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ORIGINAL RESEARCH

Mitral Regurgitation International Database (MIDA) Score Predicts Outcome in Patients With Heart Failure Undergoing Transcatheter Edge-to-Edge Mitral Valve Repair

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BACKGROUND: Optimizing risk stratification in patients undergoing transcatheter mitral valve repair is an ongoing challenge. The Mitral Regurgitation International Database (MIDA) score represents a user-friendly mortality risk stratification tool that is validated on a large-scale registry of patients with degenerative mitral regurgitation (MR). We here assessed the potential benefit of the MIDA risk score for patients with functional or degenerative MR undergoing transcatheter mitral valve repair.

METHODS AND RESULTS: In total, 680 patients undergoing MitraClip implantation were stratified according to MIDA score tertiles into a low (0–7), intermediate (8–9), and a high (10–12) MIDA score group. MR was assessed in follow-up echocardiograms in 416 patients at 323±169 days after transcatheter mitral valve repair. During 2-year follow-up, 8.2% (15/182) of patients with low, 21.3% (64/300) with intermediate, and 26.3% (52/198) with high MIDA score died (log-rank test $P<0.001$). Hazard of all-cause mortality increased by 13% (95% CI, 3%–25%) with every additional point of the MIDA score. Subanalysis of 431 patients with functional MR showed similar results. Furthermore, rates of a combined end point of mortality and hospitalization for heart failure were higher with increasing MIDA score (30% [54/182], 38% [113/300] and 48% [94/198], respectively, log-rank test $P=0.001$). Frequency of residual MR ≥II at follow-up increased with increasing MIDA score group (33%, 44%, and 59%, respectively, $P<0.001$).

CONCLUSIONS: The MIDA mortality risk score maintains its predictive utility in patients undergoing transcatheter mitral valve repair, regardless of MR cause. Moreover, it was predictive of worse event-free survival regarding a combined end point of mortality and hospitalization for heart failure, and was associated with postprocedural residual MR ≥II and MR recurrence.

Key Words: mitral regurgitation ■ percutaneous mitral valve repair ■ risk assessment

Mitral regurgitation (MR) is a common morbidity in patients with heart failure. Generally, the cause of MR is categorized according to primary and secondary pathogenesis. While degeneration of the valve is the most frequent pathology leading to primary MR, left ventricular dysfunction and remodeling is the most likely cause of secondary or functional MR.[1]

Transcatheter mitral valve repair (TMVR) via edge-to-edge MitraClip procedure is a common therapeutic option in patients with heart failure with MR, especially

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CLINICAL PERSPECTIVE

What Is New?

- The Mitral Regurgitation International Database score maintains its utility as a mortality risk score in patients undergoing MitraClip implantation, regardless of the cause of mitral regurgitation.
- Additionally, it is predictive of worse prognosis after MitraClip procedure regarding a combined end point of mortality and heart failure hospitalization, as well as postprocedural residual and recurrent mitral regurgitation.

What Are the Clinical Implications?

- The Mitral Regurgitation International Database score may be helpful in the risk stratification process, evaluating MitraClip implantation in patients with heart failure with significant mitral regurgitation, and identifying those who are in need of a more intense monitoring, with an increased hazard of reduced procedural success, sustainability, and worse postprocedural prognosis.

Nonstandard Abbreviations and Acronyms

MIDA	Mitral Regurgitation International Database
MR	mitral regurgitation
TMVR	transcatheter mitral valve repair

in those with increased surgical risk and functional MR cause.[2,3] Two major randomized controlled studies showed discordant results regarding prognostic benefits after the MitraClip procedure, emphasizing that careful patient selection is crucial.[3,4] However, regarding selection criteria, there is a lack of risk stratification tools in patients undergoing TMVR.[5]

The Mitral Regurgitation International Database (MIDA) mortality score represents a novel user-friendly risk score that was developed to help improve risk stratification in patients with primary MR who were undergoing conservative treatment or surgical mitral valve repair.[6] The score was validated on an exceptional large-scale, international registry of patients with primary MR.

In the present study, we aimed to test the utility of the MIDA score in patients who were undergoing TMVR via MitraClip procedure and assess the predictive value in patients with functional MR, separately. Moreover, we analyzed the impact of this score on a combined end point of mortality and hospitalization for heart failure (HHF), and on the incidence of postprocedural residual MR.

METHODS

Study Cohort

For the present study, we included 680 patients with available MIDA score parameters who underwent TMVR in the Heart Failure Network Rhineland (University Hospitals Bonn, Cologne, Düsseldorf) from August 2010 to September 2018, and received at least 1 Clip. All procedures were performed with the MitraClip system (Abbott Vascular Inc., Menlo Park, CA). Before TMVR, all cases were discussed in the interdisciplinary heart conference of the individual center, in which patients were considered to be at a high surgical risk and suitable for MitraClip implantation. Patients agreed to participate in our registry, which was approved by the Ethical Committee of the individual center in accordance with the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request. Echocardiographic data were evaluated according to the institutional practice of the treatment center. MR severity was scaled in 3 grades as I (mild), II (moderate), and III (severe) according to current guidelines.[7] For our outcome analysis, MR of mixed cause was considered as functional MR.

