ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Single-Center Retrospective Evaluation of Clinical Features and Life Expectancy in Mid-Range/Reduced Left Ventricular Ejection Fraction Heart Failure Patients Who Died During Hospitalization

Hastanede Yatış Sırasında Ölen Sınırda/Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliği Hastalarında Klinik Özelliklerin ve Yaşam Süresinin Tek Merkezli Retrospektif Değerlendirilmesi

Ferhat DİNDAŞ[a], Okan Onur TURGUT[a], Mehmet Birhan YILMAZ[a]

[a]Sivas Cumhuriyet University Faculty of Medicine, Department of Cardiology, Sivas, TURKEY

ABSTRACT Objective: Today, despite medical developments the frequency of heart failure is increasing. The current guidelines have categorized patients with heart failure (HF) by their phenotypes to better explain them. In our study, we aimed to compare the basic clinical features, drug treatment and the life expectancy in HF phenotypes who died during hospitalization. **Material and Methods:** 100 consecutive patients who admitted with HF between 2011 and 2018 and died of cardiac cause during last hospitalization were evaluated. Patients with left ventricle ejection fraction (LVEF) 41-49% and N-terminal pro-B type natriuretic peptide (NT-proBNP) level >125 pg/mL were classified in the study as HFmrEF. Patients with EF% ≤40 NT-proBNP level >125 pg/mL were classified in the study as HFrEF. There were 50 patients from each HF group. Patients' demographic features, major laboratory parameters, drug treatments and life expectancy were evaluated in retrospective analysis. SPSS version 17.0 program was used for statistical analysis. p<0.05 was considered statistically significant. **Results:** The LVEF values of HFrEF and HFmrEF patients were 30% (15-38) and 45% (40-49), respectively. There was no significant difference between groups in drug treatment. The life expectancy values of the groups were 15 (1-61) months in the HFmrEF group and 11 (1-49) months in the HFrEF group (p=0.043). **Conclusion:** In our study, it was concluded that the demographic characteristics of HFrEF and HFmrEF patients were different. The life expectancy in HFmrEF group was longer than in HFrEF group.

Keywords: Heart failure; death; demography; cardiology service, hospital; life expectancy

ÖZET Amaç: Günümüzde, medikal gelişmelere rağmen kalp yetersizliği (KY) sıklığı artmaktadır. Mevcut kılavuzlar kalp yetersizliği hastalarını daha iyi açıklamak için fenotiplerine göre sınıflandırmıştır. Biz çalışmamızda, hastanede ölen KY fenotiplerinin temel klinik özelliklerini, ilaç tedavilerini ve yaşam sürelerini kıyaslamayı hedefledik. **Gereç ve Yöntemler:** 2011-2018 yılları arasında kalp yetersizliği ile başvuran ve son hastaneye yatışı sırasında kardiyak nedenden ölen 100 ardışık hasta değerlendirildi. Çalışmada EF% 41-49 ve N-terminal pro-B tipi natriüretik peptit (NT-proBNP) düzeyi >125 pg/mL olan hastalar SEF-KY olarak sınıflandırıldı. Çalışmada EF%≤40 ve NT-proBNP düzeyi >125 pg/mL olan hastalar DEF-KY olarak sınıflandırıldı. Her iki KY grubunda 50 hasta vardı. Retrospektif analizimizde hastaların demografik özellikleri, başlıca laboratuvar parametreleri, ilaç tedavileri ve tahmini yaşam süreleri değerlendirildi. İstatistiksel incelemede SPSS versiyon 17.0 programı kullanıldı. p<0,05 istatiksel olarak anlamlı kabul edildi. **Bulgular:** DEF-KY ve SEF-KY hastalarının EF değerleri sırasıyla %30 (15-38) ve %45 (40-49) idi. İlaç tedavilerinde gruplar arasında anlamlı bir fark yoktu. Grupların yaşam sürelerinin değerleri SEF-KY grubunda 15 (1-61) ay ve DEF-KY grubunda 11 (1-49) ay olarak saptandı (p=0.043). **Sonuç:** Çalışmamızda DEF-KY ve SEF-KY hastalarının demografik özelliklerinin farklı olduğu sonucuna varıldı. SEF-KY grubundaki yaşam süresi DEF-KY grubuna göre daha uzundu.

