ORIGINAL RESEARCH ARTICLE

Impact of diastolic dysfunction on outcome in heart failure patients with mid-range or reduced ejection fraction

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Abstract

Aims   The role of diastolic dysfunction (DD) in prognostic evaluation in heart failure (HF) patients with impaired systolic function remains unclear. We investigated the impact of echocardiography-defined DD on survival in HF patients with mid-range (HFmrEF, EF 41–49%) and reduced ejection fraction (HFrEF, EF < 40%).

Methods and results   A total of 2018 consecutive hospitalized HF patients were retrospectively included and divided in two groups based on baseline EF: HFmrEF group (*n* = 951, aged 69 ± 13 years, 74.2% male) and HFrEF group (*n* = 1067, aged 68 ± 13 years, 76.3% male). Clinical data were collected and analysed. All patients completed ≥1 year clinical follow-up. The primary endpoint was defined as all-cause death (including heart transplantation) and cardiovascular (CV)-related death. All-cause mortality (30.8% vs. 24.9%, *P* = 0.003) and CV mortality (19.1% vs. 13.5%, *P* = 0.001) were significantly higher in the HFrEF group than the HFmrEF group during follow-up [median 24 (13–36) months]. All-cause mortality increased in proportion to DD severity (mild, moderate, and severe) in either HFmrEF (17.1%, 25.4%, and 37.0%, *P* < 0.001) or HFrEF (18.9%, 30.3%, and 39.2%, *P* < 0.001) patients. The risk of all-cause mortality [hazard ratio (HR) = 1.347, *P* = 0.015] and CV mortality (HR = 1.508, *P* = 0.007) was significantly higher in HFrEF patients with severe DD compared with non-severe DD after adjustment for identified clinical and echocardiographic covariates. For HFmrEF patients, severe DD was independently associated with increased all-cause mortality (HR = 1.358, *P* = 0.046) but not with CV mortality (HR = 1.155, *P* = 0.469).

Conclusions   Echocardiography-defined severe DD is independently associated with increased all-cause mortality in patients with HFmrEF and HFrEF.

Keywords   Heart failure with mid-range ejection fraction; Heart failure with reduced ejection fraction; Diastolic dysfunction; Echocardiography; Prognosis

Introduction

Steadily increased life expectancy worldwide[1] is associated with increased prevalence of heart failure (HF) in the aging population.[2] The overall incidence of HF has been estimated to be 100–500 per 100 000 persons at risk in the general population, based on data from European countries and the USA.[3–5] Despite recent substantial improvements in medical care,[6] the outcome related with HF remains generally ominous. A recent systematic review and meta-analysis summarized survival data from 1.5 million patients with chronic HF across 60 studies; it was reported that the pooled survival rates at 1 month, 1, 2, 5, and 10 years were 65.7%, 86.5%, 72.6%, 56.7%, and 34.9%, respectively. The 5 year survival rate between 2000 and 2009 was as high as around 60%.[7]

Understanding and defining the risk factors related to the ominous outcome of HF is paramount in the effort to reduce disease burden and improve the outcome. Echocardiographic

detected left ventricular ejection fraction (LVEF) serves as a primary parameter used for risk stratification and therapy planning in current clinical practice. Based on the recent population studies, however, the outcome of HF patients with preserved or moderately reduced LVEF appeared to be comparable with patients with severely reduced LVEF.[8] Accordingly, great efforts were made to identify additional echocardiographic markers for predicting outcomes of patients with HF.[9] Numerous studies have demonstrated prognostic impact of echocardiographic defined diastolic dysfunction (DD) in a wide variety of patients with preserved and reduced LVEF.[10–13] However, it remains not fully clear whether evaluation of DD could provide additional prognostic information in HF patients with impaired systolic function. A recent clinical study reported that echocardiographic evaluation of DD defined by tissue Doppler marker abnormality (i.e. E/E') could provide additional prognostic information in patients with non-severe systolic dysfunction (LVEF 36–49%), but not in those with severe systolic dysfunction (LVEF ≤ 35%).[13]

The purpose of the present study, therefore, was to investigate the prognostic impact of DD grade defined based on the current recommendations[14] with minor modification on all-cause mortality and cardiovascular (CV) mortality of HF patients with mid-range LVEF (HFmrEF, LVEF 41–49%) and reduced LVEF (HFrEF, LVEF < 40%) hospitalized in our centre from 2009 to 2017. We sought to confirm whether DD grade might provide incremental prognostic value on outcome of HFmrEF and HFrEF patients.

Methods

Study population

This retrospective cohort study included consecutive hospitalized HF patients in our department between July 2009 and December 2017 who underwent echocardiographic examination. Inclusion criteria were as follows: (i) hospitalized patients with echocardiography examination at baseline with sufficient image quality; (ii) echocardiography-derived LVEF < 50% at baseline; and (iii) completion of a clinical follow-up for at least 1 year after initial echocardiographic examination. We initially screened 2365 consecutive patients during this time window; data from 2018 patients meeting all these four inclusion criteria were analysed (*Figure 1*). The diagnosis of chronic HF was defined according to the most recent guidelines of the European Society of Cardiology.[15] The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee at the University of Würzburg. Written informed consent was obtained from all patients or

their guardians prior to study start. The study is registered with the NCT Number NCT03966729 (REDEAL-HF trial).

Standard echocardiography measurements

Standard transthoracic echocardiographic examination was performed (GE, Vingmed Vivid 7 or IE9, Horten, Norway). Measurements were made offline according to the current guidelines in a remote workstation (EchoPAC Version 113, GE, Horten, Norway).[16,17] Left ventricular (LV) end-diastolic dimension (LVEDD), end-diastolic thickness of the posterior wall (LVPWd), and the septum (IVSd) were measured using M-mode in the parasternal LV long-axis view. Right ventricular (RV) end-diastolic basal and mid-dimensions and end-systolic right atrial area (RAA) were measured in the RV-focused apical four-chamber view. Left atrial (LA) volume was also measured in both the apical four-chamber and two-chamber views at end-systole using the biplane disk summation technique method of disks. Left atrial volume index (LAVi) was calculated by dividing LA volume by body surface area of subjects. LVEF was measured with the biplane Simpson method in apical four-chamber and two-chamber views. Tricuspid annular plane systolic excursion (TAPSE) and mitral annular plane systolic excursion (MAPSE) at the septal and lateral sites were measured in the apical four-chamber view by M-mode imaging. LV mass indexed to body surface area was estimated by LV cavity dimension and wall thickness at end-diastole: LV mass (g) = $0.8 \times [1.04 \times (\text{LVEDD} + \text{LVPWd} + \text{IVSd})^3 - \text{LVEDD}^3] + 0.6$. Meanwhile, peak tricuspid regurgitation jet velocity (TRV$_{max}$) was measured with colour Doppler and continuous-wave Doppler. Systolic pulmonary artery pressure (sPAP) was derived from using the simplified Bernoulli equation in combination with an estimated right atrial pressure (RAP): sPAP = $4V^2$ + RAP, where V indicates the TRV$_{max}$. RAP was estimated from inferior vena cava diameter and respiratory changes.

