# The high-risk features among patients undergoing mitral valve operation for ischemic mitral regurgitation: The 3-strike score

Makoto Mori, MD, PhD,[a,b] Christina Waldron, BS,[a] Sigurdur Ragnarsson, MD,[a] Markus Krane, MD,[a] and Arnar Geirsson, MD[a]

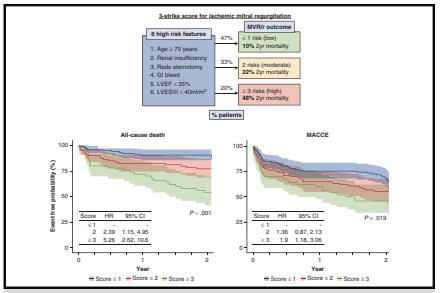
## ABSTRACT

**Objective:** Ischemic mitral regurgitation is prevalent and associated with high surgical risk. With the less-invasive option of transcatheter edge-to-edge repair, the optimal patient selection for mitral valve operation for ischemic mitral regurgitation remains unclear. We sought to identify high-risk features in this group to guide patient selection.

**Methods:** Using the Cardiothoracic Surgery Trial Network's severe ischemic mitral regurgitation trial data, we identified patient and echocardiographic characteristics associated with an increased risk of 2-year mortality using the support vector classifier and Cox proportional hazards model. We identified 6 high-risk features associated with 2-year survival. Patients were categorized into 3 groups, each having 1 or less, 2, or 3 or more of the 6 identified high-risk features.

**Results:** Among the 251 patients, the median age was 69 (Q1 62, Q3 75) years, and 96 (38%) were female. Two-year mortality was 21% (n = 53). We identified 6 high-risk preoperative features: age 75 years or more (n = 69, 28%), prior sternotomy (n = 49, 20%), renal insufficiency (n = 69, 28%), gastrointestinal bleeding (n = 15, 6%), left ventricular ejection fraction less than 40% (n = 131, 52%), and ventricular end-systolic volume index less than 50 mL/m$^2$ (n = 93, 37%). In patients who had 1 or less, 2, and 3 or more high-risk features, 90-day mortality was 4.2% (n = 5), 9.9% (n = 4), and 20.0% (n = 10), respectively ($P = .006$), and 2-year mortality was 10% (n = 12), 22% (n = 18), and 46% (n = 23) ($P < .001$), respectively.

**Conclusions:** We developed the 3-strike score by identifying high-risk preoperative features for mitral valve surgery for ischemic mitral regurgitation. Patients having 3 or more of such high-risk features should undergo careful evaluation for surgical candidacy given the high early and late mortality after mitral valve operations. (JTCVS Open 2024;18:52-63)




**The 3-strike score is a bedside risk stratification system for patients with iMR.**

### CENTRAL MESSAGE

There were 6 high-risk features for MV operation for iMR. Patients having 3 or more of such high-risk features should undergo careful evaluation for surgical candidacy.

### PERSPECTIVE

The patient selection for MV operation for iMR remains unclear. We identified 6 high-risk features: age 75 years or more, prior sternotomy, renal insufficiency, GI bleeding, ejection fraction less than 40%, and small left ventricle. Patients with 3 or more of such high-risk features should undergo extensive heart team discussion and careful evaluation for surgical candidacy.

From the [a]Division of Cardiac Surgery, Yale School of Medicine, New Haven, Conn; and [b]Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Conn.

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Address for reprints: Arnar Geirsson, MD, Division of Cardiac Surgery, Yale School of Medicine, BB204, 330 Cedar St, PO Box 208039, New Haven, CT 06510 (E-mail: arnar.geirsson@yale.edu).

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**Abbreviations and Acronyms**

CABG = coronary artery bypass grafting
CTSN = Cardiothoracic Surgical Trials Network
GI = gastrointestinal
iMR = ischemic mitral regurgitation
LVEF = left ventricular ejection fraction
LVESVI = left ventricular end-systolic volume index
MACCE = major adverse cerebrovascular and cardiac events
MR = mitral regurgitation
MV = mitral valve
MVr = mitral valve repair
MVR = mitral valve replacement

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Ischemic mitral regurgitation (iMR) is common and portends a poor prognosis.[1] Mitral valve replacement (MVR) or repair (MVr) at the time of coronary artery bypass grafting (CABG) in patients with severe iMR currently receives a Class 2a recommendation by the American Heart Association/American College of Cardiology guidelines.[2] However, survival remains suboptimal even after surgical correction, with 2-year mortality exceeding 20% in the Cardiothoracic Surgical Trials Network's (CTSN) severe iMR trial.[3] In this cohort, there likely exists a subgroup of patients who would derive substantial benefit from a mitral valve (MV) operation, whereas others portend poor prognosis even with surgery so that conservative or less-invasive treatment options may be favored.

Understanding the subgroup of patients who are at increased risk of poor outcomes after an MV operation may improve patient selection and triage between surgery and conservative alternatives. A systematic way of quantifying the risk for patients with iMR undergoing an MV operation is lacking, because the Society of Thoracic Surgeons Adult Cardiac Surgery Database risk model for an MV operation is etiology specific for primary mitral regurgitation (MR)[4] but not for iMR,[5] although the randomized controlled trial did not reproduce this outcome difference.[3] Additionally, there may be value in understanding key risk factors related to long-term outcomes. Therefore, a simple risk stratification system that accounts for perioperative and post–30-day outcomes is of value.

Using the CTSN's severe iMR trial data, we aimed to identify high-risk features among patients who underwent MV surgery for severe iMR to aid prognostication and guide the heart team discussion in patients for whom surgery may harbor extreme risk.

## MATERIALS AND METHODS

### Data Source and Patients

We used the CTSN severe iMR trial data. The trial enrolled patients with severe iMR between 2009 and 2012 across 22 sites who were eligible for surgical correction with or without concomitant CABG. Patients were randomized into MVr versus MVR 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. The trial conducted a rigorous follow-up of 2 years.