MIDA Score Assessment

Patients were included if all 7 parameters of the MIDA score (age, heart failure symptoms, atrial fibrillation, left atrial diameter, right ventricular systolic pressure, left ventricular end-systolic diameter, and left ventricular ejection fraction) were available before undergoing the TMVR procedure (Figure S1). Assessment and calculation of the MIDA score were performed as described in a prior study.[6] For each patient the score was calculated as the sum of following weightings, which were obtained previously[6] according to hazard ratios (HRs) regarding overall mortality: 3 points for age ≥65 years, 3 points for symptoms, 1 point for atrial fibrillation, 1 point for left atrial diameter ≥55 mm, 2 points for right ventricular systolic pressure >55 mm Hg, 1 point for left ventricular end-systolic diameter ≥40 mm, and 1 point for left ventricular ejection fraction ≤60%. Scores range from 0 to 12. Patients were categorized according to MIDA score tertiles into a low, intermediate, and high MIDA score group.

Follow-Up Data

Postprocedural clinical and echocardiographic follow-up of patients was monitored at regular clinic visits, telephone calls to the referring cardiologist, the general practitioner, or the patients themselves. The median follow-up of the study population was

515 (357–863) days. End points of the present study were all-cause mortality within 2 years after TMVR, a combined end point composite of 2-year all-cause mortality and first postprocedural HHF, and residual MR at follow-up that was of moderate or worse severity.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics software version 24.0.0.0 (IBM, Armonk, NY). Normal distribution was tested with the use of the Kolmogorov–Smirnov test. Categorical variables were presented in percentages, while continuous variables had nonnormal distribution and were reported as median (interquartile range). Echocardiographic follow-up time period was presented as mean days±SD. In order to assess differences between the 3 MIDA score groups, ANOVA or Kruskal–Wallis test were performed for continuous variables. Chi-square test was performed for categorical variables. A Bonferroni correction was used to correct for multiple comparisons. Kaplan–Meier method and the log-rank test were used for event-free-survival rates and statistical differences. Cox regression analysis was used to assess the predictive value of parameters regarding event-free survival. Baseline characteristics and MIDA score were tested in univariable Cox regression analysis. For the multivariable analysis, parameters were included that were significant predictors in the univariable analysis. Variables were checked for multicollinearity using variance inflation factors, which showed no indications of multicollinearity as all variance inflation factors below 5. Preprocedural NT-proBNP (N-terminal pro-B-type natriuretic peptide) values were missing for 10.4% (71/680) of patients. For multivariable tests including NT-proBNP, missing values were substituted by using multiple imputation of data. HR and 95% CI are presented. Logistic regression analysis was used, to evaluate the association of the MIDA score with residual and recurrent MR. *P* value of <0.05 was considered to be statistically significant.

RESULTS

Patient Population

Out of 1010 patients who underwent the MitraClip procedure, 680 patients with available MIDA score parameters were included in the final analysis. Median age was 78 years (73–83 years), and 40% were of female sex. Median Logistic EuroSCORE of 17% (9%–31%) revealed a high surgical risk for the patient cohort. Median NT-proBNP was 2764 ng/L (1395–5951 ng/L), while median left ventricular ejection fraction was 44% (32%–57%). Cause of MR was secondary in 63% of patients (n=431). In total, 995 clips were implanted and the median numbers of implanted clips per procedure was 1 (1–2). MitraClip (first generation) was used in 505 patients, while 148 patients received MitraClip NT (second generation), and 27 patients received the Mitra NTR/XTR (third generation).

MIDA Score in Patients Undergoing TMVR

According to the calculated MIDA score, the patient cohort was classified into 3 categories: 182 (27%) patients had a low MIDA score of 0 to 7, while 300 (44%) patients had an intermediate MIDA score of 8 to 9 and 198 (29%) patients had a high MIDA score of 10 to 12. Baseline characteristics are summarized according to these 3 groups in Table 1. All parameters of the MIDA score differed significantly among these tertiles. Moreover, compared with the low and intermediate MIDA score group, patients with a high MIDA score showed an increased Logistic EuroSCORE (14.6 [8.5–27.9] versus 14.8 [8.1–28.6] and 20.6 [12.6–36.0], respectively; *P*=0.001). NT-proBNP increased with higher MIDA score tertile (1842 pg/mL [848–3836 pg/mL], 2703 pg/mL [1513–5925 pg/mL], 3923 pg/mL [2011–7722 pg/mL], respectively; *P*<0.001), while increased with higher MIDA score tertile, while patients with low MIDA score had a higher serum glomerular filtration rate compared with patients with an intermediate or high MIDA score (56 mL/min [42–70 mL/min], 49 mL/min [35–62 mL/min], and 43 mL/min [31–58 mL/min], respectively; *P*<0.001]. No significant differences were revealed for the frequency of MR>II and MR cause (primary versus secondary). Moreover, there were no significant differences in the 3 MIDA score groups regarding number of utilized clips per procedure (1 [1–2] clip/procedure in each group, *P*=0.360), and regarding the implanted Clip generation (*P*=0.520). Analysis of the incidence of TMVR re-interventions within 2 years after first intervention showed 3/182, 4/300, and 3/198 patients with MR re-intervention in the low, intermediate, and high MIDA score group, respectively (*P*=0.960).

