Heart failure with reduced, mid-range and preserved left ventricular ejection fraction in Chinese with type 2 diabetes: risk factors and prognosis from time of first index hospitalization

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Original investigation

Keywords: Heart failure, left ventricular ejection fraction, mortality, type 2 diabetes

Posted Date: July 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-744950/v1

Abstract

Background

The clinical predictors and prognosis of heart failure (HF) by categories of left ventricular ejection fraction (LVEF) have not been well studied in people with diabetes. In a retrospective cohort of Chinese with type 2 diabetes, we examined 1) clinical factors associated with incident decompensated HF, and 2) mortality post-HF, stratified by LVEF.

Methods

We conducted a retrospective analysis of the Hong Kong Diabetes Register comprising 23,348 people with type 2 diabetes without history of HF enrolled between 1993–2015, followed for incident decompensated HF until 2017. Heart failure subtypes were defined according to LVEF on echocardiography. Multivariate Cox proportional hazards models were used to identify clinical factors associated with incident HF versus no HF, stratified by HF subtypes. All-cause mortality rates were compared by HF subtypes.

Results

Over median follow-up of 7.1 years from enrolment, 1,195 (5.1%) people developed decompensated HF. Among 611 (51.1%) people with echocardiography, 24.1% had HF with reduced LVEF (HFrEF) (LVEF < 40%), 15.2% had HF with mid-range LVEF (HFmrEF) (LVEF 41–49%), and 60.7% had HF with preserved LVEF (HFpEF) (LVEF ≥ 50%). Old age, low GFR, albuminuria and coronary artery disease were associated with increased hazards for all HF subtypes. During median follow-up of 2.1 years post-HF, 760 (63.6%) people died. One-year mortality rate was lower in people with HFpEF (16.2%) than those with HFmrEF (*vs* 26.9%,p = 0.034) and HFrEF (*vs* 31.3%,p < 0.001). At 10 years, mortality rates in HFpEF group (58.0%) remained lower than HFmrEF group (*vs* 71.0%,p = 0.38), but similar to HFrEF group (*vs* 55.8%,p = 0.651).

Conclusions

In Chinese with type 2 diabetes, HFpEF was the predominant HF subtype. One-year mortality following decompensated HF was lowest in HFpEF group but 10-year mortality was similar between HFpEF and HFrEF.

Background

Heart failure (HF) is a serious complication of type 2 diabetes resulting in impaired health-related quality of life and functional status as well as frequent hospitalization. Type 2 diabetes independently increases the likelihood of HF by 1.7-fold in men and 2.0-fold in women (1). People with type 2 diabetes and comorbid HF have a 20–30% excess risk of all-cause mortality than their counterparts with HF without diabetes (2, 3). Established risk factors for developing HF in people with type 2 diabetes include old age, obesity, poor glycemic control, impaired kidney function and pre-existing coronary heart disease (4, 5).

Several glucose-lowering drug classes such as thiazolidinediones and dipeptidyl-peptidase 4 inhibitors may potentially induce or worsen HF (6, 7), whereas sodium-glucose co-transporter 2 (SGLT2) inhibitors benefit not only diabetes but also people with HF (8). Given the rising prevalence of type 2 diabetes and changing clinical profile of people living with diabetes with many living to older ages, the burden of HF is also increasing (9, 10).

Heart failure may be classified according to left ventricular ejection fraction (LVEF) on echocardiography as HF with reduced LVEF (HFrEF), HF with mid-range LVEF (HFmrEF), and HF with preserved LVEF (HFpEF) (11). Reduced LVEF (LVEF < 40%) is frequently flagged as an adverse prognostic index and primarily denotes impaired ventricular systolic dysfunction with adverse remodelling (12, 13). Heart failure with preserved LVEF (LVEF ≥ 50%) is characterised by LV hypertrophy and impaired LV filling, also referred to as diastolic dysfunction. Heart failure with mid-range LVEF (LVEF 40–49%) is a newly defined HF subtype that remains poorly understood. Notably, LVEF is only one of the measures of cardiac function, is subjected to inter-observer variability, changes over time, and does not infer underlying aetiology or pathophysiology of HF (14, 15). Despite these limitations, LVEF is used commonly for selection of participants in clinical trials and its measurement is widely available. Previous observational studies based on HF registries have shown that clinical characteristics and outcome of HF vary according to LVEF (13, 16–18). However, limited data are available in people with type 2 diabetes (19). Using a longitudinal cohort of Hong Kong Chinese with type 2 diabetes without HF at baseline, we examined 1) clinical factors associated with incident decompensated HF, and 2) mortality post-HF, stratified by LVEF.

