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Mitral Annular Tissue Velocity Predicts Survival in Patients With Primary Mitral Regurgitation

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AUTHOR'S SUMMARY

This study assessed the prognostic role of e' velocity in chronic degenerative mitral regurgitation (MR) patients under 65 years. Among 404 participants (median age, 51.0 years; 64.1% male; 47.8% severe MR), e' velocity independently predicted both all-cause (adjusted hazard ratio [aHR], 0.770; 95% confidence interval [CI], 0.634–0.935; p=0.008) and cardiovascular death (aHR, 0.690; 95% CI, 0.477–0.998; p=0.049), regardless of other factors. Incorporating e' velocity ≤7 cm/s into the 10-year risk score improved reclassification for mortality and cardiovascular death. In conclusion, e' velocity serves as an independent predictor of all-cause and cardiovascular death in primary MR patients under 65 years.

ABSTRACT

Background and Objectives: Early diastolic mitral annular tissue (e') velocity is a commonly used marker of left ventricular (LV) diastolic function. This study aimed to investigate the prognostic implications of e' velocity in patients with mitral regurgitation (MR).
Methods: This retrospective cohort study included 1,536 consecutive patients aged <65 years with moderate or severe chronic primary MR diagnosed between 2009 and 2018. The primary and secondary outcomes were all-cause and cardiovascular mortality, respectively. According to the current guidelines, the cut-off value of e' velocity was defined as 7 cm/s.
Results: A total of 404 individuals were enrolled (median age, 51.0 years; 64.1% male; 47.8% severe MR). During a median 6.0-year follow-up, there were 40 all-cause mortality and 16 cardiovascular deaths. Multivariate analysis revealed a significant association between e' velocity and all-cause death (adjusted hazard ratio [aHR], 0.770; 95% confidence interval [CI], 0.634–0.935; p=0.008) and cardiovascular death (aHR, 0.690; 95% CI, 0.477–0.998; p=0.049). Abnormal e' velocity (≤7 cm/s) independently predicted all-cause death (aHR, 2.467; 95% CI, 1.170–5.200; p=0.018) and cardiovascular death (aHR, 5.021; 95% CI, 1.189–

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21.211; p=0.028), regardless of symptoms, LV dimension and ejection fraction. Subgroup analysis according to sex, MR severity, mitral valve replacement/repair, and symptoms, showed no significant interactions. Including e' velocity in the 10-year risk score improved reclassification for mortality (net reclassification improvement [NRI], 0.154; 95% CI, 0.308–0.910; p<0.001) and cardiovascular death (NRI, 1.018; 95% CI, 0.680–1.356; p<0.001).
Conclusions: In patients aged <65 years with primary MR, e' velocity served as an independent predictor of all-cause and cardiovascular deaths.

Keywords: Mitral regurgitation; Echocardiography, Doppler; Heart failure, Diastolic; Prognosis

INTRODUCTION

Mitral regurgitation (MR) is one of the most frequent valvular heart diseases, characterized by the backflow of blood from the left ventricle (LV) to the left atrium (LA) during systole.[1] Numerous causes contribute to MR, with mitral valve (MV) prolapse or flail leaflet as the most frequent etiology.[1] Significant primary MR often leads to LV decompensation, associated with high rates of mortality and morbidity.[2] As a consequence, MV surgery is recommended for those with symptomatic severe MR or evidence of LV systolic dysfunction.[3)4)] However, due to the slow disease progression, patients with chronic MR may fail to observe any change in the symptom status and the optimal timing of surgery or standards that advocate early intervention in patients with severe MR remain a debate.[5]

While ongoing research is being conducted for novel biomarkers that would help predict the prognosis of patients with primary MR more accurately,[6] our recent findings indicate that a substantial proportion of patients with primary MR exhibit significant impairment in echocardiographic parameters indicating diastolic dysfunction and that the outcome of these patients may be comparable to those with isolated compensatory LV dilatation.[7] However, the importance of advanced diastolic dysfunction is not emphasized in the contemporary guidelines of MR treatment.[3)4)] This is probably attributed to the difficulty in assessing the LV diastolic function with Doppler parameters of mitral inflow and pulmonary vein flow in primary MR.[8-10]

Although early diastolic mitral annular tissue (e') velocity is a commonly used parameter for evaluating LV diastolic function under the assumption that it reflects myocardial relaxation in the longitudinal axis,[11] the clinical significance of e' velocity in predicting long-term survival in patients with primary MR remains uncertain. Therefore, we aimed to evaluate whether e' velocity adds predictive value to prognosis in patients with significant primary degenerative MR.

METHODS

Ethical statement
We obtained Institutional Review Board authorization (H-2110-152-1266) before initiating the study. This study conformed with the revised Declaration of Helsinki guidelines (2013).

