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Original Research

Cross-Validation of Risk Scores for Patients Undergoing Transcatheter Edge-to-Edge Repair for Mitral Regurgitation

Rodrigo Estévez-Loureiro, MD, PhD [a,†], Neeraj Shah, MD [b,†], Sergio Raposeiras-Roubin, MD, PhD [a], Lak N. Kotinkaduwa, PhD [c], Mahesh V. Madhavan, MD, MS [c,d], William A. Gray, MD [e], JoAnn Lindenfeld, MD [f], Marianna Adamo, MD [g], William T. Abraham, MD [h], Xavier Freixa, MD, PhD [i], Paul A. Grayburn, MD [j], Dabit Arzamendi, MD, PhD [k], Saibal Kar, MD [l,m], Tomas Benito-González, MD [n], D. Scott Lim, MD [o], Antonio Montefusco, MD, PhD [p], Björn Redfors, MD, PhD [c,q], Isaac Pascual, MD, PhD [r], Luis Nombela-Franco, MD, PhD [s], Josep Rodés-Cabau, MD, PhD [t], Mony Shuvy, MD, PhD [u], Vanessa Moñivas, MD, PhD [v], Cosmo Godino, MD, PhD [w], Michael J. Mack, MD [x], Francesco Bedogni, MD, PhD [y], Gregg W. Stone, MD [z,*]

[a] *Cardiovascular Research Group, Galicia Sur Health Research Institute (IISGS), Hospital Álvaro Cunqueiro, Vigo, Spain;* [b] *East Carolina University, Greenville, North Carolina;* [c] *Clinical Trials Center, Cardiovascular Research Foundation, New York, New York;* [d] *Columbia University Irving Medical Center, NewYork-Presbyterian Hospital, New York, New York;* [e] *Division of Cardiovascular Diseases, Lankenau Heart Institute, Philadelphia, Pennsylvania;* [f] *Advanced Heart Failure and Cardiac Transplantation Section, Vanderbilt Heart and Vascular Institute, Nashville, Tennessee;* [g] *Institute of Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy;* [h] *Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio;* [i] *Clinic Barcelona, University of Barcelona, Barcelona, Spain;* [j] *Department of Internal Medicine, Division of Cardiology, Baylor Scott & White Heart and Vascular Hospitals, Plano, Texas;* [k] *Department of Cardiology, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain;* [l] *Los Robles Regional Medical Center, Thousand Oaks, California;* [m] *Bakersfield Heart Hospital, Bakersfield, California;* [n] *Department of Cardiology, University Hospital of León, León, Spain;* [o] *Division of Cardiology, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia;* [p] *Division of Cardiology, Cardiovascular and Thoracic Department, University of Turin, Città Della Salute e Della Scienza, Turin, Italy;* [q] *Department of Cardiology, Sahlgrenska University Hospital and Wallenberg Laboratory, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden;* [r] *Interventional Cardiology Unit, Hospital Universitario Central de Asturias, Oviedo, Spain;* [s] *Cardiovascular Institute, Hospital Clinico San Carlos, IdISSC, Madrid, Spain;* [t] *Cardiology Department, Quebec Heart and Lung Institute, Laval University, Quebec City, Canada;* [u] *Heart Institute Hadassah-Hebrew University Medical Center, Jerusalem, Israel;* [v] *Cardiology Department Hospital Universitario Puerta de Hierro, Madrid, Spain;* [w] *Clinical Cardiology Unit, Faculty of Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [x] *Department of Cardiothoracic Surgery, Baylor Scott & White Health, Plano, Texas;* [y] *Clinical and Interventional Cardiology Department, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy;* [z] *The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York*

ABSTRACT

Background: Risk scores may identify patients with mitral regurgitation (MR) who are at risk for adverse events, but who may still benefit from transcatheter edge-to-edge repair (TEER). We sought to cross-validate the MitraScore and COAPT risk score to predict adverse events in patients undergoing TEER.

Methods: MitraScore validation was carried out in the COAPT population which included 614 patients with FMR who were randomized 1:1 to guideline-directed medical therapy (GDMT) with or without TEER and were followed for 2 years. Validation of the COAPT risk score was carried out in 1007 patients from the MIVNUT registry of TEER-treated patients with both FMR and degenerative MR who were followed for a mean of 2.1 years. The predictive value was assessed using the area under the receiver operating characteristic curve (AUC) plots. The primary outcome was all-cause mortality.

Results: The MitraScore had fair to good predictive accuracy for mortality in the overall COAPT trial population (AUC, 0.67); its accuracy was higher in patients treated with TEER (AUC, 0.74) than GDMT alone (AUC, 0.65). The COAPT risk score had fair predictive accuracy for death in the overall MitraScore cohort (AUC, 0.64), which was similar in patients with FMR and degenerative MR (AUC, 0.64 and 0.66, respectively). There was a consistent benefit of treatment with TEER plus GDMT compared with GDMT alone in the COAPT trial population across all MitraScore risk strata.

Conclusions: The COAPT risk score and MitraScore are simple tools that are useful for the prediction of 2-year mortality in patients eligible for or undergoing treatment with TEER.

Abbreviations: AUC, area under the receiver operating characteristic curve; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; RV, right ventricle; RVSP, right ventricular systolic pressure; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation.

Keywords: COAPT; mitral regurgitation; MitraScore; mortality; risk score; transcatheter edge-to-edge repair.

* Corresponding author: gregg.stone@mountsinai.org (G.W. Stone).

† Co-first authors.

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Introduction

Transcatheter edge-to-edge mitral valve repair (TEER) with the MitraClip device (Abbott) has been established as an effective treatment for selected patients with functional mitral regurgitation (FMR) and for those with degenerative MR (DMR) who are at high surgical risk.[1,2] The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated significant reductions in 2-year mortality and heart failure hospitalization (HFH) with TEER plus guideline-directed medical therapy (GDMT) compared with GDMT alone.[3] However, clinical event rates remained high in this patient population.[4,5] Careful risk stratification and appropriate patient selection is the cornerstone for identifying patients who would benefit from TEER, enabling patients and physicians to engage in shared decision-making regarding TEER. Several early risk scores that were developed for transcatheter MR treatment have not been widely adopted due to suboptimal performance or complex calculations.[6–8] Recently a user-friendly score (MitraScore) was derived from a population of patients with symptomatic MR (both FMR and DMR) undergoing TEER.[9] Likewise, a simple risk prediction tool consisting of clinical and echocardiographic variables was derived from the COAPT trial population.[10] The MitraScore has not been validated in an FMR-only population and the COAPT risk score has not been externally validated. The aim of this study was to perform a cross-validation of both the MitraScore and COAPT risk score to determine their predictive utility across the spectrum of patients with severe MR, especially those undergoing TEER.

