Heart failure with preserved ejection fraction diagnostic scores in an Asian population

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Heart failure with preserved ejection fraction (HFpEF) is a global epidemic, with increasing prevalence especially in aging societies such as Asia.[1] Non-invasive diagnosis of HFpEF is especially challenging and currently relies on a combination of symptoms and signs, increased natriuretic peptides as well as structural and/or functional alterations on echocardiography signifying increased left ventricular filling pressures.[2] Recently, the H_2FPEF score[3] and a novel algorithm by the Heart Failure Association of the European Society of Cardiology (HFA-PEFF)[4] have been proposed for the diagnosis of HFpEF. The H_2FPEF score includes a combination of clinical characteristic [age, obesity and atrial fibrillation (AF)] and echocardiographic parameters, while the new HFA-PEFF score includes echocardiographic characteristics such as left atrial enlargement combined with natriuretic peptide elevation. Asian patients with HFpEF are almost a decade younger than their western counterparts, have a lower prevalence of obesity and AF, and generally have smaller heart sizes with less concomitant left atrial enlargement.[1] Thus, we hypothesized that both scores may be less sensitive for the diagnosis of HFpEF in Asian patients with HFpEF. Accordingly, we aimed to test the ability of the HFA-PEFF and H_2FPEF scores to distinguish HFpEF from hypertensive controls in an Asian population.

We assessed the utility of the HFA-PEFF and H_2FPEF to distinguish 233 patients with HFpEF from 273 hypertensive controls in the Singapore Heart failure Outcomes and Phenotypes (SHOP) study.[5] In brief, HFpEF cases were Asian adults with a clinical diagnosis of heart failure independently established by a cardiologist and left ventricular ejection fraction ≥50%. Patients with severe valve disease were excluded. Hypertensive controls without heart failure were asymptomatic free adults, randomly sampled within five districts in the southeastern region of Singapore by a door-to-door census,[5] who either had an established diagnosis of hypertension, on anti-hypertensive medications or systolic blood pressure >140 mmHg. We provided additional validation in a separate cohort recruited as part of the Asian neTwork for Translational Research and Cardiovascular Trials (ATTRaCT) study (https://www.a-star.edu.sg/attract), which prospectively included 122 patients with HFpEF and 57 hypertensive controls with similar inclusion and exclusion criteria as the SHOP study.

We compared sensitivity, specificity, positive and negative predictive value (PPV/NPV), and area under the receiver-operating characteristic curve (AUC) of the HFA-PEFF and H_2FPEF scores in both the SHOP and ATTRaCT cohorts. According to the HFA-PEFF and H_2FPEF scores, the diagnosis was determined by a sum score ≥5 out of a total of 6 and ≥6 out of 9, respectively. Median percentage of missing variables (25th and 75th percentile) in SHOP data was 2% (1.2–3.2%) and 3% (2.5–9.3%) in ATTRaCT. To account for missing data, we generated five imputed datasets using multichain Monte Carlo methods with Gibbs sampling, and calculated the HFA-PEFF and H_2FPEF scores in these datasets separately. The diagnosis of HFpEF was determined by majority rule for each score.

In SHOP, patients with HFpEF had a mean age of 68 ± 11.7 years, 52% were women, 26% were obese (body mass index ≥ 30 kg/m^2), 31% had a history of AF, 86% had N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 125 pg/mL, 98% had increased filling pressures (E/e′ ≥ 13 or e′ septal and lateral wall <9 cm/s) and 23% of patients had a hypertensive and 42% an ischaemic aetiology. Mean age of hypertensive controls was 62 ± 9.8 years and 52% were women. In ATTRaCT, patients with HFpEF were 60 ± 14.8 years old, 31% were female, 41% were obese, 29% had a history of AF, 71% had NT-proBNP > 125 pg/mL, and 90% had increased filling pressures. Hypertensive controls were 60 ± 14.8 years old and 56% were female.