Study design
This was a single-center, observational, retrospective cohort study of consecutive patients diagnosed with chronic MR at Seoul National University Hospital, a large-volume

tertiary hospital in Korea between 2009 and 2018. Consecutive patients with significant primary MR, defined as moderate or severe, were retrospectively identified from a 10-year echocardiographic database.

Study population

A total of 1,536 consecutive patients with significant MR diagnosed using echocardiography were enrolled in the current study. The specific eligibility criteria were the absence of 1) a previous history of open-heart surgery or percutaneous mitral balloon valvuloplasty; 2) concomitant at least moderate aortic stenosis; and 3) congenital heart diseases. Only the patients diagnosed with MV prolapse/flail leaflets were included in the analysis. Therefore, functional, rheumatic, and congenital MR etiologies were excluded as well as those with MR due to infective endocarditis or other etiologies. Furthermore, for the present analysis, we only included patients for whom measurements of the e' velocity were available while excluding cases in which the e' velocity measurement was deemed unreliable because of regional wall motion abnormalities or mitral annular calcification. No cases with constrictive physiology, which could induce an overestimation of septal e' velocity, were included. Finally, to account for the potential confounding effects of old age, the study was limited to patients aged <65 years (**Supplementary Figure 1**). Clinical decisions regarding medical management and referral for surgery were made by the attending physician for each patient.

Echocardiography

Transthoracic echocardiograms were performed with commercially available machines (Vivid 7, Vivid S70, Vivid E9, or Vivid E95, GE Healthcare; EPIQ 7, EPIQ 9, CX50, or iE33, Philips Healthcare; and ACUSON SC2000 or SEQUOIA C512, Siemens Medical Solution) according to the most up-to-date guidelines (**Supplementary Data 1**).[12-15] For patients with multiple echocardiographic examinations, the first echocardiography to diagnose either significant MR between 2009 and 2018 was used. A 2-mm-sized sample volume of the pulse wave Doppler was placed between the tips of the mitral leaflets in the apical 4-chamber view to assess the mitral inflow patterns.[15] The e' velocity was measured by tissue Doppler imaging placed at the septal side of the mitral annulus.[15] In patients with atrial fibrillation, the e' velocity was calculated by averaging velocities from more than 3 cardiac cycles. In a previous study, inter- and intra-observer variabilities of e' velocity were documented as 5% and 6.5%, respectively, endorsing the reliability of the measurements.[16]

Clinical outcomes

The primary outcome was all-cause death after the first diagnosis of at least moderate MR. The secondary outcome was cardiovascular death (**Supplementary Data 1**). Patients were censored if they were lost to follow-up. Each patient was followed up until the occurrence of the study endpoint (i.e., death), the end of the study follow-up (December 31, 2020), or 10 years, whichever came first.

Mortality risk model

The Mitral Regurgitation International Database (MIDA), which is a large-scale registry of patients with degenerative MR, provides the MIDA score to stratify mortality risk (**Supplementary Data 1**).[17] For the current study, we used the MIDA score as the reference model for predicting 10-year mortality in the study population. The presence of symptoms was defined according to the New York Heart Association functional classification of heart failure II–IV.

Statistical analysis

Continuous variables were described as mean±standard deviation or median (interquartile range) and compared with either Student's t-test or the Mann–Whitney U test. Categorical variables were summarized as frequencies (percentages) and analyzed using the chi-square test or Fisher's exact test.

The Kaplan–Meier method was used for survival analysis and the log-rank test was used to compare differences in the Kaplan–Meier curves. Hazard ratios (HR) with confidence intervals (CIs) were obtained from the results of the Cox regression analyses. We employed restricted cubic splines to investigate the relationships between a continuous variable (e.g., e' velocity) and the risk of outcomes (**Supplementary Figure 2**). Univariate and multivariate analyses of time-to-events were performed using Cox proportional hazard regression model including the e' velocity as an independent factor as either a continuous (cm/s) or categorical variable (i.e., e' velocity ≤7 cm/s). Following the current guidelines, we employed 7 cm/s as a cutoff value indicating abnormal e' velocity.[15] Significant factors with p<0.2 resulting from the univariate analysis and clinically relevant factors were included as possible covariates in a multivariate analysis. The proportional hazard assumption was tested using statistics and graphs based on scaled Schoenfeld residuals. The index date was the echocardiography date of the first diagnosis of either moderate or severe MR. We performed the competing risk analysis, treating MV replacement/repair during follow-up as competing event. Subsequently, subgroup analysis included groups stratified by sex, MR severity (moderate and severe), MV replacement/repair during follow-up, and symptoms with measurement of statistical interaction between these characteristics and the e' velocity in predicting all-cause mortality. To examine the incremental predictive value of survival based on abnormal e' velocity, we calculated Harrell's concordance index (C-index), continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI).[18]

All statistical analyses were performed using the R Statistical Software (version 4.0.1; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at p<0.05. All p values were 2 sided.