Diastolic dysfunction evaluation

Pulsed-wave Doppler echocardiography was performed in the apical four-chamber view to obtain mitral inflow velocities for LV filling patterns evaluation. Peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of E wave were measured, and the E/A ratio was calculated. Tissue Doppler derived early diastolic mitral annular velocity (E') was acquired at the septal and lateral mitral annular sites, and then septal, lateral, and average E/E' were calculated. Besides pulsed-wave Doppler parameters for the evaluation of filling patterns, we used additional parameters including LAVi, septal E/E' ratio, and TRV$_{max}$ to identify DD classification in patients with sinus rhythm and atrial fibrillation (AF), respectively. All measurements were averaged from 3 heart

Figure 1 Study protocol. E/E' ratio, the ratio of early diastolic filling velocity to mitral annular velocity; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplantation; LAVi, left atrial volume index at end-systole; LVEF, left ventricular ejection fraction; TRV$_{max}$, peak tricuspid regurgitation jet velocity.
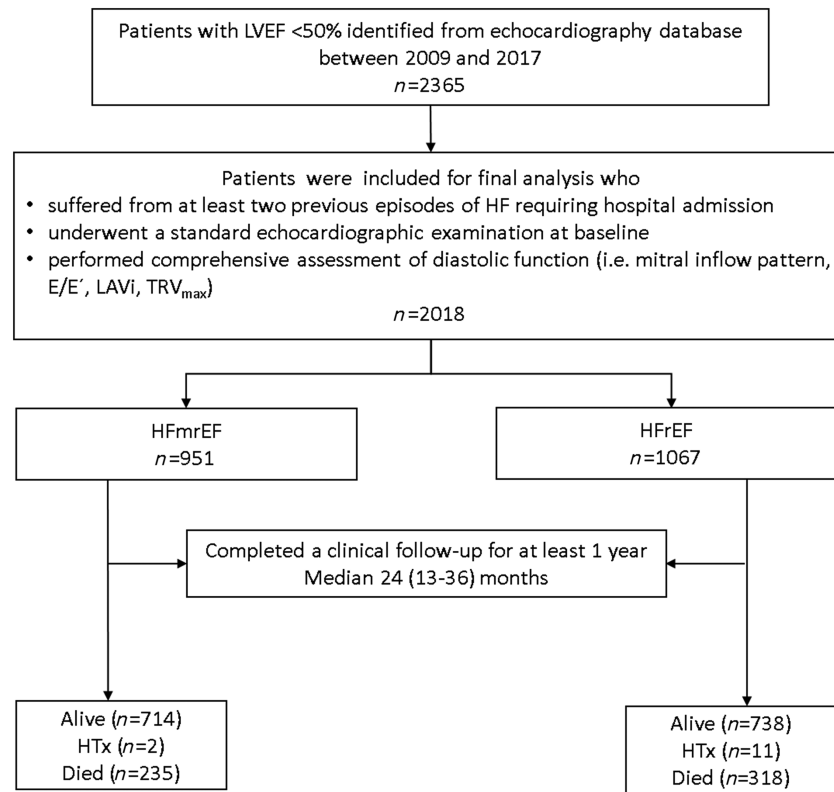
cycles in sinus rhythm and from 5 heart cycles in AF. DD was graded according to the current recommendations of the American Society of Echocardiography and European Association of Echocardiography (ASE/EAE) in 2016[14] with minor modification (*Figure 2*). We adopted the diagnostic criteria of HF patients with sinus rhythm to AF patients by the judgement of three parameters (LAVi > 34 mL/m^2, septal E/E' ratio > 14, and TRV$_{max}$ > 2.8 m/s). Similar to sinus rhythm patients, AF patients with all three positive parameters are defined as severe DD, with two positive parameters defined as moderate DD, and with one positive parameter defined as mild DD.

Clinical follow-up

All patients were clinically followed up for a median of 24 (13–36) months by reviewing the medical record information or by telephone interview. The primary endpoint was defined as all-cause death [including heart transplantation (HTx)] and CV death. CV deaths were defined as deaths from an acute myocardial infarction, sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death

due to CV haemorrhage, death due to other CV causes, and HTx.[18]

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Normal distribution of continuous variables was explored by inspecting skewness, kurtosis, and Q–Q plots. Continuous variables with normality distribution were compared using unpaired Student's *t*-test or one-way analysis of variance, and data with skewed distribution were tested by non-parametric tests: Mann–Whitney *U* test or Kruskal–Wallis *H* test, as indicated. Categorical variables, expressed as count (percentage), were compared using a similar approach employing χ^2 and Fisher's exact test, as appropriate.

Risk factors predicting primary endpoints (i.e. all-cause death and CV death) were sought using univariable and multivariable Cox proportional hazard regression models. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Clinical and echocardiographic risk factors, which significantly associated with both all-cause death including HTx and DD grade (*P* value < 0.10 for initial difference

Figure 2 An algorithm for grading diastolic dysfunction in heart failure patients with left ventricular ejection fraction < 50% in this study. DD, diastolic dysfunction; E wave, pulsed-wave Doppler derived early diastolic mitral inflow velocity; E', tissue Doppler derived early diastolic mitral annular velocity; E/A ratio, the ratio of early to late diastolic filling velocity; E/E' ratio, the ratio of early diastolic filling velocity to mitral annular velocity; LAVi, left atrial volume index at end-systole; TRV$_{max}$, peak tricuspid regurgitation jet velocity.

Results

Clinical characteristics and outcomes

comparisons), were identified as potential confounders to build multivariable Cox regression models. Prognostic performance of DD grade defined by the simplified echocardiographic algorithm was determined using multivariable Cox regression models after adjustment for clinical confounders and clinical plus other echocardiographic confounders. A two-tailed probability value of less than 0.05 was considered significant. Statistical analysis was performed using IBM SPSS, Version 25 for Windows (IBM, Armonk, NY).

Patients were divided into HFmrEF (n = 951) and HFrEF (n = 1067) groups according to systolic function at baseline visit. Clinical characteristics and outcomes of patients with HFmrEF and HFrEF are shown in *Table 1*. The mean age was 69 ± 13 years in the HFmrEF group and 68 ± 13 years in the HFrEF group; 74.2% of HFmrEF patients and 76.3% of HFrEF patients were male. The proportion of New York Heart Association (NYHA) functional class III–IV was significantly higher in the HFrEF group compared with the HFmrEF group (42.6% vs. 25.1%, P < 0.001). The prevalence of diabetes and hyperuricaemia and the proportion of implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator (CRT-D) were significantly higher in the

HFrEF group than in the HFmrEF group. Other CV co-morbidities and risk factors were similar between the two groups. Serum N-terminal pro-B-type natriuretic peptide concentration corresponding to echocardiographic measurements was available in 804 patients of this cohort (322 in HFmrEF and 482 in HFrEF). The median value of N-terminal pro-B-type natriuretic peptide was significantly higher in patients with HFrEF than that in patients with HFmrEF (median 3241 vs. 1688 pg/mL, P < 0.001). Angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, beta-blockers, mineralocorticoid receptor antagonist, digitalis glycosides, and loop diuretics were more frequently used in patients with HFrEF than in patients with HFmrEF. Additionally, during the whole observation period, 4.3% (41/951) of HFmrEF patients and 12.7% (136/1067) of HFrEF patients were treated with sacubitril/valsartan (ARNI) in this cohort, and all began after the year of 2016. Among the ARNI users in HFmrEF patients during follow-up, the proportion of EF ≤ 40% at the time of ARNI application was 78% (32/41).

During follow-up period of 24 (13–36) months, 237 patients with HFmrEF (all-cause death n = 235 and HTx n = 2) and 329 patients with HFrEF (all-cause death n = 318 and HTx n = 11) reached the primary endpoint. Of these, CV death was defined in 93 HFmrEF patients and 150 HFrEF patients. All-cause mortality (30.8% vs. 24.9%, P = 0.003) and CV mortality (14.1% vs. 9.8%, P = 0.003) were significantly higher in the HFrEF group compared with the HFmrEF group.

