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ORIGINAL RESEARCH ARTICLE

H_2FPEF score for predicting future heart failure in stable outpatients with cardiovascular risk factors

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Abstract

Aims The prediction of future heart failure (HF) in stable outpatients is often difficult for general practitioners and cardiologists. Recently, the H_2FPEF score (0–9 points) has been proposed for the discrimination of HF with preserved ejection fraction from non-cardiac causes of dyspnoea. The six clinical and echocardiographic variables that constitute the H_2FPEF score include the following: (i) obesity (H); (ii) the use of ≥2 antihypertensive drugs (H); (iii) atrial fibrillation (F); (iv) pulmonary hypertension (P); (v) an age > 60 years (E); and (vi) E/e' > 9 (F). We performed an external validation study that investigated whether the H_2FPEF score could predict future HF-related events in stable outpatients with cardiovascular risk factor(s) in Japan.

Methods and results In this prospective cohort study, after exclusion of 195 from 551 consecutive, stable Japanese outpatients with at least one cardiovascular risk factor who were enrolled between September 2010 and July 2013, the remaining 356 outpatients (171 men, 185 women, mean age 73.2 years) were eligible for the analysis. We calculated the H_2FPEF score (0–9 points), and followed up the patients for an average of 517 days. In all of the 356 patients, the mean H_2FPEF score was 3.1 ± 1.8, and 15 developed HF-related events during the follow-up period, including cardiovascular death (n = 2) and hospitalization for HF decompensation (n = 13). Multivariate Cox proportional hazards analysis showed that the H_2FPEF score was an independent predictor of future HF-related events ($P < 0.001$ for all three models). Kaplan–Meier survival curves showed a significantly higher probability of HF-related events in the outpatients with a high H_2FPEF score ($P < 0.001$). In receiver operating characteristic (ROC) curve analysis, the H_2FPEF score was significantly associated with the occurrence of future HF-related events ($P < 0.001$). In ROC curve analysis, the sensitivity, specificity, and positive likelihood ratio of a H_2FPEF score of 7 points to predict HF-related events were 47%, 96%, and 11.4%, respectively.

Conclusions The H_2FPEF score could provide useful information for future HF-related events in stable outpatients with cardiovascular risk factor(s) in Japan.

Keywords H_2FPEF score; Outpatient; Heart failure; Prognosis

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Introduction

The prevalence of heart failure (HF) has been increasing worldwide, especially in elderly populations. In the United States, the cost for HF management including healthcare services, medications, and lost productivity exceeded $30 billion in 2013, indicating that the economic burden of HF management is increasing.[1] Although it is imperative to establish improved management for HF, the prediction of HF is often difficult for general practitioners and cardiologists. To make effective use of limited medical resources, it is important to detect high-risk patients for HF in routine clinical practice.

Most recently, the H_2FPEF score (0–9 points) has been proposed for the discrimination of HF with preserved ejection fraction (HFpEF) from non-cardiac causes of dyspnoea and to assist in determination of the need for further diagnostic testing in the evaluation of patients with unexplained exertional dyspnoea in a Bayesian approach.[2,3] The six clinical and echocardiographic variables that constituted the H_2FPEF score included the following: (i) a body mass index (BMI) $>$ 30 kg/m^2 (H); (ii) the use of $\geq$2 antihypertensive drugs (H); (iii) the presence of atrial fibrillation (AF) (F); (iv) pulmonary hypertension defined as pulmonary artery systolic pressure (PAP) $>$35 mmHg (P); (v) an age $>$ 60 years (E); and (vi) elevated filling pressures evident from E/e' $>$ 9 (F). The presence of paroxysmal or persistent AF yields 3 points, a BMI $>$ 30 kg/m^2 yields 2 points, and all of the other criteria listed above yield 1 point. This score enables robust discrimination of HFpEF from non-cardiac causes of dyspnoea at low and high scores, while identifying patients at intermediate probability in whom additional testing is needed to refine the diagnosis.[2,3]

Although the H_2FPEF score provides properly derived and validated diagnostic algorithms to predict HFpEF, the relevance between the numerical value of each point indicated by this score and the prognosis for future HF events is not clear. Also, the six clinical and echocardiographic variables that are included in the H_2FPEF score are known to be important as pathogenetic and prognostic factors for HF. [1–4] These findings suggest the possible utility of the H_2FPEF score in predicting future HF events in stable outpatients with cardiovascular risk factor(s) in routine clinical practice.

