



Mitral peak early diastolic filling velocity to deceleration time ratio as a predictor of prognosis in patients with chronic heart failure and preserved or reduced ejection fraction

Flora Pirozzi, Antonella Paglia, Laura Sasso, Pasquale Abete, Angelo Carlomagno, Carlo G Tocchetti, Domenico Bonaduce, Mario Petretta

Department of Translational Medical Sciences, Section of Internal Medicine, Federico II University, Naples, Italy

Abstract

Objective Doppler derived mitral peak early diastolic filling velocity to deceleration time ratio (E/DT) has been proposed as parameter for predicting prognosis in general population. This study prospectively investigates the incremental prognostic value of E/DT over clinical, conventional echocardiographic and mitral-Doppler variables in patients hospitalized for decompensated heart failure (HF). **Methods** We analyzed 95 HF patients (mean age 64.8 ± 12.2 years) hospitalized at our institution from January 2010 to March 2012. The primary end-point was cardiac death or hospitalization, whichever occurred first. Cox regression analysis was performed to identify significant predictors of outcomes. **Results** During follow-up (median 37.7 months) 13 patients died and 44 were hospitalized for a cardiac event. At univariable analysis, New York Heart Association (NYHA) functional class, furosemide dosage, lateral tricuspidal annular plane systolic excursion, deceleration time and E/DT were predictive of outcome. At multivariable analysis, E/DT was the only predictor of prognosis (hazard ratio = 1.02, $P = 0.018$), giving incremental prognostic information to clinical and other echocardiographic measures (global chi-square from 15.4 to 25.2; $P = 0.032$). **Conclusions** E/DT gives independent and incremental prognostic information in HF patients.

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1 Introduction

Predictors of poor outcome in patients with chronic heart failure (HF) help physicians in medical decision making. Previous studies have identified a number of epidemiological, clinical and laboratory variables predictive of poor outcome.^[1–3] Multivariable models that incorporate clinical and laboratory variables, medications and devices have been developed to estimate survival of HF patients, in order to create a valid assessment of prognosis in patients with HF.^[4–6] Several risk scores are available as an interactive application to calculate the risk of mortality in ambulatory patients with HF.^[7]

Although a complete history and physical examination are important first steps in HF patients, a two-dimensional

and Doppler echocardiography, is a very useful test in the evaluation of these patients. The addition of standard echocardiographic variables to multivariable risk score models results in a significant improvement in risk prediction.^[8] Many echocardiographic variables correlate with prognosis in HF, including left ventricular (LV) volumes and function, pulmonary hypertension, right ventricular systolic function and Doppler derived diastolic filling variables.^[9–12] Recently, the ratio of mitral peak early diastolic filling velocity to deceleration time (E/DT) has been demonstrated to give important prognostic information in a middle aged to elderly population with a high prevalence of diabetes and hypertension.^[13] Our purpose was to evaluate the prognostic value of this parameter, after adjustment for conventional data, in HF patients either with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF).

2 Methods

2.1 Study population

From January 2010 to March 2012, we prospectively

Correspondence to: Mario Petretta, MD, Department of Translational Medical Sciences, Section of Internal Medicine, Federico II University, Naples, Italy. E-mail: petretta@unina.it

Telephone: +39-081-746-2262

Fax: +39-081-746-2282

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enrolled 120 patients admitted for acute decompensated heart failure to the Internal Medicine Section of our Department. All patients, after structured history and physical examination, fulfilled the Framingham criteria for diagnosis of HF.^[14] Demographic, clinical and laboratory data were collected in all patients before discharge, and after clinical stabilization. Baseline characteristics included patients demographics (age, gender), clinical data (height, weight, NYHA functional class, cardiac rhythm, blood pressure, history of coronary artery disease, smoking habits, diabetes, presence of implantable cardioverter-defibrillator), and laboratory data (serum hemoglobin, lymphocytes, cholesterol, urea nitrogen, sodium). Patients were considered to have idiopathic dilated cardiomyopathy when no obvious underlying cause of HF could be discovered during routine evaluation (electrocardiogram, two-dimensional echocardiography, stress test, perfusion imaging). The diagnosis of ischemic heart disease was based on clinical history, or evidence of previous Q-waves myocardial infarction. When after routine evaluation the diagnosis was still uncertain, coronary angiography was performed. Patients with hemodynamically significant valvular disease, myocarditis, hypertrophic obstructive cardiomyopathy, angina at rest, myocardial infarction within six months before enrollment, uncontrolled hypertension and patients undergoing biventricular pacing for resynchronization therapy were excluded. We also excluded patients in chronic dialytic treatment and patients with major cerebrovascular diseases or other severe illness. Therapy for HF consisted of furosemide in all patients, anti-aldosteronic agents in 15%, angiotensin-converting enzyme inhibitors in 42%, β -blockers in 70%, angiotensin AT₁ receptor blockers in 31% of patients.

