ORIGINAL ARTICLE

Comparison of clinical characteristics of patients with heart failure and preserved ejection fraction with atrial fibrillation versus sinus rhythm: Insights from the APOLLON registry

Atriyal fibrilasyon ve sinüs ritminde olan korunmuş ejeksiyon fraksiyonlu kalp yetersizliği hastalarının klinik özelliklerinin karşılaştırılması: APOLLON çalışmasından sonuçlar

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ABSTRACT

Objective: The aim of this study was to assess the clinical characteristics of patients with heart failure and preserved ejection fraction (HFpEF) and atrial fibrillation (AF) and compare them with those of HFpEF patients without AF.

Methods: This study was a sub-group analysis of a multicenter, observational, and cross-sectional registry conducted in Turkey (ClinicalTrials.gov identifier: NCT03026114). Patients with HFpEF were divided into 2 groups: HFpEF with AF and HFpEF with sinus rhythm (SR), and the clinical characteristics of the groups were compared.

Results: In a total of 819 HFpEF patients (median age: 67 years; 58% women), 313 (38.2%) had AF. Compared to the patients with SR, those with AF were older (70 years vs 66 years; p<0.001) and more symptomatic, with a higher rate of classification as New York Heart Association functional class III-IV, paroxysmal nocturnal dyspnea, orthopnea, palpitations, fatigue, pulmonary crepitations, and peripheral edema. The

ÖZET

Amaç: Atriyal fibrilasyonu (AF) bulunan korunmuş ejeksiyon fraksiyonlu kalp yetersizliği (KEF-KY) hastalarının klinik özelliklerini değerlendirmeyi ve bu hastaların klinik özelliklerini AF'si bulunmayan KEF-KY hastalarıyla karşılaştırmayı amaçladık.

Yöntemler: Bu çalışma, Türkiye'de yürütülmüş olan, daha kapsamlı, çok merkezli, gözlemsel ve kesitsel bir kayıt çalışmasının alt grup analizi olarak tasarlandı (NCT03026114). KEF-KY hastaları; AF ritminde olan KEF-KY hastaları ve sinüs ritminde (SR) olan KEF-KY hastaları olarak iki gruba ayrılarak, bu hastaların klinik karakteristik özellikleri karşılaştırıldı.

Bulgular: Toplam 819 KEF-KY hastası (ortanca yaş 67 yıl, %58 kadın) içinde, 313 (%38.2) hastada AF mevcuttu. SR olan hastalara kıyasla, AF mevcut olan hastalar daha yaşlı (70'e karşı 66 yıl, p<0.001) ve daha semptomatikti. NYHA III-IV fonksiyonel kapasite, paroksismal nokturnal dispne, ortopne, çarpıntı, yorgunluk, akciğerlerde krepitan ral ve periferik ödem prevalansı AF ritmindeki hastalarda daha yüksekti. Kalp

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hospitalization rate for heart failure was higher (28.4% vs 12.6%; p<0.001) in patients with AF, and participants with AF had higher level of N-terminal pro-B-type natriuretic peptide (887 pg/mL vs 394.8 pg/mL; p<0.001) and higher left atrial volume index level. Patients without AF had a higher burden of diabetes mellitus, obstructive sleep apnea, and coronary artery disease. The prescription rate of nondihydropyridine calcium blockers, digoxin, loop diuretics, and anticoagulant drugs was higher in the AF group.

Conclusion: The results of this study revealed that in a large Turkish cohort with HFpEF, significant clinical differences were present between those with and without AF and. Further prospective studies are needed to clarify the prognostic implications of AF in this growing heart failure population in our country.

yetersizliğine bağlı hastaneye yatış oranı AF hastalarında daha fazlaydı (%28.4'e karşı %12.6, p<0.001) ve AF hastaları belirgin olarak daha yüksek N-terminal pro-B-tipi natriüretik peptit (887'ye karşı 394.8 pg/mL, p<0.001) ve sol atriyum volüm indeksi değerlerine sahipti. Bununla birlikte, AF mevcut olmayan hastalar daha yüksek diabetes mellitus, obstrüktif uyku apnesi ve koroner arter hastalığı yüküne sahipti. Ayrıca AF grubunda, nondihidropiridin grubu kalsiyum kanal blokerleri, digoksin, loop diüretikleri ve antikoagülan ilaç kullanım oranları daha fazlaydı.