The present prospective cohort study was performed as an external validation study, and it examined whether the H_2FPEF score could identify stable outpatients with cardiovascular risk factors(s) at high risk for future HF-related events.

Methods

Study patients

Between September 2010 and July 2013, we enrolled 551 consecutive, stable Japanese outpatients who visited Ozawa Clinic with at least one cardiovascular risk factor, defined below in detail. Since then, we have conducted a longitudinal cohort study in those patients. We recorded each patient's medical history and relevant clinical characteristics. A detailed description of this study has been published previously.[5] In the 551 stable outpatients, we excluded 75 outpatients for the following reasons: left ventricular ejection fraction (LVEF) $<$50% (n = 29), hypertrophic or dilated cardiomyopathy (n = 29), cardiac sarcoidosis (n = 2), and greater than or equal to moderate heart valve disease or post-valve replacement (n = 15). We also excluded 120 outpatients who did not have E/e', tricuspid regurgitation peak gradient (TRPG), or inferior vena cava (IVC) diameter measured by echocardiography. The remaining 356 outpatients (171 men, 185 women) with complete data were included in the present analysis (*Figure 1*).

Unstable and high-risk outpatients were excluded at the time of enrollment. These included those with acute phase HF decompensation and those with acute coronary syndrome who required emergency coronary angiography, defined as either acute myocardial infarction or class II/III unstable angina by Braunwald's classification. Furthermore, we also excluded patients with advanced chronic obstructive pulmonary disease, advanced collagen disease, active inflammatory disease, severe liver dysfunction, neoplasms, and estimated glomerular filtration rate (eGFR) $<$ 15 mL/min/1.73 m^2 at the time of enrollment.

The cardiovascular risk factors were defined as hypertension (HT) (blood pressure $\geq$ 140/90 mmHg or taking antihypertensive drugs), dyslipidemia (DLP) (low-density lipoprotein cholesterol $\geq$ 140 mg/dL [3.6 mmol/L], high-density lipoprotein cholesterol $<$ 40 mg/dL [1.0 mmol/L], triglycerides $\geq$ 150 mg/dL [1.7 mmol/L] or taking lipid-lowering drugs), diabetes mellitus (DM) (fasting blood glucose levels $\geq$ 126 mg/dL [7.0 mmol/L], $>$200 mg/dL [11.1 mmol/L] in an oral glucose tolerance test, or taking anti-diabetic drugs), an estimated glomerular filtration rate $<$ 60 mL/min/1.73 m^2 (chronic kidney disease [CKD]), and a history of cardiac diseases (a history of coronary artery disease [CAD], left ventricular hypertrophy [LVH] due to HT and not due to cardiomyopathy, valve disease [moderate-severe heart valve disease or heart valve replacement], or paroxysmal/persistent AF). Antihypertensive drugs included angiotensin converting enzyme inhibitors (ACE-I)/angiotensin II receptor blockers (ARB), calcium channel blockers, beta-blockers, thiazide diuretics, loop diuretics, and mineralocorticoid receptor blockers (MRA) including spironolactone.

