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ORIGINAL RESEARCH ARTICLE

Diagnosis of patients with heart failure with preserved ejection fraction in primary care: cohort study

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) accounts for half of all heart failure (HF), but low awareness and diagnostic challenges hinder identification in primary care. Our aims were to evaluate the recruitment and diagnostic strategy in the Optimise HFpEF cohort and compare with recent recommendations for diagnosing HFpEF.

Methods and results Patients were recruited from 30 primary care practices in two regions in England using an electronic screening algorithm and two secondary care sites. Baseline assessment collected clinical and patient-reported data and diagnosis by history, assessment, and trans-thoracic echocardiogram (TTE). A retrospective evaluation compared study diagnosis with H_2FPEF score and HFA-PEFF diagnostic algorithm. A total of 152 patients (86% primary care, mean age 78.5, 40% female) were enrolled; 93 (61%) had HFpEF confirmed. Most participants had clinical features of HFpEF, but those with confirmed HFpEF were more likely female, obese, functionally impaired, and symptomatic. Some echocardiographic findings were diagnostic for HFpEF, but no difference in natriuretic peptide levels were observed. The H_2FPEF and HFA-PEFF scores were not significantly different by group, although confirmed HFpEF cases were more likely to have scores indicating high probability of HFpEF.

Conclusions Patients with HFpEF in primary care are difficult to identify, and greater awareness of the condition, with clear diagnostic pathways and specialist support, are needed. Use of diagnostic algorithms and scores can provide systematic approaches to diagnosis but may be challenging to apply in older multi-morbid patients. Where diagnostic uncertainty remains, pragmatic decisions are needed regarding the value of additional testing versus management of presumptive HFpEF.

Keywords Heart failure; Primary health care; Diagnostic tests; Algorithms

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome estimated to account for half of all heart failure (HF) cases, and the majority of HF in those aged over 65 years.[1] In the United Kingdom (UK), HFpEF receives relatively little focus in comparison with heart failure with reduced ejection fraction (HFrEF).[2,3] This is despite predictions that HFpEF will become the dominant form of HF by virtue of our ageing, multi-morbid population, the rise of lifestyle-related disease, and improved post-cardiac event survival.[4,5] A recent analysis of 6144 patients referred from the community with suspected HF and N-terminal pro-brain natriuretic peptide (NT-proBNP) $\geq$ 400 pg/mL found that HFpEF was the most prevalent diagnosis among those confirmed with HF (46% HFpEF, 40% HFrEF, 13% other).[6] However, some specialist centres do not accept referrals for patients with suspected or confirmed HFpEF and bespoke clinical services are rare, prompting concern over quality and sustainability.[7,8]

A diagnosis of HFpEF is difficult to establish and may not be suspected or recognized by clinicians especially in primary care.[9,10] There are variations in diagnostic pathways and a lack of relevant information in primary care records.[11–13] In addition to impeding appropriate management, lack of relevant information explicitly identifying HFpEF in patients' clinical records[12] can hamper recruitment to studies, necessitating the use of confirmatory diagnostic evaluation. Few studies describe in detail the challenges of recruiting and confirming a diagnosis in patients with suspected HFpEF recruited in the community. Such descriptions are important for informing development of diagnostic pathways that are relevant to all patients and not selected sub-populations.

The 'Optimising Management of Patients with Heart Failure with Preserved Ejection Fraction in Primary Care' (Optimise HFpEF) cohort study identified and phenotyped patients with HFpEF in primary care through diagnostic evaluation and assessment of comorbidities, functional capacity, symptoms, and quality of life.[14] The aims of this analysis are to evaluate the recruitment and diagnostic strategy used and to compare this with recent recommendations for diagnosing HFpEF.

Methods

Study design and setting

The full protocol for the Optimise HFpEF programme has been previously published.[14] The study included a Patient Advisory Group, and patients were involved from before the study started. In summary, the Optimise HFpEF cohort study was conducted in the Cambridgeshire and Oxfordshire/Thames Valley regions. The study was approved by the London–Surrey Research Ethics Committee in 2017 (REC reference: 17/LO/2136) and conforms to the standards of the Declaration of Helsinki. The National Institute for Health Research Clinical Research Networks (NIHR CRN) facilitated access to general practices. Practices that agreed to participate in the study were provided with an electronic medical record screening algorithm to identify potential HFpEF patients. To simplify the screening process and increase yield, the automated search was run within each practice's existing HF register.

