The European Research Journal 2022;8(2):266-274 Original Article

DOI: 10.18621/eurj.1049360 *Cardiology*

Baseline characteristics of outpatients with heart failure according to phenotype: preliminary analysis from SMYRNA-HF registry

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ABSTRACT

Objectives: SMYRNA-HF study is a prospective multicenter registry study to determine the profiles of patients with heart failure (HF) in Turkey. This study aimed to present the baseline characteristics of preliminary cohort by comparing them according to different HF phenotypes.

Methods: The first SMYRNA-HF cohort included outpatients with HF from 9 centers. Patients were classified into three HF phenotypes as HF with reduced ejection fraction (HFrEF), mildly reduced EF (HFmrEF), and preserved EF (HFpEF) as recommended by guidelines.

Results: Overall, 298 patients were included in this preliminary analysis that 57% of the patients were classified as having HFrEF, 33.3% as having HFpEF, and 9.7% as having HFmrEF. Female gender was more common in HFpEF (p = 0.003). Age, frequency of diabetes mellitus, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, use of beta-blocker, use of daily loop diuretic, heart rate, blood urea nitrogen levels, lipid profiles, hemoglobin, white blood cell, platelet levels were similar among three HF phenotypes. Body mass index (BMI) ($p < 0.001$), frequency of hypertension (HT) ($p < 0.001$), and atrial fibrillation (AF) ($p = 0.015$) were higher in HFpEF. Ischemic etiology ($p < 0.001$) was less frequent in HFpEF. Use of mineralocorticoid receptor antagonist was higher in HFrEF ($p < 0.001$).

Conclusions: Our study presented the baseline characteristics of outpatients with HF in Turkey. There were

Received: ***December 28, 2021;*** ***Accepted:*** ***January 31, 2022;*** ***Published Online:*** ***March 4, 2022***

How to cite this article: *Şentürk B, Çelik A, Bekar L, Uyan U, Yakar Tülüce S, Güneş H, et al. Baseline characteristics of outpatients with heart failure according to phenotype: preliminary analysis from SMYRNA-HF registry. Eur Res J 2022;8(2):266-274. DOI: 10.18621/eurj.1049360*

e-ISSN: 2149-3189

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significant differences among HF phenotypes in terms of gender, BMI, frequency of HT, AF, and ischemic etiology. Treatment implementations seem to follow the guidelines. Although the rates are low, new treatment approaches recommended in the most recent guidelines seem to enter clinical practice.
Keywords: Heart failure, registries, Turkey, phenotypes, outpatients, baseline characteristics

Heart failure (HF) is a fatal disease that occurs as a result of deterioration of cardiac functions. It is estimated that there are approximately 40 million patients with HF in the world. The number of patients with HF is anticipated to increase in the coming years [1]. Many notable improvements have been observed in the treatment of HF, and there has been a remarkable increase in the life expectancy of patients with HF [2, 3]. Nevertheless, these patients still are at risk of death or acute decompensation requiring recurrent hospitalization.

Large-scale multicenter HF cohort registry studies have been conducted in many countries [4-13]. These studies provide important data regarding the basic profiles of patients, the distribution of HF phenotypes, risk factors, treatment, mortality, and morbidity characteristics of patients with HF from different countries. The "SELFIE-TR study" that includes the basal characteristics, treatments [14], and mortality data [15] of patients with different HF phenotypes has been recently published in Turkey.

More registry studies are required to understand better the profile of the patients with HF in our country. In this multicenter HF registry study called SMYRNA-HF, it was aimed to determine the profile of outpatients with HF in our country, to define the baseline characteristics of the patients, to examine whether these features differ between different HF phenotypes, and to evaluate the treatment of the patients.

METHODS

The SMYRNA-HF study is an ongoing prospective national registry study including outpatients with HF with a plan to recruit patients from centers in Turkey under the leading role of Izmir. In this registry study, long-term follow-up of the patients is aimed. The current study, which provides the data from the preliminary cohort of the SMYRNA-HF registry, recruited patients from 9 centers between October 2019 and January 2021. Patients with acute decompensated HF and hospitalized with acute decompensation within the last month were not considered.

Demographic and clinical characteristics of the patients, laboratory, electrocardiographic and echocardiographic findings, and medications at the time of enrolment were recorded. The diagnosis and phenotype categorization of patients with HF were made according to the current guidelines. The patients were classified into three HF phenotype groups; HF with reduced ejection fraction (HFrEF) if they had left ventricular ejection fraction (LVEF) ≤ 40%, HF with mildly reduced ejection fraction (HFmrEF) if they had LVEF between 41% and 49%; and HF with preserved ejection fraction (HFpEF) if they had LVEF ≥ 50% [16, 17]. The New York Heart Association (NYHA) class was used to determine the functional capacities of patients.