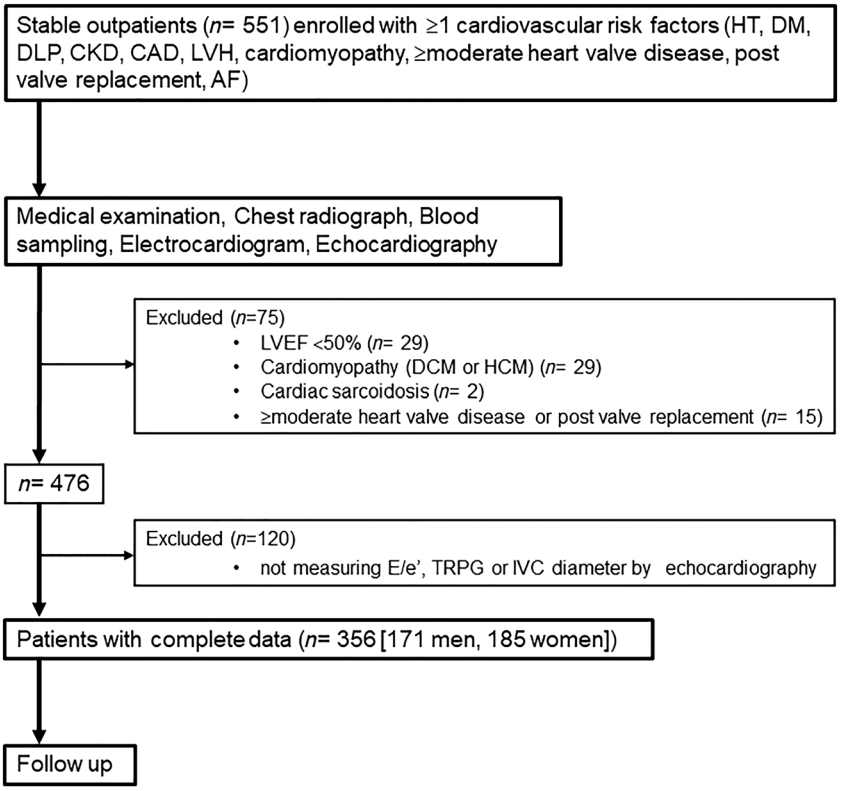
Ethics statement

This study was conducted in accordance with the principles contained in the Declaration of Helsinki. The study protocol was approved by the Human Ethics Review Committee of Kumamoto University (approval number: 1627). Signed consent was obtained from each participant. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN 000035217). Opt-out materials are available through the website: http://www.kumadai-junnai.com/en/. This study was supported by research funds from Ozawa Clinic.

Clinical variables, electrocardiogram, and echocardiography

The eGFR was calculated using the Japanese Society of Nephrology formula at the time of enrollment.[6]

Figure 1 Flow chart of patient enrollment in the present study.AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; DLP, dyslipidemia; DM, diabetes mellitus; E/e', the ratio of early transmitral flow velocity to early diastolic mitral annular velocity by tissue Doppler (septal); HCM, hypertrophic cardiomyopathy; HT: hypertension; IVC, inferior vena cava diameter; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; TRPG: tricuspid regurgitation peak gradient.



An electrocardiogram was obtained, and echocardiography was performed within 6 months after enrollment. We used commercially available ultrasound systems (EUB-7500, Hitachi, Tokyo, Japan) to evaluate cardiac function. Measurement of the LVEF was performed in the biplane apical (2-chamber and 4-chamber) views using a modified Simpson's method. The left atrial diameter, left atrial volume index (LAVI), ratio of early transmitral flow velocity to early diastolic mitral annular velocity by tissue Doppler at the septal side (E/e'[septal]), left ventricular mass index, TRPG, and IVC diameter were measured. PAP was calculated as (4 × TRPG) + right atrial pressure (estimation by IVC diameter).[7–9]

We calculated the H_2FPEF score for each outpatient and divided them into three groups (low score [0–1 point], intermediate [2–5 points], and high [6–9 points]) according to previous studies.[2,3]

Follow-up and heart failure-related events

We followed up all patients prospectively every month with information about HF-related events from the patients themselves, their families, and/or their affiliated hospitals. The primary endpoint was an HF-related event that consisted of a composite of cardiovascular death and hospitalization for HF decompensation. Cardiovascular death was defined as death because of myocardial infarction, congestive heart failure, or documented sudden death without an apparent non-cardiovascular cause. Hospitalization for HF decompensation was diagnosed if the patient was hospitalized with typical HF symptoms and objective signs of worsening HF that required intravenous drug administration.

Statistical analyses

Continuous values were expressed as the mean ± standard deviation, whereas data with a skewed distribution were expressed as the median (interquartile range). The frequencies of clinical variables and drugs were compared between three groups (low, intermediate, and high H_2FPEF score) using a X^2 analysis. For continuous variables, an ANOVA or Kruskal–Wallis test was performed to compare the three groups, as appropriate.

A Cox proportional hazards regression analysis was performed to identify independent predictors of the primary

endpoint (HF-related events). In the multivariate Cox proportional hazards analysis, we input variables that were statistically significant in the univariate Cox proportional hazards analyses. Although age, AF, E/e', and PAP were statistically significant in the univariate Cox proportional hazards analyses, we did not input these variables in the multivariate Cox proportional hazards analysis because these variables overlapped with components of the H_2FPEF score.

Survival curves for HF-related events were determined using the Kaplan–Meier method. Survival curves were compared between three groups with different H_2FPEF scores using a log-rank test, as appropriate.

Receiver operating characteristic (ROC) curves were constructed for the H_2FPEF score to predict future HF-related events. The area under the curve (AUC) was calculated to predict future HF-related events. We defined the cutoff value of the H_2FPEF score utilizing the sensitivity, specificity, and likelihood ratio for future HF-related events.