The algorithm was programmed to exclude patients with Read codes (a coded thesaurus of clinical terms) for left ventricular systolic dysfunction (LVSD) or cardiomyopathy, and a general practitioner (GP) screened outputs against study inclusion/exclusion criteria. Eligible patients were posted an invitation to participate along with study material and asked to return an expression of interest form. Participants attended a baseline assessment within designated clinical research facilities or research clinic space. Informed consent was obtained then participants provided detailed medical information, completed questionnaires, and underwent assessment. Two specialist secondary care outpatient services (an HF service in Peterborough and an older persons' clinic in London) were later added due to slow recruitment and a high percentage of subjects not meeting HFpEF diagnostic criteria.

Sample size

The target sample size was 200 based on the need for an adequate number of patients to confidently determine prevalence of symptoms, signs, and characteristics of patients with HFpEF in primary care, while considering practical constraints of recruiting from this setting. Exemplar analyses in Stata indicated that in a sample of 200 people, the 95% confidence interval for an estimate of 10% prevalence of a specific characteristic in the HFpEF population would be from 6% to 15%. Thus, the sample would have a high degree of precision to determine the prevalence of specific characteristics such as comorbid conditions, geriatric syndromes, and findings from diagnostic tests. From a previous study, we expected that 40% of patients on the HF registers would be suspected HFpEF.[12] Although we estimated that 25% of recruited patients would not have HFpEF confirmed,[15] our initial intent was to describe the characteristics of patients with HFpEF including their diagnostic features. Challenges in recruitment and diagnosis prompted an evaluation of the process and consideration of more recent recommendations in diagnosis.

Participants

The target population was people with an existing diagnosis of HFpEF. However, studies have shown primary care records hold incomplete information on HF, preventing easy and accurate identification of patients with HFpEF, and Read codes specific for HFpEF are rarely used.[12,13] GPs were asked to include patients where there was evidence of non-valvular HF and a left ventricular ejection fraction (EF) $\geq$ 50%. Exclusion criteria related both to factors excluding a diagnosis of HFpEF and to study participation: diagnosis of LVSD, cardiomyopathy, an EF $<$ 50% regardless of whether diagnosed as LVSD, or significant cognitive impairment, end of life care, or New York Heart Association (NYHA) functional class IV.

Variables and data sources

Details on HF register size, numbers screened and excluded by GPs, and recruitment outcome were collected. Once enrolled, variables designed to assess risk for, aid diagnosis of, and subsequently characterize HFpEF were collected. Validated assessments, standardized equipment, and a Manual of Operations guided data collection to ensure consistency

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across sites. A detailed protocol for the trans-thoracic echocardiogram (TTE) based on current European Society of Cardiology (ESC) guidelines[16] was produced to guide measurement. Standard echocardiogram parameters were supplemented with global longitudinal strain at one site.

Confirming the diagnosis

Heart failure with preserved ejection fraction diagnosis was adjudicated by an experienced cardiologist and was based on self-reported past medical history, assessment at study visit, clinical information, and TTE interpretation using thresholds specified in the 2016 ESC HF guidelines.[16] The ESC guidelines require the presence of signs and symptoms of HF, an EF $\geq$ 50%, elevated levels of natriuretic peptides (NP; NT-proBNP $\geq$ 125 pg/mL), and at least one of the following: relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) and/or diastolic dysfunction. Given that these were 'treated' patients on HF registers, patients were not excluded by study assessed NT-proBNP levels.

Since the study started, two diagnostic algorithms have been proposed and validated: the H_2FPEF score (*Figure 1*) and the HFA-PEFF diagnostic algorithm (*Figure 2*).[17,18] The H_2FPEF score, developed and validated by Reddy and colleagues in 2018, is designed to estimate the likelihood of HFpEF in patients with unexplained dyspnoea.[17] The four-step HFA-PEFF diagnostic algorithm, conceived in 2019 by the Heart Failure Association of the ESC, incorporates advancements in understanding since publication of the 2016 ESC guideline.[18] We undertook retrospective evaluation to compare the study diagnosis of participants with these two new diagnostic algorithms. The baseline assessment, aligning with the recommended HFA-PEFF initial work-up, included 12-lead electrocardiogram (ECG), NPs, TTE, and 6 min walk test.