Methods

The MitraScore population and risk score

The MitraScore was derived from the retrospective Percutaneous Mitral Valve Repair and Nutritional Status (MIVNUT) registry of 1119 patients with symptomatic MR who underwent TEER at 12 centers in Europe and Canada between 2012 and 2020 who had a mean 2.1-year follow-up.[9] FMR was present in 658 (59.3%) patients and the remainder had DMR. A total of 112 participants with unknown values for at least 1 of the characteristics required for the COAPT risk score were excluded. Therefore, the final MitraScore cohort from the MIVNUT registry in the present study (hereafter referred to as the "MitraScore cohort") comprised 1007 patients.

The MitraScore was derived by assigning 1 point to each of the 8 independent predictors: age ≥75 years, anemia, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, LVEF <40%, peripheral artery disease, chronic obstructive pulmonary disease, high diuretic dose use (≥80 mg of furosemide per day or use of ≥2 diuretic agents excluding aldosterone antagonists), and no therapy with renin-angiotensin system inhibitors.[9] Patients were classified into 3 risk groups of MitraScore: low-risk (0-2 points), moderate-risk (3-4 points), and high-risk (≥5 points).

The COAPT population and risk score

The COAPT trial enrolled 614 patients with heart failure (HF), left ventricular ejection fraction (LVEF) 20%-50%, and moderate-to-severe (3+) or severe (4+) FMR confirmed by an independent echocardiographic core laboratory who remained symptomatic despite maximally tolerated GDMT and cardiac resynchronization therapy (CRT) if appropriate at 78 sites in the United States and Canada.[3] Enrolled patients were randomized 1:1 to TEER with the MitraClip plus GDMT or GDMT alone.

The COAPT risk score was derived using 4 clinical, 4 echocardiographic, and 1 treatment variable.[10] Different points were assigned to each independent predictor: New York Heart Association functional class III or IV (+1 point), chronic obstructive pulmonary disease (+1 point), history of atrial fibrillation or flutter (+1 point), chronic kidney disease (CKD) stage III (eGFR 30-60 mL/min/m^2) (+1 point), CKD stage IV or greater (eGFR <30 mL/min/m^2) (+3 points), LVEF 25%-35% (+1 point), LVEF <25% (+2 points), left ventricular end-systolic diameter (LVESD) >5.5 cm (+2 points), right ventricular systolic pressure (RVSP) >45 mm Hg (+3 points), tricuspid regurgitation (TR) grade ≥2+ (+2 points), and MitraClip therapy (−3 points). Missing data for covariates was imputed. For details regarding imputed data, please refer to our manuscript on COAPT risk score derivation.[10] For the purpose of this study, we used a "modified" COAPT risk score excluding the –3 point deduction for MitraClip, since all patients in the MitraScore cohort underwent TEER. In the original study, the modified COAPT risk score was divided into the following quartiles of risk: 0 to 4, 5 to 6, 7 to 8, and 9 to 15 points. For the current analyses, the second and third quartiles of the modified COAPT risk score were combined into 1 group ("intermediate risk") and the modified COAPT risk score was divided into the following 3 risk strata: low-risk (0-4 points), intermediate-risk (5-8 points) and high-risk (9-15 points).

Study outcomes

The primary end point of the present study was all-cause mortality at 2 years. Secondary end points were HFH and the composite of death or HFH. In the absence of outcomes, follow-up time was censored at the last medical contact.

Statistical analysis

Validation of the MitraScore in the COAPT trial population. Receiver operating characteristic (ROC) curves including the 7 clinical and 1 echocardiographic variables of the MitraScore in the COAPT trial population (n = 614) were generated for the following 2-year outcomes: death, HFH, and death or HFH. The predictive value of this model was assessed using the area under curve (AUC) of the ROC plot. Subgroup analysis was performed in patients assigned to the GDMT alone group (n = 312) and to the MitraClip plus GDMT group (n = 302). Kaplan-Meier survival curves were generated for the incidence of death, HFH, and the composite of death or HFH in the 3 risk strata of the MitraScore (0-2, 3-4, 5-8 points) in all patients and separately for the GDMT alone and MitraClip plus GDMT groups, with differences assessed using the log-rank statistic. Cubic splines were generated to assess the continuous relationship between the MitraScore and outcomes in the COAPT trial.

Validation of the COAPT risk score in the MitraScore cohort. ROC curves including the 4 clinical and 4 echocardiographic variables of the modified COAPT risk score were generated in the MitraScore cohort (n = 1007 patients undergoing TEER) for the following outcomes: death, HFH, death, or HFH. The predictive value of these models was assessed using the AUC of the ROC plots. Subgroup analysis was performed in those with FMR (n = 594) and those with degenerative MR (n = 413). Kaplan-Meier survival curves were generated for the incidence of death, HFH, and the composite of death or HFH in the 3 strata of the modified COAPT risk score (0-4, 5-8, 9-15 points) in all patients and separately for the FMR and DMR groups, with differences assessed using the log-rank statistic. Cubic splines were generated to assess the continuous relationship between the COAPT risk score and outcomes in the MitraScore cohort. Additive and multiplicative interactions between treatment effect with TEER (vs GDMT) and MitraScore risk groups on event outcomes were evaluated using the relative excess risk due to interaction and Cox regression models, respectively.

Table 1. Baseline characteristics of the MitraScore cohort and the COAPT trial population.

Variables	MitraScore (n = 1007)	COAPT (n = 614)	*P* value
Age, y	73.5 ± 10.4	72.2 ± 11.2	.02
≥75 y	505 (50.1%)	291 (47.4%)	.28
Female sex	368 (36.5%)	221 (36.0%)	.82
Race and ethnicity			–
White	N/A	457 (74.4%)	
Black	N/A	88 (14.3%)	
Hispanic	N/A	40 (6.5%)	
Other	N/A	29 (4.7%)	
MR classification			
Functional MR	594 (59.0%)	614 (100%)	<.001
Degenerative MR	413 (41.0%)	0 (0%)	<.001
NYHA functional class[a]			<.001
I	3 (0.3%)	1 (0.2%)	
II	147 (14.6%)	239 (39.0%)	
III	642 (63.7%)	322 (52.5%)	
IV	215 (21.4%)	51 (8.3%)	
NYHA III-IVa	857 (85.1%)	373 (60.8%)	<.001
Comorbidities			
Hypertension	720 (71.5%)	494 (80.5%)	<.001
Hypercholesterolemia	561 (55.7%)	329 (53.6%)	.40
Diabetes mellitus	351 (34.9%)	229 (37.3%)	.32
Coronary artery disease	572 (56.8%)	446 (72.6%)	<.001
Prior myocardial infarction	N/A	316 (51.5%)	–
History of coronary artery bypass grafting	191 (19.0%)	247 (40.2%)	<.001
Prior percutaneous coronary intervention	346 (35.8%)	283 (46.1%)	<.001
Previous stroke	105 (10.4%)	72 (11.7%)	.42
History of transient ischemic attack	N/A	43 (7.0%)	–
Peripheral vascular disease	165 (16.4%)	109 (17.8%)	.48
Chronic obstructive pulmonary disease	226 (22.4%)	143 (23.3%)	.69
Atrial fibrillation	594 (59.0%)	339 (55.2%)	.14
CKD[b] stage III	485 (48.2%)	324 (53.6%)	.04
CKD[b] stage IV or greater	165 (16.4%)	142 (23.5%)	<.001
Anemia	582 (57.8%)	144 (23.5%)	<.001

Values are mean ± SD or n (%).
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MR, mitral regurgitation; NYHA, New York Heart Association.
[a] NYHA functional class data were available for 613 patients in the COAPT trial cohort. [b] CKD stages were determined by estimated glomerular filtration rate (calculated by Cockcroft-Gault equation) with stage III CKD defined as eGFR 30-60 mL/min/1.73m^2 and stage IV or greater CKD defined as eGFR <30 mL/min/1.73m^2. CKD data were available for 605 patients in the COAPT trial cohort; missing values were otherwise imputed using multiple imputations.