The investigation conformed to the principles outlined in the Declaration of Helsinki, and the study protocol was approved by our institutional committee on human research. All patients provided their written informed consent.

2.2 Two-dimensional and Doppler echocardiography

Standard M-mode, two-dimensional and Doppler examinations were performed during hospitalization after clinical stabilization. In all patients left and right ventricular systolic and diastolic function were evaluated by M-mode, two-dimensional and Doppler echocardiography using a Philips digital ultrasound machine, Model i-E-33. Left ventricular ejection fraction (LVEF) was calculated by Simpson's methods. We categorized individuals with a LVEF of $\leq 40\%$ as having HF_rEF, and those with ejection fraction of $> 40\%$ as having HF_pEF. For the study of diastolic function, the following mitral wave Doppler and tissue Doppler pa-

rameters were measured: peak early (E) and late (A) diastolic filling velocities, E/A ratio, deceleration time of E wave (DT), septal early diastolic mitral annular tissue velocity (septal-e'), lateral early diastolic mitral annular tissue velocity (lateral-e'). We also calculated E/e' ratio by dividing transmitral E peak by e', this latter averaged from the two acquisition sites. Right ventricular (RV) diameters were measured at end-diastole from a right ventricle focused apical 4-chamber view, as recommended by the American Society of Echocardiography. Using M-mode echocardiography, lateral tricuspid annular plane systolic excursion (TAPSE) was measured as the distance between the basal, end-diastolic position of the tricuspid annulus taken at the beginning of the electrocardiographic QRS complex and its greatest apical long-axis movement. Two-dimensional echocardiography-derived RV area measurements were taken from the apical four-chamber view at end-diastole and end-systole, and the fractional area change (FAC) was calculated (difference between end-diastolic and end-systolic areas divided by end-diastole area $\times 100$).^[15] A TAPSE value < 16 mm was considered abnormal, while a DT < 140 ms was considered to predict an elevated LV filling pressure. Pulmonary artery systolic pressure (PAPs) was estimated using Doppler echocardiography by calculating the RV to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, where v is the velocity of the tricuspid regurgitation jet in m/s. The tricuspid regurgitant signal was recorded by continuous wave Doppler echocardiography, and its maximal velocity was measured. Right atrial pressure, estimated on the basis of echocardiographic characteristics of the inferior vena cava and assigned a standardized value, was added to the calculated gradient to give PAPs. All mean values were derived from ≥ 3 different measurements, and five if in presence of arrhythmia. All recordings were analyzed by two operators and the results were averaged.

2.3 Follow-up

After discharge, patients periodically attended our institution outpatient unit for at least 24 months. For patients who died or were hospitalized during the follow-up, information was obtained from the attending physicians, or by phone contact and by review of hospital, or physicians' records by individuals blinded to the patient's echocardiographic data. The primary end-point was the occurrence of cardiac death or hospitalization due to cardiac events, whichever occurred first. Cardiac death, defined as due to acute myocardial infarction, ventricular arrhythmias, refractory HF, or cardiogenic shock, was confirmed by review of death certificates, hospital charts, or physician's records. Acute

coronary syndrome was defined based on the criteria of typical chest pain, enzyme levels, and ECG alterations. The date of the last examination, or consultation, was used to determine the length of follow-up.