Methods

Study cohort

We conducted a retrospective analysis of the Hong Kong Diabetes Register (HKDR) which enrolled adults aged ≥ 18 years with physician-diagnosed diabetes who underwent structured assessment of metabolic control and diabetes complications at the Diabetes and Endocrine Centre, the Prince of Wales Hospital, Hong Kong Special Administrative Region (20). Affiliated with the Chinese University of Hong Kong and governed by the Hong Kong Hospital Authority (HA), the hospital serves approximately one seventh of the Hong Kong population of 7.39 million as of 2017. Referral sources included hospital-based specialist and family medicine clinics as well as community out-patient clinics. For this study, Chinese men and women with type 2 diabetes without history of HF at baseline enrolled since inception of the HKDR on 1 Jun 1993 until 30 June 2015 were included for analysis. People with type 1 diabetes, diabetes or unknown type, who were non-Chinese, or with history of HF were excluded. All participants have provided written informed consent for the collection and analysis of their clinical information for research purpose. The study has received approval by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Baseline assessment

At enrolment, information on socio-demographics, past medical history and drug use was collected by a trained nurse. Anthropometric measurements (body weight, body height, waist circumference) and vital signs (blood pressure [BP], pulse) were collected. Fundus was examined for the presence or absence of diabetic retinopathy using ophthalmoscopy or fundus photography, interpreted by trained endocrinologists. Lower extremities were examined for evidence of sensory neuropathy using monofilaments and 256-Hz tuning fork. Sensory neuropathy was present if a person fulfilled two or more of the following criteria: reduced sensation to monofilament, reduced vibration sense on testing using tuning fork, and self-reported abnormal sensation over one or more lower limbs. After an 8-hour fast, blood samples were collected for HbA1c, plasma glucose, lipids (total cholesterol, low density-lipoprotein (LDL) cholesterol, high density-lipoprotein (HDL) cholesterol, triglyceride), and serum creatinine. Spot urine sample was collected for urine albumin-to-creatinine ratio (ACR). Estimated glomerular filtration rate (GFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration Eq. (21). Chronic kidney disease was defined as estimated GFR < 60 ml/min/1.73m^2. Albuminuria was defined as urine ACR ≥ 3.0 mg/mmol creatinine.

Follow-up and event ascertainment

The Hong Kong HA is a statutory organisation that governs all public hospitals and majority of out-patient clinics, and provides healthcare to over 90% of people living in Hong Kong. Clinical information including vital status, hospital admissions, investigations and drug prescription are stored in an electronic medical record system of the Hong Kong HA, and are retrievable using the unique Hong Kong Identity Card number compulsory for all local residents. Incident decompensated HF was identified as hospital admission with principal diagnosis of HF (ICD-9 code 428) from the date of enrolment into HKDR until 30 June 2017. Next, cases of incident HF in which rheumatic heart disease, valvular heart disease, endocarditis, congenital heart disease and other non-atherosclerotic causes of structural heart disease were recorded in secondary diagnoses were excluded (Supplementary Table 1). Finally, medical records of the remaining people with incident HF were reviewed for echocardiography performed within 24 months of the event. Left ventricular ejection fraction documented by echocardiography closest to the date of HF was used to categorise HF into HFrEF (LVEF < 40%), HFmrEF (LVEF 40–49%), and HFpEF (≥ 50%) (11). People with incident HF were followed until death or 30 June 2017, whichever came first. Additionally, repeated measurements of HbA1c, lipids, serum creatinine and urine ACR between the date of enrolment and 30 June 2017 were obtained.