The SPSS version 24.0 (IBM Japan, Tokyo, Japan), R version 3.5.1 (R Project for Statistical Computing, Vienna, Austria), and Bell Curve for Excel, version 3.00 (Social Survey Research Information, Tokyo, Japan) were used for statistical analyses, as appropriate. Statistical significance was defined as a *P* value <0.05.

Results

Baseline clinical characteristics

The clinical characteristics and H_2FPEF scores in all 356 outpatients are shown in *Table 1*, and the distribution of the H_2FPEF scores is shown in *Figure 2*, respectively. The average H_2FPEF score of all 356 outpatients was 3.1 ± 1.8. As shown in *Table 1*, the patients with a high H_2FPEF score were older and had a higher prevalence of DM and AF, lower eGFR, higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, enlarged LAVI, increased E/e' (septal), reduced LVEF, and a higher PAP. Also, the patients with a higher H_2FPEF score had a higher prescription rate of ACE-I/ARB, beta-blocker, loop diuretics, MRA, and anticoagulant drugs.

Clinical characteristics of H_2FPEF score

Supporting Information, *Table S1* shows the clinical characteristics of the H_2FPEF score in the study groups. The patients with a high H_2FPEF score had higher prevalence of BMI $\geq$30 kg/m^2, the use of $\geq$2 antihypertensive drugs, AF, PAP $\geq$30 mmHg, $\geq$60 years, and E/e' (septal) $\geq$9 compared with those in the groups with intermediate and low H_2FPEF scores.

Prediction of future heart failure-related events by the H_2FPEF score

The mean follow-up period was 517 days for all study patients. Of the 356 patients, 15 developed HF-related events during the follow-up period, including cardiovascular death (n = 2) and hospitalization for HF decompensation (n = 13) (*Table 2*). The incidence of cardiovascular death and hospitalization for HF decompensation was significantly and gradually increased according to the H_2FPEF score.

Supporting Information, *Table S2* shows the clinical characteristics of the H_2FPEF score between those with and without HF-related events. The patients with HF-related events were older and had significantly higher H_2FPEF scores. In addition, they also had a higher prevalence of LVH, AF, lower eGFR, higher NT-proBNP level, enlarged LAVI, increased E/e' (septal), and a higher PAP. Also, the patients with HF-related events had a higher prescription rate of ACE-I/ARB, loop diuretics, and anticoagulant drugs.

Univariate Cox proportional hazards analysis showed that the H_2FPEF score, age, history of AF, eGFR, NT-proBNP, LAVI, E/e' (septal), LVEF, and PAP were significantly associated with future HF-related events (*Table 3*). Multivariate Cox proportional hazards analysis including the factors that were significant in the univariate Cox proportional hazards analysis showed that the H_2FPEF score was an independent predictor of future HF-related events (*Table 4*).

Kaplan–Meier analysis showed a significantly higher probability of primary endpoints (HF-related events) over time in the patients with a high H_2FPEF score (6–9 points) in proportion to a higher H_2FPEF score during the follow-up period ($P<0.001$) (*Figure 3*).

Receiver operating characteristic curve analyses to predict future heart failure-related events

We calculated the sensitivity, specificity, and likelihood of the H_2FPEF score and constructed ROC curves to compare the ability of the different H_2FPEF scores to predict future HF-related events. The ROC curve analysis showed that the H_2FPEF score was significantly associated with the occurrence of future HF-related events (three groups: AUC 0.78, 95%, confidence interval 0.66–0.89, $P < 0.001$; 0–9 points: AUC 0.77, 95% confidence interval 0.63–0.91, $P < 0.001$). There was no significant difference of the AUC between the H_2FPEF scores in the three groups and those with an H_2FPEF score of 0–9 points for the prediction of future HF-related events (P = 0.89) (Supporting Information, *Figure S1*). The sensitivity, specificity, and positive likelihood ratio (LR+) of the ROC curve in patients with a high H_2FPEF score (6–9 points) to predict HF-related events were 60%, 90%, and 5.9, respectively. The sensitivity, specificity, and LR+ of the ROC curve in those with an H_2FPEF score of 7 points to predict future HF-related