RESULTS

A total of 404 patients with primary moderate or severe MR aged <65 years were eligible for the current study. The median age was 51.0 years (41.0–59.0 years) and 64.1% comprised of males. The baseline characteristics of the study population are shown in **Table 1**.

Prognostic value of mitral annular tissue velocity

During a median follow-up of 6.0 years (2.93–9.51 years), 40 deaths occurred, of which 16 were cardiovascular death. In the univariate analysis, e' velocity was associated with all-cause (HR, 0.692; 95% CI, 0.588–0.815; p<0.001; **Supplementary Table 1**) and cardiovascular death (HR, 0.634; 95% CI, 0.455–0.802; p<0.001; **Supplementary Table 2**). In the multivariate analysis, e' velocity was independently related to all-cause (HR, 0.770; 95% CI, 0.634–0.935; p=0.008; **Table 2** and **Supplementary Table 3**) and cardiovascular death (HR, 0.690; 95% CI, 0.477–0.998; p=0.049; **Table 2** and **Supplementary Table 4**).

Detailed demographic information and echocardiographic findings for the study population stratified by the e' velocity are provided in **Table 1**. The e' velocity ≤7 cm/s was also associated

Table 1. Baseline characteristics of the study population

Variables	Total population (n=404)	e' velocity >7 cm/s (n=265)	e' velocity ≤7 cm/s (n=139)	p value
Age (years)	51.0 (41.0–59.0)	47.0 (38.0–55.0)	57.0 (51.0–61.0)	<0.001
Male sex	259 (64.1)	173 (65.3)	86 (61.9)	0.497
Body mass index (kg/m²)	23.5 (21.1–25.7)	23.2 (20.7–25.2)	24.0 (21.9–26.6)	0.001
Systolic blood pressure (mmHg)	122.0 (111.0–132.0)	121.5 (111.2–130.0)	123.0 (110.0–135.0)	0.481
Diastolic blood pressure (mmHg)	74.0 (67.0–80.0)	73.5 (67.0–80.0)	75.0 (68.0–82.0)	0.196
Severe MR	193 (47.8)	128 (48.3)	65 (46.8)	0.769
ERO (cm²)	0.34 (0.25–0.50)	0.32 (0.22–0.55)	0.34 (0.29–0.46)	0.739
Regurgitation volume (mL)	52.0 (37.3–71.4)	51.9 (33.1–73.7)	52.0 (41.0–67.6)	0.992
MIDA score	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.208
NYHA functional class				
I	272 (67.3)	182 (68.7)	90 (64.7)	0.812
II	96 (23.8)	61 (23.0)	35 (25.2)	
III	32 (7.9)	20 (7.5)	12 (8.6)	
IV	4 (1.0)	2 (0.8)	2 (1.4)	
II–IV	132 (32.7)	83 (31.3)	49 (35.3)	0.424
Comorbidities				
Hypertension	136 (33.7)	75 (28.3)	61 (43.9)	0.001
Diabetes mellitus	52 (12.9)	21 (7.9)	31 (22.3)	<0.001
Dyslipidemia	55 (13.6)	32 (12.1)	23 (16.5)	0.275
Atrial fibrillation	78 (19.3)	56 (21.1)	22 (15.8)	0.199
Coronary artery disease	12 (3.0)	7 (2.6)	5 (3.6)	0.591
COPD/asthma	6 (1.5)	3 (1.1)	3 (2.2)	0.413
End-stage renal disease	11 (2.7)	3 (1.1)	8 (5.8)	0.007
Echocardiographic parameters				
LV end-diastolic dimension (mm)	56.0 (52.0–60.0)	56.0 (53.0–60.0)	56.0 (52.0–60.0)	0.536
LV end-systolic dimension (mm)	35.0 (32.0–38.0)	35.0 (32.0–38.0)	35.0 (31.0–38.0)	0.954
LV end-diastolic volume (mL)	125.7 (98.2–155.7)	125.9 (100.0–158.2)	123.6 (95.4–151.7)	0.430
LV end-systolic volume (mL)	45.0 (34.3–58.9)	46.0 (32.3–58.3)	42.9 (30.9–58.9)	0.175
LV ejection fraction (%)	61.0 (57.0–64.3)	61.0 (57.0–64.0)	61.0 (56.0–65.0)	0.541
Interventricular septal wall thickness (mm)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	10.0 (9.0–11.0)	<0.001
Posterior LV wall thickness (mm)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.4 (9.0–10.0)	<0.001
E velocity (m/s)	1.05 (0.84–1.30)	1.01 (0.84–1.25)	1.10 (0.84–1.30)	0.293
e' velocity (cm/s)	8.0 (7.0–10.0)	10.0 (8.0–11.0)	6.0 (5.0–7.0)	<0.001
E/e' ratio	12.6 (9.28–17.1)	10.4 (8.37–13.7)	17.5 (14.0–22.2)	<0.001
A velocity (cm/s)	0.60 (0.50–0.80)	0.59 (0.47–0.70)	0.70 (0.52–0.86)	<0.001
E/A ratio	1.67 (1.30–2.22)	1.75 (1.35–2.25)	1.53 (1.12–2.00)	0.005
TR peak velocity (m/s)	2.45 (2.18–2.83)	2.40 (2.12–2.74)	2.45 (2.24–3.04)	0.008
Pulmonary arterial systolic pressure (mmHg)	33.0 (29.0–42.0)	32.0 (28.0–40.0)	35.0 (30.8–47.3)	0.003
Left atrial dimension index (mm/m²)	27.5 (24.2–31.3)	26.7 (23.4–31.0)	29.1 (25.5–31.6)	<0.001
Left atrial volume index (mL/m²)	54.1 (37.1–75.4)	54.7 (36.4–74.1)	52.8 (39.7–76.5)	0.711

