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ORIGINAL RESEARCH ARTICLE

Applying the ESC 2016, H_2FPEF, and HFA-PEFF diagnostic algorithms for heart failure with preserved ejection fraction to the general population

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) is common in patients presenting with dyspnoea. Recently, clinical tools were developed to facilitate the diagnosis of HFpEF. Here, we apply the European Society of Cardiology (ESC) 2016 heart failure guidelines and the H_2FPEF and HFA-PEFF scores to a middle-aged sample of the general population and compared the different groups with each other.

Methods and results This study included the first 10 000 participants of the population-based Hamburg City Health Study. A total of 5613 subjects, aged 62 ± 8.7 years (51.1% women), qualified for the analysis. Unexplained dyspnoea was present in 407 (7.3%) subjects. In those, the estimated prevalence of HFpEF was 20.4% (ESC 2016), 12.3% (H_2FPEF), and 7.6% (HFA-PEFF). The majority of subjects was classified as HFpEF not excludable according to the HFA-PEFF (57.7%) and H_2FPEF (59.2%) scores. For all algorithms, subjects diagnosed with HFpEF showed elevated age and body mass index as well as a higher prevalence of atrial fibrillation, diabetes, and arterial hypertension compared with those without HFpEF or HFpEF not excludable. The distribution of those co-morbidities and risk factors varied between the differently diagnosed HFpEF groups with the highest burden in the HFpEF group defined by the H_2FPEF score. The overlap of subjects diagnosed with HFpEF according to the different algorithms was very limited.

Conclusions Unexplained dyspnoea is common in the middle-aged general population. The ESC 2016 algorithm and the H_2FPEF and HFA-PEFF scores detect different, discordant subpopulations of probands with breathlessness. Further classification of the HFpEF syndrome is desirable.

Keywords HFpEF; Heart failure; HCHS; H_2FpEF; HFA-PEFF; ESC 2016 guidelines

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Introduction

Unexplained breathlessness is the leading symptom for the diagnosis of heart failure (HF) with preserved ejection fraction (HFpEF). Pathophysiologically, the syndrome is characterized by preserved cardiac systolic function and pathologically increased cardiac filling pressures either at rest or with exertion accompanied by classical HF symptoms or signs.[1] While these parameters can be detected by detailed cardiac imaging and right heart catheterization, HFpEF is difficult to diagnose in clinical practice. Therefore, the prevalence of HFpEF in the population remains difficult to assess.

Heart failure with preserved ejection fraction is often accompanied by atrial fibrillation (AF), obesity, older age, and hypertension. In 2016, the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF proposed an algorithm to diagnose HFpEF, incorporating symptoms and signs, echocardiographic assessment, and N-terminal pro-brain natriuretic peptide (NT-proBNP).[1] In

2018, the H_2FPEF algorithm was introduced—a simple algorithm including six clinical characteristics and transthoracic echocardiography (TTE) assessment.[2] In 2019, the Heart Failure Association (HFA) of the ESC published the HFA-PEFF (HFA Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final aetiology) score, based on an expert consensus, containing two steps: a pretest for the likelihood of HFpEF and a second step for the calculation of a score based on TTE and NT-proBNP.[3] Both scores were validated in two small HFpEF cohorts and one larger elderly population-based cohort, calling for further validation and comparison.[2,4]

In the present study, we applied these three HFpEF algorithms to an unselected, middle-aged population enrolled into the Hamburg City Health Study (HCHS, http://www.uke.de/hchs). We determined the prevalence and compared the different characteristics of HFpEF according to the three algorithms in subjects with unexplained dyspnoea.

Methods

Study setting

Data from the first 10 000 participants of the HCHS were analysed. HCHS is a prospective, long-term, at random selected, population-based cohort study placed in Hamburg, Germany.[5] Of the first 10 000 study participants, 8245 received TTE. All measurements were performed between 2016 and 2019 during the baseline visit at the HCHS Epidemiological Study Centre from the University Medical Center Hamburg-Eppendorf following the published HCHS protocol.[5] All participants underwent biomarker quantification including NT-proBNP. Exclusion criteria were insufficient image quality to perform standardized measurements for calculating left ventricular ejection fraction (LVEF), lacking clinical or laboratory variables for HFpEF classification. Additionally, subjects with competing causes of dyspnoea, that is, LVEF $<$ 50%, more than mild left-sided valvular stenosis, more than moderate left-sided regurgitation, current asthma or chronic obstructive pulmonary disease, or haemoglobin $<$10 g/dL, were excluded. Our final cohort comprised 5613 subjects (*Figure 1*).

Clinical parameters

Demographics and clinical parameters were assessed by self-reported questionnaires as well as standardized interviews conducted by specifically trained medical professionals following standard operating procedures.[5] Subjects were classified in the unexplained dyspnoea group if they were lacking common causes of dyspnoea, as described earlier, or suffered from self-reported HF (including HF with reduced ejection fraction and HFpEF). In the following, those are referred to as unexplained dyspnoea.

Atrial fibrillation was considered present if it was reported in the questionnaire or if it was diagnosed on 12-lead electrocardiogram or both. We defined coronary artery disease based on the questionnaires if any of the following was stated: prior myocardial infarction, prior coronary intervention, or coronary bypass surgery.

