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ORIGINAL RESEARCH

Clinical Features of Heart Failure With Normal Ejection Fraction

Insights From the ASIAN-HF Registry

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ABSTRACT

BACKGROUND Heart failure and left ventricular ejection fraction in the normal range (HFnEF) (left ventricular ejection fraction [LVEF] of ≥55% for men and ≥60% for women) is understudied.

OBJECTIVES The authors aimed to characterize patients with HFnEF compared with those with preserved (≥50%) yet below the normal LVEF.

METHODS In an Asian HF registry, clinical characteristics, echocardiographic features, and outcomes were compared across: 1) HFnEF; 2) heart failure with preserved left ventricular ejection fraction (HFpEF) (LVEF of ≥50%) and below normal LVEF; and 3) community-based controls without HF. Cluster analysis of echocardiographic parameters was performed and validated in an external cohort.

RESULTS Among 1,765 patients with HFpEF (age 68 ± 12 years; 50% women), 1,313 (74.4%) had HFnEF. Compared with patients with HFpEF and below normal LVEF, patients with HFnEF had less coronary artery disease (33.7% vs 27.9%), greater LV wall thickness, and higher stroke volume, but similar 2-year age-adjusted all-cause mortality (HR: 0.8; 95% CI: 0.6-1.2). Five echocardiographic clusters with similar 2-year mortality were identified: 1) normal LV (normal structure despite increased filling pressure; least comorbidities) in 25%; 2) restrictive (smallest stroke volume; predominantly elderly women) in 26%; 3) hypertrophic (most concentric hypertrophy; more men) in 25%; 4) high output (greatest stroke volume; predominantly obese younger men) in 10%; and 5) atrial dominant (most left atrial myopathy; mainly elderly women with multiple comorbidities) in 10%. Similar patterns were found in the validation cohort.

CONCLUSIONS The majority of patients with HFpEF had normal LVEF, which consists of patients with different patterns of cardiac features and clinical characteristics. Results may carry implications for targeted treatment approaches in HFpEF. (JACC: Asia 2023;3:739–751) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CKD = chronic kidney disease

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFnEF = heart failure with normal ejection fraction

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LASSO = least absolute shrinkage and selection operator

LVEF = left ventricular ejection fraction

PC = principal component

Recent data suggest heterogeneity in the therapeutic benefits of neurohormonal agents among patients with heart failure (HF) across the left ventricular ejection fraction (LVEF) spectrum, wherein beneficial effects of renin-angiotensin-aldosterone and neprilysin inhibitors are most prominent in the lower LVEF ranges and become attenuated in the normal LVEF range (LVEF of ≥55% in men and 60% in women).[1-3] Recent registry data suggest a U-shaped relationship between mortality and LVEF in patients with HF, highlighting potentially heightened risk for those with supranormal LVEF.[4] However, there is still a limited understanding of heart failure with normal ejection fraction (HFnEF). We aimed to characterize patients with HFnEF, compared with those with HF and LVEF in the preserved (≥50%) yet below the normal range. Although transthoracic echocardiography remains the first-in-line assessment tool in HF, LVEF is a single echocardiographic measurement that may not fully reflect underlying cardiac structural and functional changes. Therefore, we hypothesized that subtypes of HFnEF, discernible using other echocardiographic markers, may exist.

METHODS

STUDY PATIENTS. Patients with heart failure with preserved ejection fraction (HFpEF) (LVEF ≥50%) from the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) registry and controls without HF (and with normal LVEF) from the SHOP (Singapore Heart Failure Outcomes and Phenotypes) study were analyzed.[5,6] The ASIAN-HF registry is a multinational, multi-ethnic HF registry with 46 investigation sites across 10 countries. Patients aged >18 years with ≥1 episode of decompensated HF in the last 6 months (resulting in admission or treatment in outpatient clinics) were enrolled from October 2012 to December 2017. Of note, the ASIAN-HF registry excluded HFpEF with a prior LVEF of ≤40%. Data from 1,765 patients (of 6,633 patients enrolled in the ASIAN-HF registry) with preserved ejection fraction (LVEF ≥50%) were analyzed for this study. Definitions of past medical history and the details on standard transthoracic echocardiography can be found in the Supplemental Methods.

Controls without HF from the SHOP study included 932 free-living adults recruited from the general community in Singapore by a random sampling of all residents in contiguous precincts within 5 districts in the South-Eastern region of Singapore by the door-to-door census. These were participants without coronary artery disease (CAD) or HF by history, clinical, and echocardiographic examination. Both studies adhered to the Declaration of Helsinki and were approved by the relevant human ethics committee at all participating sites. Written informed consent was obtained from all participating patients in both studies.

DEFINITION OF A NORMAL LVEF. All patients from the ASIAN-HF registry and control individuals from the SHOP study had quantitative LVEF measured with echocardiography at the time of enrolment. Based on distinct LVEF distribution between sexes (Supplemental Figure 1) and previous studies suggesting sex differences in LVEF cut-off values in defining the lower limit of normal LVEF,[7,8] we used sex-specific LVEF cut-off values of 55% for men and 60% for women.[1] However, acknowledging the absence of a universal definition of normal LVEF, we also performed the same descriptive analysis using the sex-neutral cut-off value of 60% (for both men and women) as a supplementary analysis.

STUDY OUTCOMES. The primary outcome of this study was all-cause mortality at 2 years of follow-up and was compared across all 3 groups of HFnEF, HFpEF below normal LVEF, and the controls. Secondary outcomes were the composite of all-cause death or HF hospitalization and the composite of

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cardiovascular death or HF hospitalization at 2 years of follow-up, compared between groups of patients with HFnEF and HFpEF below normal LVEF.

CLUSTER ANALYSIS. Unsupervised cluster analysis was performed in patients with HFnEF to identify mutually exclusive clusters of patients with HFnEF using echocardiographic parameters. Cluster analysis was performed in patients with HFnEF who had <50% missing data on echocardiographic variables (n = 888) (Supplemental Table 1). Missing variables were imputed using the imputePCA function of the *missMDA* package.[9,10] We predicted missing values using 5 components, before performing a principal component (PC) analysis. The PC analysis was used to minimize redundancy and collinearity from a total of 14 echocardiographic variables (interventricular septal and posterior wall thickness, LV end-diastolic and -systolic diameters and volumes, E wave, medial e', LV mass, E/A, E/e', left atrial [LA] volume, stroke volume, and cardiac output). All PCs with an eigen factor of >1 were included in the cluster analysis. Cluster analysis was performed using NbClust, with the k-means clustering using Euclidean distances.[11] NbClust determines: 1) the optimal number of cluster solution based on a combination of 30 indices (presented in Supplemental Table 2); and 2) the best clustering scheme based on varying all combinations of number of clusters, distance measures, and clustering methods (Supplemental Methods). Afterward, we performed penalized least absolute shrinkage and selection operator (LASSO) logistic regression analyses for echocardiographic parameters to find the smallest combination of the features that best identified each cluster. Details on the statistical analysis can be found in the Supplemental Methods.

