

Mustafa Karabacak<sup>1</sup>, Ahmet Peynirci<sup>1</sup>, Omer Ozdil<sup>1</sup>, Senol Tayyar<sup>2</sup>, Mevlüt Serdar Kuyumcu<sup>1</sup>

<sup>1</sup> Suleyman Demirel University, Department of Cardiology, Medical Faculty, Isparta, Turkey

<sup>2</sup> Private Meddem Hospital, Department of Cardiology, Isparta, Turkey

## THE RELATIONSHIP BETWEEN GLOBAL LEFT VENTRICULAR FUNCTION, AS INDICATED BY THE TEI INDEX, AND LONG-TERM SURVIVAL IN PATIENTS WITH NON-ISCHEMIC, DILATED CARDIOMYOPATHY

<i>Aim</i>	Idiopathic dilated cardiomyopathy (DCM) is one of the leading causes of low ejection fraction (EF) heart failure (HF). The Tei index is a reliable marker that reflects both left ventricular (LV) systolic and diastolic function, and it has prognostic value in patients with DCM. We aimed to investigate the relationship between the Tei index and long-term survival in non-ischemic, DCM patients.
<i>Material and methods</i>	The present study included 98 patients with non-ischemic DCM. The mean survival time of the patients was 59 mos.
<i>Results</i>	The Tei index was prominently higher in patients who died ( $0.64 \pm 0.08$ vs $0.71 \pm 0.12$ , respectively; $p=0.01$ ). LV end-systolic volume and LV ejection fraction (LVEF) were independent prognostic factors and predicted worse long-term survival. Additionally, the patients with LVEF $\geq 32.7\%$ and the Tei index $\leq 0.76$ had significantly longer survival.
<i>Conclusion</i>	The present study showed that the Tei index was significantly associated with mortality and the patients with both low LVEF ( $\leq 32.7\%$ ) and high Tei index ( $\geq 0.76$ ) values had a shorter life expectancy. As a result, we suggest that the Tei index may be a useful echocardiographic marker to predict long-term survival in DCM patients.
<i>Keywords</i>	Dilated cardiomyopathy; ejection fraction; Tei index
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<i>Corresponding author</i>	Mustafa Karabacak. Email: mustafakarabacak@sdu.edu.tr

### Introduction

Heart failure (HF) is a complex clinical syndrome that still has a poor prognosis and is one of the most common causes of recurrent hospitalizations despite advances in its treatment. Idiopathic dilated cardiomyopathy (DCM), a heart muscle disease, is one of the leading causes of HF with low ejection fraction (EF). DCM is characterized by ventricular dilatation and systolic dysfunction in the absence of known abnormal loading conditions or significant coronary artery disease [1–3]. In recent years, remarkable advancements have been achieved in the overall survival of DCM patients, along with advances in pharmacological and device-related therapies. However, a non-negligible, significant proportion of these patients still have a poor prognosis [4, 5].

The Tei index [6] is an echocardiographic parameter that is easy to obtain, repeatable, and suitable for long-term follow-up. It's calculated as the sum of isovolumic times (contraction and relaxation times) divided by the ejection time (ET) of LV outflow and has been validated for the assessment of global myocardial performance, particularly in HF [6]. Compared with EF, it's less dependent on heart rate, loading states, and left ventric-

ular (LV) geometry [6]. Previous studies in non-ischemic HF patients with low EF have shown that the Tei index is higher than in the normal population and is associated with the severity of HF. In addition, high values of the Tei index predict mortality and the need for heart transplantation [7–11].

Although current echocardiographic developments have facilitated the diagnosis of DCM, simple echocardiographic prognostic indicators that are easily obtainable and repeatable are still needed in daily clinical practice. Therefore, in the present study, we investigated echocardiographic indicators associated with long-term survival, and the prognostic significance of the Tei index in non-ischemic, DCM patients.