The data were obtained through the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center. Yale Institutional Review Board approved the study, and individual consent was waived (#2000034167, 12/1/2022).

### Candidate Variable Selection and Outcomes

Variables were defined per the original severe iMR trial. Echocardiographic measurements were standardized at the trial core laboratory. Candidate variables were selected in the following stepwise fashion: First, we identified all variables available to clinicians during preoperative assessment (n = 40). We then excluded those (1) with a prevalence of less than 5% in the trial cohort, (2) known to have minimal associated operative risk, or (3) with more than 20% missing values (ie, New York Heart Association class). This process excluded 10 variables. The remaining 30 variables were entered into a support vector classifier algorithm as a nonregression way of selecting variables with the highest pertinence, which has been done in a prior Society of Thoracic Surgeons CABG risk model performance evaluation.[6] We elected to use a nonregression algorithm given the low absolute number of events in the relatively small trial samples.[7] The chosen 14 variables (Table E1) were then modeled using a Cox proportional hazards model with stepwise selection for time to death as the dependent variable. A Cox model was used to provide variable coefficients to facilitate the clinical interpretability of the model. A time-dependent model was used in this step to evaluate death as a time-dependent outcome. This sequence of variable selections was applied to create a parsimonious risk stratification system for bedside use. The final set of variables retained in the model was then characterized as the high-risk features (Figure E1). Given the original trial randomized on MVr versus MVR, we conducted a sensitivity analysis, fitting a Cox model with the final set of variables and a forced input of randomization assignment (repair vs replacement).

The outcomes of interest were survival up to 2 years, major adverse cerebrovascular and cardiac events (MACCE), and quality of life as measured by Short Form 12 mental component score and physical component score at 2 years postrandomization, all of which were the original trial's secondary end points.

### Statistical Analysis

A support vector classifier algorithm[8] was applied on the split samples of 30:70 testing and validating samples,[9] with more than 1000 iterations via random sampling without replacement. We chose variables that were selected 90% or more of the time. The list of variables was then used to fit a Cox proportional hazard model. Variables with statistically significant associations with 2-year mortality hazards were chosen as high-risk features. We did not stratify the analysis by the MVr or MVR assignment because the original trial did not demonstrate a difference in survival or MACCE between the treatment assignments.

To facilitate clinical interpretation, we fitted Cox models for the time to death up to 2 years with the high-risk covariates. This identified inflection

**TABLE 1. Patient characteristics by those with and without death at 2 years**

| Variables | Overall, N = 251 | Alive, N = 198 | Died, N = 53 | *P* |
|---|---|---|---|---|
| Age, y (median, IQR) | 69 (62, 75) | 67 (62, 74) | 73 (68, 79) | <.001 |
| Female | 96 (38%) | 70 (35%) | 26 (49%) | .068 |
| Randomized to MVR | 125 (50%) | 96 (48%) | 29 (55%) | .4 |
| Race | | | | .2 |
| American Indian, Alaskan Native | 1 (0.4%) | 0 (0%) | 1 (1.9%) | |
| Asian | 2 (0.8%) | 2 (1.0%) | 0 (0%) | |
| Black | 44 (18%) | 34 (17%) | 10 (19%) | |
| White | 202 (80%) | 161 (81%) | 41 (77%) | |
| Other | 2 (0.8%) | 1 (0.5%) | 1 (1.9%) | |
| Hispanic ethnicity | 24 (9.6%) | 19 (9.6%) | 5 (9.4%) | >.9 |
| Atrial fibrillation | 80 (32%) | 60 (30%) | 20 (38%) | .3 |
| Diabetes | 89 (36%) | 72 (37%) | 17 (32%) | .5 |
| Carotid stenosis | 14 (5.6%) | 12 (6.1%) | 2 (3.8%) | .5 |
| Prior CABG | 47 (19%) | 32 (16%) | 15 (28%) | .044 |
| Cerebrovascular disease | 27 (11%) | 22 (11%) | 5 (9.4%) | .7 |
| Chronic lung disease | | | | .2 |
| None | 181 (73%) | 147 (75%) | 34 (64%) | |
| Mild | 27 (11%) | 20 (10%) | 7 (13%) | |
| Moderate | 27 (11%) | 17 (8.7%) | 10 (19%) | |
| Severe | 14 (5.6%) | 12 (6.1%) | 2 (3.8%) | |
| Dyslipidemia | 207 (83%) | 164 (83%) | 43 (81%) | .7 |
| Heart failure | 180 (72%) | 137 (69%) | 43 (81%) | .086 |
| GI bleed | 15 (6.0%) | 8 (4.1%) | 7 (13%) | .021 |
| Hypertension | 199 (79%) | 155 (78%) | 44 (83%) | .4 |
| Malignancy | 34 (14%) | 24 (12%) | 10 (19%) | .2 |
| Preoperative IABP | 6 (2.4%) | 4 (2.0%) | 2 (3.8%) | .6 |
| PCI | 90 (36%) | 67 (34%) | 23 (43%) | .2 |
| ICD | 40 (16%) | 28 (14%) | 12 (23%) | .13 |
| Myocardial infarction | 187 (75%) | 143 (72%) | 44 (83%) | .11 |
| Pacemaker | 29 (12%) | 20 (10%) | 9 (17%) | .2 |
| Peripheral arterial disease | 26 (10%) | 18 (9.2%) | 8 (15%) | .2 |
| Redo sternotomy | 49 (20%) | 34 (17%) | 15 (28%) | .069 |
| Prior surgery | 13 (5.2%) | 10 (5.1%) | 3 (5.7%) | .7 |
| Renal insufficiency | 69 (27%) | 46 (23%) | 23 (43%) | .003 |
| Stroke | 25 (10.0%) | 22 (11%) | 3 (5.7%) | .2 |
| TIA | 9 (3.6%) | 8 (4.0%) | 1 (1.9%) | .7 |
| Smoking history | 159 (64%) | 122 (62%) | 37 (70%) | .3 |
| Ventricular arrhythmias | 32 (13%) | 21 (11%) | 11 (21%) | .049 |
| Psychiatric disorder | 15 (6.0%) | 10 (5.1%) | 5 (9.4%) | .3 |
| Baseline echocardiography | | | | |
| LVESVI ($mL/m^2$) | 59 (43, 81) | 60 (45, 82) | 54 (41, 76) | .3 |
| ERO ($cm^2$) | 0.38 (0.30, 0.46) | 0.39 (0.31, 0.46) | 0.36 (0.30, 0.46) | .7 |
| LVEF (%) | 40 (32, 48) | 40 (34, 50) | 39 (30, 48) | .3 |
| Left ventricle sphericity (unitless) | 0.66 (0.60, 0.71) | 0.66 (0.61, 0.71) | 0.65 (0.59, 0.69) | .2 |
| Vena contracta (mm) | 7.50 (7.10, 8.40) | 7.55 (7.10, 8.30) | 7.50 (7.10, 8.43) | >.9 |