EXTERNAL VALIDATION OF CLUSTER ANALYSIS. To examine whether these clusters can be found in a separate cohort of patients, the results of the cluster analysis based on echocardiographic variables in the ASIAN-HF registry were validated in an external cohort of patients with HFnEF. This validation cohort consisted of 113 patients with HFnEF from ATTRaCT (Asian neTwork for Translational Research and Cardiovascular Trials) (a deeply phenotyped observational HF cohort study in Singapore[6]) and 163 patients from PROMIS-HFpEF (Prevalence of Microvascular Dysfunction in HF With Preserved Ejection Fraction) (a prospective, multinational observational study of patients with a firm diagnosis of HFpEF, designed to investigate the relationships with coronary microvascular dysfunction).[12] Cluster membership was determined by a consensus of the 5-nearest neighbors' comparison of the PCs with the 888 patients with HFnEF. The PCs were projected based on a PC analysis of the ASIAN-HF registry. Clinical characteristics and echocardiographic parameters were presented across the clusters in both the ASIAN-HF registry and the validation cohort. The study flow of the research is illustrated in Figure 1.

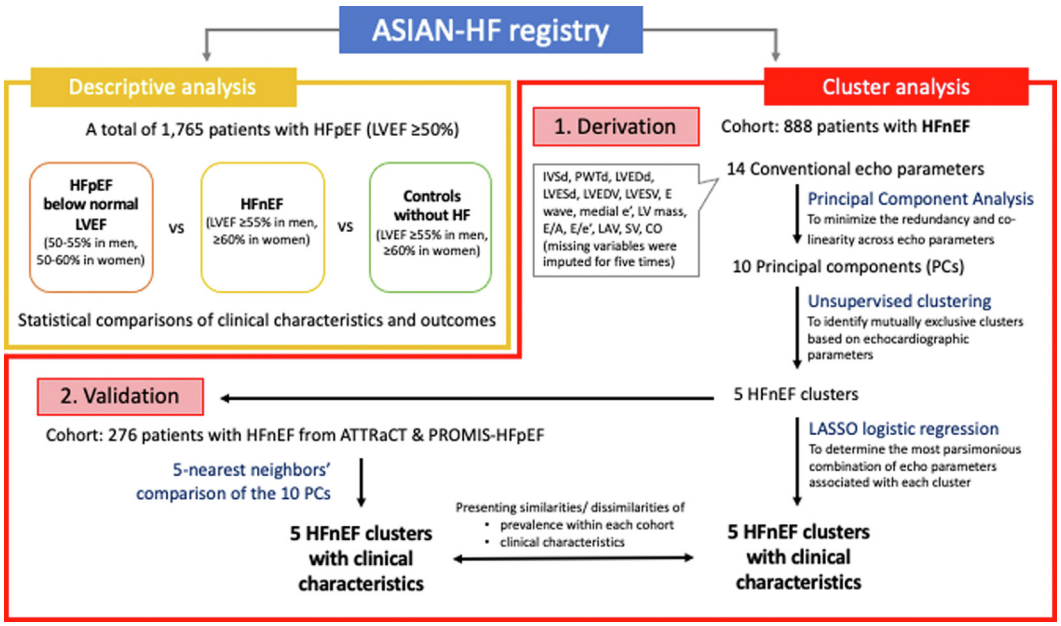
RESULTS

BASELINE CHARACTERISTICS AND CLINICAL BACKGROUND. Among a total of 1,765 patients with HFpEF (LVEF ≥50%) in the ASIAN-HF registry, 1,313 patients (74.4%) had HFnEF and 452 (25.6%) had HFpEF below normal LVEF (Table 1). Compared with controls (n = 932), patients with HFnEF were a decade older with a higher comorbidity burden. Compared with patients with HFpEF below normal LVEF, patients with HFnEF were more often men (39% vs 54% men; $P < 0.001$) and had less CAD (33.7% vs 27.9%; $P = 0.02$). The prevalence of hypertension, diabetes, and atrial fibrillation in patients with HFnEF was significantly higher than in controls but similar compared with patients with HFpEF below normal LVEF. Age- and sex-adjusted NT-proBNP levels were similar between HFnEF and HFpEF below normal LVEF (Supplemental Figure 2) (adjusted mean: 544.3 pg/mL [95% CI: 458-646 pg/mL] vs 519 pg/mL [95% CI: 109-658 pg/mL]; $P = 0.99$).

When a sex-neutral LVEF cut-off value of 60% was used to define normal LVEF, the proportion of women was higher for HFnEF compared with HFpEF below normal LVEF (Supplemental Table 3) (55% vs 40%; $P < 0.001$). Other findings were generally similar to the original analysis performed with sex-specific LVEF cut-off values.

CARDIAC STRUCTURE AND FUNCTION. Compared with controls, both HFnEF and HFpEF below normal LVEF had thicker LV walls, higher LV mass, higher mitral E/e' ratios and larger LA volumes (Table 2). Compared with HFpEF below normal LVEF, patients with HFnEF had thicker LV posterior walls with greater relative wall thickness, similar indexed end-diastolic volumes but smaller indexed LV end-systolic volumes, larger stroke volumes, and higher cardiac output; associations that persisted after adjusting for age and sex (Table 2). Concentric remodeling and concentric hypertrophic patterns were more prevalent in patients with HFnEF than those with HFpEF and below normal LVEF (Supplemental Figure 3) (30.6% and 25.9%, respectively). Although LV diastolic function was impaired in both HF groups compared with

FIGURE 1 Study Flow of the Research



Summary of the study flow of the research. CO = cardiac output; HFnEF = heart failure with normal ejection fraction; HFpEF = heart failure with preserved ejection fraction; IVSd = interventricular septal thickness at diastole; LASSO = least absolute shrinkage and selection operator; LAV = left atrial volume; LVEDd = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSd = left ventricular end-systolic dimension; PWTd = post wall thickness at diastole; SV = stroke volume.

controls, the mean mitral e' velocity was higher, the E/e' ratio was lower, and the LA volume was smaller in HFnEF compared with HFpEF below normal LVEF (Table 2).

OUTCOMES. A total of 149 all-cause deaths occurred within 2 years among patients with HF, whereas only 7 deaths occurred among controls (Table 3). When compared across the 3 groups of the controls, HFnEF, and HFpEF below normal LVEF, a trend of increasing 2-year mortality was observed ($P < 0.001$). The risk of all-cause death at 2 years was higher in HFnEF and HFpEF below normal LVEF compared with the controls (age-adjusted HR: 7.4 [95% CI: 3.4-16.1] and HR: 9.0 [95% CI: 4.0-20.4], respectively); however, the risk was not significantly different between the HF groups (age-adjusted HR: 0.8; 95% CI: 0.6-1.2). Rates of secondary outcomes including the composite of: 1) all-cause death or HF hospitalization at 2 years; and 2) cardiovascular death or HF hospitalization at 2 years were similar between HFnEF and HFpEF below normal LVEF (age-adjusted HR: 0.85 [95% CI: 0.7-1.1] and HR: 0.84 [95% CI: 0.6-1.1], respectively).