Sonuç: Bu çalışma Türkiye'deki geniş bir KEF-KY kohortunda AF ritminde olan ve olmayan hastalar arasında önemli klinik farklılıklar olduğunu göstermiştir. Ülkemizde de giderek artan bu kalp yetersizliği popülasyonunda, AF'nin prognostik etkilerini netleştirmek için daha ileri, prospektif çalışmalara ihtiyaç vardır.

Atrial fibrillation (AF) and heart failure (HF) are two epidemics that are worsening nationally and internationally.[1,2] The prevalences of both conditions are predicted to increase with the aging of the population.[1,2] HF with preserved ejection fraction (HFpEF) is an increasingly prevalent form of HF, representing nearly 50% of HF cases.[3,4] Patients with HFpEF are often underdiagnosed and less aggressively treated compared with other types of HF.[5] However, HFpEF is associated with frequent hospitalizations, increased mortality, and high medical expenditures.[6] AF remains the most common, clinically significant arrhythmia in adults and is independently associated with a greater risk of ischemic stroke, as well as poorer quality of life, higher hospitalization rates, and excess mortality.[7] AF is a common arrhythmia in patients with HFpEF,[8–10] and the link between both conditions is likely explained by shared risk factors which predispose to each condition.[11] Comorbidities such as hypertension and greater body mass index, which are commonly seen and may play an etiological role in patients with HFpEF, are also thought to represent the greatest attributable risk for the development of AF.[12] AF may also cause hemodynamic deterioration through multiple mechanisms: reduction in stroke volume, impaired diastolic filling, increase in mean atrial diastolic pressure, loss of atrioventricular synchrony, and irregularity in ventricular response.[13] Eventually, they may occur together: HFpEF can beget AF, and AF can beget HFpEF.[14] When they occur concurrently, HFpEF and AF synergistically confer a poorer prognosis compared to those without these conditions or with either condition alone.[15,16]

As patients with HFpEF tend to be older and have more cardiovascular and non-cardiovascular morbidities,[17] the prevalence of AF is presumed to be different from HF with reduced ejection fraction (HFrEF). Based on data from previous studies, the prevalence of AF in HFpEF patients ranges between 15% and 76% according to gender and age,[18,19] with a reported incidence of between 5% and 32%,[20] and is perhaps more prevalent in patients with HFpEF than in those with HFrEF.[15] Although there are many studies that have analyzed patients with HFrEF and AF, much less is known about patients with HFpEF and AF. Characterizing this vulnerable patient population and identifying clinical features is critical to improving the outcomes of those with concurrent HFpEF and AF. Turkey is a large country with a growing elderly population. However, there has been no comprehensive study focused on the clinical characteristics of HFpEF patients with AF in our

Abbreviations:

AF	*Atrial fibrillation*
APOLLON	*A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejectiON fraction*
ECG	*Electrocardiography*
EGFR	*Estimated glomerular filtration rate*
ESC	*European Society of Cardiology*
HF	*Heart failure*
HFpEF	*Heart failure and preserved ejection fraction*
HFrEF	*HF with reduced ejection fraction*
HFmrEF	*Heart failure and mid-range ejection fraction*
LA	*Left atrium*
LAVI	*Left atrial volume index*
LVEF	*Left ventricular ejection fraction*
LVMI	*Left ventricular mass index*
NT-proBNP	*N-terminal pro-B-type natriuretic peptide*
NYHA	*New York Heart Association*
SR	*Sinus rhythm*
SwedeHF	*Swedish Heart Failure Registry*
TOPCAT	*Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist*

country. This study was designed to examine clinical differences between the patients with AF and patients with sinus rhythm (SR) within a large, multicenter cohort of patients with HFpEF.

METHODS

Study participants

APOLLON (A comPrehensive, ObservationaL registry of heart faiLure with mid-range and preserved ejectiON fraction) was a multicenter, cross-sectional, and observational study conducted in Turkey (ClinicalTrials.gov identifier: NCT03026114). The present study was designed as post-hoc analysis of the APOLLON registry. The design and results of the APOLLON study have previously been published.[21,22] Briefly, a total of 1065 patients who presented at outpatient cardiology clinics with HF and mid-range ejection fraction (HFmrEF) or HFpEF were enrolled at 13 centers in 7 regions of Turkey. The study was initiated on March 31, 2018 and the last patient was enrolled on May 20, 2018.

The patients were classified as HFmrEF or HFpEF according to the European Society of Cardiology (ESC) 2016 HF guidelines.[23] These were patients with a left ventricular ejection fraction (LVEF) ≥40%, at least 1 sign or symptom of HF, an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level (>125 pg/mL), and at least 1 additional echocardiographic criterion, such as relevant structural heart disease or diastolic dysfunction.