The local ethics committee of the *Landesärztekammer Hamburg* (PV5131, Medical Association Hamburg) approved the HCHS. All participants gave written informed consent. The review board of the HCHS study approved the study protocol. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Echocardiographic data

Transthoracic echocardiography was performed at baseline in the HCHS Epidemiological Study Centre Hamburg-Eppendorf, Hamburg, Germany, using a standardized protocol according to the guidelines of the American Society of Echocardiography and the European Society of Cardiovascular Imaging. It was conducted and analysed by specially trained and internally certified medical professionals (cardiologists and sonographers) following standard operating procedures (Siemens Acuson SC2000 Prime echocardiography machines). All echocardiographers were trained and certified by HCHS. Each person underwent a 3 month training period under constant supervision by an ESC TTE-certified cardiologist. After this training period, a set of 50 TTE exams was assessed by the trainee and compared with the measurements of the ESC certified cardiologist. Only if the interobserver correlation coefficient was $\geq$0.9, the certification was successful. For continuous quality assessment, every 100th TTE exam was analysed twice. Qualitative and quantitative image analyses were performed using an offline workplace with the commercially available and established Siemens syngo SC2000 Version 4.0 software.

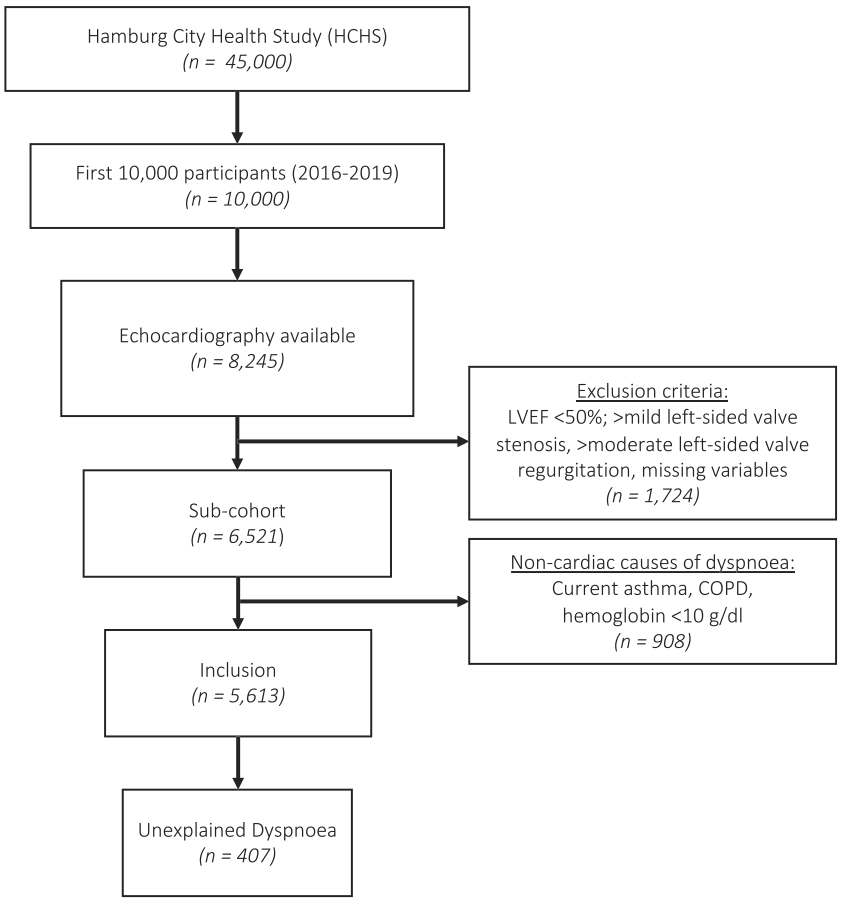
Heart failure with preserved ejection fraction scores

All parameters required for the ESC 2016, H_2FPEF, and HFA-PEFF algorithms were analysed in the primary population according to the original publications of those (Supporting Information).[1,2,3]

European Society of Cardiology 2016 algorithm

Following the dichotomous ESC 2016 algorithm, HFpEF was considered present if subjects showed the combination of symptoms/signs, echocardiographic criteria such as diastolic

Figure 1 PRISMA study. From a total of 8245 subjects providing a transthoracic echocardiography examination, 1724 were excluded because of left ventricular ejection fraction (LVEF) <50%, more than mild left-sided valve stenosis, more than moderate valve regurgitation, or missing variables. Further, 908 subjects were excluded because of non-cardiac causes of dyspnoea. Consequently, 5613 subjects were included in the study analysis. Of those, 407 subjects suffered from unexplained dyspnoea or self-reported heart failure. First, the prevalence of heart failure with preserved ejection fraction applying the European Society of Cardiology 2016, H_2FPEF, and HFA-PEFF algorithms was calculated. Second, the inter-score concordance was assessed using Cohen's kappa coefficient. COPD, chronic obstructive pulmonary disease.



dysfunction according to current recommendations, and laboratory data.[6]

H_2FPEF score

The H_2FPEF score is based on six clinical and echocardiographic variables. Subjects were categorized in three groups based on their result: HFpEF (≥6 points), HFpEF not excludable (2–5 points), and no HFpEF (≤1 point).

HFA-PEFF score

This analysis was restricted to the second step of the HFA-PEFF score based on functional and morphological echocardiographic variables as well as natriuretic peptides with different cut-off values for subjects with or without AF. Definitions were HFpEF (≥5 points), HFpEF not excludable (2–4 points), and no HFpEF (≤1 point).

