

The ventilatory abnormalities and prognostic values of H₂FPEF score in dyspnoeic patients with preserved left ventricle systolic function

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) is one of the major diagnoses in dyspnoeic subjects, and H₂FPEF score enables robust differentiation of HFpEF. Given ventilatory abnormalities prevail in subjects with HFpEF, the associations between H₂FPEF score and pulmonary function remain to be elucidated.

Methods and results Subjects who presented with exertional dyspnoea and had left ventricular ejection fraction of >50% were eligible for this study. Total lung capacity, forced expiratory volume in the 1 s, and forced vital capacity (FVC) were obtained by pulmonary function tests. Pulmonary artery systolic pressure (PASP), the ratio of early ventricular filling flow velocity to the septal mitral annulus tissue velocity (E/e'), and left ventricular mass (LVM) were measured by echocardiogram. Among a total of 5849 participants (65.6 ± 6.4 years, 54% men), 2453 (41.9%) had low H₂FPEF score (0 ~ 1) and 160 (2.7%) had high H₂FPEF score,^{6–9} respectively. Subjects with high H₂FPEF score were older and had higher proportion of restrictive and obstructive defect, more morbidities, poorer renal function, lower haemoglobin, higher LVM, E/e' ratio, and PASP. During a mean follow-up duration of 30.0 ± 20.5 months, the H₂FPEF score was significantly associated with mortality [hazard ratio and 95% confidence intervals, 1.063(1.010–1.18)], independent of sex, haemoglobin, renal function, LVM, and comorbidities.

Conclusions Either obstructive or restrictive ventilation defects prevail in subjects with high H₂FPEF score, indicating chronic obstructive pulmonary disease (COPD) is commonly associated with HFpEF. In addition, H₂FPEF score was correlated with long-term survival in dyspnoeic subjects with or without concomitant diseases of HFpEF and COPD.

Keywords Heart failure with preserved ejection fraction; Mortality; Pulmonary function

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Introduction

Heart failure with preserved ejection fraction (HFpEF) has accounted for approximately 50% of heart failure (HF) hospitalizations worldwide, and it was also related to an increased risk of mortality.^{1–4} Nevertheless, the accurate diagnosis of HFpEF was even more challenged in the absence of congestive symptoms and signs.^{5,6} Invasive hemodynamic measures with or without exercise tests would be helpful to identify

elevated left ventricular end-diastolic pressure in patients with unexplained dyspnoea.^{7,8} However, the routine application of right heart catheterization for the diagnosis of HFpEF seems to be unpractical.^{8,9} Recently, Reddy et al. developed H₂FPEF score to discriminate HFpEF from non-cardiac causes of dyspnoea, while HFpEF was recognized by elevated pulmonary arterial wedge pressure (PAWP) at rest or during exercise.⁷ H₂FPEF score was composed of clinical characteristics and echocardiography, including age, body mass index,

hypertension, atrial fibrillation, pulmonary hypertension, and elevated left ventricular filling pressure, to propose the likelihood of HFpEF.

But an elevated PAWP is not specific exclusively for HFpEF, patients with chronic obstructive pulmonary disease (COPD) may also have presented with left ventricular diastolic dysfunction and raised left ventricular end-diastolic pressure in the previous studies.^{10–12} COPD is a common cause of dyspnoea, and it is highly prevalent in patients with HFpEF.^{13,14} Because Reddy et al. have excluded subjects with significant lung diseases, we wondered whether H₂FPEF score can be generalized to the patients firstly presented with dyspnoea on exertion. In this study, we therefore investigated the associations of H₂FPEF score with clinical characteristics, echocardiographic indices, and pulmonary function in an Asian population. We further evaluated the prognostic impacts of H₂FPEF score in dyspnoeic subjects.

Methods

Study population

The study population was drawn from an administrative registry to INvestigate Heart And Lung interERaction (INHALER registry). The registry was composed of 8963 ambulatory outpatients, who complained of exertional dyspnoea from August 2005 to December 2012. All of them have received both pulmonary function tests and echocardiographic studies. Patients with left ventricular ejection fraction of <50%, significant valvular heart disease, severe hepatic disease, haematopoietic diseases, or active malignancy, were excluded from this analysis. (Figure S1) The investigation was conformed to the principles outlined in the Declaration of Helsinki. The institutional review committee of Taipei Veterans General Hospital approved the registry data to be used for study purposes.