Table 1 Patient characteristics

		H_2FPEF score			
	All patients (n = 356)	Low score group (0–1 point) (n = 45)	Intermediate score group (2–5 points) (n = 267)	High score group (6–9 points) (n = 44)	P value
H_2FPEF score	3.1 ± 1.8	0.7 ± 0.4	2.9 ± 0.9	6.7 ± 0.8	
Age (years)	73.2 ± 12.2	58.1 ± 17.5	74.8 ± 9.3	79.2 ± 10.0	<0.001
Male (%)	171 (48)	25 (56)	120 (45)	26 (59)	0.12
BMI (kg/m^2)	23.1 ± 4.3	22.6 ± 3.3	23.1 ± 4.2	23.4 ± 5.4	0.65
HT (%)	267 (75)	21 (45)	218 (82)	28 (64)	<0.001
DM (%)	83 (23)	3 (7)	65 (24)	15 (34)	0.0068
DLP (%)	177 (50)	20 (44)	138 (43)	19 (43)	0.43
Current smoking	47 (13)	9 (20)	32 (12)	6 (14)	0.34
History of CAD, LVH, or AF (%)	147 (41)	5 (11)	98 (37)	44 (100)	<0.001
History of CAD (%)	55 (15)	3 (1)	44 (16)	8 (18)	0.21
History of LVH (%)	50 (14)	3 (7)	43 (16)	4 (9)	0.15
History of AF (%)	67 (19)	0 (0)	23 (9)	44 (100)	<0.001
Blood test					
eGFR (mL/min/1.73m^2)	65 ± 20	77 ± 17	64 ± 19	55 ± 18	<0.001
hs-CRP (mg/dL)	0.065 (0.030–0.140)	0.053 (0.028–0.145)	0.060 (0.030–0.128)	0.097 (0.052–0.210)	0.089
NT-proBNP (pg/mL)	113 (52–287)	50 (25–94)	112 (56–221)	568 (189–1373)	<0.001
Electrocardiogram					
Heart rate (HR) (bpm)	69 ± 14	72 ± 17	69 ± 12	70 ± 15	0.35
Echocardiography					
LAD (mm)	38.9 ± 6.3	32.3 ± 5.3	35.5 ± 5.9	42.0 ± 6.3	<0.001
LAVI (mL/m^2)	33.7 ± 11.8	25.7 ± 6.5	33.0 ± 9.7	45.8 ± 17.4	<0.001
LVMI (g/m^2)	80.8 ± 17.2	72.2 ± 17.2	82.3 ± 18.1	79.9 ± 13.2	0.004
E/e' (septal)	12.8 ± 4.2	8.6 ± 2.7	13.1 ± 4.0	14.9 ± 4.1	<0.001
LVDd (mm)	44.5 ± 5.4	44.3 ± 3.6	44.5 ± 5.6	44.9 ± 5.8	0.85
LVEF (%)	63 ± 4	64 ± 2	63 ± 4	60 ± 6	<0.001
PAP (mmHg)	25 ± 9	25 ± 6	24 ± 8	32 ± 10	<0.001
Drugs					
ACE-I or ARB (%)	186 (52)	8 (18)	147 (55)	31 (71)	<0.001
CCB (%)	205 (57)	14 (31)	172 (64)	19 (43)	<0.001
Beta-blocker (%)	74 (21)	1 (2)	55 (21)	18 (41)	<0.001
Thiazide diuretic (%)	21 (6)	0 (0)	19 (7)	2 (5)	0.16
Loop diuretic (%)	34 (10)	0 (0)	19 (7)	15 (34)	<0.001
MRA (%)	30 (8)	0 (0)	15 (6)	15 (34)	<0.001
Antihypertensive drugs, (n)	1.5 ± 1.0	0.5 ± 0.5	1.6 ± 1.0	2.3 ± 0.9	<0.001
≥2 antihypertensive drugs (%)	174 (49)	1 (2)	134 (50)	39 (89)	<0.001
Aspirin (%)	89 (25)	5 (11)	78 (29)	6 (14)	0.0061
Anticoagulant drug (%)	72 (20)	0 (0)	28 (11)	44 (100)	<0.001
HMG-CoA reductase inhibitor (%)	104 (29)	4 (9)	88 (33)	12 (27)	0.0053

ACE-I, angiotensin converting enzyme inhibitor; AF, paroxysmal/persistent atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; DLP, dyslipidemia; DM, diabetes mellitus; E/e' (septal), the ratio of early transmitral flow velocity to tissue doppler early diastolic mitral annular velocity (septal); eGFR, estimated glomerular filtration rate; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; hs-CRP, high-sensitivity C-reactive protein; HT: hypertension; LAD, left atrial diameter; LAVI: left atrial volume index; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide PAP: pulmonary artery systolic pressure.
Data are number of patients (%), mean ± standard deviation and median (interquartile range)

events were 47%, 96%, and 11.4, respectively (Supporting Information *Table S3*).