MIDA Score and 2-Year Mortality

During 2-year follow-up, 19% (131/680) of patients died. Mortality rates according to MIDA score tertiles were 8.2% (15/182), 21.3% (64/300), and 26.3% (52/198), respectively (*P*<0.001). Kaplan–Meier curve and log rank analysis confirmed a lower rate of 2-year mortality in patients with low MIDA score (Figure 1A) (*P*<0.001). Univariable Cox regression analysis revealed that a 1-point increase in the MIDA score was associated with a 21% higher hazard rate of mortality (95% CI, 10%–34%, *P*<0.001). After multivariable adjustment, the MIDA score remained a significant

Table 1. Baseline Characteristics According to MIDA Score

	Low MIDA Score	Intermediate MIDA Score	High MIDA Score	*P* Value
Patients, n	182 (27%)	300 (44%)	198 (29%)	
Clinical characteristics				
Age, y	76 (63–82) ^{inter,high}	79 (74–83)^{low}	79 (75–83)^{low}	<0.001*
Female sex	76 (42%)	116 (39%)	81 (41%)	0.772
BMI, kg/m^2	25.3 (22.6–28.7)	25.2 (22.9–28.1)	26.0 (23.3–28.7)	0.295
Log EuroSCORE, %	14.6 (8.5–27.9)^{high}	14.8 (8.1–28.6)^{high}	20.6 (12.6–36.0)^{low,inter}	<0.001*
Diabetes mellitus	44 (24%)^{high}	82 (27%)	70 (35%)^{low}	0.042*
Arterial hypertension	156 (86%)	251 (84%)	167 (84%)	0.834
Prior stroke	28 (15%)	37 (12%)	30 (15%)	0.548
COPD	25 (14%)	58 (19%)	43 (22%)	0.120
Coronary artery disease	104 (57%)	201 (67%)	130 (66%)	0.071
Prior CABG	44 (24%)	93 (31%)	70 (35%)	0.059
Prior valvular surgery	20 (11%)	43 (14%)	29 (15%)	0.501
Atrial fibrillation	82 (45%)^{inter,high}	208 (69%)^{low,high}	160 (81%)^{low,inter}	<0.001*
NYHA class >II	86 (47%)^{inter,high}	286 (96%)^{low,high}	198 (100%)^{low,inter}	<0.001*
Carotid stenosis	42 (23%)	89 (30%)	48 (24%)	0.206
Echocardiographic data				
Functional MR	114 (63%)	186 (62%)	131 (66%)	0.622
MR>II	147 (83%)	254 (86%)	160 (82%)	0.475
TR>II	34 (19%)	75 (25%)	49 (25%)	0.239
LVEF, %	51 (33–62)^{high}	45 (32–57)	42 (32–53)^{low}	0.004*
LVESD ≥40 mm	111 (61%)^{inter,high}	221 (74%)^{low}	159 (80%)^{low}	<0.001*
LA ≥55 mm	17 (9%)^{high}	17 (6%)^{high}	66 (33%)^{low,inter}	<0.001*
Systolic PAP, mm Hg	43 (34–54)^{high}	43 (32–50)^{high}	60 (54–69)^{low,inter}	<0.001*
Laboratory assessment				
NT-proBNP, pg/mL	1842 (848–3836)^{inter,high}	2703 (1513–5925)^{low,high}	3923 (2011–7722)^{low,inter}	<0.001*
GFR, mL/min	56 (42–70)^{inter,high}	49 (35–62)^{low}	43 (31–58)^{low}	<0.001*
Leukocytes, G/L	7.0 (5.9–8.4)	7.0 (5.9–8.3)	6.9 (5.6–8.5)	0.785

Values are n (%) or median (interquartile range). Superscript description denotes groups from which the value is significantly different in pairwise comparisons (Bonferroni correction). BMI indicates body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GFR, estimated serum glomerular filtration rate; inter, intermediate; LA, left atrium; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MIDA, Mitral Regurgitation International Database; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary artery pressure; and TR, tricuspid regurgitation.

*P value <0.05 is considered as statistically significant.

predictor of mortality (HR, 1.13 [95% CI, 1.03–1.25; P=0.013]) (Table 2). Moreover, compared with a low MIDA score, an intermediate and high MIDA score class was associated with a HR of 2.46 (95% CI, 1.39–4.3; P=0.002) and 2.67 (95% CI, 1.48–4.81 P=0.001). Other independent predictors of mortality were tricuspid regurgitation severity, diabetes mellitus, and renal function.

2-Year Mortality According to MR Cause

We further analyzed the predictive value of the MIDA score for both MR causes separately, focusing on functional MR. According to low, intermediate, and high MIDA score, 2-year mortality rates for functional MR cause were 10% (11/114), 22% (41/186), and 28% (37/131) (P=0.001), respectively, while mortality rates for patients with primary MR were 6% (4/68), 20% (23/114), and 22% (15/67), respectively (P=0.017). For patients with functional MR, Kaplan–Meier curve and result of the log-rank test are shown in Figure 1B. In this subanalysis, Cox regression analysis regarding the MIDA score revealed a HR of 1.21 (95% CI, 1.07–1.36; P=0.002) in the univariable analysis, while the multiple variable analysis showed a HR of 1.15 (95% CI, 1.01–1.3; P=0.032) for 1-point increase in the MIDA score (Table S1). Another 2-year mortality predictor was diabetes mellitus.

Hospitalization for Heart Failure

One hundred eighty-one patients were readmitted for heart failure during 2-year follow-up after TMVR. Categorized by low, intermediate, and high MIDA score,

