Circulation

ORIGINAL RESEARCH ARTICLE

Heart Failure With Preserved Ejection Fraction in the Young

BACKGROUND: Heart failure with preserved ejection fraction (HFpEF), traditionally considered a disease of the elderly, may also affect younger patients. However, little is known about HFpEF in the young.

METHODS: We prospectively enrolled 1203 patients with HFpEF (left ventricular ejection fraction ≥50%) from 11 Asian regions. We grouped HFpEF patients into very young (<55 years of age; n=157), young (55–64 years of age; n=284), older (65–74 years of age; n=355), and elderly (≥75 years of age; n=407) and compared clinical and echocardiographic characteristics, quality of life, and outcomes across age groups and between very young individuals with HFpEF and age- and sex-matched control subjects without heart failure.

RESULTS: Thirty-seven percent of our HFpEF population was <65 years of age. Younger age was associated with male preponderance and a higher prevalence of obesity (body mass index ≥30 kg/m^2; 36% in very young HFpEF versus 16% in elderly) together with less renal impairment, atrial fibrillation, and hypertension (all P<0.001). Left ventricular filling pressures and prevalence of left ventricular hypertrophy were similar in very young and elderly HFpEF. Quality of life was better and death and heart failure hospitalization at 1 year occurred less frequently (P<0.001) in the very young (7%) compared with elderly (21%) HFpEF. Compared with control subjects, very young HFpEF had a 3-fold higher death rate and twice the prevalence of hypertrophy.

CONCLUSIONS: Young and very young patients with HFpEF display similar adverse cardiac remodeling compared with their older counterparts and very poor outcomes compared with control subjects without heart failure. Obesity may be a major driver of HFpEF in a high proportion of HFpEF in the young and very young.

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Clinical Perspective

What Is New?

- We investigated age-related differences in clinical characteristics, cardiac structure and function, quality of life, and clinical outcomes in patients with heart failure with a preserved ejection fraction (HFpEF).
- Younger patients with HFpEF are more often obese and have fewer comorbidities yet similar filling pressures and left ventricular hypertrophy.
- Quality of life and mortality were better in younger patients with HFpEF, yet mortality was markedly worse compared with age- and sex-matched control subjects without heart failure.

What Are the Clinical Implications?

- HFpEF is often considered a disease of the elderly; however, our results show that HFpEF also occurs in younger patients who are often obese.
- Therefore, the diagnosis of HFpEF might easily be missed in younger, more obese patients and deserves further consideration.
- In addition, obesity seems to be an important factor for developing HFpEF at a young age.
- Future interventions could specifically target obesity to both prevent and treat HFpEF in the young.

Heart failure (HF), particularly HF with preserved ejection (HFpEF), is considered a disease of the elderly.[1] Nevertheless, earlier studies have shown that HF also affects younger patients who are frequently working productively and helping to raise a family. Asian patients with HF are considerably younger than their Western peers.[2] However, the characteristics and outcomes of young patients with HFpEF have not been well described. Prior studies either reported undifferentiated HF or focused exclusively on HF with a reduced ejection fraction (HFrEF).[3–6] This can be explained by the relatively high proportion of HFrEF, including most young patients with HF, in earlier studies.[3–7] Greater understanding of the clinical and echocardiographic characteristics, quality of life, and outcomes in young patients with HFpEF is of particular importance given the global epidemiological rise of risk factors for developing HFpEF, including obesity, diabetes mellitus, and hypertension.[8,9]

The ASIAN-HF registry (Asian Sudden Cardiac Death in Heart Failure) indicates that Asian patients with HF are almost a decade younger than their Western counterparts,[2] making the ASIAN-HF registry uniquely suited to study any possible young HFpEF phenotype. Therefore, we aimed to compare clinical and echocardiographic characteristics, quality of life, and outcomes across age groups in patients with HFpEF. To address any concern that young patients with HFpEF may not truly have HF, we ensured all participants' diagnosis and compared our young HFpEF group with age- and sex-matched community-based participants without HF.

METHODS

Study Population

For legal reasons, study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure. We studied clinical and echocardiographic characteristics and outcomes in 1203 patients with HFpEF from the ASIAN-HF registry, the design and initial results (of patients with HFrEF) of which have been published previously.[10] In brief, ASIAN-HF is a multinational registry of Asian patients with HF from 46 medical centers across 11 Asian regions (Taiwan, Hong Kong, China, India, Malaysia, Thailand, Singapore, Indonesia, the Philippines, Japan, and Korea). Recruitment was undertaken in cardiology and HF specialty units with considerable experience in following up and treating chronic HF. Inclusion criteria for ASIAN-HF included a diagnosis of HF (based on signs and symptoms, as well as response to therapy) with a recent episode of decompensation (within 6 months) that resulted in hospitalization (HF as primary diagnosis) or treatment as an outpatient. Patients were excluded if they had valve disease, had a life-threatening comorbidity with life expectancy of <1 year, were unable or unwilling to give consent, or were participating in a concurrent clinical therapeutic trial that requires patient consent and a documented history of reduced left ventricular (LV) ejection fraction (<50%). Echocardiography was performed at recruitment. Data on demographics, medical history, clinical symptoms, and functional status were collected. Patients underwent standard 12-lead ECG and transthoracic echocardiography at inclusion according to protocol.[10] Patients with HFpEF were grouped by age into very young (<55 years of age), young (55–64 years of age), older (65–74 years of age), and elderly (≥75 years of age).

We compared our very young (<55 years of age) patients with HFpEF with age- and sex-matched control subjects without HF from the SHOP study (Singapore Heart Failure Outcomes and Phenotypes), the design of which has been previously described.[11] Control subjects included 972 free-living adults without HF identified from the general community of Singapore via random sampling of all residents in continuous precincts within 5 districts of Singapore by door-to-door census. Control subjects underwent standardized clinical examination and echocardiography identically applied to patients with HF and were followed up for outcomes.

