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ORIGINAL PAPER

Visual echocardiographic scoring system of the left ventricular filling pressure and outcomes of heart failure with preserved ejection fraction

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Aims Elevated left ventricular filling pressure (LVFP) is a powerful indicator of worsening clinical outcomes in heart failure with preserved ejection fraction (HFpEF); however, detection of elevated LVFP is often challenging. This study aimed to determine the association between the newly proposed echocardiographic LVFP parameter, visually assessed time difference between the mitral valve and tricuspid valve opening (VMT) score, and clinical outcomes of HFpEF.

Methods and results We retrospectively investigated 310 well-differentiated HFpEF patients in stable conditions. VMT was scored from 0 to 3 using two-dimensional echocardiographic images, and VMT ≥2 was regarded as a sign of elevated LVFP. The primary endpoint was a composite of cardiac death or heart failure hospitalization during the 2 years after the echocardiographic examination. In all patients, Kaplan–Meier curves showed that VMT ≥2 ($n = 54$) was associated with worse outcomes than the VMT ≤1 group ($n = 256$) ($P < 0.001$). Furthermore, VMT ≥2 was associated with worse outcomes when tested in 100 HFpEF patients with atrial fibrillation (AF) ($P = 0.026$). In the adjusted model, VMT ≥2 was independently associated with the primary outcome (hazard ratio 2.60, 95% confidence interval 1.46–4.61; $P = 0.001$). Additionally, VMT scoring provided an incremental prognostic value over clinically relevant variables and diastolic function grading (χ^2 10.8–16.3, $P = 0.035$).

Conclusions In patients with HFpEF, the VMT score was independently and incrementally associated with adverse clinical outcomes. Moreover, it could also predict clinical outcomes in HFpEF patients with AF.

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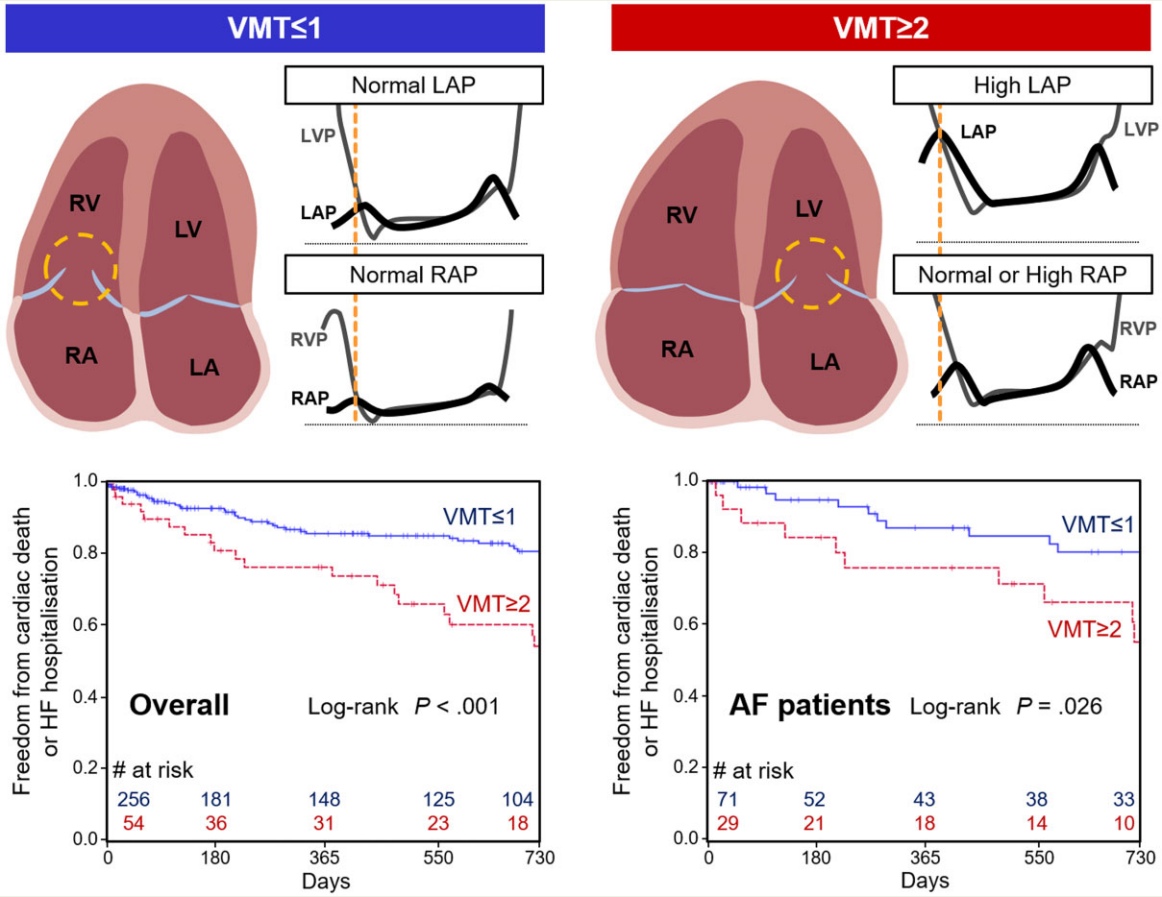
Graphical Abstract



Graphical Abstract Pathophysiology and prognostic impact of VMT scoring in HFpEF patients. Early-diastolic pressure crossover between the left atrial pressure and left ventricular pressure happens earlier with the increase in the LA v wave. In addition, reduced right ventricular (RV) relaxation owing to passive pulmonary hypertension delays early-diastolic pressure crossover between the right atrial pressure and RV pressure. Therefore, early mitral valve opening which precedes tricuspid valve opening pathophysiologically reflects the LAP elevation. HFpEF patients with higher VMT scores were characterized by elevated LAP and subsequent higher RVP, resulting in a higher prevalence of advanced right heart remodelling. As a result, VMT ≥2 was associated with adverse clinical outcomes in HFpEF patients. Notably, VMT ≥2 was also associated with worse outcomes when tested in atrial fibrillation patients. Orange dashed circles indicate the atrioventricular valve which opens earlier in early diastole. Orange vertical lines indicate the timing of pressure crossover between the atrium and ventricle which occurs earlier in early diastole. AF, atrial fibrillation; HF, heart failure; LA, left atrial; LAP, left atrial pressure; LV, left ventricular; LVP, left ventricular pressure; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVP, RV pressure; VMT, visually assessed time difference between mitral and tricuspid valves opening.

