Association between the proportionality of functional mitral regurgitation and survival after mitral valve operation

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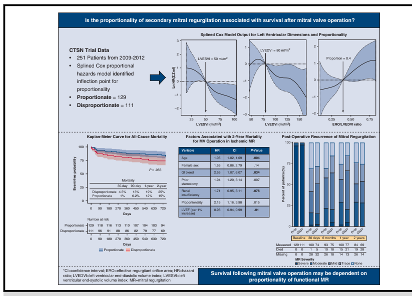
ABSTRACT

Objective: The concept of proportionate and disproportionate functional mitral regurgitation suggests that transcatheter edge-to-edge mitral repair may benefit patients with a smaller left ventricle relative to a higher regurgitant burden. The clinical relevance of proportionality remains unknown in mitral operations for ischemic mitral regurgitation. We aimed to characterize the association between mitral regurgitation proportionality and outcomes after mitral valve operations.

Methods: By using the Cardiothoracic Surgery Trial Network's severe ischemic mitral regurgitation trial, we first identified the inflection point at which the risk of 2-year mortality changed along the spectrum of the mitral regurgitation proportionality (defined as effective regurgitant orifice area/left ventricular end-diastolic volume index) using a splined multivariable Cox proportional hazards model. Patients were dichotomized by the mitral regurgitation proportionality value. The Cox model evaluated the hazard of 2-year all-cause mortality between proportionate and disproportionate mitral regurgitation.

Results: Among the 240 patients, the median age was 69 years (interquartile range, 62-75), and 38% (n = 90) were women. Patients with effective regurgitant orifice/left ventricular end-diastolic volume index proportion greater than 0.40 (more disproportionate mitral regurgitation) had a higher hazard of death compared with those with more proportionate mitral regurgitation. The 90-day and 1-year mortality were higher in patients with disproportionate mitral regurgitation (13% vs 6.2% for 90 days and 19% vs 12% for 1 year). In a multivariable Cox model, the disproportionate mitral regurgitation group had a statistically significantly higher hazard of death compared with the proportionate mitral regurgitation group (hazard ratio, 2.15, 95% CI, 1.16-3.98, $P = .015$).

Conclusions: The clinical relevance of the proportionality of functional mitral regurgitation proposed in the transcatheter edge-to-edge mitral repair population may not generalize to surgical patient populations. (JTCVS Open 2024;22:176-88)



Event-free survival from all-cause death by disproportionate versus proportionate MR.

CENTRAL MESSAGE

The clinical relevance of the proportionality of functional MR proposed in the TEER population may not generalize to surgical patient populations.

PERSPECTIVE

Patients undergoing MV operations with a small LV and disproportionate ischemic MR had increased hazard of death, mostly occurring in the early postoperative period despite having a better baseline LVEF. Survival after MV operations may be dependent on the proportionality of functional MR and likely informs designing future trials comparing alternative therapeutic options in ischemic MR.

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Abbreviations and Acronyms

CTSN = Cardiothoracic Surgery Trial Network
ERO = effective regurgitant orifice
LV = left ventricle
LVEDVI = left ventricular end-diastolic volume index
LVEF = left ventricular ejection fraction
LVESVI = left ventricular end-systolic volume index
MACCE = major adverse cardiac and cerebrovascular events
MR = mitral regurgitation
MV = mitral valve
NHLBI = National Heart, Lung, and Blood Institute
TEER = transcatheter edge-to-edge repair

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Recent trials comparing medical therapy and transcatheter edge-to-edge repair (TEER) in patients with secondary mitral regurgitation (MR) emphasized the concept of proportionality of MR as a key factor in dictating whether the mechanical correction of secondary MR is beneficial over medical therapy.[1] Specifically, in the COAPT trial[2] that was enriched with patients with disproportionate MR, in whom the effective regurgitant orifice (ERO) size was larger relative to left ventricular (LV) dimensions, TEER conferred a survival benefit compared with medical therapy. This is in contrast to the MITRA-FR trial[3] that did not show benefit of TEER in the patients who had more proportionate MR. The theory argues that disproportionate MR resembles the pathophysiology of primary MR, resulting in the benefit of mechanical correction of MR. It remains unknown how the proportionality of MR relates to the outcome in mitral valve (MV) operations in secondary MR. If the presence of disproportionality between LV size and degree of MR is decisive for a better outcome in mechanically correcting the MR, this concept should be applicable to surgical patients, although this remains unknown.

By using the Cardiothoracic Surgery Trial Network's (CTSN) severe ischemic MR trial data, we aimed to better understand the relationship between the proportionality of secondary MR and the surgical outcomes and survival.

MATERIAL AND METHODS

Data Source and Patients

We used the CTSN severe ischemic MR trial data obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). The trial enrolled 251 patients with severe ischemic MR between 2009 and 2012 across 22 sites who were eligible for surgical correction, with or without concomitant coronary artery bypass grafting. Patients were randomized into MV repair versus replacement groups. The trial's primary end point, left ventricular end-systolic volume index (LVESVI), was not significantly different between the groups. However, the trial demonstrated a substantially higher incidence of recurrent MR in the repair group.[4] Echocardiographic measurements were validated in a core laboratory. The trial conducted a follow-up of 2 years.

The data were obtained through the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. The Yale Institutional Review Board approved the study, and individual consent was waived (Protocol ID: 2000034167, approval date: December 1, 2022).