### Material and methods

#### Study Population

The present research, a retrospective cohort study, included 98 non-ischemic, idiopathic DCM patients with diagnosed mild or moderate symptomatic HF [New York Heart Association (NYHA) functional class (FC) II to III] treated at the Department of Cardiology, Süleyman Demirel University. Patients with low

LVEF (<35%) on echocardiography despite at least 3 mos of optimal HF treatment were included in the study. Patients with normal coronary arteries or with non-critical coronary stenoses (stenosis <40%) on coronary angiography were defined as non-ischemic.

Initially, the eligibility of 314 non-ischemic HF patients was assessed in detail. 113 patients were excluded from the study due to echocardiographic EF  $\geq 35\%$  or due to insufficient echocardiographic data, atrial fibrillation, NYHA FC IV HF, moderate-severe valvular disease, hypo- hyperthyroidism, chronic renal failure, or severe chronic obstructive pulmonary disease. 103 patients were excluded due to lack of baseline clinic or echocardiographic data. A further 17 patients were excluded because they did not meet the diagnostic criteria for DCM. Other exclusion criteria were congenital heart disease, previous intolerance to beta-blocker therapy, history of chronic obstructive pulmonary disease, hematological disorders, history of malignancy, inflammatory, or infectious disease, serious obstructive sleep apnea syndrome, hepatic failure, and serious rhythm disturbances.

### Study Design

The patients were divided into two groups according to survival. During the follow-up period, 66 patients (41 females and 25 males; mean age  $63 \pm 11$  yrs) died and 32 patients (23 females and 9 males; mean age  $59 \pm 11$  yrs) were alive.

### Collection of Demographic and Clinical Characteristics

The demographic and cardiovascular risk factors were collected and recorded for all patients. Body mass index was calculated as the ratio of body weight to height squared. Body surface area [BSA ( $m^2$ )] was calculated as height (cm)  $\times$  weight (kg) / 3600. Cardiovascular risk factors included smoking status, history of hypertension, previous diagnosis of diabetes, and history of hyperlipidemia.

### Echocardiographic Evaluation

Two-dimensional, M-mode, conventional, and tissue Doppler echocardiographic measurements were obtained according to the recommendations of international guidelines [12]. The mean of three cardiac cycles of the electrocardiography record was considered the final measurement. The left atrial size and the LV diameter and wall thickness were measured using M-Mode echocardiography. LVEF was calculated by Simpson's method. For transmitral flow, the pulsed-wave Doppler sample volume was positioned at the mitral leaflet tips in the apical, four-chamber view. Early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), and deceleration time (DT) were measured by the conventional, transmitral Doppler method, and then the mitral E/A ratio was calculated. Septal  $a'$ ,  $e'$ , and  $s'$  velocities, as well as, isovolumic relaxation times (IVRT), isovolumic contraction time (IVCT), and ET were measured using the tissue Doppler imaging (TDI) method. As previously defined, the Tei index was calculated as the sum of isovolumic

times, i.e., the time spent in IVCT and IVRT, divided by the ET [6]. The  $E/e'$  and  $e'/a'$  ratios were calculated. Systolic and diastolic durations were measured from the pulsed tissue Doppler image recorded at the septal mitral annulus. The systolic duration consisted of IVCT and ET and was defined as the interval in the electrocardiographic QRS onset to the end of the  $S'$  wave. The diastolic duration consisted of IVRT, septal  $e'$ ,  $a'$  wave and was defined as the remainder of the cardiac cycle, i.e., the interval between  $S'$  termination to QRS onset in the subsequent cardiac cycle. The systolic and diastolic duration ratios were calculated. The presence of DCM was defined by an LV end-diastolic diameter greater than two standard deviations (SD) of the predicted and by LVEF <35%. Predicted values were calculated according to the formula of Henry, corrected for age and body surface area, and are expressed as a percentage of the predicted diameter: Predicted LV end-diastolic diameter =  $(45.3 \times \text{body surface area } 0.3 - (0.03 \times \text{age}) - 7.2)$ . A value of LV end-diastolic diameter  $> 112\%$  ( $> 2$  SD) was a diagnostic criterion for DCM [2, 13].

