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Echo-Doppler determinants of outcomes in patients with unoperated significant mitral regurgitation in current era

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ABSTRACT

Objective: One-half of patients with severe symptomatic mitral regurgitation (MR) do not undergo surgery due to comorbidities. We evaluated prognosticators of outcomes in patients with unoperated significant MR.

Methods: In this observational study, we retrospectively evaluated medical records of 75 consecutive patients with unoperated significant MR.

Results: All-cause mortality was 39% at 5 years. Non-survivors (n=29) versus survivors (n=46) were: older (77 ± 9.8 vs 68 ± 14, p=0.006), had higher New York Heart Association (NYHA) class (2.7 ± 0.8 vs 2.3 ± 0.8, p=0.037), higher brain natriuretic peptide (1157 ± 717 vs 427 ± 502 pg/mL, p=0.024, n=18), more coronary artery disease (61% vs 35%, p=0.031), more frequent left ventricular ejection fraction <50% (20.7% vs 4.3%, p=0.026), more functional MR (41% vs 22%, p=0.069), higher mitral E/E' (12.7 ± 4.6 vs 9.8 ± 4, p=0.008), higher pulmonary artery systolic pressure (PASP; 52.6 ± 18.7 vs 36.7 ± 14, p <0.001), more ≥3+ tricuspid regurgitation (28% vs 4%, p=0.005) and more right ventricular dysfunction (26% vs 6%, p=0.035). Significant predictors of 5-year mortality were PASP (p=0.001) and E/E' (p=0.011) using multivariate regression analysis.

Conclusions: Patients with unoperated significant MR have high mortality. Elevated PASP and mitral E/E' were the most significant predictors of 5-year survival in patients with unoperated significant MR. Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines provide a limited incorporation of echo-Doppler parameters in the preoperative risk stratification of patients with severe MR.

KEY QUESTIONS

What is already known about this subject?
► Patients with uncorrected severe symptomatic mitral regurgitation (MR) have a significantly increased risk of morbidity and mortality. Several clinical and echocardiographic prognosticators of outcomes in patients with unoperated severe MR have been described in the past, but limited data exist in the current era.

What does this study add?
► This study provides an updated analysis of echo-Doppler parameters in determining outcomes in patients with severe MR who are not candidates for surgery or percutaneous repair in the context of current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.

How might this impact on clinical practice?
► This study will help clinicians to better risk stratify patients with severe MR and highlights that the current ACC/AHA guidelines provide limited incorporation of echo-Doppler parameters in the preoperative risk stratification of patients with severe MR.

patients with unoperated severe MR to determine the prognostic value of various echo-Doppler and clinical variables. The objective of our study was to identify clinical and echo-Doppler predictors of 5-year outcomes in patients with significant symptomatic MR who did not undergo surgical intervention in the current era.

INTRODUCTION

Patients with uncorrected severe symptomatic mitral regurgitation (MR) have a significantly increased risk of morbidity and mortality.[1–4] However, in the EuroHeart survey, approximately one-half of patients with severe symptomatic MR did not undergo surgery, most frequently due to comorbidities.[5] However, there are no data from the current era, which addresses the natural history of

METHODS

In this observational study, we retrospectively evaluated the medical records of consecutive patients with significant MR (≥3+) from December 2005 through December 2008, who were considered high risk and did not undergo surgery during a 5-year follow-up and were not deemed to be candidates for

the MitraClip procedure.[6] [7] We excluded patients with concomitant moderate or greater aortic stenosis or aortic regurgitation, and patients with prior percutaneous or surgical repair or replacement of the mitral and/or aortic valves.[6] [7] Hospital medical records and the social security death index were used to obtain and verify the 5-year mortality data. Patients were stratified into two groups as survivors versus non-survivors at 5 years of follow-up. The Institutional Review Board approved the study, and the waiver for patient consent was granted because of the retrospective nature of the study.