Discussion

The major findings of the present study were as follows: (i) the average H_2FPEF score was 3.1 ± 1.8 in stable outpatients with cardiovascular risk factor(s); (ii) stable outpatients with a higher H_2FPEF score developed HF-related events more frequently during the follow-up period than those with low and intermediate scores; (iii) multivariate Cox proportional hazards analysis showed that the H_2FPEF score was an independent predictor of future HF-related events in stable outpatients with cardiovascular risk factor(s); (iv) Kaplan–Meier analysis showed that the outpatients with a higher H_2FPEF score had increased HF-related events compared with those in the groups with low and intermediate H_2FPEF scores; and (v) the best cutoff level of the H_2FPEF score for HF-related

Figure 2 The distribution of H_2FPEF scores.

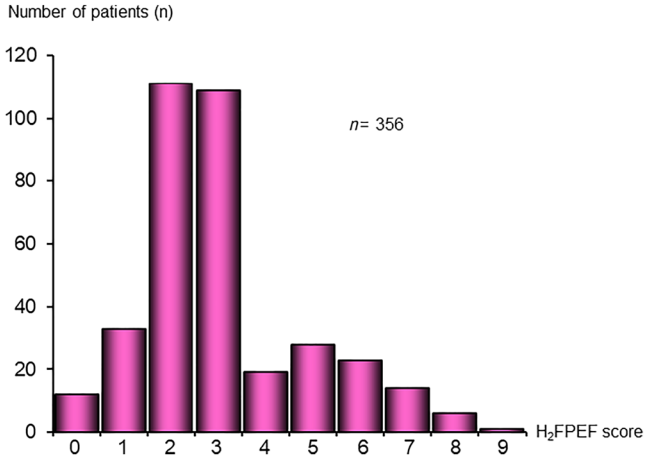


Table 2 HF-related events in the study groups according to the H_2FPEF score

	All patients (n = 356)	H_2FPEF score			
		Low score group (0–1 point (n = 45)	Intermediate score group (2–5 points) (n = 267)	High score group (6–9 points) (n = 44)	P value
Primary endpoint (HF-related Events) (%)	15	0 (0)	6 (2)	9 (20)	<0.001
Cardiovascular death	2	0 (0)	0 (0)	2 (4)	<0.001
Hospitalization for HF decompensation (%)	13	0 (0)	6 (2)	7 (16)	<0.001

HF, heart failure.
Data are number of patients (%)

events was 7 points. To the best of our knowledge, the present study is the first to report that the H_2FPEF score can provide a useful prognostic tool for HF management in stable outpatients with cardiovascular risk factor(s).

The H_2FPEF score was proposed to discriminate HF from non-cardiac causes of dyspnoea in patients with high scores (6–9 points) and to assist in the determination of the need for further diagnostic testing in the evaluation of patients with unexplained exertional dyspnoea.[2,3] The six clinical variables that composed the H_2FPEF score were (i) a BMI $>$ 30 kg/m^2; (ii) use of $\geq$2 antihypertensive drugs; (iii) AF; (iv) PAP $>$ 35 mmHg; (v) age $>$ 60 years; and (vi) E/e' $>$ 9. These six variables have been reported to be not only risk factors for HF, but also prognostic factors,[1,10–14] suggesting that the H_2FPEF score has the ability to predict future HF-related events in stable outpatients with cardiovascular risk factor (s). Especially, the presence of paroxysmal or persistent AF yields 3 points in calculating the H_2FPEF score (other components yield 1 or 2 points).[2] In the present study, all patients with a high H_2FPEF score (6–9 points) had AF (*Table 1*). Previous reports indicated that AF is a particularly important factor for HF management among several factors (e.g. aging, obesity, smoking, HT, DM, DLP, anaemia, CKD, depression, etc.).[1,15,16] It is also necessary to examine the association between AF and HF in detail because HF patients with AF would have a high rate of mortality and rehospitalization.[17,18] Thus, the H_2FPEF score, including the component of AF, could be a useful tool for HF management in routine clinical practice.