Anahtar Kelimeler: Kalp yetersizliği; ölüm; demografi; kardiyoloji servisi, hastane; yaşam beklentisi

Correspondence: Ferhat DİNDAŞ
Sivas Cumhuriyet University Faculty of Medicine, Department of Cardiology, Sivas, TURKEY/TURKEY
E-mail: frhtys@hotmail.com

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Heart failure (HF) a clinical complex that has become a real public health problem, may not only appear alone but also as a morbidity of other cardiovascular diseases.[1,2] Therefore, despite all the advances that modern medicine has brought to the field of cardiology, the mortality of HF patients is still very high.[3] Determining the phenotypes of patients with HF has serious importance in clinical practice in terms of prognosis and treatment.[4] The results of effective HF treatment have manifested itself in certain patient groups, resulting in the classification of HF patients.[5] In 2013, the American Society of Cardiology defined HF patients with LVEF 41-50% as borderline.[6] The European Heart Association then updated their HF guideline in 2016, and one of the most important innovations of the guideline is that it divides patients with HF into three groups according to their LVEF values.[7] This grouping, which is more accepted by clinicians, consists of protected ejection fraction HF (HFpEF), HFrEF and HFmrEF. HmrHF patients, identified as a gray area between HFpEF and HFrEF patients, have different features than other groups such as diagnosis, demographic characteristics, comorbidities.[8] In spite of these differences, since the HFmrEF group was included in the HFpEF or HFrEF group in the initial HF studies, it shows similar characteristics with other groups such as hospitalization and mortality.[9] There have recently been many studies in the field of HFrEF. In these studies, large data were established that provided significant improvements in patients' prognosis.[10] However, the clinic, prognosis and treatment of the HFmrEF group, which constitutes a quarter of all HF patients, are still unclear.[11,12] In our country, studies describing the subgroups of HF patients with an increasing number are limited. In our study, we aimed to investigate the demographic characteristics and life expectancy of patients with HFrEF and HFmrEF comparatively.

MATERIAL AND METHODS

SETTING

We analyzed data from tertiary care and academic Cumhuriyet University Medicine Faculty Hospital.

PATIENTS

We reviewed the medical records of all heart failure patients admitted from 2011 to 2018. The study population consisted of patients diagnosed as HFmrEF and HFrEF according to current guidelines. In our retrospectif analyse, we included 100 consecutively patients who were identified all stage of the New York Heart Association (NYHA) classification in admission and who died of cardiac cause during last hospitalization. We excluded the patients who were younger than 18 years old, admitted to the hospital once, had non-cardiac cause in admission for last hospitalization, diagnosed with advanced cancer, died of non-cardiac cause and died in another hospital or were transported before death. Patients with LVEF 41-49% and N-terminal pro-B type natriuretic peptide (NT-proBNP) level >125 pg/mL were classified in the study as HFmrEF.[7] Patients with EF% ≤40 NT-proBNP level >125 pg/mL were classified in the study as HFrEF.[7] There were 50 patients in the HFrEF group and 50 patients in the HFmrEF group. Functional class was scored according to the NYHA classification scale in initial admission. In our study, demographic characteristics of patient groups, including age and gender, were evaluated.

LABORATORY ANALYSIS

An automated blood cell counter (Beckman Coulter analyzer, California) was used for complete blood count. Glucose, TG, LDL, HDL, BUN, creatinine, sodium, potassium, calcium, total protein, albumin, ALT, AST, LDH, HGB, HCT, WBC, RBC, PLT, NT-proBNP values in the blood taken of the first of the patient groups were examined. Transthoracic echocardiography (TTE) was performed with Vivid E7 (GE Vingmed Ultrasound) echocardiography device and MS5 (1.5-4.5 MHz) ultrasound probe in all patients. All patients were evaluated by the same echocardiography specialist. Left ventricular ejection fraction (LVEF) was measured by the Simpson method in initial admission. The evaluation of the treatment of the patients was made by considering the drugs they used in their last hospitalization. The evaluation of the groups' life expectancy was calculating the time from their diagnosis of HF and to the last

hospitalization. Absolute time was calculated as month.