Patients with an LVEF of <40%; significant chronic pulmonary disease; primary severe heart valve disease requiring intervention or surgery; any history of surgically corrected heart valve disease (e.g., mechanical or bioprosthetic heart valve); myocardial infarction, stroke, or coronary artery bypass graft surgery in the past 90 days; percutaneous coronary intervention or pacemaker implantation in the past 30 days; heart transplant recipients; known infiltrative or hypertrophic obstructive cardiomyopathy or known pericardial constriction; congenital heart diseases or cor pulmonale; hospitalized patients with HF; and pregnant patients were excluded from the study.[21] Patients with an LVEF of ≥50% were diagnosed with HFpEF and were included in the present subgroup analysis.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by local institutional review boards (01/03/2018–01/VI). Written informed consent was obtained from all of the patients.

Data collection

All of the participants underwent a comprehensive clinical evaluation that included a clinical history, physical examination, blood pressure measurement, electrocardiography (ECG) and echocardiography assessment, and a blood test. Demographic, clinical, and other objective data were collected for each participant at the time of the visit. Patient characteristics were obtained with a survey recording demographic data, including age, gender, body mass index, status of tobacco and alcohol use, comorbid conditions, current and previous therapies or interventions to treat HF, and all medications. Blood samples were obtained at admission to measure laboratory variables, including NT-proBNP. The diagnosis of AF was based on a 12-lead standard ECG performed at the time of inclusion in the study. All of the patients were screened using transthoracic echocardiography during their first admission at the outpatient clinic, and LVEF was assessed using the conventional apical 2- and 4-chamber views and the modified Simpson's method. For the definition of HFpEF, at least 1 additional echocardiographic criterion was required, such as diastolic dysfunction or relevant structural heart disease. Key diastolic dysfunction criteria were accepted as an E/e′ of ≥13 and a mean e' septal and lateral wall of <9 cm/second. Key structural alterations were defined as a left atrial volume index (LAVI) of >34 mL/m^2 or a left ventricular mass index (LVMI) of ≥115 g/m^2 for males and ≥95 g/m^2 for females.[22]

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.[24] Chronic kidney disease was defined as an eGFR of <60 mL/minute/1.73 m^2. The blood pressure value used was the average of 2 seated measurements, and hypertension was defined based on current guidelines. Diabetes mellitus was defined as a fasting glucose of ≥126 mg/dL, random glucose of ≥200 mg/dL, or the use of hypoglycemic medications. Anemia was defined as a hemoglobin value of <13 g/dL in men and <12 g/dL in women. Body mass index was calculated as weight divided by height^2 and expressed as kg/m^2. Individual risk factors were evaluated and hyperlipidemia was defined according to the 2016 European Society of Cardiology/ European

Atherosclerosis Society Guidelines for the Management of Dyslipidaemias.[25] A prior history of coronary heart disease was ascertained using a combination of self-report (a history of myocardial infarction, coronary revascularization, or angiographic evidence of stenosis in 1 or more coronary arteries of >50% of the luminal diameter), electrocardiogram, review of all available prior medical records, and physician contact. Other comorbid conditions were determined according to a review of all available previous medical records and clinician contact.[22]

The participating clinicians were asked to identify the underlying leading causes of HF development according to clinical and laboratory findings and a physical examination. The leading etiology of HFpEF was defined according to the following algorithm: "atrial fibrillation," when the patient had atrial fibrillation, but had no other significant or uncontrolled risk factor for HF; "hypertensive," if the participant had resistant, untreated, or uncontrolled hypertension, but had no other substantial or uncontrolled risk factor for HF; "ischemic," if the patient had obstructive coronary artery disease, but had no other significant or uncontrolled risk factor for HF; or "valvular," when the patient had mild or moderate valvulopathy, but had no other substantial or uncontrolled risk factor for HF. Patients whose leading etiology could not be attributed to a single main cause and/or could not be determined clinically were categorized in the "other" group.[22]

Study design

A total of 819 HFpEF patients (median age: 67 years; 58% women) were included in the present study. The participants were divided into 2 groups: HFpEF with AF and HFpEF with SR. The clinical characteristics, laboratory findings, etiology, and management of HFpEF patients with AF were compared with HFpEF patients with SR.