Values are presented as median (interquartile range) or number (%).
The MIDA score ranged from 0 to 12 depending on the total score of the risk factors (age ≥65 years, 3 points; symptoms, 3 points; atrial fibrillation, 1 point; LV ejection fraction ≤60%, 1 point; LV end-systolic dimension ≥40 mm, 1 point; left atrial dimension ≥55 mm, 1 point; pulmonary arterial systolic pressure >50 mmHg, 2 points). Symptoms were defined according to the NYHA functional classifications of II–IV.
COPD = chronic obstructive pulmonary disease; E velocity = early diastolic transmitral velocity; ERO = effective regurgitant orifice; e' velocity = early diastolic mitral annular tissue velocity; LV = left ventricular; MIDA = Mitral Regurgitation International Database; MR = mitral regurgitation; NYHA = New York Heart Association; TR = tricuspid regurgitation.

Table 2. Cox proportional hazards regression analysis in patients with primary mitral regurgitation

Outcomes	No. of subjects	No. for event	e' velocity, cm/s (as a continuous variable)			e' velocity ≤7 cm/s (as a categorical variable)		
			aHR[*]	95% CI	p value	aHR[*]	95% CI	p value
All-cause death	404	40	0.770	0.634–0.935	0.008	2.467	1.170–5.200	0.018
Cardiovascular death	404	16	0.690	0.477–0.998	0.049	5.021	1.189–21.211	0.028

aHR = adjusted hazard ratio; CI = confidence interval; e' velocity = early diastolic mitral annular tissue velocity.
[*]Adjusted for age (years), sex, symptoms, hypertension, diabetes mellitus, coronary artery disease, end-stage renal disease, atrial fibrillation, pulmonary arterial systolic pressure >40 mmHg, and left atrial dimension index.

with all-cause death (HR, 2.467; 95% CI, 1.171–5.200; p=0.018; **Supplementary Tables 1** and **3**) and cardiovascular death (HR, 5.021; 95% CI, 1.189–21.21; p=0.028; **Supplementary Tables 2** and **4**). Kaplan-Meier curves demonstrate a significantly higher risk of all-cause and cardiovascular death in patients with e' velocity ≤7 cm/s (both log-rank test p<0.001, **Figure 1**). In multivariate analysis, the e' velocity ≤7 cm/s was an independent predictor for all-cause (HR, 2.190; 95% CI, 1.032–4.647; p=0.041) and cardiovascular death (HR, 2.151; 95% CI, 1.013–4.564; p=0.046; **Table 2**). Furthermore, in the multivariate analysis adjusted by risk factors included in the MIDA score, the e' velocity as a continuous variable and the e' velocity ≤7 cm/s were both independent predictors of all-cause and cardiovascular death in subjects aged <65 years (**Supplementary Tables 5**).

Subgroup analysis and competing risk analysis

In the subgroup analysis by sex, MR severity, MV replacement/repair during follow-up, and symptoms, e' velocity as a continuous variable and e' velocity ≤7 cm/s as a categorical variable were consistently associated with all-cause and cardiovascular death without significant interaction (**Figure 2**). Competing risk analysis, accounting for MV interventions as competing events, demonstrated a consistent trend (**Supplementary Table 6**).