2.4 Statistical analysis

Continuous variables were expressed as mean \pm SD and categorical data as percentages. Differences between groups were analyzed by *t*-test and chi-square test, as appropriate. A *P* value $<$ 0.05 was considered statistically significant. Event-free survival curves were estimated with Kaplan-Meier analysis and compared by the log-rank test. Univariable associations with cardiac events were determined by Cox proportional hazards regression. For this purpose, clinical, laboratory and echocardiographic variables were considered. Before performing the regression analysis, the proportional hazard assumption was validated by visual inspection of the log $[-\log(\text{survivor function})]$ for categorical variables and with statistical tests based on Schoenfeld residuals for continuous variables. The proportional hazard assumption was not rejected for any covariate included in the Cox model. Finally, a stepwise multivariable Cox regression analysis was performed (*P* $<$ 0.10 for model entry and *P* $<$ 0.15 for model retention), considering all variables showing a *P* value $<$ 0.10 at univariable analysis.

3 Results

The study group consisted of 120 HF patients, 13 of which were excluded because the diastolic function could not be reliably determined, whereas 12 were lost at follow-up. Thus, the outcome cohort included 95 patients (69 men and 26 women, mean age 64.8 ± 12.2 years). The echocardiographic parameters of patients with HFrEF (*n* = 51) and patients with HFpEF (*n* = 44) are reported in Table 1.

During a median follow-up of 37.7 months (5th to 95th percentile, 24.7 to 49.5 months) we observed 57 combined events (death or cardiovascular hospitalization). A fatal cardiac event occurred in 13 patients, five sudden cardiac death and eight worsening of cardiac disease. Furthermore, 44 patients were hospitalized, 41 for decompensated HF, two for occurrence of acute coronary syndrome and one for arrhythmic episode. Baseline characteristics of patients with or without events at follow-up are reported in Table 2. The two groups were comparable for demographic, clinical and laboratory data. Also there was no significant difference for medications between the two groups. The echocardiographic parameters in patients with, or without events, are reported in Table 3 in patients with cardiac events a signifi-

Table 1. Echocardiographic parameters of patients with HFrEF and with HFpEF.

	HFpEF (<i>n</i> = 51)	HFrEF (<i>n</i> = 44)	<i>P</i> value
Left ventricle parameters			
LVEF (%)	47 \pm 5	32 \pm 5	0.000*
LVIDd (mm)	55 \pm 6.3	60 \pm 5.9	0.000*
LVIDs (mm)	41 \pm 6.2	49 \pm 7.5	0.000*
LVEDV (mL)	138 \pm 42	169 \pm 42	0.001*
LVESV (mL)	73 \pm 26	116 \pm 35	0.000*
Mitral E-wave (cm/s)	73.6 \pm 29.5	81.4 \pm 31.6	0.21
Mitral DT (ms)	195 \pm 62	212 \pm 70	0.22
E/e'	16.2 \pm 7.5	15.7 \pm 6.7	0.68
E/DT (m/s ²)	50.5 \pm 34.4	41.4 \pm 27.1	0.15
Right ventricle parameters			
TAPSE	19 \pm 4	19 \pm 4	0.96

Data are presented as mean \pm SD. **P* $<$ 0.05 compared with HFpEF and HFrEF groups. E/DT: mitral peak early diastolic filling velocity to deceleration time ratio; E/e': mitral peak early diastolic filling velocity and early diastolic velocity by Doppler tissue imaging ratio; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end systolic volume; LVIDd: diastolic left ventricular internal diameter; LVIDs: systolic left ventricular internal diameter; Mitral E wave: peak early diastolic filling velocity; TAPSE: tricuspid annular plane systolic excursion.

cantly lower TAPSE (18.3 ± 3.4 mm vs. 20 ± 3.8 mm; *P* = 0.03) compared to patients without events was observed.

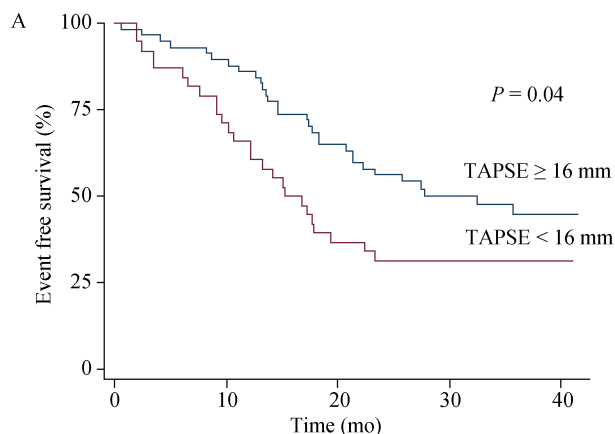
At univariable analysis we found that NYHA class (HR = 1.76; *P* = 0.02), furosemide dosage (HR = 1.01; *P* = 0.04), TAPSE (HR = 0.93; *P* = 0.04), DT (HR = 0.99; *P* = 0.03) and E/DT (HR = 1.01; *P* = 0.017) were predictive for occurrence of events. Kaplan-Meier survival estimates for TAPSE or DT are reported in Figure 1. As shown, patients with TAPSE $<$ 16 mm had lower event free survival than patients with TAPSE \geq 16 mm (*P* = 0.02). Similarly, the outcome was poorer in patients with DT $<$ 140 ms than in patients with DT \geq 140 ms (*P* = 0.04).