Statistical analysis

Signs, symptoms, and risk factors for HFpEF were described using proportions, frequencies, and measures of central tendency appropriate for categorical and continuous variables. Comparisons were made between participants with and without clinically adjudicated HFpEF using *t*-tests, χ^2 tests, and non-parametric methods based on the data. Continuous variables were assessed for normality with Qplots and the Shapiro–Wilk test. TTE parameters were compared between participants with and without HFpEF using these methods. Final analysis compared the two groups by HFA-PEFF score and H_2FPEF score. Analysis was conducted using SPSS Version 27.

Results

Participants

Between July 2018 and November 2019, 152 patients from four sites in England [Cambridge (n = 67), Oxford (n = 64),

Figure 1 H_2FPEF score *reprinted with the kind permission of Walter Kluwer Health, Inc.* HFpEF, heart failure with preserved ejection fraction

	Clinical Variable	Values	Points
H_2	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
H_2FPEF score			Sum (0-9)

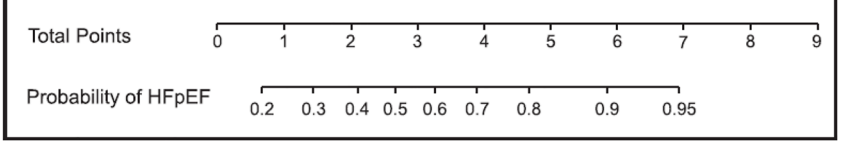

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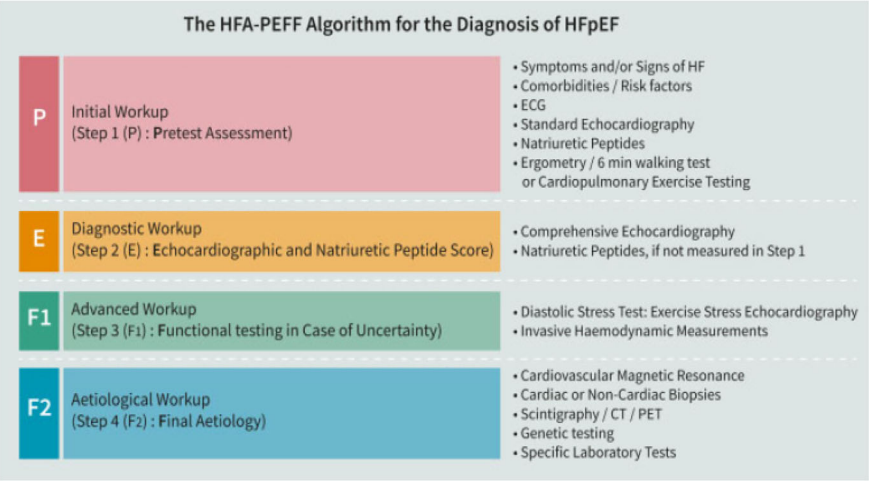
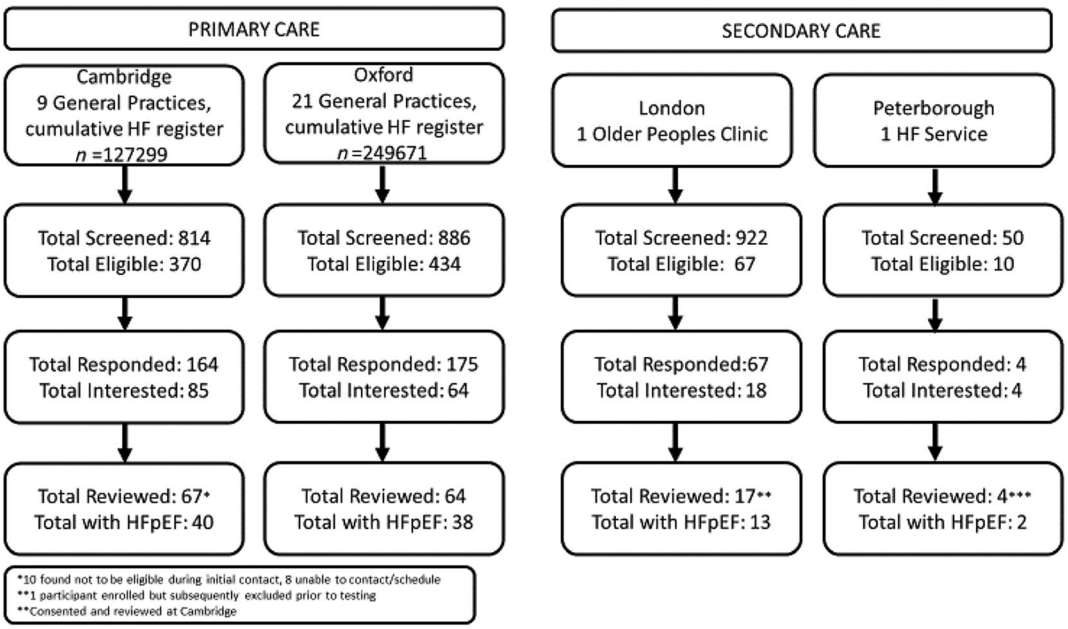
Figure 2 HFA-PEFF algorithm for the diagnosis of HFpEF *reprinted with the kind permission of John Wiley & Sons, Inc.* CT, computed tomography; ECG, electrocardiogram; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; PET, positron emission tomography