Candidate Variable Selection, Proportionality, and Outcomes

Variables were defined per the original trial. Echocardiographic variables are defined in Table E1. Candidate variables were selected from the prior analysis that identified parsimonious high-risk features that were associated with 2-year mortality in this trial dataset using the combination of support vector classifier and Cox proportional hazards model.[5] The covariates include in the models were age, sex, gastrointestinal bleed, prior sternotomy number, renal insufficiency, and baseline LVEF.

Proportional hazards assumption was evaluated for the dependent variables using the survival plot.[6] The final variables were then modeled using Cox proportional hazards model with stepwise selection for time to death as the dependent variable.

MR proportionality was defined as a ratio between ERO area and left ventricular end-diastolic volume index (LVEDVI).[7] The association between the risk of 2-year mortality and baseline proportionality was modeled using multivariable Cox proportional hazards model with cubic splining of proportionality across the range to determine the inflection point in the risk of mortality at a particular ERO/LVEDVI proportion value. This inflection point was used to dichotomize patients into proportionate versus disproportionate MR. Patient characteristics and outcomes were compared between proportionate and disproportionate MR.

The outcomes of interest were survival up to 2 years and major adverse cerebrovascular and cardiac events (MACCE) at 2 years postrandomization. We evaluated the recurrence of moderate or severe MR to evaluate whether MR recurrence among patients undergoing MV repair had a correlation with the original MR proportionality. We also evaluated LV dimension changes on echocardiograms obtained at postoperative day 30, month 6, month 12, and month 24, stratified by baseline LV dimension and MR proportionality. Percent difference from the baseline was calculated for LV dimension at each follow-up time point.

Statistical Analysis and Missing Value

Baseline ERO measurements were missing in 11 patients and were excluded from the analysis because of the inability to calculate proportionality with the missing value.

To facilitate mechanistic understanding of outcome differences between proportionate and disproportionate MR cases, we graphically characterized postoperative echocardiography measurements (ejection fraction, LVESVI, LVEDVI) and recurrence of MR during the follow-up period at 3, 6, 12, and 24 months postrandomization.

Patients' characteristics were summarized using median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. Survival was compared using Kaplan–Meier plots. Multivariable Cox proportional hazards model was fitted to quantify the adjusted hazard of death over the 2-year follow-up period. The proportional hazards assumption was tested for the proportionality variable via Kaplan–Meier plots. Test of normality was performed using Q-Q plot. All analyses were conducted with RStudio 1.3.1073 (R Foundation). We used the packages smoothHR, survival, and Hmisc.

RESULTS

Among 240 patients analyzed, the median age was 69 years (IQR, 62-75), and 38% (n = 90) were women. Death occurred in 20% (n = 48) at 2 years. Splined Cox model demonstrated a higher hazard of mortality with more disproportionate MR (Figure 1), with patients with ERO/LVEDVI proportion greater than 0.40 (more disproportionate MR) having a higher hazard of death compared with those with more proportionate MR with lower ERO/LVEDVI ratio (Figure 2).

Compared with patients with proportionate MR, those with disproportionate MR were older (median 70 years [IQR, 65-77 years] vs 68 years [61-74 years], $P = .049$), had a similar proportion of women, less commonly had implantable cardioverter-defibrillator at baseline, had higher baseline ejection fraction (44% [IQR, 38-54] vs 37% [30-44], $P < .001$), had lower LVESVI (46 mL/m^2 [IQR, 37-58] vs 72 mL/m^2 [58-97], $P < .001$, and had larger ERO (44 mm^2 [IQR, 38-53] vs 32 mm^2 [26-40], $P = .001$)