At multivariable analysis E/DT (HR = 1.02; *P* = 0.017) was the only independent predictor of poor prognosis after adjustment for NYHA class, furosemide dosage, TAPSE, and DT (Table 4). Values for the chi-square statistics as an index of the incremental predictive power of clinical variables, echocardiographic data, and E/DT are reported in Figure 2. As shown, E/DT increased the prognostic power of the model after considering clinical and echocardiographic parameters (global chi-square from 15.4 to 25.2; *P* = 0.032).

Table 2. Baseline characteristics of patients with and without events at follow-up.

Clinical and laboratory characteristics	Events (n = 57)	No events (n = 38)	P value
Age (yr)	65.9 ± 11.8	63.3 ± 12.6	0.3
Gender (M/F)	42/15	27/11	0.8
Weight (kg)	78.9 ± 17.1	74.5 ± 15.6	0.2
	I = 1 (1.7)	I = 3 (7.8)	
NYHA class	II = 29 (50.8)	II = 24 (63.2)	0.1
	III = 27 (47.3)	III = 11 (29)	
CAD	44 (57)	28 (74)	0.7
Smoking	20 (35)	12 (32)	0.7
Diabetes	19 (33)	12 (32)	0.9
SBP (mmHg)	125 ± 17	124 ± 13	0.7
Haemoglobin (g/dL)	12.7 ± 2.1	13.2 ± 1.7	0.2
Lymphocytes (%)	22.7 ± 7.5	22.2 ± 7.3	0.7
Total cholesterol (mg/dL)	163.9 ± 50.8	179.7 ± 36.3	0.2
Serum uric acid (mg/dL)	5.7 ± 1.9	6.2 ± 1.9	0.3
Serum sodium (mEq/L)	140.4 ± 3.6	140.4 ± 2.8	0.9
Sinus rhythm	41 (72)	29 (76)	0.6
ICD	7 (12)	4 (10.5)	0.8
Medications			
β-blockers	42 (74)	24 (63)	0.3
ACE-I	22 (39)	18 (47)	0.4
ARB	19 (33)	11 (29)	0.6
Antialdosteronic agents	9 (16)	5 (13)	0.7
Statins	30 (53)	23 (61)	0.4
Allopurinol	7 (12)	6 (16)	0.6
Furosemide (mg/day)	48.6 ± 94.1	29.8 ± 48.4	0.3

Data are presented as mean ± SD or n (%). ACE-I: Angiotensin converting enzyme-inhibitors; ARB: angiotensin receptor blockers; CAD: coronary artery disease; ICD: implantable cardioverter defibrillator; NYHA: New York Heart Association; SBP: systolic blood pressure; SD: standard deviation.

**Table 3. Echocardiographic measures of patients with and without events at follow-up.**

	Events	No-events	P value
Left ventricular parameters			
LVEF (%)	40 ± 10	39 ± 9	0.53
LVIDd (mm)	57.6 ± 6.7	57.8 ± 6.9	0.91
LVIDs (mm)	45.5 ± 7.9	46.2 ± 8	0.67
LVEDV (mL)	149.5 ± 45.5	162.9 ± 42.7	0.15
LVESV (mL)	91.6 ± 36.6	102.7 ± 40.1	0.17
LVM (g/m ²)	248.6 ± 65.3	246.6 ± 62.4	0.88
Mitral E-wave (cm/s)	79.2 ± 31.2	74.1 ± 30	0.43
Mitral DT (ms)	197.2 ± 66.4	215.4 ± 65.9	0.2
e' (cm/s)	5.1 ± 1.2	5 ± 1.5	0.8
E/e'	16.4 ± 7.8	15.3 ± 5.6	0.5
E/DT (m/s ²)	49.16 ± 33.94	40.23 ± 25.11	0.17
Right ventricular parameters			
TAPSE (mm)	18.3 ± 3.4	20 ± 3.8	0.03*
FAC (%)	35.4 ± 13.2	32.1 ± 11.8	0.2
PAPs (mmHg)	35.4 ± 13.2	32.0 ± 11.7	0.2
RVD basal (mm)	38 ± 5.5	36.5 ± 4.5	0.2