Statistical analysis

Continuous variables are presented as median and inter-quartile range (IQR), and categorical variables are presented as absolute numbers and percentages. Comparisons between subjects classified as 'HFpEF', 'HFpEF not excludable', or 'no HFpEF' as well as between the different HFpEF groups were performed using one-way analysis of variance for continuous variables and χ^2 test for categorical variables. For analysing differences between the HFpEF groups, subgroups that were not overlapping were compared with each other.

The concordance between the three classifications was determined using Cohen's kappa coefficients and proportion of agreement. The concordance was defined as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), and optimal (0.81–1). The reclassification percentage was determined as 100 − proportion of agreement. A *P*-value of

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<0.05 was considered as statistical significant. All tests were two tailed. Data analysis was performed using R Version 3.5.1.

Results

The analysed population of 5613 subjects of the first 10 000 HCHS participants showed the expected characteristics of a middle-aged European population, with 2868 (51.3%) women, mean age of 62 ± 8.7 years, and mean body mass index (BMI) of 25.7 [IQR: 23.4–28.6] kg/m^2 (*Table 1*). Arterial hypertension was present in 3386 (63.5%) subjects, AF in 269 (5.3%), and diabetes in 362 (6.8%). The median NT-proBNP was 78.0 [IQR: 43.0–137.0] ng/L, and the median LVEF was 58.8% [IQR: 56.0–62.0]; 407 (7.3%) subjects suffered from unexplained dyspnoea. Those were older and more often female and showed higher proportions of co-morbidities and tendencies towards worse functional and morphological echocardiographic parameters compared with those who were asymptomatic.

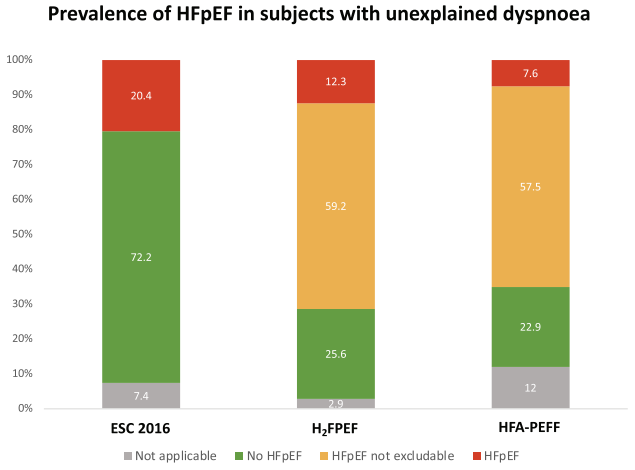
The prevalence of HFpEF as defined by the ESC 2016 algorithm (ESC HFpEF group) or high likelihood group of HFpEF according to an HFA-PEFF score of $\geq$5 (HFA-PEFF HFpEF group) or an H_2FPEF score of $\geq$6 (H_2FPEF HFpEF group) significantly differed.

In subjects with unexplained dyspnoea, 83 (20.4%) were diagnosed with HFpEF according to the ESC 2016 algorithm, the HFA-PEFF HFpEF group comprised 31 (7.6%), and 50 (12.3%) were in the H_2FPEF HFpEF group (*Figure 2*). Of those, more than half were classified as 'HFpEF not excludable' according to the proposed cut-off values by the authors of the HFA-PEFF score (234 subjects, 57.5%) and the H_2FPEF score (241 subjects, 59.2%), respectively. In subjects without unexplained dyspnoea, only 5 (0.1%) were part of the ESC 2016 HFpEF group, and 24 (0.5%) were part of the H_2FPEF HFpEF group whereas 193 (3.7%) were part of the HFA-PEFF HFpEF group. The H_2FPEF score could be determined in 395/407 (97.1%) of all subjects with unexplained dyspnoea, the ESC 2016 algorithm in 377/407 (92.6%), and the HFA-PEFF score in 358/407 (88%) of subjects with unexplained dyspnoea (*Table 2*).

Table 1 Baseline characteristics of the study population divided in subjects with and without (asymptomatic) unexplained dyspnoea