Statistical analysis

The statistical analysis for this subgroup analysis was independent from the previous, larger study. The Komolgorov-Smirnov test was used to determine normal distribution. The baseline continuous variables are presented as mean±SD or the median and the first and third quartile, depending on the distribution of the data. The categorical variables are expressed as frequencies and percentages. The continuous variables were compared using a t-test or the Mann-Whitney U-test, as appropriate. Univariate analysis was performed for continuous variables and a chi-square or Fisher's exact test was applied for categorical variables. Fisher's exact test was used if at least 1 cell had a value of <5, a chi-square test with continuity correction was used if the cell value was 5–25; otherwise, Pearson's chi-square test was used. A p value of <0.05 was considered statistically significant in all of the tests. Analyses were performed using the statistical package IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Among the participants with HFpEF, 313 (38.2%) patients had AF. The prevalence of AF in patients with HFpEF differed by age and gender. The rate of AF was higher in women in all age groups under aged 80, whereas AF was more common in men aged 80 and older. However, there was an increasing trend in AF with age in all age groups and in both sexes (Fig. 1).

The baseline characteristics and comorbid conditions of HFpEF patients with AF and SR are provided in Table 1. Compared to patients with SR, the patients with AF were older and there were more New York Heart Association (NYHA) class III or IV patients in the AF group. Similar to functional class, the prevalence of paroxysmal nocturnal dyspnea, orthopnea, palpitations, fatigue, syncope, dizziness, pulmonary crepitations, and peripheral edema was higher in patients with AF. However, there were fewer smokers among the patients with AF, and the chest pain rate was higher in patients with SR. Systolic blood pressure was higher in patients with SR, whereas the me-

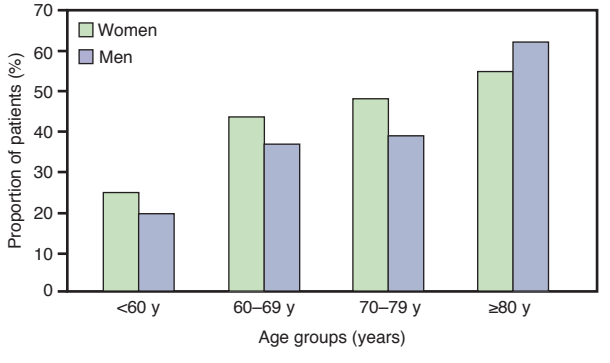

Figure 1. Prevalence of atrial fibrillation in patients with heart failure and preserved ejection fraction according to age and gender.

Table 1. Patient demographics, characteristics, and comorbid conditions

	HFpEF patients with atrial fibrillation (n=313)	HFpEF patients with sinus rhythm (n=506)	*p* value
Female sex	194 (62)	279 (55.1)	0.054
Age, years	70 (63–77)	66 (58–73)	<0.001
Smoking	26 (8.3)	103 (20.4)	<0.001
Alcohol use	6 (1.9)	23 (4.5)	0.052
New York Heart Association			
I	40 (12.8)	138 (27.2)	
II	181 (57.8)	273 (54.0)	<0.001
III	78 (24.9)	83 (16.4)	
IV	14 (4.5)	12 (2.4)	
Paroxysmal nocturnal dyspnea	134 (42.8)	143 (28.3)	<0.001
Orthopnea	115 (36.7)	124 (24.5)	0.001
Palpitations	216 (69)	192 (37.9)	<0.001
Reduced exercise tolerance	267 (85.3)	410 (81)	0.116
Fatigue, tiredness	216 (69)	304 (60.1)	0.010
Chest pain	58 (18.5)	143 (28.3)	0.002
Syncope	24 (7.7)	12 (2.4)	<0.001
Dizziness	87 (27.8)	75 (14.8)	<0.001
Body mass index (kg/m^2)	29 (25–32)	28 (25–32)	0.686
Systolic blood pressure (mmHg)	130 (120–140)	135 (120–145)	0.007
Diastolic blood pressure (mmHg)	80 (70–85)	80 (70–88)	0.451
Heart rate, bpm	89 (76–105)	76 (68–85)	<0.001
Pulmonary crepitations	86 (27.5)	98 (19.4)	0.007
Peripheral edema	126 (40.3)	139 (27.5)	<0.001
Cachexia	16 (5.1)	12 (2.4)	0.036
History of hospitalization for HF in the last year	88 (28.4)	64 (12.6)	<0.001
Comorbidities			
Hypertension	233 (74.4)	390 (77.1)	0.391
Diabetes mellitus	71 (22.7)	173 (34.2)	<0.001
Anemia	107 (34.1)	178 (35.1)	0.838
Chronic kidney disease	31 (9.9)	57 (11.3)	0.541
Obstructive sleep apnea	14 (4.5)	41 (8.1)	0.044
Hyperlipidemia	50 (16)	143 (28.3)	<0.001
Coronary artery disease	55 (17.6)	216 (42.7)	<0.001
Peripheral artery disease	7 (2.2)	14 (2.8)	0.821
Cerebrovascular accident/TIA	38 (12.1)	12 (2.4)	<0.001
Chronic obstructive pulmonary disease	44 (14.1)	64 (12.6)	0.562
Hepatic failure	7 (2.2)	7 (1.4)	0.360
Depression	15 (4.8)	29 (5.7)	0.563
Malignancy	5 (1.6)	8 (1.6)	1.000
Etiology of heart failure			
Ischemic	16 (5.1)	163 (32.2)	
Atrial fibrillation	249 (79.6)	0 (0)	
Hypertension	16 (5.1)	235 (46.5)	<0.001
Valvular disease	30 (9.6)	77 (15.2)	
Other	2 (0.6)	31 (6.1)	

HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; TIA: Transient ischemic attack.

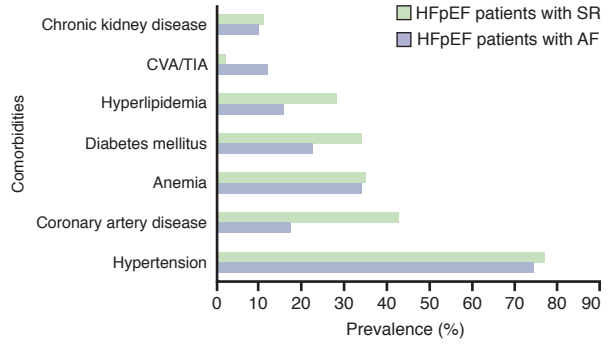

Figure 2. Comorbid diseases in patients with heart failure and preserved ejection fraction with atrial fibrillation and sinus rhythm. AF: Atrial fibrillation; CVA: Cerebrovascular accident; HFpEF: Heart failure with preserved ejection fraction; SR: Sinus rhythm; TIA: Transient ischemic attack.

dian heart rate was higher in patients with AF. Patients with SR had a higher burden of diabetes mellitus, hyperlipidemia, obstructive sleep apnea, and coronary artery disease. As expected, the frequency of cerebrovascular accident or transient ischemic attack was higher in the AF group. There were no significant differences between the 2 groups in other comorbidities (e.g., hypertension, anemia, chronic kidney disease, peripheral artery disease, and chronic obstructive pulmonary disease) (Fig. 2). In addition, a history of hospitalization for HF in the prior year was higher in patients with AF (28.4% vs 12.6%; p<0.001). The main cause of HF varied between HFpEF patients with AF and SR. Hypertension and ischemic heart disease were the leading etiological factors for the development of HF in patients with SR, whereas valvular disease was the principal etiology of HF in AF group.

A comparison of blood tests and 2-dimensional transthoracic echocardiographic data of HFpEF patients with AF and SR is shown in Tables 2 and 3. Compared to patients without AF, patients with AF had considerably lower fasting blood glucose, serum potassium, serum calcium, and thyrotropin-stimulating hormone levels. Although the median LVEF value was higher in patients with AF, NT-proBNP levels were also significantly higher (887 pg/mL vs 394.8 pg/mL; p<0.001) in AF patients. Grade 3 left ventricle diastolic dysfunction was more prevalent, the e' level was lower, and the E/e' ratio was significantly higher in the SR group compared with the AF group. As expected, the LAVI, the prevalence of left atrial (LA) enlargement (68.7% vs 34.9%; p<0.001), and the rate of valvular heart disease (e.g., mitral regurgitation, aortic regurgitation, and tricuspid regurgitation) were higher in the HFpEF patients with AF. Pulmonary artery systolic pressure was also higher in AF patients.

There were also some differences between the 2 groups in prescribed medications (Table 4). The pre-