Table 2. Baseline laboratory and echocardiographic data and therapies of the MitraScore cohort and the COAPT trial population.

Variables	MitraScore (n = 1007)	COAPT (n = 614)	*P* value
Baseline creatinine[a], g/dL	1.5 ± 1.0	1.8 ± 1.3	<.001
Baseline eGFR[b], mL/min	52.9 ± 23.1	49.3 ± 26.8	.005
Baseline hemoglobin[c], g/dL	12.2 ± 1.9	12.1 ± 1.7	.29
Left ventricular ejection fraction[d], %	39.7 ± 15.9	31.3 ± 9.3	<.001
<40%	547 (54.3%)	465 (80.9%)	<.001
25%-35%	339 (33.7%)	250 (43.5%)	<.001
<25%	142 (14.1%)	159 (27.7%)	<.001
LV end-systolic dimension[e], cm	4.6 ± 1.1	5.3 ± 0.9	<.001
>5.5 cm	171 (17.0%)	236 (38.9%)	<.001
LV end-diastolic dimension[f], cm	6.2 ± 1.8	6.2 ± 0.7	1.0
Right ventricular systolic pressure[g], mm Hg	49.2 ± 14.9	44.3 ± 13.7	<.001
>45 mm Hg	484 (48.1%)	238 (45.1%)	.27
Tricuspid regurgitation[h]			<.001
0 (none)	30 (3.0%)	27 (4.4%)	
1+	435 (43.2%)	489 (79.6%)	
2+	264 (26.2%)	92 (15.0%)	
3+	182 (18.1%)	5 (0.8%)	
4+	96 (9.5%)	1 (0.2%)	
TR ≥2+	542 (53.8%)	98 (16.0%)	<.001
Left atrial size[i]			<.001
Normal (LAVI <34 mL/m^2)	42 (9.1%)	145 (24.0%)	
Mild-moderately dilated (LAVI 34-48 mL/m^2)	19 (4.1%)	213 (35.2%)	
Severely dilated (LAVI >48 mL/m^2)	402 (86.9%)	247 (40.8%)	
Therapies			
TEER	1007 (100%)	302 (49.2%)	<.001
High diuretic dose	307 (30.5%)	287 (46.7%)	<.001
No therapy with RAS inhibitors	360 (36.7%)	203 (33.1%)	.27

Values are mean ± SD or n (%).
LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NYHA, New York Heart Association; RAS, renin-angiotensin system; RVSP, right ventricular systolic pressure; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation.
[a] Baseline creatinine data were available for 606 patients in the COAPT trial cohort. [b] Baseline eGFR data were available for 601 patients in the COAPT trial cohort. [c] Baseline hemoglobin data were available for 587 patients in the COAPT trial cohort. [d] Baseline LVEF data were available for 575 patients in the COAPT trial cohort. [e] LVESD data were available for 607 patients in the COAPT trial cohort. [f] LV end-diastolic dimension data were available for 608 patients in the COAPT trial cohort. [g] RVSP estimates were available for 528 patients in the COAPT trial cohort (in the remainder RVSP could not be estimated because of the absence of a TR jet). These 86 missing values were imputed as normal RVSP (ie, placed in the <45 mm Hg). [h] There were 15 missing values for TR in the COAPT trial cohort which were treated as absent or no TR ie, TR grade 0. [i] LAVI data were available for only 463 patients in the MitraScore cohort and 605 patients in the COAPT trial cohort. Missing values were otherwise imputed using multiple imputations.

Differences in baseline characteristics were evaluated using the χ^2 test for categorical variables, *t* test for continuous variables that were normally distributed and the Kruskal Wallis test for continuous variables that were not normally distributed. AUC values of 0.5 to 0.6 were considered as poor discrimination, 0.6 to 0.7 as fair discrimination, 0.7 to 0.8 as good discrimination, and ≥0.8 as excellent discrimination.[11] Two-sided *P* values <.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute).

Results

Patient populations and outcomes

From the MIVNUT registry, there were no significant differences in the baseline characteristics of the 1007 patients that were included in this analysis compared with the 112 patients that were excluded (Supplemental Table S1). In the MitraScore cohort included in the final analysis (n = 1007), the average duration of follow-up was 2.1 ± 1.8 years and 59.0% of patients had FMR. During follow-up, 313 patients died (14.6 per 100 patient-years), 297 HFH were reported (16.2 per 100 patient-years) and 452 patients died or had a HFH (24.6 per 100 patient-years).

In the COAPT trial population, 125 (40.1%), 158 (50.6%), and 201 (64.4%) patients in the GDMT alone group and 83 (27.5%), 95 (31.5%), and 133 (44.0%) patients in the MitraClip plus GDMT group experienced death, HFH, or a composite of death or HFH respectively during the 2-year follow-up period (*P* < .001 for all 3 comparisons).

As shown in Tables 1 and 2, the COAPT trial population compared with the MitraScore cohort had higher proportions of patients with hypertension, coronary artery disease, CKD-III, and CKD-IV or greater, and treatment with higher diuretic doses. The

Table 3. AUC values (with 95% CI) of the modified COAPT risk score and the MitraScore for 2-year outcomes in the COAPT trial.