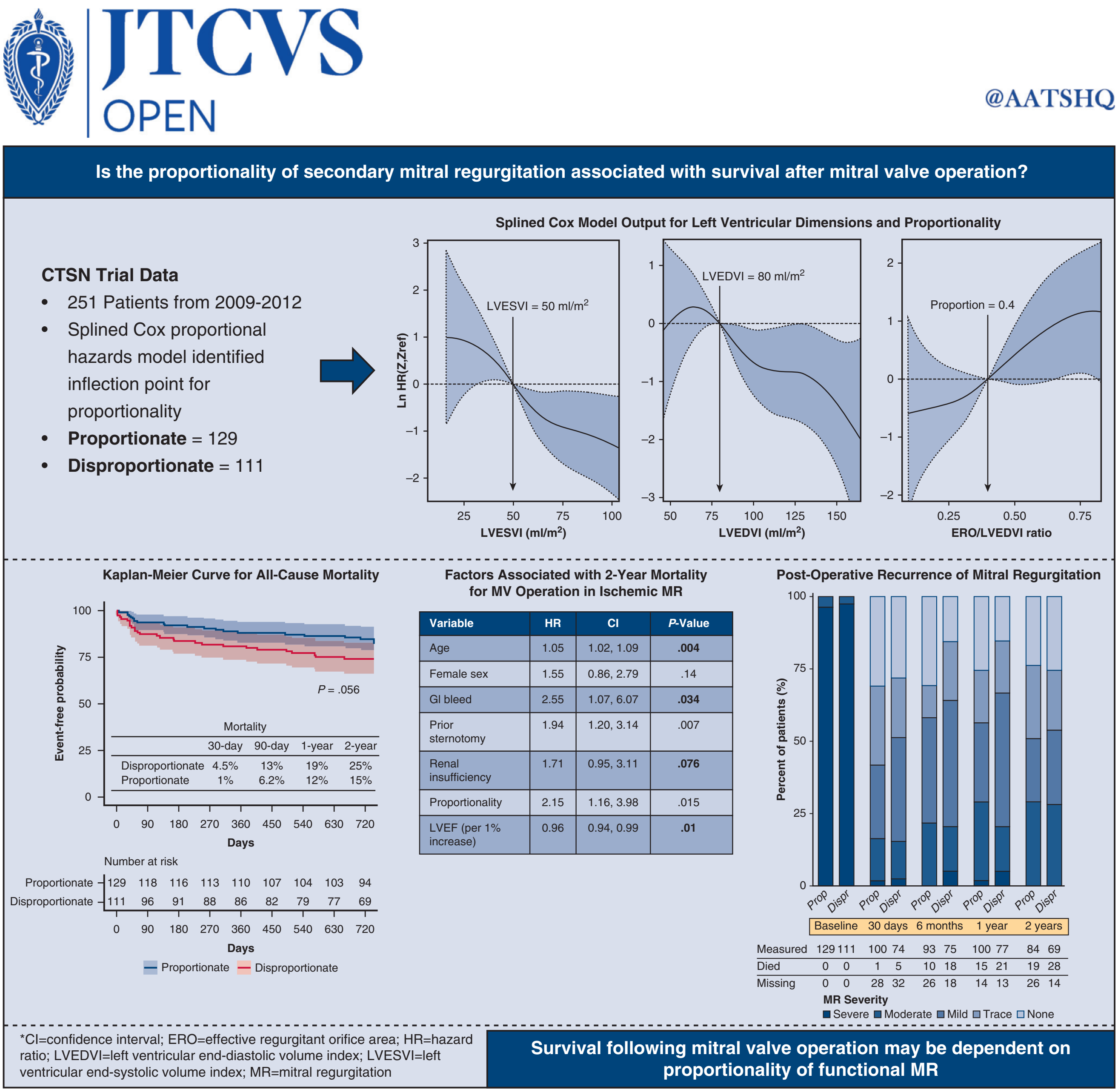

FIGURE 1. The impact of proportionality on the outcome and survival of patients undergoing MV operations.

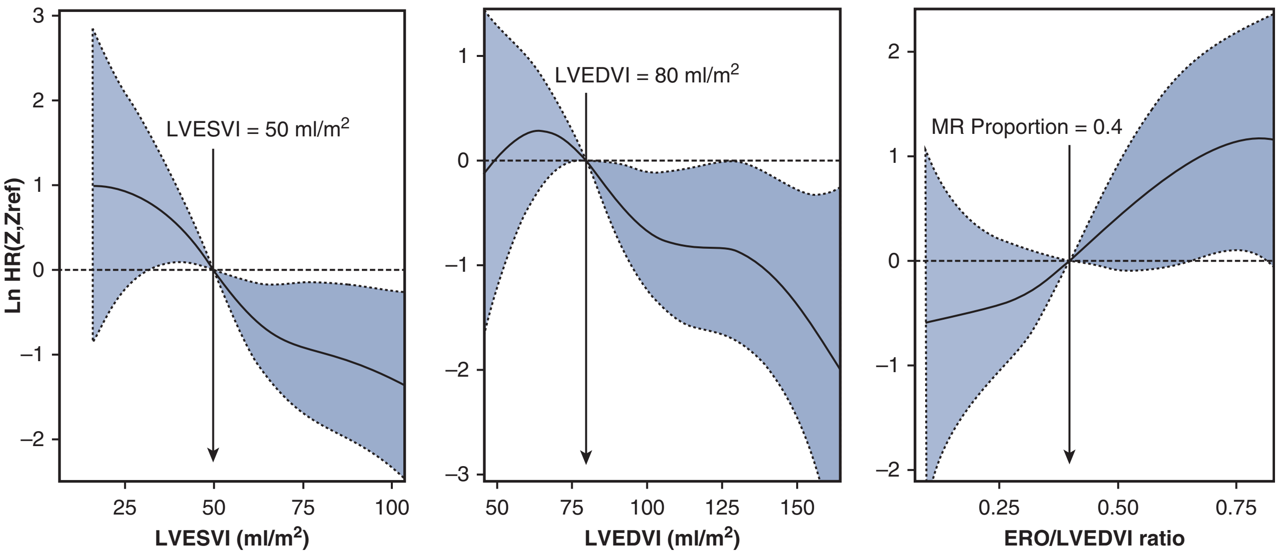

FIGURE 2. Splined Cox model output for LV dimensions and proportionality. The hazard ratios for 2-year mortality across ranges of continuous variables: LVESVI (*left*), LVEDVI (*middle*), and proportion of ERO area and LVEDVI (*right*). *Arrows* indicate reference points at which the natural log (Ln) of the hazard ratio is zero. *LVESVI*, Left ventricular end-systolic volume index; *LVEDVI*, left ventricular end-diastolic volume index; *MR*, mitral regurgitation; *ERO*, effective regurgitant orifice.

(Table 1). Patient characteristics by LV dimension are summarized in Table E2.

Ninety-day and 1-year mortality were higher in disproportionate MR cases (13% vs 6.2% for 90 days and 19% vs 12% for 1 year, respectively). Survival on Kaplan–Meier log–rank test was not statistically significantly different between the 2 groups ($P = .056$) (Figure 3).