STATISTICAL ANALYSIS

All analyses were done in SPSS 17.0 for Windows package software with a 95% confidence interval and 0.05 significance level. Nominal and ordinal data were described with frequency analysis, and measurement data were described by mean and standard deviation values. Kolmogorov Smirnov test was used to analyze whether the measurement values fit the normal distribution. Independent Sample T-Test was used for the dual group difference of the normally distributed parameters, and Mann Whitney U test was used for the dual group difference of the parameters that did not fit the normal distribution. For the difference analysis of the nominal and ordinal data, the Chi-Square Test and the Chi-square Similarity Ratio (likelihood ratio) analyses were used.

ETHICS

Institutional permission from the university hospital where the study was conducted and approval from the ethics committee of the university were obtained. Ethics committee approval code numbered 2018-11/31 was obtained on 07.11.2018. This research was carried out in accordance with the principles of the Helsinki Declaration. The eboard waived there quirement for informed patient consent because of the retrospective nature of the study.

RESULTS

One hundred consecutive patients (62% male, 38% female) who were diagnosed with HF and died due to cardiac causes between 2010/2018 were included in our study. 50 patients were in the HFrEF group and 50 patients were in the HFmrEF group. 20% of all patients in the groups were diagnosed with HF for the first time in 2011, 20% in 2012, 28% in 2013, 16% in 2014, 8% in 2015, 4% in 2016, and 4% in 2017. The baseline characteristics of the groups were similar (Table 1). There was no significant difference between the groups in terms of glucose, TG, LDL, HDL, BUN, creatinine, sodium, potassium, calcium, total protein, albumin, ALT, LDH, HGB, HCT, WBC, RBC, PLT, NT-proBNP and NYHA class ($p>0.05$ for all variables). However, there was a significant difference in demographic characteristics of the groups in terms of age and gender. In the HFmrEF group, the rate of female was higher and older (HFrEF 26% female; HFmrEF 50% female, HFrEF 72.18±9.67 mean years, HFmrEF 75.86±8.55 mean years) ($p<0.05$ for all variables). AST median (min-max) values of the groups were 24 (8-750) U/L in the HFmrEF group and 31 (10-490) U/L in the HFrEF group. Although ALT and LDH values did not differ significantly between two groups, the AST value was statistically significantly higher in the HFrEF group ($p=0.021$). The median LVEF (min-max) values of HFrEF and HFmrEF were 30% (15-38) and 45% (40-49), respectively (Table 1, Figure 1). In addition, no significant difference was observed between the groups regarding the drugs routinely used by patients at the time of their last hospitalization. HFrEF group, there was angiotensin converting enzyme inhibitor (ACEI) use in 48.9%, beta beta blocker (BB) in 77.8%, calcium channel blocker (CCB) in 2.2%, loop diuretics (LD) in 82.2%, and mineralocorticoid receptor antagonist (MRA) in 57.8%. In the HFmrEF case group, there was ACEI use in 60%, BB in 82.5%, CCB in 12.5%, LD in 75.02%, and MRA in 60.0% ($p>0.05$ for all variables) (Figure 2). The life expectancy median (min-max) values of the groups were 15 (1-61) months in the HFmrEF group and 11 (1-49) months in the HFrEF group (Table 1). The life expectancy in the HFmrEF group was statistically significantly longer than in the HFrEF group ($p=0.043$).

DISCUSSION

The target of our single-center, retrospective study was to investigate the demographic characteristics, drug treatments, and life expectancy of patients with HF grouped according to the latest guidelines. It is the first study to evaluate the life expectancy of HF phenotypes in our country. The results of our study showed that life expectancy of patients with HFrEF had significantly shorter than patients with HFmrEF.

Cardiovascular diseases are among the most deadly diseases.[13,14] The frequency of cardiovascular

TABLE 1: Baseline characteristics of HFrEF and HFmrEF groups.