Statistical analysis

We compared baseline clinical characteristics across HF subtypes among people with incident HF, and between people with and without incident HF. Data were expressed as mean ± standard deviation (SD), median (interquartile range [IQR]), or percentages. χ^2 test was used for between-group comparison of categorical variables, t test for normally distributed continuous variables, and Kruskal-Wallis test for continuous variables with skewed distribution. P-values for multiple comparisons were adjusted using the Benjamini-Hochberg method. We performed multivariate Cox proportional hazards model to determine the association of clinical factors (expressed as hazard ratios [HR] with 95% confidence intervals [CI])

with incident HF, separated by HF subtypes. The variables included in multivariate Cox regression model for each HF subtype were based on demonstration of statistically significant association with HF subtype, versus no incident HF, on univariate analysis. High density-lipoprotein cholesterol, LDL-cholesterol, estimated GFR, HbA1c, log urine ACR, history of coronary heart disease (CHD), and history of stroke were treated as time varying covariates. The proportional hazards assumption in each Cox model was verified by evaluating the weighted Schoenfeld residuals (22), and there was no evidence to support that the assumption was violated, with all p-values > 0.05. We estimated all-cause mortality rates and mortality rates at 1-year, 5-year and 10-year post-HF for each HF subtypes. Pairwise comparisons were conducted by using log-rank test and p-values were adjusted using the Benjamini-Hochberg method. Kaplan-Meier analysis was used to plot cumulative all-cause mortality post-HF, separated by HF subtypes. All statistical analyses were conducted using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value < 0.05 was considered statistically significant.

Results

Baseline clinical characteristics of the study cohort

Among 25,075 people enrolled into the HKDR, 809 with type 1 diabetes or diabetes of unknown type, 230 non-Chinese and 688 with history of HF at baseline were excluded (Supplementary Fig. 1). Of the remaining 23,348 people, 1,195 (5.1%) developed de novo HF over a median follow-up of 7.1 (IQR 6.8) years. People with available echocardiography were younger and had lower frequencies of chronic kidney disease, diabetic retinopathy and stroke compared with those without echocardiography (Supplementary Table 2).

Stratified by LVEF, 147 (24.1%) had HFrEF, 93 (15.2%) had HFmrEF, and 371 (60.7%) had HFrEF. Compared with those without incident HF, people with HF, irrespective of HF subtypes, were older, had longer diabetes duration, higher HbA1c levels and worse control of other metabolic risk factors at baseline (Supplementary Table 3). In addition, those with HF were more likely to have microvascular complications and coronary heart disease (CHD), and had more frequent use of renin-angiotensin-aldosterone system (RAAS) inhibitors, BP lowering drugs and insulin (Supplementary Table 3). Some differences were detected in baseline clinical characteristics between the HF subgroups. Compared with people with HFrEF, those with HFpEF and HFmrEF were older, had longer diabetes duration, higher body mass index (BMI), systolic BP, lower estimated GFR and higher urine ACR (Table 1). A female preponderance was observed in people with HFpEF (Table 1). Sex differences in baseline characteristics among people with incident HF are shown in Supplementary Table 4.

Table 1
Baseline clinical characteristics of 611 people with type 2 diabetes and incident heart failure

	HFrEF	HFmrEF	HFpEF	p for trend between HF subtypes
Number	147	93	371	
Demographics				
Male sex, n (%)	79 (53.7)	47 (50.5)	153 (41.2)	0.007
Age at enrolment, years	63.8 ± 11.2	66.8 ± 10.5	66.2 ± 10.0	0.040
Cardio-metabolic risk factors				
Duration of diabetes, years	8.0 [3.0, 13.0]	10.0 [6.0, 18.0]	9.0 [4.0, 15.0]	0.599
Smoking, n (%)				0.010
Previous	34 (23.3)	24 (25.8)	73 (19.7)	
Current	24 (16.4)	8 (8.6)	35 (9.5)	
BMI, kg/m^2	25.4 ± 3.7	25.7 ± 4.7	26.6 ± 4.4	0.004
Systolic BP, mmHg	142.1 ± 21.0	148.2 ± 23.3	146.0 ± 21.2	0.112
Diastolic BP, mmHg	76.8 ± 11.5	77.1 ± 11.7	76.2 ± 12.2	0.523
HbA1c, %	8.2 ± 2.1	7.8 ± 1.8	8.0 ± 1.8	0.359
HDL-cholesterol, mmol/L	1.25 ± 0.36	1.23 ± 0.39	1.30 ± 0.36	0.123
LDL-cholesterol, mmol/L	3.1 ± 1.0	3.0 ± 1.1	3.0 ± 1.0	0.420
Triglyceride, mmol/L	1.5 [1.1, 2.2]	1.6 [1.1, 2.6]	1.5 [1.0, 2.3]	0.480
Estimated GFR, ml/min/1.73m^2	68.6 ± 24.4	58.0 ± 26.9	65.1 ± 23.6	0.364
Urine ACR, mg/mmol	5.4 [1.5, 23.6]	28.3 [8.0, 157.1]	15.6 [2.5, 91.4]	0.066