On multivariable Cox model, the disproportionate MR group had a statistically significantly higher hazard of death compared with the proportionate MR group (hazard ratio, 2.15, 95% CI, 1.16-3.98, $P = .015$). In the model, higher age, gastrointestinal bleed, prior sternotomy, and lower LVEF were significantly associated with higher hazards of death (Table 2). Female sex was not significantly associated with a higher hazard of death. In the same model replacing proportionality with LVEDVI, LVEDVI less than 80 mL/m^2 was associated with increased hazard of death (hazard ratio, 2.59, 95% CI, 1.32-5.09, $P = .006$) compared with LVEDVI 80 mL/m^2 or greater (Table E3). Lower LVEDVI was associated with increased hazard of MACCE (Table E4). Proportionality was also significantly associated with survival when treated as continuous variable (Table E5).

The incidence of severe MR recurrence was higher in disproportionate MR groups across the follow-up period: 1% versus 2.7% at 30 days, 0% versus 4% at 6 months, and 1% versus 4% at 12 months in this groups with balanced proportions of MV repair (Figure 4). From the baseline LVEF, the proportionate MR group had a positive percent change in LVEF (+3%), and the disproportionate MR group had a negative percent change in LVEF (−5%) at 24 months (Figure E1). Compared with disproportionate MR, the proportionate MR group had greater percent reduction in LVEDVI at 24 months (−33% vs −14%) (Figure E1).

DISCUSSION

Ischemic MR is prevalent,[8] and optimal patient selection for MV operation, TEER, and medical therapy remains unclear. Proportionality of MR has been proposed as a way to identify those who would benefit from TEER over medical therapy, but its importance remained unclear in patients undergoing MV operations.[9] In this study, we demonstrated that smaller LVs and more disproportionate MR were associated with increased hazard of death, with most of the mortality difference occurring within the first 90 days of randomization, despite patients with smaller LVs having higher ejection fraction at baseline. Although our study did not directly compare alternative therapies, the finding partly contrasts with the prior theory that mechanical correction of secondary MR preferentially benefits patients with more disproportionate, primary-like MR.

Our study is important for several reasons. First, there are no robust data on outcomes associated with proportionality of MR in patients undergoing MV operations.[9] At first glance, the finding of proportionate MR being associated with increased hazard of mortality contradicts existing data indicating that a less dilated LV signifies lesser extent of adverse LV remodeling and is a favorable prognosticator.[10]

TABLE 1. Patient characteristics by proportionate and disproportionate mitral regurgitation

Characteristic	Overall (N = 240)	Proportionate (N = 129)	Disproportionate (N = 111)	*P*
Age (y)	69 (62-75)	68 (61-74)	70 (65-77)	.049
Female	90 (38%)	46 (36%)	44 (40%)	.5
Randomized to MV repair	124 (52%)	64 (50%)	60 (54%)	.5
Race				.4
American Indian, Alaskan Native	1 (0.4%)	0 (0%)	1 (0.9%)	
Asian	2 (0.8%)	1 (0.8%)	1 (0.9%)	
Black	41 (17%)	26 (20%)	15 (14%)	
White	194 (81%)	100 (78%)	94 (85%)	
Other	1 (0.4%)	1 (0.8%)	0 (0%)	
Hispanic ethnicity	23 (9.6%)	11 (8.5%)	12 (11%)	.5
Atrial fibrillation	79 (33%)	34 (26%)	45 (41%)	.02
Diabetes	86 (36%)	45 (35%)	41 (37%)	.8
Prior CABG	46 (19%)	25 (19%)	21 (19%)	>.9
Cerebrovascular disease	27 (11%)	13 (10%)	14 (13%)	.6
Chronic lung disease				.6
None	174 (73%)	89 (70%)	85 (77%)	
Mild	26 (11%)	15 (12%)	11 (9.9%)	
Moderate	25 (11%)	14 (11%)	11 (9.9%)	
Severe	13 (5.5%)	9 (7.1%)	4 (3.6%)	
Heart failure	170 (71%)	93 (72%)	77 (69%)	.6
GI bleed requiring transfusion	14 (5.8%)	7 (5.4%)	7 (6.3%)	.9
Hypertension	192 (80%)	103 (80%)	89 (80%)	>.9
Malignancy	31 (13%)	15 (12%)	16 (14%)	.5
Preoperative IABP	6 (2.5%)	4 (3.1%)	2 (1.8%)	.7
Prior PCI	86 (36%)	47 (36%)	39 (35%)	.8
ICD	38 (16%)	26 (20%)	12 (11%)	.048
Liver disease	2 (0.8%)	1 (0.8%)	1 (0.9%)	>.9
Myocardial infarction	177 (74%)	96 (74%)	81 (73%)	.8
Pacemaker	27 (11%)	14 (11%)	13 (12%)	.8
Peripheral arterial disease	26 (11%)	15 (12%)	11 (9.9%)	.6
Prior sternotomy	48 (20%)	25 (19%)	23 (21%)	.8
Renal insufficiency	65 (27%)	33 (26%)	32 (29%)	.6
Ventricular arrhythmia	31 (13%)	13 (10%)	18 (16%)	.2
Psychiatric disorder	14 (5.8%)	8 (6.2%)	6 (5.4%)	.8
Stroke	25 (10%)	14 (11%)	11 (9.9%)	.8
Tobacco use	153 (64%)	80 (62%)	73 (66%)	.6
Baseline echo characteristics				
LVESVI (mL/m^2)	89 (37%)	21 (16%)	68 (61%)	<.001
LVEDDI (mL/m^2)	101 (83-123)	117 (101-139)	87 (74-96)	<.001
ERO (mm^2)	38 (30-46)	32 (26-40)	44 (38-53)	<.001
LVEF (%)	40 (33-48)	37 (30-44)	44 (38-54)	<.001
Vena contracta (mm)	7.60 (7.10-8.40)	7.50 (7.00-8.10)	7.80 (7.10-8.60)	.088
MR proportion (ERO/LVEDVI)	0.38 (0.29-0.50)	0.29 (0.23-0.34)	0.50 (0.45-0.59)	<.001