*(Continued)*

**TABLE 1. Continued**

| Variables | Overall, N = 251 | Alive, N = 198 | Died, N = 53 | *P* |
|---|---|---|---|---|
| MR severity | | | | .4 |
| Moderate | 10 (4.0%) | 7 (3.5%) | 3 (5.8%) | |
| Severe | 240 (96%) | 191 (96%) | 49 (94%) | |
| Concomitant CABG | 187 (75%) | 148 (75%) | 39 (74%) | .9 |

*IQR*, Interquartile range; *MVR*, mitral valve replacement; *CABG*, coronary artery bypass grafting; *GI*, gastrointestinal; *IABP*, intra-aortic balloon pump; *PCI*, percutaneous coronary intervention; *ICD*, intracardiac defibrillator; *TIA*, transient ischemic attack; *LVESVI*, left ventricular end-systolic volume index; *ERO*, effective regurgitant orifice; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation.

points for continuous variables in relation to the hazard of death using a spline curve fit. Martingale residuals for each continuous variable were obtained from the fitted Cox model and plotted against the hazard of death across the continuous variable spectrum using a penalized smoothing spline.[10] The inflection point was used to convert the continuous variables to binary risk factors. Using the number of high-risk features present in each patient, we constructed patient groups with 0 or 1, 2, or 3 or more high-risk features. Three high-risk features was defined as the threshold for the high-risk group because the 2-year mortality was similar between patients with 3 and more than 3 high-risk features (Figure E1). We then compared these 3 groups with respect to the outcomes of interest.

To characterize the discriminatory ability of the identified high-risk features, we fitted logistic regression models for binary 2-year mortality by splitting the dataset by 30:70 testing and validation samples, iterating over 100 times to derive c-statistics as a discrimination metric, Brier scores as a calibration metric, and CIs.

Patients' characteristics were summarized using median and interquartile range for continuous variables and frequency and percentage for categorical variables. Unadjusted survival was analyzed using Kaplan–Meier analysis, with statistical significance tested with a log-rank test. The significance level was 2-sided for all statistical tests. All analyses were conducted with Python (version 3.5) and the open-source packages available in Scikit-Learn and RStudio 1.3.1073 (R studio, PBC) with packages "smoothHR, survival," and "survminer."

## RESULTS

Among 251 randomized patients, the median age was 69 (interquartile range, 62-75) years, including 38% (n = 96) women. Death occurred in 21.2% (n = 53) at 2 years. Compared with the survivors, patients who died were older, more frequently had prior CABG, and had histories of gastrointestinal (GI) bleed, renal insufficiency, and ventricular arrhythmias (Table 1). Echocardiographic characteristics, including left ventricular ejection fraction (LVEF), LVESVI, and effective regurgitant orifice, were not significantly different.

**TABLE 2. High-risk features for mitral valve operation in ischemic mitral regurgitation**

| Variables | HR | 95% CI | *P* |
|---|---|---|---|
| Age (per 1-y increase) | 1.05 | 1.02-1.09 | .003 |
| Renal insufficiency | 1.69 | 0.97-2.96 | .063 |
| Prior sternotomy | 2.02 | 1.28-3.18 | .002 |
| GI bleed | 3.60 | 1.55-8.36 | .003 |
| LVEF (per 1% increase) | 0.93 | 0.89-0.96 | <.001 |
| LVESVI (per 1 unit increase) | 0.97 | 0.95-0.99 | <.001 |
| Stroke | 0.37 | 0.11-1.21 | .1 |

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

The variable selection process using the combination of clinician input, support vector classifier, and stepwise multivariable Cox proportional hazards model for the hazard of 2-year mortality identified 6 high-risk variables: older age, renal insufficiency, prior sternotomy, GI bleed, lower preoperative LVEF, and lower LVESVI (Table 2). The Cox model output categorizing all continuous variables as binary categories is shown in Table E2. Stroke did not have statistically significant association with the outcome but was retained in the model in the process of stepwise selection. Consequently, stroke was not included in the derivation of the final risk score. The sensitivity analysis model adding MVr versus MVR as an input variable did not demonstrate a significant association between repair or replacement and survival (Table E3). The multivariable Cox model splining for continuous variables identified a linear relationship without a clear inflection point between LVEF and the hazard of death, and inflection points around the age of 75 years and around LVESVI of 50 mL/m$^2$ (Figure E2). Given no clear inflection point in LVEF, we chose the median value for the LVEF threshold. High-risk thresholds for these variables were determined as age 75 or more years, ejection fraction less than 40%, and LVESVI less than 50 mL/m$^2$. There were 14, 106, 81, 41, and 9 patients with 0, 1, 2, 3, and 4 high-risk features, respectively. None of the patients had more than 4 high-risk features. Because the number of patients in 0 and 4 high-risk features were low and 2-year mortality incidences were similar to the neighboring groups, we created 3 groups with 0 or 1 (low risk), 2 (intermediate risk), and 3 or more (high risk) high-risk features (Figure E1).