Peterborough (n = 4), and London (n = 17)] were enrolled. Thirty general practices participated. Across all sites, 2672 records were screened yielding a potential sample of 881 subjects that were subsequently contacted. Based on the HF register size and potentially eligible participant list generated by the automated search, prevalence of possible HFpEF was 0.6% (Cambridge) and 0.3% (Oxford) lower than calculated prevalence in the population.[19] Of the 881 subjects contacted, 410 responded, 41% of which (n = 171) were positive responses (*Figure 3*).

From 171 positive responses, 152 patients attended for baseline assessments. Ninety-three (61%) were clinically determined to have HFpEF by ESC reference standards. Although differential diagnosis for participants not meeting the ESC HFpEF criteria was not planned, the majority of non-HFpEF participants presented with other HF phenotypes such as HFrEF (some with recovered EF), hypertrophic cardiomyopathy, isolated atrial myopathy, or valve disease. On baseline TTE, 3.4% of participants had an EF $<$ 40%, 11.5% an EF 40–49%, and 85% had an EF $\geq$ 50%.

Figure 3 Patient flow chart. HF, heart failure; HFpEF, heart failure with preserved ejection fraction



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Clinical assessment of recruited sample

Clinical information collected as part of the diagnostic process included assessment of signs, symptoms, and risk factors for HF (*Table 1*), corresponding with Stage 'P' of the HFA-PEFF algorithm as seen in *Figure 2*. The majority of participants presented with or reported signs and symptoms of HF. Fatigue/tiredness and exercise intolerance, as assessed by NYHA class, were the most common followed by breathlessness. Breathlessness and fatigue were significantly more frequent in participants confirmed as HFpEF. The mean age of the sample was 78.5 years, half had a body mass index above 30 kg/m^2, and most had hypertension. Risk factors such as chronic kidney disease, diabetes, and atrial fibrillation (AF) were present in about a third. Overall comorbidity burden was high in the entire cohort by the Charlson Comorbidity Index [median 4, interquartile range (IQR) 3 to 6]. All participants with confirmed HFpEF had at least one risk factor for HFpEF, and the diagnosis was significantly more likely in women and if obesity was present. ECGs indicated that 45% of participants were in sinus rhythm, 34% in AF, and 21% in other baseline rhythms (primarily paced), with 15% having ventricular or supraventricular beats. Inverted *t* waves (27%), *q* waves (14%), ST segment depression (4%), and ST segment elevation (1.4%) were infrequent.

N-terminal pro-brain natriuretic peptide was not normally distributed. Removal of one patient who presented with an extremely elevated level (>18 000 pg/mL) revealed a median of 314 pg/mL (IQR 124 to 1055). Median values and distribution of NP levels were not different by presence or absence of an HFpEF diagnosis (P = 0.841). Seventy-four per cent of the total sample and 70% of patients with HFpEF had NT-proBNP levels greater than 125 pg/mL and 44% and 42.5%, respectively, had levels above 400 pg/mL. Patients with AF had a median NT-proBNP of 855 pg/mL (IQR 255 to 1596) compared with median 131 pg/mL (IQR 41 to 360) for those in sinus rhythm ($P < 0.001$). Twelve patients (six in each group) presented with NT-proBNP levels of 2000 pg/mL or more.