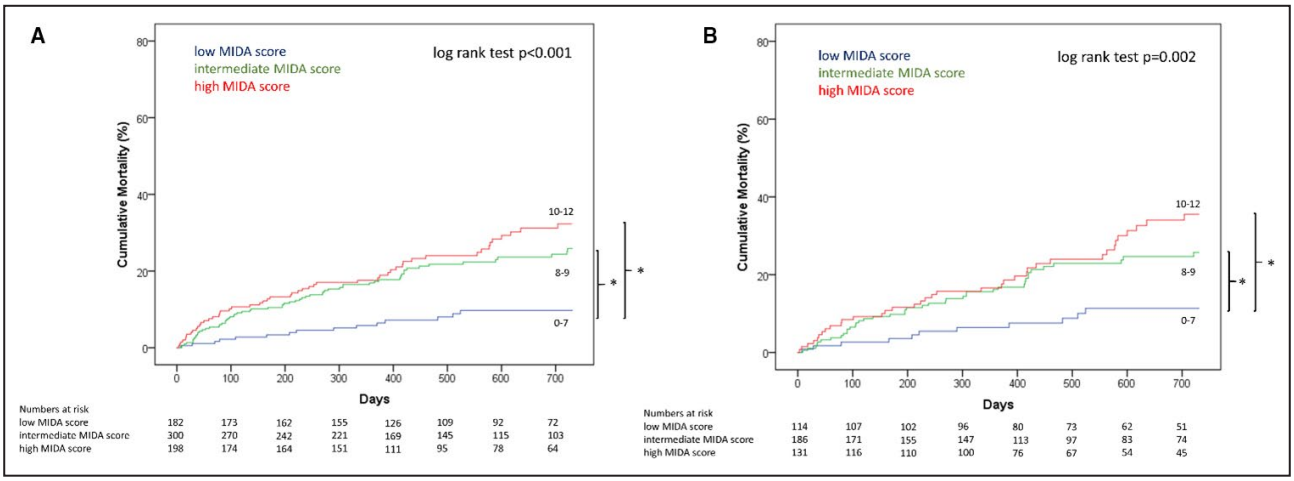

Figure 1. Kaplan–Meier survival curves stratified by MIDA score.
Low MIDA score was associated with lower mortality rates after transcatheter mitral valve repair for the total cohort (**A**) and patients with functional mitral regurgitation (**B**). *Indicates *P*<0.050. MIDA indicates Mitral Regurgitation International Database.

a composite end point of death or HHF occurred in 30% (54/182), 38% (113/300), and 48% (94/198) of patients, respectively (*P*=0.002). Kaplan–Meier curve and log-rank test results are shown in Figure 2A. One-point increase in the MIDA score was associated with a 10% (95% CI, 3%–19%, *P*=0.006) hazard of death or HHF during 2-year follow-up. In the multivariable analysis, the MIDA score remained a predictor of the combined end point (HR, 1.07 [95% CI, 1.002–1.15; *P*=0.042]) (Table S2). Subanalysis of patients with functional MR showed higher rates of events with increasing MIDA score; however, there was no statistical significance (38%, 42%, and 50% in the low, intermediate, and high MIDA score group, respectively; log-rank test *P*=0.083) (Figure 2B). Regarding this combined end point, Cox analysis confirmed a HR, which is slightly above the threshold of significance (HR, 1.08 [95 CI, 0.999–1.17]; *P*=0.052).

Residual MR ≥II After TMVR

Postprocedural echocardiographic assessments were available for 654 patients before discharge. Follow-up echocardiograms were available in 416 patients. Mean echocardiographic follow-up time period after intervention was 323±169 days. While there were no significant differences in the distributions of MR ≥II in the low, intermediate, and high MIDA score group (98%, 99%, and 99% respectively, *P*=0.340), postprocedural rates of residual MR ≥II was highest in the high MIDA score group (30%, 27%, and 39%, respectively, *P*=0.022). Moreover, differences of residual MR ≥II score were more pronounced at follow-up: residual MR ≥II increased with ascending MIDA score classification (33%, 44%, and 59%, respectively, *P*<0.001) (Figure 3). Subgroup analysis of functional MR confirmed similar results. While at baseline distributions of residual MR ≥II showed no significant differences between the 3 MIDA score groups (96%, 99%, and 99%, respectively, *P*=0.294), distributions of MR ≥II were 29%, 25%, and 38%, respectively (0.054) before discharge, and 31%, 43%, and 61% at follow-up (*P*=0.001). Regression analysis confirmed a predictive power of the MIDA score regarding residual MR ≥II at discharge (odds ratio [OR], 1.13 [95% CI, 1.004–1.26], *P*=0.043, per 1 point increase) and highly significantly at follow-up (OR, 1.23 [95% CI, 1.1–1.37], *P*<0.001, per 1-point increase). To distinguish whether the MIDA score identifies MR deterioration during follow-up, we defined MR recurrence as MR <II at discharge (indicating successful TMVR), which worsened to MR ≥II at follow-up. Of 284 patients with MR <II at discharge, 97/284 (34%) showed recurrent MR ≥II at follow-up. For each additional point increase of the MIDA score, the hazard of MR recurrence was 1.18-fold (95% CI, 1.03–1.35, *P*=0.019). We further assessed a *marked MR progression*, defined as a none or mild MR at discharge that showed a MR ≥II at follow-up (of 228 patients with none or mild MR at discharge, 66 [29%] showed this MR deterioration). MIDA score tended to be associated with *marked MR progression* with an OR of 1.17 (95% CI, 1–1.37, *P*=0.051). In this analysis, significance was reached when using the MIDA score tertiles instead of continuous score points (OR, 1.61 [95% CI, 1.14–2.23], *P*=0.008].