We validated the predictive utility of the identified high-risk features by constructing and validating a risk model based on those variables. With iterative sampling, the model had a c-statistic of 0.72 $\pm$ 0.06 and a Brier score of 0.15 $\pm$ 0.01 for predicting 2-year mortality.

There were 119 (47.4%) low-risk patients, 81 (32.3%) intermediate-risk patients, and 50 (19.9%) high-risk patients. Among them, high-risk features were all significantly higher in the high-risk group compared with lower-risk groups. Additionally, patients in the high-risk group had a

**TABLE 3. Patient characteristics by the risk strata**

| Variables | Low risk, N = 119 | Intermediate risk, N = 81 | High risk, N = 50 | *P* |
|---|---|---|---|---|
| Age (y) | 66 (59-70) | 72 (64-79) | 76 (72-80) | <.001 |
| Female | 43 (36%) | 31 (38%) | 22 (44%) | .6 |
| Diabetes | 45 (38%) | 29 (36%) | 15 (30%) | .6 |
| Prior CABG | 3 (2.5%) | 21 (26%) | 23 (46%) | <.001 |
| Chronic lung disease | | | | .2 |
| None | 88 (75%) | 58 (72%) | 34 (68%) | |
| Mild | 13 (11%) | 9 (11%) | 5 (10%) | |
| Moderate | 7 (5.9%) | 11 (14%) | 9 (18%) | |
| Severe | 10 (8.5%) | 2 (2.5%) | 2 (4.0%) | |
| Heart failure | 80 (67%) | 54 (67%) | 45 (90%) | .005 |
| GI bleed | 2 (1.7%) | 3 (3.7%) | 10 (20%) | <.001 |
| Hypertension | 89 (75%) | 65 (80%) | 44 (88%) | .15 |
| Malignancy | 6 (5.0%) | 11 (14%) | 17 (34%) | <.001 |
| On IABP | 4 (3.4%) | 0 (0%) | 2 (4.0%) | .2 |
| PCI | 42 (35%) | 28 (35%) | 20 (40%) | .8 |
| ICD | 9 (7.6%) | 17 (21%) | 14 (28%) | .001 |
| Myocardial infarction | 90 (76%) | 57 (70%) | 40 (80%) | .4 |
| Pacemaker | 5 (4.2%) | 10 (12%) | 14 (28%) | <.001 |
| PAD | 12 (10%) | 10 (12%) | 4 (8.0%) | .7 |
| Redo sternotomy | 3 (2.5%) | 23 (28%) | 23 (46%) | <.001 |
| Renal insufficiency | 6 (5.0%) | 27 (33%) | 36 (72%) | <.001 |
| Stroke | 9 (7.6%) | 9 (11%) | 7 (14%) | .4 |
| LVESVI (mL/m$^2$) | 66 (51, 83) | 52 (39, 77) | 48 (39, 79) | .009 |
| ERO | 0.41 (0.31, 0.47) | 0.38 (0.30, 0.44) | 0.36 (0.29, 0.43) | .2 |
| LVEF (%) | 40 (31, 48) | 41 (35, 51) | 38 (31, 48) | .4 |
| Left ventricle sphericity | 0.66 (0.61-0.70) | 0.66 (0.58-0.71) | 0.65 (0.59-0.71) | .5 |
| Vena contracta | 7.60 (7.20-8.45) | 7.30 (7.00-8.40) | 7.60 (7.03-8.20) | .3 |
| Baseline MR | | | | .12 |
| Moderate | 2 (1.7%) | 6 (7.5%) | 2 (4.0%) | |
| Severe | 117 (98%) | 74 (92%) | 48 (96%) | |
| Concomitant CABG | 104 (87%) | 56 (69%) | 27 (54%) | <.001 |

*CABG*, Coronary artery bypass grafting; *GI*, gastrointestinal; *IABP*, intra-aortic balloon pump; *PCI*, percutaneous coronary intervention; *ICD*, intracardiac defibrillator; *PAD*, peripheral artery disease; *LVESVI*, left ventricular end-systolic volume index; *ERO*, effective regurgitant orifice; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation.

significantly higher prevalence of heart failure and malignancy (Table 3).

In the low, intermediate, and high-risk groups, the 90-day mortality rates were 4.2% (n = 5), 9.9% (n = 8), and 20% (n = 10), respectively ($P = .006$), and the 2-year mortality rates were 10% (n = 12), 22% (n = 18), and 46% (n = 23), respectively ($P < .001$) (Figure 1, left). The incidence of MACCE also differed among the 3 risk groups (Figure 1, right), with higher risk groups showing higher MACCE incidences (Figure 2). Quality of life scores in both Short Form 12 physical component score and mental component score at 2 years for the survivors did not differ significantly across the 3 risk strata (Table 4).

In the high-risk stratum, 4 of 6 high-risk features were present in more than half of the patients, except a history of GI bleed (present in 20%) and redo sternotomy (present in 46%) (Figure 3).

## DISCUSSION

iMR is prevalent, and patients tend to have high surgical risks. With the recently demonstrated effectiveness of transcatheter edge-to-edge repair for functional MR,[11,12] improved surgical risk stratification of patients with severe iMR is in need. In this secondary analysis of the CTSN severe iMR trial, we identified 6 high-risk features that together defined low-, intermediate-, and high-risk

