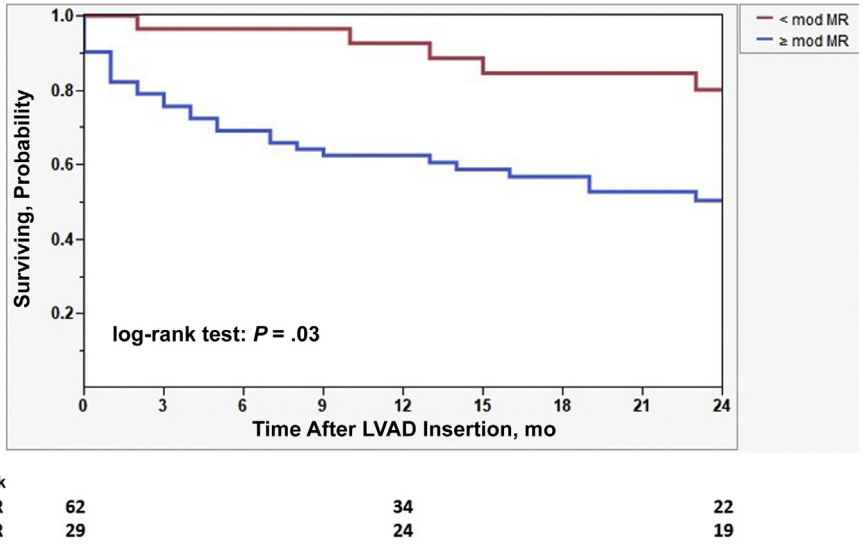

Fig 1. Kaplan-Meier survival curves estimating survival at defined time points for patient groups. Abbreviations: mod, moderate; MR, mitral regurgitation; LVAD, left ventricular assist device.