### Follow-up

Patients with regular follow-up data and meeting the study criteria were included in the study. The patients were enrolled in the study between 2009 and 2016, and the date of the last follow-up was August 2021. The patients data were obtained by office visits records, by telephone contacts, or national health system records when necessary. Patients who could not be accessed regular follow-up data were excluded from the study.

### Ethics

The study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects, and it was approved by the Health Research Ethics Board of Süleyman Demirel University.

### Statistical Analysis

Data were analyzed with the SPSS software version 23.0 for Windows (SPSS, Chicago, IL, USA). Continuous variables were expressed as means  $\pm$  standard deviation or median (25<sup>th</sup>–75<sup>th</sup> percentile), as normally or not normally distributed, respectively. To compare continuous variables, Student t tests or Mann-Whitney U tests were used, as appropriate. Categorical variables were compared using the Chi-square test. Median overall survival probability was calculated using the product-limit method of Kaplan-Meier. Differences in survival between two groups were determined using the log rank test. Univariate and multivariate analyses for survival differences were performed using the Cox proportional hazards model. Overall survival was calculated from the diagnosis of the patient to either the date of death from any cause or the date of the last follow-up. Receiver operating characteristic curve analysis was used to determine the cut-off values for the Tei index (0.76) and LVEF (32.7). For all statistical procedures, a p-value less than 0.05 was considered statistically significant.

## Results

### Patients Characteristics

Baseline demographic and clinical features were comparable between the two groups (Table 1). There was no significant difference between the FC classes of the patients included in the study ( $p=0.28$ ). The concomitant medications did not differ between the two groups, except for using furosemide and lipid-lowering therapy (Table 2). In deceased patients, while furosemide use was significantly higher ( $p<0.01$ ), lipid-lowering treatment use tended to be lower ( $p=0.05$ ). In a small number of patients (18%) who developed angiotensin-converting enzyme inhibitors intolerance, angiotensin-II receptor blocker therapy was given.

The echocardiographic parameters were generally similar between groups (Table 3). However, in deceased patients, while LVEF and septal  $s'$  wave were significantly lower, LV end-dia-

stolic volume, LV end-systole volume and IVCT were significantly higher. Moreover, the Tei index ( $0.64\pm0.08$  vs  $0.71\pm0.12$ , respectively;  $p=0.01$ ) was prominently higher in patients who died. Similarly, left atrium width was also significantly higher in patients who died. The diastolic duration tended to be higher in the group of living patients ( $p=0.06$ ). However, there was no significant difference between the groups in terms of systolic duration ( $p=0.95$ ) and diastolic to systolic duration ratio ( $p=0.14$ ).

### Survival and Prognostic Factors

At the last follow-up, the number of patients who had died was 66 (67%). The mean survival time of all patients was 59 (3-144) mos. In the Kaplan–Meier analysis, the overall survival was significantly longer in patients with LVEF $\geq$ 32.7% [90.6 (76.1–105.2) mons] vs [54.8 (43.3–66.3) mons];  $p<0.0001$ , Figure 1]. Similarly, the patients with the Tei index

**Table 1. Comparisons of the demographic, clinical and prognostic values of the DCM patients**

Variable	Alive, n=32	Deceased, n=66	p
Age, yrs	59 $\pm$ 11	63 $\pm$ 11	0.11
Male/Female	9/23	25/41	0.37
Systolic BP, mmHg	135 $\pm$ 20	139 $\pm$ 20	0.34
Diastolic BP, mmHg	83 $\pm$ 14	85 $\pm$ 13	0.40
Heart rate, bpm	75 $\pm$ 10	78 $\pm$ 10	0.10
Body mass index, kg/m <sup>2</sup>	28 $\pm$ 3	28 $\pm$ 7	0.89
Waist circumference, cm	96 $\pm$ 11	97 $\pm$ 17	0.90
Hypertension	9 (28)	27 (41)	0.27
Diabetes mellitus	8 (25)	10 (15)	0.27
Hyperlipidemia	9 (28)	14 (21)	0.46
Smoking	12 (37)	22 (33)	0.82
FC II/III	17/15	26/40	0.28
Survival time, mos	107 (86-144)	37 (5-103)	<0.01

Data are mean $\pm$ SD, median (25<sup>th</sup>–75<sup>th</sup> percentile), n/n, or n (%). BP, blood pressure; FC, functional class.