CLUSTER ANALYSIS OF ECHOCARDIOGRAPHIC PARAMETERS. A total of 7 echocardiographic clusters was identified as the optimal number of clusters based on the 10 PCs selected with an Eigen factor of >1 in patients with HFnEF from the ASIAN-HF registry. Two clusters were omitted owing to a small number of patients (<5%). Supplemental Table 4 presents the results of penalized LASSO logistic regression on echocardiographic parameters of the 5 major clusters. An absence of LV remodeling was associated with higher odds of cluster 1 (OR: 9.9; 95% CI: 6.5-15.0). Thickening of the LV wall was associated with higher odds of both clusters 2 and 3, yet a smaller LV cavity and a concentric LV remodeling pattern were predominantly associated with cluster 2 (concentric remodeling: OR: 4.3; 95% CI: 2.7-6.9), whereas concentric LV hypertrophy was strongly associated with higher odds of cluster 3 (OR: 1.9; 95% CI: 1.2-3.0). Increased cardiac output was the essential attribute of cluster 4 (OR: 1.9; 95% CI: 1.2-3.0), whereas an elevated E/e' was associated with higher odds of cluster 5 (OR: 1.2; 95% CI: 1.1-1.3). There were no statistical differences in survival rate

TABLE 1 Clinical Characteristics of Patients With HFnEF, HFpEF With Below Normal LVEF, and Controls

	Overall HFpEF (N = 1,765)	HFpEF With Below Normal LVEF (n = 452)	HFnEF (n = 1,313)	Controls (n = 932)
Age, y	67.9 ± 12.4[a]	66.9 ± 12.5[a]	68.3 ± 12.3[a]	57.2 ± 10.3
Women	876 (49.6)	274 (60.6)[a]	602 (45.8)[b]	470 (50.4)
BMI, kg/m^2	27.1 ± 5.9[a]	27.6 ± 6.3[a]	26.9 ± 5.7[a]	24.9 ± 4.0
NYHA functional class III/IV	308 (23.1)	95 (24.5)	213 (22.5)	-
KCCQ-os	75.7 ± 21.8	70.7 ± 22.9	77.3 ± 21.1[b]	-
In-patient enrolment	535 (30.3)	152 (33.6)	383 (29.2)	-
Comorbidities				
Hypertension	1,275 (72.2)[a]	310 (68.6)[a]	965 (73.5)[a]	268 (29.0)
Diabetes	761 (43.1)[a]	206 (45.6)[a]	555 (42.3)[a]	81 (8.8)
Atrial fibrillation	446 (25.3)[a]	128 (28.3)[a]	318 (24.2)[a]	6 (0.6)
Prior stroke	132 (7.5)[a]	30 (6.6)[a]	102 (7.8)[a]	2 (0.2)
Coronary artery disease	518 (29.4)	152 (33.7)	366 (27.9)[b]	-
CKD	666 (50.0)[a]	189 (53.4)	477 (48.8)	-
COPD	145 (8.2)	47 (10.4)	98 (7.5)	-
Anemia	580 (58.4)[a]	169 (57.3)	411 (58.9)	-
Physical examination and test results				
Heart rate, beats/min	76.1 ± 14.7[a]	77.2 ± 15.0[a]	75.7 ± 14.6[a]	59.1 ± 8.8
Systolic blood pressure, mm Hg	132.4 ± 21.1	131.8 ± 22.6	132.7 ± 20.6	130.9 ± 18.5
eGFR, mL/min/1.73 m^2	60.0 (39.2-81.6)[a]	56.8 (37.3-80.6)	60.3 (39.9-81.8)	-
Hemoglobin (g/L)	11.8 (10.3-13.6)[a]	11.7 (10.2-13.6)[a]	11.8 (10.3-13.6)[a]	13.7 (12.9-14.8)
Pulmonary edema on chest radiograph[c]	204 (24.8)	62 (25.6)	142 (24.4)	-
Pulmonary effusion on chest radiograph[c]	204 (24.8)	53 (21.9)	151 (25.9)	-
Medication use				
ACEI or ARB	1101 (66.0)	265 (63.1)	836 (67.0)	-
MRA	343 (20.6)	111 (26.4)	232 (18.6)[b]	-
Beta-blockers	1,083 (65.0)	292 (69.5)	791 (63.4)[b]	-
Diuretics	1,109 (66.5)	283 (67.4)	826 (66.2)	-
Calcium channel blocker	638 (43.9)	127 (36.4)	511 (46.3)[b]	-

Values are mean ± SD, n (%), or median (25th-75th percentile). [a]Bonferroni adjusted *P* values of <0.05 compared with controls. [b]Bonferroni adjusted *P* values of <0.05 compared with HFpEF below normal LVEF. [c]Number of observations are limited to subset of patients.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HFnEF = heart failure with normal ejection fraction; HFpEF = heart failure with preserved ejection fraction; KCCQ-os = Kansas City cardiomyopathy questionnaire; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist.

over 2 years across the 5 clusters (Supplemental Figure 4) (log-rank $P = 0.10$).

VALIDATION AND THE CLINICAL CHARACTERISTICS OF THE 5 CLUSTERS. The cluster analysis was validated in a total of 276 patients with HFnEF from the combined validation cohort of the ATTRaCT and PROMIS-HFpEF study. The prevalence of the 5 clusters in the ASIAN-HF registry and the validation cohort were similar (**Figure 2**). **Table 4** presents the clinical characteristics and echocardiographic findings of the 5 clusters in both cohorts. All clusters from both cohorts shared similar clinical characteristics: cluster 1 from both cohorts consisted of patients with the least prevalence of comorbidities (hypertension: 79% and 74%; chronic kidney disease [CKD]: 40% and 36%, respectively). Their LV wall thickness, LV cavity, and strain measurements were within normal limits. Of note, compared with controls without HF (**Table 2**), cardiac structural measurements were similar, yet the E/e' was higher in those with HFnEF within this cluster. Patients in cluster 2 from both cohorts were predominantly elderly (age 71 ± 11 years and 70 ± 12 years) women (65% and 59%) with substantially small LV cavity (left ventricular end-diastolic volume index: 40 ± 10 mL/m^2 and 35 ± 8 mL/m^2; left ventricular end-systolic volume index: 15 ± 5 mL/m^2 and 15 ± 18 mL/m^2) that is smaller than that of controls. Cluster 3 from both cohorts included more men (57% and 70%) with the highest prevalence of concentric LV hypertrophy (61% and 67%). Cluster 4 from both cohorts consisted of relatively young (age 65 ± 12 years and 69 ± 10 years) men (70% and 92%) with a high body mas index (29 ± 9 kg/m^2 and 39 ± 9 kg/m^2). Notably, patients in this cluster from the PROMIS-HFpEF had the worst LV global longitudinal

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TABLE 2 Echocardiographic Characteristics of Patients With HFnEF, HFpEF With Below Normal LVEF, and Controls