	Total cohort n = 5613	Asymptomatic n = 5206	Unexplained dyspnoea n = 407	P-value
Demographics				
Age (years)	62.0 [55.0, 69.0]	62.0 [54.0, 69.0]	66.0 [59.0, 71.5]	<0.001
Female	2868 (51.1)	2648 (50.9)	220 (54.1)	0.235
BMI (kg/m^2)	25.7 [23.4, 28.6]	25.6 [23.3, 28.5]	27.8 [24.9, 31.7]	<0.001
Current smoker	1052 (18.8)	970 (18.7)	82 (20.3)	0.462
Co-morbidity				
Hypertension	3386 (63.5)	3071 (62.2)	315 (79.9)	<0.001
Diabetes	362 (6.8)	296 (6.0)	66 (17.1)	<0.001
Coronary artery disease	274 (6.4)	195 (4.9)	79 (27.6)	<0.001
Atrial fibrillation	269 (5.3)	202 (4.3)	67 (18.2)	<0.001
Peripheral artery disease	146 (2.7)	109 (2.2)	37 (9.8)	<0.001
Medication				
Aldosterone antagonists	22 (0.4)	13 (0.3)	9 (2.3)	<0.001
Loop diuretics	68 (1.3)	39 (0.8)	29 (7.5)	<0.001
Beta-blocker	814 (15.2)	691 (14.0)	123 (31.7)	<0.001
ACEi/ARBs	1452 (27.2)	1266 (25.6)	186 (47.9)	<0.001
Laboratories				
GFR (mL/min)	86.2 [75.5, 94.3]	86.4 [76.0, 94.6]	82.0 [68.6, 91.2]	<0.001
NT-proBNP (ng/L)	78.0 [43.0, 137.0]	76.0 [43.0, 133.0]	106.5 [56.0, 197.8]	<0.001
Haemoglobin (g/dL)	14.3 [13.6, 15.1]	14.3 [13.6, 15.1]	14.2 [13.4, 14.9]	0.038
HbA1c	5.5 [5.3, 5.7]	5.5 [5.3, 5.7]	5.7 [5.4, 6.0]	<0.001
LDL cholesterol (mg/dL)	121.0 [97.0, 145.0]	121.5 [98.0, 146.0]	117.0 [86.0, 142.0]	<0.001
Echocardiographic data				
LVEF (%)	58.8 [56.0, 62.0]	58.8 [56.1, 62.1]	58.0 [55.1, 61.3]	<0.001
LV mass index (g/m^2)	81.7 [71.5, 95.4]	81.6 [71.4, 95.0]	84.7 [72.2, 102.7]	0.007
LVEDV (mL)	110.8 [92.5, 132.7]	110.9 [92.5, 133.0]	108.3 [91.8, 127.2]	0.196
LAVI (mL/m^2)	25.3 [20.4, 30.7]	25.3 [20.4, 30.6]	25.8 [20.7, 32.4]	0.163
LV lateral s′ (mm/s)	8.2 [6.9, 9.9]	8.2 [6.9, 9.9]	8.1 [6.9, 9.4]	0.143
LV lateral e′ (mm/s)	10.3 [8.5, 12.4]	10.3 [8.5, 12.5]	9.5 [7.9, 11.7]	<0.001
LV septal e′ (mm/s)	8.5 [7.1, 10.2]	8.6 [7.1, 10.2]	7.7 [6.3, 9.5]	<0.001
E/e′ mean ratio	7.3 [6.2, 8.6]	7.2 [6.1, 8.5]	7.7 [6.6, 9.4]	<0.001
E/A ratio	1.0 [0.8, 1.2]	1.0 [0.8, 1.2]	0.9 [0.7, 1.1]	<0.001
TR Vmax (m/s)	2.2 [1.9, 2.4]	2.1 [1.9, 2.4]	2.2 [1.9, 2.5]	0.003
TAPSE (mm)	24.2 [21.5, 27.0]	24.3 [21.5, 27.2]	23.1 [20.5, 25.7]	<0.001
RV s′ (mm/s)	13.5 [12.0, 15.4]	13.5 [12.0, 15.4]	13.2 [11.6, 15.0]	0.015

Figure 2 Prevalence of heart failure with preserved ejection fraction (HFpEF) according to the European Society of Cardiology (ESC) 2016 algorithm and the H_2FPEF and HFA-PEFF scores in subjects with unexplained dyspnoea. According to the ESC 2016 algorithm, 20.4% were diagnosed with HFpEF, the H_2FPEF HFpEF group included 12.3%, and 7.6% were in the HFA-PEFF HFpEF group; 59.2% and 57.5% were classified as 'HFpEF not excludable' according to the H_2FPEF and HFA-PEFF scores.



Concordance between the HFA-PEFF algorithm and the ESC 2016 algorithm was fair with a kappa coefficient (κ) of 0.38 and a reclassification rate of 16% (*Table 3* and *Figure 3*); 23 (5.7%) individuals were equally diagnosed with HFpEF according to both algorithms. In contrast, 47 (11.5%) subjects without HFpEF according to the HFA-PEFF algorithm were diagnosed with HFpEF following the ESC 2016 algorithm. A κ of 0.27 with a reclassification rate of 20.8% demonstrated similar discrepancies between the ESC 2016 algorithm and the H_2FPEF score (*Table 4* and *Figure 3*). Whereas 24 (5.9%) study participants were equally diagnosed with HFpEF, the application of the H_2FPEF score led to a reclassification of 54 (13.3%) subjects as no HFpEF or HFpEF not excludable. However, the poorest concordance was found between the HFA-PEFF score and the H_2FPEFF score with a κ of 0.13 and a reclassification rate = 39.9% (*Table 5* and *Figure 3*). Only 9 (2.2%) individuals were concordantly classified as HFpEF according to both scores.

Table 2 demonstrates a comparison of patient characteristics and echocardiographic data diagnosed with HFpEF or HFpEF not excludable by ESC 2016 algorithm, HFA-PEFF score, or H_2FPEF score for subjects with unexplained dyspnoea. For all three algorithms, we discovered consistent differences between the HFpEF, HFpEF not excludable, and no HFpEF groups of most studied variables, including anthropometric data, major cardiovascular risk factors, medication, laboratories, and echocardiographic data. Furthermore, comparing the three HFpEF groups with each other, we observed the following intergroup differences: in contrast to the ESC 2016 group and the HFA-PEFF group, the majority of subjects was male in the H_2FPEF group (64%). Additionally, the H_2FPEF group did not only present the highest BMI of 31.3 cm/m^2 [IQR: 27.8–33.4] but demonstrated the highest prevalence of coronary artery disease (55.6%) and AF (38.0%).

Discussion

The present study applied and compared three current algorithms for diagnosing HFpEF in a large, middle-aged population cohort. Major findings include that unexplained dyspnoea and among those with HFpEF appear to be very common in a population-based middle-aged sample. The prevalence of HFpEF varies extensively depending on the diagnostic algorithm and the precision (definitive HFpEF, possible HFpEF) applied. Each algorithm identified different HFpEF subgroups, with different co-morbid and imaging features as well as little concordance between those.