**Table 2. Concomitant medications in deceased and surviving DCM patients**

Medication	Alive, n=32	Deceased, n=66	p
ACEI	24 (75)	54 (81)	0.44
ARB	7 (21)	11 (17)	0.78
Beta-Blocker	43 (95)	94 (97)	0.96
ASA/ Clopidogrel	24 (75)	52 (78)	0.79
Lipid-lowering therapy	12 (37)	12 (18)	0.05
Aldosterone antagonist	24 (75)	51 (77)	0.80
Thiazide	10 (31)	28 (42)	0.25
Furoceramid	11 (34)	32 (48)	<0.01
Digoxin	3 (9)	9 (14)	0.51
Ivabradine	4 (12)	10 (15)	0.35
Nitrate	5 (16)	12 (18)	0.38

Data are n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-1 receptor blockers; ASA, acetylsalicylic acid.

**Table 3. Echocardiographic characteristics**

Variable	Alive, n=32	Deceased, n=66	p
LVEF, %	32.1 $\pm$ 3.5	28.5 $\pm$ 4.4	<0.01
LVEDV, cm <sup>2</sup>	198 $\pm$ 60	239 $\pm$ 59	<0.01
LVEDD, mm	59.8 $\pm$ 3.3	63.9 $\pm$ 4.9	<0.01
LVESV, cm <sup>2</sup>	134 $\pm$ 44	165 $\pm$ 45	<0.01
LVESD, mm	45.5 $\pm$ 1.9	48.6 $\pm$ 4.7	<0.01
Septal thickness, mm	12.0 $\pm$ 1.3	11.7 $\pm$ 1.5	0.15
Posterior wall, mm	11.1 $\pm$ 1.0	10.8 $\pm$ 1.3	0.10
Left atrium, mm	42.8 $\pm$ 4.7	45.4 $\pm$ 8.2	0.02
Systolic duration, ms	328 $\pm$ 40	329 $\pm$ 40	0.95
Diastolic duration, ms	483 $\pm$ 96	435 $\pm$ 97	0.06
Diastolic/systolic duration ratio	1.44 $\pm$ 0.28	1.32 $\pm$ 0.33	0.14
Mitral E wave, m/s	0.86 $\pm$ 0.26	0.83 $\pm$ 0.28	0.58
Mitral A wave, m/s	0.73 $\pm$ 0.26	0.81 $\pm$ 0.24	0.92
Mitral deceleration time, ms	199 $\pm$ 50	193 $\pm$ 58	0.46
Mitral E/A ratio	1.2 $\pm$ 0.7	1.0 $\pm$ 0.6	0.61
Septal e' wave, cm/s	4.4 $\pm$ 2.4	4.4 $\pm$ 2.2	0.96
Septal a' wave, cm/s	6.5 $\pm$ 3.7	6.2 $\pm$ 3.2	0.46
Septal e'/a' ratio	0.76 $\pm$ 0.35	0.70 $\pm$ 0.33	0.58
Septal E/e' ratio	16.8 $\pm$ 8.3	17.0 $\pm$ 6.2	0.80
Septal s' wave, cm/s	5.4 $\pm$ 1.1	4.8 $\pm$ 1.2	0.04
TDI-ET, ms	272 $\pm$ 39	259 $\pm$ 37	0.12
TDI-IVRT, ms	112 $\pm$ 13	112 $\pm$ 16	0.94
TDI-IVCT, ms	62 $\pm$ 11	70 $\pm$ 11	<0.01
TDI-Tei index	0.64 $\pm$ 0.08	0.71 $\pm$ 0.12	0.01

Data are mean $\pm$ SD. LVEF, left ventricular ejection fraction; LVEDD-V, left ventricle end diastolic diameter – volume; LVESD-V, left ventricle end systolic diameter – volume; TDI-ET, pulse wave tissue doppler-derived ejection time; TDI-IVCT, pulse wave tissue doppler-derived isovolumic contraction time; TDI-IVRT, pulse wave tissue doppler-derived isovolumic relaxation time; TDI-Tei index, pulse wave tissue doppler-derived myocardial performance.