Ethical approval for this study was provided by the Non-Invasive Research Ethics Committee of Dokuz Eylül University (date: 16.09.2019, approval No: 2019/23-39), the coordinating center, and each center approved participation in the study in accordance with established legislation.

Statistical Analysis

The Kolmogorov-Smirnov test was used to evaluate whether the data showed a normal distribution. Since all continuous variables showed a non-normal distribution, non-parametric analysis methods were used. The continuous variables were expressed as median (quartile 1-3), and the categorical variables were presented as numbers (%). Differences in continuous variables between the three groups according to HF phenotype were analyzed with the Kruskal Wallis-H test. Differences between categorical variables were analyzed with the chi-square test. The significance level for all tests was determined as $p < 0.05$. Statistical analysis was performed using the IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 298 patients with HF were included in this analysis. 57% of the patients were classified as having HFrEF, 33.3% as having HFpEF, and 9.7% as having HFmrEF (Fig. 1). The median age of the patients was 67 (59-76) years, and 37% of them were female. Previous acute coronary syndrome (ACS) was present in 54.7% of the patients. In addition, 30.9% of the patients had hypertension, and 28.2% had diabetes mellitus (DM). In the whole cohort, the median LVEF was 40% (30%-52%).Beta-blocker use was reported in 85.6%, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB) use was reported in 63.4%, mineralocorticoid receptor antagonist (MRA) use was reported in 40.9%, and daily loop diuretic use was reported in 79.2%. In the whole cohort, the frequency of use of angiotensin receptor neprilysin inhibitors (ARNI) and sodium-glucose co-transporter-2 (SGLT2) inhibitors was 4.4% and 1.3%, respectively. The frequency of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) was 10.4% and 2.3%, respectively. The rhythm was atrial fibrillation in 24.2% of the patients. The baseline characteristics of patients, including demographic, clinical features, electrocardiographic and echocardiographic findings, laboratory parameters, and medications are presented in Table 1.

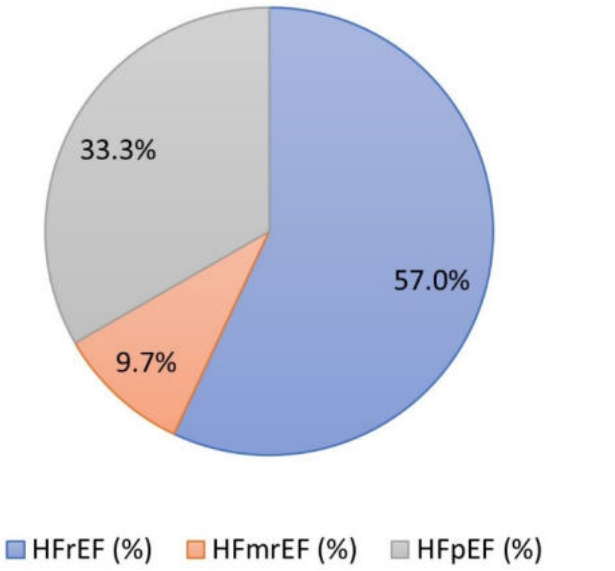

Fig. 1. Ratio of patients according to heart failure phenotypes. HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction.

Median LVEF was 31.5% in the patients with HFrEF, 45% in HFmrEF, and 55% in HFpEF ($p < 0.001$). Age, frequency of DM, use of ACEI/ARB, use of beta-blocker, use of daily loop diuretic, heart rate, blood urea nitrogen levels, lipid profiles, hemoglobin, white blood cell, platelet levels were similar among three HF phenotypes (Table 2). Female gender was more common in the patients with HFpEF ($p = 0.003$). The median body mass index (BMI) value ($p < 0.001$) and the frequency of hypertension, atrial fibrillation was higher ($p < 0.001$ and $p = 0.015$, respectively), and the frequency of previous ACS was lower in the patients with HFpEF ($p < 0.001$). The median systolic blood pressure (SBP), diastolic blood pressure (DBP), and sodium level were lower in patients with HFrEF ($p < 0.001$, $p < 0.001$, $p = 0.002$, respectively). The median creatinine level and the frequency of use of MRA were higher in patients with HFrEF ($p = 0.003$, $p < 0.001$, respectively). In addition, there were no significant differences among the groups with regard to frequency of poor NYHA functional class (NYHA class III-IV) ($p = 0.210$) and echocardiographic parameters, including left atrium diameter, right ventricle diameter, and systolic pulmonary artery pressure (SPAP) ($p = 0.272$, $p = 0.094$, $p = 0.309$, respectively). Left ventricle end-diastolic diameter (LVEDD), end-systolic diameter (LVESD) were higher ($p < 0.001$, $p < 0.001$), and tricuspid annular plane systolic excursion (TAPSE) was lower in patients with HFrEF ($p = 0.024$). The comparison results of patients' characteristics according to HF phenotypes are presented in Table 2.