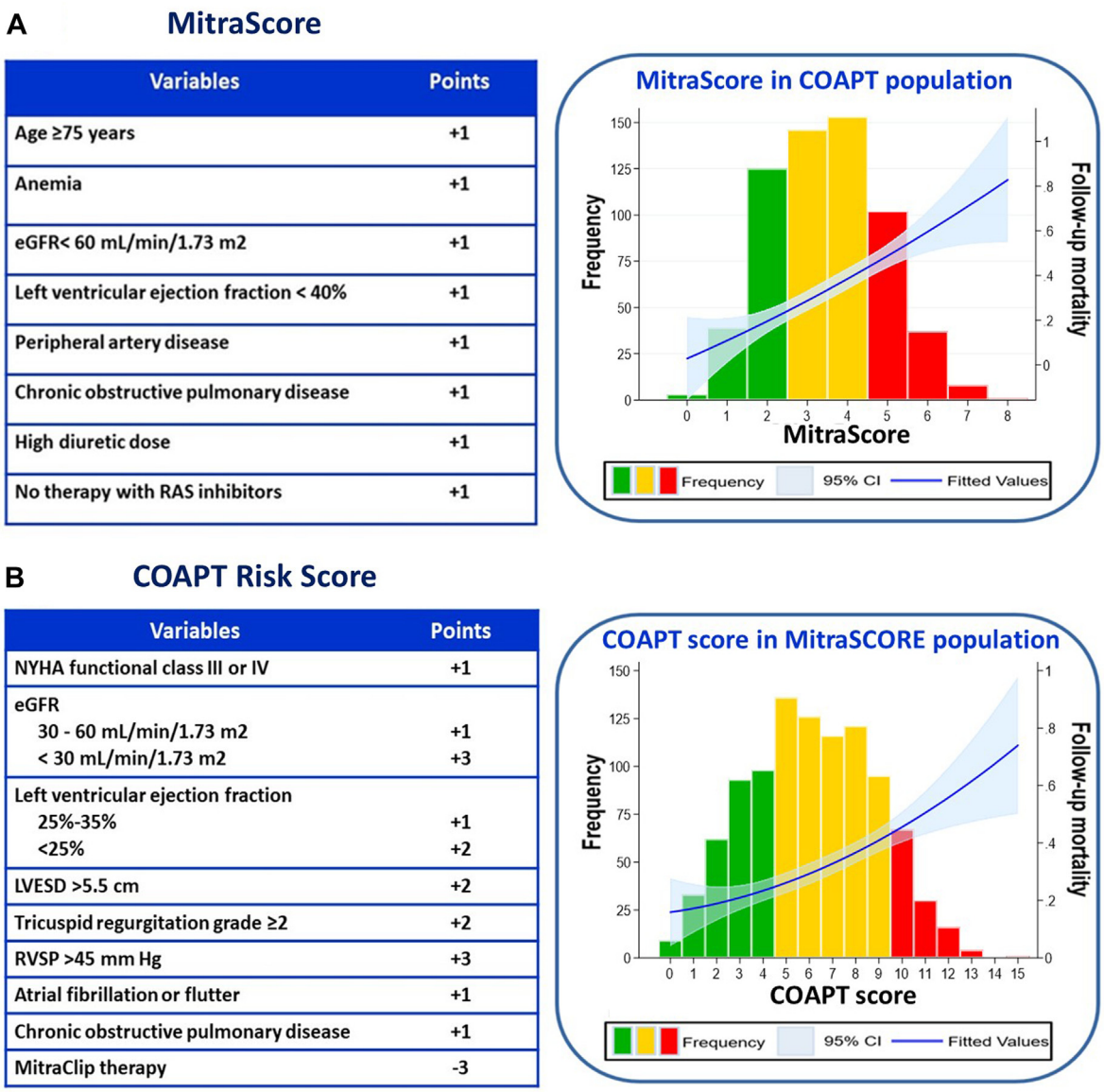
Outcomes	Modified COAPT risk score AUC	MitraScore AUC
Overall COAPT population (n = 614)		
Death	0.74 (0.69-0.78)	0.67 (0.63-0.72)
HFH	0.68 (0.65-0.77)	0.57 (0.54-0.63)
Death or HFH	0.71 (0.66-0.77)	0.60 (0.57-0.65)
COAPT GDMT-alone group (n = 312)		
Death	0.76 (0.69-0.83)	0.65 (0.60-0.73)
HFH	0.69 (0.66-0.79)	0.57 (0.51-0.70)
Death or HFH	0.71 (0.66-0.79)	0.57 (0.52-0.68)
COAPT MitraClip plus GDMT group (n = 302)		
Death	0.72 (0.67-0.82)	0.74 (0.69-0.80)
HFH	0.74 (0.68-0.82)	0.57 (0.53-0.67)
Death or HFH	0.76 (0.69-0.83)	0.65 (0.59-0.71)

AUC, area under the receiver operating characteristic curve; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization.

COAPT population also had a lower mean LVEF and a higher mean LVESD but was slightly younger and had a lower proportion of patients with New York Heart Association III/IVa functional class, history of anemia and TR ≥2+, and had lower mean RVSP. There were also significant differences in the baseline characteristics between the patients enrolled in COAPT and the FMR cohort of MitraScore (Supplemental Tables S2 and S3).

External validation of MitraScore in the COAPT trial population

As shown in Table 3, the MitraScore had fair to good accuracy for predicting 2-year mortality in the overall COAPT trial population (AUC 0.67). Its predictive accuracy was numerically better among COAPT patients who underwent TEER than those who were treated with GDMT alone (AUC 0.74 vs 0.65, respectively, $P = .06$). The AUC for the MitraScore in the COAPT TEER plus GDMT group was similar to that of the modified



Central Illustration.

Distribution of MitraScore and COAPT risk score. (**A**) Frequency distribution of MitraScore in the COAPT trial population superimposed over a cubic spline analysis demonstrating the continuous relationship between the MitraScore and the primary outcome or 2-year death in the COAPT trial population. (**B**) Frequency distribution of the modified COAPT risk score in the MitraScore cohort superimposed over a cubic spline analysis demonstrating the continuous relationship between the modified COAPT risk score and primary outcome of death at a mean follow-up of 2.1 years in the MitraScore cohort. AUC, area under curve; eGFR, estimated glomerular filtration rate; LVESD, left ventricular end-systolic dimension; NYHA, New York Heart Association; RAS, renin-angiotensin system; RVSP, right ventricular systolic pressure.