Table 2. Laboratory data

	HFpEF patients with atrial fibrillation (n=313)	HFpEF patients with sinus rhythm (n=506)	*p* value
NT-proBNP (pg/mL)	887 (382.5–1557)	394.8 (196–795.7)	<0.001
Fasting blood glucose (mg/dL)	101 (92–120)	110 (95–133)	<0.001
Blood urea nitrogen (mg/dL)	18 (13–22.2)	17 (13–22)	0.650
Serum creatinine (mg/dL)	0.81 (0.7–1.0)	0.86 (0.7–1.0)	0.545
Serum sodium (mmol/L)	141 (139–143)	141 (138–143)	0.869
Serum potassium (mmol/L)	4.5 (4.2–4.8)	4.6 (4.3–5)	0.003
Serum calcium (mg/dL)	9.2 (8.9–9.5)	9.3 (9–9.8)	<0.001
Uric acid (mg/dL)	5.5 (4.6–6.7)	5.5 (4.7–6.7)	0.899
Hemoglobin (g/dL)	13 (11.7–14.2)	13 (11.8–14.2)	0.655
Leukocyte (x10^3/μL)	7.7 (6.5–9.2)	7.9 (6.6–9.3)	0.356
C-reactive protein (mg/dL)	3.4 (2–8)	3.5 (1.7–7)	0.281
Ferritin (ng/mL)	55 (26.3–101)	53 (26.6–101)	0.878
TSH (μIU/mL)	1.38 (0.82–2)	1.6 (1–2.5)	0.005

Data are presented as median with the first and third quartile (Q1–Q3). HFpEF: Heart failure with preserved ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; TSH: Thyrotropin-stimulating hormone.

Table 3. Two-dimensional transthoracic echocardiographic findings

	HFpEF patients with atrial fibrillation (n=313)	HFpEF patients with sinus rhythm (n=506)	*p* value
Left ventricle ejection fraction (%)	61 (55–65)	60 (55–62)	0.005
e', cm/sn	7.4 (6.5–8.4)	7 (6–8)	<0.001
E/e'	9 (7.4–12)	10 (8–12)	0.047
LV diastolic dysfunction			
None	59 (18.9)	45 (8.9)	0.001
Grade 1	62 (19.8)	163 (32.2)	
Grade 2	131 (41.8)	180 (35.5)	
Grade 3	61 (19.5)	118 (23.3)	
LVED dimension (mm)	47 (44–51)	48 (44–51)	0.214
Left ventricular end-systolic dimension (mm)	31 (28–35)	32 (29–35)	0.483
Interventricular septum dimension (mm)	11 (10–12)	12 (10–13)	0.002
LVPW dimension (mm)	11 (10–11)	11 (10–12)	0.117
Left atrial volume index (mL/m^2)	38 (32–45)	31 (27–36)	<0.001
Left atrium enlargement	215 (68.7)	177 (34.9)	<0.001
Left ventricular mass index (g/m^2)	104 (88–122)	107 (89–127)	0.058
Left ventricle concentric hypertrophy	160 (51.1)	282 (55.7)	0.262
Pulmonary artery systolic pressure (mmHg)	32 (25–40)	25 (15–33)	<0.001
Mitral regurgitation			
None	52 (16.6)	218 (43.1)	<0.001
Mild	168 (53.7)	237 (46.8)	
Moderate	93 (29.7)	48 (9.5)	
Severe	0 (0)	3 (0.6)	
Mitral stenosis			
None	299 (95.5)	489 (96.6)	0.540
Mild	10 (3.2)	10 (2.0)	
Moderate	4 (1.3)	7 (1.4)	
Aortic stenosis			
None	304 (97.1)	492 (97.2)	0.732
Mild	5 (1.6)	10 (2.0)	
Moderate	4 (1.3)	4 (0.8)	
Aortic regurgitation			
None	214 (68.3)	412 (81.4)	<0.001
Mild	92 (29.5)	76 (15.0)	
Moderate	7 (2.2)	18 (3.6)	
Tricuspid regurgitation			
None	74 (23.7)	226 (44.7)	<0.001
Mild	129 (41.2)	206 (40.7)	
Moderate	94 (30.0)	64 (12.6)	
Severe	16 (5.1)	10 (2.0)	

Data are presented as median with the first and third quartile (Q1-Q3) or number (%).
HFpEF: Heart failure with preserved ejection fraction; LVED: Left ventricular end-diastolic; LVPW: Left ventricular posterior wall.

Table 4. Prescribed medications

	HFpEF patients with atrial fibrillation (n=313)	HFpEF patients with sinus rhythm (n=506)	*p* value
Angiotensin-converting enzyme inhibitor	103 (32.9)	162 (32)	0.791
Angiotensin receptor blocker	85 (27.2)	143 (28.3)	0.732
Beta blocker	173 (55.3)	279 (55.1)	0.970
Aldosterone antagonists	55 (17.6)	65 (12.8)	0.063
Amiodarone	8 (2.6)	6 (1.2)	0.169
Propafenone	1 (0.3)	1 (0.2)	1.000
Nondihydropyridine calcium blockers	69 (22.0)	33 (6.5)	<0.001
Dihydropyridine calcium blockers	65 (20.8)	114 (22.5)	0.553
Digoxin	43 (13.7)	7 (1.4)	<0.001
Statin	39 (12.5)	149 (29.4)	<0.001
Loop diuretic	120 (38.3)	130 (25.7)	<0.001
Thiazide	99 (31.6)	141 (27.9)	0.250
Antiaggregant	58 (18.5)	272 (53.8)	<0.001
Anticoagulant	216 (69)	24 (4.7)	<0.001
Nonsteroidal anti-inflammatory drug	25 (8)	30 (5.9)	0.253
Oral antihyperglycemic	58 (18.5)	131 (25.9)	0.015
Insulin	14 (4.5)	47 (9.3)	0.011