Baseline characteristics	HFrEF (n=50)	HFmrEF (n=50)	p
Demographics			
Male (%)	74.0	50.0	0.013 *
Age (years)	72.18±9.67	75.86±8.55	0.047 *
Laboratory findings			
Glucose (mg/dL)	123 (57-557)	119.5 (68-359)	0.452
Low density lipoprotein (mg/dL)	104.23±43.65	94.94±29.40	0.243
High density lipoprotein (mg/dL)	33.44±11.93	38.07±15.76	0.135
Blood urea nitrogen (mg/dL)	28.45 (7-85.7)	23 (8-90)	0.354
Serum creatinine (mg/dL)	1.25 (0.4-5.6)	1.15 (0.6-8.3)	0.722
Sodium (mg/dL)	136.2 (123-145)	137 (117-145)	0.299
Potassium (mg/dL)	4.52±0.66	4.47±0.67	0.717
Calcium (mg/dL)	8.7 (6.6-10.1)	8.7 (7-10.3)	0.402
Total protein (g/dL)	6.41±0.61	6.49±0.68	0.588
Albumin (g/dL)	3.51±0.54	3.58±0.44	0.513
Alanine transferase (U/L)	22.5 (5-497)	16 (5-396)	0.127
Aspartate transaminase (U/L)	31 (10-490)	24 (8-750)	0. 021 *
Lactate dehydrogenase (U/L)	280 (163-1791)	298.5 (128-806)	0.761
Hemoglobin (g/dL)	12.55±2.18	12.76±1.77	0.594
Hematocrit (%)	38.45±6.05	39.16±5.87	0.554
White blood cell ($x10^3$/μL)	10.26±4.30	10.36±4.79	0.914
Red blood cell ($x10^6$/μL)	4.49±0.80	4.46±0.70	0.834
Platelet ($x10^3$/μL)	256.45±105.17	247.62±111.93	0.687
NT-proBNP pg/ml	5096 (1890-11829)	10347.5 (6860-20393.5)	0.144
Left ventricular ejection fraction. %	30 (15-38)	45 (40-49)	< 0.001 *
Life expectancy (month)	11 (1-49)	15 (1-61)	0.043*
NYHA class n (%)			
I	4 (8.0)	3 (6.0)	0.980
II	16 (32.0)	18 (36.0)	
III	16 (32.0)	16 (32.0)	
IV	14 (28.0)	13 (26.0)	

Variables that fit the normal distribution were expressed as Mean±SD, variables that did not fit the normal distribution were indicated as median (minimum-maximum).

*p value less than 0.05 was.

risk factors in our society, whether they can be changed or not, has increased mortality and morbidity in this field. It was stated in the HAPPY study that the frequency of HF in our country was 2.8%.[15] According to another study conducted abroad, its prevalence can be up to 2%, and up to 8%, especially in the population over 65 years of age.[16] It is clear how great dangers await us in the field of HF in the future. Therefore, many studies and published guides around the world still continue in order to understand HF. In order to better explain the pathogenesis and clinical course of HF, patients with HF were divided into groups according to their EF values in the 2016 ESC guidelines.[7] Thanks to this change, the number of studies in patients with HF has greatly increased.[7] In the recent SELFIE-TR study based on the subgroups of HF in our country, 76% of alive HF patients were categorized as HFrEF, 16.7% HFmrEF, and 7.3 %HFpEF. Even if the incidence of HFrEF and HFpEF is different, the incidence of HFmrEF in our country is similar to that in the international clinical studies conducted.[13] In two large-scale studies conducted in 2015 and 2016, the accepted rate of HFmrEF in HF was within the range of 13-24%.[17-19] In