The prevalence of HFpEF in subjects with unexplained dyspnoea from the first 10 000 participants of HCHS applying the ESC 2016 guidelines was as high as 20.4%. According to the H_2FPEF and HFA-PEFF scores, the prevalence of HFpEF was much lower with 12.3% and 7.6%, respectively. As the prevalence of HFpEF depends on the chosen thresholds of the two scores, a different definition of the cut-offs modulates HFpEF prevalence. However, defining HFpEF seems crucial not only for clinical decision-making but also for epidemiologically estimating the disease burden. Data on the prevalence of HFpEF in subjects with unexplained dyspnoea are sparse ranging from 10.2% in the Atherosclerosis Risk In Communities study (ARIC) to 12% in a study from the Netherlands.[7,8] However, both results originate from elderly cohorts. They are rather in line with our results applying the HFA-PEFF and H_2FPEF scores than with applying the ESC algorithm, favouring the applied cut-off values.

Each algorithm incorporates different focuses and limitations. Choosing reliable and applicable criteria for diagnosing HFpEF remains challenging.[9] The HFA-PEFF score, as well as the ESC algorithm, is based on expert opinion but has been validated in two independent, prospective HFpEF cohorts.[4] As a limitation, the diagnosis of HFpEF in these cohorts mostly relied on expert opinion itself and only partly on invasive testing. Strikingly, in our study, the prevalence of HFpEF was 3.7% applying the HFA-PEFF score to subjects without unexplained dyspnoea. These results might question the specificity of the HFA-PEFF score. Step 2 of the HFA-PEFF score relies on morphological and functional cardiac measurements. One of the three major diagnostic columns consists of natriuretic peptides. Applying the ESC score, normal natriuretic peptides even fully exclude HFpEF. However, natriuretic peptides may be normal in HF patients, for example, in obese patients or patients with dyspnoea only on exertion.[10] The H_2FPEF score, which was derived from invasive testing in subjects with unexplained dyspnoea, found no additional discrimination using

Table 2 Clinical characteristics of subjects with unexplained dyspnoea classified as HFpEF or HFpEF not excludable according to the ESC 2016 algorithm and the H_2FPEF and HFA-PEFF scores