Table 1 Baseline clinical characteristics in patients with HFmrEF and HFrEF

	HFmrEF N = 951	HFrEF N = 1067	P value
Age (years)	69 ± 13	68 ± 13	0.399
Male [n (%)]	706 (74.2)	814 (76.3)	0.268
Body mass index (kg/m^2)	27.5 ± 5.1	27.2 ± 5.1	0.223
NYHA class III–IV [n (%)]	239 (25.1)	455 (42.6)	<0.001
Cardiac risk factors and co-morbidities [n (%)]			
Obesity	373 (39.2)	403 (37.8)	0.503
Atrial fibrillation	312 (32.8)	362 (33.9)	0.595
Dyslipidaemia	286 (30.1)	337 (31.6)	0.464
Hypertension	650 (68.3)	711 (66.6)	0.412
Diabetes	265 (27.9)	348 (32.6)	0.021
Smoking	305 (32.1)	354 (33.2)	0.597
Hyperuricaemia	82 (8.6)	126 (11.8)	0.019
Anaemia	537 (56.5)	595 (55.8)	0.751
Renal dysfunction (eGFR < 60 mL/min/1.73 m^2)	384 (40.4)	483 (45.3)	0.027
Coronary artery disease	558 (58.7)	592 (55.5)	0.148
Percutaneous coronary intervention	335 (35.2)	312 (29.2)	0.004
Coronary artery bypass grafting	155 (16.3)	181 (17.0)	0.689
Stroke/transient ischaemic attack	82 (8.6)	95 (8.9)	0.824
Chronic obstructive pulmonary disease	110 (11.6)	139 (13.0)	0.319
Peripheral vascular disease	68 (7.2)	89 (8.3)	0.319
Implantable cardioverter defibrillator	73 (7.7)	169 (15.8)	<0.001
Cardiac resynchronization therapy defibrillator	19 (2.0)	69 (6.5)	<0.001
NT-proBNP (pg/mL)			
No.	322	482	
Median (25th–75th)	1688 (658–4629)	3241 (1377–7892)	<0.001
HF-related medications [n (%)]			
ACEis or ARBs	696 (73.2)	832 (78.0)	0.012
Beta-blockers	718 (75.5)	878 (82.3)	<0.001
Mineralocorticoid receptor antagonists	186 (19.6)	450 (42.2)	<0.001
Digitalis glycosides	93 (9.8)	166 (15.6)	<0.001
Loop diuretics	461 (48.5)	712 (66.7)	<0.001
Clinical outcomes			
Follow-up duration (months)	24 (14–36)	24 (12–37)	0.308
All-cause death [n (%)]	235 (24.7)	317 (29.7)*	
HTx [n (%)]	2 (0.2)	12 (1.1)*	
Cause of death [n (%)]			0.047
CV death (HTx included)	128 (54.0)	204 (62.0)	
Non-CV death	103 (43.5)	111 (33.7)*	
Undetermined	6 (2.5)	14 (4.3)	
All-cause mortality (HTx included) [n (%)]	237 (24.9)	329 (30.8)	0.003
CV mortality (HTx included) [n (%)]	128 (13.5)	204 (19.1)	0.001

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplantation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
*$P < 0.05$ vs. HFmrEF.

Comparisons of baseline clinical and echocardiographic characteristics between HF patients with ischaemic and non-ischaemic aetiology are displayed in Supporting Information, *Tables S1* and *S2*. Patients with ischaemic HF aetiology were older and had higher prevalence of male sex, hypertension, diabetes, dyslipidaemia, smoking, peripheral vascular disease, and use of digitalis glycosides compared with patients with non-ischaemic HF aetiology in both the HFmrEF and HFrEF groups. Additionally, the prevalence of renal dysfunction and chronic obstructive pulmonary disease was higher in HFrEF patients with ischaemic aetiology. Besides smaller RV and right atrial diameters in the HFmrEF patients with ischaemic aetiology, the majority of echocardiographic parameters were similar between

HFmrEF patients with ischaemic or non-ischaemic aetiology. LV end-diastolic diameter and RAA values and the prevalence of severe mitral regurgitation were lower, while LVEF and lateral MAPSE values are higher in the HFrEF patients with ischaemic aetiology than those with non-ischaemic aetiology. All-cause mortality rate was lower in HFmrEF patients with ischaemic aetiology than in HFmrEF patients with non-ischaemic aetiology (all-cause mortality 21.7% vs. 29.5%, $P = 0.006$; CV mortality 12.7% vs. 14.5%, $P = 0.428$). In contrast, all-cause mortality and CV mortality were higher in HFrEF patients with ischaemic aetiology than in HFrEF patients with non-ischaemic aetiology (all-cause mortality 35.0% vs. 25.7%, $P = 0.001$; CV mortality 22.8% vs. 14.5%, $P = 0.001$).

Impact of simplified echocardiographic algorithm-defined diastolic dysfunction grades on all-cause mortality

The proportion of mild, moderate, and severe DD defined by simplified echocardiographic algorithm was 33.1% (315/951), 47.5% (452/951), and 19.3% (184/951) in HFmrEF patients, respectively (*Table 2*). All-cause mortality increased in proportion to DD severity: 17.1% (54/315) in the mild DD group, 25.4% (115/452) in the moderate DD group, and 37.0% (68/184) in the severe DD group (*P* < 0.001, *Figure 3A*). As shown in *Table 2*, besides DD-related parameters, lower TAPSE, MAPSE_septal, and severe mitral regurgitation were also closely related to higher all-cause mortality in HFmrEF patients after adjustment for age and sex.

In patients with HFrEF (*Table 3*), mild, moderate, and severe DD were identified in 21.4% (228/1067), 45.2% (482/1067), and 33.5% (357/1067) of patients, respectively. Similar to HFmrEF patients, all-cause mortality increased in proportion to DD severity: 18.9% (43/228) in the mild DD group, 30.3% (146/482) in the moderate DD group, and 39.2% (140/357) in the severe DD group (*P* < 0.001, *Figure 3B*). Higher RVD_basal, RVD_mid, RAA, and lower TAPSE, MAPSE_septal, and MAPSE_lateral values were significantly related to higher all-cause mortality in HFrEF patients after adjustment for age and sex.

In addition, echocardiographic parameters significantly associated with both all-cause mortality and DD severity (*P* < 0.10) were defined as confounders entered into the multivariable Cox regression models in the HFmrEF and HFrEF groups (Supporting Information, *Tables S3* and *S4*).

Cardiac risk factors and cardiovascular co-morbidities associated with all-cause mortality and diastolic dysfunction grades

Univariable Cox regression models showed that age, NYHA class III–IV, AF, diabetes, dyslipidaemia, coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease, renal dysfunction, and the use of HF medications were predictors of all-cause mortality rate in the HFmrEF group. Of these risk factors, age, male gender, NYHA class, AF, diabetes, peripheral vascular disease, renal dysfunction, and the use of mineralocorticoid receptor antagonists, digitalis glycosides, and loop diuretics also significantly related to DD severity in HFmrEF patients. Same analyses were made to determine the clinical confounders in HFrEF patients, showing that age, male gender, NYHA class III–IV, AF, diabetes, renal dysfunction, CRT-D, and the use of mineralocorticoid receptor antagonists, digitalis glycosides, and loop diuretics were associated with both all-cause mortality and DD severity (*Table 4*). The use of ARNI was associated

with lower all-cause mortality in both HFmrEF (unadjusted HR = 0.258, 95% CI 0.083–0.808, *P* = 0.020) and HFrEF (unadjusted HR = 0.398, 95% CI 0.244–0.648, *P* < 0.001) patients. However, the association between the use of ARNI and DD severity is not significant in both groups (HFmrEF group: 2.9% in mild DD, 4.6% in moderate DD, and 6.0% in severe DD, *P* = 0.226; HFrEF group: 13.6% in mild DD, 11.8% in moderate DD, and 13.4% in severe DD, *P* = 0.714). ARNI was therefore not added into Cox models as a potential confounder in this study.

Independently prognostic performance of diastolic dysfunction grades for all-cause mortality

As shown in *Table 5*, severe DD was significantly and independently associated with increased all-cause mortality risk after adjustment for clinical plus other echocardiographic confounders (vs. mild or moderate DD: HR 1.358, 95% CI 1.005–1.834, *P* = 0.046) in HFmrEF patients. For HFrEF patients, severe DD also significantly and independently associated with increased all-cause mortality risk after adjustment for clinical and echocardiographic confounders (vs. mild or moderate DD: HR 1.347, 95% CI 1.059–1.713, *P* = 0.015).