	Overall HFpEF (N = 1,765)	HFpEF With Below Normal LVEF (n = 452)	HFnEF (n = 1,313)	Controls (n = 932)
IVSd, mm	10.9 ± 2.4[a]	10.7 ± 2.5[a]	11.0 ± 2.4[a]	8.9 ± 1.7
PWTd, mm	10.6 ± 2.1[a]	10.4 ± 2.2[a]	10.7 ± 2.1[a,b]	8.6 ± 1.5
RWT	0.46 ± 0.12[a]	0.44 ± 0.14[a]	0.46 ± 0.12[a,b]	0.37 ± 0.07
LVDd, mm	47.4 ± 7.1[a]	48.8 ± 7.8[a]	47.3 ± 6.8[b]	46.9 ± 4.4
LVSd, mm	30.4 ± 6.2[a]	33.4 ± 6.8[a]	29.5 ± 5.7[a,b]	28.1 ± 4.1
LVEDVI, mL/m^2	56.8 ± 22.9	58.3 ± 26.2	56.2 ± 21.4	55.2 ± 14.1
LVESVI, mL/m^2	24.9 ± 14.1[a]	29.2 ± 13.6[a]	23.0 ± 14.0[a,b]	19.9 ± 6.1
Stroke volume, mL	61.3 ± 24.7	54.1 ± 25.4[a]	63.4 ± 24.0[a,b]	59.7 ± 15.7
Cardiac output, L/min	4.6 ± 2.0[a]	4.1 ± 2.0[a]	4.7 ± 2.0[a,b]	3.5 ± 1.0
Cardiac index, L/min/m^2	2.5 ± 1.2[a]	2.3 ± 1.2[a]	2.6 ± 1.2[a,b]	2.1 ± 0.5
LVMI, g/m^2	108.2 ± 41.3[a]	108.6 ± 38.9[a]	108.1 ± 42.4[a]	81.3 ± 19.6
E wave, cm/s	83.2 ± 29.9[a]	85.9 ± 31.7[a]	82.3 ± 29.3[a]	70.6 ± 16.1
e' medial, cm/s	5.9 ± 4.6[a]	5.3 ± 2.1[a]	6.1 ± 5.3[a,b]	7.6 ± 2.1
E/e' medial	17.3 ± 9.3[a]	18.2 ± 9.8[a]	16.8 ± 9.0[a,b]	9.9 ± 3.5
LA volume, mL	63.3 ± 42.3[a]	69.6 ± 58.2[a]	60.1 ± 30.9[a,b]	45.2 ± 12.1

Values are mean ± SD. [a]Bonferroni adjusted *P* values of <0.05 against controls. [b]Bonferroni adjusted *P* values of <0.05 between HFnEF and HFpEF below normal LVEF.

IVSd = interventricular septal thickness at diastole; LA = left atrial; LVDd = left ventricular dimension at end-diastole; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVH = left ventricular hypertrophy; LVMI = left ventricular mass; LVSd = left ventricular dimension at end-systole; PCWP = pulmonary capillary wedge pressure; PWTd = post wall thickness at diastole; RWT = relative wall thickness; other abbreviations as in Table 1.

strain (absolute LVGLS of 16.0% ± 4.2%). Finally, cluster 5 from both cohorts comprised mainly elderly women with a high prevalence of atrial fibrillation (51% and 63%) and CKD (61% and 71%). Patients in cluster 5 had the highest prevalence of disproportionate LA myopathy (84%, defined as abnormality in LA reservoir strain relative to the decrease in LVGLS (Supplemental Methods) in addition to the worst LA reservoir strain (11.8% ± 4.6%), across the clusters in the PROMIS-HFpEF cohort.

DISCUSSION

We found that three-quarters of Asian patients with HFpEF (LVEF ≥50%) had a normal LVEF (≥55% for men and ≥60% for women). Compared with patients with HFpEF below normal LVEF, patients with HFnEF were more often men and had less CAD. A female predominance was observed if a sex-neutral LVEF cut-off of 60% was used to define a normal LVEF. HFnEF hearts had greater LV wall thickness and higher stroke volume despite similar indexed LV end-diastolic volume, compared with HFpEF with below normal LVEF. Despite a normal LVEF, the 2-year age-adjusted all-cause mortality was 7-fold greater for patients with HFnEF compared with controls without HF. Cluster analyses based on echocardiography identified 5 mutually exclusive clusters of patients with HFnEF characterized by distinct structural and functional cardiac features with a similarly reduced 2-year survival rate: 1) normal LV (normal structure despite increased filling pressure; fewest comorbidities) in 25%; 2) restrictive (smallest LV cavity and stroke volume; predominantly elderly women) in 26%; 3) hypertrophic (most concentric hypertrophy; more men) in 25%; 4) high output (largest LV cavity and stroke volume; predominantly obese younger men) in 10%; and 5) atrial dominant (most LA myopathy; mainly elderly women with atrial

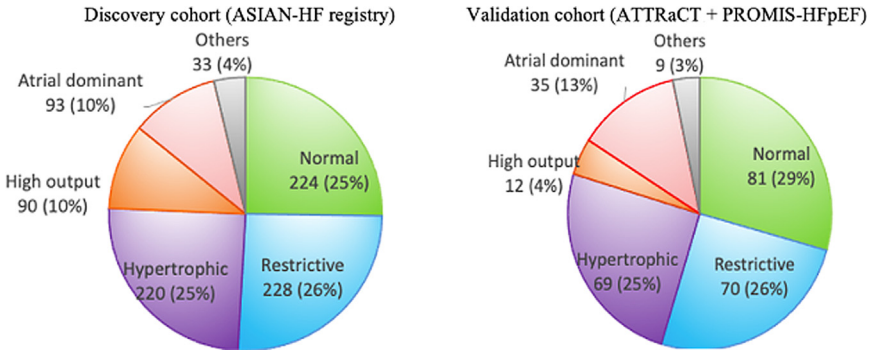
TABLE 3 Prognostic Outcomes in HFnEF, HF With Below Normal LVEF, and Controls

	N	No. of Events	Event Rate[a]	Age-Adjusted HR	95% CI	*P* Value
Primary outcome						
All-cause death at 2 y						
Controls	901	7 (0.8)	4.2		Ref	
HFnEF	1,242	106 (8.5)	49.7	7.38[b]	3.37-16.14	<0.001
HFpEF below normal LVEF	424	43 (10.1)	58.9	9.04	4.00-20.42	<0.001
Secondary outcomes						
All-cause death or HFH at 2 y						
HFnEF	1,242	205 (16.5)	101.2	0.85	0.65-1.10	0.207
HFpEF below normal LVEF	424	79 (18.6)	115.6		Ref	
CV death or HFH at 2 y						
HFnEF	1,242	177 (14.3)	102.6	0.84	0.64-1.11	0.219
HFpEF below normal LVEF	424	69 (16.3)	120.9		Ref	

Values are n (%) unless otherwise indicated. [a]Event rate in 1,000 patient-years. Cox models are adjusted for age. [b]HR of 0.8 (95% CI: 0.6-1.2) when referencing HFpEF below normal LVEF.

CV = cardiovascular; HFH = heart failure hospitalization; Ref = reference; other abbreviations as in Table 1.