	ESC 2016	H_2FPEF		HFA-PEFF		ESC vs. H_2FPEF	ESC vs. HFA-PEFF	H_2FPEF vs. HFA-PEFF
	HFpEF	Not excludable	HFpEF	Not excludable	HFpEF	*P*-value	*P*-value	*P*-value
n	83 (20.4)	241 (59.2)	50 (12.3)	234 (57.5)	31 (7.6)			
HFA-PEFF score	3.97	2.50	3.25	2.9	5.29			
H_2FPEF score	4.06	3.33	6.54	3.31	4.06			
Demographics								
Age (years)	70.0 [63.0–73.0]	66.0 [61.0–72.0]	68.5 [62.0–72.8]	67.0 [60.2–72.8]	70.0 [67.5–73.0]	0.683	0.044	0.002
Female	45 (54.2)	133 (55.2)	18 (36.0)	123 (52.6)	17 (54.8)	0.001	0.825	0.001
BMI (kg/m^2)	28.1 [25.3–32.4]	28.9 [25.4–33.1]	31.3 [27.8–33.4]	28.3 [25.2–32.3]	27.2 [24.9–30.8]	0.075	<0.001	<0.001
Current smoker	15 (18.3)	44 (18.3)	7 (14.0)	45 (19.4)	5 (16.1)	0.366	0.521	1.000
Co-morbidities								
Hypertension	15 (19.5)	197 (84.9)	49 (98.0)	193 (85.0)	30 (96.8)	0.450	0.849	0.431
Diabetes	24 (42.9)	36 (15.8)	15 (31.2)	38 (17.0)	7 (24.1)	0.214	0.224	0.018
Coronary artery disease	26 (35.1)	52 (30.2)	20 (55.6)	45 (27.4)	10 (41.7)	1.00	<0.001	<0.001
Atrial fibrillation	12 (15.6)	39 (17.5)	19 (38.0)	40 (18.2)	10 (33.3)	0.016	<0.001	<0.001
Peripheral artery disease	15 (19.5)	23 (10.3)	6 (14.3)	19 (8.6)	4 (13.8)	0.316	0.010	0.502
Self-reported heart failure	32 (38.1)	70 (3.4)	46 (42.2)	73 (2.7)	11 (5.0)	0.164	<0.001	<0.001
Medication								
Aldosterone antagonists	2 (2.5)	5 (2.2)	3 (6.1)	5 (2.2)	0 (0.0)	0.476	0.157	0.026
Loop diuretics	11 (13.9)	18 (7.8)	9 (18.4)	20 (8.9)	3 (10.3)	0.834	0.040	0.326
Beta-blockers	38 (48.1)	81 (35.2)	31 (63.3)	81 (36.2)	17 (58.6)	0.395	0.052	0.005
ACEi/ARBs	40 (50.6)	121 (52.6)	38 (77.6)	116 (51.8)	15 (51.7)	0.004	0.108	<0.001
Laboratories								
GFR (mL/min)	77.0 [63.1–85.5]	82.5 [69.5–90.7]	72.1 [58.2–90.1]	81.3 [66.4–89.3]	73.6 [63.5–80.8]	0.996	0.304	0.245
NT-proBNP (ng/L)	278.0 [187.5–683.0]	98.0 [52.0–191.8]	202.0 [94.5–622.8]	101.0 [57.2–194.0]	305.0 [270.0–686.5]	0.631	0.002	0.054
Haemoglobin (g/dL)	13.9 [13.1–14.6]	14.2 [13.5–14.9]	14.5 [13.2–15.4]	14.3 [13.5–15.0]	14.0 [13.3–14.6]	0.002	0.203	<0.001
HbA1c	5.7 [5.4–6.0]	5.7 [5.4–6.0]	5.8 [5.6–6.2]	5.7 [5.4–6.0]	5.8 [5.4–6.0]	0.195	0.179	0.012
LDL cholesterol (mg/dL)	109.5 [85.0–136.0]	119.0 [86.2–145.0]	102.0 [68.0–135.0]	114.0 [83.5–143.0]	95.0 [85.0–128.0]	0.234	0.017	0.012
Echocardiographic data								
LVEF (%)	56.7 [53.3–59.8]	58.0 [55.1–61.7]	56.7 [54.2–59.2]	58.0 [55.3–61.2]	57.2 [54.1–59.5]	0.935	0.027	0.056
LV mass index (g/m^2)	107.4 [88.0–122.1]	84.9 [72.3–102.9]	100.2 [81.1–125.6]	86.9 [74.2–103.7]	106.0 [91.5–128.2]	0.222	0.408	0.055
LVEDV (mL)	114.7 [89.8–138.5]	107 [89–126]	121 [106–149]	108 [91–126]	111 [88–143]	0.652	0.400	0.384
LAVI (mL/m^2)	36.1 [26.6–42.4]	26.0 [21.1–30.7]	33.9 [28.6–42.4]	26.2 [19.8–32.8]	32.6 [27.2–42.0]	0.305	0.004	0.004
LV lateral s′ (mm/s)	7.6 [6.8–8.6]	8.0 [6.9–9.5]	7.9 [7.0–9.0]	7.9 [6.8–9.5]	7.5 [6.8–8.0]	0.032	0.414	0.003
LV lateral e′, mm/s	9.8 [7.7–12.4]	9.2 [7.6–11.7]	10.3 [7.9–11.6]	8.9 [7.5–10.3]	8.9 [6.6–9.9]	0.029	<0.001	<0.001
LV septal e′ (mm/s)	7.3 [6.1–9.0]	7.4 [6.2–8.9]	7.5 [6.3–8.7]	7.1 [6.1–8.4]	6.3 [5.6–7.3]	0.441	0.001	<0.001
E/e′ mean ratio	8.7 [7.0–11.1]	8.1 [6.9–9.7]	9.4 [7.5–11.0]	8.2 [6.9–9.7]	9.4 [6.8–11.7]	0.890	0.547	0.625
E/A ratio	0.9 [0.7–1.2]	0.9 [0.7–1.1]	1.0 [0.8–1.3]	0.8 [0.7–1.0]	0.9 [0.7–1.1]	0.092	0.008	<0.001
TR Vmax (m/s)	2.4 [2.2–2.6]	2.2 [1.9–2.5]	2.4 [2.1–2.6]	2.2 [1.9–2.5]	2.5 [2.2–2.6]	0.307	0.179	0.650
TAPSE (mm)	22.8 [19.8–25.4]	23.0 [20.6–25.4]	22.0 [19.2–25.7]	23.1 [20.4–25.5]	22.0 [18.9–23.3]	0.257	0.187	0.148
RV s′ (mm/s)	12.8 [11.1–15.1]	12.7 [11.6–14.8]	12.6 [10.6–15.0]	13.2 [11.6–15.0]	11.7 [11.0–14.2]	0.142	0.825	0.266

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; ESC, European Society of Cardiology; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LDL, low-density lipoprotein; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular peak systolic excursion; TR, tricuspid regurgitation.

Continuous variables are presented as median and inter-quartile range, and categorical variables are presented as absolute numbers and percentages. *P*-value for intergroup differences between ESC 2016, HFA-PEFF, and H_2FPEF HFpEF groups.

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Table 3 Reclassification table of HFpEF prevalence using the ESC 2016 algorithm and the HFA-PEFF score

	HFA-PEFF			
ESC 2016	HFpEF	No HFpEF	NA	Total
HFpEF	23 (5.7%)	47 (11.5%)	13 (3.2%)	83 (20.4%)
No HFpEF	7 (1.7%)	260 (63.9%)	27 (6.6%)	294 (72.2%)
NA	1 (0.2%)	20 (4.9%)	9 (2.2%)	30 (7.4%)
Total	31 (7.6%)	327 (80.3%)	49 (12%)	407 (100%)