Independently prognostic performance of diastolic dysfunction grades for cardiovascular mortality

For HFmrEF patients, although there was a trend of increased CV mortality rate with increasing grade of DD (5.4% vs. 11.7% and 12.5%, *P* = 0.006), the significance between DD grades and CV mortality rate disappeared after adjustment for clinical and other echocardiographic confounders (*P* > 0.05). For HFrEF patients, severe DD remained as independent determinant for increased CV mortality risk (vs. mild or moderate DD: HR 1.493, 95% CI 1.059–2.105, *P* = 0.022) after adjustment for clinical and echocardiographic confounders.

Discussion

Diastolic dysfunction was graded based on the ASE/EAE 2016 recommendations[14] with minor modification, in that DD was graded with LAVi, E/E', and TRV$_{max}$ not only for HFmrEF and HFrEF patients in sinus rhythm; we also adopted the criteria for patients in sinus rhythm to AF patients in this study. Their impact of DD on predicting all-cause mortality and CV mortality in patients with HFmrEF or HFrEF was investigated in a real-world clinical cohort. The main findings of this study are as follows. (i) All-cause mortality increases in proportion to DD severity in both HFmrEF and HFrEF patients. (ii)

Table 2 Echocardiographic characteristics in patients with heart failure with mid-range ejection fraction

	Total N = 951	Survivors N = 714	Non-survivors/HTx N = 237	P value	Univariable HR (95% CI)	P value	Age-adjusted and sex-adjusted HR[a] (95% CI)	P value
Diastolic function								
DD grade [n (%)]				<0.001				
Mild	315 (33.1)	261 (36.6)	54 (22.8)		Reference		Reference	
Moderate	452 (47.5)	337 (47.2)	115 (48.5)		1.487 (1.076–2.056)	0.016	1.189 (0.856–1.651)	0.303
Severe	184 (19.3)	116 (16.2)	68 (28.7)		2.438 (1.705–3.486)	<0.001	1.818 (1.261–2.620)	0.001
LAVi (mL/m^2)	40.0 ± 20.2	38.3 ± 18.7	45.3 ± 23.5	<0.001	1.009 (1.005–1.013)	<0.001	1.006 (1.002–1.011)	0.007
E wave (cm/s)	82 ± 31	79 ± 29	92 ± 3330	<0.001	1.010 (1.007–1.014)	<0.001	1.009 (1.005–1.013)	<0.001
DT (ms)	201 ± 79	204 ± 81	191 ± 73	0.032	0.998 (0.996–0.999)	0.010	0.998 (0.996–0.999)	0.008
E/A[b]	1.29 ± 0.85	1.26 ± 0.80	1.38 ± 1.00	0.129	1.193 (1.011–1.406)	0.036	1.177 (1.001–1.384)	0.048
Septal E' (cm/s)	5.1 ± 1.9	5.2 ± 1.9	5.0 ± 1.9	0.186	0.957 (0.892–1.027)	0.222	—	—
Septal E/E'	17.9 ± 9.6	17.0 ± 8.9	20.7 ± 10.9	<0.001	1.028 (1.017–1.040)	<0.001	1.019 (1.008–1.031)	0.001
Lateral E' (cm/s) n = 907	7.4 ± 2.9	7.4 ± 2.9	7.4 ± 3.0	0.997	1.01 (0.966–1.058)	0.641	—	—
Lateral E/E' n = 907	12.9 ± 7.4	12.3 ± 7.0	14.5 ± 8.3	<0.001	1.024 (1.010–1.038)	0.001	1.020 (1.004–1.037)	0.013
Average E' (cm/s) n = 907	6.3 ± 2.1	6.3 ± 2.1	6.2 ± 2.1	0.569	0.993 (0.932–1.057)	0.820	—	—
Average E/E' n = 907	14.4 ± 7.0	13.8 ± 6.8	16.3 ± 7.3	<0.001	1.033 (1.018–1.049)	<0.001	1.024 (1.007–1.041)	0.006
TRV$_{max}$ (m/s)	2.61 ± 0.61	2.54 ± 0.58	2.83 ± 0.65	<0.001	2.059 (1.688–2.513)	<0.001	1.691 (1.363–2.099)	<0.001
sPAP (mmHg)	35 ± 14	33 ± 13	40 ± 15	<0.001	1.029 (1.022–1.036)	<0.001	1.023 (1.015–1.031)	<0.001
Cardiac sizes								
LVEDD (mm)	52 ± 7	53 ± 7	51 ± 7	0.011	0.968 (0.951–0.986)	<0.001	0.984 (0.966–1.002)	0.088
IVSd (mm)	10.1 ± 2.1	10.0 ± 2.1	10.3 ± 1.9	0.059	1.055 (0.992–1.122)	0.086	—	—
LVPWd (mm)	9.6 ± 1.8	9.6 ± 1.8	9.8 ± 1.9	0.068	1.043 (0.975–1.117)	0.222	—	—
LVMi (g/m^2)	101 ± 30	101 ± 30	103 ± 31	0.300	1.001 (0.996–1.005)	0.807	—	—
RVD_basal (mm)	37.2 ± 7.8	36.8 ± 7.6	38.1 ± 8.5	0.033	1.020 (1.003–1.038)	0.022	1.015 (0.997–1.032)	0.095
RVD_mid (mm)	28.0 ± 7.5	27.7 ± 7.3	28.9 ± 8.2	0.038	1.017 (0.999–1.035)	0.057	—	—
RAA (cm^2)	18.6 ± 6.7	18.2 ± 6.5	19.7 ± 7.0	0.003	1.025 (1.007–1.043)	0.006	1.017 (0.999–1.035)	0.065
Systolic function								
LVEF (%)	44.9 ± 2.9	45.0 ± 2.8	44.6 ± 2.9	0.043	0.964 (0.923–1.008)	0.106	—	—
TAPSE (mm)	18.6 ± 5.4	18.9 ± 5.4	17.7 ± 5.5	0.004	0.963 (0.940–0.986)	0.002	0.975 (0.952–0.998)	0.037
MAPSE_septal (mm)	7.7 ± 2.4	7.8 ± 2.5	7.3 ± 2.4	0.015	0.900 (0.851–0.951)	<0.001	0.941 (0.888–0.996)	0.037
MAPSE_lateral (mm)	10.1 ± 2.8	10.2 ± 2.7	9.9 ± 2.9	0.125	0.951 (0.908–0.996)	0.032	0.971 (0.926–1.019)	0.232
Mitral regurgitation								
No or mild	762 (80.1)	595 (83.3)	167 (70.5)	<0.001	Reference		Reference	
Moderate	127 (13.4)	83 (11.6)	44 (18.6)		1.781 (1.277–2.484)	0.001	1.318 (0.935–1.856)	0.115
Severe	62 (6.5)	36 (5.0)	26 (11.0)		2.581 (1.705–3.906)	<0.001	1.972 (1.292–3.009)	0.002

CI, confidence interval; DD, diastolic dysfunction; DT, deceleration time of the mitral E wave; E, pulsed-wave Doppler derived early diastolic mitral inflow velocity; E', tissue Doppler derived early diastolic mitral annular velocity; E/A ratio, the ratio of early to late diastolic filling velocity; E/E' ratio, the ratio of early diastolic filling velocity to mitral annular velocity; HR, hazard ratio; HTx, heart transplantation; IVSd, interventricular septum wall thickness at end-diastole; LAVi, left atrial volume index at end-systole; LVEDD, left ventricular dimension at end-diastole; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LVPWd, left ventricular posterior wall thickness at end-diastole; MAPSE, mitral annular plane systolic excursion; RAA, right atrial area at end-systole; RVD, right ventricular diameter at end-diastole; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TRV$_{max}$, peak tricuspid regurgitation jet velocity.

[a]Cox regression models adjusted for age and sex using the backward elimination method (likelihood ratio test).