Keywords echocardiography • heart failure with preserved ejection fraction • left ventricular filling pressure • VMT score • outcome • prognosis

Introduction

Heart failure with preserved ejection fraction (HFpEF) comprises approximately half of the cases of heart failure (HF),[1] and the morbidity and mortality in HFpEF are similar to that observed in patients with HF with reduced ejection fraction (EF).[2] With limited preferential treatment, HFpEF has been a major global public health problem.[3] Over the past decade, the pathophysiological diversity of HFpEF has been well recognized;[3] however, the presence of left ventricular (LV) diastolic dysfunction manifested by elevated LV filling pressure (LVFP) is a fundamental haemodynamic abnormality in HFpEF.[4,5]

In the outpatient setting, the diagnosis of HFpEF is frequently challenging and relies on identifying direct or indirect evidence of elevated LVFP.[6] In addition, high LVFP in the non-decompensated state is a powerful indicator of worse clinical outcomes in HFpEF patients.[7,8] Therefore, elevated LVFP could be a potential therapeutic target in stable HFpEF patients.[9] Although multiple echocardiographic parameters of LVFP for HFpEF have been proposed, the detection

of elevated LVFP in HFpEF remains challenging.[5,6,10] A recent study highlighted that a two-dimensional echocardiographic scoring system, the visually assessed time difference between mitral valve (MV) and tricuspid valve (TV) opening (VMT) score, was associated with elevation of LVFP in HF patients.[11] We thus hypothesized that the VMT score could be a useful indicator of HFpEF prognosis and aimed to evaluate the association between the VMT scoring and clinical outcomes in patients with HFpEF.

Methods

Study population

This was a retrospective, two-centre, observational study that assessed the VMT score and clinical outcomes in patients with HFpEF. Some participant data from this study have been recently published;[12] however, they were not regarding VMT scoring. Any patients included in the former invasive-echocardiographic study[11] were not included in the present investigation. A total of 27 633 subjects who were referred to the echocardiographic laboratories of the Gunma University Hospital ($n = 17\,507$) or Hokkaido University Hospital ($n = 10\,126$) between January 2014 and December 2018 were screened. HFpEF was defined by the typical clinical symptoms of HF (exertional dyspnoea, fatigue, and oedema), EF ≥50%, and evidence of elevated LVFP [invasively measured pulmonary arterial wedge pressure >15 mmHg, B-type natriuretic peptide (BNP) levels >200 pg/mL or N-terminal pro-BNP >400 pg/mL, E/e′ >15, left atrial (LA) volume index >34 mL/m^2 (see the echocardiographic measurements section for further details), or previous HF hospitalization].[12] Subjects with (i) reduced EF (EF < 50%), (ii) recovered EF (previous EF < 40%), (iii) pulmonary arterial hypertension, (iv) significant left-sided valvular heart disease (>moderate regurgitation, >mild stenosis), (v) previous atrioventricular valve replacement, (vi) acute coronary syndrome, (vii) constrictive pericarditis, (viii) congenital heart disease, or (ix) cardiomyopathies were excluded. From this group, patients with comprehensive echocardiographic evaluation in a compensated state (outpatient or discharge from HF hospitalization) were identified. When patients had multiple echocardiograms during this period, the oldest study was used as an index echocardiographic evaluation. The study was approved by the Institutional Review Boards of the two hospitals.

Data on clinical demographics, medical history, current medications, and laboratory data were extracted from a detailed chart review. Based on a previous study, we defined atrial fibrillation (AF) as AF rhythm in patients during the echocardiographic assessment, that is, current AF.[12]

Echocardiographic examination

A comprehensive echocardiographic examination was performed in accordance with the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines.[13] LV end-diastolic volume, end-systolic volume, EF, and LA volume were measured using the biplane disc summation method. LV mass was calculated by using the Devereux formula. Stroke volume was calculated from the time velocity interval of the LV ejection flow and the diameter of the LV outflow tract. Peak early-diastolic velocity (E), deceleration time of E, and the ratio of the E to the peak late-diastolic velocity (E/A) were measured in the apical LV long-axis view. Early-diastolic mitral annular velocity at the septal annulus (e′) was measured from the apical four-chamber view, and the ratio of E to the septal e′ (E/e′) was calculated. LV isovolumic relaxation time was measured as the time interval between the end of ejection and the onset of the E wave. The right ventricular (RV) to right atrial (RA) pressure gradient was estimated from the peak systolic tricuspid regurgitation (TR) velocity. LV diastolic dysfunction was then segregated into three severity grades, with grades 2/3 diastolic dysfunction regarded as elevated LVFP.[13] In patients with AF, the peak systolic TR velocity >2.8 m/s and E/e′ ratio ≥11 were used to determine LVFP elevation according to the previous reports.[8,11]

In line with our recent study,[11] the VMT score was assessed as a marker of LVFP elevation. Based on earlier opening of the MV than TV in the presence of a higher LVFP compared to RA pressure,[11] this scoring system consists of (i) visual assessment of the time sequence of atrioventricular valve openings and (ii) estimated RA pressure based on inferior vena cava (IVC) findings. Briefly, from the cine loops (6–9 beats) of the apical four-chamber view, the time sequence of the MV and TV openings was visually assessed by slow playback, if necessary, and scored into three grades: 0 = TV opening first, 1 = simultaneous, and 2 = MV opening first. When a marker of abnormal RA pressure (the IVC dimension was >21 mm and collapsed to <20% with quiet inspiration) was observed,[11] 1 point was added and the VMT score was calculated as four grades from 0 to 3 (*Figure 1*). The VMT 2/3 was then regarded as elevated LVFP.[11]