Two independent reviewers (RJS and AMR) evaluated the echocardiograms. Significant MR was defined as per the ACC/AHA guidelines, using a combination of qualitative and quantitative parameters including MR colour jet area to left atrial area ratio (JA/LAA) ≥40%, Doppler vena contracta width (VC) ≥0.7 cm, mitral regurgitant volume (Rvol) ≥60 mL/beat, regurgitant fraction ≥50%, effective regurgitant orifice area (EROA) ≥40 mm^2, density and width of MR continuous wave (CW) jet, pulmonary vein flow (PVF) with systolic reversal, and enlarged left atrium (LA) and left ventricle (LV).[6–8]

Transmitral early (E) peak velocity, its deceleration time (DT) and transmitral atrial (A) wave velocity were obtained with a pulsed wave sample at the tip of the mitral valve.[9] Early diastolic velocity of the lateral aspect of the mitral annulus (E$'$) was measured by Doppler tissue imaging (TDI). PVF was obtained on an apical four-chamber view.[9] [10]

The maximum velocity of the tricuspid regurgitation (TR) jet was measured using CW Doppler as per American Society of Echocardiography (ASE) recommendations.[8] [11] Right ventricle (RV) systolic pressure was estimated based on the modified Bernoulli equation and assumed to be equal to the pulmonary artery systolic pressure (PASP) in the absence of RV outflow obstruction. PASP was calculated by adding the tricuspid valve pressure gradient to the estimated right atrial pressure (RAP).[11] RAP was considered as: 3 mm Hg for inferior vena cava (IVC) diameter <1.7 cm and ≥50% collapse with inspiration; 7 mm Hg for IVC diameter ≥1.7 cm and ≥50% decrease in the diameter with inspiration; 12 mm Hg if <50% collapse on inspiration; ≥15 mm Hg if the IVC was dilated without any collapse.[8] [11]

Statistical analysis

Statistical analysis was performed with the statistical software program IBM SPSS V.21.0 (IBM Inc). Continuous data were presented as mean±SD. Categorical data were presented as an absolute number or percentages. Between-groups comparisons of baseline data were performed using the independent-samples t-test. All categorical variables were compared between the two groups using the Pearson χ^2 test. Clinical and statistical variables were entered into Cox regression models to evaluate the independent predictors of 5-year survival.

Kaplan-Meier analysis was used to estimate survival. The log-rank test was used to compare survival across two groups. A p value <0.05 was considered statistically significant. Given the retrospective and observational nature of the study, the sample size was not calculated.

RESULTS

Medical records of 83 patients with significant MR and available 5-year follow-up data were reviewed. Eight patients were excluded due to: prior mitral valve repair (MVR; n=2), MitraClip treatment (n=1), or MVR/mitral valve replacement (MVRe; n=3) during the follow-up period, or absence of a reliable TR signal on echocardiography (n=2). We included 75 patients (45 male) with a mean age of 72±11 years. The mean mitral EROA was 54±30 mm^2, the mitral Rvol was 80±37 mL/beat, the VC was 0.6±0.2 cm and the mean mitral JA/LAA was 42.3 ±12 mm Hg. TDI of the lateral mitral annulus was available for 64 (85%) patients, and PVF was interpretable in 62 (83%) patients. The reasons for non-operability are shown in table 1.

Overall, 29 (39%) patients died during the 5 years of follow-up. As shown in table 2, non-survivors (n=29) compared with survivors (n=46) were older (77±9.8 vs 68 ±14 years, p=0.006); had more coronary artery disease (61% vs 35%, p=0.031), diabetes (21% vs 6.5%, p=0.057), pulmonary hypertension (71% vs 37%, p=0.004), atrioventricular block (14% vs 2.3%, p=0.073), higher New York Heart Association (NYHA) class (2.7 ±0.8 vs 2.3±0.8, p=0.037), higher brain natriuretic peptide (BNP) level (1157±717 vs 427±502, p=0.024, n=18) and a trend for a higher incidence of syncope (7.1% vs 0%, p=0.066). Overall, there was no significant difference in the prevalence of symptoms between the two study groups (93.1% vs 84.8%, p=0.281). Other comorbidities and medical treatment were comparable between the two groups.

Table 1	Reasons for not performing mitral valve surgery
Variable	**n**
Advanced age ≥90 years	4
Frailty	8
Severe mitral calcification	3
Redo surgery	7
Severe PVD	2
Poor bypass targets	1
Severe kyphosis	1
Malignancy	4
Other comorbidities*	8
Other reasons†	37

*Other comorbidities included infection, gastrointestinal bleeding (GIB), cirrhosis, severe COPD, vasculitis.
†Other reasons included non-compliance, patient preference (n=17), lost to follow-up (n=9) or no obvious reason (n=3).
COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

Table 2 Comparison of baseline clinical variables between non-survivors and survivors