[b]E/A ratio values were derived from patients with sinus rhythm.

Figure 3 Kaplan–Meier curves displaying the estimated survival probability for patients with HFmrEF and HFrEF stratified by mild, moderate, and severe DD. DD, diastolic dysfunction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction.
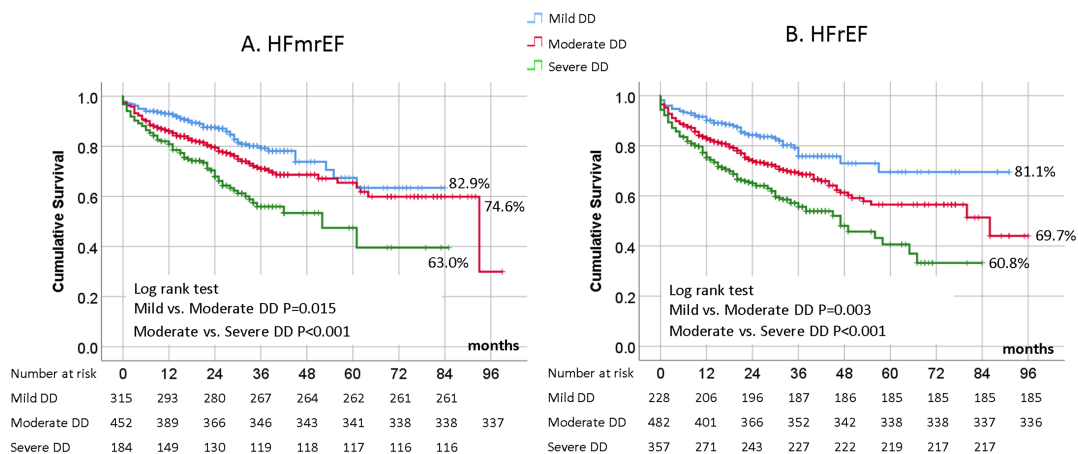
Multivariable survival analysis shows that severe DD remains as independent determinant of increased risk of all-cause mortality and CV mortality in patients with HFrEF, after adjusted for identified cardiac risk factors and co-morbidities, CRT-D, the use of HF medications, and other echocardiographic parameters associated with mortality in this cohort. (iii) Severe DD remains as independent determinant of increased risk of all-cause mortality in patients with HFmrEF after adjusted for cardiac risk factors and co-morbidities, the use of HF medications, and other echocardiographic indices. To our best knowledge, this is the first clinical analysis showing the incremental prognostic value of DD severity in HFmrEF and HFrEF patients.

The present study confirmed findings from previous studies reporting that severity of systolic dysfunction as expressed by reduced LVEF is a determinant of mortality in HF patients.[19] All-cause mortality was significantly higher in HFrEF patients than in HFmrEF patients (30.8% vs. 24.9%, $P = 0.003$). The impact of DD in HF patients with impaired systolic function, however, remained elusive until now. A cross project analysis from the German Competence Network Heart Failure demonstrated that the echocardiographic evaluation of DD could provide further prognostic information in particular in subject with non-severe systolic dysfunction (i.e. LVEF 35–50%) but not in subjects with severe systolic dysfunction (LVEF $< 35\%$), in whom DD was graded by the Doppler parameter E/E' > 15 only.[13] In the current study, our data show that severe DD is significantly and independently associated with increased all-cause mortality risk and CV mortality risk in HFrEF patients. The main reason for the divergent results between our study and previous observations might be that the compressive assessment of DD with three parameters (LAVi, E/E', and TRV_{max}) might be superior to using one single parameter (E/E' > 14).[13] The results from our study thus suggest comprehensive assessment of DD

valuable for predicting outcome of HFmrEF and HFrEF patients. Moreover, DD grade also remained as a powerful independent predictor of outcome after adjustment of numerous well-known clinical and echocardiographic risk factors.

Diastolic dysfunction is just one side of the coin; other clinical and echocardiographic parameters certainly play a crucial role on the outcome of HFmrEF and HFrEF patients as well. The prevalence of NYHA class III–IV, diabetes, hyperuricaemia, and renal dysfunction was significantly higher in HFrEF patients than in HFmrEF patients. These factors might jointly be responsible for the higher mortality rate in HFrEF patients as compared with HFmrEF patients. Univariable regression analysis showed that age, NYHA class III–IV, AF, diabetes, and renal dysfunction are common risk factors for mortality rate in HFmrEF and HFrEF patients, while peripheral vascular disease and coronary artery disease serve as additional risk factors for HFmrEF and HFrEF patients. Targeting these (co-)morbidities might be crucial to improve general outcome of HFmrEF and HFrEF patients.

In line with previous research,[20,21] HFrEF patients with ischaemic aetiology present distinct clinical characteristics and worse prognosis compared with patients with non-ischaemic HF in this study. Conversely, HFmrEF patients with ischaemic HF present better prognosis compared with patients with non-ischaemic HF. These results should be considered in the risk stratification among HFrEF and HFmrEF patients with either ischaemic or non-ischaemic aetiology.

Besides DD-related echocardiographic parameters, our results showed that reduced TAPSE and MAPSE_septal are risk factors for mortality rate in HFmrEF patients, while increased RVD_basal, RVD_mid, and RAA values and reduced TAPSE, MAPSE_septal, and MAPSE_lateral were risk factors for mortality rate in HFrEF patients after adjustment of age and sex. These results indicate more significantly reduced longitudinal systolic function and RV function contributed to the worse

Table 3 Echocardiographic characteristics in patients with heart failure with reduced ejection fraction