**Table 4.** Results of univariate and multivariate analyses and the Cox proportional hazard model regarding mortality

Characteristic	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
LVEF, %	0.88 (0.84-0.93)	<0.001	0.90 (0.85-0.95)	<0.001
LVESV, cm <sup>3</sup>	1.010 (1.004-1.016)	0.001	1.006 (1.000-1.012)	0.04
LVEDV, cm <sup>3</sup>	1.007 (1.002-1.012)	0.004		
TDI-IVCT, ms	1.035 (1.014-1.057)	0.001		
TDI-Tei Index	18.3 (2.5-136.8)	0.005		
FC	1.60 (0.96-2.67)	0.04		

FC, functional class; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; TDI-IVCT, pulse wave tissue doppler-derived isovolumic contraction time; TDI-Tei index, pulse wave tissue doppler-derived myocardial performance.

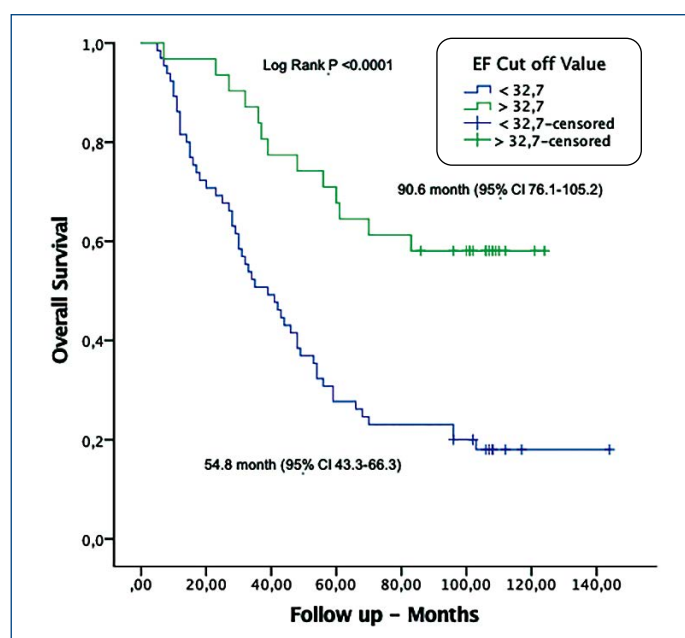
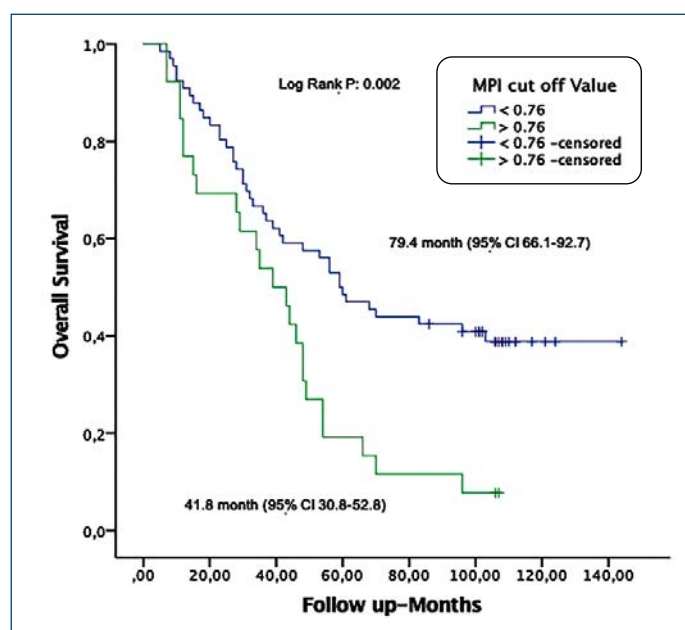
≤0.76 had prominently longer survival [79.4 (66.1–92.7) vs 41.8 (30.8–52.8) mos;  $p=0.002$ , Figure 2].