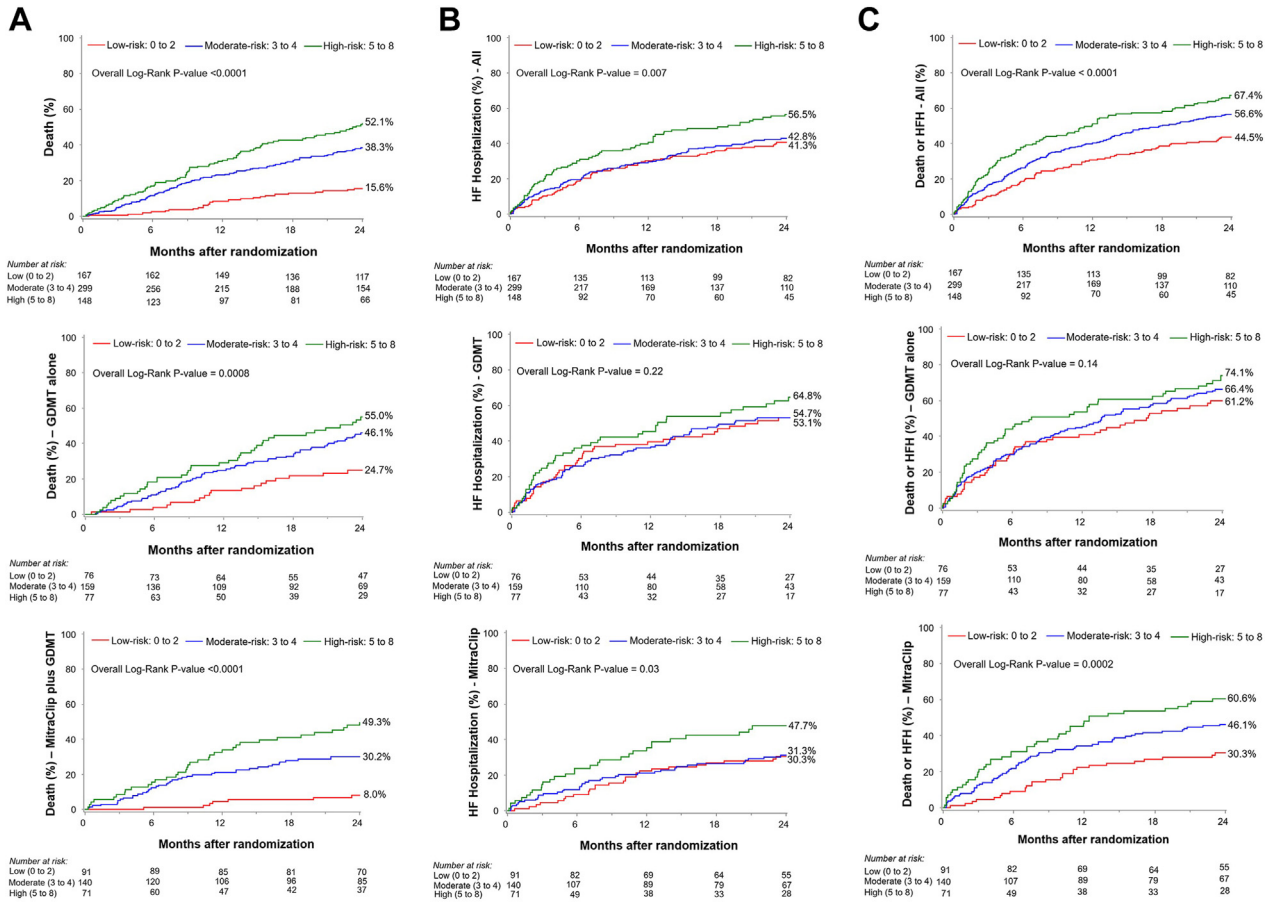


Figure 1.

Kaplan-Meier hazard curves in the COAPT trial population according to MitraScore risk groups. (**A**) Mortality. (**B**) Heart failure hospitalization. (**C**) The composite of death or heart failure hospitalization. Top: All patients; Center: GDMT alone group; Bottom: MitraClip plus GDMT group. GDMT, guideline-directed medical therapy.

COAPT risk score (0.74 and 0.72 respectively). The MitraScore had poor accuracy for predicting 2-year HFH in the overall COAPT trial population and in those treated with TEER plus GDMT or GDMT alone (AUC 0.57 in all 3 groups). As seen in the Central Illustration and Figure 1A, there was a continuous increase in the primary outcome of 2-year mortality in the COAPT trial population with increasing MitraScore values. As also seen in Figure 1, there was a steady increase in 2-year mortality with increasing MitraScore values in both the TEER plus GDMT group as well as the GDMT alone group of the COAPT trial population. Figure 1 also demonstrates that the MitraScore was associated with HFH and the composite of death or HFH in the overall population as well as in the TEER plus GDMT group but not in the GDMT alone group. Supplemental Table S4 shows the AUC for the MitraScore in predicting 1-year mortality in the MitraScore and COAPT trial populations.

External validation of the modified COAPT risk score in the MitraScore cohort

As shown in Table 4, the modified COAPT risk score had fair accuracy for predicting death at mean 2.1-year follow-up in the overall MitraScore cohort (AUC 0.64), with similar predictive accuracy for patients with FMR and DMR (AUC 0.64 and 0.66, respectively). The AUC values for the modified COAPT risk score to predict HFH and the composite of death or HFH ranged between 0.60 to 0.65 in the overall MitraScore cohort as well as in those with FMR and DMR. As seen in the Central Illustration and Figure 2, there was a steady increase in the 2.1-year rate of mortality, HFH, and the composite of mortality or HFH with increasing values of the modified COAPT risk score in the overall MitraScore cohort as well as the FMR and DMR subgroups. Supplemental Table S4 shows the AUC for the modified COAPT risk score in predicting 1-year mortality in the COAPT trial and MitraScore populations.

FMR patients undergoing TEER

Restricting the analyses to patients with FMR undergoing TEER in the COAPT trial, the MitraScore had good accuracy (AUC 0.74) in

Table 4. AUC values (with 95% CI) of the modified COAPT risk score and the MitraScore for 2.1-year outcomes in the MitraScore cohort.

Outcomes	Modified COAPT risk score AUC	MitraScore AUC
Overall MitraScore cohort (n = 1007)		
Death	0.64 (0.60-0.68)	0.69 (0.65-0.72)
HFH	0.61 (0.57-0.65)	0.58 (0.54-0.62)
Death or HFH	0.64 (0.61-0.67)	0.66 (0.63-0.70)
MitraScore functional MR subgroup (n = 594)		
Death	0.64 (0.59-0.70)	0.68 (0.63-0.72)
HFH	0.64 (0.59-0.69)	0.58 (0.53-0.63)
Death or HFH	0.63 (0.58-0.68)	0.65 (0.61-0.70)
MitraScore degenerative MR subgroup (n = 413)		
Death	0.66 (0.60-0.71)	0.70 (0.64-0.75)
HFH	0.60 (0.54-0.66)	0.58 (0.51-0.64)
Death or HFH	0.65 (0.59-0.70)	0.67 (0.62-0.73)

AUC, area under the receiver operating characteristic curve; DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; HFH, heart failure hospitalization; MR, mitral regurgitation.