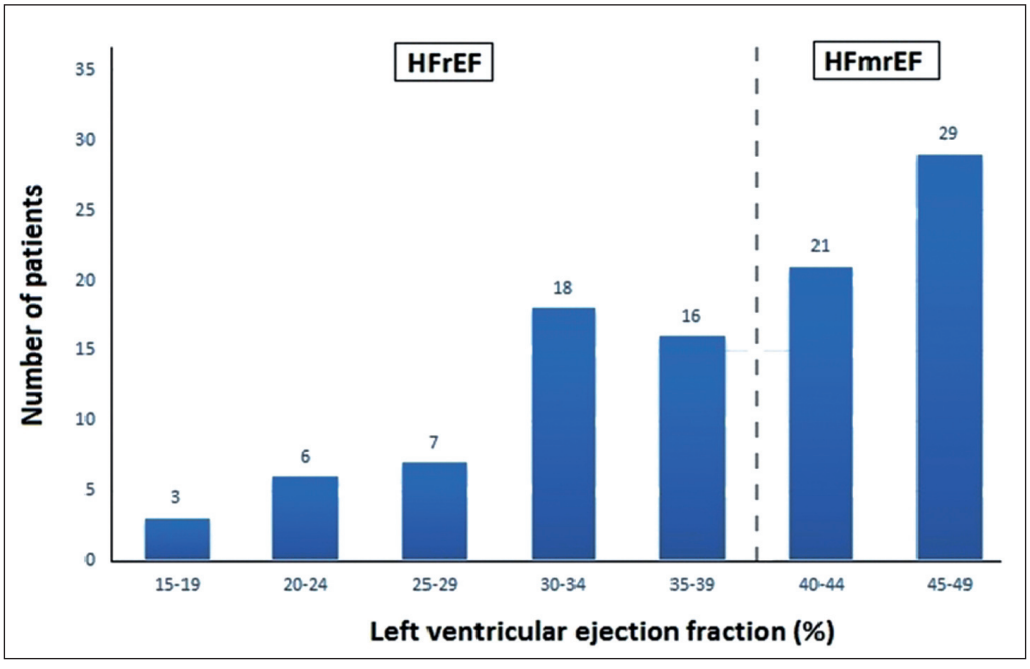

FIGURE 1: Histogram of left ventricular ejection fraction (LVEF) among patients with heart failure and who died of cardiac cause during hospital (n=100).

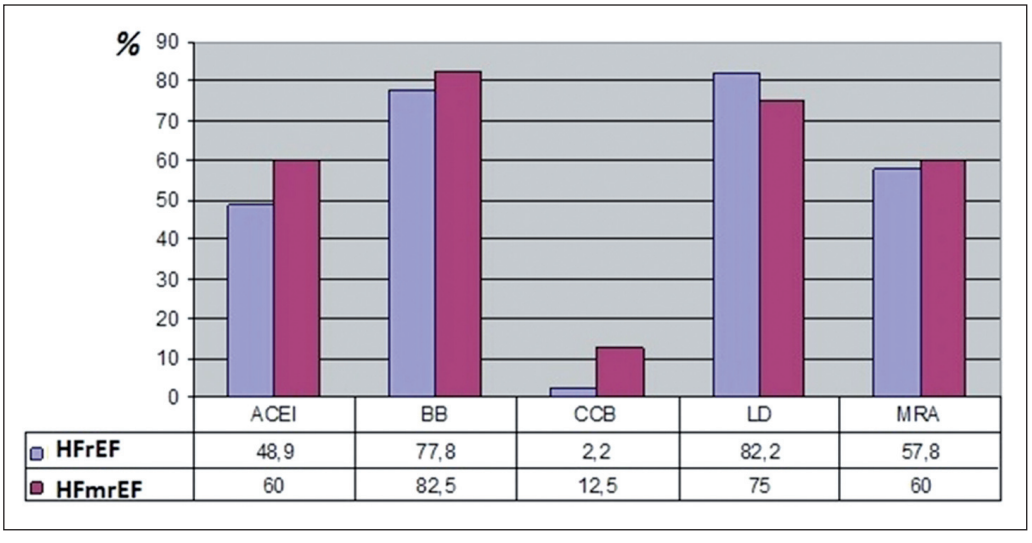

FIGURE 2: Angiotensin converting enzyme inhibitors, beta blocker, non-dihydropyridine calcium channel blocker, loop diuretics, mineralocorticoid receptor antagonist medication percentage of HFrEF and HFmrEF groups at the time of last hospitalization.