Data are expressed as number (percentage), mean ± standard deviation, or median (inter-quartile range)

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

	HFrEF	HFmrEF	HFpEF	p for trend between HF subtypes
Diabetes-related complications, n (%)				
Albuminuria	88 (61.5)	73 (82.0)	256 (70.9)	0.118
Chronic kidney disease	56 (38.1)	51 (54.8)	150 (40.4)	0.983
Diabetic sensory neuropathy	41 (27.9)	32 (34.4)	110 (29.6)	0.842
Diabetic retinopathy	46 (46.5)	35 (56.5)	115 (46.7)	0.834
Coronary heart disease	29 (19.7)	18 (19.4)	69 (18.6)	0.758
Stroke	7 (4.8)	9 (9.7)	18 (4.9)	0.760
Cancer	5 (3.4)	8 (8.6)	11 (3.0)	0.491
Use of medications, n (%)				
RAAS inhibitor	52 (35.4)	44 (47.3)	145 (39.1)	0.649
BP lowering drugs	99 (67.3)	73 (78.5)	272 (73.3)	0.272
Lipid lowering drugs	48 (32.7)	31 (33.3)	116 (31.3)	0.720
Insulin	32 (21.8)	33 (35.5)	120 (32.3)	0.036
Non-insulin glucose lowering drugs	115 (78.2)	71 (76.3)	275 (74.1)	0.316

Data are expressed as number (percentage), mean ± standard deviation, or median (inter-quartile range)

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

Clinical predictors of incident HF, stratified by HF subtypes

Multivariate Cox proportional hazards models were conducted to identify clinical factors associated with incident HF (Table 2). Only variables that showed significant association with incident HF in univariate analysis were included (Supplementary Table 5). Old age, low estimated GFR, high urine ACR and history of CHD were independently associated with increased hazards of incident HF, irrespective of HF subtypes. In addition, female sex, BMI and history of sensory neuropathy were associated with increased hazards of incident HFpEF, and HDL-cholesterol was inversely associated with incident HFmrEF.

Table 2
Multivariate Cox proportional hazard models showing the association between clinical factors and incident heart failure according to heart failure subtypes

	HFrEF *vs* without HF		**HFmrEF *vs* without HF**		**HFpEF *vs* without HF**	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	0.91 (0.53, 1.57)	0.738	0.87 (0.41, 1.86)	0.717	0.69 (0.52, 0.92)	0.010
Age at enrollment	1.03 (1.01, 1.06)	0.018	1.06 (1.02, 1.10)	0.002	1.05 (1.04, 1.07)	< 0.001
Duration of diabetes	1.00 (0.97, 1.03)	0.972	1.00 (0.96, 1.04)	0.956	1.00 (0.99, 1.02)	0.654
Previous smoking	1.24 (0.67, 2.30)	0.491	0.85 (0.36, 2.05)	0.724	-	-
Current smoking	1.69 (0.87, 3.28)	0.121	0.91 (0.28, 2.91)	0.875	-	-
BMI	-	-	-	-	1.10 (1.07, 1.14)	< 0.001
Systolic BP	1.01 (0.99, 1.02)	0.388	1.00 (0.99, 1.02)	0.867	1.00 (0.99, 1.01)	0.723
HDL-cholesterol_time varying variable	0.76 (0.38, 1.50)	0.424	0.15 (0.05, 0.47)	0.001	-	-
LDL-cholesterol_time varying variable	0.91 (0.71, 1.17)	0.469	-	-	0.85 (0.72, 1.00)	0.053
Estimated GFR_time varying variable	0.99 (0.98, 1.00)	0.027	0.97 (0.96, 0.99)	0.005	0.98 (0.97, 0.99)	< 0.001
HbA1c_ time varying variable	1.02 (0.87, 1.19)	0.795	0.98 (0.78, 1.24)	0.872	0.98 (0.89, 1.08)	0.713

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; CI, confidence interval; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