Data of demographic characteristics, electrocardiogram, laboratory data, echocardiography, and medications were prospectively inputted in a web-based medical recording system. Estimated glomerular filtration (eGFR) rate was calculated using the Chinese Modification of Diet in Renal Disease equation.¹⁵ Body mass index was universally expressed in kg/m².

Left ventricular end-diastolic dimension, end-systolic dimension, left ventricular end-diastolic volume, left ventricular mass (LVM), left atrial (LA) dimension, and left ventricular ejection fraction were obtained.¹⁶ E/A ratio represented the ratio of left ventricular early (E) to late (A) filling flow velocity. E/e' was the ratio of early ventricular filling flow velocity (E) to the septal mitral annulus tissue velocity (e'). Pulmonary artery systolic pressure (PASP) was also estimated. Left ventricular diastolic dysfunction was defined if ≥ 3 of the following

measures were fitted¹: septal e' velocity < 7 cm/s,² septal E/e' ratio > 15,³ PASP > 35 mmHg, and⁴ LA dimension >40 mm.

Pulmonary function test was performed standardly by body plethysmograph (MasterScreen Body Plethysmograph, Erich Jaeger GmbH, Würzburg, Germany) and spirometry (CPFS/D USB, Medical Graphics, St Paul, Minnesota, USA). According to the statement of American Thoracic Society standards, residual volume, total lung capacity (TLC), forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were presented as the percentage of their predicted values. The obstructive and restrictive ventilation defects were defined as the ratio of FEV1 to FVC below 70% and the predicted %TLC below 80%, respectively.¹⁷ COPD was diagnosed by the clinical physicians and a pre-bronchodilator FEV1/FVC ratio of <0.7. Subjects who were diagnosed as asthma or had received monotherapy with inhaled corticosteroid were excluded.

H₂FPEF score was determined by six variables, including, 3 points for atrial fibrillation, 2 points for obesity, and 1 point for each of the follows: two or more hypertensive drugs, pulmonary hypertension (PASP > 35 mmHg), elder (age > 60), and elevated filling pressures (E/e' ratio > 9).⁷

Follow-up

We would identify the causes and dates of death of the study population by linking to the National Death Registry.¹⁸ The study population was followed for up to 60 months.

Statistical analysis

Continuous and categorical variables were presented as mean \pm standard deviation and the absolute numbers and relative frequencies, respectively. The differences between groups were compared by Chi-square tests and Student's *t*-test as appropriate. Cox proportional hazards models were used to evaluate the independence of H₂FPEF in the prediction of mortality with adjustments for sex, haemoglobin, eGFR, and comorbidities. All the statistics were performed using SPSS v.22.0 software (SPSS, Inc., Chicago, IL, USA). All the tests performed were two-sided and a *P* value of <0.05 was considered statistically significant.

Results

The study population was composed of 5849 patients (age 65.6 \pm 16.4 years, 54% men, and mean H₂FPEF score 2.04 \pm 1.50), presented with dyspnoea on exertion to the outpatient clinics. The baseline characteristics were presented in *Table 1*, stratified by H₂FPEF score. In short, patients with