Incremental predictive value of mitral annular tissue velocity

The model performance considerably improved when the e' velocity ≤7 cm/s was added to the modified MIDA mortality risk score, leading to a significantly higher Harrell's C-index for prediction of all-cause death (model with plus 1 point for e' velocity ≤7 cm/s on top of the modified MIDA mortality risk score, 0.635 [95% CI, 0.547–0.723], p=0.004; model with plus 2 points for e' velocity ≤7 cm/s on top of the modified MIDA mortality risk score, 0.657 [95% CI, 0.570–0.744], p=0.008), as well as cardiovascular death (**Table 3**). The NRI and IDI for all-cause and cardiovascular mortality were calculated to assess the incremental predictive value of e' velocity added to the modified MIDA mortality risk score (**Table 3**). Based on the HR of e' velocity ≤7 cm/s in the range of 2.190 (95% CI, 1.032–4.647), we added 1 or 2 points of e' velocity to the modified MIDA mortality risk score. The model including e' velocity ≤7 cm/s
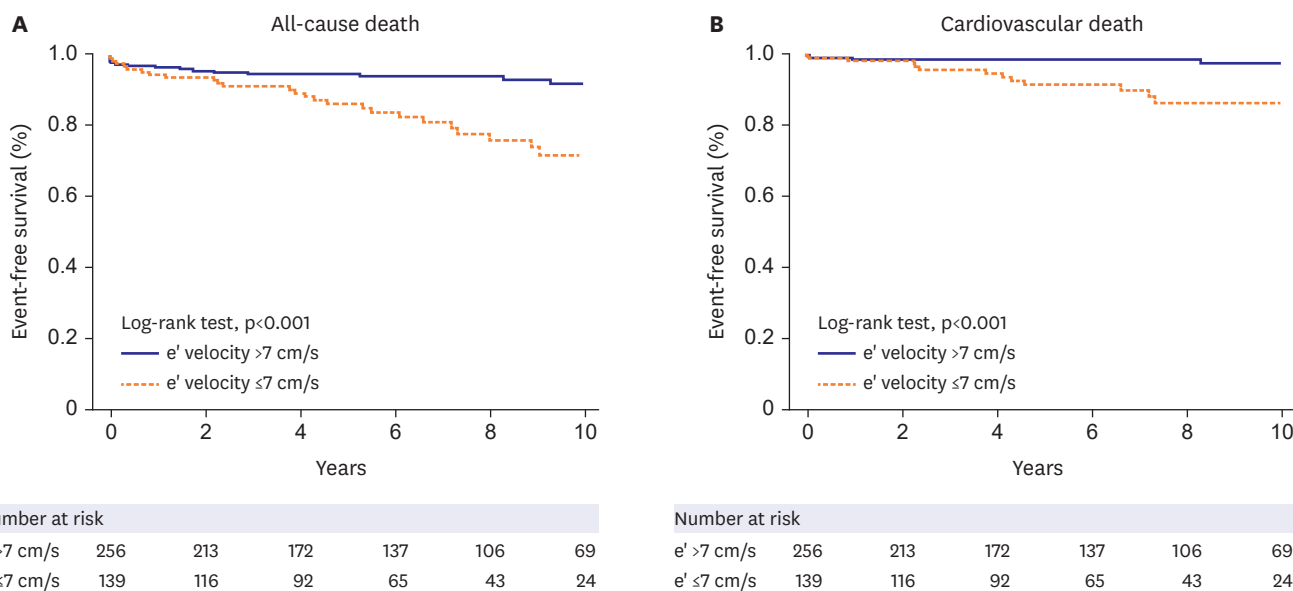