FIGURE 2 **Prevalence of Clusters in the Derivation and Validation Cohorts**



The number and proportion of patients with HFnEF in each cluster found in the derivation and validation cohorts. ASIAN-HF = the Asian Sudden Cardiac Death in Heart failure; ATTRaCT = Asian neTwork for Translational Research and Cardiovascular Trials; PROMIS-HFpEF = Prevalence Of Microvascular Dysfunction in Heart Failure with Preserved Ejection Fraction.

fibrillation and CKD) in 10% (**Central Illustration**). The 5 clusters were well-validated in an external cohort of patients with HFnEF.

EPIDEMIOLOGY AND CHARACTERISTICS OF OVERALL HFnEF AND HFpEF BELOW NORMAL LVEF. In the absence of a universal definition of HFnEF, previous HF trials reported that 40% to 50% of patients with HFpEF had HFnEF, depending on the threshold used to define normal LVEF.[13,14] Data from the U.S. regional health care system reported that, among patients with HFpEF (LVEF ≥50%), approximately 40% had an LVEF of ≥60%.[4] In contrast, in BIOSTAT-CHF (BIOlogy Study to Tailored Treatment in Chronic Heart Failure), only 12.9% of patients with HFpEF (LVEF ≥50%) had a normal LVEF (defined as ≥62% for men and ≥64% for women).[15] The high proportion of HFnEF among our Asian patients with HFpEF may relate to intrinsic ethnic differences in LV size and LVEF[8] (smaller LV volumes and higher LVEF among Asian compared with White individuals). Still, the published data to date are consistent in showing that a sizeable proportion of patients with HFpEF have truly normal LVEF, and, depending on the specific cut-off used and population studied, HFnEF may even represent the majority of patients with HFpEF.

Similar to previous reports, we found that patients with HFpEF, including HFnEF, were elderly with a high comorbidity burden.[13,14,16] Overall clinical characteristics were similar between patients with HFnEF and those with HFpEF below normal LVEF, except for a lower prevalence of CAD in the former group (27.9% vs 33.7%, respectively). We found significant echocardiographic differences between the HF groups, where those with HFpEF below normal LVEF had less thick LV walls, less LV concentricity, smaller stroke volumes, and lower cardiac output compared with those with HFnEF. Whether these echocardiographic changes represent early/mild LV adverse remodeling, or herald future more severe LV dilatation and reduced LVEF, remains to be determined.

We have also added to published data on clinical outcomes in HFnEF and HFpEF with lower LVEF, showing that although survival was clearly decreased in both groups compared with controls without HF, overall outcomes were similar between HFnEF and HFpEF with a below normal LVEF. There are few prior data on outcomes in patients with HFnEF, and they are conflicting. The Digitalis Investigation Group trial reported comparable overall mortality between patients with an LVEF between 46% and 55% vs those with an LVEF of ≥55% (mortality rate: 23.3% vs 23.5% over a median follow-up of 37 months, respectively; $P = 0.25$).[13] A study using data from a regional health care system in Pennsylvania reported a higher mortality rate among patients hospitalized for HF with an LVEF of ≥70% compared with an LVEF of 60% to 65%.[4] In the validation cohort of BIOSTAT-CHF, the risk of the combined outcomes of all-cause mortality or HF hospitalization was lower in those with HFnEF compared with patients with HFpEF with below normal LVEF.[15] The reasons for these differing results across studies may relate to the different LVEF cut-offs used, HF population differences, or different lengths of follow-up. We note striking similarity in the outcomes of patients with HFpEF below normal LVEF compared with patients with HF with mildly

TABLE 4 Clinical Features Across Clusters in Discovery Cohort (ASIAN-HF Registry) and Validation Cohort (ATTRaCT+PROMIS-HFpEF)

	Overall		Cluster 1 (Normal LV)		Cluster 2 (Restrictive)	
	ASIAN-HF (N = 855)	Validation Cohort (N = 267)	ASIAN-HF (n = 224, 25.3%)	Validation Cohort (n = 81, 29.3%)	ASIAN-HF (n = 228, 25.7%)	Validation Cohort (n = 70, 25.3%)
Age, y	69.7 ± 11.6	69.7 ± 11.4	69.1 ± 11.4	64.4 ± 11.6	71.3 ± 11.1	70.0 ± 11.7
Women	447 (52.3)	113 (42.3)	121 (54.0)	30 (37.0)	148 (64.9)	41 (58.6)
BMI, kg/m^2	27.1 ± 6.0	30.3 ± 8.3	26.2 ± 5.3	27.8 ± 6.5	26.3 ± 5.7	29.5 ± 7.1
NYHA functional class III/IV	141 (25.1)	49 (18.5)	45 (28.1)	4 (5.0)	37 (21.5)	14 (20.0)
KCCQ-os	77.7 ± 20.3	62.4 ± 24.3	78.9 ± 20.3	67.9 ± 22.5	74.4 ± 18.8	58.6 ± 23.4
Comorbidities						
Hypertension	725 (84.8)	224 (84.5)	176 (78.6)	59 (73.8)	195 (85.5)	62 (89.9)
Diabetes	409 (47.8)	115 (43.4)	100 (44.6)	30 (37.5)	105 (46.1)	34 (49.3)
Atrial fibrillation	211 (24.7)	111 (41.9)	53 (23.7)	30 (37.5)	47 (20.6)	20 (29.0)
Coronary artery disease	223 (26.1)	88 (34.9)	54 (24.2)	28 (37.3)	48 (21.1)	24 (37.5)
CKD	346 (47.2)	128 (49.8)	79 (39.7)	27 (36.0)	77 (44.8)	29 (43.3)
Echocardiographic parameters						
Left heart structure and function						
IVSd, mm	11.0 ± 2.4	12.4 ± 2.8	8.8 ± 1.6	10.1 ± 1.8	11.7 ± 2.2	12.4 ± 2.2
PWTd, mm	10.8 ± 2.1	10.5 ± 2.1	8.8 ± 1.5	9.2 ± 1.5	11.2 ± 1.9	10.6 ± 1.8
RWT	0.47 ± 0.12	0.47 ± 0.12	0.38 ± 0.07	0.38 ± 0.07	0.56 ± 0.12	0.54 ± 0.15
LVEDVI, mL/m^2	53.2 ± 18.9	42.8 ± 12.7	57.4 ± 15.2	48.5 ± 12.1	39.5 ± 10.0	34.8 ± 7.6
LVESVI, mL/m^2	21.5 ± 10.9	16.6 ± 9.8	24.8 ± 11.2	18.2 ± 5.5	14.7 ± 5.2	15.0 ± 18.2
SV, mL	62.1 ± 24.0	70.6 ± 29.4	63.6 ± 16.1	66.5 ± 16.6	42.2 ± 16.0	53.1 ± 32.2
CO, L/min	4.6 ± 2.0	4.6 ± 1.9	4.7 ± 1.4	4.4 ± 1.2	3.1 ± 1.3	3.5 ± 2.2
LVMI, g/m^2	107.1 ± 42.4	103.6 ± 36.0	82.3 ± 20.6	90.9 ± 23.5	95.7 ± 26.4	91.0 ± 27.2
LV remodeling patterns						
Normal	136 (28.2)	72 (27.5)	104 (72.2)	48 (60.0)	6 (4.8)	7 (10.3)
Concentric remodeling	129 (26.7)	82 (31.3)	21 (14.6)	15 (18.8)	70 (55.6)	42 (61.8)
Concentric hypertrophy	151 (31.3)	85 (32.4)	6 (4.2)	9 (11.2)	41 (32.5)	18 (26.5)
Eccentric hypertrophy	67 (13.9)	23 (8.8)	13 (9.0)	8 (10.0)	9 (7.1)	1 (1.5)
e' medial, cm/s	6.0 ± 4.5	6.8 ± 2.4	6.4 ± 2.6	7.6 ± 2.7	5.9 ± 2.1	6.6 ± 2.0
E/e' medial	16.9 ± 9.2	14.5 ± 7.0	13.3 ± 4.0	12.0 ± 5.4	13.6 ± 5.0	12.2 ± 4.5
LAVI, mL/m^2	38.8 ± 19.6	37.3 ± 15.0	38.9 ± 17.8	35.5 ± 13.0	30.8 ± 15.4	30.7 ± 10.9
LVGLS, %, absolute	-	17.3 ± 2.9	-	18.6 ± 2.5	-	17.9 ± 2.8
LASr, %	-	17.2 ± 8.3	-	18.8 ± 8.3	-	19.9 ± 9.3
Disproportionate LA myopathy,[a] %	-	87 (54.7)	-	15 (51.7)	-	15 (45.5)
Right heart structure and function						
RVGLS, %	-	22.1 ± 5.3	-	24.5 ± 5.2	-	22.6 ± 5.4
TAPSE, cm	-	1.9 ± 0.4	-	2.0 ± 0.3	-	1.8 ± 0.3
PASP, mm Hg	-	43.4 ± 14.0	-	41.8 ± 10.9	-	39.2 ± 10.2