DISCUSSION

The SMYRNA-HF study provides a real-life dataset of chronic HF outpatients with different HF phenotypes in reference to the European Society of Cardiology (ESC) guidelines published in 2021 [17]. SMYRNA-HF registry study aimed to reflect outpatients with HF in our country. The characteristics of the patients for each HF phenotype were determined and whether patients were on guideline-directed medical therapy or not considered thoroughly in this analysis. Of note, these patients have been on follow-up for outcomes. This registry overall purposes of determin-

Table 1. Baseline characteristics of the whole cohort (n = 298)

	Median (Quartiles 1-3)
Age (years)	67 (59-76)
Female gender, n (%)	110 (37.0)
Body mass index (kg/m^2)	27.26 (24.24-31.33)
NYHA functional classification, n (%)	
Class I/II	218 (73.2)
Class III/IV	80 (26.8)
Systolic blood pressure (mmHg)	120 (110-136.5)
Diastolic blood pressure (mmHg)	70 (69.5-80)
Previous acute coronary syndrome, n (%)	163 (54.7)
Diabetes mellitus, n (%)	84 (28.2)
Hypertension, n (%)	92 (30.9)
Atrial fibrillation, n (%)	72 (24.2)
Heart rate (beats/min)	75 (66-83.5)
ICD, n (%)	31 (10.4)
CRT-D, n (%)	7 (2.3)
Echocardiography characteristics	
LV end-diastolic diameter (mm)	53 (48-58)
LV end-systolic diameter (mm)	39.5 (34-46)
LVEF (%)	40 (30-52)
SPAP (mmHg)	38 (34.5-45)
TAPSE (mm)	16 (14-18)
Left atrium (mm)	44 (41-48)
Right ventricle (mm)	37 (32-40.3)
Medication, n (%)	
Use of ACEI/ARB	189 (63.4)
Use of betablocker	255 (85.6)
Use of MRA	122 (40.9)
Use of daily loop diuretic	236 (79.2)
Use of SGLT2 inhibitor, n (%)	4 (1.3)
Use of ARNI, n (%)	13 (4.4)
Laboratory findings	
Glucose (mg/dL)	110 (95-145)
Blood urea nitrogen (mg/dL)	18.5 (15-27.8)
Creatinine (mg/dL)	1.0 (0.8-1.3)
Sodium (mEq/L)	139 (136-141)
Potassium (mEq/L)	4.4 (4.1-4.8)
Hemoglobin (g/dL)	13.0 (11.4-14.2)
Platelet ($\times 10^9$/L)	245.5 (201.0-311.8)
White blood cell ($\times 10^9$/L)	8.0 (6.7-10.0)
Low-density lipoprotein (mg/dL)	100.5 (75.8-128.0)
High-density lipoprotein(mg/dL)	43.0 (36.0-54.0)
Triglyceride (mg/dL)	115.0 (90.8-170.0)
Total cholesterol (mg/dL)	172.0 (141.8-200.0)

NYHA = New York Heart Association, ICD = implantable cardioverter defibrillator, CRT-D = cardiac resynchronization therapy-defibrillator, LV = left ventricle, LVEF = left ventricular ejection fraction, SPAP = systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, ACEI = angiotensin- converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist, SGLT2 = sodium-glucose cotransporter-2, ARNI = angiotensin receptor neprilysin inhibitor

Table 2. Comparison of baseline characteristics according to heart failure phenotypes (n = 298)