	Total N = 1067	Survivors N = 738	Non-survivors/HTx N = 329	P value	Univariable HR (95% CI)	P value	Age and sex-adjusted HR[a] (95% CI)	P value
Diastolic function								
DD grade [n (%)]				<0.001				
Mild	228 (21.4)	185 (25.1)	43 (13.1)		Reference		Reference	
Moderate	482 (45.2)	336 (45.5)	146 (44.4)		1.649 (1.174–2.318)	0.004	1.427 (1.014–2.009)	0.041
Severe	357 (33.5)	217 (29.4)	140 (42.6)		2.536 (1.801–3.571)	<0.001	2.308 (1.637–3.254)	<0.001
LAVi (mL/m²)	45.0 ± 20.2	43.9 ± 20.6	47.7 ± 19.0	0.005	1.008 (1.004–1.012)	<0.001	1.005 (1.001–1.010)	0.014
E wave (cm/s)	86 ± 29	84 ± 29	91 ± 29	<0.001	1.006 (1.003–1.010)	<0.001	1.005 (1.002–1.009)	0.003
DT (ms)	168 ± 74	172 ± 77	159 ± 66	0.004	0.998 (0.996–0.999)	0.007	0.997 (0.995–0.999)	<0.001
E/A[b]	1.65 ± 1.09	1.59 ± 1.07	1.78 ± 1.14	0.030	1.177 (1.046–1.324)	0.007	1.215 (1.083–1.362)	0.001
Septal E' (cm/s)	4.4 ± 1.6	4.6 ± 1.7	4.1 ± 1.4	<0.001	0.851 (0.791–0.916)	<0.001	0.888 (0.824–0.958)	0.002
Septal E/E'	22.1 ± 11.5	20.8 ± 11.0	25.0 ± 12.2	<0.001	1.021 (1.013–1.029)	<0.001	1.018 (1.010–1.027)	<0.001
Lateral E' (cm) n = 993	6.6 ± 2.8	6.7 ± 2.8	6.4 ± 2.8	0.198	0.985 (0.945–1.026)	0.473	—	—
Lateral E/E'	15.4 ± 8.7	14.9 ± 8.5	16.7 ± 9.2	0.003	1.015 (1.003–1.026)	0.013	1.012 (1.000–1.024)	0.051
Average E' (cm/s) n = 993	5.5 ± 1.9	5.6 ± 1.9	5.2 ± 1.8	0.004	0.933 (0.877–0.992)	0.026	0.954 (0.896–1.016)	0.141
Average E/E'	17.3 ± 8.4	16.5 ± 8.2	19.0 ± 8.7	<0.001	1.022 (1.010–1.034)	<0.001	1.018 (1.006–1.031)	0.003
TRV$_{max}$ (m/s)	2.74 ± 0.64	2.68 ± 0.62	2.87 ± 0.66	<0.001	1.576 (1.327–1.873)	<0.001	1.324 (1.109–1.581)	0.002
sPAP (mmHg)	38.1 ± 14.9	36.6 ± 14.5	41.6 ± 15.4	<0.001	1.021 (1.014–1.028)	<0.001	1.014 (1.007–1.022)	<0.001
Cardiac sizes								
LVEDD (mm)	59 ± 9	59 ± 9	58 ± 10	0.311	0.988 (0.976–1.001)	0.062	—	—
IVSd (mm)	9.5 ± 2.1	9.5 ± 2.1	9.7 ± 2.1	0.112	1.034 (0.982–1.088)	0.205	—	—
LVPWd (mm)	9.4 ± 2.0	9.3 ± 2.0	9.5 ± 1.9	0.247	1.014 (0.960–1.070)	0.628	—	—
LVMi (g/m²)	116 ± 35	115 ± 34	119 ± 37	0.064	1.001 (0.998–1.004)	0.466	—	—
RVD_basal (mm)	38.9 ± 8.5	38.4 ± 8.3	40.2 ± 8.8	0.002	1.025 (1.012–1.038)	<0.001	1.023 (1.010–1.037)	<0.001
RVD_mid (mm)	29.4 ± 8.8	28.8 ± 8.4	30.7 ± 9.5	0.001	1.024 (1.011–1.037)	<0.001	1.024 (1.012–1.037)	<0.001
RAA (cm²)	19.7 ± 7.3	19.0 ± 6.9	21.3 ± 8.0	<0.001	1.037 (1.023–1.052)	<0.001	1.032 (1.017–1.046)	<0.001
Systolic function								
LVEF (%)	29.6 ± 7.0	29.9 ± 6.9	29.0 ± 7.1	0.047	0.985 (0.970–1.000)	0.054	—	
TAPSE (mm)	16.0 ± 5.0	16.3 ± 4.9	15.3 ± 5.0	0.003	0.956 (0.934–0.978)	<0.001	0.966 (0.944–0.989)	0.003
MAPSE_septal (mm)	6.1 ± 2.2	6.2 ± 2.2	5.8 ± 2.1	0.004	0.886 (0.841–0.933)	<0.001	0.904 (0.858–0.953)	<0.001
MAPSE_lateral (mm)	8.3 ± 2.6	8.5 ± 2.7	7.9 ± 2.5	0.002	0.914 (0.875–0.954)	<0.001	0.912 (0.873–0.953)	<0.001
Mitral regurgitation				<0.001				
No or mild	721 (67.6)	531 (72.0)	190 (57.8)		Reference		Reference	
Moderate	221 (20.7)	139 (18.8)	82 (24.9)		1.572 (1.213–2.038)	<0.001	1.408 (1.085–1.828)	0.010
Severe	125 (11.7)	68 (9.2)	57 (17.3)		2.180 (1.620–2.932)	<0.001	2.223 (1.650–2.994)	<0.001

CI, confidence interval; DD, diastolic dysfunction; DT, deceleration time of the mitral E wave; E, pulsed-wave Doppler derived early diastolic mitral inflow velocity; E', tissue Doppler derived early diastolic mitral annular velocity; E/A ratio, the ratio of early to late diastolic mitral filling velocity; E/E' ratio, the ratio of early diastolic filling velocity to mitral annular velocity; HR, hazard ratio; HTx, heart transplantation; IVSd, interventricular septum wall thickness at end-diastole; LAVi, left atrial volume index at end-systole; LVEDD, left ventricular dimension at end-diastole; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; LVPWd, left ventricular posterior wall thickness at end-diastole; MAPSE, mitral annular plane systolic excursion; RAA, right atrial area at end-systole; RVD, right ventricular diameter at end-diastole; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TRV$_{max}$, peak tricuspid regurgitation jet velocity.
[a]Cox regression models adjusted for age and sex using the backward elimination method (likelihood ratio test).
[b]E/A ratio values were derived from patients with sinus rhythm.

Table 4 Cardiac risk factors and co-morbidities associated with all-cause death/heart transplantation rate in patients with HFmrEF and HFrEF

	Univariable HR (95% CI)	P value	Mild DD	Moderate DD	Severe DD	P value
HFmrEF (n = 951)			N = 315	N = 452	N = 184	
Age (10 years)	1.565 (1.390–1.761)	<0.001	64 ± 14	71 ± 11	73 ± 12	<0.001
Male	0.813 (0.611–1.082)	0.155	251 (79.7)	322 (71.2)	133 (72.3)	0.025
NYHA class III–IV	1.903 (1.459–2.481)	<0.001	40 (12.7)	122 (27.0)	77 (41.8)	<0.001
Obesity	0.783 (0.598–1.027)	0.077	117 (37.1)	188 (41.6)	68 (37.0)	0.362
Atrial fibrillation	1.594 (1.231–2.064)	<0.001	59 (18.7)	138 (30.5)	115 (62.5)	<0.001
Diabetes	1.412 (1.078–1.849)	0.012	67 (21.3)	141 (31.2)	57 (31.0)	0.006
Dyslipidaemia	0.516 (0.378–0.705)	<0.001	92 (29.2)	135 (29.9)	59 (32.1)	0.791
Coronary artery disease	0.662 (0.513–0.855)	0.002	190 (60.3)	263 (58.2)	105 (57.1)	0.744
Peripheral vascular disease	1.857 (1.235–2.793)	0.003	15 (4.8)	34 (7.5)	19 (10.3)	0.061
Chronic obstructive pulmonary disease	2.321 (1.693–3.182)	<0.001	34 (10.8)	57 (12.6)	19 (10.3)	0.624
Renal dysfunction	2.350 (1.815–3.042)	<0.001	82 (26.0)	198 (43.8)	104 (56.5)	<0.001
Implantable cardioverter defibrillator	0.741 (0.432–1.272)	0.277	26 (8.3)	34 (7.5)	13 (7.1)	0.878
Cardiac resynchronization therapy defibrillator	0.913 (0.340–2.455)	0.857	5 (1.6)	7 (1.5)	7 (3.8)	0.149
HF medications						
ACEis or ARBs	0.451 (0.347–0.585)	<0.001	239 (75.9)	328 (72.6)	138 (75.0)	0.563
Beta-blockers	0.635 (0.481–0.839)	0.001	232 (73.7)	348 (77.0)	148 (80.4)	0.215
Mineralocorticoid receptor antagonists	0.639 (0.448–0.912)	0.014	63 (20.0)	79 (17.5)	48 (26.1)	0.048
Digitalis glycosides	2.447 (1.782–3.361)	<0.001	12 (3.8)	48 (10.6)	37 (20.1)	<0.001
Loop diuretics	2.347 (1.789–3.078)	<0.001	102 (32.4)	240 (53.1)	119 (64.7)	<0.001
HFrEF (n = 1067)			N = 228	N = 482	N = 357	
Age (10 years)	1.532 (1.386–1.695)	<0.001	65 ± 12	70 ± 12	68 ± 14	<0.001
Male	1.065 (0.824–1.376)	0.631	172 (75.4)	352 (73.0)	290 (81.2)	0.021
NYHA class III–IV	1.628 (1.311–2.022)	<0.001	69 (30.3)	196 (40.7)	190 (53.2)	<0.001
Obesity	0.986 (0.787–1.235)	0.901	79 (34.6)	172 (25.7)	152 (42.6)	0.069
Atrial fibrillation	1.511 (1.212–1.884)	<0.001	47 (20.6)	152 (31.5)	163 (45.7)	<0.001
Diabetes	1.408 (1.128–1.759)	0.003	58 (25.4)	161 (33.4)	129 (36.1)	0.024
Dyslipidaemia	1.024 (0.815–1.287)	0.837	80 (35.1)	158 (32.8)	99 (27.7)	0.131
Coronary artery disease	1.520 (1.215–1.901)	<0.001	122 (53.5)	285 (59.1)	185 (51.8)	0.087
Peripheral vascular disease	2.031 (1.477–2.793)	<0.001	18 (7.9)	42 (8.7)	29 (8.1)	0.919
Chronic obstructive pulmonary disease	1.430 (1.068–1.915)	0.016	27 (11.8)	65 (13.5)	47 (13.2)	0.828
Renal dysfunction	2.734 (2.177–3.435)	<0.001	70 (30.7)	222 (46.1)	191 (53.5)	<0.001
Implantable cardioverter defibrillator	1.353 (1.028–1.782)	0.031	35 (15.4)	65 (13.5)	69 (19.3)	0.071
Cardiac resynchronization therapy defibrillator	1.620 (1.106–2.374)	0.013	7 (3.1)	29 (6.0)	33 (9.2)	0.011
HF medications						
ACEis or ARBs	0.540 (0.425–0.686)	<0.001	188 (82.5)	387 (80.3)	270 (75.6)	0.101
Beta-blockers	0.674 (0.514–0.884)	0.004	192 (84.2)	403 (83.6)	299 (83.8)	0.979
Mineralocorticoid receptor antagonists	0.706 (0.564–0.883)	0.002	107 (46.9)	185 (38.4)	167 (46.8)	0.021
Digitalis glycosides	1.355 (1.036–1.773)	0.026	17 (7.5)	77 (16.0)	74 (20.7)	<0.001
Loop diuretics	1.663 (1.296–2.134)	<0.001	117 (51.3)	329 (68.3)	266 (74.5)	<0.001