Variable	Non-survivors mean±SD (n=29)	Survivors mean±SD (n=46)	p Value
Age (years)*	76.7±9.8	68.2±14	0.006
Gender (female)	38%	41%	0.772
BSA (m^2)	1.8±0.3	1.8±0.2	0.696
SBP (mm Hg)	124±19	126±22	0.804
Symptoms			
Angina	10.7%	8.7%	0.774
Dyspnoea	85.7%	82.6%	0.725
NYHA class*	2.7±0.8	2.3±0.8	0.037
Cardiovascular risk factors			
Diabetes mellitus*	21%	6.5%	0.057
Hypertension	71.4%	65.2%	0.581
Cardiovascular comorbidities			
CHF	89.3%	82.6%	0.434
CAD*	60.7%	34.8%	0.031
Previous MI	25%	19.6%	0.582
Atrialfibrillation/flutter	44%	30%	0.228
CVA	7.1%	6.5%	0.918
PVD	14.3%	4.3%	0.129
Pacemaker	22.2%	13%	0.307
Pulmonary hypertension*	71.4%	37%	0.004
Non-cardiac comorbidities			
CKD±dialysis	35.7%	19.6%	0.123
COPD	14.3%	6.5%	0.268
Cancer	25%	10.9%	0.111
Medications			
Aspirin	60.9%	52.6%	0.531
β-Blockers	64%	46.20%	0.163
ACEi/ARB	72%	56.8%	0.211
Statins	57.7%	50%	0.545
Vasodilators†	21%	29%	0.477
Diuretics‡	67%	57%	0.439
Digoxin	36%	21.1%	0.191
Coumadin	37.50%	27%	0.388
Antiarrhythmics	16%	18.9%	0.768
Laboratory			
Sodium (mmol/L)	138±6	141±3	0.093
Creatinine (mg/dL)	2.1±2.8	1.9±2.5	0.852
Haemoglobin (g/dL)	12.5±1.4	13.1±1.8	0.231
Platelet counts (1000/μL)	224±56	229±94	0.851
INR	1.5±0.4	1.3±0.6	0.341
LDL (mg/dL)	69.4±34.9	80.3±42.3	0.546
BNP (pg/mL)*	1158±717	427±503	0.024
HbA1c (%)	7.1±1.7	5.4±0.2	0.22

*$p<0.05$.
†Vasodilators included calcium channel blockers, α-blockers, hydralazine and nitrates.
‡Diuretics included Lasix, thiazides, spironolactone.
ACEi, ACE inhibitors; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; HbA1c, glycated haemoglobin; INR, international normalised ratio; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease; SBP, systolic blood pressure.

The use of β-blockers, ACE inhibitors or angiotensin receptor blockers, or spironolactone was significantly higher in non-survivors compared with survivors (87% vs 61%, p=0.033). The use of these medications tended to be more frequent in non-survivors compared with survivors both in functional MR (FMR; 100% vs 78%, p=0.134) and degenerative MR (DMR; 79% vs 56%, p=0.147). Patients on these medications tended to have worse: NYHA class (2.6±0.7 vs 2.1±0.9, p=0.044), left ventricular ejection fraction (LVEF; 58±17% vs 65±12%, p=0.182), forward stroke volumes (47±19 vs 71±42, p=0.051), PASP (43±16 vs 36±16, p=0.176), RAP (9±6 vs 8±6, p=0.782), BNP (896±1232 vs 491±195, p=0.561) and creatinine (2.1±2.9 vs 1.0±0.4, p=0.289).

Table 3 Comparison of echocardiographic variables between non-survivors and survivors

	Non-survivors mean±SD(n=29)	Survivors mean±SD(n=46)	p Value
LVEDD (mm)	55.5±9.7	53.6±6.8	0.369
LV mass (g)	243±111	246±107	0.89
LVESV (mL)	52.7±41.4	38.4±33.6	0.105
LVEDV (mL)	102±48	105±65	0.839
LVEF (%)	54±20	59±15	0.243
LVOT VTI (cm)	15±4.4	16.2±4	0.247
3+TR grade (%)*	28%	4%	0.0045
RV dysfunction (%)*	26%	6%	0.0351
MV E velocity (cm/s)*	116±29	100±31	0.024
MV E/A	1.7±0.9	1.5±0.6	0.296
MV DT (ms)	188±59	203±62	0.301
MV E/E′*	12.7±4.6	9.8±4	0.008
E/E′≥15*	32%	10.5%	0.034
LAA (cm^2)	24.9±6.4	26.8±7.7	0.285
PASP systolic (mm Hg)*	52.6±18.7	36.7±14	<0.001
PASP≥50 mm Hg*	58.6%	13.3%	<0.001
RAP (mm Hg)*	10.6±6.5	7.7±4.6	0.042

*$p < 0.05$.
DT, deceleration time; EDD, end diastolic dimension; EDV, end diastolic volume; EF, ejection fraction; ESD, end systolic dimension; ESV, end systolic volume; IVS, interventricular septum; LAA, left atrial area; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve; PASP, pulmonary artery systolic pressure; PV, pulmonary vein; PWT, posterior wall thickness; RAP, estimated right atrial pressure; RV, right ventricle; TR, tricuspid regurgitation; VTI, velocity time integral.