DISCUSSION

In the present study, we evaluated whether the MIDA score maintains its relevance as risk score in patients undergoing TMVR with the MitraClip system, regardless of MR cause. We demonstrate (1) that rates of all-cause mortality increase with increasing MIDA score

Table 2. Cox Regression Analysis of Parameter Associated With 2-Year Mortality

Clinical Data	Total Cohort			
	Univariable Predictor of 2-Year Mortality		Multivariable Predictor of 2-Year Mortality	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
MIDA score classification*				
Low MIDA score	1.00 [Ref.]		1.00 [Ref.]	
Intermediate MIDA score	2.9 (1.65–5.08)	<0.001†	2.46 (1.39–4.34)	0.002†
High MIDA score	3.57 (2.01–6.33)	<0.001†	2.67 (1.48–4.81)	0.001†
MIDA score (per 1 increase)*	1.22 (1.10–1.34)	<0.001†	1.13 (1.03–1.25)	0.013†
Female sex	0.65 (0.45–0.94)	0.023†	0.68 (0.47–1.002)	0.051
BMI (per kg/m^2)	0.99 (0.95–1.03)	0.650		
Logistic EuroSCORE (per %)	1 (0.998–1.001)	0.915		
Diabetes mellitus	1.65 (1.16–2.34)	0.005†	1.54 (1.08–2.2)	0.018†
Arterial hypertension	0.96 (0.60–1.54)	0.877		
Prior stroke	1.43 (0.92–2.22)	0.115		
Coronary artery disease	1.46 (1.001–2.14)	0.050†	1.27 (0.86–1.88)	0.230
Prior CABG	1.331 (0.92–1.88)	0.134		
Prior valvular surgery	1.48 (0.95–2.33)	0.086		
Carotid stenosis	0.69 (0.45–1.07)	0.096		
Number of clips per procedure	1.21 (0.92–1.6)	0.177		
Echocardiographic data				
Functional MR	1.13 (0.78–1.63)	0.510		
MR (per grade)	1.36 (1.05–1.75)	0.019†	1.04 (0.77–1.4)	0.798
TR (per grade)	1.38 (1.12–1.70)	0.003†	1.33 (1.06–1.66)	0.013†
Laboratory assessment				
NT-proBNP, pg/mL	1 (1.000006–1.00002)	0.001†	1 (1–1.00002)	0.061
GFR, mL/min	0.98 (0.97–0.99)	0.001†	0.99 (0.98–0.999)	0.027†
Leukocytes, G/L	1.02 (0.96–1.09)	0.546		

BMI indicates body mass index; CABG, coronary artery bypass grafting; GFR, estimated serum glomerular filtration rate; MIDA, Mitral Regurgitation International Database; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and TR, tricuspid regurgitation.

*Included in multivariable analysis separately.

†*P* values <0.05 are considered statistically significant.

tertile and patients with low MIDA score have a particular low 2-year mortality rate of 8.2% after TMVR; (2) that each point in the MIDA score is associated with a 1.13-fold increase in the risk of mortality, and a 1.07-fold increase in the risk of mortality or HHF after TMVR; (3) that in patients with functional MR, the predictive value of the MIDA score remained regarding all-cause mortality, although it was first developed as a prognostic model for degenerative MR; and finally (4) that the MIDA score was associated with MR recurrence and postprocedural residual MR ≥II at discharge and follow-up, indicating its predictive usefulness regarding TMVR efficiency and sustainability.

Because of their limited procedural invasiveness, TMVR procedures such as the MitraClip intervention represent emerging alternative therapeutic options in patients with MR.[2] Consecutively, current guidelines recommend TMVR in symptomatic patients at high-to-prohibitive surgical risk and reasonable life expectancy (>1 year).[8,9] However, estimation of postprocedural survival in this group of patients with a high burden of comorbidities is complex. The MIDA score represents a user-friendly risk score that recently was developed and validated on an exceptional large-scale registry of patients with primary MR.[6] Here, we tested the MIDA score on consecutive patients with heart failure undergoing TMVR with the MitraClip system. These patients with multiple morbidities were at a high surgical risk with increased median Logistic EuroSCORE and elevated median NT-proBNP. The score maintained its utility as risk stratification tool in these patients as postprocedural mortality rates increased with increasing MIDA score. Each point increase in the MIDA score was associated with a 13% higher hazard rate of mortality, after adjusting for possible confounders. In addition, an intermediate and high MIDA score class was associated with a 2.46-fold and 2.67-fold increased risk of mortality, respectively, compared with a low MIDA score. Moreover, the predictive value of the MIDA score remained in the subanalysis of patients

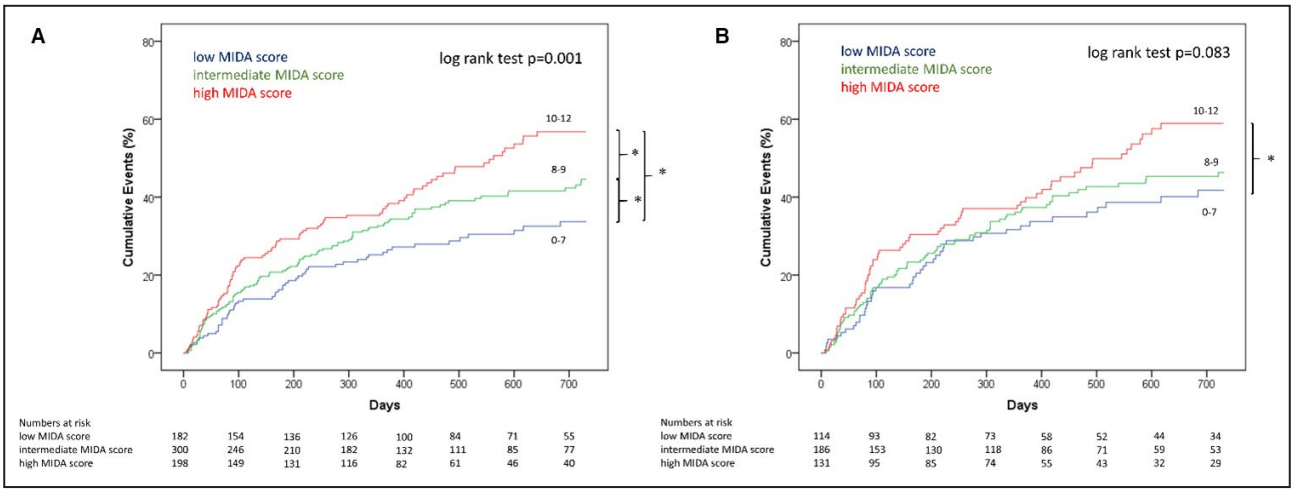

Figure 2. Combined end point of mortality and HHF stratified by MIDA score.
Assessing the combined end point of mortality and HHF, low MIDA score was associated with favorable event-free survival rates for the total cohort (**A**). Moreover, assessing patients with functional mitral regurgitation high MIDA score showed higher rates of the combined end point (**B**). *Indicates *P*<0.050. HHF indicates hospitalization for heart failure; and MIDA, Mitral Regurgitation International Database.