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; CI, confidence interval; DD, diastolic dysfunction; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NYHA, New York Heart Association.

outcome in HFmrEF and HFrEF patients. Assessing and monitoring these parameters might be helpful on risk stratification of HFmrEF and HFrEF patients.

Atrial fibrillation is common in HF patients, and E/A ratio is not available in these patients. We adopted the ASE/EAE algorithm for sinus rhythm patients and used LAVi, septal E/E', and TRV_{max} to grade DD for HF patients with AF, since the structural and functional properties of DD might be similar in sinus rhythm and AF patients except A wave is not available in AF patients. This modification makes the DD comparison between sinus rhythm and AF patients more objective with the identical criteria. Other parameters like mitral deceleration time and isovolumic relaxation time could also be used to define DD in AF patients as suggested by ASE/EAE guidelines. Nevertheless, these time-dependent parameters could be significantly affected by heart rate, which is

always irregular in AF patients; thus, these parameters might be linked with much larger variabilities as that of LAVi, E/E', and TRV_{max}. Subgroup analysis indicated that all-cause mortality was significantly higher in AF patients with severe DD in both the HFmrEF and HFrEF groups as compared with AF patients with non-severe DD (Supporting Information, *Figure S1*). Future studies are warranted to validate if these criteria are also feasible to predict the all-cause mortality in HFmrEF and HFrEF patients with AF.

Andersen *et al.* reported that about 40% of patients with reduced EF might still have normal filling pressure.[22] It is to note that there is no report of filling pressure in untreated HF patients. It thus remains unknown if the normal filling pressure detected in these HF patients was the consequence of effective HF medication or not. Normal filling pressure alone could not deny the presence of DD, especially in the

Table 5 Multivariable Cox regression models of DD for predicting all-cause mortality and CV mortality in patients with HFmrEF and HFrEF

	Events	Event rate	P value	Model 1 Clinical covariates adjusted HR (95% CI)	P value	Model 2 Clinical plus other echo covariates adjusted HR (95% CI)	P value
All-cause mortality							
HFmrEF[a] (*n* = 951)	237/951	24.9%					
DD grade							
Mild	54/315	17.1%		Reference		Reference	
Moderate	115/452	25.4%		1.003 (0.718–1.400)	0.987	0.963 (0.689–1.348)	0.827
Severe	68/184	37.0%	<0.001	1.419 (0.972–2.072)	0.070	1.321 (0.896–1.947)	0.160
Severe vs. non-severe		37.0 vs. 22.0%	<0.001	1.416 (1.056–1.899)	0.020	1.358 (1.005–1.834)	0.046
HFrEF[b] (*n* = 1067)	329/1067	30.8%					
DD grade							
Mild	43/228	18.9%		Reference		Reference	
Moderate	146/482	30.3%		1.228 (0.870–1.735)	0.243	1.110 (0.781–1.576)	0.561
Severe	140/357	39.2%	<0.001	1.826 (1.284–2.595)	0.001	1.466 (1.008–2.133)	0.045
Severe vs. non-severe		39.2 vs. 26.6%	<0.001	1.559 (1.245–1.951)	<0.001	1.347 (1.059–1.713)	0.015
CV mortality							
HFmrEF[a] (*n* = 951)	128/951	13.5%					
DD grade							
Mild	22/315	7.0%		Reference			
Moderate	70/452	15.5%		1.445 (0.884–2.362)	0.142		
Severe	36/184	19.6%	<0.001	1.535 (0.875–2.693)	0.135		
Severe vs. non-severe		19.6 vs. 12.0%	0.007	1.155 (0.772–1.729)	0.483		
HFrEF[b] (*n* = 1067)	204/1067	19.1%					
DD grade							
Mild	23/228	10.1%		Reference		Reference	
Moderate	84/482	17.4%		1.260 (0.789–2.013)	0.334	1.164 (0.726–1.867)	0.529
Severe	97/357	27.2%	<0.001	2.212 (1.326–3.393)	0.002	1.707 (1.044–2.792)	0.033
Severe vs. non-severe		27.2 vs. 15.1%	<0.001	1.771 (1.334–2.351)	<0.001	1.508 (1.118–2.036)	0.007

CI, confidence interval; CV, cardiovascular; DD, diastolic dysfunction; HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio.
Model 1: Clinical covariates were included into the Cox models using the backward elimination method (likelihood ratio) for every observed variable. Model 2: Both clinical and echocardiographic covariates were included into the Cox models using the backward elimination method (likelihood ratio) for every observed variable.
[a]Clinical covariates for patients with HFmrEF included age, sex, New York Heart Association class III–IV, atrial fibrillation, diabetes, peripheral vascular disease, renal dysfunction, mineralocorticoid receptor antagonists, digitalis glycosides, and loop diuretics; other echocardiographic covariates included interventricular septum wall thickness at end-diastole, septal mitral annular plane systolic excursion, tricuspid annular plane systolic excursion, basal right ventricular diameter at end-diastole, right atrial area at end-systole, and mitral regurgitation.
[b]Clinical covariates for patients with HFrEF included age, sex, New York Heart Association class III–IV, atrial fibrillation, diabetes, coronary artery disease, renal dysfunction, mineralocorticoid receptor antagonists, digitalis glycosides, loop diuretics, and cardiac resynchronization therapy; other echocardiographic covariates included left ventricular dimension at end-diastole, left ventricular ejection fraction, septal mitral annular plane systolic excursion, tricuspid annular plane systolic excursion, basal right ventricular diameter at end-diastole, right atrial area at end-systole, and mitral regurgitation.

case of enlarged LA, higher E/E′, and TRV$_{max}$ values. Defining the association between comprehensive non-invasive assessments of DD with the three parameters used in the current study with invasively measured filling pressure in untreated HF patients in a dedicated study might clarify this issue, because invasive filling pressure measurements are often not available in daily clinical practice. The ASE/EAE recommendations, which emphasize the role of non-invasive echocardiographic indexes, might offer more convenience on evaluating DD status in patients with reduced EF. A modified algorithm based on the current guideline might also favour the DD grading for AF patients as shown in our study. In addition, identifying DD severity by using diastolic filling pattern derived from pulsed-wave Doppler suffers some uncertainties. Suboptimal Doppler signals could lead to misinterpretation. A presence of E/A ratio > 2 might be found in a heart with normal or mildly impaired diastolic function but not always a sign of severe DD with a restrictive pattern.