Outcome assessment

All subjects were followed up from the day of echocardiographic examination. The primary endpoint of the current study was a composite of cardiac death and hospitalization for HF. The secondary endpoint was a composite of all-cause mortality and hospitalization for HF. HF hospitalization was defined as dyspnoea and pulmonary oedema on chest X-ray requiring intravenous diuretic treatment.[12] As elevated LVFP and subsequent lung congestion are associated with short-term cardiac events,[14] the observation period was set at 2 years.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median (interquartile range), as appropriate. Parametric one-way analysis of variance with the Tukey–Kramer *post hoc* test or nonparametric Kruskal–Wallis test followed by the Steel–Dwass *post hoc* test were used for comparisons of quantitative variables among the different VMT score groups. Categorical variables were presented as numbers (%) and compared using the χ^2 test or Fisher's exact test, as appropriate. Survival curves were constructed using Kaplan–Meier estimates and compared using the log-rank test. The independent prognostic power of the VMT scoring was assessed using univariable and multivariable Cox proportional hazards models, in which non-normally distributed data were log-transformed. The covariates in the multivariable model were chosen from the well-established predictors of adverse events in HF.[12,15] The variables with a *P*-value <0.05, in the univariate analyses, were entered into the multivariable models. E/e′ and LV mass index were also entered into the multivariable models based on a priori knowledge.[4] To avoid overfitting, the number of covariates that were incorporated into the multivariable model was limited to five based on the number of events for the primary composite endpoints and we constructed three independent multivariable models: (i) model 1 adjusted for age, systolic blood pressure, LV mass index, and LV diastolic dysfunction grade by the 2016 ASE/EACVI recommendations; (ii) model 2 adjusted for age, history of HF, BNP level, and E/e′; (iii) model 3 adjusted for age, history of HF, LV mass index, and E/e′. The incremental prognostic value of the VMT score was defined by a significant increase in the global χ^2 value, c-index, and the continuous net reclassification improvement. All statistical analyses were conducted using IBM SPSS version 25 for Windows (IBM Co., Armonk, NY, USA) and R software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). For all tests, the threshold for significance was set at *P*-value <0.05.

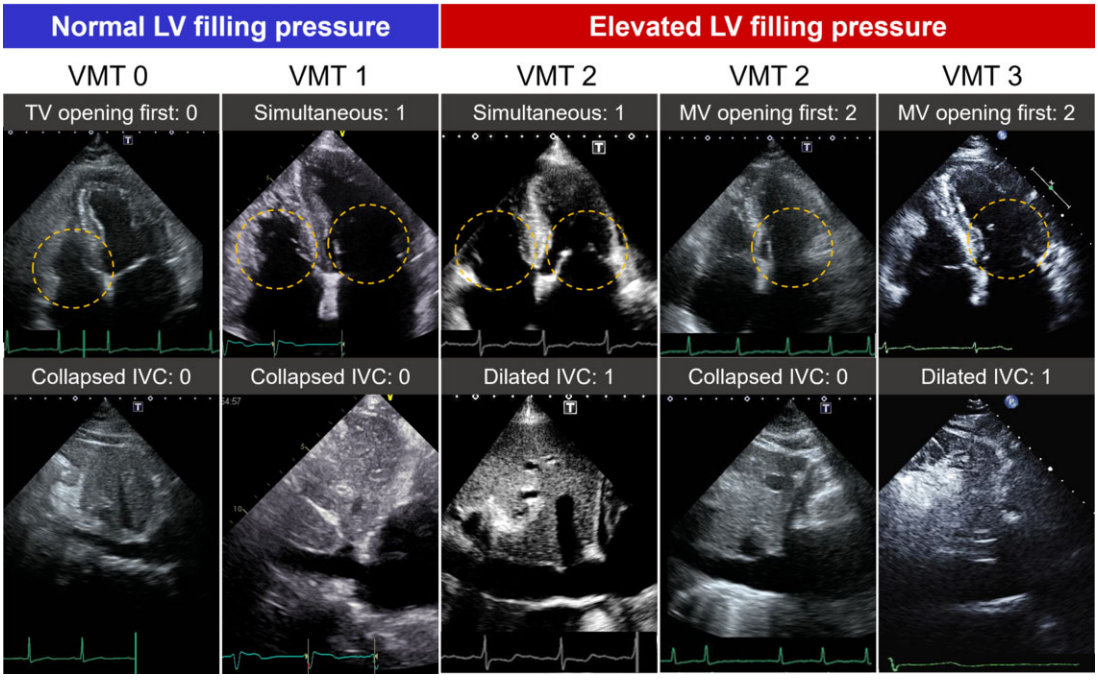


Figure 1 VMT scoring. Apical four-chamber views in early diastole (upper panels) and corresponding subcostal views (lower panels) are presented. Time sequence of opening of MV and TV was visually assessed in the apical four-chamber view and scored as follows: 0, TV opening first; 1, simultaneous; and 2, MV opening first. When the IVC diameter was >21 mm and collapsed to <20% during normal respiration, 1 point was added and VMT score was calculated as 4 grades from 0 to 3. Orange dashed circles highlight the atrioventricular valves which open in early diastole. IVC, inferior vena cava; LV, left ventricular; MV, mitral valve; TV, tricuspid valve; VMT, visually assessed time difference between MV and TV opening.

Results

Patient characteristics according to VMT score

Of 335 HFpEF patients who met the inclusion criteria, 25 were excluded because of the lack of available echocardiographic images, and the remaining 310 patients participated in the final analysis. *Table 1* displays patient demographics according to the VMT score. Because the echocardiographic data were obtained in a haemodynamically stable state, a small proportion of the patients were judged to have elevated LVFP, that is, VMT score of 2 (50 patients, 16%) or VMT score of 3 (4 patients, 1%). When the clinical demographics were compared among VMT 0, 1, and 2/3, higher VMT scores were associated with a higher prevalence of current AF, more frequent use of implantable cardiac devices, and higher BNP level. The use of neurohormonal antagonists and diuretics was similar among the groups.

Cardiac structure and function according to VMT score

Table 2 displays cardiac structure and function according to the VMT score. While LV volume was increased in patients with VMT 2/3, LV wall thickness and EF were similar among the groups, resulting in greater LV mass index and stroke volume in this group. Mitral E wave velocity, E/A, LA volume index, TR pressure gradient, and E/e′ were increased, and the deceleration time of the E wave and LV isovolumic relaxation time were shortened in accordance with the VMT score, resulting in the higher prevalence of elevated LVFP judged by the 2016 ASE/EACVI recommendations in VMT 2/3. There was an increase in the prevalence of significant mitral regurgitation in the higher VMT scores. RV dimensions and RA volume were also increased with the VMT score which could be associated with a higher prevalence of significant TR in VMT 2/3. While RV systolic function was similar between the groups, the VMT 2/3 was characterized by a larger IVC diameter and lower its respiratory change.