Study Definitions

The definitions of common risk factors and comorbidities in ASIAN-HF have previously been described.[2,10] Obesity was defined according to standard body mass index (BMI) cutoffs defined by World Health Organization (underweight, BMI <18.5 kg/m^2; overweight, BMI ≥25 kg/m^2; obese, BMI ≥30 kg/m^2). Coronary artery disease included the angiographically documented presence of significant coronary obstruction, history of myocardial infarction, or prior revascularization. Hypertension was defined as the clinical diagnosis (blood

pressure ≥140/90 mm Hg) and/or receiving antihypertensive therapy. Diabetes mellitus was defined as the presence of the clinical diagnosis (fasting plasma glucose ≥7 mmol/L, random plasma glucose ≥11.1 mmol/L, hemoglobin A_{1c} ≥6.5%, and/or receiving antidiabetic therapy). The estimated glomerular filtration rate was calculated with the MDRD study (Modification of Diet in Renal Disease) equation. Chronic kidney disease (CKD) was determined with an estimated glomerular filtration rate cutoff point of <60 mL·min^{-1}·1.73 m^{-2}. Ethnicity was self-reported and grouped as Chinese, Indian, Malay, Japanese/Korean, and other. Health status was measured with the Kansas City Cardiomyopathy Questionnaire, a 23-item self-administered HF-specific questionnaire that has been validated in multiple HF-related disease states[12,13] and in several languages.[14–16] Computed Kansas City Cardiomyopathy Questionnaire domain scores ranged from 0 to 100; higher scores represent better health status. Non–English-speaking participants used certified versions of the Kansas City Cardiomyopathy Questionnaire translated into their native languages.[17]

Outcomes

The primary outcome of this study was all-cause death or HF rehospitalization at 1 year. A total of 1111 patients (92%) had outcomes data available, whereas 92 patients (8%) were lost to follow-up. Patients followed up for <1 year were censored at their last known visit date. All data were captured prospectively in an electronic database, and registry operations and data management were handled by Quintiles Outcomes as the contract research organization appointed by the academic Executive Committee. Ethics approvals were obtained from relevant institutions at all sites. All participants provided informed consent, and this study adheres to the principles of medical research as laid down in the Declaration of Helsinki.

Echocardiography

The collection and processing of echocardiographic data have been reported previously.[10] Echocardiography was performed at each center according to internationally accepted guidelines.[18] In addition to LV ejection fraction and LV dimensions, left atrial size, LV diastolic function, stroke volume, and cardiac output were documented. The Cardiovascular Imaging Laboratory of the National University Health System, Singapore, provided oversight and imaging protocol guidelines and quality assurance of the echocardiograms. Echocardiographic measurements were performed at the site level with standardized protocols provided by the echocardiography laboratory in Singapore. LV mass was calculated from linear dimensions and indexed to height$^{2.7}$ and to body surface area.[18] Relative wall thickness (RWT) was calculated by the following formula: (2×diastolic posterior wall thickness)/diastolic LV internal diameter. LV hypertrophy (LVH) was determined as LV mass indexed to body surface area >115 g/m^2 in men and >95 g/m^2 in women.[18] Normal LV geometry was defined as having no LVH and an RWT ≤0.42. Abnormal LV geometry was classified as concentric remodeling (no LVH and RWT >0.42), concentric hypertrophy (LVH and RWT >0.42), and eccentric hypertrophy (LVH and RWT ≤0.42). Left atrial size was indexed to body surface area.[18]

Statistical Analysis

Baseline descriptive statistics are stratified and presented according to age categories, as means plus SD, medians plus interquartile range, or numbers and percentages. Differences between groups were tested with 1-way ANOVA, the Kruskal-Wallis test, or the χ^2 test when appropriate. Associations of clinical characteristics and age were studied in multivariable analysis with logistic regression. Here, we dichotomized age to compare cases <65 with those ≥65 years of age and performed multivariable logistic regression analysis correcting for sex, economic status, obesity, diabetes mellitus, hypertension, coronary artery disease, CKD, atrial fibrillation, ethnicity, and New York Heart Association class. Differences in survival were depicted with Kaplan-Meier graphs and tested with the log-rank test. For multivariable survival analysis, Cox regression analysis was used with correction for sex, economic status, obesity, diabetes mellitus, hypertension, coronary artery disease, CKD, atrial fibrillation, ethnicity, New York Heart Association class, and medication use. We performed additional analysis for all-cause mortality and hospitalizations for HF separately. In the latter case, we set all-cause mortality as a competing risk. We tested the proportionality of hazards assumption and found it to be valid. We performed sensitivity analyses in a subset of patients in whom plasma brain natriuretic peptide (BNP) or NT-proBNP (N-terminal pro-B-type natriuretic peptide) results (n=455) were available. Notably, in 90% of these cases, BNP/NT-proBNP levels fell above guideline-recommended cutoff values.[19] Last, we performed sensitivity analyses in patients included as inpatients or outpatients. All tests were performed 2-sided, and values of P<0.05 were considered statistically significant. Statistical analyses were performed with STATA 14.0 (Stata Corp, College Station, TX).

RESULTS

Baseline Characteristics

Among 1203 patients with HFpEF (mean age, 68.4±12.2 years; 50% women), 37% were <65 years of age, including 157 (13%) very young (<55 years of age) and 284 (24%) young (55–64 years of age) patients. Compared with older age groups (Table 1), very young patients with HFpEF were more often men (61%), had better New York Heart Association functional class (86% class I–II), were more likely to be obese (36%), and had a similar prevalence of coronary artery disease but a lower prevalence of CKD, diabetes mellitus, prior stroke, atrial fibrillation, and hypertension. In sensitivity analysis with Asian-specific cutoff points for BMI, very young (<55 years of age) patients had even higher rates (54%) of obesity. Young patients with HFpEF were more often on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-blockers and less often on diuretics. Overall, >90% of patients had classic signs or symptoms of HF at inclusion.