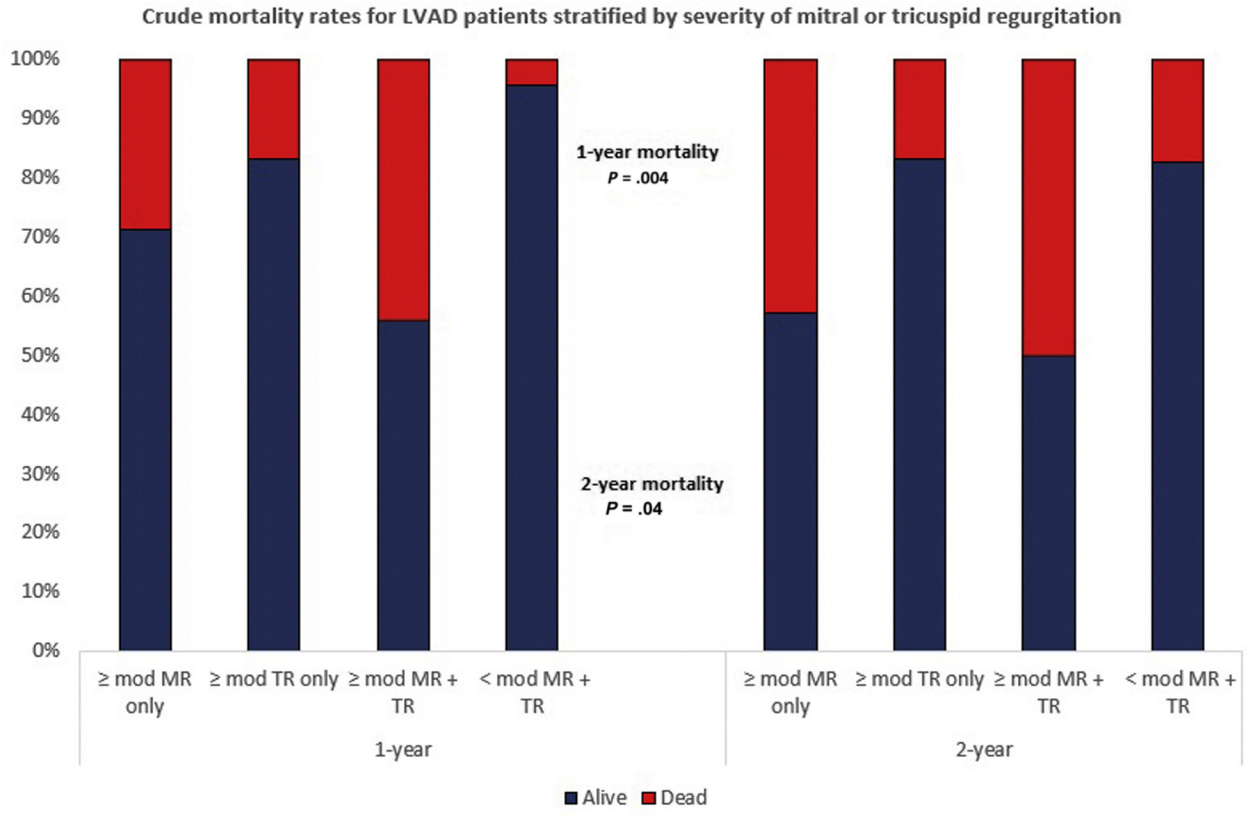

Fig 2. Subgroup analysis of unadjusted mortality at 1 year and 2 years in patients based on severity of MR and TR. Abbreviations: mod, moderate; MR, mitral regurgitation; TR, tricuspid regurgitation.

pulmonary hypertension, worse right ventricle function, and death [11]. It is possible that this effect is more pronounced with worse survival in DT LVAD patients whose duration of LVAD support is longer than the BTT population. However, our study did not investigate the progression of right heart parameters during follow-up and is therefore limited in its assessment.

Although there are several studies that reviewed outcomes of MR after LVAD implantation, most did not differentiate outcomes based on BTT and DT. In the analysis of Interagency Registry for Mechanically Assisted Circulatory Support data on patients with MR, Robertson et al stratified outcomes based on BTT or DT. There was a trend toward a long-term survival advantage when DT patients with moderate to severe MR underwent an MV procedure. This suggests that a concomitant MV procedure may be beneficial in this population and may explain worse survival in DT patients with moderate to severe MR in our study.

An important finding from this study is the impact of concurrent ≥ moderate MR and TR on survival in DT-LVAD patients. In our study, ≥ moderate TR alone was an independent predictor of mortality with a frequency of 44%, which is slightly higher than the 39% reported by Song et al. Similar to our findings, Song et al found ≥ moderate TR to be an independent predictor of mortality but did not find concomitant intervention of the tricuspid valve to be protective against worse survival [12].

Regardless of the debate surrounding intervention on MR, it is well known that, the development of right heart failure is

Table 3. Cox Proportional Hazard Model Showing Factors Associated With Overall All-Cause Mortality After LVAD Implantation

	Univariable Analysis		Multivariate Analysis	
Variable, No. (%)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age ≥ 60 y	1.1 (1.1–1.2)	.001	1.1 (1.0–1.4)	<.001
Sex, female	0.4 (0.2–0.8)	.01	4.0 (1.8–8.8)	.006
Preop EKG (ASR)	2.4 (1.2–4.5)	.009	1.6 (0.8–3.2)	.22
Preop ≥ moderate MR	2.3 (1.1–5.4)	.02	2.3 (0.9–6.2)	.05
Preop ≥ moderate TR	1.8 (0.9–3.5)	.08	2.4 (1.2–4.9)	.01

Abbreviations: ASR, abnormal sinus rhythm; EKG, electrocardiogram; HR, hazard ratio; MR, mitral regurgitation; Preop, preoperative; TR, tricuspid regurgitation.

associated with worse survival in LVAD patients [13–15]. For this reason, the treatment goal should include prevention or slowing progression of right heart failure. Intervention may not be warranted in LVAD patients with ≥ moderate MR alone; however, coexisting ≥ moderate TR should raise consideration for mitral repair especially in the DT-LVAD population who will require long-term support.

Limitations

Our case series is limited by a small number of patients and retrospective assessment of data, and it is subject to all limitations inherent in such studies. In this observational study, sample sizes of patients with moderate to severe MR and less than moderate MR were not balanced. Failure to detect a difference may be a result of low power from small sample size. Cause of deaths were not clear in all the patients who died in the study. Postoperative echocardiographic findings were not shown in this study, and whether resolution of MR occurred in our DT population needs to be confirmed in the future study.

In conclusion, moderate to severe MR is a significant risk factor for increased mortality after LVAD implantation in DT patients. Moderate to severe MR and moderate to severe TR portends worst survival and MV intervention should therefore be considered.

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