	HFrEF (n = 170)	HFmrEF (n = 29)	HFpEF (n = 99)	*p* value
Age (years)	66 (58-75)	67 (57-75)	69 (62-77)	0.289
Female gender, n (%)	51 (30.2)	9 (31.0)	50 (50.5)	**0.003***
Body mass index (kg/m^2)	25.9 (23.4-29.4)	28.1 (25.1-32.1)	29.4 (26.3-33.5)	**< 0.001***
NYHA functional classification – Class III/IV, n (%)	46 (27.1)	4 (13.8)	30 (30.3)	0.210
Systolic blood pressure (mmHg)	120 (110-130)	130 (120-140)	130 (115-140)	**< 0.001***
Diastolic blood pressure (mmHg)	70 (62-75)	80 (70-90)	70 (70-80)	**< 0.001***
Previous acute coronary syndrome, n (%)	110 (64.7)	21 (72.4)	32 (32.3)	**< 0.001***
Diabetes mellitus, n (%)	42 (24.7)	11 (37.9)	31 (31.3)	0.240
Hypertension, n (%)	30 (17.6)	13 (44.8)	49 (49.5)	**<0.001***
Atrial fibrillation, n (%)	35 (22.7)	3 (11.1)	34 (35.4)	**0.015***
Heart rate (beats/min)	75.5 (67-85)	70 (61-80)	76 (67-84)	0.177
Echocardiography characteristics				
LV end-diastolic diameter (mm)	56 (52-61.5)	52 (48-56)	48 (43-51)	**< 0.001***
LV end-systolic diameter (mm)	44 (40-50)	38.5 (37-41)	33 (30-36)	**< 0.001***
LVEF (%)	31.5 (25-40)	45 (45-46.5)	55 (51-60)	**< 0.001***
SPAP (mmHg)	40 (34-46)	35 (30-40)	38 (35-45)	0.309
TAPSE (mm)	16 (13-18)	16.5 (16-19)	17 (15-19)	**0.024***
Left atrium (mm)	44 (41-48)	43 (38-46)	45 (42-48)	0.272
Right ventricle (mm)	38 (33-40)	32 (28-39)	37 (31-41)	0.094
Medication, n (%)				
Use of ACEI/ARB	108 (63.5)	20 (69.0)	61 (61.6)	0.769
Use of betablocker	151 (88.8)	26 (89.7)	78 (78.8)	0.063
Use of daily loop diuretic	137 (80.3)	19 (65.5)	80 (80.8)	0.161
Use of MRA	90 (52.9)	12 (41.4)	20 (20.2)	**< 0.001***
Laboratory findings				
Glucose (mg/dL)	110.5 (96-148)	111 (85.5-138)	108 (94.5-131)	0.491
Blood urea nitrogen (mg/dL)	20 (16-30)	17.5 (16.5-20.5)	17 (14-24)	0.059
Creatinine (mg/dL)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	**0.003***
Sodium (mEq/L)	138 (136-140)	140 (138-142)	140 (137-141)	**0.002***
Potassium (mEq/L)	4.4 (4.08-4.8)	4.4 (4.2-4.6)	4.4 (4.1-4.8)	0.986
Hemoglobin (g/dL)	13 (11.5-14.3)	12.7 (11-13.8)	12.9 (11.4-14.1)	0.878
Platelet ($\times 10^9$/L)	242 (193-307)	234 (207-299)	255 (209-319.5)	0.253
White blood cell ($\times 10^9$/L)	7.9 (6.8-9.5)	9.4 (7-11.4)	8.1 (6.4-10)	0.210
Low-density lipoprotein (mg/dL)	99 (77.5-124.5)	90 (63-143)	104 (77-128)	0.801
High-density lipoprotein(mg/dL)	44 (36-53)	41 (35-56)	43.5 (37-54)	0.905
Triglyceride (mg/dL)	113 (83-155)	139 (105-195)	114.5 (91-161)	0.541
Total cholesterol (mg/dL)	173 (142-210)	161 (144-200)	170.5 (141-194)	0.804

Data are presented as median (Quartiles 1-3) unless otherwise stated. *$p < 0.05$. HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, NYHA = New York Heart Association, LV = left ventricle, LVEF = left ventricular ejection fraction, SPAP = systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist

ing the barriers to the management of HF and identifying predictors of mortality and recurrent hospitalization. Baseline characteristics of this preliminary cohort were presented herein.