Univariable associations of younger age groups (<65 years of age) were male sex, Malay ethnicity, and obesity. After multivariable adjustment, independent corre-

Table 1. Baseline Characteristics

	Control Subjects	HFpEF					
	<55 y	<55 y	55–65 y	65–74 y	≥75 y	*P* Value*	*P* for Trend*
n	157	157	284	355	407		
Demographics							
Age, y	46.9 (7.2)	46.8 (7.6)	60.4 (2.9)	69.9 (2.9)	81.1 (4.5)	NA	NA
Women, n (%)	61 (38.9)	61 (38.9)	119 (41.9)	179 (50.4)	238 (58.5)	<0.001	<0.001
Race, n (%)						<0.001	<0.001
Chinese	100 (64.5)	43 (27.4)	115 (40.5)	171 (48.2)	259 (63.6)		
Indian	18 (11.6)	62 (39.5)	91 (32.0)	94 (26.5)	59 (14.5)		
Malay	37 (23.9)	29 (18.5)	53 (18.7)	30 (8.5)	25 (6.1)		
Japanese/Korean	0 (0.0)	23 (14.6)	21 (7.4)	55 (15.5)	61 (15.0)		
Others	0 (0.0)	0 (0.0)	4 (1.4)	5 (1.4)	3 (0.7)		
Clinical characteristics							
New York Heart Association class, n (%)						<0.001	<0.001
I	NA	47 (33.8)	38 (16.5)	43 (15.5)	35 (10.5)		
II	NA	72 (51.8)	153 (66.2)	166 (59.9)	191 (57.5)		
III	NA	19 (13.7)	37 (16.0)	60 (21.7)	92 (27.7)		
IV	NA	1 (0.7)	3 (1.3)	8 (2.9)	14 (4.2)		
BMI, mean (SD), kg/m^2	24.9 (3.9)	28.9 (6.2)†	29.0 (7.0)	26.8 (5.7)	25.5 (4.8)	<0.001	<0.001
BMI categories, n (%)						<0.001	<0.001
Underweight (BMI <18.5 kg/m^2)	5 (3.2)	2 (1.6)	3 (1.3)	13 (4.7)	11 (3.4)		
Normal (18.5 kg/m^2≤BMI<25 kg/m^2)	82 (52.6)	34 (27.0)	63 (28.1)	97 (35.4)	153 (46.8)		
Overweight (25 kg/m^2≤BMI<30 kg/m^2)	52 (33.3)	45 (35.7)	76 (33.9)	101 (36.9)	111 (33.9)		
Obese (BMI ≥30 kg/m^2)	17 (10.9)	45 (35.7)	82 (36.6)	63 (23.0)	52 (15.9)		
Heart rate, mean (SD), bpm	68.1 (10.3)	77.9 (16.7)†	79.2 (15.2)	74.6 (15.3)	75.6 (15.1)	<0.001	0.001
Estimated GFR, mean (SD), mL·min^{-1}·1.73 m^{-2}	107.3 (20.4)	80.8 (35.6)†	65.1 (30.6)	61.7 (27.3)	53.9 (23.9)	<0.001	<0.001
LV ejection fraction, mean (SD), %	62.6 (8.1)	58.4 (6.3)†	60.7 (7.2)	60.8 (7.2)	62.1 (7.3)	<0.001	<0.001
Systolic blood pressure, mean (SD), mm Hg	122.7 (13.5)	130.2 (23.4)†	132.5 (23.9)	133.2 (21.3)	132.2 (21.8)	0.59	0.297
Diastolic blood pressure, mean (SD), mm Hg	74.7 (11.1)	78.0 (14.6)†	75.4 (12.9)	71.2 (12.3)	69.7 (12.1)	<0.001	<0.001
Ischemic pathogenesis of HF, n (%)	NA	40 (25.6)	100 (35.7)	120 (34.2)	109 (27.0)	0.058	0.567
Previous hospitalization for HF, n (%)	NA	69 (43.9)	150 (52.8)	202 (56.9)	270 (66.3)	<0.001	0.001
Shortness of breath on exertion, n (%)	1 (0.6)	85 (54.1)†	174 (61.5)	205 (57.7)	253 (62.3)	0.25	0.191
Shortness of breath on rest, n (%)	0 (0.0)	21 (13.4)†	21 (7.4)	40 (11.3)	58 (14.3)	0.043	0.143
Reduction in exercise tolerance, n (%)	6 (3.8)	85 (54.1)†	173 (61.1)	196 (55.2)	248 (61.1)	0.19	0.347
Nocturnal cough, n (%)	0 (0.0)	19 (12.1)†	33 (11.7)	37 (10.4)	68 (16.7)	0.054	0.069
Orthopnea, n (%)	0 (0.0)	22 (14.0)†	37 (13.1)	49 (13.8)	73 (18.0)	0.25	0.105
Paroxysmal nocturnal dyspnea, n (%)	0 (0.0)	17 (10.8)†	30 (10.6)	38 (10.7)	39 (9.6)	0.95	0.636
Angina, n (%)	0 (0.0)	15 (9.6)†	25 (8.9)	25 (7.1)	35 (8.6)	0.75	0.675
Elevated JVP, n (%)	8 (5.1)	17 (10.9)†	24 (8.5)	37 (10.5)	45 (11.1)	0.72	0.557
Peripheral edema, n (%)	3 (1.9)	38 (24.4)	86 (30.4)	112 (31.6)	150 (37.0)	0.027	0.003
Pulmonary rales, n (%)	0 (0.0)	12 (7.7)†	41 (14.5)	52 (14.7)	78 (19.3)	0.007	0.041
Hepatomegaly, n (%)	1 (0.6)	1 (0.6)	14 (4.9)	11 (3.1)	4 (1.0)	0.004	0.194
Hepatojugular reflux positive, n (%)	24 (15.4)	9 (5.8)†	20 (7.1)	25 (7.1)	22 (5.4)	0.75	0.645
Medical history, n (%)							
Coronary heart disease	0 (0.0)	35 (22.4)†	93 (33.6)	94 (27.1)	124 (30.7)	0.066	0.354
CKD	0 (0.0)	29 (27.1)†	93 (43.9)	138 (48.9)	221 (62.4)	<0.001	<0.001