Additionally, prognostic risk factors were evaluated by univariate analysis (Table 4). According to this analysis LVEF ( $p<0.001$ ), LV end-diastolic volume ( $p=0.004$ ), LV end-systolic volume ( $p=0.001$ ), FC ( $p=0.04$ ), IVCT ( $p=0.001$ ), the Tei index ( $p=0.005$ ) were significantly associated with survival. However, no significant difference in long-term survival was noted regarding the septal  $s'$  wave ( $p=0.14$ ), IVRT ( $p=0.88$ ), ET ( $p=0.16$ ), DT ( $p=0.24$ ), E to A ratio ( $p=0.23$ ), diastolic duration ( $p=0.87$ ), systolic duration ( $p=0.12$ ), and diastolic to systolic duration ratio ( $p=0.82$ ). Subsequently, all significant prognostic factors were evaluated with multivariate analysis and the Cox proportional hazards model. LV end-systolic volume (odds ratio (OR) 1.006; 95% CI 1.000–1.012;  $p=0.04$ ), and LVEF (OR 0.90; 95% CI 0.85–0.95;  $p<0.001$ ) were independent prognostic factors and predicted worse long-term survival in DCM patients. Results of all multivariate survival analyses are presented in Table 4.

## Discussion

In this study, we investigated current, echocardiographic markers associated with long-term survival and the prognostic significance of the Tei index in patients with non-ischemic DCM. Shorter life expectancy was associated with  $LVEF \leq 32.7\%$  and the Tei index  $\geq 0.76$ . However, in the multivariate analysis, LVEF and LV end-systolic volume were predictors of long-term survival in DCM patients.

HF is a complex clinical syndrome with a high mortality rate [1]. Idiopathic DCM, a heart muscle disease, is one of the leading causes of HF with low EF. It is characterized by ventricular dilatation and systolic dysfunction in the absence

**Figure 1.** Kaplan–Meier median overall survival curves reflect the differences in survival rates relative to the cut-off LVEF values in DCM patients**Figure 2.** Kaplan–Meier median overall survival curves reflect the differences in survival rates relative to the TDI-Tei index values in DCM patients

of known abnormal loading conditions or significant coronary artery disease [1–3]. In recent decades, the survival of patients with DCM has improved in developed countries. The most important reasons for this are significant improvements in pharmacological therapy, e.g., angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and in devices, e.g., implanted cardioverter-defibrillators and cardiac resynchronization therapy. However, despite all these positive advances in the management of patients with DCM, it is still a major cause of mortality [4, 5, 14].

The major cause of cardiovascular death in DCM is ventricular arrhythmias secondary to progressive HF [14]. In other words, the poor prognosis of these patients has been associated with the degree of LV systolic dysfunction. On the basis of randomized clinical trials, LVEF  $\leq 35\%$  has been set as the threshold for a high risk of sudden death [15]. Thus, in this study, we determined the LVEF threshold value as 35%. Like the results of prior clinical studies, we demonstrated that LVEF is an independent prognostic factor and predicts poor long-term survival in these patients. Moreover, the cut-off value of LVEF was calculated as 32.7%, and the patients with LVEF  $\geq 32.7\%$  were associated with significantly higher long-term survival. Like our study, Merlo et al also demonstrated that LVEF was independently associated with all-cause mortality [5].

Numerous studies have been conducted on non-invasive predictors of sudden death in DCM patients. In a meta-analysis of 45 studies, Goldberger et al investigated the relationship between arrhythmic events and non-invasive predictive tests, such as heart rate variability, LVEF, non-sustained ventricular tachycardia, signal-averaged electrocardiogram, and fragmented QRS. These techniques provided only modest risk stratification for sudden cardiac death in non-ischemic DCM patients. Hence, they reported that combinations of these indicators, or new ones, are required to optimize risk stratification in this population [16].