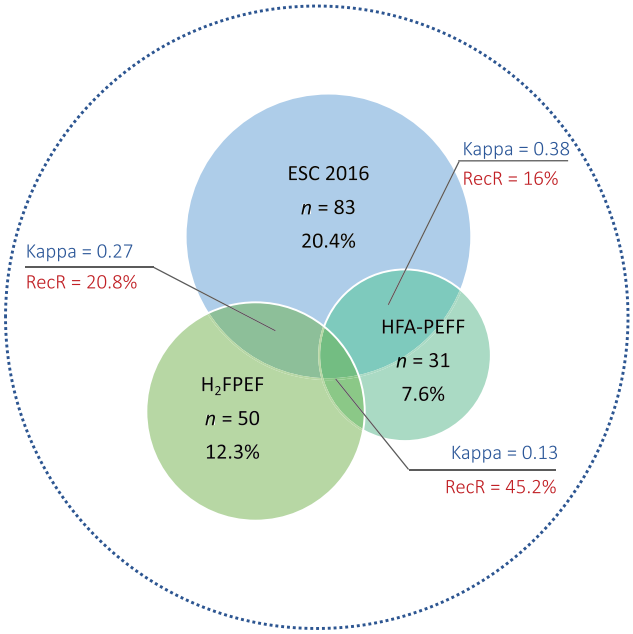
ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; NA, not applicable.
'HFpEF not excludable' has been classified as 'no HFpEF'. The concordance between the ESC 2016 and HFA-PEFF score was fair (κ = 0.39) with a reclassification rate of 16.4%. Subjects for whom at least one classification could not be determined (n = 10) were excluded.

Table 4 Reclassification table of HFpEF prevalence using the ESC 2016 algorithm and the H_2FPEF score

	H_2FPEF			
ESC 2016	HFpEF	No HFpEF	NA	Total
HFpEF	24 (5.9%)	54 (13.3%)	5 (1.2%)	83 (20.4%)
No HFpEF	22 (5.4%)	265 (65.1%)	7 (1.7%)	294 (72.2%)
NA	4 (1%)	26 (6.4%)	0 (0%)	30 (7.4%)
Total	50 (12.3%)	345 (84.8%)	12 (2.9%)	407 (100%)

ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; NA, not applicable.
'HFpEF not excludable' has been classified as 'no HFpEF'. The concordance between the ESC 2016 and H_2FPEF score was fair (κ = 0.28) with a reclassification rate of 21.2%. Subjects for whom at least one classification could not be determined (n = 1) were excluded.

Figure 3 Prevalence and concordance of the three heart failure with preserved ejection fraction algorithms in subjects with unexplained dyspnoea. Of the 407 subjects with unexplained dyspnoea or self-reported heart failure, the prevalence ranged from 20.4% [n = 83, European Society of Cardiology (ESC) 2016 guideline] to 12.3% (n = 50, H_2FPEF score) and 7.6% (n = 31, HFA-PEFF score). The concordance was highest between the ESC 2016 guidelines and the HFA-PEFF score reflected by a kappa coefficient of 0.38 and a reclassification rate (RecR) of 16%.



natriuretic peptides. On the other hand, natriuretic peptides are established biomarkers for diagnosing HF and provided accurate prognostic information in HFpEF patients.[11,12] All three scores include the prognostically relevant echocardiographic parameters E/e′ and the peak velocity of the tricuspid regurgitation (TR Vmax) indicating diastolic dysfunction.[13,14] In contrast to the HFA-PEFF score and the ESC algorithm, the H_2FPEF score additionally relies on co-morbidities such as AF, BMI, and arterial hypertension, which expectedly leads to higher prevalence of these co-morbidities in subjects with HFpEF according to the H_2FPEF score. However, both the H_2FPEF and HFA-PEFF scores have demonstrated a comparable prognostic utility for HF hospitalization or death in the elderly ARIC population with unexplained dyspnoea.[7]

As a limitation of both the HFA-PEFF and H_2FPEF scores, most subjects had intermediate scores indicating that HFpEF is not excludable. In line with these results, Barandiarán Aizpurua *et al*. reported that 36% of subjects with known HFpEF were categorized as HFpEF not excludable according to the HFA-PEFF validation study.[4] Translating these results into clinical practice would imply that the majority of patients with unexplained dyspnoea would have to undergo further testing for finally diagnosing or ruling out HFpEF. Whereas stress echocardiography is proposed as the next step in this group with inconclusive results according to the HFA-PEFF algorithm, Obokata *et al*. demonstrated a specificity of only 71% compared with invasive testing, which is still considered the gold standard for diagnosing HFpEF.[15,1] Invasive testing at rest or during exercise, as alternatively proposed by the authors of both the HFA-PEFF and H_2FPEF scores, would be the consequence in this large group.[3,16] However, invasive testing is limited because of its potential complications and high costs. Indeed, the ESC 2016 guidelines propose a more practical approach as HFpEF is dichotomously defined. On the other hand, in an analysis of the HFpEF TOPCAT trial study population, a lower H_2FPEF score was associated with a potential benefit of spironolactone.[17] These findings might suggest a future clinical application for therapeutic decision-making of the H_2FPEF and possibly the HFA-PEFF score beyond clearly differentiating HFpEF from non-HFpEF patients.

Each algorithm diagnosed, excluded, or considered HFpEF in the same study population differently. The concordance between the HFA-PEFF and H_2FPEF scores was poor in our cohort with only 2.2% of subjects with unexplained dyspnoea identified as HFpEF by both scores. Confirmatory evidence for large discrepancies between HFpEF populations identified by either the HFA-PEFF or H_2FPEF score comes from an

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Table 5 Reclassification table of HFpEF prevalence using the HFA-PEFF and H_2FPEF score

	H_2FPEF				
HFA-PEFF	HFpEF	HFpEF not excludable	No HFpEF	NA	Total
HFpEF	9 (2.2%)	18 (4.4%)	4 (1%)	0 (0%)	31 (7.6%)
HFpEF not excludable	32 (7.9%)	152 (37.3%)	50 (12.3%)	0 (0%)	234 (57.5%)
No HFpEF	7 (1.7%)	50 (12.3%)	34 (8.4%)	2 (0.5%)	93 (22.9%)
NA	2 (0.5%)	21 (5.2%)	16 (3.9%)	10 (2.5%)	49 (12%)
Total	50 (12.3%)	241 (59.2%)	104 (25.6%)	12 (2.9%)	407 (100%)