	HFrEF *vs* without HF		HFmrEF *vs* without HF		HFpEF *vs* without HF	
Log urine ACR_time varying variable	1.25 (1.09, 1.44)	0.001	1.23 (1.00, 1.52)	0.050	1.39 (1.28, 1.52)	< 0.001
History of diabetic retinopathy	1.30 (0.81, 2.11)	0.278	1.48 (0.75, 2.94)	0.258	1.25 (0.93, 1.68)	0.132
History of diabetic sensory neuropathy	1.31 (0.79, 2.15)	0.297	0.94 (0.45, 1.96)	0.863	1.42 (1.04, 1.93)	0.026
History of coronary heart disease_time varying variable	16.65 (9.94, 27.87)	< 0.001	13.50 (6.60, 27.60)	< 0.001	3.29 (2.47, 4.40)	< 0.001
History of stroke_time varying variable	1.98 (1.18, 3.33)	0.010	1.26 (0.55, 2.90)	0.583	1.44 (1.01, 2.04)	0.043
Use of RAAS inhibitor	0.85 (0.49, 1.46)	0.553	0.87 (0.43, 1.76)	0.700	0.97 (0.71, 1.34)	0.867
Use of BP lowering drugs	1.02 (0.56, 1.85)	0.948	1.69 (0.61, 4.67)	0.309	1.00 (0.68, 1.48)	0.999
Use of lipid lowering drugs	-	-	-	-	0.90 (0.66, 1.23)	0.517

ACR, albumin-to-creatinine; BMI, body mass index; BP, blood pressure; CI, confidence interval; GFR, glomerular filtration rate; HDL, high density-lipoprotein; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LDL, low density-lipoprotein; RAAS, renin-angiotensin-aldosterone system

Mortality rates post-HF

Over a median time of 2.1 [IQR 0.7, 4.8] years after HF, 760 people died. The mortality rate post-HF for the entire cohort was 189.4 per 1,000 person-year, and the mortality rates for people with HFrEF, HFmrEF and HFpEF were 162.3, 209.0 and 153.2 per 1,000 person-year, respectively, with no between-group difference (Table 3). Mortality rates at 1 year post-HF was lower in people with HFpEF (16.2%) than those with HFmrEF (*vs* 26.9%, p = 0.034) and HFrEF (*vs* 31.3%, p < 0.001) (Table 3). Mortality rates at 5 years and 10 years post-HF remained lower in people with HFpEF than those with HFmrEF, but were similar between HFpEF and HFrEF, and between HFmrEF and HFrEF (Table 3).

Table 3
Mortality rates after development of heart failure among Chinese with type 2 diabetes

	HFrEF	HFmrEF	HFpEF	All HF	p-value for HFrEF *vs* HFpEF*	p-value for HFmrEF *vs* HFpEF*	p-value for HFrEF *vs* HFmrEF*
Follow-up time from onset of HF, years (IQR)	2.21 [0.55, 5.20]	2.34 [0.79, 4.52]	2.89 [1.12, 5.61]	2.41 [0.73, 4.82]			
Number of deaths	85	67	223	760			
1-year mortality, n (%)	46 (31.3)	25 (26.9)	60 (16.2)	304 (25.4)	< 0.001	0.034	0.363
5-year mortality, n (%)	72 (49.0)	59 (63.4)	169 (45.6)	629 (52.6)	0.199	0.008	0.199
10-year mortality, n (%)	82 (55.8)	66 (71.0)	215 (58.0)	744 (62.3)	0.651	0.038	0.203
Overall mortality rate, per 1,000 person-year	162.3	209.0	153.2	189.4	0.659	0.073	0.287

HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IQR, interquartile range

* P-values for multiple comparisons were adjusted using the Benjamini-Hochberg method.

Discussion

Type 2 diabetes and HF are both age-related conditions. As life expectancy of the population increases, the prevalence of comorbid diabetes and HF is expected to rise. In our longitudinal cohort of Chinese with type 2 diabetes followed for incident decompensated HF, we report the following observations: 1) Heart failure with preserved LVEF was the predominant HF subtype accounting for 60% of acute HF in people with type 2 diabetes; 2) Clinical predictors for incident HF were similar across HF subtypes with a few salient differences. Correlation of female sex, high BMI and sensory neuropathy was detected with incident HFpEF but not with other HF subtypes, and low HDL cholesterol was associated only with HFmrEF; 3) Mortality at 1 year post-HF was the lowest in the group with HFpEF but longer term mortality rates were similar between HFpEF and HFrEF with a tendency of higher mortality in the group with HFmrEF.