Echocardiographic analyses revealed few differences between those with HFpEF and those not meeting criteria. Although EF was slightly higher in those with HFpEF compared with those without, only mitral valve early diastolic inflow (MV-E), E/A ratio, and septal e′ were significantly different between the groups (*Table 2*). Using the threshold proposed by the ESC of an E/e′ ratio $\geq$ 13, patients with confirmed HFpEF were slightly more likely to meet that criterion than those without, and similarly with an E/e′ > 15. Using the five criteria of diastolic dysfunction in the ESC guidelines,[16] patients with HFpEF were significantly more likely to have both two or more and three or more abnormal diastolic parameters than those without HFpEF. There were no significant differences between groups in relative wall thickness, pulmonary artery systolic pressures (PASP), and global longitudinal strain (measured in a subset). Only 76 patients had PASP documented, but 66% of patients with HFpEF had a level above 35 mmHg, compared with 44% of those without (P = 0.071).

Step 'E' in the HFA-PEFF algorithm consists of a more detailed comprehensive echocardiogram and NPs if not done previously. The study TTE protocol was designed to provide that comprehensive level of assessment, but acquisition was not possible to achieve in all patients given characteristics such as AF, obesity, and procedure tolerance. However, consistent with the algorithm, the HFA-PEFF score was

Table 1 Signs, symptoms, and risk factors for heart failure with preserved ejection fraction

	Number of patients	Total sample n = 152	Confirmed HFpEF n = 93	Non-HFpEF n = 59	P value
Signs and symptoms of heart failure at baseline assessment					
Breathlessness/daytime dyspnoea	148	56%	63%	46%	0.035
Orthopnoea	152	22%	22%	25%	0.743
Fatigue/tiredness	152	71%	81%	61%	0.012
Leg oedema	152	45%	46%	43%	0.707
Exercise intolerance	152				0.118
NYHA class I		22%	17%	31%	
NYHA class II		57%	62%	48%	
NYHA class III		20%	20%	21%	
Risk factors					
Mean age	152	78.5 (8.6)	79.3 (7.1)	77 (10.5)	0.156
Female sex	152	40%	46%	29%	0.039
Obesity (≥30 kg/m^2)	151	50%	57%	39%	0.029
BMI mean	151	30.4 (6.6)	30.9 (6.2)	29.4 (7.1)	0.179
Hypertension	150	79%	81.5%	72%	0.522
Moderate to severe CKD	150	33%	34%	32%	0.789
Diabetes	150	29%	31.5%	26%	0.498
Pulmonary disease	150	29%	31.5%	23%	0.251
Atrial fibrillation	149	34%	32%	39%	0.435

BMI, body mass index; CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association.

Table 2 Echocardiographic parameters

	Number of patients	HFpEF	Non-HFpEF	*P* value
Left ventricular ejection fraction (%)	148	58.1 (7.1)	54.4 (10.8)	0.023
LV mass index, g/m^2	147	105.4 (32)	103.1 (32)	0.809
LAVI, mL/m^2	124	44.98 (16.5)	50.3 (27.3)	0.178
MV-E, m/s	147	0.85 (.32)	0.97 (.34)	0.046
MV-A, m/s	83	0.86 (.26)	0.75 (.24)	0.068
DecT, m/s	136	218 (71.2)	206 (68.1)	0.349
E/A	81	0.88 (.31)	1.3 (.77)	0.024
Septal e′, cm/s	123	6.2 (1.8)	6.96 (2.1)	0.037
e′ mean sep-lat, cm/s	117	7.75 (2.4)	8.5 (2.3)	0.110
E/e′ mean sep-lat, cm/s	127	12.8 (5.4)	11.6 (5.1)	0.192
E/e′ ≥ 13	125	44%	30%	0.124
E/e′ > 15	125	27%	15%	0.118
IVRT				
2 or more abnormal (ESC criteria) diastolic function parameters	138	69%	36%	0.003
3 or more		32%	23%	
RWT	147	0.45 (0.11)	0.44 (0.12)	0.511
GLS	65	−16.3 (6.5)	−15.4 (5.2)	0.558
PASP	76	39.8 (10.1)	36.2 (11.4)	0.164

DecT, deceleration time; E, early mitral diastolic inflow; E/A, ratio between peak early (E) and late (A) diastolic filling velocities; E/e′, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; e′, early diastolic tissue velocity; ESC, European Society of Cardiology; GLS, global longitudinal strain; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LV, left ventricular; MV, mitral valve; PASP, pulmonary artery systolic pressure; RWT, relative wall thickness.

calculated in 87 patients who had sufficient data from the initial analysis to calculate a score in the functional, morphological, and biomarker domains.[18] Scores were not significantly different between the two groups when analysed in their clinically adjudicated category (*Table 3*).