HFpEF, heart failure with preserved ejection fraction; NA, not applicable.
The concordance between the H_2FPEF and HFA-PEFF scores was poor ($\kappa = 0.13$) with a reclassification rate of 45.2%. Subjects for whom at least one classification could not be determined ($n = 10$) were excluded.

elderly subgroup of the population-based ARIC cohort: only 4% of subjects with unexplained dyspnoea were concordantly diagnosed with HFpEF, whereas 26% were diagnosed with HFpEF by the HFA-PEFF score and 11% by the H_2FPEF score.[7] Accordingly, even in an HFpEF cohort from the Maastricht, the Netherlands, HFpEF outpatient clinic, applying the HFA-PEFF and the H_2FPEF resulted in large discrepancies.[18]

The ESC algorithm showed a slightly better concordance with both scores. One major reason might be that HFpEF is rather considered a clinical syndrome than a separate entity.[19] Therefore, different phenotypes of HFpEF have been described before with potentially different underlying aetiologies.[20,21] Hence, HFpEF according to the different scores might refer in part to different HFpEF phenotypes. HFpEF is equally distributed between men and women according to the ESC 2016 algorithm and the HFA-PEFF score in line with some recent epidemiological HFpEF data. Nevertheless, other data support a female dominance of HFpEF patients.[22,23] In contrast to these data as well as to data from the ARIC study, the HFpEF group consisted of only 36% women applying the H_2FPEF score in our study.[7] Additionally, the H_2FPEF score is the only algorithm considering major co-morbidities. Especially AF, a major risk factor for HFpEF, was distributed unevenly between the different algorithms with the highest burden in the H_2FPEF group. Thus, according to our results, the H_2FPEF score might emphasize a male-dominated, co-morbidity-based phenotype of HFpEF.

Limitations

Our study cohort originates from a sample of the middle-aged population of Hamburg enrolled at random. Most of the participants are of Caucasian ascend, restricting the translation of our results into other populations necessitating further validation of our findings in other ethnic groups. Furthermore, the mean BMI in our study population was considerably lower than in comparable population-based cohorts from the Americas, for example, ARIC, possibly limiting the generalizability of our results.[7]

Concerning the application of the different scores, four relevant limitations have to be addressed: (i) the HFA-PEFF algorithm consists of four diagnostic steps. In our study, only the major step, Step 2, was fully performed, possibly restricting its diagnostic accuracy. (ii) As we applied the high probability threshold of the HFA-PEFF and H_2FPEF scores for diagnosing HFpEF, the calculated prevalence might underestimate the true prevalence of HFpEF according to the scores if full testing was performed. (iii) TR Vmax, as one of the echocardiographic variables in the HFA-PEFF score, was missing in 47% of subjects. As a result, in case of missing data, a normal value <2.8 m/s was assumed. Thus, HFpEF prevalence might be underestimated. Nevertheless, our approach is in line with clinical practice and a complete case sensitivity analysis showed no conflicting results. (iv) Global longitudinal strain, a minor parameter in the HFA-PEFF score, was not available in our study cohort, possibly resulting in a lower HFpEF prevalence. However, in an HFA-PEFF validation study, adding global longitudinal strain <16 as a criterion only reclassified very few individuals.[4] Next, dyspnoea, as the leading symptom of HFpEF, was assessed by a validated questionnaire, but without clinical testing. Notably, there was no specific gold standard to diagnose HFpEF, for example, by invasive measurement. Hence, our study could not assess the diagnostic accuracy of the three different algorithms. Finally, we analysed a cross-sectional dataset. Therefore, only associations were described, while no causal conclusions could be drawn.

Conclusions

Our study provides new data on the application of the ESC 2016 algorithm, the HFA-PEFF score, and the H_2FPEF score for diagnosing HFpEF in the general population. The prevalence of HFpEF in subjects with unexplained dyspnoea largely varied depending on the algorithm applied. The clinical applicability of both the HFA-PEFF and H_2FPEF scores might be challenged as most individuals were classified as HFpEF not excludable. Furthermore, each algorithm identified diverging subpopulations with dyspnoea underlining the need for further classification of the HFpEF syndrome.

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Conflict of interest

S.B. reports honoraria from Abbott, Siemens, Thermo Fisher, and Roche, outside of the submitted work. P.K. receives additional research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last 3 years. P.K. is listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571 and Markers for Atrial Fibrillation WO 2016012783). C.M. receives speaker fees from AstraZeneca, Novartis, and Löwenstein Medical unrelated to the submitted work. R.B.S. has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 648131, from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No. 847770 (AFFECT-EU), German Centre for Cardiovascular Research (DZHK e.V.) (81Z1710103), German Ministry of Research and Education (BMBF 01ZX1408A), and ERACoSysMed3 (031L0239). R.B.S. has received lecture fees and advisory board fees from BMS/Pfizer outside this work.

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Declaration of Helsinki

The authors do hereby declare that their study complies with the Declaration of Helsinki.

Illustrations and figures

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

Data availability statement

The data underlying this article cannot be shared publicly because of the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Supporting information

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

Data S1. Supporting information.

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