Table 4 Comparison of echocardiographic variables related to MV anatomy and function

	Non-survivors mean±SD (n=29)	Survivors mean±SD (n=46)	p Value
MV VC (cm)	0.61±0.15	0.57±0.14	0.213
MV JA/LAA (%)*	0.48±0.14	0.39±0.1	0.001
PISA radius (cm)	0.99±0.24	1.09±0.26	0.091
Vr (cm/s)	36.3±2.5	36.9±4.5	0.535
MR Vmax (m/s)	5.08±0.79	4.99±0.75	0.615
MR VTI (cm)	160.1±25.8	155.9±38.2	0.604
EROA (mm^2)	46.7±23	59.2±32.3	0.074
MR Rvol (mL/beat)	73.2±33.9	83.4±38.7	0.249
MR RF (%)	59±11%	56±15%	0.511
Abnormal PV flow (%)	48%	54%	0.639
MR functional (%)	41%	22%	0.069
MR eccentric (%)	64%	78%	0.242
Annular calcification (%)*	70%	36%	0.021

*$p < 0.05$.
EROA, effective regurgitant orifice area; JA/LAA, ratio of jet area to left atrial area; MR, mitral regurgitation; MV, mitral valve; PV, pulmonary vein; PISA, proximal isovelocity surface area; RF, regurgitant fraction; Rvol, regurgitant volume; VC, vena contracta; VFR, volume flow rate; Vr, aliasing velocity at the radial distance r (cm/s) (Vr); VTI, velocity time integral.

As shown in table 3, non-survivors compared with survivors had: similar LV systolic (36.4±13.1 vs 34.3±9.2, p=0.448) and LV diastolic (55.5±9.7 vs 53.6±6.8, p=0.369) dimensions, with a higher prevalence of an LVEF<50% (20.7% vs 4.3%, p=0.026), lower LV stroke volume (49.5±21.8 vs 66.7±47.8, p=0.038), higher mitral E velocity (116.1±28.9 vs 99.5±30.7, p=0.024), higher E/E′ (12.7±4.6 vs 9.8±4, p=0.008), higher prevalence of E/E′≥15 (32% vs 10.5%, p=0.034), higher PASP (52.6±18.7 vs 36.7±14, p<0.001), similar E/A≥2 (18.2% vs 26.3%, p=0.473), similar DT<140 ms (21.4% vs 10.9%, p=0.216), and more TR and RV dysfunction (26% vs 4%, p=0.035).

Non-survivors compared with survivors had: severe MR (72% vs 70%, p=0.791), FMR (41% vs 22%, p=0.069), eccentric MR jet (64% vs 78%, p=0.242), mitral annular calcification (70% vs 36%, p=0.021), JA/LAA (72.4% vs 45.7%, p 0.023), VC≥0.7 (34.5% vs 22.2%, p=0.246), Rvol≥60 mL (58.6% vs 76.1%, p=0.11), EROA≥40 mm^2 (51.7% vs 76.1%, p=0.029) and mean EROA (47±23 vs 59±32, p=0.074; table 4). Of the 22 patients with FMR, the 5-year mortality was 54% compared with 32% of 53 patients with DMR (p=0.032).