Figure 1. Kaplan–Meier survival curves for (A) all-cause and (B) cardiovascular mortality in patients with degenerative mitral regurgitation.
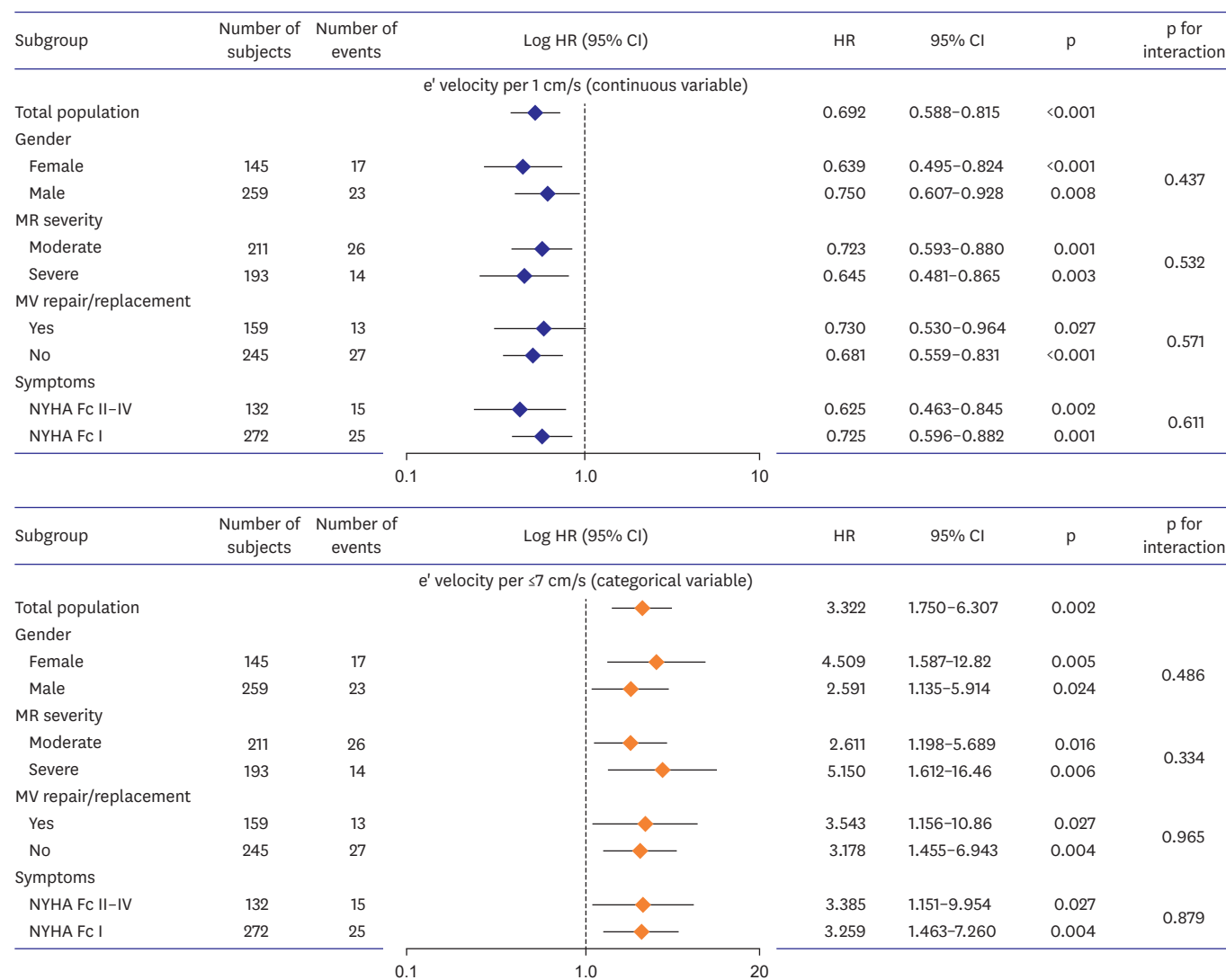e' velocity = early diastolic mitral annular tissue velocity.

Subgroup	Number of subjects	Number of events	Log HR (95% CI)	HR	95% CI	p	p for interaction
			e' velocity per 1 cm/s (continuous variable)				
Total population				0.692	0.588–0.815	<0.001	
Gender							
Female	145	17		0.639	0.495–0.824	<0.001	0.437
Male	259	23		0.750	0.607–0.928	0.008	
MR severity							
Moderate	211	26		0.723	0.593–0.880	0.001	0.532
Severe	193	14		0.645	0.481–0.865	0.003	
MV repair/replacement							
Yes	159	13		0.730	0.530–0.964	0.027	0.571
No	245	27		0.681	0.559–0.831	<0.001	
Symptoms							
NYHA Fc II–IV	132	15		0.625	0.463–0.845	0.002	0.611
NYHA Fc I	272	25		0.725	0.596–0.882	0.001	

0.1　　1.0　　10

Subgroup	Number of subjects	Number of events	Log HR (95% CI)	HR	95% CI	p	p for interaction
			e' velocity per ≤7 cm/s (categorical variable)				
Total population				3.322	1.750–6.307	0.002	
Gender							
Female	145	17		4.509	1.587–12.82	0.005	0.486
Male	259	23		2.591	1.135–5.914	0.024	
MR severity							
Moderate	211	26		2.611	1.198–5.689	0.016	0.334
Severe	193	14		5.150	1.612–16.46	0.006	
MV repair/replacement							
Yes	159	13		3.543	1.156–10.86	0.027	0.965
No	245	27		3.178	1.455–6.943	0.004	
Symptoms							
NYHA Fc II–IV	132	15		3.385	1.151–9.954	0.027	0.879
NYHA Fc I	272	25		3.259	1.463–7.260	0.004	

0.1　　1.0　　20

Figure 2. Subgroup analysis for all-cause death.
CI = confidence interval; e' velocity = early diastolic mitral annular tissue velocity; HR = hazard ratio; MR = mitral regurgitation; MV = mitral valve; NYHA Fc = New York Heart Association functional classification.