Values are mean ± SD or n (%). KCCQ-os score, strain measurements, LA myopathy, PASP, and TAPSE were only available for patients from PROMIS-HFpEF. [a]Disproportionate LA myopathy was defined by estimating the residuals from a linear association between the LVGLS and LA reservoir strain. Continuous studentized residual values were assigned to each patient indicating disproportionate LA myopathy when a studentized residual was <0. The prevalence of disproportionate LA myopathy was shown as a percentage in each cluster.

CO = cardiac output; HF = heart failure; LASr = left atrial reservoir strain; LAVI = left atrial volume indexed to body surface area; LVGLS = left ventricular global longitudinal strain; PASP = pulmonary arterial systolic pressure; PWTd = posterior wall thickness at diastole; RVGLS = right ventricular global longitudinal strain; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Tables 1 and 2.

Continued on the next page

reduced EF (HFmrEF) (LVEF of 40%-49%) prospectively recruited in our Singapore Heart Failure Outcomes and Phenotypes study (2-year mortality of 10.1% vs 9.8%, respectively).[17] In aggregate, the resemblance of patient characteristics, echocardiographic changes, and clinical outcomes of HFpEF below normal LVEF to HFmrEF calls for consideration of grouping these patients together; thus extending the definition of HFmrEF from LVEF 40% to 55% in men and 60% in women.

HFnEF CLUSTERS BASED ON CONVENTIONAL ECHOCARDIOGRAPHY. Recent phenotyping research in HFpEF has identified 3 to 6 clusters of patients with HFpEF, depending on the analytical approach and clustering variables.[18-23] Acknowledging the

TABLE 4 Continued

Cluster 3 (Hypertrophic)		Cluster 4 (High Output)		Cluster 5 (Atrial Dominant)	
ASIAN-HF (n = 220, 24.8%)	**Validation Cohort (n = 69, 25.0%)**	**ASIAN-HF (n = 90, 10.1%)**	**Validation Cohort (n = 12, 4.3%)**	**ASIAN-HF (n = 93, 10.5%)**	**Validation Cohort (n = 35, 12.7%)**
69.6 ± 11.6	72.9 ± 9.7	65.3 ± 11.8	68.9 ± 9.5	71.5 ± 12.2	75.0 ± 9.3
95 (43.2)	21 (30.4)	27 (30.0)	1 (8.3)	56 (60.2)	20 (57.1)
28.4 ± 5.2	33.0 ± 10.2	29.2 ± 9.4	38.6 ± 8.6	27.5 ± 5.9	29.8 ± 6.8
27 (25.7)	19 (27.9)	13 (25.0)	1 (9.1)	19 (26.0)	11 (31.4)
82.3 ± 19.1	62.9 ± 24.9	79.3 ± 21.6	54.9 ± 29.5	69.2 ± 21.8	62.4 ± 25.5
198 (90.0)	60 (87.0)	79 (87.8)	12 (100)	77 (82.8)	31 (88.6)
115 (52.3)	27 (39.1)	37 (41.1)	7 (58.3)	52 (55.9)	17 (48.6)
35 (15.9)	33 (47.8)	29 (32.2)	6 (50.0)	47 (50.5)	22 (62.9)
69 (31.5)	21 (31.3)	24 (26.7)	5 (41.7)	28 (30.1)	10 (29.4)
97 (50.0)	40 (58.8)	43 (50.0)	7 (58.3)	50 (61.0)	25 (71.4)
12.1 ± 1.5	14.3 ± 2.4	12.2 ± 2.6	14.6 ± 2.6	11.1 ± 2.7	12.7 ± 3.1
12.0 ± 1.4	11.8 ± 1.7	11.8 ± 2.0	12.8 ± 2.6	10.5 ± 2.0	10.2 ± 2.3
0.49 ± 0.07	0.49 ± 0.09	0.42 ± 0.09	0.48 ± 0.10	0.48 ± 0.12	0.46 ± 0.12
58.4 ± 13.5	41.6 ± 9.8	83.5 ± 22.7	58.7 ± 17.7	44.8 ± 16.0	40.3 ± 13.2
22.0 ± 8.2	16.0 ± 4.4	32.7 ± 10.3	22.4 ± 5.9	18.7 ± 13.4	14.9 ± 5.6
70.5 ± 13.7	81.0 ± 23.3	99.9 ± 19.7	116.3 ± 36.3	47.9 ± 23.4	67.6 ± 28.8
5.1 ± 1.2	5.2 ± 1.5	7.7 ± 1.9	7.5 ± 2.7	3.5 ± 1.9	4.2 ± 1.6
132.7 ± 27.8	126.2 ± 41.6	164.8 ± 71.5	142.6 ± 53.5	103.0 ± 38.2	100.0 ± 26.2
6 (5.7)	4 (6.0)	5 (11.1)	4 (33.3)	15 (23.8)	9 (25.7)
19 (18.1)	12 (17.9)	1 (2.2)	2 (16.7)	18 (28.6)	11 (31.4)
64 (61.0)	45 (67.2)	21 (46.7)	5 (41.7)	19 (30.2)	8 (22.9)
16 (15.2)	6 (9.0)	18 (40.0)	1 (8.3)	11 (17.5)	7 (20.0)
6.5 ± 9.5	6.7 ± 2.1	6.1 ± 2.0	6.7 ± 1.9	5.2 ± 1.7	6.0 ± 2.4
16.0 ± 5.6	14.0 ± 4.9	19.0 ± 7.6	15.9 ± 4.6	29.2 ± 13.8	25.2 ± 8.7
35.3 ± 12.4	37.0 ± 11.8	55.5 ± 32.7	46.8 ± 15.3	49.2 ± 17.6	51.3 ± 20.4
-	16.7 ± 2.7	-	16.0 ± 4.2	-	17.1 ± 2.8
-	17.5 ± 7.9	-	15.4 ± 10.1	-	11.8 ± 4.6
-	29 (47.5)	-	7 (63.6)	-	21 (84.0)
-	21.0 ± 4.6	-	19.9 ± 5.6	-	22.3 ± 6.0
-	1.8 ± 0.4	-	2.0 ± 0.5	-	1.8 ± 0.4
-	41.5 ± 13.4	-	56.5 ± 25.0	-	49.8 ± 13.9