MV, Mitral valve; *CABG*, coronary artery bypass grafting; *GI*, gastrointestinal; *IABP*, intra-aortic balloon pump; *PCI*, percutaneous coronary intervention; *ICD*, implantable cardioverter defibrillator; *LVESVI*, left ventricular end-systolic volume index; *LVEDDI*, left ventricular end-diastolic diameter index; *ERO*, effective regurgitant orifice; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation; *LVEDVI*, left ventricular end-diastolic volume index.

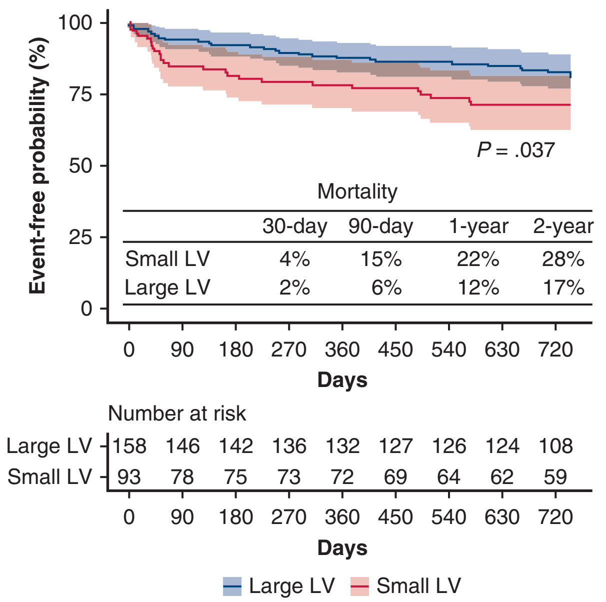

FIGURE 3. All-cause mortality and MACCE. Event-free survival probability from all-cause death by disproportionate (*green*) versus proportionate MR (*red*). *P* values were derived from log-rank test. 95% CI. *LV*, Left ventricle.

Our finding suggests that among patients with ischemic disease advanced enough to induce severe ischemic MR, patients with smaller LVs and more disproportionate MR undergoing MV operation constitute a distinct risk subgroup that behaves differently than the general population with ischemic heart disease. Cause of death was not available in the dataset, limiting the further interpretation of this finding. However, the occurrence of a mortality difference between large and small LV groups within the first 90 days suggests that the mechanism is related to the short-term impact of the operation.

TABLE 2. Factors associated with 2-year mortality for mitral valve operation in ischemic mitral regurgitation

Variable	HR	95% CI	*P*
Age (per 1-y increase)	1.05	1.02-1.09	.004
Female sex	1.55	0.86-2.79	.14
GI bleed	2.55	1.07-6.07	.034
Prior sternotomy	1.94	1.20-3.14	.007
Renal insufficiency	1.71	0.95-3.11	.076
Proportionality (>0.4)	2.15	1.16-3.98	.015
LVEF (per 1% increase)	0.96	0.94-0.99	.01

Variables that were retained in the final multivariable Cox proportional hazards model for the outcome of time to death during the 2-year follow-up. *GI*, Gastrointestinal; *HR*, hazard ratio; *LVEF*, left ventricular ejection fraction.

A possible explanation of the higher short-term mortality in those with smaller LVs may be the trial patient cohort was enrolled predominantly with the MR mechanism of leaflet tethering, downsizing of the annulus, as specified by the trial protocol, may have resulted in increased tethering of the leaflet in systole, rendering the papillary muscle more arrhythmogenic, leading to mortality related to ventricular arrhythmia.[11]

The mechanistic pathway of the increased risk of adverse events remains unclear upon evaluating postoperative changes in echocardiographic measurements. The incidence of severe MR recurrence was numerically higher in the disproportionate MR group. Trajectories of measures indicating LV remodeling, including LVEF and LVEDVI, were not discernibly different at 30 days, the period before the divergence in survival curve occurred. However, at 24 months, the disproportionate MR group seemed to have had smaller relative remodeling compared with the proportionate MR group. Although less remodeling and residual MR after TEER is associated with reduced survival,[12,13] it is unclear whether such small differences in remodeling and MR recurrence provide adequate explanation for the increased perioperative mortality risk. The lack of significant difference in MR recurrence based on MR proportionality, as observed in the COAPT trial,[14] could be explained by the prosthetic annular fixation during MV repair or replacement.