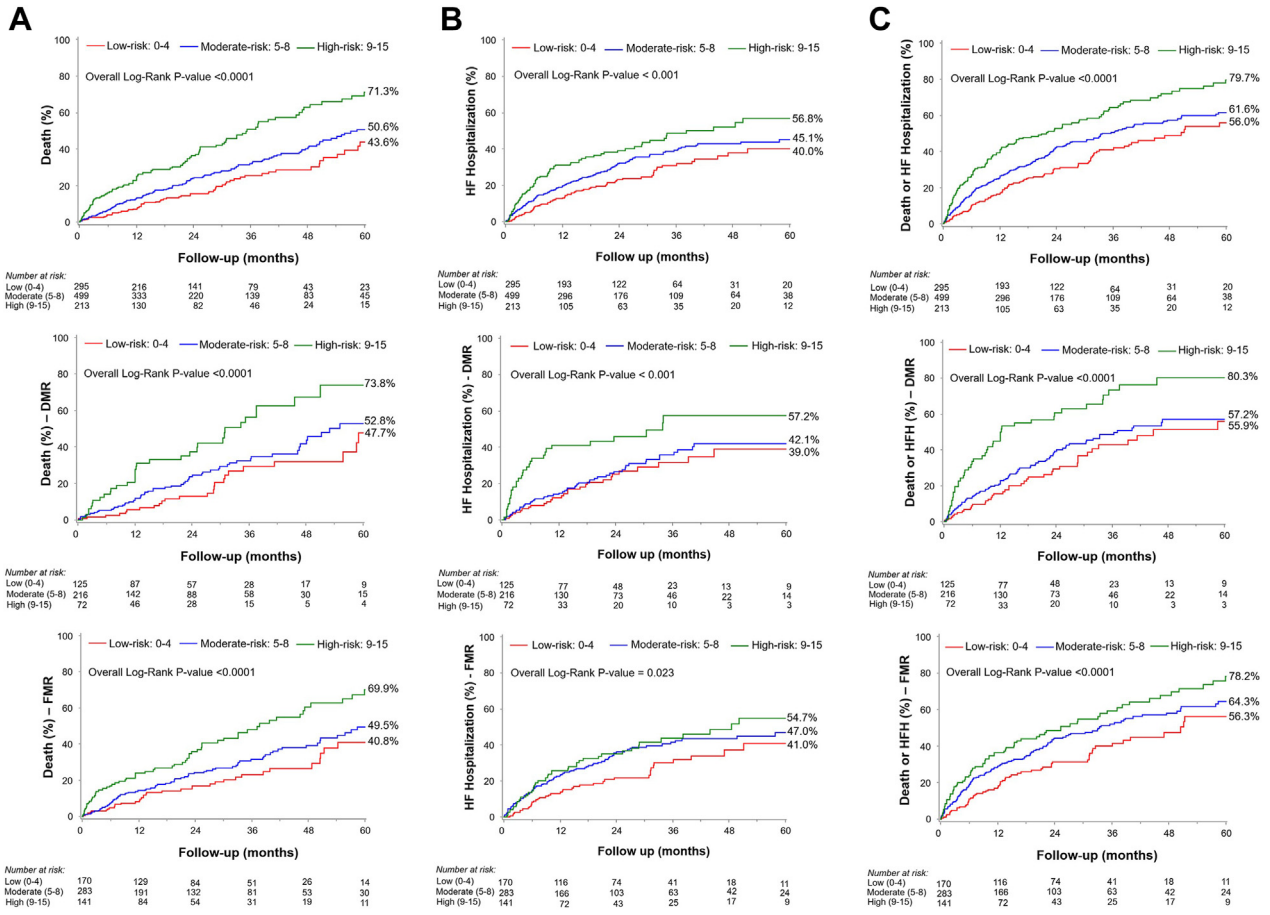


Figure 2.
Kaplan-Meier hazard curves in the MitraScore population according to COAPT risk groups. (**A**) Mortality. (**B**) Heart failure hospitalization. (**C**) The composite of death or heart failure hospitalization. Top: All patients; Center: DMR group; Bottom: FMR group. DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; HFH, heart failure hospitalization.

predicting 2-year all-cause mortality, similar to that of the COAPT risk score (AUC 0.72) (Table 3). However, the COAPT risk score had numerically better accuracy in predicting the 2-year rate of HFH compared to the MitraScore in the COAPT trial population (AUC 0.74 vs 0.57, respectively). Among patients with FMR undergoing TEER in the MIVNUT registry, the COAPT risk score had fair accuracy (AUC 0.64) to predict 2.1-year all-cause mortality, similar to that of the MitraScore (AUC 0.68), and at least as good predictive accuracy for the 2.1-year rate of HFH (AUC 0.61 vs 0.58, respectively) (Table 4).

Benefit of TEER in the COAPT trial population according to MitraScore risk score groups

There were no significant interactions between treatment with TEER plus GDMT compared with GDMT alone and the risk strata of the MitraScore for the absolute and relative risk reduction in 2-year outcomes in patients from the COAPT trial (Figure 3). However, by cubic spline analysis, the greatest risk reductions in death and the composite of death or HFH were observed in the lower risk strata of the MitraScore (Figure 4).

Discussion

This present analysis reports the cross-validation of 2 recently developed risk scores to predict clinical events in patients with MR and in those undergoing TEER. Both the COAPT risk score and MitraScore demonstrated fair to good accuracy for the prediction of mortality in the external validation cohorts. The predictive utility of the MitraScore in the COAPT trial population was better among TEER-treated patients than in those treated with GDMT alone. The MitraScore had lower accuracy for predicting HFH than mortality. Conversely, the COAPT risk score showed fair predictive accuracy in the MitraScore cohort (all of whom had TEER) for predicting both death and HFH, including both FMR and DMR patients (even though the COAPT risk score was derived from a pure FMR population). TEER had a positive effect among randomized patients in the COAPT trial in reducing death and HFH in all risk categories of the MitraScore compared with GDMT alone, although the magnitude of reduction appeared to be greater in the lower risk strata.

TEER is presently indicated for select patients with FMR (principally those meeting COAPT criteria) and for those with DMR at high surgical risk.[1,2] However, patients still have high rates of early and late adverse events after TEER principally due to their associated comorbidities and underlying degree of ventricular dysfunction. In this regard, scoring systems may assist heart teams and patients in shared decision-making as well as create awareness in patients and family members regarding the expected outcome of a procedure. Choosing cost-effective therapies is also important in the contemporary era of precision medicine,[12] a consideration for which risk score can also assist.

An important prerequisite for the acceptance of generalizable risk stratification models is the demonstration of external validity. The present study demonstrates that both the COAPT risk score and the MitraScore have acceptable accuracy in predicting survival in patients