(*Continued*)

Table 1. Continued

	Control Subjects	HFpEF					
	<55 y	<55 y	55–65 y	65–74 y	≥75 y	*P* Value*	*P* for Trend*
Diabetes mellitus	10 (6.4)	51 (32.7)†	147 (53.1)	160 (45.7)	178 (44.1)	<0.001	0.481
Stroke	0 (0.0)	4 (2.6)†	16 (5.8)	30 (8.6)	46 (11.4)	0.002	<0.001
Atrial fibrillation	0 (0.0)	23 (14.7)†	44 (15.9)	105 (30.0)	166 (41.1)	<0.001	<0.001
Hypertension	24 (15.5)	76 (48.7)†	188 (67.9)	252 (72.0)	326 (80.7)	<0.001	<0.001
Peripheral arterial disease	0 (0.0)	1 (0.6)	5 (1.8)	8 (2.3)	10 (2.5)	0.55	0.179
COPD	3 (1.9)	10 (6.4)†	18 (6.5)	31 (8.9)	49 (12.1)	0.043	0.007
Medication, n (%)							
ACE inhibitor/ARB	NA	82 (67.8)	178 (71.8)	213 (68.5)	220 (60.4)	0.021	0.014
β-Blocker	NA	91 (75.2)	186 (75.0)	210 (67.5)	220 (60.4)	<0.001	<0.001
MRA	NA	36 (29.8)	44 (17.7)	69 (22.2)	75 (20.6)	0.065	0.301
Diuretics	NA	75 (62.0)	154 (62.1)	228 (73.3)	283 (77.7)	<0.001	<0.001
Laboratory							
NT-proBNP, median (IQR), pg/mL	36 (19–57)	665 (107–1809)†	1518 (456–3524)	1392 (613–2624)	1722 (671–3643)	0.008	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; JVP, jugular venous *pressure*; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NA, not available; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

**P* value for difference between different age groups of patients with HFpEF.

†*P*≤0.05 for very young patients with HFpEF versus control subjects (age <55 years).

lates of younger age in HFpEF included male sex (odds ratio [OR], 2.5; 95% CI, 1.7–3.7), Malay (OR, 5.1; 95% CI, 2.9–8.8), or Indian (OR, 2.3; 95% CI, 1.1–4.7) rather than Chinese ethnicity, and obesity (OR, 3.2; 95% CI, 2.0–4.9; Figure 1). NT-proBNP levels were lower with decreasing age (*P*=0.008); however, this was attenuated when corrected for sex, BMI, and atrial fibrillation. On sensitivity analysis, results in the subgroup with natriuretic peptide levels above the guideline-endorsed cutoff values confirmed those from the entire cohort (Figure I in the online-only Data Supplement). Additional sensitivity analyses repeating our analyses in patients included as inpatients or outpatients showed similar results (Figure II in the online-only Data Supplement).

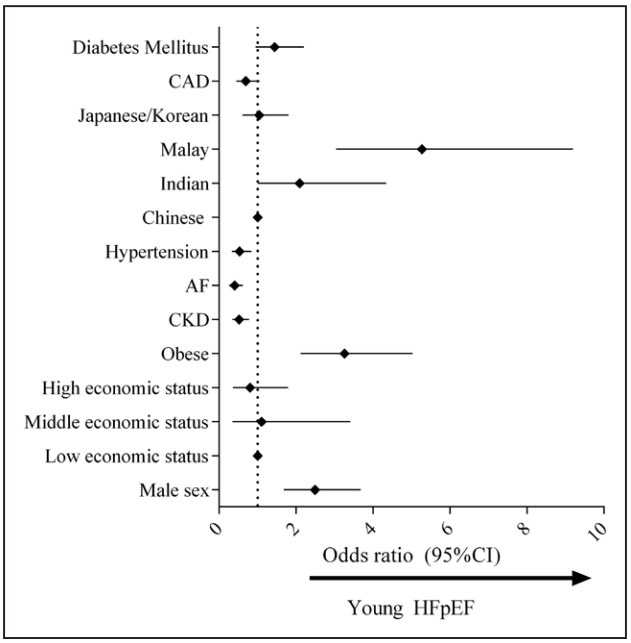

Figure 1. Forest plot depicting associations between young (<65 years of age) and older patients with heart failure with preserved ejection fraction (HFpEF) in multivariable analysis.

AF indicates atrial fibrillation; CAD, coronary artery disease; and CKD, chronic kidney disease.