Table 1 Baseline characteristics of the study population

Characteristic	HF2PEF score 0 ~1 (n = 2453)	HF2PEF score 2–5 (n = 3236)	HF2PEF score 6–9 (n = 160)	P value
Age (years)	55.0 ± 16.4	72.7 ± 11.4	79.7 ± 7.05	<0.001
Male gender, n (%)	1,189 (48.6)	1869 (58.1)	109 (68.1)	<0.001
Body mass index	23.4 ± 3.3	26.3 ± 14.0	32.6 ± 26.9	<0.001
Co-morbidity, n (%)				
COPD	148 (6.0)	456 (14.1)	41 (25.6)	<0.001
Diabetes mellitus	285 (11.6)	835 (25.9)	66 (41.3)	<0.001
Coronary artery disease	881 (35.9)	1,433 (44.3)	68 (42.5)	<0.001
Hypertension	618 (25.2)	1840 (56.9)	129 (80.6)	<0.001
Atrial fibrillation	0 (0)	198 (6.1)	138 (86.3)	<0.001
Echocardiography				
LV diastolic dysfunction, n (%)	1 (0.0)	255 (7.8)	47 (29.3)	<0.001
LVEF (%)	71.5 ± 8.7	71.5 ± 9.5	69.9 ± 9.2	0.097
LVM (g)	159.3 ± 67.6	191.3 ± 70.1	203.3 ± 64.7	<0.001
Septal E/e'	8.5 ± 3.0	13.6 ± 5.6	15.6 ± 6.1	<0.001
Mitral E/A ratio	1.10 ± 0.48	0.89 ± 0.43	1.08 ± 0.69	<0.001
LA diameter (mm)	35.5 ± 7.3	41.2 ± 8.7	49.2 ± 9.6	<0.001
LVIDd (mm)	47.1 ± 12.6	48.3 ± 7.5	48.5 ± 7.1	<0.001
LVIDs (mm)	27.5 ± 5.6	28.3 ± 6.5	29.0 ± 6.0	<0.001
PASP (mmHg)	28.6 ± 11.9	39.4 ± 16.4	49.9 ± 16.0	<0.001
Hemogram and Biochemistry, on admission				
Haemoglobin (g/dL)	12.7 ± 2.1	12.0 ± 2.1	11.7 ± 2.0	<0.001
eGFR (mL/min/1.73m ²)	87.1 ± 28.5	71.4 ± 30.8	57.4 ± 29.0	<0.001
Sodium (mEq/L)	139.2 ± 3.3	139.0 ± 3.6	139.2 ± 4.0	0.138
Potassium (mEq/L)	4.08 ± 0.68	4.12 ± 0.56	4.07 ± 0.64	0.788
Pulmonary function test				
Predicted RV%	106.9 ± 33.6	104.8 ± 33.9	102.9 ± 30.7	0.109
Predicted TLC%	92.5 ± 17.2	88.9 ± 22.4	83.6 ± 16.0	<0.001
Predicted VC%	85.5 ± 19.7	78.1 ± 20.4	69.6 ± 20.5	<0.001
RV/TLC ratio, %	38.5 ± 10.9	46.2 ± 11.1	50.9 ± 11.6	<0.001
FEF 25% to 75%, (L/s)	2.35 ± 1.20	1.50 ± 0.90	1.21 ± 0.79	<0.001
Predicted FEV1%	86.7 ± 22.0	78.6 ± 24.2	70.5 ± 24.3	<0.001
Predicted FVC%	85.2 ± 20.0	75.8 ± 21.6	66.8 ± 21.1	<0.001
FEV1/FVC ratio, %	80.1 ± 10.8	75.7 ± 12.0	73.8 ± 13.2	<0.001

COPD, chronic obstructive pulmonary disease; E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; E/E', ratio of early ventricular filling velocity (E) to early diastolic tissue velocity mitral annulus; eGFR, estimated glomerular filtration; FEF 25% to 75%, forced expiratory flow at 25%–75% of the pulmonary volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LV mass, left ventricular mass; PASP, pulmonary artery systolic pressure; RV, residual volume; TLC, total lung capacity; VC, vital capacity

high H₂FPEF score (*n* = 160, 2.7%) were older, more likely to be men, and have COPD, diabetes, hypertension, and atrial fibrillation. Haemoglobin and eGFR decreased along with the order of low, intermediate, and high H₂FPEF score. In contrast, LVM, septal E/e', LA dimension, left ventricular internal diameter in diastole, left ventricular internal dimension in systole, and PASP increased along with the increase of H₂FPEF score. Regarding the pulmonary function indices, predicted %TLC, predicted %FEV1, predicted %FVC, and FEV1/FVC ratio declined and residual volume/TLC ratio increased in subjects with higher H₂FPEF score.

Pulmonary function and H₂FPEF score

On one hand, the prevalence of obstructive ventilation defect¹⁹ was 12.8%, 26%, and 36.9% in subjects with low, intermediate, and high H₂FPEF score. (Figure 1) On the other hand, restrictive ventilation defects were presented in

17.7%, 26.4%, and 38.1% of the patients with low, intermediate, and high H₂FPEF score, respectively. (Figure 1) H₂FPEF score was positively related to the prevalence of pulmonary function abnormalities.

Among the subpopulation without COPD, 44.2% of them had low H₂FPEF score of 0 or 1. (Figure 2) In contrast, only 22.9% of the subpopulation with COPD had low H₂FPEF score. H₂FPEF score was significantly higher in subjects with COPD than those without (2.57 ± 1.44 vs. 1.91 ± 1.45, *P* < 0.001). (Figure 2).