Distribution of HF subtypes

The distribution of HF subtypes as reported in HF registries varies depending on the region, setting (in-patient *vs* out-patient), age range, and calendar period. Heart failure with reduced LVEF was the predominant HF subtype in earlier studies but more recent studies found a larger representation of HFpEF

among those with acute or chronic HF, independent of diabetes status (16, 18, 23, 24). In the U.S-based National Cardiovascular Data Registry Practice Innovation and Clinical Excellence Registry of 1,103,386 participants with chronic HF, 57% had HFpEF and 36% had HFrEF (24). Several East Asian registries also found a preponderance of HFpEF (25, 26). In the present study, almost two third of people with decompensated HF and underlying type 2 diabetes had preserved LVEF and another 10% had mid-range LVEF on echocardiography. Collectively, the high prevalence of HFmrEF and HFpEF in contemporary cohorts of people with HF may reflect a shift in risk profile of predisposed individuals including aging and rise in obesity.

Clinical predictors of incident HF according to subtypes

The pathophysiologic processes leading to HFpEF is not well elucidated. Besides myocardial ischemia due to coronary heart disease, endothelial dysfunction in coronary microvasculature, disturbed cardiac metabolism and systemic low grade inflammation may be contributory (27). In the PRevalence Of MIcrovascular dySfunction in Heart Failure with Preserved EjectionFraction study, local microvascular dysfunction as assessed using adenosine stress Doppler echocardiography, was correlated with markers of systemic endothelial dysfunction and albuminuria (28). In the Asian Sudden Cardiac Death in Heart Failure registry, among 2,800 people with diabetes and HF, the presence of microvascular complications was associated with 1.8-fold higher odds of HFpEF versus HFrEF, independent of other clinical confounders (19). In the present study, we found that age, low GFR, albuminuria and pre-existing coronary heart disease were independent predictors of all subtypes of HF. On the other hand, female sex, BMI and sensory neuropathy were associated with incident HFpEF but not with other HF subtypes. Our results are consistent with the notion that metabolic comorbidities, as indicated by obesity, insulin resistance and microvascular disease, favor the development of HFpEF (19, 29). Notably, coronary heart disease increased the hazard of HFrEF by 16-fold and that of HFpEF by 3-fold, suggesting a larger influence on development of HFrEF versus HFpEF by atherosclerotic stenosis or occlusion, similar to findings in people without diabetes (13, 23, 29, 30).

The association between female sex and incident HFpEF has also been shown in other studies (23, 24, 30, 31). Reasons underpinning the propensity for HFpEF in women are unclear but may be due to sex differences in the distribution of risk factors. In the present study, among people with incident HF, women were older, had longer diabetes duration, worse metabolic control and a higher frequency of diabetes retinopathy, whereas men were more likely to smoke and have coronary heart disease. Although glycemic and metabolic parameters have been adjusted for in the regression model, residual confounding of unmeasured metabolic factors cannot be excluded. Men have a higher risk of premature mortality and might not have lived long enough to have HFpEF, which is also driven by age (10).

Short- and long-term mortality post-HF

Our observation of lower mortality rate at 1 year after HF in the group with HFpEF as compared with the other HF subtypes concur with results from other studies (16, 18, 25). Findings on mid- to longer-term mortality after HF are conflicting in the literatures with some studies reporting similar rates (30, 32) and in

others, lower mortality in those with HFpEF (13, 16, 26). In the present cohort of people with type 2 diabetes, we detected similar mortality rates at 5 and 10 years after HFpEF and HFrEF. People with HFrEF were more likely than those with HFpEF to have pre-existing coronary heart disease and possibly more liberal use of life-saving drugs such as statins. Conventional drug therapies for HF are effective in reducing all-cause and cardiovascular mortality in people with HFrEF but not in those with HFpEF (33–38). Mineralocorticoid receptor antagonists and angiotensin-receptor blockers may prevent HF-related hospitalization in people with HFpEF albeit with modest impact (37, 38). More recently, SGLT2 inhibitors have been shown to confer survival advantage in people with HFrEF independent of diabetes status, but evidence for those with HFpEF is pending (8). Given the high frequency of HFpEF in people with diabetes whose long-term prognosis is similar to their counterparts with HFrEF, there is an urgent need to develop new therapy with the aim to improve quality of life, reduce morbidity and mortality in this group.