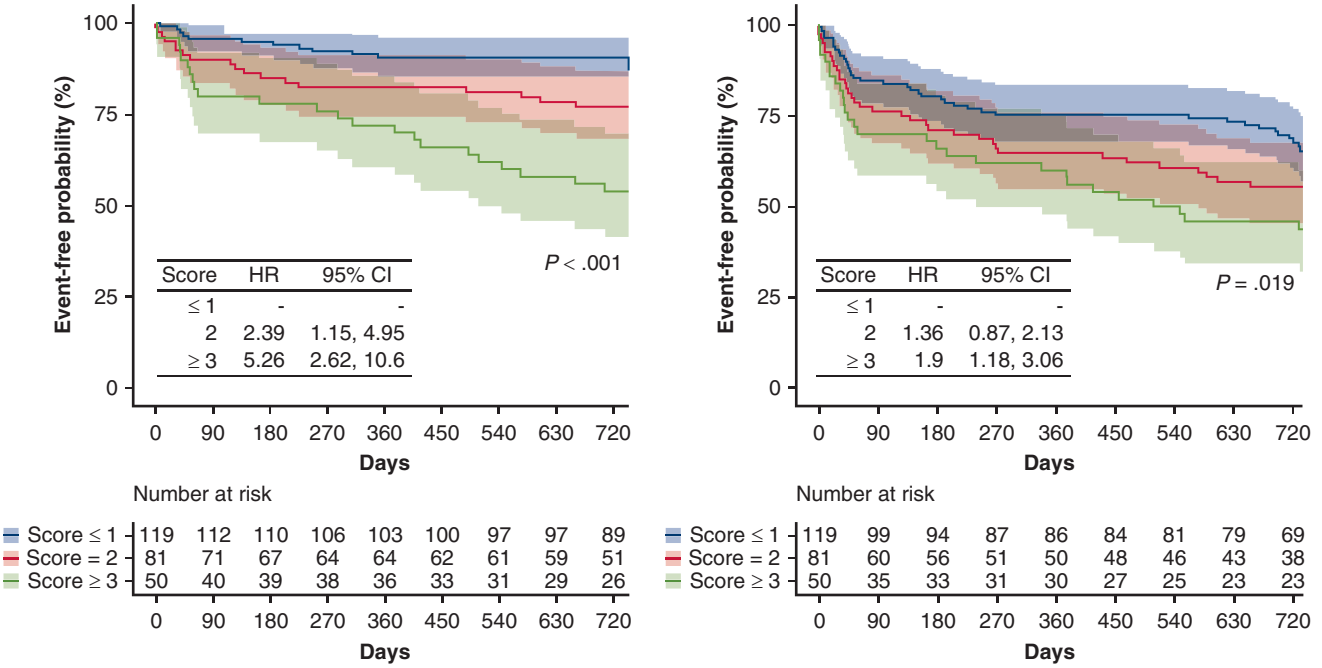


**FIGURE 1.** Survival by the number of high-risk features. The figures show event-free survival probability from all-cause death (*left*) and MACCE (*right*) by the number of high-risk features: 1 or less (*red*), 2 (*green*), and 3 or more (*blue*). *MACCE*, Major adverse cardiac and cerebrovascular events; *HR*, hazard ratio. *P* values were derived from Kaplan–Meier analysis.

subgroups based on the 2-year postoperative mortality risk. The model had a good discriminatory performance as judged by the c-statistics. The high-risk group, which comprised 20% of the patients who underwent MV operation, had a 2-year mortality approaching 50%, likely representing suboptimal surgical candidates, whereas that of the low-risk group was approximately 10%. This risk stratification can be performed at the bedside based on having "3 strikes" among the 6 high-risk features and may facilitate improved patient triage between MV surgery and alternative therapies.

Our study is important for several reasons. First, the current gold standard, the Society of Thoracic Surgeons Adult Cardiac Surgery Database risk model for MV operation is not specific to iMR. The severe iMR trial suggested that perioperative and midterm mortality are not significantly different between those undergoing MVR or MVr, although survival was not the primary end point of the trial. These observations highlighted the gap in estimating the surgical risks and outcomes of patients undergoing MV surgery for iMR using the existing tools. The multicenter trial data with rigorous 2-year follow-up and core laboratory–validated echocardiographic data allowed us to identify parsimonious clinical features that separate patients with low surgical risk from patients with high surgical risk. Of note, our risk stratification yielded the separation in survival early in the postoperative course, with 90-day mortality in the low-risk group being 4% versus 20% in the high-risk group. These data are likely valuable to preoperative patient counseling and shared decision making.

Second, some of the clinical features, including advanced age, renal insufficiency, low ejection fraction, and redo sternotomy, were known to increase surgical risks, but lower LVESVI as a risk factor had not been demonstrated in this population to our knowledge. The high coefficient associated with the history of GI bleed, although low in prevalence, also differs from prior risk models. The preoperative GI bleed history may increase the bleeding risk associated with routine postoperative anticoagulation for the MV prosthetics, which is practiced in approximately 40% of patients after MVR,[13] or it could represent a broad marker of the patient's higher comorbidity status. Concomitant CABG was performed at comparable incidences between those who survived and those who died but was performed more commonly in the lower-risk groups. This may be due to the surgeons' perception of the patient risk profile that led them to preferentially perform concomitant surgical revascularization in those with a lower-risk profile.

LVESVI's inverse association with mortality hazard warrants further investigation, as conventionally, a more dilated ventricle represents a more advanced disease and portends a poor prognosis. The significance of this relationship within the iMR, the group already with an advanced disease, remains unclear. Two randomized controlled trials on transcatheter edge-to-edge repair versus medical therapy for