Sensitivity for distinguishing HFpEF from hypertensive controls was higher for HFA-PEFF score (73.8%), and lower for the H_2FPEF score (24.9%), with corresponding specificities of 81.3% and 87.9%, respectively. In the ATTRaCT cohort, the sensitivities were lower, but specificities higher, compared to the SHOP cohort, with similar patterns comparing the HFA-PEFF and H_2FPEF scores. The best discrimination of HFpEF from controls was achieved using HFA-PEFF in SHOP [AUC 0.776; 95% confidence interval (CI) 0.739–0.776]. Discrimination was better using continuous values than the cutoff for clinical diagnosis. All scores had prognostic properties, with hazard ratios for 1-year mortality in SHOP of 2.88 (95% CI 1.57–5.28; $P = 0.0007$) and 1.42 (95% CI 1.13–1.79; $P = 0.0028$) per point increase for HFA-PEFF and H_2FpEF, respectively.

Figure 1 shows the prevalence of patients with HFpEF that fulfilled each component of the various diagnostic algorithms. For the H_2FPEF score, the components most frequently fulfilled were hypertension and increased filling pressures, whereas the least frequently satisfied components were AF, obesity and pulmonary hypertension. We included the 2016 European Society of Cardiology (ESC) sub-criteria in this figure. The biomarker and structural heart disease criteria of ESC 2016 were most frequently satisfied; for the HFA-PEFF score, the biomarker and morphological domains were similarly most frequently fulfilled. This suggests that the H_2FPEF score was disadvantaged in our Asian population by not including a natriuretic peptide criterion and by including the AF and obesity criteria – given the high prevalence of raised natriuretic peptide levels, and low prevalence of AF and obesity in our Asian HFpEF population.[1,6–8] Lowering the obesity cutoff from 30 to 27 kg/m^2 increased sensitivity (from 24.9% to 30.9%), while maintaining the same specificity in SHOP for the H_2FPEF score. Conversely, the lack of gold standard invasive exercise haemodynamics for diagnosing HFpEF and potential clinical use of natriuretic peptides in identifying patients with HFpEF, might have led to a relative overestimation of diagnostic accuracy of the HFA-PEFF score, which are also largely based on increased natriuretic peptides, increased atrial size and filling pressures (E/e′).

In secondary analyses stratified by ethnicity, the AUC for the H_2FPEF score was lowest in Malay (0.64) compared to Chinese (0.74) and

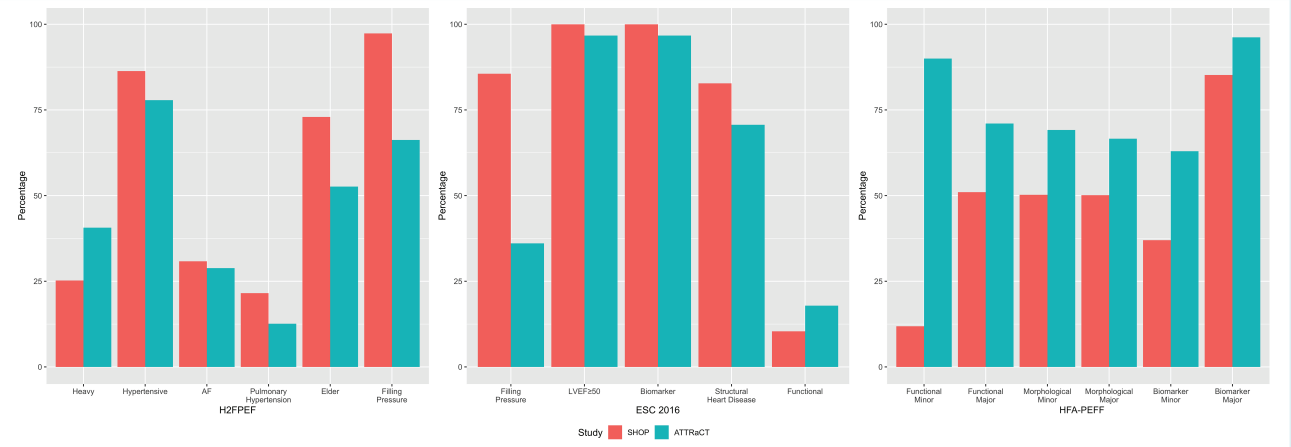

Figure 1 Sub-scores of the H_2FPEF, 2016 European Society of Cardiology heart failure with preserved ejection fraction (HFpEF) criteria and HFA-PEFF scores in the HFpEF population of SHOP and ATTRaCT. Percentage of patients with a positive score for each sub-category of each score. AF, atrial fibrillation; HFA, Heart Failure Association; LVEF, left ventricular ejection fraction.