Echocardiographic Parameters

Across age groups among patients with HFpEF (Table 2), younger age was associated with larger LV end-diastolic and end-systolic volumes (before and after indexation for body size) and smaller left atrial volume. There was no difference in mean LV mass index, RWT, or mitral E/e' ratio among age groups of HFpEF. The distribution of LV geometry across age groups is shown in Figure 2. There was no statistical difference in prevalence of LVH (≈46% in the entire cohort) across age strata on echocardiography (*P*=0.263). RWT was more often (*P*=0.021) abnormal (>0.42) in very young patients (58%) compared with the elderly (51%). The prevalence of LVH remained similar between age groups after correction for sex and BMI (*P*=0.432). After adjustment for sex and BMI, younger age was associated with a higher prevalence of abnormal cardiac remodeling (RWT >0.42; OR, 1.02 [per additional year]; 95% CI, 1.01–1.03; *P*=0.007). The 2016 European Society of Cardiology criteria for diastolic dysfunction (E/e' ≥13, E' medial/lateral <9 milliseconds, left atrial enlargement,

Table 2. Echocardiographic Characteristics

	Controls	HFpEF					
	<55 y	<55 y	55–65 y	65–74 y	≥75 y	*P* Value*	*P* for Trend*
n	157	157	284	355	407		
LV end-diastolic volume, median (IQR), mL	97 (81–114)	112 (84–148)†	100 (81–128)	94 (75–119)	87 (65–111)	<0.001	<0.001
LV end-systolic volume, median (IQR), mL	36 (29–44)	48 (34–63)†	39 (29–52)	38 (28–53)	33 (25–47)	<0.001	<0.001
LV end-diastolic volume, indexed to BSA, median (IQR), mL/m^2	57.1 (46.9–66.7)	55.3 (46.4–71.6)	55.0 (44.0–71.9)	53.0 (40.7–66.3)	51.0 (36.4–65.5)	0.022	<0.001
LV end-systolic volume, indexed to BSA, median (IQR), mL/m^2	21.1 (16.8–25.2)	25.8 (18.8–33.9)†	23.2 (17.1–31.2)	22.4 (17.4–32.3)	19.8 (14.2–29.5)	0.004	0.001
Interventricular septal thickness in diastole, median (IQR), mm	8.0 (7.0–10.0)	10.0 (10.0–12.0)†	11.0 (9.3–13.0)	10.0 (9.0–12.0)	10.0 (9.0–12.0)	0.068	0.029
PWT in diastole, median, (IQR), mm	8.0 (7.0–9.0)	10.0 (9.4–11.0)†	11.0 (9.6–12.0)	10.0 (9.0–12.0)	10.0 (9.0–11.8)	0.037	0.040
LV mass, median, (IQR), g	129 (105–157)	181 (153–239)†	186 (153–241)	181 (149–220)	170 (136–207)	0.007	0.001
LV mass, indexed to height$^{2.7}$, median, (IQR), g/m$^{2.7}$	34.0 (28.6–40.2)	48.6 (40.3–62.9)†	52.6 (40.0–66.5)	51.5 (42.2–62.8)	50.5 (40.7–65.4)	0.36	0.480
LV mass, indexed to BSA, median, (IQR), g/m^2	75.5 (63.9–87.3)	95.7 (85.5–118.1)†	105.3 (80.2–133.5)	103.9 (85.2–125.1)	100.7 (85.8–130.6)	0.36	0.176
Relative wall thickness, median, (IQR)	0.35 (0.30–0.39)	0.43 (0.38–0.49)†	0.45 (0.38–0.52)	0.43 (0.36–0.52)	0.42 (0.37–0.52)	0.16	0.365
Relative wall thickness >0.42, n (%)	14 (8.9)	65 (57.5)†	138 (64.1)	147 (53.9)	154 (50.8)	0.021	0.015
LV ejection fraction, median (IQR), %	63 (61–65)	58 (54–61)†	60 (55–65)	60 (55–65)	62 (56–67)	<0.001	<0.001
E wave, median (IQR), cm/s	71 (62–84)	79 (60–97)†	80 (60–101)	77 (62–96)	82 (63–105)	0.58	0.248
A wave, median (IQR), cm/s	53 (45–63)	68 (55–87)†	76 (61–92)	84 (67–99)	86 (67–101)	<0.001	<0.001
E' medial, median (IQR), cm/s	9.0 (7.0–10.0)	5.0 (4.0–7.0)†	5.5 (4.1–6.7)	5.0 (4.0–7.0)	5.0 (4.0–6.3)	0.43	0.192
E/e' medial, median (IQR)	8.2 (6.8–9.7)	14.6 (10.9–18.8)†	15.0 (11.4–20.0)	15.4 (11.8–20.0)	16.7 (12.0–22.2)	0.29	0.065
E/a' medial, median (IQR)	1.3 (1.1–1.6)	1.1 (0.9–1.4)†	1.0 (0.8–1.3)	0.9 (0.7–1.2)	0.8 (0.6–1.3)	<0.001	<0.001
Left atrial volume, median (IQR), mL	44 (36–50)	54 (40–84)†	52 (37–70)	60 (40–81)	69 (48–90)	<0.001	<0.001
Left atrial volume, indexed to BSA, median (IQR), mL/m^2	26.6 (21.8–28.0)	28.3 (20.6–39.7)	29.9 (20.5–39.9)	35.2 (23.0–47.1)	41.8 (30.1–54.7)	<0.001	<0.001

BSA indicates body surface area; HFpEF, heart failure with preserved ejection fraction; IQR, interquartile range; LV, left ventricular; and PWT, posterior wall thickness.
**P* value for difference between different age groups of patients with HFpEF.
†*P*≤0.05 for very young patients with HFpEF versus control subjects (age <55 years).

or LVH) were fulfilled by 99.5% of patients with no difference between centers or age strata (*P*>0.3) in additional sensitivity analyses.[19]

Compared with age- and sex-matched control subjects without HF, very young patients with HFpEF had larger LV volumes, a thicker posterior wall,