Prognostic impacts of H₂FPEF score

During a mean follow-up duration of 30.0 ± 20.5 months, there were 897 deaths and 230 cardiovascular mortalities. The long-term survival probabilities were 88.5%, 82.3%, and 75.0% of patients with low, intermediate, and high H₂FPEF score, respectively. The Kaplan–Meier survival curve analysis

Figure 1 The distributions of the pulmonary function abnormalities, stratified by H₂FPEF score of 0–1, 2–5, and 6–9. The obstructive and restrictive ventilation defects were defined as forced expiratory volume in 1 s/forced vital capacity of <0.7 and the predicted %TLC of <80%, respectively.

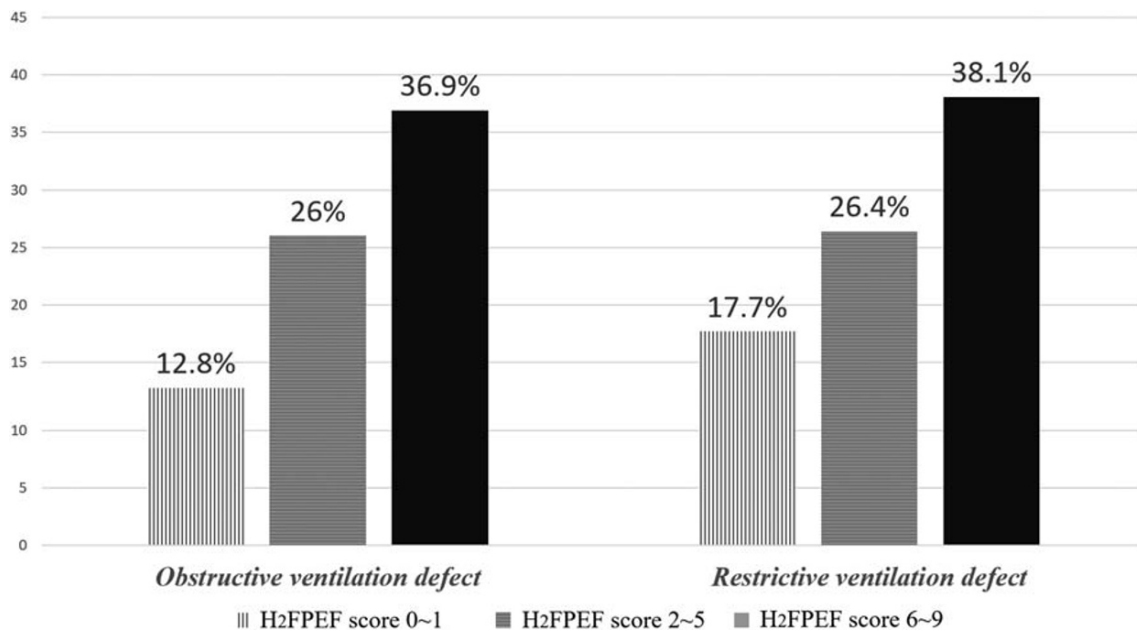
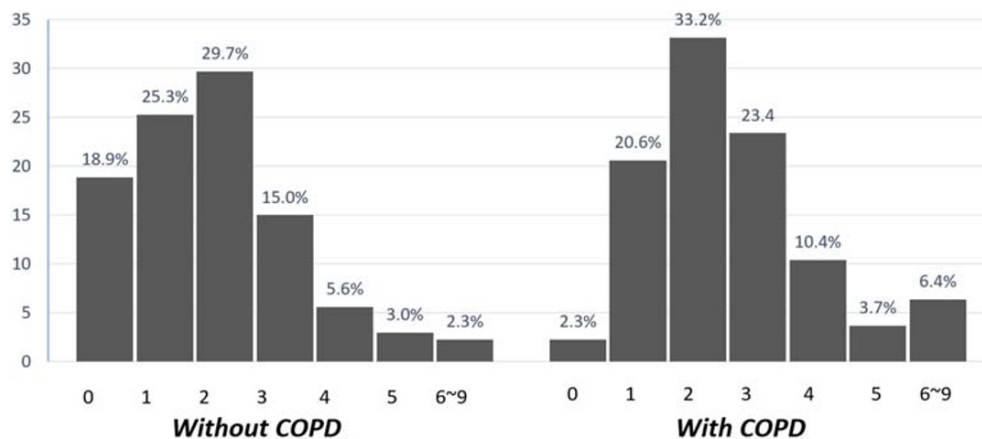


Figure 2 The distributions of H₂FPEF score in subjects with or without chronic obstructive pulmonary disease (COPD).