In the ESC registry study, including outpatients with HF, 60% of the patients had HFrEF, 24% had HFmrEF, and 16% had HFpEF [18]. Similar to the ESC registry study, 57% of the patients were found to have HFrEF in our study. While 42.9% of patients with HF had ischemic etiology in the ESC registry study, this rate was 54.7% in our study. Similar to our study, ischemic etiology was found in more than half (52.6%) of the patients in the chronic HF group of the SELFIE-TR study [14]. The higher rate of ischemic etiology in HF (i.e., previous ACS) in our country compared to Europe indicates that we need to move faster in diagnosis and hyperacute treatment, especially in ST-segment elevation myocardial infarction, and improve the quality of primary percutaneous coronary interventions [19]. In our study, the frequency of HFpEF was found to be 33.3%. In the SELFIE-TR study, the frequency of HFpEF was only 7.3% in the whole cohort [14]. In general, patients with HFpEF have multiple comorbidities; the diagnosis with HF and follow-up by a cardiologist is delayed due to overlapping symptoms. Compared to the SELFIE-TR study, the higher frequency of HFpEF in our study can be interpreted as an increased awareness of HFpEF in both physicians and patients.

In general, patients with HFpEF are older and more frequently women than patients with HFrEF and HFmrEF. Patients with HFpEF have more frequent atrial fibrillation compared to patients with HFrEF and HfmrEF [20]. In the HAPPY study investigating the prevalence of HF in Turkey, the male gender ratio was higher in the subgroup of HF with LVEF < 50%, and the female gender ratio was higher in the subgroup of HF with LVEF ≥ 50% [21]. In our study, half of the patients with HFpEF were women; although the median age was numerically higher in patients with HFpEF, it did not reach statistical significance.

HFmrEF is more akin to HFrEF than the HFpEF phenotype; patients with these two phenotypes (HFmrEF and HFrEF) have a higher male gender ratio, younger age, are more likely to have ischemic etiology, and are less likely to have atrial fibrillation compared to patients with HFpEF [22-24]. In the APOLLON study comparing the clinical features of patients with HFmrEF and HFpEF in Turkey, the mean ages of the two groups were similar; the female gender ratio was higher in patients with HFpEF, and the ratio of previous myocardial infarction was higher in those with HFmrEF [25]. Consistent with the literature, in our study, approximately 70% of patients with HFmrEF and HFrEF were male, their median age was similar, and the underlying ischemic etiology was higher in patients with HFmrEF and HFrEF than in those with HFpHF. While more than half of the patients with HFmrEF and HFrEF had previous ACS, this rate was 32.3% in those with HFpEF.

Obesity is one of the major causes of HFpEF [20, 26-28]. BMI assessment is important in patients with HF. In our study, the HF phenotype with the highest BMI was HFpEF. Hypertension is the most important cause of HFpEF [29]. In our study, nearly half of the patients with HFpEF were found to have hypertension. In our study, the proportions of patients with NYHA functional class III-IV were similar in patients with HFrEF and HFpEF (27.1% vs. 30.3%, respectively) along with similar age distribution. However, the NYHA functional class assessment is based on symptoms only. Non-cardiac comorbidities are more common in HFpEF, and it may be difficult to distinguish whether symptoms are primarily and solely caused by HF or by other non-cardiac diseases [30]. Therefore, the frequency of patients with poor NYHA functional class may have been found to be similar in patients with HFrEF and HFpEF.

In our study, SBP and DBP were found to be lower in patients with HFrEF. Similarly, in the ESC registry study, SBP was lower, and hypotension (SBP ≤ 110 mmHg) was more frequent in patients with HFrEF [13]. These results may simply be associated with a high frequency of hypertension in patients with HFpEF.

Most of the deaths are caused by electrical disturbances, including ventricular arrhythmias in patients with HFrEF. ICD or CRT-D are recommended to reduce mortality in these patients when specific indications are provided [17]. In our study, all patients with ICD/CRT-D were in the HFrEF phenotype. The rate of ICD and CRT-D were 18.2% and 4.1%, respectively in patients with HFrEF. In the ESC registry study, the same rates were 34.8 % and 22.4 %, respectively [18]. Although it is difficult to make a comparison due to the small number of patients, the rate of patients with

ICD/CRT-D was low in our cohort. In the CRT Survey-II study, 11,088 patients who are candidates for CRT were recruited from 288 centers, the median number of CRT implantations per year in Turkey was found to be significantly lower than in other European countries [31]. Management of HF especially device threapy is expensive [32]. The lower rate of device therapy in HF in our country may be due to cost-effectiveness problem. Conservative approach of patients and physicians may also be another reason. Nevertheless, it would be appropriate to improve the implementation of ICD and CRT-D in eligible patients.