We measured both septal and lateral E′ and calculated septal, lateral, and average E/E′ in this study. Although averaged E/E′ was finally used as recommended,[14] the data of this cohort indicate that prognostic performance of septal E/E′ might be comparable with lateral E/E′ or averaged E/E′ in patients with HFmrEF [area under the ROC curve (AUC): 0.619, 0.597, and 0.616, respectively, *P* > 0.05]. Moreover, prognostic performance of septal E/E′ was even better than lateral E/E′ (AUC: 0.615 vs. 0.568, *P* = 0.007) and comparable with average E/E′ (AUC: 0.615 vs. 0.597, *P* = 0.118) in patients with HFrEF (Supporting Information, *Figure S2*). This is in line with findings from previous clinical studies also suggesting that septal and lateral E/E′ are equally useful in predicting cardiac events in the general population. On the other hand,

measuring both sites does not provide further predictive value than measuring a single site.[23] Accordingly, septal E/E' was selected as a predominant component for grading DD instead of average E/E' in our study.

Clinical implication

The present study highlights prognostic value of echocardiographic determination of DD in HFmrEF and HFrEF patients. The echocardiographic algorithm including three predominant parameters (i.e. LAVi, septal E/E', and TRV$_{max}$) is easy to obtain in clinical practice and feasible for defining DD severity and predicting the outcome in HFmrEF and HFrEF patients with various cardiac rhythms. Severe DD serves as an independent determinant for all-cause mortality for both HFmrEF and HFrEF patients after adjustment of clinical and other echocardiographic covariates. It is to note that DD grade was not found independently associated with CV mortality in patients with HFmrEF after adjusted for identified clinical risk factors. This might reflect the ability of modern medication and intervention on reducing the cardiac mortality in HFmrEF patients, and the benefit achieved by these targeted strategies might thus outweigh the impact of or normalize DD in these patients. This finding might be interpreted as a hint for DD being the 'straw that breaks the camel's back' for CV death in HFrEF, but not in HFmrEF patients.

Limitation

Patients with HF with preserved EF were not included in the urrent study. Current echocardiographic recommendations suggest a different algorithm for grading DD in patients with HF with preserved EF as compared with patients with reduced EF (<50%). Careful investigation of the ideal diagnostic workup for DD grading and clarification of clinical implications in this particularly heterogeneous patient collective remains a main task for the future. Another study limitation is that we did not acquire data on hospitalizations due to HF in our current study. The impact of DD on rehospitalization due to HF in patients with HFmrEF and HFrEF therefore also needs to be explored in future studies. In addition, the drug regimens and titration/optimization during follow-up are not available in this retrospective cohort.

Conclusions

Echocardiography-derived DD is an independent prognostic indicator of increased all-cause mortality in both HFmrEF and HFrEF patients. Future studies are warranted to investigate potential incremental value of serial measurements and changes seen over time for therapy planning and improving prognosis.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline clinical characteristics in HFmrEF and HFrEF patients stratified by heart failure etiology.
Table S2. Baseline echocardiographic characteristics in HFmrEF and HFrEF patients stratified by heart failure etiology.
Table S3. Cardiac sizes and systolic function associated with both all-cause mortality and diastolic dysfunction grades in patients with HFmrEF.
Table S4. Cardiac sizes and systolic function associated with both all-cause mortality and diastolic dysfunction grades in patients with HFrEF.
Figure S1. Kaplan–Meier curves displaying the estimated survival probability stratified by non-severe and severe DD for HFmrEF and HFrEF patients with and without atrial fibrillation (AF). Severe DD is significantly associated with lower survival rate both in HFmrEF and HFrEF patients without AF (A and C) and with AF (B and D) as compared to non-severe DD. HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; DD, diastolic dysfunction.
Figure S2. Comparison of prognostic performance among septal, lateral, and average E/E' for all-cause mortality by Receiver Operating Characteristic (ROC) curves. Prognostic performance of septal E/E' is comparable with lateral E/E' or averaged E/E' in patients with HFmrEF (A, AUC: 0.619, 0.597, and 0.616, respectively, $P > 0.05$). Moreover, prognostic performance of septal E/E' is better than lateral E/E' (B, AUC: 0.615 vs. 0.568, $P = 0.007$), and comparable with

average E/E' (AUC: 0.615 vs. 0.597, P = 0.118) in patients with HFrEF. HFmrEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction;

E/E' ratio, the ratio of early diastolic filling velocity to mitral annular velocity; AUC, area under ROC curve.

References

1. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *Lancet* 2017; **389**: 1323–1335.

2. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016; **18**: 242–252.

3. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999; **20**: 421–428.

4. Ohlmeier C, Mikolajczyk R, Frick J, Prutz F, Haverkamp W, Garbe E. Incidence, prevalence and 1-year all-cause mortality of heart failure in Germany: a study based on electronic healthcare data of more than six million persons. *Clin Res Cardiol* 2015; **104**: 688–696.

5. Stork S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, Hupfer S, Klebs S. Epidemiology of heart failure in Germany: a retrospective database study. *Clin Res Cardiol* 2017; **106**: 913–922.

6. Jackevicius CA, Page RL, Buckley LF, Jennings DL, Nappi JM, Smith AJ. Key articles and guidelines in the management of heart failure: 2018 update. *J Pharm Pract* 2019; **32**: 77–92.

7. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019; **21**: 1306–1325.

8. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016; **13**: 368–378.

9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–2200.

10. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; **289**: 194–202.

11. Halley CM, Houghtaling PL, Khalil MK, Thomas JD, Jaber WA. Mortality rate in patients with diastolic dysfunction and normal systolic function. *Arch Intern Med* 2011; **171**: 1082–1087.

12. Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of left ventricular diastolic dysfunction in a general population. *J Am Heart Assoc* 2014; **3**: e000789.

13. Luers C, Edelmann F, Wachter R, Pieske B, Mende M, Angermann C, Ertl G, Dungen HD, Stork S. Prognostic impact of diastolic dysfunction in systolic heart failure—a cross-project analysis from the German Competence Network Heart Failure. *Clin Cardiol* 2017; **40**: 667–673.

14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29**: 277–314.

15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891–975.

16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39 e14.

17. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23**: 685–713 quiz 786-688.

18. Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MTT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018; **137**: 961–972.

19. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; **112**: 3738–3744.

20. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OO, Savarese G, Dahlstrom U, Lund LH. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail* 2017; **10**: e003875.

21. Shen L, Ramires F, Martinez F, Bodanese LC, Echeverria LE, Gomez EA, Abraham WT, Dickstein K, Kober L, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Jhund PS, Gimpelewicz CR, McMurray JJV, Paradigm HF, Investigators A, Committees. Contemporary characteristics and outcomes in chagasic heart failure compared with other nonischemic and ischemic

cardiomyopathy. *Circ Heart Fail* 2017; **10**: e004361.

22. Andersen OS, Smiseth OA, Dokainish H, Abudiab MM, Schutt RC, Kumar A, Sato K, Harb S, Gude E, Remme EW, Andreassen AK, Ha JW, Xu J, Klein AL, Nagueh SF. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol* 2017; **69**: 1937–1948.

23. Wang JN, Biering-Sorensen T, Jorgensen PG, Jensen JS, Mogelvang R. Left ventricular filling pressure by septal and lateral E/e' equally predict cardiovascular events in the general population. *Int J Cardiovasc Imaging* 2017; **33**: 653–661.