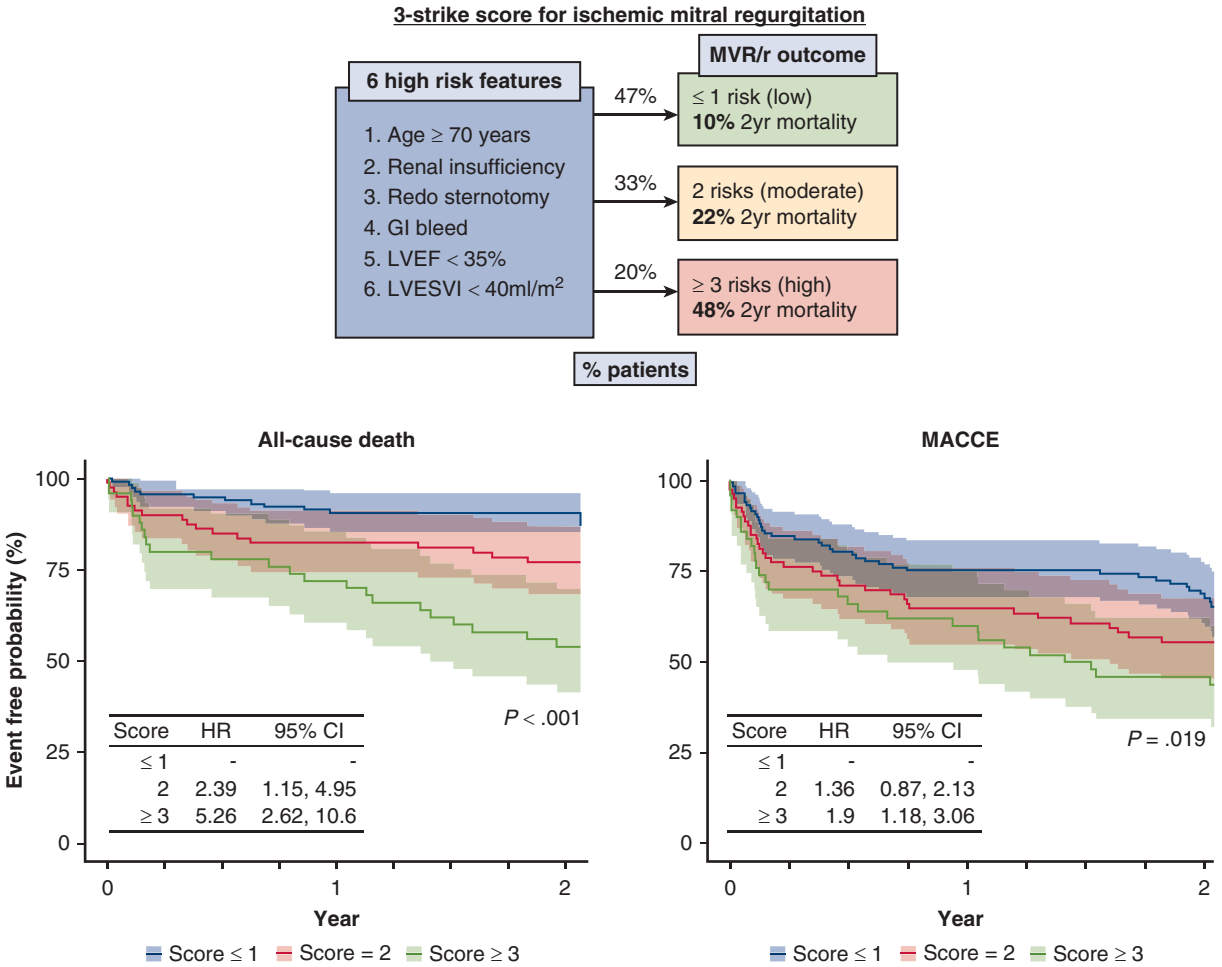


**FIGURE 2.** The figure shows a summary of 3-strike score components and associated 2-year survival. *MVR*, Mitral valve replacement; *MVr*, mitral valve repair; *GI*, gastrointestinal; *LVEF*, left ventricular ejection fraction; *LVESVI*, left ventricular end-systolic volume index; *HR*, hazard ratio; *MACCE*, major adverse cardiac and cerebrovascular events.

secondary MR birthed the concept of proportionate and disproportionate MR, where the ratio between the effective regurgitant orifice and ventricular dimension is used to identify those with smaller ventricles and relatively large regurgitant burden who are likely to benefit from intervention on the leaflet apparatus alone.[14] It is possible that MVR or MVr, both with annular remodeling components, may be more beneficial to those with larger ventricles regardless of the regurgitant burden. Trials have consistently demonstrated a reduction in left ventricle dimension after MV operations.[15,16] Further investigation on the proportionality of MR may identify a subgroup with proportionate MR that may yield benefits from MV operations, in contrast to disproportionate MRs benefitting from transcatheter edge-to-edge repair focused on the treatment of the leaflet apparatus.

A prior secondary analysis of the CTSN iMR trial showed worse survival in women.[17] Our analysis, which focused on identifying high-risk features and not specifically the sex-based differences, did not find sex to be significantly associated with survival. This may be due to our inclusion of risk features that were higher in coefficients that may have superseded the sex variable effect. Considering the identified association between lower LVESVI and worse survival, it is possible that sex was a confounder of this association in the prior analysis, with female patients having a lower threshold of LVESVI (male > 42 mL/m$^2$ and female > 37 mL/m$^2$)[18] to meet the severe dilation category even after indexing for the body surface area.

The number of patients seeking multidisciplinary valve team evaluation for IMR is expected to increase. Moderate or severe MR is found in 2.3% of older adults,[19] of whom approximately two-thirds have functional MR.[1] Among those with functional MR, 60% are of ischemic etiology.[1,20] This already high number of patients with severe iMR seeking treatment is likely to further increase with the recent Food and Drug Administration approval of the MitraClip for severe secondary MR,[21] similar to the impact of the adoption of transcatheter aortic valve replacement and its "halo"

**TABLE 4. Outcomes by the risk strata**

| Variables | Low risk, N = 119 | Intermediate risk, N = 81 | High risk, N = 50 | *P* |
|---|---|---|---|---|
| LVESVI at 2 y (mL/m$^2$) | 55 (36, 68) | 44 (27, 75) | 47 (31, 63) | .6 |
| Missing* | 31 | 33 | 30 | |
| MACCE | 43 (36%) | 35 (43%) | 28 (56%) | .057 |
| Days alive out of hospital | 713 (668, 722) | 702 (369, 717) | 530 (211, 716) | .001 |
| SF-12 MCS at 2 y | 48 (43, 53) | 51 (46, 54) | 51 (47, 54) | .1 |
| Missing* | 31 | 39 | 30 | |
| SF-12 PCS at 2 y | 44 (38, 50) | 43 (38, 49) | 40 (33, 48) | .3 |
| Missing* | 31 | 39 | 30 | |
| 30-d mortality | 1 (0.8%) | 4 (4.9%) | 2 (4.0%) | .2 |
| 90-d mortality | 5 (4.2%) | 8 (9.9%) | 10 (20%) | .006 |
| 1-y mortality | 11 (9.2%) | 14 (17%) | 14 (28%) | .008 |
| 2-y mortality | 12 (10%) | 18 (22%) | 23 (46%) | <.001 |