Data are presented as number (%). HFpEF: Heart failure with preserved ejection fraction.

scription rate of nondihydropyridine calcium blockers, digoxin, loop diuretics, and anticoagulant drugs was higher in the patients with AF, whereas the use of statins, antiaggregant drugs, and antidiabetic medications was higher in the SR group. The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, dihydropyridine calcium blockers, and thiazide profiles was similar in both groups.

DISCUSSION

The present study is a real-world, epidemiological survey of HFpEF patients with AF in a large Turkish cohort, and several substantial findings were revealed. We found that the prevalence of AF was 38.2% in patients with HFpEF, and that AF demonstrated an increasing trend with age in men and women. Second, HFpEF patients with AF were older and more symptomatic compared to patients with SR. Third, patients with AF had higher hospitalization rates due to HF. Finally, there were important differences in the echocardiographic findings, comorbid diseases, and prescribed medications between HFpEF patients with AF and SR.

The coexistence of AF and HFpEF is common; however, a causal relationship between these pathologies has not been fully identified.[26] The prevalence of AF in patients with HFpEF varies in different studies (e.g., cohorts, registries, trials, insurance claim data). In the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial, 29.3% of the HFpEF patients had a history of AF at baseline,[27] and the prevalence of AF was almost 20% in the HFpEF patients in the Framingham Heart Study.[14] A total of 19% of patients in the HFpEF (defined as LVEF >40%) group had AF at the time of enrollment in the CHARM (Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity) study.[20] Eapen et al.[16] conducted a retrospective cohort study of clinical registry data linked to Medicare insurance claims for US patients with HFrEF and HFpEF stratified by the presence of AF at admission. A total of 36,577 HFpEF patients were included in the study, and the analysis revealed that the prevalence of AF was 47.6% in patients with HFpEF. In the PARAGON-HF (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin Receptor Blocker Global Outcomes in HFpEF) trial, which comprised 4,822

HFpEF patients, AF was present in 32% of participants.[28] On the other hand, a prevalence of 65% was determined in the SwedeHF (Swedish Heart Failure Registry), which was much higher than many other studies.[19] Consistent with these data, the AF rate was 38.2% in our study, which reflects real-world data of the first, large, Turkish HFpEF cohort.

Sartipy et al.[19] analyzed data from 2000 to 2012 in the SwedeHF registry. In this study, they compared 6250 HFpEF patients with AF and 3345 HFpEF patients with SR. As in our results, the SwedeHF registry examination showed that compared to patients with SR, patients with AF were older and that the prevalence of NYHA III-IV functional class, valve disease, and prior stroke was higher in the AF group. The presence of hypertension, peripheral artery disease, and pulmonary disease was similar in both groups; however, patients with SR had a higher rate of diabetes mellitus and ischemic heart disease. Compared with the SR group, participants with AF also had considerably higher NT-proBNP levels. The use of diuretics, digoxin, and anticoagulant drugs was higher in the AF group, whereas patients with SR had a higher prescription rate for statins and antiaggregant medications in this study. In comparison with previous HFpEF data,[19,29] it was observed that the prevalence of chronic kidney disease and chronic obstructive pulmonary disease was lower in both the AF and SR groups in our analysis, likely because the APOLLON registry included only outpatients, and hospitalized HFpEF patients were excluded from the study. In contrast to our study, the SwedeHF registry analysis revealed that the prevalence of AF in all age groups was higher in men.[19] Some other studies also found that men were more likely to have AF, especially in HFrEF.[16,20,30] However, in HFpEF, where more women are included, the prevalence of AF in men and women could be similar.[7] Our results indicated that the prevalence of AF was higher in men aged 80 and older, although the rate was higher in women under the age of 80. This could be explained by the fact that 58% of the HFpEF population in our study was female.