limited discernible findings that echocardiography can offer in phenotyping HFpEF, it still plays a significant role in the management of HF. We extended prior framework of HFpEF to patients with HFnEF to further identify novel phenotypes in HFnEF that can be classified by echocardiographic findings. Although we cannot draw etiologic conclusions from our study, our results highlight that despite similar clinical presentation (HF), prognosis, and LVEF, patients with HFnEF can have very different underlying cardiac structural and functional changes. Our identified patterns may form a framework for considering results from more selected studies. For instance, Rosch et al[24] recently described 35 patients with HF and an LVEF of >60% (median age: 72 years; 80% women; 97% hypertensive) who had notably smaller LV volumes, increased LV systolic and diastolic elastance, and diminished preload reserve, compared with patients with HF and an LVEF of 50% to 60%.[24] These patients bear a striking resemblance to our cluster 2 restrictive HFnEF. Although consistent, our results also suggest that there may be other patients presenting with the clinical syndrome of HFnEF who are volume overloaded, with eccentric LV hypertrophy (cluster 4, high output). In marked contrast with the elderly hypertensive women with the restrictive phenotype, patients with the high-output phenotype are predominantly younger obese men.[25]

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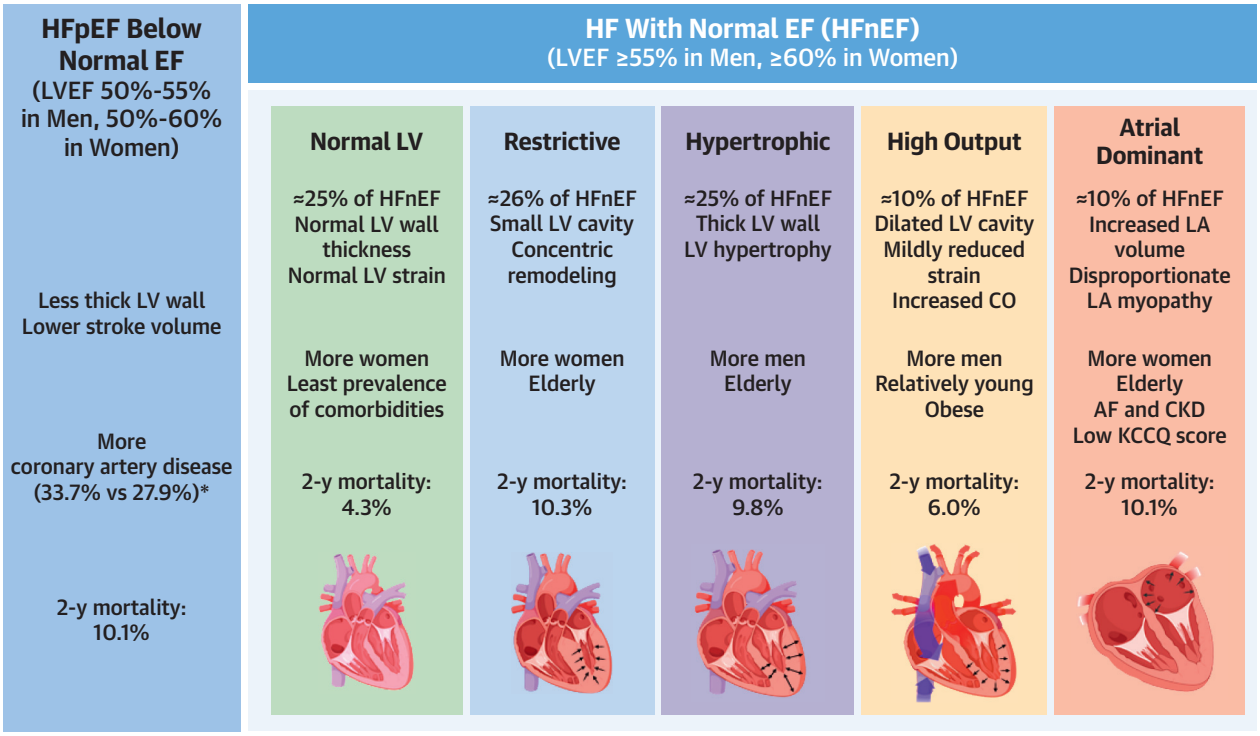
CENTRAL ILLUSTRATION **Clinical Characteristics of the HFnEF Clusters**



Teramoto K, et al. JACC: Asia. 2023;3(5):739–751.

Clinical characteristics of each cluster were determined based on the LASSO logistic regression and descriptive analysis of clinical characteristics and echocardiographic parameters. *Compared with HF with normal EF ($P = 0.02$). AF = atrial fibrillation; CKD = chronic kidney disease; CO = cardiac output; HFnEF = heart failure with normal ejection fraction; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrial; LASSO = least absolute shrinkage and selection operator; LV = left ventricular.

The recognition of different patterns of LV remodeling in patients with HFnEF may also offer clues to differential diagnoses and underlying pathophysiology. For example, in patients with the hypertrophic phenotype of HFnEF, it would be important to rule out differential diagnoses such as hypertrophic cardiomyopathy or cardiac amyloidosis. Among patients with LA-dominant HFnEF, disproportionate LA myopathy may be a key pathophysiological mechanism that has been associated with worse hemodynamics and a unique proteomic signature.[26-29]

SEX-SPECIFIC DEFINITION FOR HFnEF. In this analysis, sex-specific LVEF cut-off values were used to define the normal LVEF, because the LVEF is known to be higher in women among healthy and young individuals[8,30] and patients with HF.[31] Previous studies have shown bimodal distributions of LVEF in both sexes.[32] Generally, the peak of LVEF in women is higher than that of men with HF, as it was in the ASIAN-HF registry. With emerging evidence suggesting extended therapeutic benefit of neurohormonal agents in patients with HF to a higher LVEF range in women compared with men,[3] the use of sex-specific LVEF cut-off values of 55% for men and 60% for women has been proposed.[1] Of note, a slight male predominance in HFnEF, revealed using sex-specific cut-offs, was reversed (female predominance) using a sex-neutral cut-off of an LVEF of 60%, with other results remaining generally consistent. This result illustrates the impact of sex-specific cut-offs on epidemiologic estimates and suggests that prior reported female predominance in patients with HF and higher LVEF may be partially an artifact of using a sex-neutral cut-off (which fails to account for intrinsic sex differences).