*LVESVI*, Left ventricular end-systolic volume index; *MACCE*, major adverse cardiac and cerebrovascular events; *SF-12*, Short Form 12; *MCS*, mental component score; *PCS*, physical component score. *Number of patients with missing values, including 53 deaths within 2 years.

effect on surgical aortic valve replacement volume.[22] In multidisciplinary evaluation, the practical use of our risk stratification algorithm may be as the first broad-stroke identification of the low-risk group, which is expected to do very well from surgery, and separating them from the high-risk group, which likely would have poor surgical outcomes. The intermediate-risk group warrants elaborate evaluation to further decide on the optimal therapeutic approach. Given that the grouping of high-risk features was based on the average treatment effect of the model, the risk score must be applied carefully with the recognition that there are patients with many high-risk features who may exhibit lower-risk phenotypes not captured in the risk score.

## Study Limitations

This is a secondary analysis of a randomized controlled trial. Therefore, the retrospective nature of the analysis harbors potential biases. The number of patients included was relatively small, leading to a concern that some variables that are clinically significant may not have been detected because of the underpowered nature of the analysis. Of note, the high-risk features identified via this retrospective analysis need to be validated prospectively because the causal pathway between some of the high-risk features and the risk of death remains undetermined. The categorization of continuous variables, although based on spline curves, introduced some

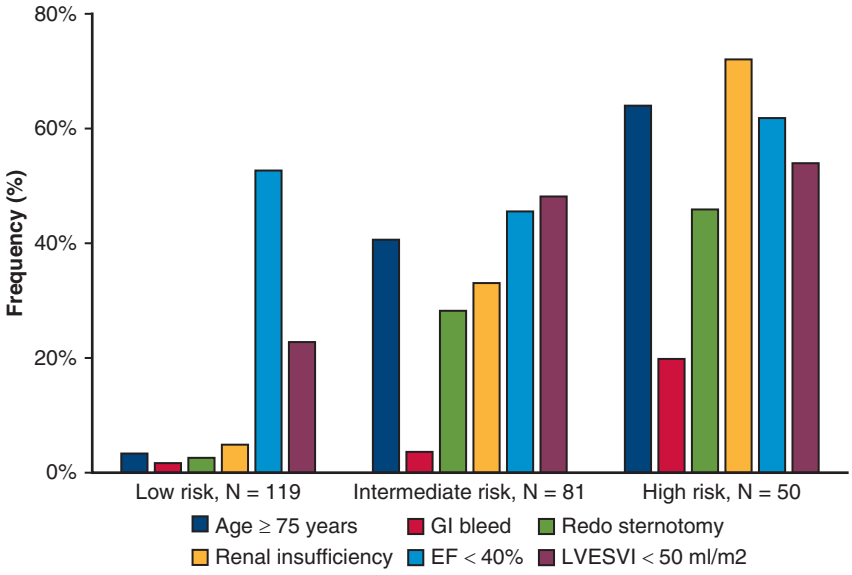


**FIGURE 3.** Frequencies of high-risk features within the risk strata. The frequencies of each high-risk feature among the risk strata: advanced age (*blue*), prior GI bleed (*red*), redo sternotomy (*green*), renal insufficiency (*yellow*), low EF (*cyan*), and low LVESVI (*mauve*). *GI*, Gastrointestinal; *EF*, ejection fraction; *LVESVI*, left ventricular end-systolic volume index.

arbitrariness because the inflection point was evaluated graphically, and potential clinical utility guided the determination of the threshold. This may be defined more rigorously in a larger dataset. Regardless, the variables identified have clinical face validity and likely would serve as useful screening tools to triage patients for those at both extremes of the risk spectrums. The available dataset did not contain left ventricular end-diastolic volume, which precluded the assessment of the proportionate/disproportionate MR concept.

## CONCLUSIONS

We developed the 3-strike score via identified high-risk preoperative features for MV surgery for iMR: advanced age, preoperative history of renal insufficiency, prior sternotomies, GI bleeding, lower ejection fraction, and lower LVESVI. Patients who have 3 or more of such high-risk features should undergo careful evaluation for surgical candidacy given the high early and late mortality after MV operations.

### Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/high-risk-subgroup-of-patients-undergoing-mitral-valve-operation-for-ischemic-mitral-regurgitation-the-3-strike-score.


### Conflict of Interest Statement

Dr Krane is a physician proctor and a member of the medical advisory board for JOMDD, is a physician proctor for Peter Duschek, is a medical consultant for EVOTEC and Moderna, and has received speakers' honoraria from Medtronic and Terumo. Dr Geirsson 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.