Sex-based differences have been demonstrated in a prior analysis of the CTSN ischemic MR trial, demonstrating worse outcomes in women without accounting for LV dimension variables.[15] Our model included sex as a covariate, which was not significantly associated with death or MACCE risk after adjusting for the LV dimension or proportionality. Considering the identified association between lower LVESVI with worse survival, it is possible that sex was a confounder of this association in the prior analysis. Concordant with prior knowledge that women, on average, having a smaller LV than men even after indexing for body size,[16] we demonstrated that women tended to have smaller indexed LV size than men, whereas this sex-based difference was not apparent in the MR proportionality. This observation may offer an explanation for the previously observed sex-based difference in surgical outcomes for MV operations.

As the number of patients seeking multidisciplinary valve team evaluation for ischemic MR is expected to increase with the recent Food and Drug Administration approval of the MitraClip for severe secondary MR,[17] our finding of disproportionate MR having worse outcomes with MV operations warrants further validation to define subgroups of patients who derive benefit from each of the therapeutic alternatives including surgery, TEER, and medical therapy. This study does not inform the comparative effectiveness of MV operation versus TEER or medical therapy, as the study focuses

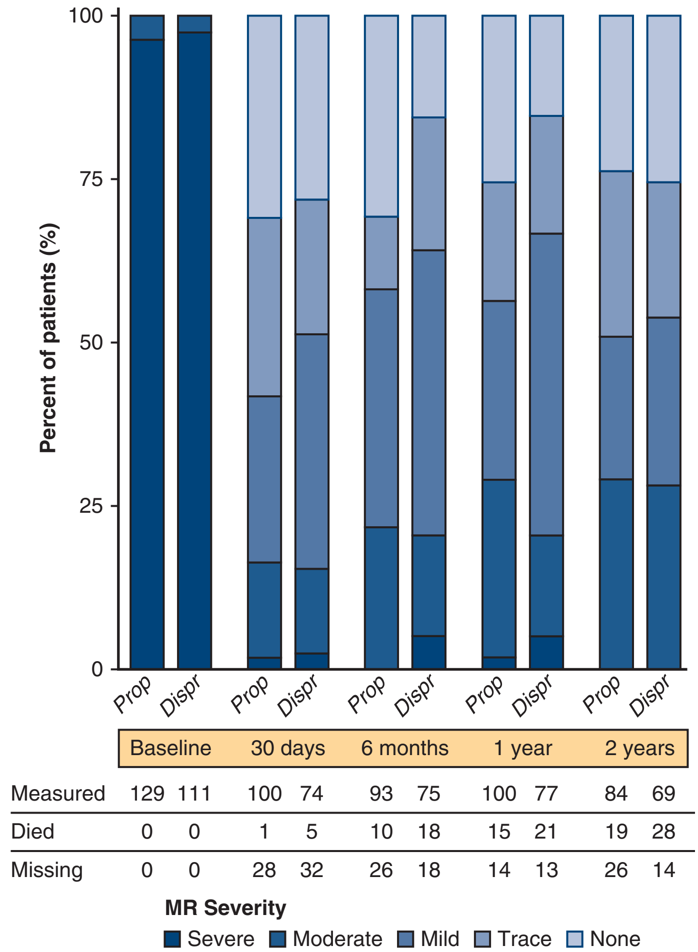

FIGURE 4. Postoperative recurrence of MR. Proportions of postoperative MR recurrence by patients grouped as proportionate MR (Prop) and disproportionate MR at baseline. *MR*, Mitral regurgitation.

exclusively on patients who underwent MV operations. However, this subgrouping based on proportionality of ischemic MR likely forms important subgroups for future trials comparing different treatments for secondary MR, as the increased perioperative risk of MV operation in proportionate MR patients may favor such patients to undergo conservative treatment alternatives.

Study Limitations

This is a secondary analysis of a randomized controlled trial. Therefore, the retrospective nature of the analysis harbors potential biases. The original trial was published in 2014, and practice of MV operation for ischemic MR has changed during the time. The number of patients included was relatively small, although the trial data provided the benefit of extensive data points with standardized definitions and rigorous end point validation. Body surface area data were not available, limiting the analysis to the indexed LV dimensions and proportionality based on indexed values. Cause of death data were not available, limiting the insights into understanding the driver of mortality risk difference based on proportionality and LV dimensions. The comparisons we made are among those who underwent MV operation, and therefore the comparative effectiveness of different treatment strategies including MV operation, TEER, and medical therapy was not evaluated. Center- and surgeon-level variation in outcomes and their contributions toward observed outcome difference remain unknown.

CONCLUSIONS

Patients undergoing MV operation with a small LV and disproportionate ischemic MR had an increased hazard of death, mostly occurring in the early postoperative period despite having a better baseline LVEF. This suggests that survival after MV operations may be dependent on the proportionality of functional MR and likely informs designing future trials comparing alternative therapeutic options in ischemic MR.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/lb7-association-between-the-proportionality-of-functional-mitral-regurgitation-and-survival-insights-from-cardiothoracic-surgery-trial-network-severe-ischemic-mr-trial.

Conflict of Interest Statement

M.K. is a physician proctor and a member of the medical advisory board for JOMDD, a physician proctor for Peter Duschek, and a medical consultant for EVOTEC and Moderna, and has received speakers' honoraria from Medtronic and Terumo. A.G. receives a consulting fee from Medtronic and Edwards Lifesciences. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

This manuscript was prepared using Severe Ischemic Mitral Regurgitation Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the original trial investigators or the NHLBI.