Figure 1 shows the areas under the curve (AUC) from receiver-operator characteristic curve for the various
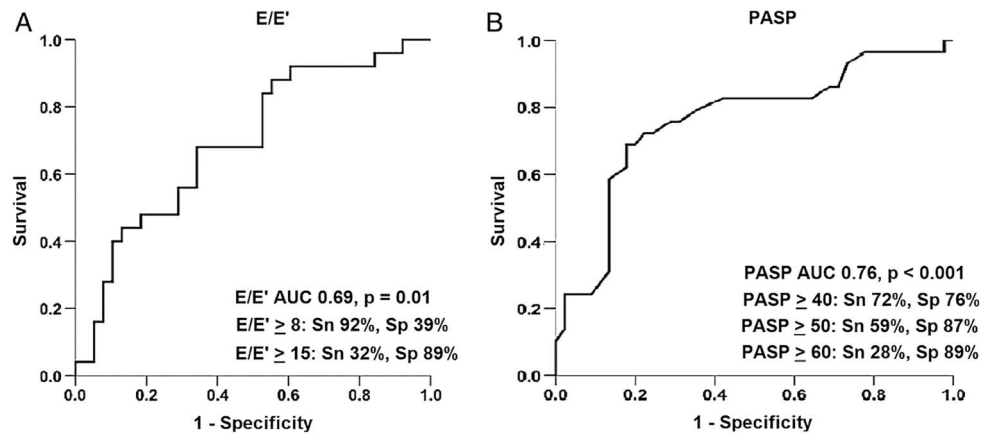
Figure 1 (A) ROC for the prediction of 5-year mortality in unoperated significant MR. AUCs and corresponding p values are shown for lateral annulus E/E$^{'}$ (AUC=0.69, 95% CI 0.56 to 0.83, p=0.01). (B) ROC for the prediction of 5-year mortality in unoperated significant MR. AUCs and corresponding p values are shown for PASP (AUC=0.76, 95% CI 0.64 to 0.88, p<0.001). AUC, area under curve; PASP, pulmonary artery systolic pressure; ROC, receiver-operator characteristic curve.
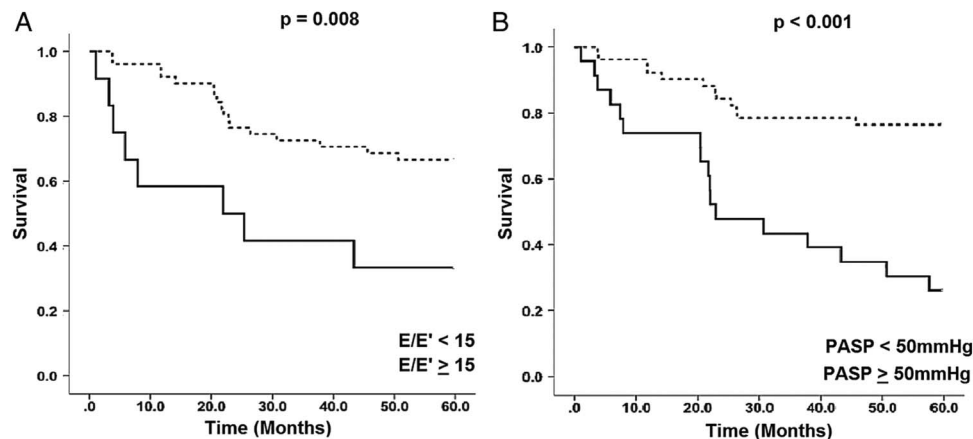

Figure 2 (A): Five-year mortality in unoperated patients with severe MR with E/E$^{'}$≥15 was significantly higher compared with patients with E/E$^{'}$<15 (67% vs 33%, p=0.008). (B): Five-year mortality in unoperated patients with severe MR with PASP≥50 was significantly higher compared with patients with PASP<50 (76% vs 23%, p<0.001). DMR, degenerative MR; EROA, effective regurgitant orifice area; FMR, functional MR; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure.

parameters. Lateral E/E$^{'}$≥8 was 92% sensitive and 39% specific; lateral E/E$^{'}$≥15 was 32% sensitive and 89% specific; PASP≥50 mm Hg was 59% sensitive and 87% specific; PASP≥60 mm Hg was 28% sensitive and 89% specific; RAP≥10 mm Hg was 36% sensitive and 81% specific (AUC=0.62, 95% CI 0.48 to 0.76, p=0.098); mitral E velocity ≥120 cm/s was 43% sensitive and 80% specific (AUC 0.66, 95% CI 0.53 to 0.78, p=0.027); and mitral JA/LAA ≥40% was 66% sensitive and 60% specific (AUC 0.71, 95% CI 0.60 to 0.83, p <0.01) to predict 5-year mortality.

Using Kaplan-Meier curves, the 5-year all-cause mortality was 67% in patients with E/E$^{'}$≥15 compared with 33% in patients with E/E$^{'}$<15 (p=0.008, figure 2A). Using Kaplan-Meier curves, the 5-year mortality was 74% for patients with a PASP≥50 mm Hg compared with 23% for patients with PASP<50 mm Hg (p<0.001, figure 2B).