The HFA-PEFF algorithm proposes that patients with intermediate scores (2–4) go to Step F1, which includes other testing such as a stress TTE. This was not part of the study protocol, so a decision regarding confirmation of HFpEF was made based on clinical assessment, history, and resting TTE, as would be common in clinical practice.

Sixty-four patients had full information to calculate the H_2FPEF score.[17] Seventy-two per cent of the patients with confirmed HFpEF by our assessment had a score of 5 of more (>80% probability of HFpEF) compared with 59% of the non-HFpEF group (P = 0.214). About a quarter of both groups had scores indicative of 50–70% probability of HFpEF. The H_2FPEF score requires assessment of PASP and E/e′, which were not consistently available in all patients.

Table 3 Results by HFA-PEFF and H_2FPEF scores

HFA-PEFF score	HFpEF (n = 67)	Non-HFpEF (n = 36)	*P* value
≤1 HFpEF unlikely	7.5%	11.4%	0.402
2–4 requires further evaluation	34.3%	44.4%	
>5 diagnostic of HFpEF	58.2%	44.4%	
H_2FPEF score	HFpEF (n = 50)	Non-HFpEF (n = 27)	*P* value
Score 0–2	4%	14.8%	0.214
Score 3–4	26%	24%	
Score ≥ 5	72%	59%	

HFpEF, heart failure with preserved ejection fraction.

Discussion

Key findings

Our study reinforces that finding patients in primary care that were then confirmed with HFpEF was difficult using HF registers, due to a lack of identification in general practice. Only 32% of screened patient records with a code for HF had features suggestive of or consistent with HFpEF, and of those subsequently enrolled and evaluated, 39% did not have HFpEF based on assessment against the ESC guidelines. Confirmation of HFpEF was challenging using the standard clinical diagnostic pathways of clinical features, history, and resting TTE. In general, patients with confirmed HFpEF had higher rates of specific risk factors for HFpEF (obesity and female sex), more symptoms (daytime dyspnoea and fatigue), and specific and cumulative parameters of abnormal diastolic function than patients without HFpEF.

Although the ESC guidelines provide thresholds for measures of structural heart disease and diastolic function considered abnormal, there will be interpretation of the findings such as how many measures are abnormal, degree of abnormality, and other components of the echocardiogram within the context of the clinical assessment of the patient. The ESC guidelines in 2016 did not specify how many measures need to be abnormal, although other guidelines[19] state that at least half of five recommended variables of diastolic function need to be abnormal to diagnose diastolic dysfunction. Guidelines also differ on exact thresholds for abnormal results on diastolic dysfunction. Our intent was not to diagnose patients without HFpEF, but ageing and conditions found such as hypertrophic cardiomyopathy, valvular

heart disease, and atrial myopathy can lead to echocardiogram abnormalities similar to HFpEF.[20–22] Studies evaluating the performance of HFpEF diagnostic criteria against haemodynamic evidence or cardiac magnetic resonance imaging have found limitations in accuracy of classification.[20–22]

New recommendations for HFpEF diagnosis have sought to overcome these limitations, using the HFA-PEFF or H_2FPEF score. However, in this cohort, neither of these scores consistently discriminated between older multi-morbid patients on HF registers with or without HFpEF. Retrospective application of the HFA-PEFF algorithm and H_2FPEF score was equivocal, although more patients with HFpEF than without had scores indicating high probability or considered diagnostic. A substantial proportion of patients had intermediate scores on the HFA-PEFF, and confirmation of diagnosis would have required additional tests, out with our ethical approvals and funding. In addition, 44% of patients not considered to have HFpEF in our evaluation had scores considered diagnostic for HFpEF on the HFA-PEFF, and 59% had scores indicating high probability on H_2FPEF score.