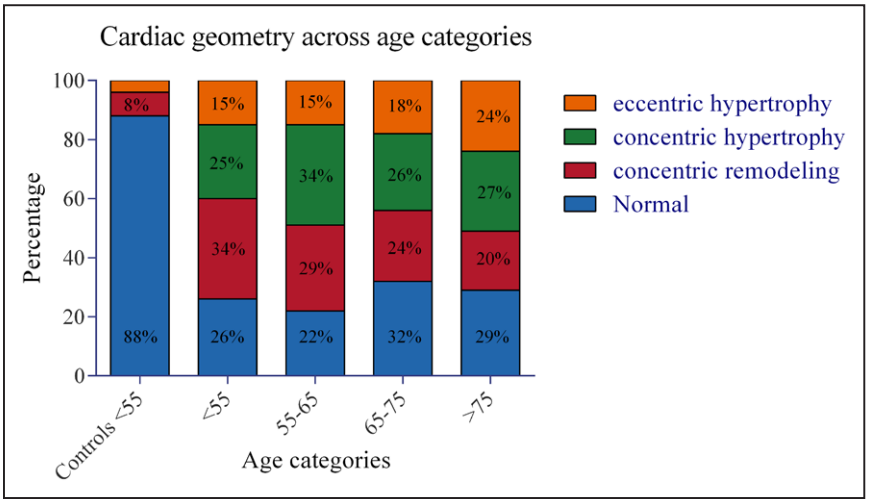

Figure 2. Cardiac geometry for age- and sex-matched control subjects (<55 years of age) and across age categories in heart failure with preserved ejection fraction.

Table 3. Quality of Life

	Age <55 y (n=157)	Age 55–65 y (n=284)	Age 65–74 y (n=355)	Age ≥75 y (n=407)	*P* Value	*P* for Trend
KCCQ Physical Limitation score	80.3 (22.3)	75.9 (23.1)	74.2 (25.0)	69.1 (27.0)	<0.001	<0.001
KCCQ Symptom Stability score	67.7 (25.5)	58.8 (25.4)	60.9 (25.9)	55.5 (25.7)	<0.001	<0.001
KCCQ Symptom Frequency score	75.4 (24.4)	73.6 (26.5)	72.5 (25.7)	67.9 (28.8)	0.021	0.011
KCCQ Symptom Burden score	80.4 (23.8)	78.4 (25.1)	79.0 (22.1)	77.0 (23.2)	0.530	0.038
KCCQ Total Symptom score	77.9 (23.2)	75.9 (24.8)	75.7 (22.8)	72.5 (24.8)	0.120	0.020
KCCQ Self-Efficacy score	74.7 (23.8)	71.8 (24.8)	67.1 (24.2)	63.0 (26.4)	<0.001	<0.001
KCCQ Quality of Life score	70.0 (23.4)	67.7 (26.7)	66.4 (23.4)	65.1 (22.3)	0.260	0.011
KCCQ Social Limitation score	81.0 (25.8)	77.0 (30.0)	72.8 (30.9)	69.4 (31.1)	0.003	<0.001
KCCQ Overall Summary score	77.4 (20.2)	74.1 (22.8)	72.5 (21.8)	69.1 (22.5)	0.002	<0.001
KCCQ Clinical Summary score	79.3 (20.2)	76.2 (21.7)	75.0 (21.3)	70.5 (23.3)	<0.001	<0.001

Values are mean (SD).
KCCQ indicates Kansas City Cardiomyopathy Questionnaire.

considerably greater LV mass, higher E/e' ratios, and larger left atria (Table 2), as well as >10 times (40% versus 4%) the incidence of LVH and >4 times the incidence of concentric remodeling (Figure 2). In addition, age- and sex-matched control subjects did not have any concentric hypertrophy compared with 25% of very young patients with HFpEF (Figure 2). These differences remained significant after adjustment for BMI, hypertension, diabetes mellitus, coronary artery disease, CKD, and atrial fibrillation (*P*<0.0001). In a sensitivity analysis, very young patients with natriuretic peptides above the recommended cutoff point had rates of LVH and E/e' ratios similar to those of the total very young subcohort. Results were similar when stratified to patients enrolled as inpatients or outpatients.

Quality of Life

Compared with the elderly, very young patients with HFpEF had better Kansas City Cardiomyopathy Questionnaire scores for both the individual components and the overall and clinical summary scores (Table 3).

Outcomes

Among patients with HFpEF, increasing age was associated with a higher risk of the composite outcome of all-cause mortality or HF hospitalization (Figure 3). This association remained significant after adjustment for clinical covariates such as BMI, hypertension, diabetes mellitus, coronary artery disease, CKD, atrial fibrillation, and medication (hazard ratio, 1.04 per 1-year increase in age; 95% CI, 1.02–1.07; *P*<0.001). After further ad-

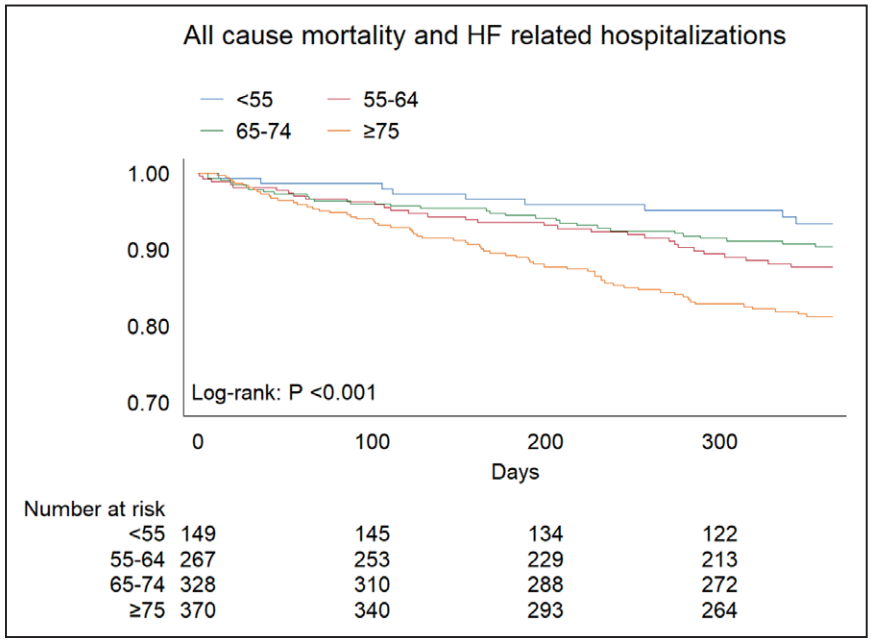

Figure 3. Kaplan-Meier curves depicting differences in outcomes for the combined outcome of all-cause mortality and heart failure (H)–related hospitalizations at 1 year between age categories.