with functional MR, extending the target patients of this risk score. Other predictive parameters were tricuspid regurgitation, diabetes mellitus, and glomerular filtration rate, which are known predictors of mortality. However, tricuspid regurgitation and glomerular filtration rate revealed a lack of predictive ability in the

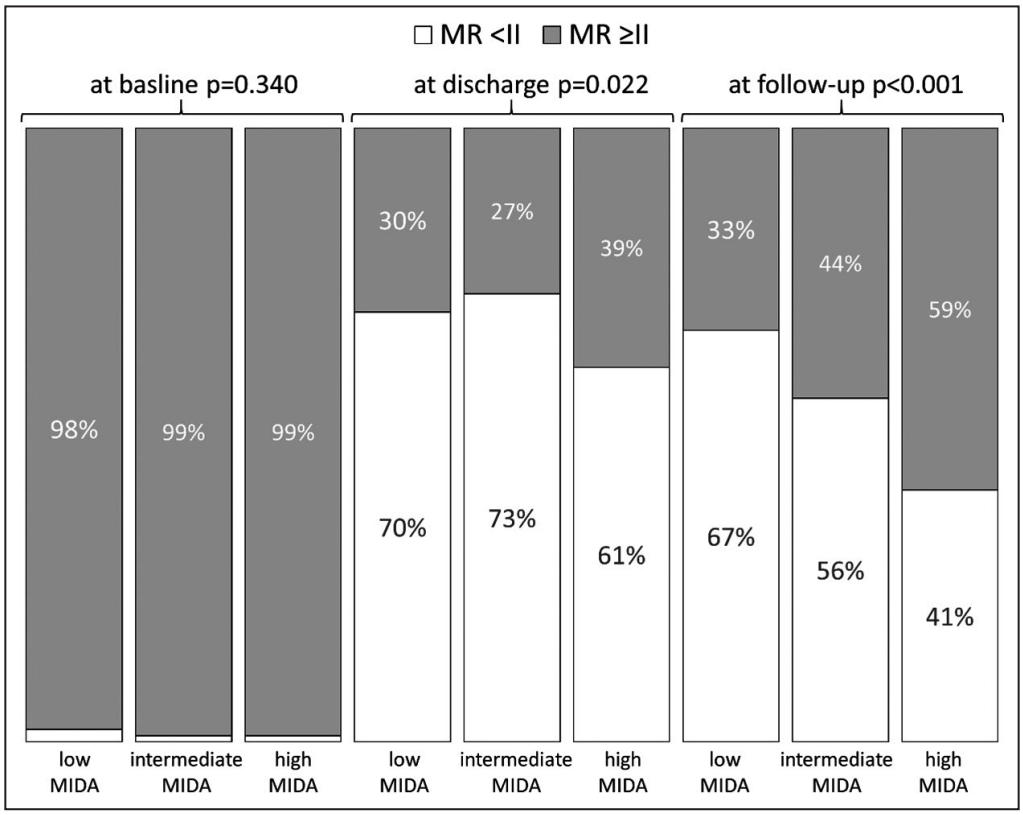

Figure 3. MR ≥II according to MIDA score.
While at baseline there were no significant differences between the MIDA score tertiles, MR ≥II was more frequent in the high MIDA score group at discharge and follow-up. MIDA indicates Mitral Regurgitation International Database; and MR ≥II, residual mitral regurgitation.

subanalysis of patients with functional MR, while diabetes mellitus showed a deficiency regarding the composite end point of mortality or HHF. Of note is that the score identifies patients with a relatively low rate of postprocedural mortality: in total, patients with a low MIDA score of <8 points had a mortality rate of 8.2%, while the 2-year mortality rate was 10% in patients with functional MR. In comparison, overall mortality rates of MitraClip patients with functional MR were 29.1% at 2 years in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial and 24.3% at 1 year in the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) study. Because of a lack of a control group in the present study, it is not possible to derive recommendations regarding TMVR in different MIDA score subgroups, or to evaluate the impact of TMVR in the different subgroups. Future controlled studies are needed to investigate this matter.

As 2 major randomized-controlled studies in this field, the COAPT and MITRA-FR trials showed apparently discordant results regarding the beneficial impact of the MitraClip intervention in patients with functional MR, focusing attention on finding appropriate patient selection criteria.[3,4] Differences between both trials regarding proportions of left ventricular end-diastolic volume and effective regurgitate orifice area represented the main focus in the attempt to identify the key components leading to the varying results.[10,11] However, accuracy of the effective regurgitate orifice area and left ventricular volume in the COAPT study is considered to be a limitation in the attempt to explain trial differences based on MR severity and left ventricular size.[12] Ultimately, development of appropriate patient selection criteria for TMVR is an ongoing process that is very challenging, but of immense importance. The MIDA score represents a risk stratification tool, which includes several parameters that are known to be associated with worse prognosis. Moreover, the score combines clinical parameters such as age and burden of heart failure symptoms, which are more obvious predictors of prognosis,[13,14] with relevant echocardiographic characteristics such as left ventricular end-systolic[15] and left atrial dimensions[16] that are known to be associated with worse outcomes in patients with TMVR.