Doppler and 2D echocardiography remain the primary method for diagnosing DCM [17]. The Tei index is an echocardiographic parameter that is easy to obtain, repeatable, not subject to a geometric structure, and suitable for long-term follow-up. More importantly, in recent studies, it has been demonstrated that Tei index is associated with global myocardial performance, i.e., systolic and diastolic function [6]. It is derived from conventional Doppler or TDI data. However, the conventional Doppler method has some limitations. Firstly, the IVCT, IVRT, and ET are measured sequentially and not during the same cycle. Hence, the accuracy of the results may be affected by heart rate fluctuations. TDI enables simultaneous measurements of both intervals [6, 18]. In the current study, while there was no correlation between the Tei index and heart rate ( $r=+0.15$ ,  $p=0.22$ ), there was a moderate negative correlation with LVEF ( $r=-0.40$ ,  $p<0.001$ ). The second limitation is that significant changes in preload may cause significant alterations in the conventional Tei index. However, TDI is relatively independent of the volume loading condition [19, 20]. Moreover, Düzenli et al suggested that TDI-Tei index has a stronger correlation with LVEF and FC than the conventional Tei index [21, 22]. It has been shown that the Tei index has a prognostic value in patients with DCM [10, 23, 24]. In our study, the Tei index was significantly higher in the patients who died and associated with mortality. This result was related to the significantly prolonged IVCT and prominently shortened but non-significant ET. Moreover, the patients with a Tei index  $\geq 0.76$  had worse long-term sur-

vival. These results were also consistent with the results of other research conducted on patients with HF [6, 25, 26].

Compared to the LVEF, the Tei index is much less affected by pre-and after-load, location of sample volume, and poor image quality. More importantly, the interobserver variability in the Tei index measurements is lower than that of the LVEF measurement [27]. In the current study, while there was a moderately negative correlation between the Tei index and LVEF ( $r=-0.30$ ,  $p=0.004$ ), there was a moderately positive correlation between the Tei index and LV end-diastolic volume ( $r=+0.28$ ,  $p=0.03$ ). Moreover, although there was a significant association between the Tei index and mortality in the univariate analysis, only LVEF and LV end-systolic volume were associated with mortality in the multivariate analysis. In addition, the patients with LVEF  $\leq 32.7\%$  and the Tei index  $\geq 0.76$  had prominently worse long-term survival. As in the current study, Dujardin et al showed that the Tei index, an independent prognostic factor for mortality, is prominently correlated with EF and ventricular volumes, and values  $\geq 0.77$  are associated with higher long-term mortality [10]. Similarly, Møller et al. suggested that the Tei index was correlated with LVEF and associated with an increased cardiac death risk and LV dilatation. Moreover, they reported that the patients with a Tei index  $\geq 0.63$  and LVEF  $\leq 40\%$  were significantly associated with poor overall survival [28]. Similar to our results, Szymanski et al. also found that the Tei index  $\geq 0.55$ , LVEF  $\leq 40\%$  and LV end-systolic volume  $>65$  ml were associated with the risk of cardiac death [29]. Despite all these studies, the threshold value of the Tei index associated with poor outcomes is still unclear. In addition, more studies are needed to determine the prognostic value of the combination of the Tei index and EF, which is the most important result of our study.

There are several limitations to our study. Firstly, the small size of our study limits its statistical power, since we applied strict non-inclusion criteria for the study. Secondly, this study cannot comment on the effects of changes in data during follow-up. Thirdly, the patient's volume status was not considered. Fourthly, our findings reflect the situation only in DCM patients with non-ischemic HF.

## Conclusions

This study showed that the Tei index was significantly associated with all-cause mortality. Moreover, patients with low LVEF ( $\leq 32.7\%$ ) and high TDI-Tei index ( $\geq 0.76$ ) had a much shorter life expectancy. In conclusion, we suggest that the Tei index may be a useful echocardiographic marker to predict long-term survival with LVEF in DCM patients.

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