Patients with PASP≥50 mm Hg and E/E$^{'}$≥15 (n=8) had a 5-year mortality of 75% while patients with PASP<50 mm Hg and E/E$^{'}$<15 (n=38) had a lower 5-year

mortality of 21%. Only seven patients had LVEF<50%, so further stratification was not possible. In the subgroup of patients with LVEF≥50%, patients with PASP≥50 mm Hg had a significantly worse survival than patients with PASP<50 mm Hg (22% vs 67%, p<0.001).

In the multivariate Cox regression analysis presented in table 5, the only significant predictor predictive of 5-year mortality was a PASP≥50 mm Hg (HR 2.2, 95% CI 1.4 to 3.3, p<0.001). Age, gender, NYHA class ≥3, LVEF<50%, E/E$^{'}$≥15, EROA≥40 and MR Rvol≥60, aetiology were not significant independent predictors in the multivariate model. Using the above parameters as continuous variables in the linear regression model, the significant predictors included PASP (p=0.001) and E/E$^{'}$ (p=0.011).

DISCUSSION

Patients with moderate to severe or severe MR who do not undergo surgical repair or replacement because of

Table 5 Cox regression model using clinical and echocardiographic variables

	HR	95% CI	Univariate p Value	Multivariate p Value
PASP ≥50 (mm Hg)*	2.2	1.41 to 3.34	<0.001	<0.001
E/E' ≥15	0.96	0.27 to 3.44	0.034	0.948
JA/LAA ≥40%	2.24	0.87 to 5.79	0.023	0.128
RV ≥60 (mL/beat)	1.09	0.12 to 10.2	0.11	0.942
EROA ≥40 (mm^2)	0.87	0.09 to 8.54	0.029	0.917
LVEF <50 (%)	2.83	0.79 to 10.2	0.026	0.112
NYHA class ≥3	0.66	0.21 to 2.04	0.085	0.466
Gender (male)	1.23	0.43 to 3.53	0.772	0.706
Age (years)	1.04	1.00 to 1.02	0.006	0.047

*p<0.05.
EF, ejection fraction; EROA, effective regurgitant orifice area; JA/LAA, ratio of jet area to left atrial area; LV, left ventricular; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RV, right ventricle; Rvol, regurgitant volume.

comorbidities have a high 5-year mortality. In the multivariate analysis, significant predictors of 5-year mortality were PASP and E/E'. We did not find EROA, Rvol and VC to be predictive of mortality in patients with significant MR.

The likely mechanisms of increased mortality in patients with elevated and persistent PASP most likely include more advanced LV and LA remodelling in response to chronic volume overload from severe MR resulting in irreversible changes in the myocardium due to fibrosis and the permanent dysfunction of endothelium in the pulmonary vasculature. Elevated filling parameters in the setting of pulmonary hypertension therefore represent a more advanced disease stage where early intervention is warranted. Early optimisation of medical therapy for congestive heart failure (CHF) is prudent to improve pulmonary hypertension (PH) and hence outcomes in patients with MR by preventing late LV irreversible remodelling.[12] The role of specific therapy for PH should be evaluated in patients with MR with an elevated transpulmonary gradient. MVR/MVRe is now an alternative treatment for patients with severe symptomatic MR who are not operative candidates.[13–15] It is important to carefully evaluate the patients undergoing MVR/MVRe or MitraClip as increasingly more complex and sick patients are being referred for these procedures.[16–18] Swaans et al[19] showed that high surgical-risk patients with severe symptomatic MR treated with transcatheter MV repair show similar survival rates comparable to patients undergoing surgery, with both groups showing a survival benefit compared with conservative treatment. Appropriate risk stratification and proper selection of these high-risk patients and optimisation of filling pressures may improve outcomes of these patients with poor surgical options and with an increased mortality with medical therapy alone.

CONCLUSIONS
Patients with unoperated significant MR have a high mortality rate. Elevated filling pressures as determined by PASP and mitral E/E' were most significant predictors of 5-year survival in patients with unoperated significant MR. Optimisation of filling pressure preprocedure or earlier intervention preceding development of irreversible changes may further improve outcomes in patients undergoing evaluation for MVR/MVRe or MitraClip.

Limitations
This is a retrospective study; however, few studies have evaluated the prognosis of untreated MR in the modern era as most patients with severe MR undergo surgery or percutaneous intervention. This study is unique in providing an updated evaluation of echo-Doppler prognosticators in patients with severe MR. PASP was evaluated using echocardiography, which reflects the filling pressure under true resting conditions, avoiding the impact of analgesia or sedation and intravenous fluids on cardiac haemodynamics.

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