Next to mortality, HHF represents another end point of importance in patients with heart failure, which is also a major cost driver in health care. Here, we demonstrate that the utility of the MIDA score may be expanded to also predict an end point composite of mortality and HHF after TMVR. In our study cohort, the MIDA score was associated with this end point in the multivariable analysis. Moreover, patients had lower rates of event-free survival with increasing MIDA score group. In the subgroup analysis of patients with functional MR, the *P* values exceeded the threshold of statistical significance, representing a lack of the predictive value for these patients regarding this combined end point. However, there was an apparent trend in the Kaplan–Meier curves (Figure 2B). This marginal exceeding of statistical significance may also be a result of reduced sample size in this subanalysis. Another reason for this shortage might be that in functional MR, an underlying advanced left ventricular dysfunction might gain in relevance, especially regarding the end point of heart failure hospitalization. Consecutively, the MIDA score might need an adjustment to optimize its utility, when used for this particular MR cause and end point.

There is evidence that residual MR following TMVR is associated with worse outcome[17,18]; however, there is a lack of data regarding parameters that are predictive of residual MR. In the present study cohort, residual MR ≥II was assessed at discharge and follow-up echocardiography (mean of 323±169 days after TMVR). While at baseline there were no differences in the distributions of MR ≥II in the low, intermediate, and high MIDA score group, postprocedural rates of residual MR ≥II were highest in the high MIDA score group compared with the low and intermediate MIDA score groups. This difference was more pronounced and highly significant at follow-up: frequency of residual MR ≥II increased with increasing MIDA score group (33%, 44%, and 59%). These results were similar in the subanalysis of patients with functional MR. Moreover, the association of the MIDA score with residual MR was confirmed in the regression analysis. Regression analysis also revealed a relationship between MIDA score and higher risk of MR recurrence as well as marked MR progression during follow-up. Consecutively, the MIDA score may be helpful in identifying TMVR patients who are in need of a more intense echocardiographic monitoring, regardless of MR cause.

Study Limitations

Although the current study included a multicenter patient cohort on a large scale, several limitations must be acknowledged. First, the study`s observational character warrants cautious interpretation and confirmation by controlled prospective studies. Second, MIDA score parameters were missing in 33% of MitraClip patients. These patients were excluded from the study. Third, the number of follow-up echocardiographic assessments was also limited. Fourth, there is no control arm; thus, conclusions regarding the impact of TMVR on the individual MIDA score groups cannot be made. Finally, in analysis

with multiple variables, possible confounders may not be fully controlled and absence of statistical significance may be because of sample size.

CONCLUSIONS

The MIDA score maintains its utility as a mortality risk score in patients undergoing TMVR with the MitraClip system, regardless of MR cause. Moreover, it was predictive of worse event-free survival regarding the combined end point of mortality and HHF. The score was also associated with the presence of residual MR ≥II at discharge, and more strongly at follow-up. Conclusively, the MIDA score may be helpful in the risk stratification process, evaluating TMVR in patients with heart failure with severe MR. Moreover, the score might help to identify TMVR patients who are in need of a more intense monitoring, with an increased hazard of reduced procedural success and sustainability.

ARTICLE INFORMATION

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Supplementary Material

Table S1–S2
Figure S1

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Supplemental Material

Table S1. Cox Regression Analysis for Patients with Functional Mitral Regurgitation.

	Patients with Functional Mitral Regurgitation			
	Univariable Predictor of 2-Year Mortality		Multivariable Predictor of 2-Year Mortality	
Clinical data	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
MIDA score classification *				
Low MIDA score	1.00 [Ref.]		1.00 [Ref.]	
Intermediate MIDA score	2.48 (1.27-4.82)	**0.008**	2.13 (1.09-4.17)	**0.028**
High MIDA score	3.27 (1.67-6.42)	**0.001**	2.56 (1.29-5.1)	**0.008**
MIDA score (per 1 increase) *	1.21 (1.07-1.36)	**0.002**	1.15 (1.01-1.3)	**0.032**
Female sex	0.87 (0.56-1.36)	0.547		
BMI (per kg/m²)	1.01 (0.96-1.05)	0.839		
Logistic EuroSCORE (per %)	1 (1-1.002)	0.739		
Diabetes	1.66 (1.09-2.52)	**0.019**	1.61 (1.06-2.46)	**0.027**
Arterial hypertension	0.86 (0.49-1.49)	0.585		
Prior stroke	1.31 (0.76-2.25)	0.326		
Coronary artery disease	1.12 (0.75-1.90)	0.446		
Prior CABG	1.30 (0.85-1.99)	0.227		
Prior valvular surgery	1.26 (0.68-2.3)	0.461		
Carotid stenosis	0.62 (0.34-1.11)	0.106		
Number of Clips per procedure	1.14 (0.81-1.58)	0.458		
Echocardiographic data				
MR (per grade)	1.2 (0.87-1.67)	0.275		
TR (per grade)	1.32 (1.02-1.71)	**0.037**	1.22 (0.93-1.6)	0.152
Laboraty assessment				
NT-proBNP, pg/mL	1 (1.000003-1.00002)	**0.013**	1 (1-1.00002)	0.063
GFR, ml/min	0.98 (0.97-0.995)	**0.007**	0.99 (0.98-1.001)	0.063

Leucozytes, G/l	1.03 (0.96-1.10)	0.485

* included in multivariable analysis separately. P value <0.05 is considered as statistically significant (bolt). Abb.: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GFR, estimated serum glomerular filtration rate, MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation.