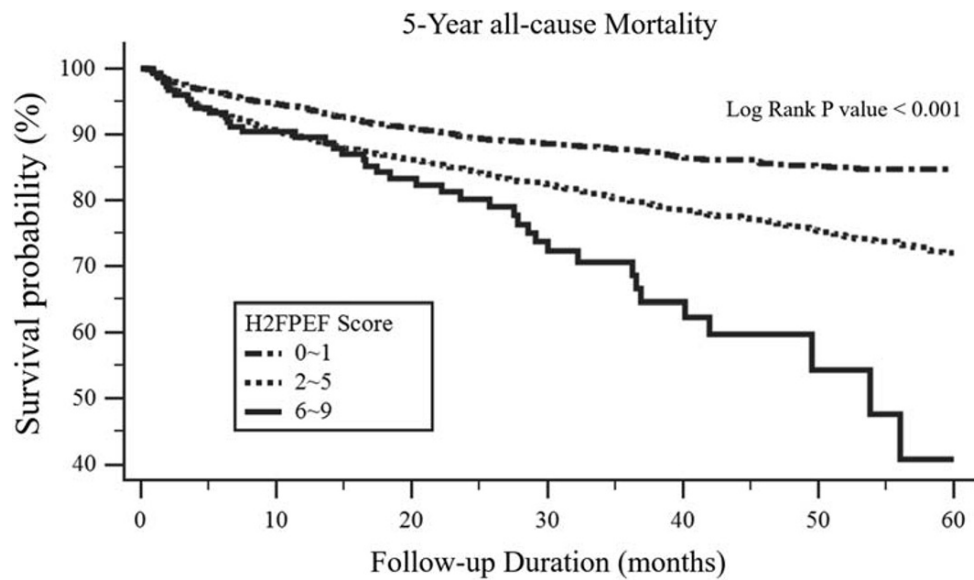


demonstrated significantly survival discrepancies among the three groups. (Figure 3).

Among the study population, H₂FPEF score, male gender, LVM, haemoglobin, eGFR, the presence of COPD, and diabetes were all related to long-term survival in univariate Cox regression analysis. (Table 2) The multivariate Cox regression analysis suggested H₂FPEF score was associated with mortality [Hazard ratios and 95% confidence interval: 1.063 (1.010–1.118)], independently of gender, haemoglobin, LVM, eGFR, COPD, and diabetes. (Table 2).

Discussion

While H₂FPEF score may have provided the probability of HFpEF in dyspnoeic patients,⁷ ventilatory abnormalities also prevail in subjects with high H₂FPEF score. The present study demonstrated patients with high H₂FPEF score were more likely to have either obstructive or restrictive ventilation defects. The results may support to survey pulmonary function in dyspnoeic patients with high H₂FPEF score, in addition to

Figure 3 The Kaplan–Meier survival curve analysis of the study population, stratified by H₂FPEF score of 0–1, 2–5, and 6–9.**Table 2** Predictors of 5-year mortality identified by univariable and multivariable Cox regression analysis

Characteristic	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
H ₂ FPEF score	1.126 (1.178–1.276)	<0.001	1.063 (1.010–1.118)	0.019
Sex (male)	1.527 (1.332–1.752)	<0.001	1.341 (1.142–1.575)	<0.001
Presence of COPD	1.502 (1.248–1.807)	<0.001	1.343 (1.083–1.666)	0.007
Presence of diabetes	1.401 (1.204–1.629)	<0.001	1.017 (1.142–1.575)	0.849
LVM (g)	1.003 (1.002–1.004)	<0.001	0.999 (0.998–1.001)	0.120
Haemoglobin (g/dL)	0.803 (0.778–0.829)	<0.001	0.846 (0.817–0.877)	<0.001
eGFR (mL/min/1.73 m ²)	0.988 (0.986–0.990)	<0.001	0.994 (0.991–0.996)	<0.001

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVM, left ventricular mass.

the evaluation of HFpEF. Furthermore, the study may firstly show the long-term prognostic values of H₂FPEF score in dyspnoeic subjects, regardless of patients with or without COPD.