Table 3. Incremental predictive power of adding e' velocity over MIDA mortality risk score

Variables	C-index			NRI			IDI		
	Value	95% CI	p value	Value	95% CI	p value	Value	95% CI	p value
All-cause death									
MIDA score	0.597	0.504–0.691	Ref.		Ref.			Ref.	
+ 1 point for e' velocity ≤7 cm/s	0.635	0.547–0.723	0.004	0.469	0.150–0.789	0.004	0.010	0.004–0.015	<0.001
+ 2 points for e' velocity ≤7 cm/s	0.657	0.570–0.744	0.008	0.609	0.308–0.910	<0.001	0.019	0.009–0.030	<0.001
Cardiovascular death									
MIDA score	0.628	0.491–0.765	Ref.		Ref.			Ref.	
+ 1 point for e' velocity ≤7 cm/s	0.675	0.543–0.807	0.004	0.976	0.582–1.369	<0.001	0.007	0.002–0.011	0.002
+ 2 points for e' velocity ≤7 cm/s	0.710	0.580–0.839	0.002	1.018	0.680–1.356	<0.001	0.013	0.005–0.020	<0.001

The MIDA score ranged from 0 to 12 depending on the total score of the risk factors (age ≥65 years, 3 points; symptoms, 3 points; atrial fibrillation, 1 point; LV ejection fraction ≤60%, 1 point; LV end-systolic dimension ≥40 mm, 1 point; left atrial dimension ≥55 mm, 1 point; pulmonary arterial systolic pressure >50 mmHg, 2 points). Symptoms were defined according to the New York Heart Association functional classifications of II–IV.
C-index = concordance index; CI = confidence interval; e' velocity = early diastolic mitral annular tissue velocity; IDI = integrated difference improvement; LV = left ventricular; MIDA = Mitral Regurgitation International Database; NRI = net reclassification improvement.

as 1 point showed an NRI of 0.469 (95% CI, 0.150–0.789; p=0.004) and IDI of 0.010 (95% CI, 0.004–0.015; p<0.001) for all-cause mortality. The model including e' velocity ≤7 cm/s as 2 points revealed an NRI of 0.154 (95% CI, 0.308–0.910; p<0.001) and IDI of 0.019 (95% CI, 0.009–0.030; p<0.001) for all-cause mortality. The NRI and IDI for cardiovascular mortality were statistically significant (**Table 3**).

DISCUSSION

In patients with significant chronic degenerative MR, e' velocity obtained via tissue Doppler imaging was an independent prognosticator of all-cause and cardiovascular mortality, regardless of the determinants of MR surgery outlined in the contemporary guidelines such as symptoms, LV end-systolic dimension and ejection fraction,[3)4)] or the MIDA mortality risk score.[17)] Additionally, the e' velocity had an incremental value for predicting mortality over the MIDA risk score. Current guidelines recommend intervention for primary MR in patients with symptoms or in those with LV systolic dysfunction even if asymptomatic.[3)4)] However, the presence of symptoms in chronic MR may be attributable not only to systolic dysfunction but also, to diastolic dysfunction. Therefore, the criteria for MV surgery in chronic MR that only consider LV dilation or systolic dysfunction may be far from complete.[19)] Thus, our findings that the e' velocity contributes predictive value for long-term prognosis may assist in establishing the optimal timing for surgery in patients with primary MR.

Several pathophysiologic mechanisms are accountable for the development of diastolic dysfunction in valvular heart disease, such as increased ventricular wall stress, myocardial structure alterations, decrease in subendocardial perfusion, and/or diastolic calcium overload.[20)] Ventricular remodeling following chronic MR, which includes LV dilation and eccentric hypertrophy, occurs to accommodate the regurgitant volume with the primary goal of maintaining cardiac output at a physiological level of LV and LA pressure.[21)22)] Regurgitant MR flow increases the end-diastolic volume, altering LV recoil property and leading to a more spherical LV shape, ultimately increasing passive diastolic stiffness.[20)] Moreover, the sarcomere lengthening rate is decreased in chronic MR with a decrease in the restoring force.[23)] Hence, these compensatory mechanisms of the LV in primary MR would be not as smooth as expected in patients with diastolic dysfunction, given that the diastolic properties of the LV are influenced by ventricular geometry, as well as myocardial stiffness.[24)]