VMT score and clinical outcomes

During a follow-up period of 2 years, 55 primary composite endpoints (18%) occurred, including 4 cardiac deaths and 51 HF hospitalizations. The causes of the non-cardiac 24 deaths were cancer ($n = 6$), unknown ($n = 5$), pneumonia ($n = 4$), liver injury ($n = 3$), multiple organ dysfunction ($n = 1$), polycythaemia vera ($n = 1$), sepsis ($n = 1$), intracerebral haemorrhage ($n = 1$), ruptured aortic aneurysm ($n = 1$), and lymphatic diseases ($n = 1$). *Figure 2* shows the Kaplan–Meier event-free curves according to the VMT score for the primary and secondary composite endpoints. Patients with VMT ≥2 had worse outcomes than those with VMT ≤1 in the overall cohort. Notably, similar results were observed in patients with AF. In

Table 1 Patients' demographics according to VMT score

	All patients	VMT 0	VMT 1	VMT 2 or 3	*P*-value
Number, *n* (%)	310	55 (18)	201 (65)	54 (17)	NA
Age (years)	74 ± 12	71 ± 15	74 ± 12	75 ± 10	0.285
Female, *n* (%)	154 (50)	30 (55)	101 (50)	23 (43)	0.442
Body mass index (kg/m^2)	22 ± 4	21 ± 3	23 ± 5[a]	23 ± 4[a]	0.009
Systolic blood pressure (mmHg)	127 ± 21	129 ± 20	128 ± 21	121 ± 22	0.090
Heart rate (bpm)	74 ± 17	72 ± 16	74 ± 17	75 ± 17	0.484
History of HF hospitalization	194 (63)	38 (69)	126 (63)	30 (56)	0.344
Comorbidity, *n* (%)					
Hypertension	251 (81)	44 (80)	164 (82)	43 (80)	0.895
Coronary artery disease	71 (23)	15 (27)	46 (23)	10 (19)	0.554
Current atrial fibrillation	100 (32)	1 (2)	70 (35)	29 (54)	<0.001
Diabetes mellitus	100 (32)	16 (29)	68 (34)	16 (30)	0.722
Cardiac implantable electrical devices	22 (7)	6 (11)	8 (4)	8 (15)	0.011
Medications, *n* (%)					
ACEI or ARB	149 (48)	27 (49)	95 (47)	27 (50)	0.925
Beta-blocker	132 (43)	28 (51)	79 (39)	25 (46)	0.253
Diuretic	207 (67)	35 (64)	132 (66)	40 (74)	0.438
Mineralocorticoid receptor antagonists	116 (37)	22 (40)	71 (35)	23 (43)	0.563
Laboratories					
Haemoglobin (g/dL)	11.6 ± 2.3	11.3 ± 2.1	11.7 ± 2.3	11.5 ± 2.4	0.454
Albumin (g/dL)	3.7 (3.3–4.0)	3.7 (3.4–4.1)	3.7 (3.2–4.0)	3.8 (3.2–4.1)	0.685
Creatinine (mg/dL)	0.9 (0.7–1.3)	0.9 (0.7–1.1)	0.9 (0.7–1.3)	1.0 (0.7–1.5)	0.521
B-type natriuretic peptide (pg/mL)	193 (92–371)	108 (45–283)	191 (100–361)[a]	321 (163–472)[a,b]	<0.001
γ-Glutamyl transferase (IU/L)	28 (17–52)	25 (16–43)	27 (18–51)	34 (17–72)	0.139
Total bilirubin (mg/dL)	0.7 (0.5–0.9)	0.6 (0.5–0.8)	0.7 (0.5–0.8)	0.7 (0.6–1.1)	0.035

Continuous data are expressed as mean ± standard deviation if normally distributed and as median (interquartile range) if not normally distributed, whereas categorical data are presented as *n* (%). *P*-values are from analysis of variance, Kruskal–Wallis test, or χ^2 test.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; HF, heart failure; VMT, visually assessed time difference between mitral and tricuspid valves opening.
[a]$P < 0.05$ vs. VMT score 0.
[b]$P < 0.05$ vs. VMT score 1 by Tukey–Kramer's or Steel–Dwass' *post hoc* test.

univariable Cox proportional hazard analyses, VMT ≥2 was associated with an increased risk of the primary composite endpoint along with age; systolic blood pressure; history of HF hospitalization; BNP levels; and the 2016 ASE/EACVI recommendations (*Table 3*). Importantly, the association of the VMT ≥2 with the primary composite endpoint remained significant after adjustment for age, systolic blood pressure, LV mass index, and the 2016 ASE/EACVI recommendations (model 1); age, history of HF hospitalization, BNP level, and E/e′ (model 2); and age, history of HF hospitalization, LV mass index, and E/e′ (model 3).

Incremental prognostic value of the VMT scoring over the 2016 ASE/EACVI recommendations

VMT scoring stratified the 77 patients with indeterminate LVFP according to the 2016 ASE/EACVI recommendations [normal: 61 (79%), elevated: 16 patients (21%)]. Of these, the reclassified high LVFP group showed a significantly higher incidence of the secondary composite endpoint ($P = 0.005$), while the differences in primary composite endpoint did not reach statistical significance ($P = 0.096$) (*Figure 3*). Additionally, we analysed the incremental predictive ability of the VMT scoring over the 2016 ASE/EACVI recommendations for the primary composite endpoint. The nested regression model showed that VMT ≥2 had significant incremental value in addition to clinically relevant factors (age, sex, BNP level, AF), and elevated LVFP judged by the 2016 ASE/EACVI recommendations for the prediction of the primary composite endpoint (*Figure 4*). Furthermore, adding the VMT scoring to the 2016 ASE/EACVI recommendations also resulted in an improvement of the prediction model with the c-index (*Figure 5*) and net reclassification improvement of 0.42 (95% confidence interval 0.15–0.68; $P = 0.002$).