The higher mortality in people with HFmrEF deserves further consideration. Mortality rates at 1, 5 and 10 years were higher in people with HFmrEF than HFpEF, and numerically higher than those with HFrEF. These findings are consistent with a prospective follow-up study of 1,405 consecutive individuals in whom 37–40% had diabetes attending heart failure clinic that have shown the strongest independent association between HFmrEF and the combined endpoint of all-cause mortality and HF-related hospitalization, particularly in those with frailty or fragility (39). Heart failure with mid-range LVEF may represent improved HFrEF on guideline-directed medical therapy (recovered HFrEF), worsened HFpEF with adverse cardiac remodelling and disease progression, or a discrete condition (11). In our study, the group with HFmrEF resembled those with HFrEF with respective to smoking status and BMI at baseline. In the regression analysis, the strength of the association between history of coronary heart disease and incident HF was comparable between HFmrEF and HFrEF. Additionally, HDL-cholesterol, involved in reverse cholesterol transport and has anti-atherogenic properties, was inversely related to incident HFmrEF. Taken together, these findings point to a heavier atherosclerosis burden in people with HFmrEF, as also shown in other studies (23, 24). The distinct risk profile in this group may also contribute to the higher mortality rates when compared against people with HFpEF. Current European guidelines support the management of people with HFmrEF in a manner as for those with HFrEF (10).

Limitations

Our study has several limitations. Firstly, only 51% of people with incident HF had echocardiography. As people with diabetes tend to have silent ischaemia, it is possible that those with advanced coronary disease and myocardial ischaemia might not have experienced symptoms due to potential ischaemic cardiomyopathy that could have prompted echocardiographic examinations. Those who had echocardiography were younger and had fewer vascular complications at baseline. This may have reflected the clinical practice pattern with the understanding that early development of diabetes carried with it significant later life disease burden and devastating complications. Regardless, given the healthier baseline profile of people with echocardiography, the mortality rates post-HF may be underestimated, although it is not possible to determine how this may bias comparison of clinical characteristics and prognosis by HF subtypes. Second, echocardiography was performed as part of routine clinical care, by

different operators and using different instruments over time. Reporting was not standardised and we acknowledge the potential risk of misclassification. Third, LVEF is not static and may change over time as a result of drug or device therapy or natural progression. Previous studies have shown that LVEF deteriorated in up to 40% of people and improved in another 30–40% in 1–4 years (15, 40). In the present study, we did not assess LVEF longitudinally nor examine the association between change in LVEF and mortality. In addition, other conditions that may affect LVEF (e.g. atrial fibrillation) were not captured or adjusted for. Fourth, the diagnosis of HF was based on physician coding and was not independently adjudicated. Biomarkers (e.g. brain natriuretic peptide [BNP]) were not available in the public healthcare system during the study period. Availability of BNP or N-terminal prohormone of BNP could potentially have added diagnostic value and precision to risk estimates. Fifth, only people with acute HF requiring hospitalization were captured, and our results cannot be generalized to chronic HF. Last, our results were based on a single centre with a well-developed, dedicated diabetes clinic and management team. Generalizability and external validity may be achieved in larger multicenter studies.

Conclusion

In Chinese with type 2 diabetes, HFpEF is the most common HF subtype. The overall survival rate in people with comorbid type 2 diabetes and HF is poor, as one quarter have died at 1 year and up to 60% by 10 years. Our results highlight the need to identify new treatment strategy to improve symptoms and prolong life in those with decompensated as well as pre-existing HF, especially as people with HFpEF have a reduced survival that is comparable to those with HFrEF.

Abbreviations

ACR, albumin-to-creatinine ratio

BMI, body mass index

BNP, brain natriuretic peptide

BP, blood pressure

CHD, coronary heart disease

GFR, glomerular filtration rate

HA, Hospital Authority

HDL, high density-lipoprotein

HF, heart failure

HFmrEF, heart failure with mid-range ejection fraction

HFpEF, heart failure with preserved ejection fraction

HFrEF, heart failure with reduced ejection fraction

HKDR, Hong Kong Diabetes Register

IQR, interquartile range

LDL, low density-lipoprotein

LVEF, left ventricular ejection fraction

RAAS, renin-angiotensin-aldosterone system

SD, standard deviation

SGLT-2, sodium-glucose co-transporter 2

Declarations

Ethics approval and consent to participate

All participants provided written informed consent for anonymised use of their clinical data for research purpose. The study has received approval from the Joint-Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no funding.