Scores on HFA-PEFF are summed for major (2 points) and minor (1 point) specific criteria in three categories: functional (diastolic function parameters and global longitudinal strain), morphological or structural (left atrial volume, left ventricular mass, and relative wall thickness), and NPs (thresholds differ for sinus rhythm and AF). However, only one abnormal finding meeting major criteria in each category is necessary for maximum points. For example, a patient with one sufficiently abnormal parameter for diastolic function, left atrial volume of 34 mL/m^2, and an NT-proBNP of 125 pg/mL would have a score of 5, which could occur in non-HFpEF patients. In a sample of patients with mixed HF diagnoses, it is not surprising that some would score highly.

The H_2FPEF score gives the greatest weight to two specific risk factors, AF and obesity, with less emphasis on specific echocardiographic parameters. The H_2FPEF score gives the most points (3) to the presence of AF, which was found in 39% of our non-HFpEF patients. Clinicians may disagree as to the differentiation between atrial myopathy due to AF and HFpEF.[18] AF and HFpEF share common pathophysiologic origins and features, and some postulate AF may indicate the presence of HFpEF in patients with obesity and diabetes, while others diagree.[18,23] Obesity (given 2 points in the H_2FPEF score) is highly prevalent in most HFpEF cohorts but was also fairly common (39%) in our non-HFpEF patients. Thus, a patient with obesity and AF would have a score of 5 ($>$80% probability of HFpEF) on the H_2FPEF score, regardless of other findings. Ironically because obesity also suppresses NPs,[24] some patients with obesity would not be further evaluated for HF if NP levels were below threshold values. The H_2FPEF score was derived in a very different population from our sample, patients with indeterminate dyspnoea after other cardiac conditions had been ruled out.[17]

Comparison with other studies

There are a number of potential explanations for why many people with HFpEF in the community remain undiagnosed and recruiting patients from primary care for studies in HFpEF is challenging. Firstly, general practice registers do not hold sufficient clinical information nor employ specific coding for HFpEF to enable identification of different HF phenotypes on their registers.[12,13] Cuthbert and colleagues[25] and our own research have shown that the proportion of patients included on a typical practice HF register is much lower than expected based on epidemiological data[26] and that these patients are more likely to have HFrEF.[27] Secondly, our qualitative work has demonstrated low awareness of HFpEF in primary care.[9,28] Lastly, there is variable access to HF specialist services for non-HFrEF referrals to obtain a definitive diagnosis.[7–9]

The challenge of HFpEF diagnosis using the standard clinical pathway has been observed in other studies. A study of patients in the Alberta HEART cohort found that echocardiographic criteria for HFpEF can be fairly common in non-HFpEF patients and that guideline criteria for diagnosis and adjudication by experienced clinicians often differ in determination of HFpEF.[21] Imaging with cardiac magnetic resonance has found patients with hypertrophic cardiomyopathy and constrictive pericarditis included in HFpEF cohorts.[22] Similar to our experience, imaging by echocardiogram can be adversely affected by common comorbidities such as obesity, AF, and lung disease.[22]

Implications for practice

This study reinforces findings from our previous research that patients with HFpEF cannot be readily identified within primary care HF registers and that guidance and specialist support is needed to improve diagnosis.[12] It also confirms that HFpEF is a difficult diagnosis to make and can be equivocal when non-invasive diagnostic criteria are used. Cost and availability of recommended confirmatory tests will likely limit their use in many healthcare systems. Diagnostic pathways need to be robust when patients present with signs and symptoms potentially indicating HF. Primary care clinicians need greater awareness of HFpEF, its risk factors, and that neither a normal or near-normal EF nor a lower NT-proBNP value than the 400 pg/mL threshold proposed by the UK guidelines[29] rule out HFpEF in a patient with clinical signs and symptoms of HF. Echocardiogram reports should state clearly whether there is diastolic dysfunction, left ventricular hypertrophy, and increased left atrial volume and that these factors could indicate HFpEF if EF is $\geq$50%. Increased support for diagnosis and management is needed from specialist services and clear guidance regarding patients with possible but indeterminate HFpEF when further testing is not considered appropriate.