The associations between heart failure with preserved ejection fraction and abnormalities of ventilation function

While lung function abnormalities were prevalent in patients with HFpEF,²⁰ Obokata and Ries *et al.* have further demonstrated the reduced ventilation reserve and significant restrictive change along with the increase of PAWP and pulmonary artery pressures in patients undergoing cardiac catheterization.^{21,22} In contrast, the obstructive change of ventilation related to submucosal oedema in decompensated HF was also anticipated.²³

In the present study, subjects with high H₂FPEF score were more likely to have restrictive and/or obstructive ventilatory defects. The predicted TLC, FEV_{25–75} and FEV₁/FVC decreased along with the increase of H₂FPEF score. Given H₂FPEF score may indicate the probability and severity of HFpEF, the study results would support the ventilatory abnormalities prevails in patients with HFpEF.

The identification and treatment of concomitant heart failure and chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is prevalent in patients with HFpEF, and it is associated with adverse clinical outcomes and poor quality of life.^{24,25} The efficacy and safety of cardioactive inhaled pulmonary drugs is controversial in treating HF patients with or without lung comorbidities.^{5,26–28} Therefore, it is critical to identify the subjects with

concomitant HF and COPD. In our study, up to 14.1% and 25.6% of the patients with intermediate and high H2FPEF score had documented COPD by spirometry, respectively. The comprehensive echocardiography and pulmonary function tests would be helpful to demonstrate cardiac or pulmonary abnormalities objectively, especially when it was challenging to differentiate a cardiac disease from pulmonary disease and vice versa by clinical findings.²⁹

About 70.7% and 53.3% of patients with and without COPD had a H2FPEF score of 2 to 5, respectively, indicating that the majority of the study population warrants further survey for HFpEF. However, only 2.3% to 6.4% of the dyspnoeic patients, regardless of COPD had high H2FPEF score. While HFpEF was highly suspected, subjects should therefore undergo right heart catheterization for confirmation.

Prognostic impacts of H2FPEF score

The long-term outcomes of HFpEF remain dismal, while the mortality rate and HF hospitalization of HFpEF are as high as those with reduced left ventricular ejection fraction.^{30,31} Although H2FPEF score was designed to evaluate the probability of HFpEF rather than to predict the clinical outcomes, its component variables, including PASP, body mass index, and atrial fibrillation have been related to survival in HFpEF.^{32–34} The prognostic associations with H2FPEF score could have been anticipated. However, in the present study, we might firstly demonstrate H2FPEF score was correlated with increased risks of long-term mortality in dyspnoeic patients, independent of morbidities, LVM, haemoglobin, and eGFR. The findings may support that H2FPEF score could not only identify a specific population with increased risk of HFpEF but also adverse clinical outcomes, regardless of diabetes, pulmonary disorders, anaemia, chronic kidney disease, or left ventricular hypertrophy. Given the baseline characteristics of HFpEF were heterogeneous, the study results also suggested the clinical application of H2FPEF score for risk stratifications and tailored therapies.

Study limitations

There were several study limitations in this work. First, we did not conduct the right heart catheterization for the diagnosis of HFpEF in all participants, because this was not a validation study of H2FPEF score. In addition, we were not able to diagnose HFpEF precisely while the data of left atrial volume and brain natriuretic peptide was lack. But we did show the prevalence of HFpEF increased along with the increased H2FPEF score. In this study, we did further extend its clinical associations with pulmonary functions and long-term survival. Second, selection bias could not be excluded, giving that this

was an observational study. But we have adjusted for all the available confounders to evaluate the independent prognostic values of H2FPEF. Third, the diagnosis of HFpEF is very difficult in patients with concomitant COPD, while both diseases may share similar risk factors, such as old age and obesity. And COPD could consequently cause atrial fibrillation, pulmonary hypertension, and abnormal E/e' ratio. Fourth, data of HF hospitalization were not fully available in this study. Further studies are needed to address the correlations of H2FPEF score with morbidity.

Conclusion

While H2FPEF score has been validated to evaluate the probability of HFpEF, the present study further extended its correlations with pulmonary functions. Although it could be difficult to identify HFpEF in patients with concomitant COPD, subjects with high H2FPEF score would more likely to have either obstructive or restrictive ventilatory defects. In addition, H2FPEF score was independently associated with long-term survival in the study population, who presented with exertional dyspnoea. Because the underline aetiologies of HFpEF were heterogeneous, this study may also have proposed the prognostic values of H2FPEF score in HFpEF. Further studies may be needed to survey the clinical application of H2FPEF score for the diagnosis of HFpEF, and a multidisciplinary approach is indicated to manage patients with concomitant COPD.

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Conflict of interest

None declared.

Supporting information

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

Figure S1. The flow chart of analyzed study population

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