Table 1 Diagnostic performance of the HFA-PEFF and H_2FPEF scores in SHOP and ATTRaCT

Cohort and comparison	Sensitivity	Specificity	PPV	NPV	AUC (95% CI)	*P*-value	AUC (continual scale) (95% CI)	*P*-value
SHOP HFpEF vs. control								
HFA-PEFF	73.8%	81.3%	77.1%	78.4%	0.776 (0.739–0.776)	–	0.821 (0.784–0.821)	–
H_2FPEF	24.9%	99.6%	98.3%	60.9%	0.623 (0.595–0. 651)	0.0003	0.822 (0.788–0.857)	0.9
ATTRaCT HFpEF vs. control								
HFA-PEFF	57.4%	91.2%	93.3%	50.0%	0.743 (0.685–0.743)	–	0.729 (0.655–0.729)	–
H_2FPEF	47.5%	98.2%	98.3%	46.7%	0.729 (0.681–0.729)	0.685	0.818 (0.758–0.818)	0.02

Youden index optimized scores	Sensitivity	Specificity	AUC	Youden score
SHOP HFpEF vs. control				
HFA-PEFF	86.3%	57.9%	0.808	0.441
H_2FPEF	61.8%	87.9%	0.822	0.497
ATTRaCT HFpEF vs. control				
HFA-PEFF	69.7%	80.7%	0.818	0.504
H_2FPEF	57.4%	91.2%	0.729	0.486

AUC, area under the receiver-operating characteristic curve; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; NPV, negative predictive value; PPV, positive predictive value.

Indian (0.71) participants. The AUC for the HFA-PEFF score was lowest in Indian (0.57) compared to Chinese (0.77) and Malay (0.75) participants. Lastly, we optimized the Youden index for our cohorts, and found that the optimal cutoffs were 3 and 5 for both SHOP and ATTRaCT for H_2FPEF and HFA-PEFF, respectively. This increased sensitivity, but decreased specificity, as compared to the original diagnostic cutoffs (*Table 1*).

Our study shows that the H_2FPEF and HFA-PEFF scores have reasonable specificities, but limited sensitivities for the diagnosis of HFpEF in an Asian population. Two recent studies independently validated the H_2FPEF score and HFA-PEFF score in predominantly Caucasian and western populations.[9,10] However, like the current study, these prior studies did not definitively ascertain HFpEF or non-HFpEF status using invasive testing. Both studies showed that the scores were good at identifying patients with HFpEF, but poor at ruling out HFpEF. Our data extend upon this previous work by showing that both the HFA-PEFF and H_2FPEF scores may have lower diagnostic performance in Asian populations with HFpEF compared to western populations. Possible reasons include younger age and lower prevalence of obesity and AF, despite high natriuretic peptide levels, in Asian patients with HFpEF. We acknowledge that HFpEF diagnostic criteria are best tested in patient populations presenting with general dyspnoea, all of whom also undergo gold standard testing with exercise invasive haemodynamics; however, in the absence of such data we attempted to get as close as possible to the comparison of clinical interest by including hypertensive controls rather than healthy controls. The performance of diagnostic scores might also be different in populations with lower NT-proBNP levels.

Strengths of our approach included prospective recruitment of HFpEF cases and controls from the same nationwide population, with standardized echocardiographic and blood sampling protocols. Our data suggest that the application of existing diagnostic

criteria and scores to Asian populations may miss some cases with HFpEF. Potential ethnic differences and need to recalibrate diagnostic cutoffs in Asians deserve further study.

Conflict of interest: none declared.

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