Cikes et al.[31] investigated the relationship between AF and outcomes in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial. A total of 1765 patients with HFpEF in North and South America were divided into 3 groups: no known AF (56.9%), a history of AF without AF at enrollment (17.8%), and AF determined based on the electrocardiogram at enrollment (25.3%). The study assessed outcomes and treatment response to spironolactone in all groups, and the association between post-randomization AF and outcomes in patients free of AF at baseline. Cikes et al.[31] found that AF at enrollment was associated with increased cardiovascular risk in HFpEF patients in the TOPCAT study. Also, post-randomization AF was associated with an increased risk of mortality and morbidity, including HF hospitalization. Similarly, we determined that HFpEF patients with AF had a significantly higher rate of HF hospitalization compared to HFpEF patients without AF.

The association between AF and exercise capacity, NT-proBNP, and LAVI in patients with HFpEF is an interesting issue. Lam et al.[32] studied 94 patients with symptomatic HF and an LVEF of ≥45% using treadmill cardiopulmonary exercise testing, and right- and/or left-sided cardiac catheterization with simultaneous echocardiography. In that study, 62 patients were in SR, and 32 patients had AF. There were no significant differences in age, gender, body mass index, comorbid conditions, or medications between groups; however, patients with AF had a lower peak oxygen consumption compared with those with SR. In addition, the median NT-proBNP level was higher in the AF group, and the LAVI was also higher in the AF group compared with the SR group. Lam et al. demonstrated that AF was independently associated with greater exertional intolerance, natriuretic peptide elevation, and LA remodeling in patients with HFpEF. Consistent with these findings, patients with AF at enrollment were more symptomatic, there was a higher rate of NYHA III-IV functional class, paroxysmal nocturnal dyspnea, orthopnea, palpitations, fatigue, syncope, dizziness, pulmonary crepitations, and peripheral edema, and the NT-proBNP levels were significantly higher in the AF group in the APOLLON registry.

There is a complex, synergistic relation between HFpEF, AF, and LA dysfunction causing poor clinical outcomes. Atrial fibrosis may not only lead to AF, but also further worsening of the HFpEF itself.[33] LA dysfunction secondary to HFpEF causes to LA overload, and has been associated with decreased peak oxygen consumption, and HF hospitalization.[33–35] It is likely that patients with severe mechanical LA

dysfunction also have a substantial AF burden, which further worsens left ventricle filling. Significantly abnormal LA mechanics with increased LA volumes may account for the increased burden of AF in the HFpEF population compared to the HFrEF cohort.[33] O'Neal et al.[36] studied the association between several echocardiographic measures of diastolic dysfunction and incident AF in 573 patients with HFpEF from the TOPCAT trial who were free of baseline AF.[36] The study revealed that increasing values of the E/A ratio, LA volume, and LA area were associated with an increased risk of AF. However, diastolic parameters of LA function possibly were more important predictors of AF than LA dilation in HFpEF.[36] In our study, compared to patients with SR, HFpEF patients with AF had significantly higher LAVI values.

Study limitations

The results of the current study are based on post-hoc analyses of the APOLLON registry. The present study had a cross-sectional design, and the main limitation is the lack of follow-up data. Therefore, the potential prognostic implications of AF in patients with HFpEF cannot be analyzed in our cohort. Patients were defined as HFpEF according to the ESC 2016 HF guidelines in our study, and we used the same NT-proBNP cut-off values for the diagnosis of HFpEF patients with AF and SR. However, AF may have a differential influence on plasma natriuretic peptide levels, and previous studies have reported that AF was most strongly associated with higher NT-proBNP levels in HFpEF.[37] Therefore, the diagnostic criteria of the ESC guidelines may overestimate the diagnosis of HFpEF in patients with AF. We evaluated the clinical differences between AF group and SR group in patients with HFpEF, but we cannot demonstrate causality. Another limitation is that our study was limited to outpatient cardiology units; hospitalized HFpEF patients were not included in the research. In addition, a "clinician-judged HF" diagnosis in terms of signs and/or symptoms of HF was one of the limitations of the APOLLON registry.

Conclusion

The present study is the first to analyze the clinical and laboratory characteristics of AF in a large, multicenter HFpEF cohort in Turkey. We found that the prevalence of AF was 38.2% in this cohort; and compared to participants without AF, HFpEF patients with AF were older, more symptomatic, and had higher hospitalization rates due to HF. We also demonstrated important differences in echocardiographic data, laboratory findings, comorbid conditions, and prescribed drugs between HFpEF patients with AF and without AF. Although the identification of the clinical characteristics of patients with AF in HFpEF is important in clinical practice, further prospective studies are needed to clarify the prognostic implications of AF in this growing HF population in our country.

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