justment for LV geometry, the association between age and outcomes remained significant. For mortality alone, older age was associated with higher rates of mortality in the fully adjusted model (hazard ratio, 1.09; 95% CI, 1.04–1.15; *P*<0.001). Equally, older age was associated with higher rates of HF hospitalizations within 1 year of recruitment in the fully adjusted model (hazard ratio, 1.02; 95% CI, 1.01–1.05; *P*=0.012). On sensitivity analysis, in patients with natriuretic peptide values above the recommended cutoff values, older age was associated with more adverse outcomes in multivariable analyses (hazard ratio, 1.09; 95% CI, 1.01–1.17; *P*=0.027). Strikingly, very young patients more often died of cardiovascular-related causes (100%) versus the elderly (63%; *P* for trend=0.004). The association between age and clinical outcomes was not affected by enrollment status ($P_{interaction}$=0.790).

Compared with age- and sex-matched control subjects without HF, very young patients with HFpEF had worse survival (*P*<0.001) with >3-fold higher crude deaths within 1 year (Table 1).

DISCUSSION

These are the first data on the clinical and echocardiographic characteristics, quality of life, and outcomes of young (<65 years of age) and very young (<55 years of age) patients with HFpEF compared with their older counterparts and age-matched control subjects without HF. Young and very young patients with HFpEF were primarily men with high rates of obesity, and of Malay or Indian rather than Chinese ethnicity in our Asian cohort. Young and very young patients with HFpEF displayed similarly raised LV filling pressures and LVH compared with older patients with HFpEF but carried a lower burden of comorbidities. Overall quality of life was better, but symptom burden/total symptoms impaired health-related quality of life to a similar extent in young and very young versus old patients with HFpEF. Abnormalities in cardiac remodeling and reduction in survival were clearly demonstrated in young and very young patients with HFpEF compared with age- and sex-matched control subjects without HF. The present analysis extends information from prior studies as (1) being the first multinational, multicenter prospective study on HFpEF in the young in Asia with standardized characterization, systematic follow-up, and adjudication of outcomes; (2) providing comparisons with age- and sex-matched control subjects without HF, confirming abnormal cardiac structure and function commensurate with HFpEF; and (3) providing novel data on echocardiographic characteristics and quality of life in these patients. These data show that a third of HFpEF cases in Asia occur at <65 years of age and that young HFpEF contributes substantially to the diversity of the HFpEF syndrome.

A striking finding in our study was that obesity was twice as common in young and very young versus elderly patients with HFpEF, suggesting that obesity may play a key role in the development of HFpEF in the young. Obesity is known to be associated with LVH and LV dysfunction that may be attributable to systemic metabolic derangement in addition to the mechanical load of increased body weight.[20,21] Given the challenges of making a diagnosis of HFpEF and the perception of HFpEF as a disease of the elderly, very young and young obese patients with HFpEF may be particularly prone to being misdiagnosed or misclassified as not having HF. Our data demonstrate the presence of the cardinal features of the syndrome of HFpEF in these patients, including symptoms and signs, objective evidence of cardiac structural abnormalities comparable to the typical elderly HFpEF, and poor outcomes compared with age- and sex-matched control subjects. These data are consistent with those of Obokata et al[22] in Olmsted County showing that the obese HFpEF phenotype is indeed "real" HFpEF and extend this to a lower BMI spectrum than previously studied (obese HFpEF defined as BMI ≥35 kg/m^2 in the prior study but ≥30 kg/m^2 in the present study). The prevalence of subclinical LV dysfunction has been shown to occur at lower BMI cutoffs in Asians compared with traditional cutoffs defined by international standards in mainly Western populations.[23] This, in turn, has been related to a greater extent of central adiposity and insulin resistance in Asians versus whites at a similar BMI. Indeed, the prevalence of diabetes mellitus among Asian patients with HFpEF was far greater compared with white patients with HFpEF despite a lower average BMI.[24] The fact that young patients with HFpEF had a very high prevalence of obesity, which was even higher according to Asian cutoff points, supports a strong cardiometabolic basis for young HFpEF in Asia. In addition, these findings call for further studies on body composition and fat distribution/function, as well as preventive strategies to curb obesity in Asia.[25] Although there was a trend toward diabetes mellitus being an independent predictor of very young and young versus old HFpEF in the present study (Figure 1), we postulate that there was a large proportion of prediabetes that may not have been detected in our young obese HFpEF group.[26] Future studies are clearly needed to address the role of insulin resistance and obesity, as well as the effects of treatment (eg, sodium glucose cotransporter inhibitors) and weight loss, on the pathogenesis of HFpEF, especially in the young.

Our study also extends results from prior studies of HF in the young, albeit not specifically in HFpEF. Wong et al[4] reported HF in the young (<40 years of age) from the CHARM program (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) and showed that young patients primarily had HFrEF, milder signs and symptoms, and better outcomes but