STUDY LIMITATIONS. Our results were derived in an exclusively Asian population, and generalizability to other ethnicities and regions may be limited, although our results were validated independently in the multinational PROMIS-HFpEF study (predominantly European and American White patients). Even among Asian countries, regional differences in clinical characteristics of patients with HF have been reported; however, the echocardiographic subgroups were too small to allow meaningful comparisons by region. Biomarker data in the ASIAN-HF registry were available in only a subset of patients. Biopsy, invasive hemodynamic, exercise, and specialized tests for differential diagnoses (eg, amyloidosis) were not available. The availability of the echocardiographic parameters differed across the parameters; therefore, we only included a limited number of echocardiographic parameters in our clustering analysis (eg, no right heart parameters were included, which may have resulted in different clusters). Patients with substantial missing echocardiographic measurements (≥50%) were excluded from the cluster analysis and in the remaining patients, imputation for unavailable variables may have resulted in penalized LASSO regression odds ratios with high instability. Only a limited number of clustering techniques are included in the NbClust analytic framework (eg, we did not examine Bayesian clustering techniques). Although there were no significant differences in outcomes across the clusters, the results may have been underpowered because of the small number of patients and events in each cluster, and a longer follow-up period may be revealing. Our results should, therefore, be considered hypothesis generating, and future prospective studies are warranted.

CONCLUSIONS

HFnEF (LVEF (≥55% for men and ≥60% for women) comprises three-quarters of Asian patients with HFpEF (LVEF of ≥50%). Patients with HFpEF below normal LVEF had a higher prevalence of CAD (33.7% vs 27.9%), less thick LV walls, less LV concentricity, smaller stroke volumes, and lower cardiac output compared with those with HFnEF. Among patients with HFnEF, distinct patterns of cardiac structural, functional, and clinical characteristics may be discerned. Future studies are needed to corroborate these findings, which may carry implications for inclusion of HFpEF with below normal LVEF in the HFmrEF category, and targeted treatment approaches in HF with higher LVEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HFnEF is highly prevalent among Asian patients with HFpEF, carries the same mortality risk as that of HFpEF with below normal LVEF, and consists of patients with different patterns of cardiac structural, functional, and clinical characteristics.

TRANSLATIONAL OUTLOOK: The recognition of different patterns of LV remodeling in patients with HFnEF may offer clues to differential diagnoses and underlying pathophysiology, as well as provide a framework for considering results from more selected studies.

REFERENCES

1. Lam CSP, Solomon SD. Classification of heart failure according to ejection fraction: JACC review topic of the week. *J Am Coll Cardiol*. 2021;77:3217–3225.

2. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620.

3. Dewan P, Jackson A, Lam CSP, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail*. 2020;22:898–901.

4. Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J*. 2020;41:1249–1257.

5. Lam CSP, Anand I, Zhang S, et al. Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry. *Eur J Heart Fail*. 2023;15:928–936.

6. Santhanakrishnan R, Ng TP, Cameron VA, et al. The Singapore Heart Failure Outcomes and Phenotypes (SHOP) study and Prospective Evaluation of Outcome in Patients with Heart Failure with Preserved Left Ventricular Ejection Fraction (PEOPLE) study: rationale and design. *J Card Fail*. 2013;19:156–162.

7. Gori M, Lam CS, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2014;16:535–542.

8. Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL Study. *J Am Coll Cardiol Img*. 2015;8:656–665.

9. Josse Julie, Husson François. Handling missing values in exploratory multivariate data analysis methods. *Journal de la société française de statistique*. 2012;153:79–99. Accessed June 26, 2023. http://www.numdam.org/item/JSFS_2012__153_2_79_0/

10. Josse J, Husson F. missMDA: A package for handling missing values in multivariate data analysis. *J Stat Softw*. 2016;70:1–31.

11. Charrad M, Ghazzali N, Boiteau V, Niknafs A. NbClust: an R package for determining the relevant number of clusters in a data set. *J Stat Softw*. 2014;61:1–36.

12. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J*. 2018;39:3439–3450.

13. Curtis JP, Sokol SI, Wang Y, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. *J Am Coll Cardiol*. 2003;42:736–742.

14. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112:3738–3744.

15. Baumhove L, Tromp J, Figarska S, et al. Heart failure with normal LVEF in BIOSTAT-CHF. *Int J Cardiol*. 2022;364:85–90.

16. van Essen BJ, Tromp J, Ter Maaten JM, et al. Characteristics and clinical outcomes of patients with acute heart failure with a supranormal left ventricular ejection fraction. *Eur J Heart Fail*. 2023;25:35–42.

17. Lam CSP, Gamble GD, Ling LH, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. *Eur Heart J*. 2018;39:1770–1780.

18. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269–279.

19. Kao DP, Lewsey JD, Anand IS, et al. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. *Eur J Heart Fail*. 2015;17:925–935.

20. Segar MW, Patel KV, Ayers C, et al. Phenomapping of patients with heart failure with preserved ejection fraction using machine learning-based unsupervised cluster analysis. *Eur J Heart Fail*. 2020;22:148–158.

21. Cohen JB, Schrauben SJ, Zhao L, et al. Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone. *J Am Coll Cardiol HF*. 2020;8:172–184.

22. Woolley RJ, Ceelen D, Ouwerkerk W, et al. Machine learning based on biomarker profiles identifies distinct subgroups of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:983–991.

23. Uijl A, Savarese G, Vaartjes I, et al. Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:973–982.

24. Rosch S, Kresoja KP, Besler C, et al. Characteristics of heart failure with preserved ejection fraction across the range of left ventricular ejection fraction. *Circulation*. 2022;146:506–518.

25. Reddy YNV, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-output heart failure: a 15-year experience. *J Am Coll Cardiol*. 2016;68:473–482.

26. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015;8:295–303.

27. Khan MS, Memon MM, Murad MH, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail*. 2020;22:472–485.

28. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol*. 2020;76:1051–1064.

29. Patel RB, Lam CSP, Svedlund S, et al. Disproportionate left atrial myopathy in heart failure with preserved ejection fraction among participants of the PROMIS-HFpEF study. *Sci Rep*. 2021;11:4885.

30. Chung AK, Das SR, Leonard D, et al. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume: the Dallas Heart Study. *Circulation*. 2006;113:1597–1604.

31. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme– a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J*. 2003;24:442–463.

32. Henneges C, Morbach C, Sahiti F, et al. Sex-specific bimodal clustering of left ventricular ejection fraction in patients with acute heart failure. *ESC Heart Fail*. 2022;9:786–790.

KEY WORDS cluster analysis, heart failure, left ventricular hypertrophy, normal ejection fraction, preserved ejection fraction

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.