* $P < 0.05$. DT: deceleration time; E: mitral peak early diastolic filling velocity and early diastolic velocity by Doppler tissue imaging ratio; e': early diastolic velocity by Doppler tissue imaging; FAC: fractional area change; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end systolic volume; LVIDd: diastolic left ventricular internal diameter; LVIDs: systolic left ventricular internal diameter; LVM: left ventricular mass; Mitral E wave: peak early diastolic filling velocity; PAPs: pulmonary artery systolic pressure; RVD: right ventricular diameter; TAPSE: tricuspid annular plane systolic excursion.

4 Discussion

This study demonstrates that E/DT gives independent and incremental prognostic information in a cohort of

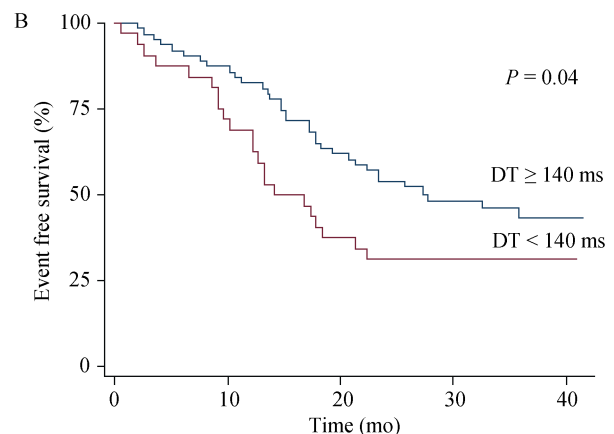


Figure 1. Kaplan-Meier event-free survival estimates. Kaplan-Meier plots showed the time of the combined end point of death and cardiac hospitalization for patients with (A) TAPSE < 16 mm vs. ≥ 16 mm and (B) DT < 140 ms vs. ≥ 140 ms. DT: deceleration time; TAPSE: tricuspid annular plane systolic excursion.

Table 4. Predictors of events at Cox univariable and multivariable analysis.

	Univariable analysis		
	Hazard ratio	95% CI	P value
NYHA class I, II or III	1.76	1.09–2.84	0.02
Furosemide dosage (mg/day)	1.01	1.001–1.006	0.04
DT (ms)	0.99	0.991–0.910	0.03
TAPSE (mm)	0.93	0.88–0.99	0.04
E/DT (m/s ²)	1.01	1.001–1.018	0.017

DT: deceleration time; E/DT: mitral peak early diastolic filling velocity and deceleration time ratio; NYHA: New York Heart Association; TAPSE: tricuspid annular plane systolic excursion.

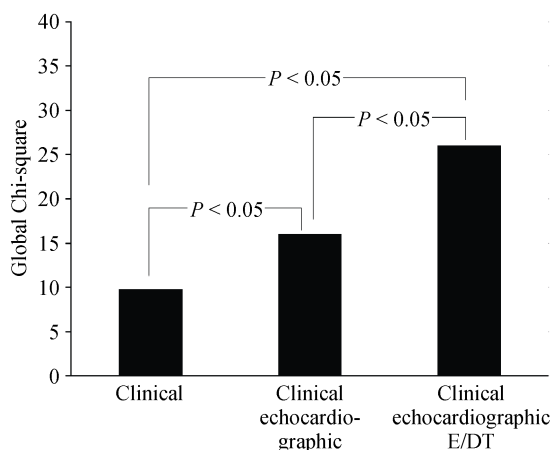


Figure 2. Incremental prognostic value of clinical, echocardiographic data and E/DT added sequentially. Global Chi-square on Y axis indicates incremental prognostic value of clinical, echocardiographic data and E/DT added sequentially. E/DT: mitral peak early diastolic filling velocity and deceleration time ratio.

patients hospitalized for HF after adjustment for clinical, laboratory and conventional echocardiographic parameters. Of note, we considered consecutive patients with reduced, or preserved LVEF, so our data may be applied to a population of HF patients with different LV functional abnormalities.