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Key Words: functional mitral regurgitation, ischemic heart disease, mitral valve repair, transcatheter edge-to-edge repair

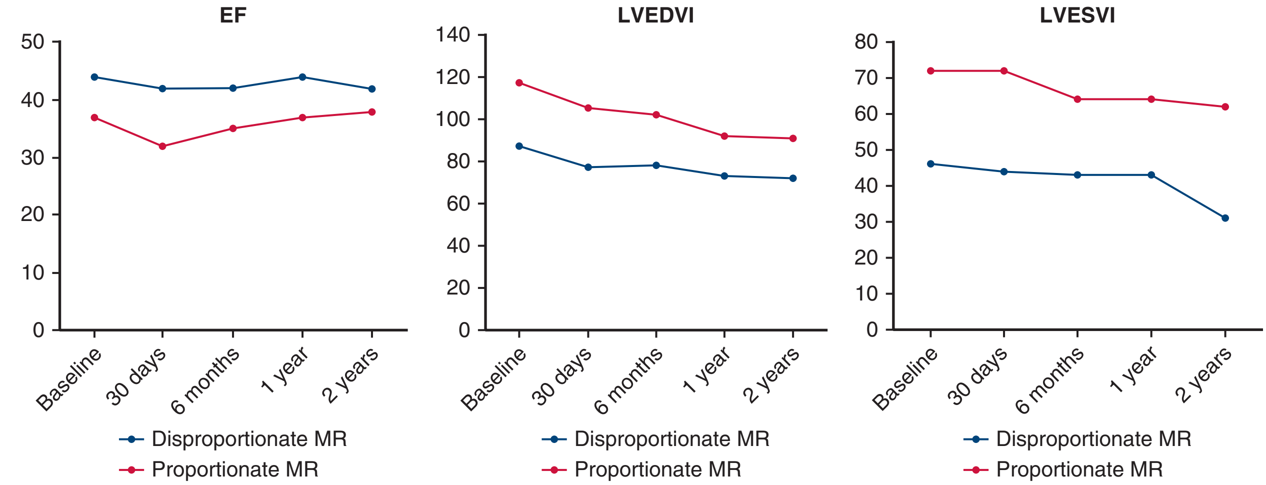

FIGURE E1. Postoperative trajectories of LV remodeling. LVEF (*left*) showed minimal change over 2-year follow-up in both proportionate and disproportionate MR groups. LVEDVI (*middle*) showed similar improvement over 2-year follow-up. LVESVI (*left*) also demonstrated improvement. *LVEF*, Left ventricular ejection fraction; *MR*, mitral regurgitation; *LVEDVI*, left ventricular end-diastolic volume index; *LVESVI*, left ventricular end-systolic volume index; *EF*, ejection fraction.

TABLE E1. Echocardiographic variable definitions

Variables	Definition
Baseline echocardiography characteristics	
LVESVI (mL/m^2)	Left ventricular end-systolic volume index was calculated using biplane volumetric method, adjusted for body surface area (mL/m^2).
LVEDDI (mL/m^2)	Left ventricular end-diastolic diameter index, adjusted for body surface area (mL/m^2).
ERO (m^2)	Calculated using 2 methods: a) proximal isovelocity surface area method and b) quantitative flow method.
LVEF (%)	Measured by the biplane Simpson's volumetric method (a combination of apical 4- and 2-chamber views). The LV endocardial border was traced contiguously from one side of the mitral annulus to the other side excluding the papillary muscles and trabeculations. LVEF will be determined from LV volumes using the formula LVEF = (EDV-ESV)/EDV.
Vena contracta (mm)	Measured from multiple views noting that only a binary classification will be used with this measure (severe and not severe).
MR proportion (ERO/LVEDVI)	MR proportion is determined by the division of ERO and LVEDVI.

LVESVI, Left ventricular end-systolic volume index; *LVEDDI*, left ventricular end-diastolic diameter index; *ERO*, effective regurgitant orifice; *LVEF*, left ventricular ejection fraction; *LV*, left ventricle; *EDV*, end-diastolic volume; *ESV*, end-systolic volume; *MR*, mitral regurgitation; *LVEDVI*, left ventricular end-diastolic volume index.