Discussion

Our findings can be summarized as follows: (i) patients with higher VMT scores were characterized by a higher prevalence of AF, severe LV diastolic dysfunction, and greater right heart remodelling; (ii) VMT

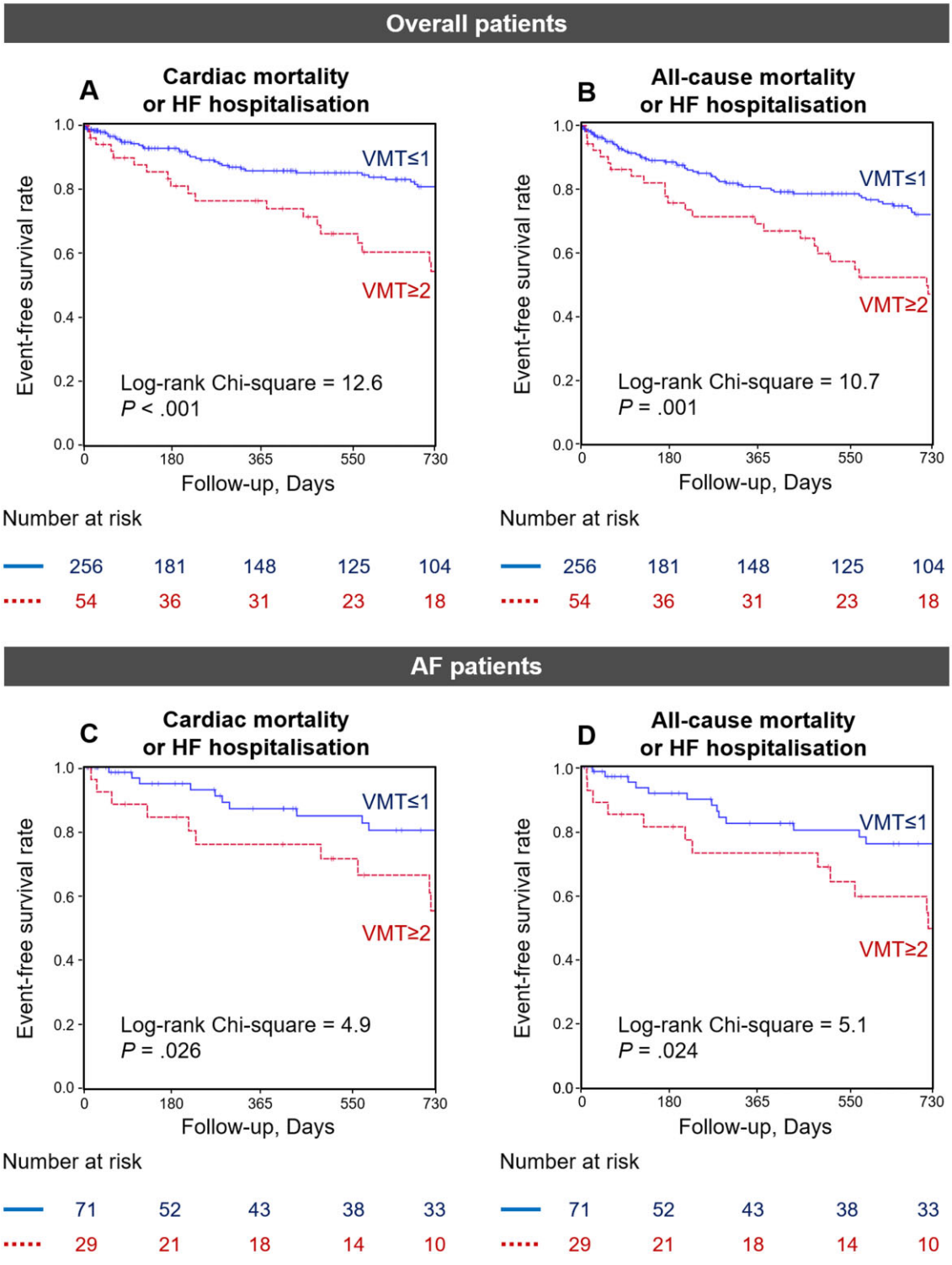


Figure 2 Kaplan–Meier analysis of event-free survival. (*A*) A composite outcome of cardiac mortality or HF hospitalization in the overall patients, (*B*) a composite outcome of all-cause mortality or HF hospitalization in the overall patients, (*C*) a composite outcome of cardiac mortality or HF hospitalization in AF patients, and (*D*) a composite outcome of all-cause mortality or HF hospitalization in AF patients. AF, atrial fibrillation; HF, heart failure; VMT, visually assessed time difference between mitral valve and tricuspid valve opening.

Table 2 Cardiac structure and function stratified by VMT score

	All patients	VMT 0	VMT 1	VMT 2 or 3	*P*-value
Number, *n* (%)	310	55 (18)	201 (65)	54 (17)	NA
Left heart					
LV end-diastolic volume (mL)	89 ± 35	94 ± 36	84 ± 32	104 ± 39[a]	0.001
Interventricular septal thickness (mm)	10 ± 2	10 ± 2	10 ± 2	11 ± 3	0.271
LV mass index (g/m^2)	105 ± 31	107 ± 30	102 ± 32	114 ± 31[a]	0.049
LV ejection fraction (%)	61 ± 7	60 ± 6	61 ± 7	62 ± 7	0.351
Stroke volume (mL)	52 ± 19	53 ± 18	49 ± 17	62 ± 24[a,b]	<0.001
E (cm/s)	84 ± 25	60 ± 21	86 ± 25[b]	99 ± 29[a,b]	<0.001
E/A	0.8 (0.7–1.2)	0.7 (0.5–0.8)	0.9 (0.7–1.3)[b]	1.2 (0.8–1.9)[b]	<0.001
Deceleration time of E (ms)	207 ± 75	244 ± 76	202 ± 70[b]	189 ± 90[b]	<0.001
Isovolumic relaxation time (ms)	82 ± 34	108 ± 41	78 ± 33[b]	69 ± 29[b]	<0.001
e′ (cm/s	5.6 ± 2.1	4.5 ± 1.6	5.8 ± 2.2[b]	5.9 ± 2.1[b]	<0.001
E/e′	16.2 ± 6.1	14.5 ± 5.3	16.0 ± 5.9	18.4 ± 7.6[a,b]	0.005
LA volume index (mL/m^2)	50 (34–65)	38 (28–48)	51 (32–64)[b]	64 (51–76)[a,b]	<0.001
Tricuspid regurgitant pressure gradient (mmHg)	27 ± 9	24 ± 7	26 ± 9	33 ± 11[a,b]	<0.001
LA pressure judged by the guidelines, *n* (%)					<0.001
Elevated LA pressure	118 (38)	13 (24)	74 (37)	31 (57)	
Normal LA pressure	115 (37)	38 (69)	70 (35)	7 (13)	
Indeterminate LA pressure	77 (25)	4 (7)	57 (28)	16 (30)	
Significant mitral regurgitation, *n* (%)	24 (8)	1 (2)	12 (6)	11 (20)	<0.001
Right heart					
RV basal diameter (mm)	36 ± 8	33 ± 6	35 ± 8	40 ± 7[a,b]	<0.001
RV mid diameter (mm)	29 ± 7	27 ± 6	28 ± 7	32 ± 7[a,b]	<0.001
TAPSE (mm)	18 ± 5	18 ± 5	18 ± 5	16 ± 6	0.103
RA maximum volume (mL)	38 (25–56)	25 (16–36)	37 (25–53)[b]	60 (41–93)[a,b]	<0.001
IVC dimension (mm)	16 ± 5	13 ± 4	15 ± 5[b]	19 ± 6[a,b]	<0.001
IVC respiratory change (%)	47 ± 19	53 ± 17	48 ± 18	37 ± 25[a,b]	<0.001
Significant tricuspid regurgitation, *n* (%)	63 (20)	7 (13)	37 (18)	20 (37)	0.003