In our study, among clinical variables, NYHA class and furosemide dosage were predictive of the outcome at univariable analysis. The NYHA functional class and furosemide dosage have long been recognized in HF patients as important indicators of the severity of cardiovascular impairment and of survival.^[16,17] Our data also confirm the prognostic utility of TAPSE (Figure 1A), an echocardiographic parameter of RV function, easy to obtain in all patients irrespective of heart rate and rhythm. Previous studies reported that TAPSE adds significant prognostic information to the NYHA functional class, echocardiographic

evaluation of LV function, and mitral Doppler variables.^[18,19]

In our two-dimensional Doppler echocardiographic study, DT (a measure of LV relaxation) was shorter in patients with events at follow-up compared to those without events and was, therefore, a predictor of the outcome at follow-up either in HFrEF or in HFpEF patients (Figure. 1B). Several studies have shown that noninvasive Doppler measurements of LV relaxation and filling pressures are predictors of outcome in patients with HFrEF and HFpEF.^[20,21] In particular, Giannuzzi, *et al.*^[22] found that in patients with LV systolic dysfunction a short DT adds important prognostic information to the other clinical, functional and echocardiographic variables.

Interestingly, our results do not confirm the prognostic value of tissue Doppler echocardiography. Hirata, *et al.*^[23] found that E/e' ratio > 15 was an excellent predictor of adverse outcome in HF patients and demonstrated the usefulness of a combination of systolic function by LVEF and diastolic function by E/e'. Nevertheless, it must be outlined that the value of E/e' has been recently questioned.^[24,25] In particular Mullens, *et al.*^[25] demonstrated that E/e' ratio may not be reliable in predicting intra-cardiac filling pressures in patients with severe HF and extensive reverse remodeling.

Instead, our study shows that an increase in E/DT is associated with a poor prognosis. Nguyen, *et al.*^[26] in an animal model of pressure overload induced HF, found that the mitral Doppler parameter E/DT reliably predicts the presence of lung remodeling better than E/e', suggesting that this parameter could be useful in other models of HF and in humans.

Opposite to our findings, Mishra, *et al.*^[13] showed that lower E/DT predicted cardiovascular events, whereas peak E velocity and DT alone did not in a population of 3,102 subjects free of prevalent cardiovascular disease and after adjustment for traditional clinical cardiovascular risk factors. These different results may be explained by taking into account the study population composition. Mishra, *et al.*^[13] studied middle aged to elderly patients with high prevalence of diabetes or hypertension without prevalent cardiovascular disease. In these patients active relaxation of LV is attenuated, resulting in a reduced atrio-ventricular pressure gradient and in a decreased mitral peak early diastolic filling velocity.^[27] The slow ventricular filling also reduces the atrio-ventricular pressure gradient that, after peak E velocity, is a determinant of DT; so this latter parameter is prolonged. On the other hand, in our HF population, atrial pressure is increased in account of loading conditions, atrio-ventricular gradient is higher irrespective of LV relaxation, and as a consequence, peak E velocity increases. Under these cir-

cumstances rapid ventricular filling time (DT) shortens. Therefore, in such conditions of increased loading, E/DT is increased. Of note, in our study population, DT was < 140 ms in 32 out of 95 HF patients, a value that is a commonly observed in patients with elevated filling pressures.^[28]

There are limitations to this study. First, this is a single centered study, with a small study population. For this reason, we did not perform separate analyses for patients with HFrEF or HFpEF. Second, pseudo-normalization could be a problem in evaluating the prognostic value of E/DT in patients with severe HF. Finally, the predictive value of echocardiographic parameters was not compared with other prognostic parameters, such as brain natriuretic peptide. However, at our Institution, brain natriuretic peptide levels are not routinely evaluated, and thus, we cannot perform this analysis.

In conclusion, our results demonstrate that E/DT gives independent and incremental prognostic information at follow-up after considering clinical and echocardiographic parameters in HF patients.

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