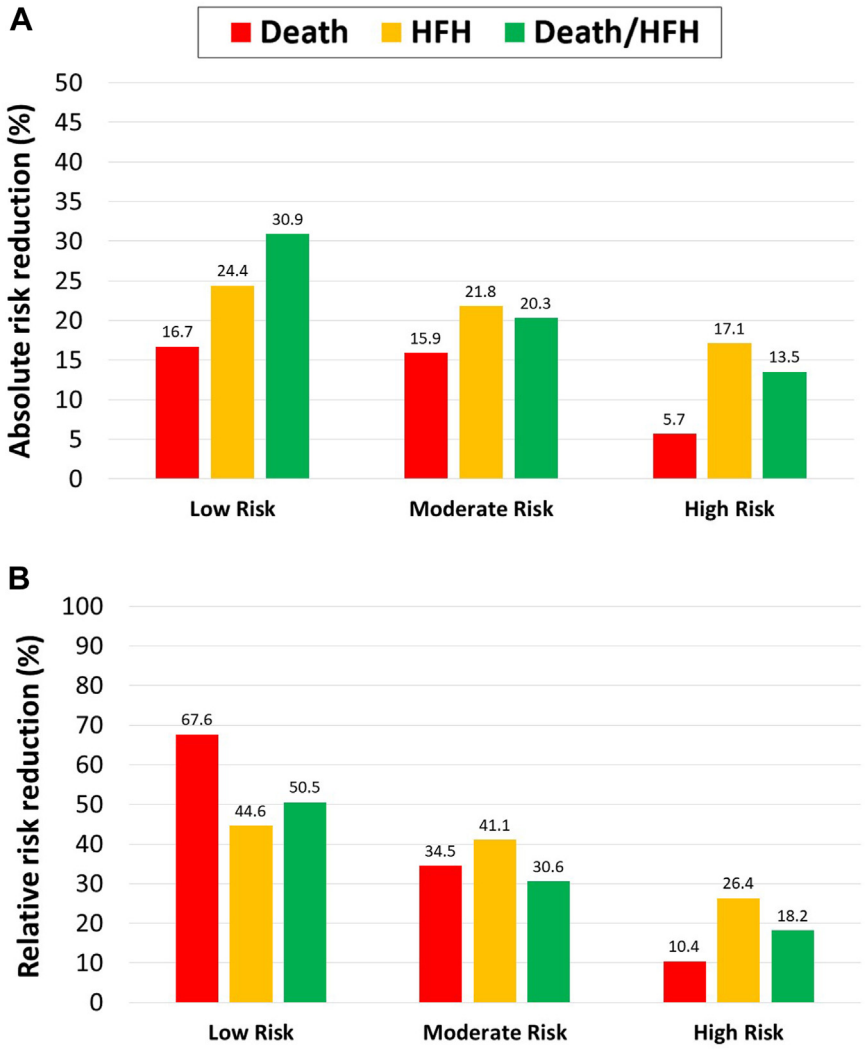


Figure 3.
Absolute and relative risk reductions in 2-year outcomes with TEER plus GDMT compared with GDMT alone in the COAPT trial population by risk strata of the MitraScore. Top: Absolute risk reduction. *P* value for additive interaction (for ARR) between treatment and MitraScore risk group on death = .41; *P* value for additive interaction between treatment and MitraScore risk group on HFH = .09; *P* value for additive interaction between treatment and MitraScore risk group on death or HFH = .62. Bottom: Relative risk reduction. *P* value for multiplicative interaction (for RRR) between treatment and MitraScore risk group on death = .09; *P* value for multiplicative interaction between treatment and MitraScore risk group on HFH = .62; *P* value for multiplicative interaction between treatment and MitraScore risk group on death or HFH = .15. ARR, absolute risk reduction; GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization; TEER, transcatheter edge-to-edge repair.

with severe MR considered for TEER. A major advantage of both scoring systems is that they are derived from clinical and echocardiographic data that are readily available prior to the procedure, without additional costs beyond the standard of care. The MitraScore uses 7 preprocedural clinical and laboratory-based measures and 1 echocardiographic variable (LVEF) for mortality prediction. Despite its simplicity, the MitraScore has shown a good ability to predict death in both patients with FMR and DMR undergoing TEER. Perhaps not surprisingly, the MitraScore (derived from a patient population that had undergone TEER), showed better predictive accuracy in the TEER plus GDMT group of the COAPT trial population (AUC 0.74 for mortality) than the GDMT alone group (AUC 0.65 for mortality). In contrast, the 9-variable COAPT risk score showed good predictive ability for 2-year all-cause mortality in both the TEER plus GDMT as well as GDMT alone groups of the COAPT trial population (AUC 0.72 and 0.76, respectively [Table 3]), and also was moderately accurate for the prediction of HFH and the composite of death or HFH from COAPT. Moreover, although the COAPT risk score was derived from an FMR patient population, it showed fair predictive accuracy for both mortality and HFH in both the FMR and DMR groups of the MitraScore cohort. This wider utility may be explained by the inclusion of risk variables in the COAPT risk score that are known to impact outcomes in both FMR and DMR, including pulmonary hypertension, the presence of significant TR, reduced LVEF, and LV dilatation.[13–15]

Other risk scores have been developed to predict outcomes in patients with MR but have additional limitations. The GRASP (Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation) score,[7] derived from a small cohort of patients undergoing TEER, is computationally complex as it requires weighting and logarithmic terms for the predictor variables, and cannot be implemented easily. The MITRALITY risk score for patients undergoing TEER was developed with machine learning techniques and uses 6 baseline clinical features for prediction.[6] However, despite good predictive value (AUC 0.78 for mortality), this score is also computationally complex, requiring an online calculator. Additionally, the variables included in this score are not specific for TEER and reflect general factors prognostic for most cardiac procedures. In contrast to these risk scores, the COAPT risk score and the MitraScore offer advantages since they comprise readily available variables and include disease-specific variables that predict post-TEER outcomes, and from spline analysis may identify which patients benefit most from TEER, as also previously reported from the COAPT risk score derivation data.[10] Nonetheless, acknowledging the limitations of cross-study comparisons, future studies are warranted to examine the relative utility of these risk scores compared with the COAPT risk score and MitraScore from a common external study population.

The present findings highlight the importance of patient selection to optimize the outcomes of the TEER procedure. Nonetheless, the benefit from TEER is also realized in patients with advanced disease, ie,