Authors' contributions

A.O.Y.L. contributed to conception of the article, data acquisition, interpretation of data, drafted the manuscript and approved the final version. X.Z. contributed to conception of the article, statistical

analysis and approved the final version. E.F., H.W., E.S.H.L., A.Y., E.C., A.P.S.K., R.C.W.M. and J.C.N.C. contributed to conception of the article and approved the final version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriate investigated, resolved, and the resolution documented in the literature. A.O.Y.L. is the guarantor of this work, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The authors thank all medical and nursing staff of the Diabetes and Endocrine Centre at the Prince of Wales Hospital for patient recruitment and assessment. R.C.W.M. acknowledged support from the Research Grants Council Research Impact Fund (R4012-18).

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Figures

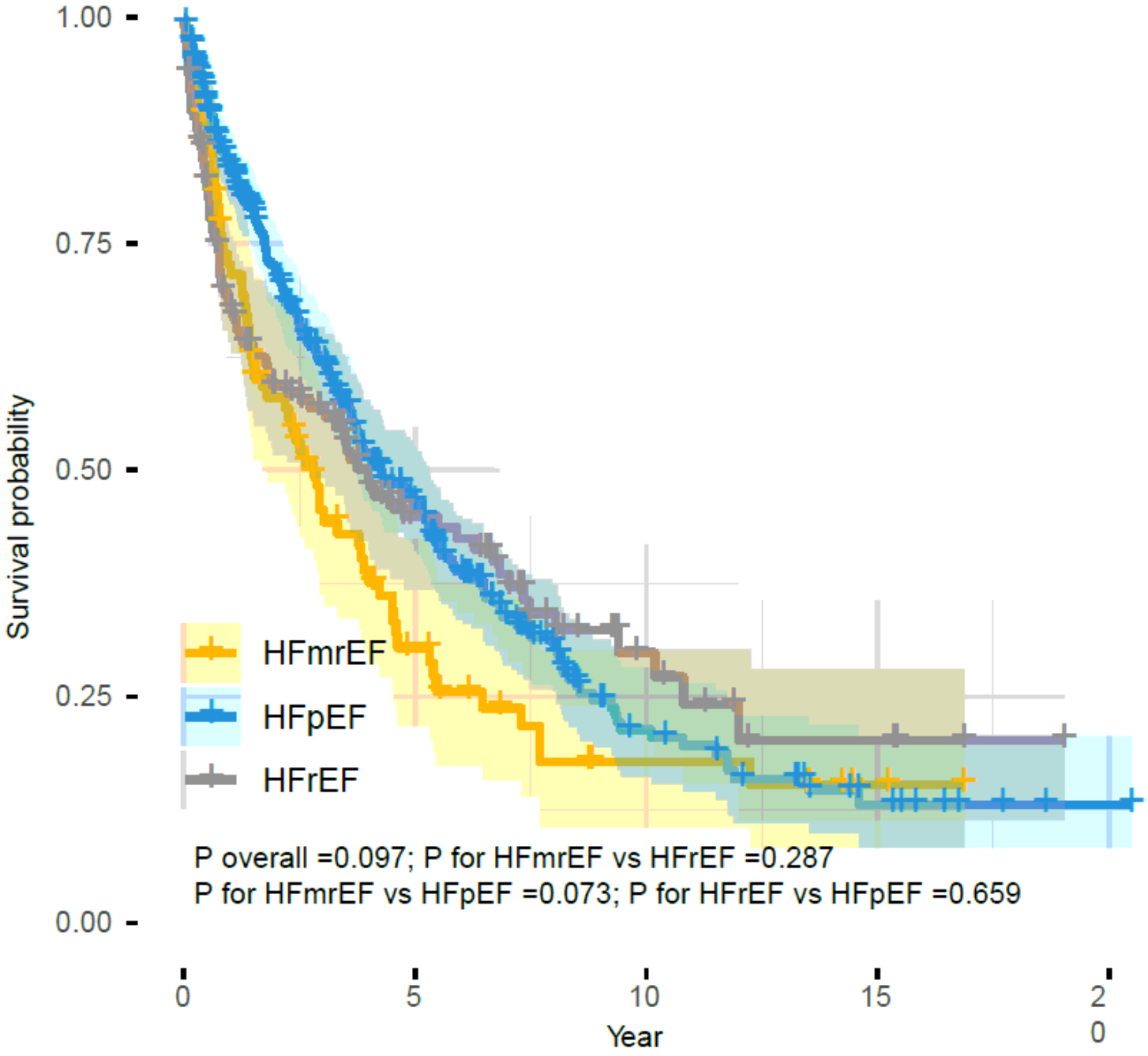

Figure 1

Survival curve for mortality after incident heart failure according to heart failure subtypes

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