Together with an aging society, cases of HF are steadily increasing, and 500 000 individuals are newly diagnosed in the United States annually with HF, especially in elderly populations.[1,19,20] Moreover, it has been reported that HF patients have a high mortality risk and high rate of rehospitalization.[21,22] For HF, which is also a social problem, our previous reports have shown that plasma natriuretic peptide level,[23] serum aldosterone level,[24] peripheral endothelial dysfunction,[25] plasma pentraxin 3,[26] plasma neopterin concentration,[27] and pulse pressure[28] were potent factors for pathogenesis as well as prognosis. However, the prediction of future HF events is still difficult for general practitioners and cardiologists. Therefore, the establishment of a new and simple risk stratification tool for HF prediction is needed in modern society for decreasing the economic burden of HF. Based on these observations, we performed an external

Table 3 Univariate cox proportional hazards analysis to identify predictors of HF-related events

Variable	Univariate analysis	
	HR (95% CI)	p value
H_2FPEF score	1.94 (1.50–2.50)	<0.001
Age (years)	1.09 (1.03–1.16)	0.0032
Sex, male	0.46 (0.15–1.45)	0.19
BMI	0.91 (0.80–1.04)	0.16
HT	1.62 (0.37–7.21)	0.52
DM	1.48 (0.47–4.67)	0.50
DLP	0.33 (0.11–1.04)	0.059
Current smoking	0.99 (0.22–4.41)	0.99
History of CAD	2.24 (0.72–7.07)	0.17
History of LVH	2.81 (0.96–8.23)	0.060
History of AF	9.33 (3.28–26.55)	<0.001
eGFR	0.96 (0.93–0.98)	0.0013
hs-CRP	1.17 (0.014–100.13)	0.95
NT-proBNP per 100 pg/mL	1.06 (1.03–1.90)	<0.001
Dipstick proteinuria ≥ +	2.13 (0.78–5.90)	0.14
HR	0.99 (0.97–1.03)	0.71
LVMI	1.03 (1.00–1.06)	0.054
E/e' (septal)	1.12 (1.03–1.22)	0.0063
LVDd	1.08 (0.99–1.17)	0.090
LVEF	0.89 (0.80–0.99)	0.03
PAP	1.26 (1.17–1.35)	<0.001

AF, paroxysmal/persistent atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; DLP, dyslipidemia; DM, diabetes mellitus; E/e' (septal), the ratio of early transmitral flow velocity to tissue doppler early diastolic mitral annular velocity (septal); eGFR, estimated glomerular filtration rate; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; HT: hypertension; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide PAP: pulmonary artery systolic pressure.

validation study to determine whether the H_2FPEF score could predict future HF in stable outpatients with cardiovascular risk factor(s). Based on our results, we propose that the H_2FPEF score could be a simple and useful tool for the prediction of future HF-related events for general practitioners as well as cardiologists.

In the present study, the H_2FPEF score was an independent predictor of future HF-related events by multivariate Cox proportional hazards analysis (*Tables 3 and 4*). On the other hand, eGFR, NT-proBNP, LAVI, and LVEF were significant in univariate Cox proportional hazards analysis, but failed to be associated with future HF-related events in multivariate Cox proportional hazards analysis. These factors have been reported to be associated with the occurrence of HF.[1,5,10,20–23,29,30] However, in the original paper that proposed the H_2FPEF score, these factors did not add incremental information to clinical factors in diagnosing HF among patients with unexplained dyspnoea.[2] Additionally, in the present study, eGFR, NT-proBNP, LAVI, and LVEF were significantly correlated with the H_2FPEF score in multiple regression analysis (eGFR: P = 0.013, NT-proBNP: P <0.001, LAVI: P <0.001, LVEF: P = 0.0028). Based on these observations, the H_2FPEF score could serve as an important alternative to these factors. A further large-scale clinical trial is needed in an independent study population.

We proposed a cutoff value of 7 points for the H_2FPEF score to predict future HF-related events in stable outpatients with cardiovascular risk factor(s) in the present study. The sensitivity, specificity, and LR+ of an H_2FPEF score of 7 points to predict future HF-related events were 47%, 96%, and 11.4, respectively (Supporting Information, *Table S3*). Some reports indicated that likelihood ratios above 10 provide strong evidence to make a definitive diagnosis in most circumstances.[31,32] Thus, we considered that an H_2FPEF score of 7 points was a clinically meaningful cutoff point from the viewpoint of specificity and LR+ in the present study. This suggests that more careful observation and intensive risk reduction treatment could be needed to treat outpatients with a high H_2FPEF score (≥7 points).