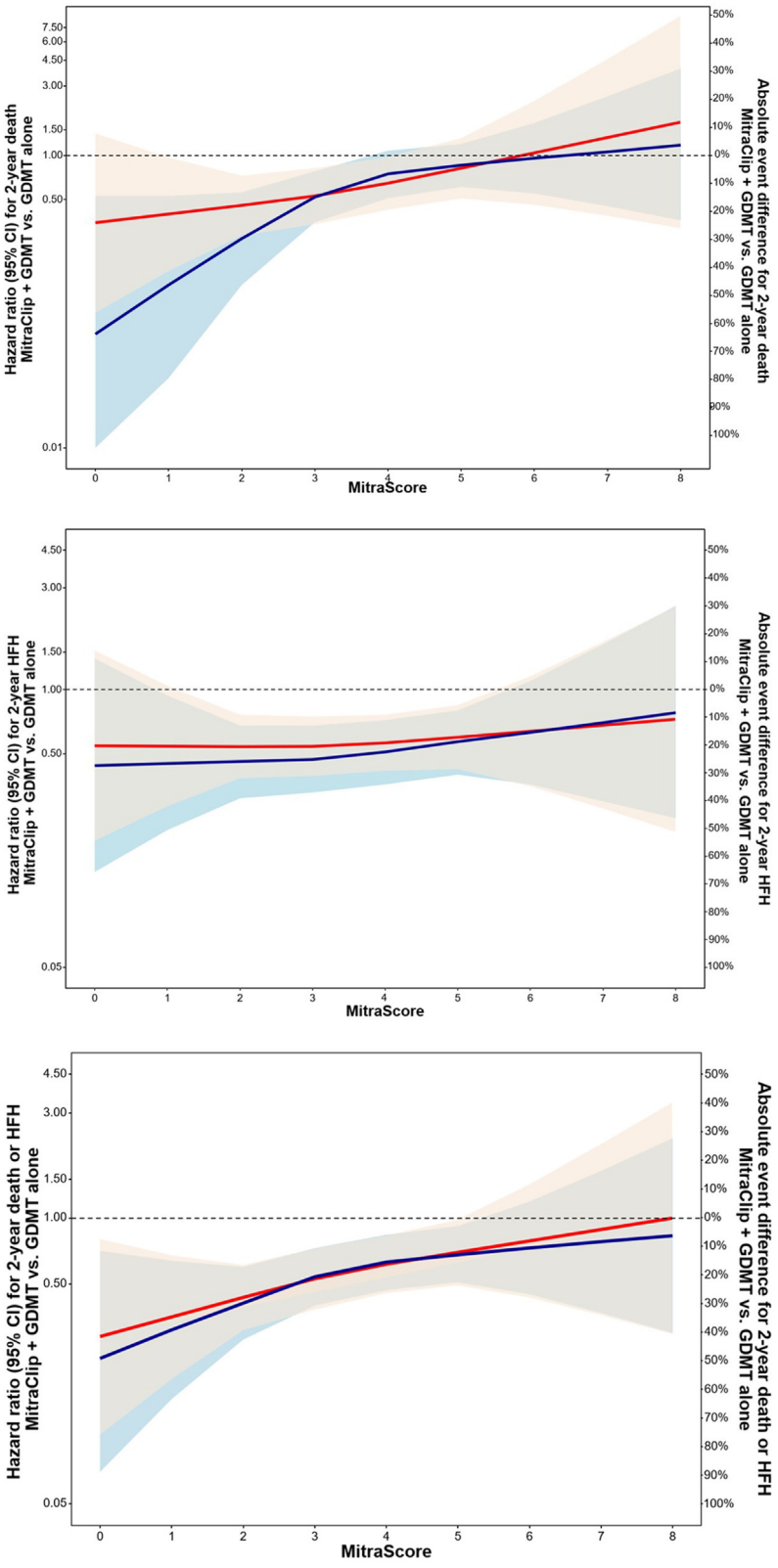


Figure 4.

Cubic spline analysis relating the MitraScore to the absolute and relative risks of 2-year outcomes in patients treated with MitraClip plus GDMT vs GDMT alone. Top: Death. Center: HFH. Bottom. Death or HFH. The figure shows restricted cubic splines with 3 knots located at risk score values of 2, 3, and 5. HR (blue line and blue shadow for 95% CI) and absolute risk difference (red line and red shadow for 95% CI) for the 2-year rate of outcomes (death, HFH, death or HFH) after treatment with MitraClip plus GDMT compared with GDMT alone across the range of Mitra-Score values. *P* values for nonlinearity in the HR relationship were 0.21, 0.80, and 0.49 for death, HFH, and death or HFH respectively indicating that the relative treatment effects of the MitraClip plus GDMT compared with GDMT alone were independent of the risk score. GDMT, guideline-directed medical therapy; HFH, heart failure hospitalization; HR, hazard ratio.

those in the "high-risk" categories of the MitraScore and COAPT risk score. Knowledge of potential outcomes with continued GDMT vs benefit from TEER in these "high-risk" populations can enable patients and physicians to make an informed decision about the best course of action. In some cases, there may only be a modest benefit expected in terms of life expectancy, but the rate of HFH may be reduced and quality of life may be improved.[16,17] Although a formal comparison between the MitraScore and COAPT risk score has not been performed as it would require an additional external validation dataset, the main advantage of the former is the simplicity of the score, and of the latter

the inclusion of echocardiographic MR-specific variables and improved prediction for HFH (as well as its greater utility in a GDMT-alone–treated patient population). Both scores have now been externally validated and consequently represent valid instruments for evaluating patients with severe MR referred for consideration of TEER.

Limitations

First, the methods used to derive and validate the models were simple and based on C-statistic or AUC. We did not perform more sophisticated analyses such as the net reclassification index or the integrated discrimination index. Nonetheless, the AUC is a widely accepted tool to assess predictive models. Second, the strength of both scores is that the majority of predictors in our final models are measures that are routinely available. However, the overall predictive ability of both risk scores was moderate at best (although somewhat better in the FMR TEER treatment subgroup). Although other risk scores may perform well or slightly better,[6] the computational complexity of these scores challenges their practical use. Third, many of the variables included in the COAPT risk score and MitraScore are dynamically affected by HF medications and CRT; however, it is assumed that all patients are treated with maximally tolerated GDMT (including CRT as appropriate) prior to TEER (which was confirmed by a central eligibility committee in COAPT). RVSP and TR, which are included only in the COAPT risk score, are sensitive to volume status and may be elevated in patients with decompensated HF. However, the COAPT trial only included stabilized patients after maximal GDMT optimization, including diuretics. Neither score includes a measure of natriuretic peptides, an important prognostic biomarker. Several parameters such as posttreatment reduction in MR grade, severity of residual MR, posttreatment RVSP, right ventricular (RV) function, and RV-pulmonary artery coupling which afford additional prognostic insights in this patient population[18,19] were not included in either risk score. The extent to which these variables alter or further improve the predictive accuracy of the COAPT risk score and the MitraScore is unknown. We also did not explore whether either score could be simplified by removing 1 or more variables without substantially affecting predictive accuracy. Finally, there are important differences between the COAPT and MIVNUT cohorts: the COAPT trial only included patients with FMR, but this cohort underwent treatment with GDMT alone as well as TEER plus GDMT, whereas the MIVNUT registry included both DMR and FMR patients, but all were treated with TEER. Despite the notable variations between the 2 study cohorts, each score showed its potential for generalizability by demonstrating at least moderate predictive accuracy in the other cohort.

Conclusions

The present analysis provides external validation of both the COAPT risk score and the MitraScore in independent cohorts, with both risk scores exhibiting overall fair to good predictive value for 2-year mortality after TEER. The COAPT risk score also provided fair to good accuracy in predicting 2-year HFH and was equally prognostic in both DMR and FMR patients undergoing TEER, as well as in FMR patients treated with GDMT alone. Both risk scores are simple to use in practice, being readily derived from clinical, laboratory, and echocardiographic variables that are routinely measured as standard of care, and both provide utility for the prediction of outcomes in patients eligible for or undergoing treatment with TEER. Use of these risk scores may aid in the early identification and referral of appropriate patients for transcatheter MR therapies.

Declaration of competing interest

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Ethics statement and patient consent

Both the MIVNUT registry and the COAPT trial were conducted according to the relevant ethical guidelines and all patients provided written informed consent.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.101227.

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