Continuous data are expressed as mean ± standard deviation if normally distributed and as median (interquartile range) if not normally distributed. *P*-values are from analysis of variance or Kruskal–Wallis test.
E, early-diastolic transmitral flow velocity; E/A, the ratio of E to late-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; IVC, inferior vena cava; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; VMT, visually assessed time difference between mitral and tricuspid valves opening.
[a]$P < 0.05$ vs. VMT score 1 by Tukey–Kramer's or Steel–Dwass' *post hoc* test.
[b]$P < 0.05$ vs. VMT score 0.

≥2 was associated with adverse clinical outcomes even after adjusting for established prognostic markers in HFpEF patients; and (iii) VMT scoring improved the predictive ability of clinical outcomes when used in addition to the diastolic function grading recommended by ASE/EACVI. Importantly, the VMT score was predictable in patient subgroups of complicating AF and those in whom LVFP was indeterminate according to the guidelines. Although the association of VMT score and clinical outcome has been found in a previous study,[11] the present findings first elucidated the application of VMT score for well-differentiated HFpEF patients.

Prognostic impact of elevated LVFP on HFpEF

Elevated LVFP indicates two pathophysiological abnormalities: the congestive state to be managed to reduce the cardiac overload and the severe diastolic dysfunction which requires a high filling pressure to maintain adequate cardiac output even after optimal management. Because both of these are prone to haemodynamic stress, elevated LVFP in the non-decompensated state should be a powerful indicator of worsening HF.[7,8] In fact, signs of elevated LVFP, such as the presence of lung congestion,[16] invasively measured pulmonary artery wedge pressure,[7] and echocardiographic diastolic function[4] assessed in a stable state are recognized as prognostic markers in hospitalized HF patients irrespective of EF. The prognostic significance of diastolic function grading in line with the ASE/EACVI algorithms in patients regardless of EF has recently been recognized.[15,17] Considering that elevated LVFP requires intensive management, this condition could be an important therapeutic target in stable HFpEF patients.[9] Accordingly, non-invasive assessment of LVFP remains a critical issue in outpatient HFpEF clinics.

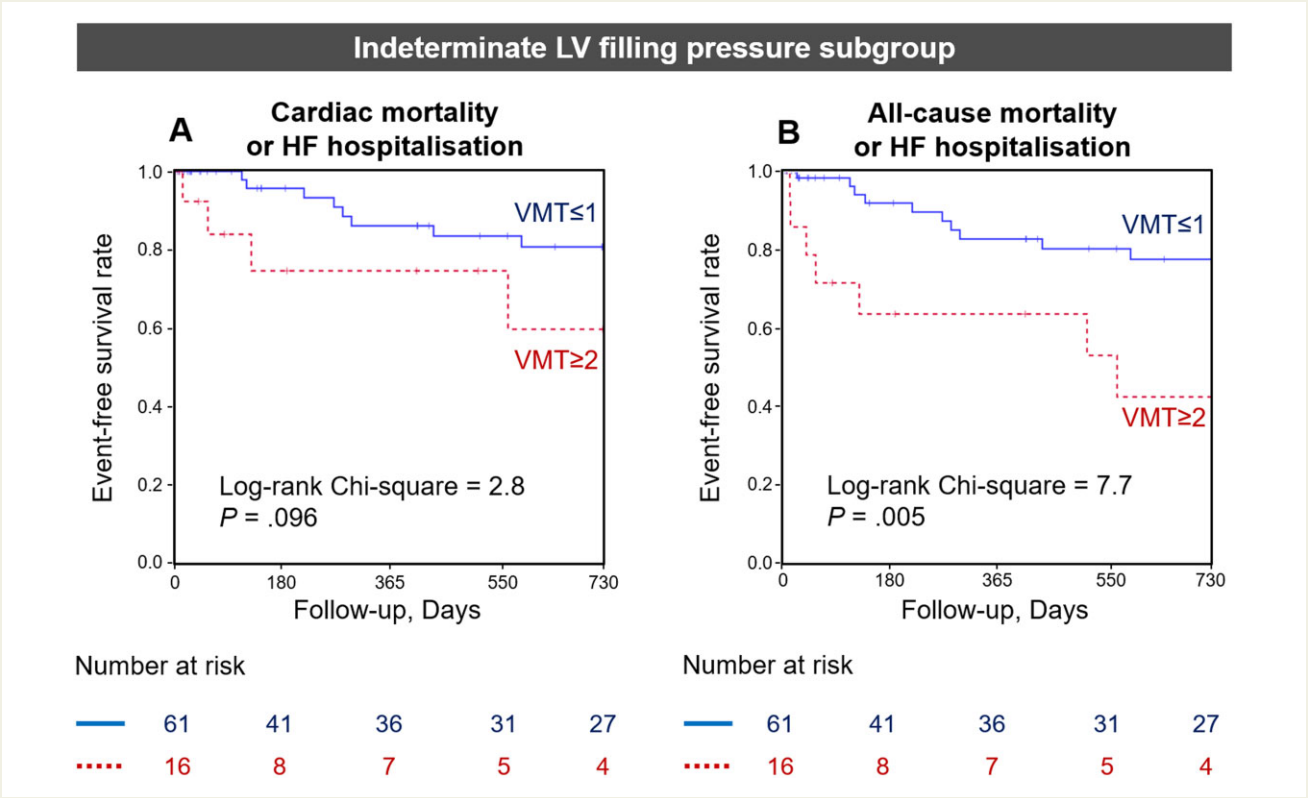


Figure 3 Kaplan–Meier analysis of event-free survival in indeterminate LV filling pressure subgroup by the 2016 ASE/EACVI guidelines. (*A*) A composite outcome of cardiac mortality or HF hospitalization and (*B*) a composite outcome of all-cause mortality or HF hospitalization. HF, heart failure; LV, left ventricular; VMT, visually assessed time difference between mitral valve and tricuspid valve opening.