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The stepwise approach in HFA-PEFF is intuitively appealing, as it begins with consideration of risk of HFpEF, signs and symptoms indicative of HF, and then parameters in domains related to NP testing and echocardiogram. HFA-PEFF provides alternative major and minor criteria in each domain and a more nuanced comprehensive consideration of the three domains, although not without limitations. The authors themselves note that it is a limitation to suggest an algorithm can reduce a complex clinical syndrome to a single diagnosis and that patient mix may affect test results.[18] The initial steps of the HFA-PEFF algorithm could begin in primary care and be continued for confirmation in specialist services. Scoring needs to be considered in light of other factors that can affect test results and evaluation by a skilled clinician. Decisions about further imaging, stress testing, and invasive testing in patients with intermediate risk are likely to be affected by concerns over cost, risk in frail populations, and value if management unlikely to change.

An important question when considering the challenges in diagnosing HFpEF is the utility of a diagnostic label in the context of limited pharmacological options specific to HFpEF. However, there are actions that can be taken. Current recommendations are to manage fluid overload with diuretics and control comorbid conditions.[16] Physical activity has been shown to improve quality of life and cardiorespiratory fitness, and intentional weight loss in obese patients may be beneficial.[30,31] Importantly, patients value a clinical diagnosis,[9] and patients with HFpEF can benefit from support for HF self-management (e.g. monitoring weight and symptoms). Furthermore, if lack of evidence-based pharmacological therapy undermines the initiative to diagnose HFpEF, failure to identify patients with HFpEF undermines development of the evidence base.

Strengths and limitations

The sample was drawn mainly from primary care (86%) and represents the types of complex multi-morbid patients with uncertain HF diagnoses being managed in the community. The study highlights the lack of consistency in HF clinical coding and the challenges of diagnosis, which are inevitably influenced by the diagnostic criteria and available testing applied in the clinical setting. Echocardiograms were reviewed by an experienced echocardiographer with relevant expertise, and decisions about HFpEF diagnosis were made by a cardiologist with specific expertise in HFpEF consistent with usual clinical practice. This study highlights the importance of improving identification of HF and HFpEF in primary care and suggests some strategies that can be used to improve the diagnostic pathway.

The study has limitations in that the planned sample size was not reached, and the proportion of sampled patients found not to have HFpEF was higher than estimated. The electronic and practice screening process may have introduced selection bias regarding which patients were invited. Lack of a consistent systematic approach to identification and screening was a limitation, as this needed to be conducted by the practices. The search algorithm and inclusion/exclusion criteria were meant to provide a systematic approach to identification of patients, but practices likely varied as to their application of criteria, understanding of HFpEF, and accuracy and completeness of HF registers and medical records. Data quality when using clinical records will inevitably be a limitation of observational studies. Although reasons for screening exclusion were requested, they were not consistently provided. Reasons recorded were EF $<$ 50%, valvular heart disease or palliation, frailty syndrome, cognitive impairment, and mental illnesses. Lack of corresponding data on eligible non-participants prevented assessment of volunteer bias in the cohort, but patients with more advanced HF or more severe illnesses may have declined participation. Future studies should develop search algorithms using codes relating to or suggestive of HF (e.g. hypertension combined with diuretics) and apply to the entire register.[25] Having searches conducted by someone with relevant expertise in HFpEF could also improve appropriateness of invited patients.

Despite our detailed protocol, not all echocardiograms were performed at the standard expected, and not all needed parameters for assessment were available, which limited the number of patients for whom we could apply HFA-PEFF and H_2FPEF criteria. The criteria were also applied retrospectively to an older multi-morbid patient group with suspected HFpEF, which was not the intended approach of the developers of HFA-PEFF and H_2FPEF.

Conclusions

Patients with HFpEF in primary care are difficult to identify, and greater awareness of the condition among community clinicians, with clear diagnostic pathways and specialist support, are needed. Use of diagnostic algorithms and scores can provide systematic approaches but may be more difficult to apply in older multi-morbid patients. The diagnostic pathway should incorporate these systematic approaches to determining HFpEF, beginning in primary care, but driven by specialist teams taking a greater role in diagnosis and management of HFpEF. Echocardiogram reports should report key parameters for assessing cardiac structure and diastolic function especially when EF is ≥50%. Where diagnostic uncertainty continues, pragmatic decisions will have to be made regarding the value of additional testing versus management of presumptive HFpEF.

Conflict of interest

C.T. reports personal fees from Vifor and Novartis, and non-financial support from Roche outside the submitted work. The other authors declare that there is no conflict of interest.

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Author contributions

All authors have approved the manuscript and agree to be accountable for all aspects of work. C.D. is the senior and corresponding author.

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