TABLE E2. Baseline characteristics by left ventricular dimension

Characteristic	Overall (N = 251)	Large LV (N = 158)	Small LV (N = 93)	*P*
Age (y)	69 (62-75)	67 (61-73)	72 (66-79)	**<.001**
Female	96 (38%)	47 (30%)	49 (53%)	**<.001**
Randomized to MV repair	126 (50%)	77 (49%)	49 (53%)	.5
Race				.8
American Indian, Alaskan Native	1 (0.4%)	0 (0%)	1 (1.1%)	
Asian	2 (0.8%)	1 (0.6%)	1 (1.1%)	
Black	44 (18%)	27 (17%)	17 (18%)	
White	202 (80%)	128 (81%)	74 (80%)	
Other	1 (0.4%)	1 (0.6%)	0 (0%)	
Hispanic ethnicity	24 (9.6%)	14 (8.9%)	10 (11%)	.6
Atrial fibrillation	80 (32%)	45 (28%)	35 (38%)	.13
Diabetes	89 (36%)	54 (34%)	35 (38%)	.6
Prior CABG	47 (19%)	31 (20%)	16 (17%)	.6
Cerebrovascular disease	27 (11%)	19 (12%)	8 (8.7%)	.4
Chronic lung disease				.3
None	181 (73%)	111 (71%)	70 (76%)	
Mild	27 (11%)	20 (13%)	7 (7.6%)	
Moderate	27 (11%)	15 (9.6%)	12 (13%)	
Severe	14 (5.6%)	11 (7.0%)	3 (3.3%)	
Heart failure	180 (72%)	123 (78%)	57 (61%)	**.005**
GI bleed requiring transfusion	15 (6.0%)	10 (6.3%)	5 (5.4%)	>.9
Hypertension	199 (79%)	123 (78%)	76 (82%)	.5
Malignancy	34 (14%)	16 (10%)	18 (19%)	**.039**
Preoperative IABP	6 (2.4%)	4 (2.5%)	2 (2.2%)	>.9
Prior PCI	90 (36%)	58 (37%)	32 (34%)	.7
ICD	40 (16%)	34 (22%)	6 (6.5%)	**.002**
Liver disease	2 (0.8%)	0 (0%)	2 (2.2%)	.14
Myocardial infarction	187 (75%)	120 (76%)	67 (72%)	.5
Pacemaker	29 (12%)	16 (10%)	13 (14%)	.4
Peripheral arterial disease	26 (10%)	17 (11%)	9 (9.8%)	.8
Prior sternotomy	49 (20%)	33 (21%)	16 (17%)	.5
Renal insufficiency	69 (27%)	42 (27%)	27 (29%)	.7
Ventricular arrhythmia	32 (13%)	22 (14%)	10 (11%)	.5
Psychiatric disorder	15 (6.0%)	10 (6.3%)	5 (5.4%)	.8
Stroke	25 (10.0%)	17 (11%)	8 (8.6%)	.6
Tobacco use	159 (64%)	105 (67%)	54 (58%)	.2
Baseline echo characteristics				
LVESVI (mL/m^2)	59 (43-81)	73 (60-93)	39 (33-45)	**<.001**
LVEDVI (mL/m^2)	101 (83-123)	116 (101-138)	78 (68-88)	**<.001**
ERO (cm^2)	0.38 (0.30-0.46)	0.38 (0.30-0.45)	0.40 (0.31-0.47)	.6
LVEF (%)	40 (32-48)	36 (29-40)	52 (45-57)	**<.001**
Vena contracta (mm)	7.50 (7.10-8.40)	7.50 (7.10-8.30)	7.60 (7.00-8.50)	.8

Bold signifies $P < .05$. *LV*, Left ventricle; *MV*, mitral valve; *CABG*, coronary artery bypass grafting; *GI*, gastrointestinal; *IABP*, intra-aortic balloon pump; *PCI*, percutaneous coronary intervention; *ICD*, implantable cardioverter defibrillator; *LVESVI,* left ventricular end-systolic volume index; *LVEDVI*, left ventricular end-diastolic volume index; *ERO*, effective regurgitant orifice; *LVEF*, left ventricular ejection fraction.

TABLE E3. Cox model for all-cause mortality including left ventricular end-diastolic dimension index to define small left ventricle

Variable	HR	95% CI	*P*
Age (per 1-y increase)	1.05	1.02-1.09	.003
Female sex	1.48	0.84-2.60	.2
GI bleed	2.47	1.11-5.51	.027
Prior sternotomy	2.04	1.28-3.23	.002
Renal insufficiency	1.66	0.95-2.91	.074
Small LV (by LVEDVI)	2.59	1.32-5.09	.006
LVEF (per 1% increase)	0.96	0.93-0.99	.004

Variables that were retained in the final multivariable Cox proportional hazards model for the outcome of time to death during the 2-year follow-up. *HR*, Hazard ratio; *GI*, gastrointestinal; *LV*, left ventricle; *LVEDVI*, left ventricular end-diastolic volume index; *LVEF*, left ventricular ejection fraction.

TABLE E4. Cox model for major adverse cardiac and cerebrovascular events including left ventricular end-diastolic dimension index to define small left ventricle

Variable	HR	95% CI	*P*
Age (per 1-y increase)	1.05	1.02-1.09	.003
Female sex	1.48	0.84-2.60	.2
GI bleed	2.47	1.11-5.51	.027
Prior sternotomy	2.04	1.28-3.23	.002
Renal insufficiency	1.66	0.95-2.91	.074
Small LV (by LVEDVI)	2.59	1.32-5.09	.006
LVEF (per 1% increase)	0.96	0.93-0.99	.004

List of variables that were retained in the final multivariable Cox proportional hazards model for the outcome of time to death during the 2-year follow-up. *HR*, Hazard ratio; *GI*, gastrointestinal; *LV*, left ventricle; *LVEDVI*, left ventricular end-diastolic volume index; *LVEF,* left ventricular ejection fraction.

TABLE E5. Cox model for survival including the proportionality as continuous variable

Variable	HR	95% CI	*P*
Concomitant CABG	1.75	0.75-4.08	.2
Age (per 1-y increase)	1.05	1.02-1.09	.005
Female sex	1.49	0.83-2.68	.2
GI bleed	2.62	1.07-6.45	.036
Prior sternotomy	2.61	1.48-4.61	<.001
Renal insufficiency	1.87	1.01-3.44	.045
Proportionality (per 0.1 increase)	1.23	1.04-1.45	.016
LVEF (per 1% increase)	0.96	0.93-0.99	.007

List of variables that were retained in the final multivariable Cox proportional hazards model for the outcome of time to death during the 2-year follow-up. *HR*, Hazard ratio; *CABG*, coronary bypass grafting; *GI*, gastrointestinal; *LVEF,* left ventricular ejection fraction.