Echocardiographic diagnosis of elevated LVFP in HFpEF

Over the last few decades, various echocardiographic parameters have been established as markers of LVFP, and echocardiography plays a critical role in the evaluation of LVFP and management of patients with HF.[13] However, despite a large body of accumulated evidence, the diagnosis of elevated LVFP in HFpEF patients is often challenging.[5,6,10] While the algorithm recommended by the current guidelines has been invasively validated in large multicentre studies both in HF with reduced EF and HFpEF,[18] there is a substantial population of HFpEF patients in whom the algorithm cannot be applied because of monophasic LV inflow such as AF.[8,13] Moreover, ~10–20% of HFpEF patients were reported to be judged as undetermined LVFP mainly because of unavailability or discrepancy of the measurers.[8,15] Although E/A and E/e′ are the main parameters to distinguish elevated LVFP in the current guidelines,[13] their associations with invasively measured LVFP have been reported to be weak in HFpEF patients.[6,10,19] Besides, one might speculate that significant mitral annular calcification, which is often coincident in elderly HFpEF patients, could deteriorate the value of E/e′.[20] Although LV isovolumic relaxation time is related to the VMT score, they might show somewhat different behaviours. In healthy individuals, a short isovolumic relaxation time is observed resulting from rapid LV relaxation, which is similar to patients with elevated LVFP.[13] The VMT score, on the other hand, conceptually shows 0 or 1 in patients with normal LVFP because the early-diastolic opening of TV usually precedes that of MV under normal conditions because of the differences of pulmonary to systemic blood pressure.[11] Therefore, the VMT score might be considered as an indicator that escapes the pseudo-normalization compared to the conventional parameters such as isovolumic relaxation time and E/A.

In the present study, we applied VMT scoring, which is a novel parameter of LVFP[11] and found that VMT ≥2 was associated with future cardiac events in a well-differentiated HFpEF population even after adjusting for other established risk markers. Notably, VMT ≥2 was still prognostic even in the subgroup where the guideline-recommended algorithm was judged as indeterminate LVFP as well as in AF patients. As a result, VMT scoring showed an incremental prognostic value for the algorithm. Based on the substantial HFpEF population in whom the algorithm cannot be applied, VMT scoring is expected to add a diagnostic option for HFpEF patients.

VMT scoring and prognosis in HFpEF

Along with the association between VMT scoring and LVFP, we observed concomitant changes in cardiac structures with an increase in VMT score in the current study, that is, a higher TR pressure gradient and significant chamber remodelling in the right heart with a higher VMT score (*Table 2*). As deterioration in the right heart structure and function associated with post-capillary

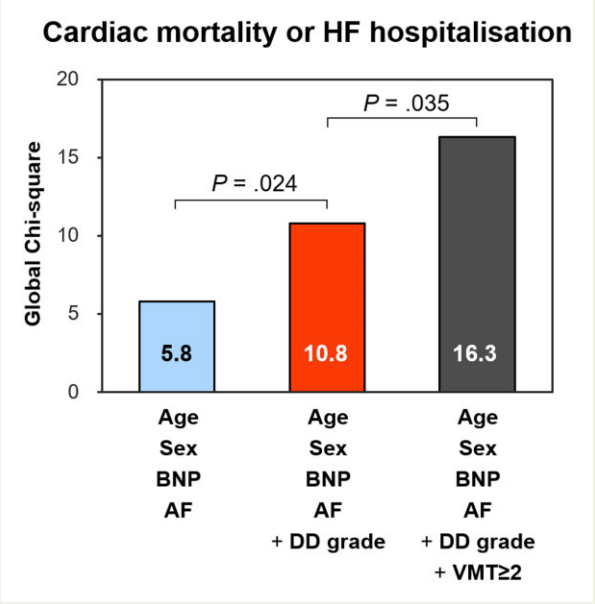


Figure 4 Incremental prognostic value of VMT score. Addition of VMT score to clinical variables (age, sex, BNP, AF) and DD grade significantly increased the predictive ability for cardiac mortality or HF hospitalization. AF, atrial fibrillation; BNP, B-type natriuretic peptide; DD grade, LV diastolic dysfunction grade by the 2016 ASE/EACVI recommendations; HF, heart failure; LV, left ventricular; VMT, visually assessed time difference between mitral valve and tricuspid valve opening.

pulmonary hypertension is common and contributes to reduced aerobic capacity and poor prognosis in HFpEF patients,[3,4] worse clinical outcomes with higher VMT scores would be accentuated by right heart remodelling due to passive pulmonary hypertension in addition to elevated LVFP at the time of echocardiography. Additionally, several studies have demonstrated that plethoric IVC identifies patients with adverse outcomes irrespective of LV EF.[14] Therefore, the association between higher VMT scores and adverse clinical outcomes is physiologically plausible.

Clinical implications

Optimal reduction of LVFP with diuretics, vasodilator, and optimal neurohormonal antagonist therapies is one of the limited options for the relief of symptoms and reduced readmission in HFpEF patients. Recently developed transcatheter intracardiac shunt device showed favourable results in HFpEF patients.[21] LVFP is thus a key therapeutic target in HFpEF patients, and accurate detection of elevated LVFP is pivotal for their management.[9] The VMT score is expected to provide an accurate detection of elevated LVFP in these patients. In particular, VMT scoring could be an additional option for precise risk stratification of HFpEF patients complicating AF and those with indeterminate LVFP according to the 2016 ASE/EACVI recommendations.