The presence of MR itself renders it difficult to reliably assess the LV filling pressure,[8-10)] partially because the mitral and pulmonary vein flow are directly influenced by MR flow.[15)] Moreover, although the early filling is influenced by several physiologic factors, such as LV relaxation, elastic recoil, passive compliance, and LA driving pressure, they could be changed in chronic MR, further increasing the complexity of the early diastolic assessment.[25)] Meanwhile, the e' velocity has long been applied to assess the LV diastolic function based on the assumption that it reflects longitudinal myocardial relaxation, suggesting the potential abnormalities in longitudinal relaxation become evident earlier than a clinical sign of global LV relaxation abnormality.[11)] Considering that the longitudinal tissue velocity of MV annulus during early filling is determined by the LV relaxation rate, decreased e' velocity might indicate that the LV of these patients cannot adequately compensate for the enhanced filling of LV by MR. In the current study, e' velocity was not only valuable for risk stratification of patients with remarkable primary MR but was independent of other echocardiographic parameters indicative of LV function.

In this study, we deliberately excluded older adult patients aged ≥65 years from this study. The significance of age ≥65 years as an independent prognostic factor is well-established, as indicated by the 3-point assignment in the MIDA score. This exclusion was established based on the understanding that e' velocity naturally decreased in the older adult population secondary to the increased degree of myocardial fibrosis with age, coupled with the change of the myocardial energetics.[26][27] Age-related LV diastolic dysfunction arises from increased LV myocardial stiffness and decreased LV compliance.[28] Therefore, an interaction between the e' velocity and age for predicting survival could exist, influenced by the natural changes in the LV diastolic function where the e' velocity is already decreased enough in the elderly and the prognostic impact of e' velocity loses its significance.[29] We believe that this careful selection process ensured a homogenous study population to explore the impact of e' velocity on their prognosis.

There have been major advances in surgical skills and interventional procedures, which may have affected the consideration of intervention in fragile patients who may not have been surgical candidates in the past.[30] Furthermore, surgical risks related to early intervention have considerably decreased. Consequently, there is an essential need for novel criteria and risk stratification strategies in primary MR to identify patients who would benefit from early intervention and/or surgery effectively. We consider the assessment of diastolic dysfunction to be a remaining crucial aspect that requires further attention in this process. Although our findings only provide evidence for the interaction between the e' velocity in those aged <65 years, further prospective studies are warranted to elucidate the clinical significance of diastolic dysfunction at any age.

One of the limitations of this study was its retrospective nature. We retrospectively obtained echocardiographic parameters from various machines, which potentially resulted in measurements depending on the vendor. Despite adjustment for confounders in the multivariable analysis, differences in baseline comorbidities between individuals with normal and abnormal e' velocity could introduce a bias. Second, the diastolic function of the LV may not be fully assessed with e' velocity alone, as e' velocity is partially volume-dependent. However, compared to other parameters commonly used to assess the diastolic function of the LV, such as the Doppler velocities, tissue Doppler is relatively more robust against volume status changes.[11] Furthermore, other parameters of the LV such as the mass index, and TR velocity in our cohort suggest that those with decreased e' velocity are indeed more likely to have a worse diastolic function. Third, we obtained e' velocity at the septal annulus only, and the reliability of e' velocity could be affected by conditions such as poor atrial fibrillation and bundle branch block.[31] However, the septal annular velocity alone is known to correlate very well with LV filling pressure.[21] Furthermore, despite adhering to the e' velocity cutoff as per guidelines, survival analysis confirmed its association with clinical outcomes. Additionally, we incorporated e' velocity as a continuous variable in the analysis to adrress potential limitations. Finally, this study underscored on individuals aged <65 years, further research covering a broader age range is necessary to enhance the generalizability of our findings.

The e' velocity is an independent predictor of long-term survival with an incremental predictive value in chronic primary MR. Thus, assessment of the mitral annular tissue velocity, especially in those aged <65 years, is helpful for the prediction of their prognosis.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1
Detailed methods

Supplementary Table 1
Univariate Cox proportional hazards regression analysis for all-cause death in patients with primary mitral regurgitation

Supplementary Table 2
Univariate Cox proportional hazards regression analysis for cardiovascular death in patients with primary mitral regurgitation

Supplementary Table 3
Multi-variate Cox proportional hazards regression analysis for all cause death in patients with primary mitral regurgitation

Supplementary Table 4
Multi-variate Cox proportional hazards regression analysis for cardiovascular death in patients with primary mitral regurgitation

Supplementary Table 5
Cox proportional hazards regression analysis in patients with primary mitral regurgitation, adjusted for factors included in the MIDA risk score

Supplementary Table 6
Cox proportional hazards competing risks regression

Supplementary Figure 1
Flow chart for the study population. Flow chart showing the definition of the study population and reasons for exclusion.

Supplementary Figure 2
Restricted cubic spline curves for the relationship between e' velocity with all-cause death (A) and cardiovascular death (B).

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