The ACE-I/ARB/ARNI, beta-blocker, and MRA triad are the cornerstone of treatment for patients with HFrEF [13, 33, 34]. In these study, 63.5% of patients with HFrEF were on ACE-I or ARB and 88.8% of those on beta-blocker. In the ATA study, including patients with HFrEF from Turkey, renin-angiotensin system (RAS) inhibitors and beta-blocker usage were 78.2% and 90.2%, respectively [35]. In our country, the rate of use of beta-blocker was satisfactory in patients with HFrEF, but the same cannot be said for RAS inhibitors. Replacement of ACE-I or ARB with ARNI is recommended in symptomatic patients with ambulatory HFrEF [17], but only 7.6% of patients with HFrEF were on ARNI in this cohort. The low usage rate of this drug can be explained by the lack of reimbursement in our country. SGLT2 inhibitors have been reported to reduce the risk of death in patients with HFrEF [36, 37]; thus, SGLT2 inhibitors were recommended for all patients with HFrEF in the recent ESC guideline [17]. In our study, only 2.3% of the patients with HFrEF were on SGLT2 inhibitors. This rate was quite low. However, SGLT2 inhibitors have recently entered the guidelines. We think that the use of SGLT2 inhibitors will increase significantly in the coming years.

There are no specific studies on medical therapy in patients with HFmrEF [17]. However, many patients with HFmrEF are also treated with ACE-I/ARBs because of ischemic heart disease, hypertension, or systolic dysfunction after ACS. A beta-blocker is used in many patients with HFmrEF because of atrial fibrillation or angina [17]. Of note, to date, only empagliflozin has been demonstrated to improve outcomes in patients with HFpEF [38]. Nevertheless, most of the patients with HFpEF have hypertension and atrial fibrillation; these patients are also on ACE-I/ARBs and beta-blockers. In a large randomized controlled study involving 4822 patients with HFpEF, it was reported that 86% of the patients were on ACE-I/ARBs, and 80% of them were on beta-blockers [39]. In our study, we think that the rate of use of ACE-I/ARBs and beta-blockers was similar in all three HF phenotypes due to other compelling cardiovascular indications. MRAs are recommended for all patients with HFrEF to reduce mortality [40, 41], but MRAs do not have clear-cut indications for patients with HFpEF and HFmrEF. Consistent with these findings, the use of MRAs was found to be significantly higher in patients with HFrEF in our study. However, only 52.9% of the patients with HFrEF were on MRAs; this ratio was 55.4% in the ATA study [35]. In the light of these data, it should be aimed to increase the use of RAS inhibitors and MRAs in patients with HFrEF unless severe renal dysfunction, symptomatic hypotension and hyperkalemia. In the Hit-Point trial, the clinical benefits of enhanced HF education with a telephone follow-up program were demonstrated in patients with HFrEF [42]. Therefore, these patients should be monitored more closely to improve patient compliance and optimize medical therapy.

Limitations

First, our study has a small sample size. In addition, the patients were recruited only from cardiology clinics, and we did not consider patients with chronic HF examined by other physicians such as internists. Since echocardiography was administered during routine outpatient practice, it was limited to assessing cardiac functions and structure. Detailed echocardiography and hemodynamic assessment were not part of the evaluation of these patients in the majority of the cases. Due to the multicenter nature of our study, standardization could not be made for LVEF measurement. Some patients with LVEF values, especially close to the cutoff values, may have been misclassified due to the differences between the performing physicians.

CONCLUSION

Our study presented the baseline characteristics of patients with HF in our country. It was determined that there were significant differences in patients with dif-

ferent HF phenotypes in terms of BMI, gender, frequency of having ischemic etiology, hypertension, and atrial fibrillation. Treatment approaches were generally in accordance with the guidelines. In addition, although the rates are low, new treatment approaches recommended in the most recent guidelines seem to enter clinical practice.

Authors' Contribution

Study Conception: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., BA, İG, CA, YÖ, MKK, EK, MÖ, TE, NY, MBY; Study Design: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., BA, İG, CA, YÖ, MKK, EK, MÖ, TE, NY, MBY; Supervision: BŞ, Ah.Çe., MBY; Funding: N/A; Materials: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., MÖ, TE, MBY; Data Collection and/or Processing BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., MÖ, TE; Statistical Analysis and/or Data Interpretation: BŞ, MBY; Literature Review: BŞ, MBY; Manuscript Preparation: BŞ, MBY and Critical Review: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., BA, İG, CA, YÖ, MKK, EK, MÖ, TE, NY, MBY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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