Study limitations

This study has some limitations. First, this was a retrospective study from tertiary referral centres; hence, has inherent flaws related to selection and referral bias. Second, because the echocardiographic data were obtained in a haemodynamically stable state, the sample size of patients with a VMT score of 2 was modest, and those showing a VMT score of 3 were very few, resulting in a potential increase in the risk of failing to detect a significant group difference. The relatively small sample included multivariable corrections in the outcome analyses. Third, the results of the VMT scoring are dependent on the temporal resolution of the two-dimensional echocardiogram. Therefore, simultaneous atrioventricular valve opening should be interpreted with caution especially in insufficient frame rate, and if necessary, high temporal resolution methods such as dual-Doppler

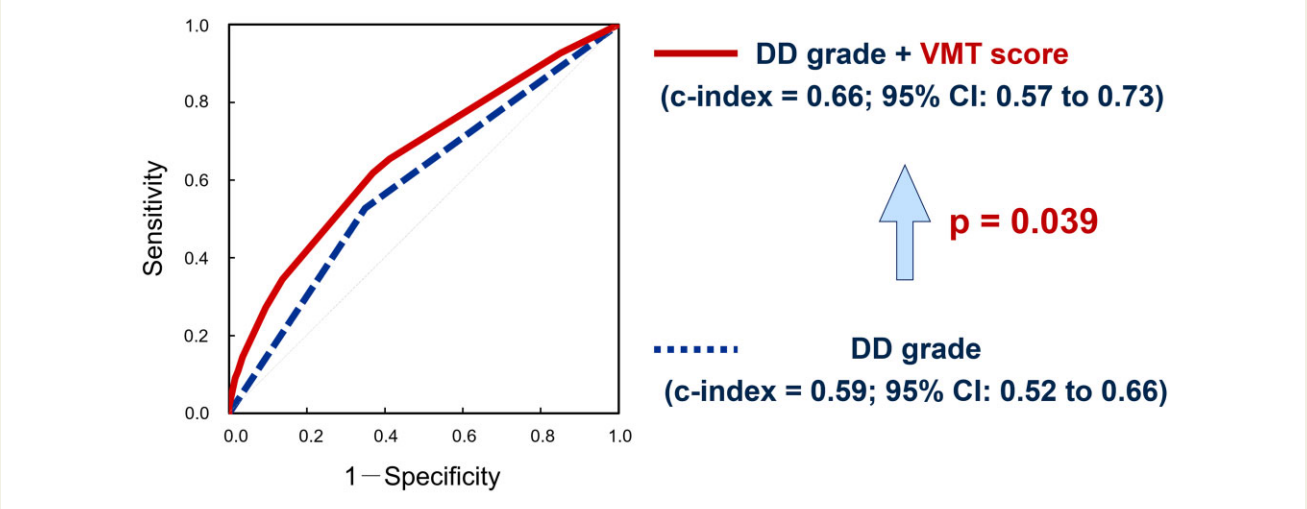


Figure 5 Receiver operating curve analysis of incremental association value of the VMT score when added to the LV diastolic dysfunction grade by the 2016 ASE/EACVI recommendations. CI, confidence interval; DD grade, LV diastolic dysfunction grade by the 2016 ASE/EACVI recommendations; LV, left ventricular; VMT, visually assessed time difference between mitral valve and tricuspid valve opening.

Table 3 Univariate and multivariate Cox proportional hazards for the association with the cardiac death or HF hospitalization

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (per 1 year)	1.03 (1.00–1.05)	0.032	1.03 (1.00–1.06)	0.025	1.02 (0.99–1.05)	0.091	1.03 (1.01–1.06)	0.018
Female	0.94 (0.55–1.59)	0.815						
Body mass index (per 1 kg/m^2)	0.93 (0.87–1.00)	0.052						
Systolic BP (per 1 mmHg)	0.99 (0.97–0.99)	0.037	0.99 (0.97–1.00)	0.078				
Heart rate (per 1 bpm)	0.99 (0.97–1.01)	0.212						
History of HF hospitalization	3.42 (1.68–6.99)	<0.001			4.16 (1.86–9.28)	<0.001	3.26 (1.59–6.68)	0.001
Hypertension	1.22 (0.59–2.49)	0.583						
Coronary artery disease	1.24 (0.68–2.24)	0.479						
Current atrial fibrillation	1.14 (0.66–1.98)	0.640						
Diabetes mellitus	0.91 (0.51–1.61)	0.740						
ACEI or ARB	1.09 (0.65–1.86)	0.737						
Beta-blocker	0.78 (0.45–1.33)	0.357						
MRA	1.10 (0.64–1.89)	0.727						
Creatinine (per 1 mg/dL)	1.25 (0.99–1.57)	0.053						
Log BNP (per 1.0 log unit)	1.64 (1.26–2.14)	<0.001			1.51 (1.12–2.05)	0.007		
LV mass index (per 1 g/m^2)	1.01 (1.00–1.02)	0.062	1.01 (1.00–1.01)	0.149			1.01 (0.99–1.01)	0.191
E/e′ (per unit)	1.03 (0.99–1.06)	0.181			1.00 (0.96–1.04)	0.979	1.01 (0.97–1.04)	0.693
Elevated LAP by the guidelines	1.91 (1.12–3.24)	0.017	1.46 (0.84–2.53)	0.181				
Significant MR	1.56 (0.67–3.65)	0.302						
VMT ≥2	2.64 (1.51–4.59)	<0.001	1.96 (1.08–3.54)	0.026	2.29 (1.24–4.23)	0.008	2.60 (1.46–4.61)	0.001

Model 1: adjusted for age, systolic blood pressure, LV mass index, and elevated LAP by guidelines. Model 2: adjusted for age, history of HF, BNP level, and E/e′. Model 3: adjusted for age, history of HF, LV mass index, and E/e′.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BP, blood pressure; BNP, plasma brain natriuretic peptide; CI, confidence interval; E, early-diastolic transmitral flow velocity; e′, early-diastolic mitral annular velocity; HF, heart failure; HR, hazard ratio; LAP, left atrial pressure; LV, left ventricular; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; VMT, visually assessed time difference between mitral and tricuspid valves opening.

echocardiography assessment might be needed. Fourth, LA reservoir and pump strain analyses which have been known as a marker of LVFP[22] were not performed in this study. Finally, LVFP is often normal at rest but becomes elevated only during exercise stress in patients with HFpEF.[5,6] Further studies are expected to elucidate the diagnostic utility of VMT scoring for detecting elevated LVFP during exercise.

Conclusions

Higher VMT scores were associated with adverse clinical outcomes of HFpEF. Notably, the VMT scoring was prognostic in patients with AF and those with indeterminate LVFP status. Additionally, the VMT scoring showed an incremental benefit over the clinical variables and the 2016 ASE/EACVI recommendations for predicting clinical outcomes. Our findings provide evidence that incorporating VMT scoring with the algorithms as one of the LVFP markers may provide additional prognostic information for the management of HFpEF patients.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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