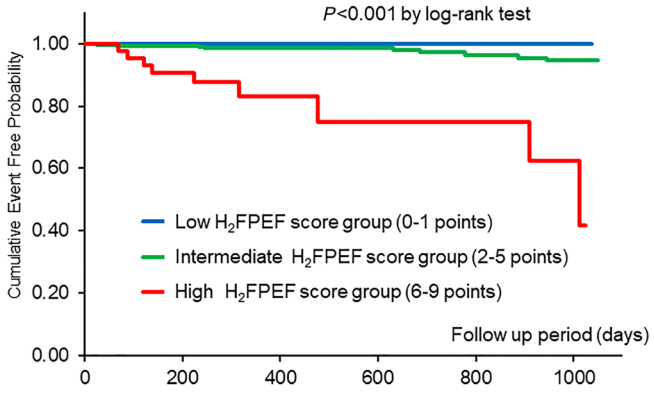
To our best knowledge, the present external validation study is the first to investigate the association between the H_2FPEF score and future HF-related events in stable outpatients with cardiovascular risk factor(s). Although the H_2FPEF score was originally proposed to discriminate HFpEF from non-cardiac causes of dyspnoea in the evaluation of patients with unexplained exertional dyspnoea,[2,3] the present study suggested that the H_2FPEF score could also be a useful tool to predict future HF-related events, even in stable outpatients with cardiovascular risk factor(s). Each of the components of the H_2FPEF score is simple, low cost, and widely applicable, and calculating the score is easy in routine clinical practice. The H_2FPEF score could be a useful tool not only for

Table 4 Multivariate cox proportional hazards analysis to identify predictors of heart failure-related events using forced inclusion models

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
H_2FPEF score	1.89 (1.45–2.46)	<0.001	1.84 (1.41–2.42)	<0.001	1.91 (1.46–2.50)	<0.001
eGFR	0.97 (0.94-0.99)	0.015	-		-	
NT-proBNP, per 100pg/mL	-		1.02 (0.99-1.06)	0.13	-	
LVEF	-		-		0.98 (0.87–1.10)	0.70

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Figure 3 Kaplan–Meier analysis for the probability of future heart failure-related events.Kaplan–Meier analysis was performed after the patients were divided into three groups (low, intermediate, and high H_2FPEF score), and it showed that there was a gradual increase in the frequency of heart failure-related events with an increasing H_2FPEF score.



cardiologists, but also general practitioners in routine clinical practice.

Study limitations

The present study has several limitations. First, it was a single-centre study with a relatively small sample size. Second, the H_2FPEF score was originally proposed to discriminate HFpEF from non-cardiac causes of dyspnoea in the patients with unexplained exertional dyspnoea,[2,3] not in stable outpatients with cardiovascular risk factor(s). Third, the present study included only Japanese outpatients. Our results may not be applicable to other ethnic populations. Fourth, the present study was observational (prospective cohort study), and the patients received no specific intervention or therapy. Further analyses and recalibration may be needed in a larger and independent population.

Conclusions

A high H_2FPEF score was associated with future HF-related events in stable outpatients with cardiovascular risk factor(s), and we propose a cutoff of 7 points for the H_2FPEF score for future HF-related events in those outpatients.

Conflict of interest

K.K. has received significant research grant support from Bayer Yakuhin, Ltd., Daiichi Sankyo Co., Ltd., Novartis Pharma AG., and SBI Pharma Co., Ltd., and has received Honoraria from Bayer Yakuhin, Ltd. and Daiichi Sankyo Co., Ltd. K.T. has received honoraria from Bayer Yakuhin, Ltd., Daiichi Sankyo Co., Ltd., Kowa Pharmaceutical Co. Ltd., MSD K.K., Sanofi K.K., and Takeda Pharmaceutical Co., Ltd.; has received trust research/joint research funds from AstraZeneca K.K., Sugi Bee Garden, and Japan Medical Device Technology Co., Ltd.; and has received grants from ITI Co., Ltd., Astellas Pharma Inc, Abbott Vascular Japan Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Kaneka Medix Co., Ltd., Goodman Co., Ltd., GM Medical Co., Ltd., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma, Chugai Pharmaceutical Co., Ltd., TERUMO Co., Ltd., Boehringer Ingelheim Japan, Medtronic Japan Co., Ltd., Japan Lifeline Co., Ltd., Novartis Pharma K.K., Fides-One, Inc., Bristol-Myers K.K., Boston Scientific Japan K.K., Cardinal Health Japan, and MSD K.K.

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Supporting information

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

Table S1. Clinical Characteristics According to H_2FPEF Score
Table S2. Comparison of the Clinical Characteristics of the H_2FPEF Score Between the Groups With and Without HF-related Events
Table S3. Sensitivity, Specificity and Likelihood Ratio in H_2FPEF Score for Future HF-related Events
Figure S1. Receiver Operating Characteristic Curves to Predict Future HF-related Events Using H_2FPEF Scores
AUC: area under curve, LR+: positive likelihood ratio.

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