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**Key Words:** ischemic mitral regurgitation, mitral valve repair, mitral valve replacement, risk score

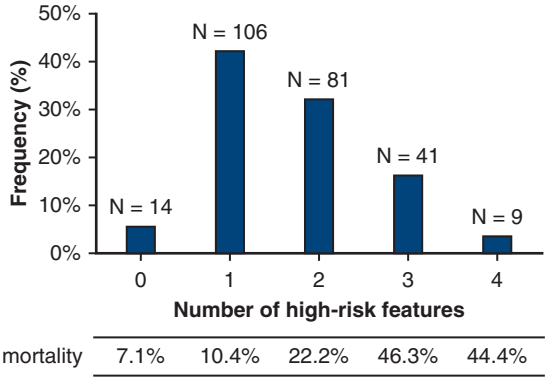


**FIGURE E1.** The 2-year mortality by high-risk feature score group. The number (*N*) and percentage of patients having zero to 4 high-risk features are shown. The 2-year mortality rate for each group is displayed in the *bottom bar.*

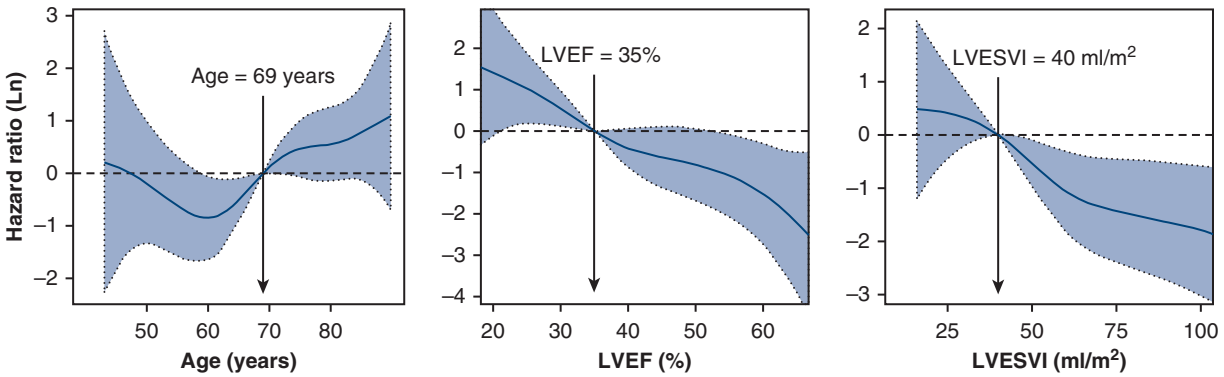


**FIGURE E2.** Splined Cox model output for continuous variables. The HRs for 2-year mortality across ranges of continuous variables: age (*left*), LVEF (*middle*), and LVESVI (*right*). *Arrows* indicate reference points at which the natural log (*Ln*) of the HR is zero. *LVEF*, Left ventricular ejection fraction; *LVESVI*, left ventricular end-systolic volume index.

**TABLE E1. Variable selection using support vector classifier**

| Rank | Variables | No. of times selected |
|---|---|---|
| 1 | Age | 1000 |
| 2 | LVESVI | 1000 |
| 3 | LVEF | 1000 |
| 4 | GI bleed | 995 |
| 5 | Stroke | 991 |
| 6 | Peripheral arterial disease | 986 |
| 7 | Renal insufficiency | 986 |
| 8 | Chronic lung disease | 976 |
| 9 | Prior sternotomy | 974 |
| 10 | Race | 963 |
| 11 | Myocardial infarction | 936 |
| 12 | Vena contracta | 935 |
| 13 | Mitral regurgitation severity | 915 |
| 14 | Sex | 902 |
| 15 | Carotid stenosis | 898 |
| 16 | Diabetes | 892 |
| 17 | Ethnicity | 889 |
| 18 | Psychiatric disorder | 874 |
| 19 | CABG | 856 |
| 20 | PCI | 843 |
| 21 | NYHA class | 843 |
| 22 | Prior valve replacement | 808 |
| 23 | ICD | 773 |
| 24 | Malignancy | 771 |
| 25 | Atrial fibrillation | 753 |
| 26 | Ventricular arrhythmia | 747 |
| 27 | LV sphericity | 747 |
| 28 | Hypertension | 712 |
| 29 | Prior valve repair | 703 |
| 30 | ERO | 652 |
| 31 | Cerebrovascular disease | 640 |
| 32 | Pacemaker | 634 |
| 33 | On IABP support | 458 |

Variables entered into the support vector classifier algorithm are listed, along the number of times the variables were selected out of 1000 sampling iterations. Variables selected in more than 90% of the sampling iterations were then entered into the Cox proportional hazards model for further variable selection. *LVESVI*, Left ventricular end-systolic volume index; *LVEF*, left ventricular ejection fraction; *GI*, gastrointestinal; *CABG*, coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *NYHA*, New York Heart Association; *ICD*, intracardiac defibrillator; *ERO*, effective regurgitant orifice; *IABP*, intra-aortic balloon pump.

**TABLE E2. Cox proportional hazard analysis using binary categorization of continuous variables**

| Characteristic | HR | 95% CI | *P* |
|---|---|---|---|
| Age >70 y | 1.6 | 1.02-2.74 | .05 |
| GI bleed | 2.36 | 1.05-5.31 | .04 |
| Redo operation | 1.68 | 0.91-3.08 | .1 |
| Renal insufficiency | 2.06 | 1.18-3.60 | .01 |
| Ejection fraction <35% | 2.16 | 1.04-4.49 | .04 |
| LVESVI <40 mL/m$^2$ | 2.92 | 1.39-6.15 | .01 |

*HR*, Hazard ratio; *GI*, gastrointestinal; *LVESVI*, left ventricular end-systolic volume index.

**TABLE E3. Cox proportional hazard analysis including mitral valve replacement versus repair**

| Variables | HR | 95% CI | *P* |
|---|---|---|---|
| Age (per 1-y increase) | 1.06 | 1.02-1.09 | .002 |
| MVr (ref. = replacement) | 0.74 | 0.42-1.28 | .3 |
| Renal insufficiency | 1.61 | 0.92-2.82 | .094 |
| Prior sternotomy | 2.05 | 1.29-3.27 | .003 |
| GI bleed | 3.28 | 1.43-7.53 | .005 |
| LVEF (per 1% increase) | 0.93 | 0.89-0.97 | <.001 |
| LVESVI (per 1 unit increase) | 0.97 | 0.95-0.99 | .001 |

*HR*, Hazard ratio; *MVr*, mitral valve repair; *GI*, gastrointestinal; *LVEF*, left ventricular ejection fraction; *LVESVI*, left ventricular end-systolic volume index.