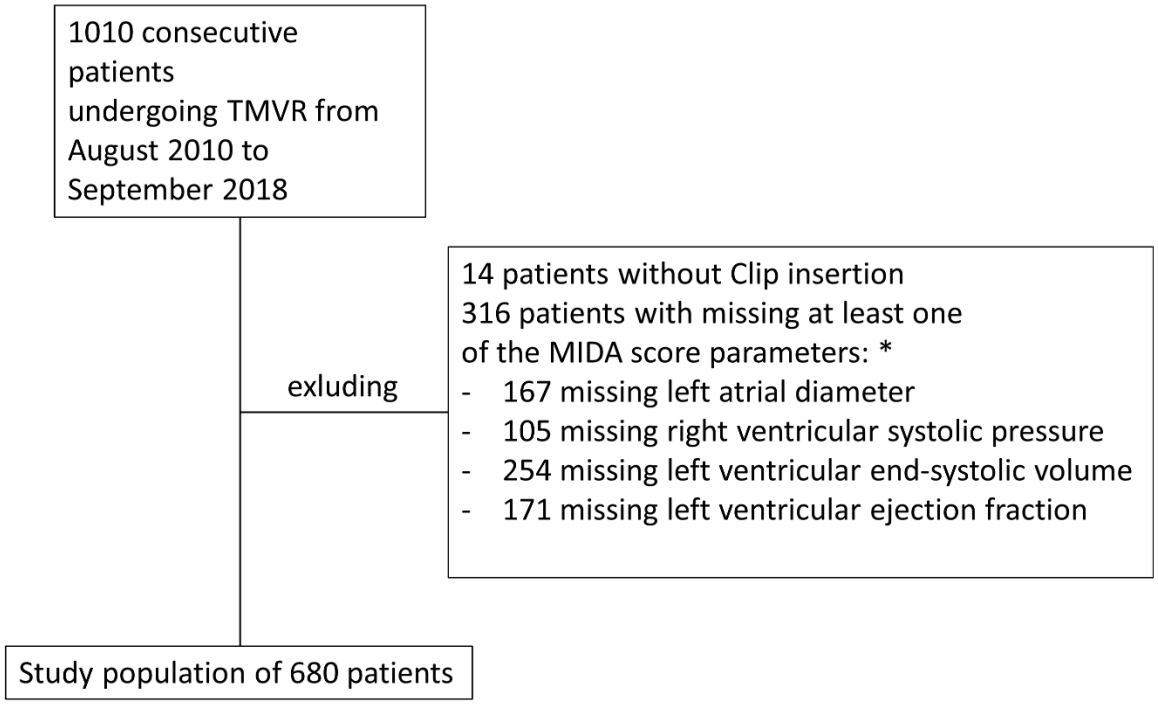
Table S2. Cox Regression Analysis for the Combined Endpoint of Mortality and Hospitalization for Heart Failure.

	Univariable Predictors		Multivariable Predictors	
Clinical data	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
MIDA score classification *				
Low MIDA score	1.00 [Ref.]		1.00 [Ref.]	
Intermediate MIDA score	1.4 (1.01-1.93)	**0.043**	1.22 (0.88-1.7)	0.235
High MIDA score	1.86 (1.33-2.6)	**<0.001**	1.55 (1.1-2.19)	**0.013**
MIDA score (per 1 increase) *	1.12 (1.05-1.19)	**0.001**	1.07 (1.002-1.15)	**0.042**
Female sex	0.75 (0.58-0.97)	**0.027**	0.84 (0.64-1.09)	0.187
BMI (per kg/m²)	1 (0.97-1.03)	0.930		
Logistic EuroSCORE (per %)	1 (0.999-1.001)	0.786		
Diabetes	1.26 (0.98-1.64)	0.075		
Arterial hypertension	0.93 (0.67-1.3)	0.682		
Prior stroke	1.27 (0.91-1.76)	0.161		
Coronary artery disease	1.43 (1.09-1.86)	**0.009**	1.18 (0.87-1.6)	0.278
Prior CABG	1.48 (1.15-1.9)	**0.002**	1.28 (0.97-1.7)	0.087
Prior valvular surgery	1.18 (0.84-1.67)	0.339		
Carotid stenosis	1.01 (0.76-1.34)	0.942		
Number of Clips per procedure	1.22 (1-1.49)	0.053		
Echocardiographic data				
Functional MR	1.48 (1.13-1.93)	**0.005**	1.35 (1.02-1.77)	**0.034**
MR (per grade)	0.93 (0.76-1.14)	0.481		
TR (per grade)	1.26 (1.08-1.46)	**0.003**	1.23 (1.06-1.44)	**0.008**
Laboraty assessment				
NT-proBNP, pg/mL	1 (1.000004-1.00002)	**0.001**	1 (1.000002-1.00002)	**0.018**

GFR, ml/min	0.99 (0.986-0.999)	**0.021**	0.995 (0.98-1.002)	0.159
Leucozytes, G/l	1.01 (0.96-1.07)	0.691		

* included in multivariable analysis separately. P value <0.05 is considered as statistically significant (bolt). Abb.: CABG, coronary artery bypass grafting; GFR, estimated serum glomerular filtration rate, MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation.

Figure S1. Flow Chart of the Study Population. In the present study population, patients were included if at least one clip was inserted and all MIDA score parameters were available.



*Numbers sum up to more than 316, since some patients had more than one missing variable