worse quality of life.[4] Similar results were seen in the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) meta-analysis[3] and the PROTECT trial (Placebo-Controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) of acutely decompensated HF.[5] Specifically for HFpEF, Zacharias et al[27] retrospectively studied patients hospitalized for HFpEF in central Massachusetts, 357 (14.9%) of whom were <65 years old, and found that these young patients with HFpEF were primarily obese, nonwhite men. Echocardiographic parameters, quality of life data, and adjudicated outcomes were not available in this prior study. Furthermore, the study did not include age-matched control subjects without HF. Our present findings are therefore consistent with the prior findings that obesity, male sex, and ethnicity are key discriminators of young and very young versus old HFpEF and extend this to an even younger age range and Asian ethnicities. Overall, very young and young patients with HFpEF displayed equally adverse cardiac remodeling and increased filling pressures compared with their elderly peers. Furthermore, very young patients with HFpEF showed a similar or higher prevalence of concentric hypertrophy (25%) compared with contemporary cohorts of patients with HFpEF included in I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; 29%), the Olmsted County study (26%), and the PARAMOUNT study (Prospective Comparison of ARNI with ARB on Management of Heart Failure With Preserved Ejection Fraction; 7%).[28] Similar to earlier publications with primarily patients with HFrEF with similarly young patients, older age was an important predictor of more adverse clinical outcomes in patients with HFpEF.[3–5,29] NT-proBNP levels were lower in younger patients despite their larger LV volumes. This age difference in NT-proBNP was attenuated after adjustment for sex, BMI, and atrial fibrillation, suggesting that lower NT-proBNP in younger patients may be explained, at least in part, by higher BMI and less atrial fibrillation. Overall, the majority of patients with HFpEF had natriuretic peptide levels above the diagnostic cut point of the European Society of Cardiology guidelines, even despite a higher BMI, which may be expected to lower natriuretic peptide levels; this strengthens our confidence in the diagnosis of HFpEF. Last, sensitivity analyses in patients included as inpatients or outpatients and patients who had natriuretic peptide values above the diagnostic cutoff points did not affect our main findings. Furthermore, the association of age with clinical outcomes was not modified by enrollment status. HFpEF is a challenging diagnosis to make with confidence, and we acknowledge potential misdiagnosis in a multinational registry of this scale. Nonetheless, we expect that the inclusion of patients without true HFpEF would have biased our results to the neutral, and if any misdiagnosed cases were confidently excluded, both clinical outcomes and quality of life would have been even worse compared with those of control subjects. Several pathogeneses (eg, constrictive pericarditis, complex adult congenital heart disease, hypertrophic cardiomyopathy, eosinophilic myocarditis, cardiac amyloid, and acute chemotherapy-induced cardiomyopathy) were not excluded in the ASIAN-HF registry, but the initial experience in Singapore showed that these constituted only 2% of 4418 screened cases.[30]

Ethnic differences have been demonstrated in both HFrEF and HFpEF.[3–5,19] In North America, prominent ethnic differences in HFpEF have been described: Black patients with HFpEF were younger and more often obese.[20] The consistency of the association between obesity and young HFpEF across different ethnicities reinforces the concept that obesity may be the central driver of HFpEF in the young. We postulate the following explanations for the predisposition of specific ethnic groups in our cohort (Malay and Indian) to young HFpEF: (1) Patients of a particular ethnicity may be genetically at risk for developing HFpEF at a young age. This extends on known ethnic differences in the distribution of LV mass, LVH, and other related phenotypes although described mainly in black versus white populations.[31–35] Furthermore, self-reported ethnicity has been shown to closely agree with genetic-based measures of ancestry and to be valuable in controlling the effect of population stratification and admixture in association tests for LV mass and LV ejection fraction in a multiethnic cohort.[36] (2) Ethnicity could also be a surrogate of culture and/or lifestyle that could place patients at higher risk for developing HFpEF at a younger age. For instance, there is a strikingly high prevalence of tobacco smoking in Indonesia (>36%) and physical inactivity in Malaysia (>50%), both countries with large majority populations of Malays.[37] (3) Genetic and environmental factors may interact, acting independently or synergistically to increase risk for HFpEF in different populations. (4) Socioeconomic factors may play a role in determining access to health care and risk factor control leading up to the onset of HFpEF. We previously reported an interesting interaction between ethnicity and regional income level in ASIAN-HF whereby the adjusted odds of diabetes mellitus were almost 5 times higher among Indians with HFrEF from high- versus low-income regions in Asia, suggesting a strong influence of socioeconomic factors.[2] Although our study does not provide definitive answers for the differential risk of young HFpEF in Malay and Indian patients, our data are hypothesis-generating and open the field to further research (genetics and gene-environment interactions) wherein these patients may potentially represent "extreme phenotypes" providing mechanistic insights.

The clinical implications of this study are 2-fold. First, because HFpEF is often considered a disease of the elderly and patients with HFpEF and obesity are often misdiagnosed as having no HF, young patients with HFpEF are at high risk for being falsely classified as not having HF. Our data indicate that even at a younger age, HFpEF should be considered in the presence of unexplained signs and symptoms of HF and the presence of risk factors such as obesity. Second, strong determinants of HFpEF in the young are obesity and ethnicity. This suggests that lifestyle factors might play a large role in developing HFpEF at a young age.

Limitations and Strengths

We acknowledge potential bias in site selection and willingness of patients to participate in a prospective registry. Site selection in ASIAN-HF was based on the size of the country, geographic location of the site within the country, patient population served, HF patient volume, and availability of expertise in echocardiography. Screening logs were encouraged but not available from all sites. Nevertheless, every effort was made to ensure protocol adherence and standardization, including language translations specific to each region, on-site investigator training, regular monitoring (both in person and remote), and centralized database management. Although every effort was made to standardize echocardiography readings at site level by providing standardized protocols and training, no centralized reading of echocardiography results was available in ASIAN-HF. Particular strengths of this study include the prospective design, uniform comprehensive data collection, detailed echocardiographic characterization, close follow-up with independent adjudication of outcomes, and comparison with age-matched community-based control subjects without HF. Unfortunately, quality of life measurements were not available in the control population.

Conclusions

We show that HFpEF not only is a disease of the elderly but also affects young patients who display similar adverse cardiac remodeling compared with their older counterparts and poor outcomes compared with age-matched control subjects without HF. Obesity is twice as common in very young versus elderly HFpEF and may be a central driver of HFpEF in the young.

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