ACEI: Angiotensin converting enzyme inhibitors; BB: Beta blocker; CCB: Non-dihydropyridine group calcium channel blocker; LD: Loop diuretics; MRA: Mineralocorticoid receptor antagonist. Other abbreviations as in Table 1.

order to illuminate the basic clinical features of the HF subgroups, the basic clinical features are as important as the incidence and prevalence of the groups. As a result of the myocardial ischemia suffered by HFpEF patients and effective treatment of HFrEF patients, the HFmrEF zone was formed.[20,21] In other words, the HFmrEF zone formed by the transition between the groups can bear the features of the other two groups. In addition, this zone is not fixed and is open to dynamic fluctuations in EF.[22,23] As expected, the positive development in LVEF desired by clinicians is seen mostly in young patients.[21] HF in de-

veloped countries is diagnosed after the age of 70 and before the age of 70 in the developing countries.[24] In other words, the mean age of HF groups provides information not only for the demographic categorization, but also about clinical competence in countries. In the meta-analysis conducted in Denmark in 2017, the mean age of the HFrEF group was 72.3±9.3, and the mean age of the HFmrEF group was 73.6±9.8.[25] The SELFIE-TR study conducted in 2019, showing the snapshot of HF in our country, reported the mean age of the HFrEF group as 62.1±13.2, and the mean age of the HFmrEF group as 65.9±12.3.[13] In the study conducted on more than 1 million patients in America in the same year, the authors reported the mean age as 67.8±13.5 in the HFrEF group and 70.1±12.8 in the HFmrEF group.[23] These recent studies found that the mean age of the HFmrEF group was significantly higher than that of the HFrEF group. In our study, the mean age of the HFrEF patients was lower than the mean age of the HFmrEF patients. HFmrEF was statistically significantly more common in older individuals. These results inform us that the increasing elderly population in the world and the incidence of HFmrEF in the elderly will further increase the prevalence of HFmrEF in the coming years.[26] In the GWTG-HF (Get With The Guidelines) study conducted in 2014, the rate of male patients was 60% in the HFrEF group and 50% in the HFmrEF group.[19] In the recent studies conducted in different centers, the rate of men in the HFrEF group was higher than in HFmrEF.[27-30] In our study, the rate of male patients in the HFrEF group showed a significant difference compared to the HFmrEF group.

In a study conducted by Tsuji et al. in 2017 in Berlin, they reported that the levels of HGB, BUN, creatinine, TG, HDL, LDL and BNP levels differed significantly in the HFmrEF, HFrEF and HFpEF groups.[22] In our study, glucose, LDL, BUN, potassium, albumin, ALT, AST, LDH, RBC, PLT, NT-proBNP levels were higher in the HFrEF group. TG, HDL, creatinine, sodium, calcium, total protein, HG, HCT and WBC levels were higher in the HFmrEF group. According to the results of the difference analysis, AST levels showed a significant difference between the groups, while the differences in the other parameters between the groups were not statistically significant.

In a study conducted in 2019, ACEI and BB were reported to differ significantly in the HFmrEF, HFrEF and HFpEF groups, while they were lower in the HFpEF group and close to each other in the HFrEF and HmrHF groups.[23] Chen et al. did not find any difference between HFmrEF and HFrEF groups in terms of ACEI, BB, MRA in a 1-year observational study conducted in China in 875 patients in 2019.[31] In our study, drug treatments of the HFrEF and HFmrEF groups were similar. Even though there was no significant difference, only LD use was higher in the HFrEF group among the drug treatments. ACEI, BB and MRA use were higher in the HFmrEF group. This distinction shows us that the clinicians' approach to LD is arranged according to LVEF. The fact that CCB and ACE treatments are higher in the HFmrEF group shows both that they have sufficient arterial pressure and that the non-dihydropyridine group CCB is utilized for its relative contraindication of the patients in the HFmrEF group. Due to the presence of atherothrombotic identity in the HFmrEF group, its use for myocardial infarction has been proven by several studies.[23] Drug treatments in our study are not only specific to HF but also include ischemia treatment. It can be concluded that ischemia treatment is also more stringent in the HFmrEF group. Although the current guidelines report that the treatment of HFmrEF is like the HFpEF treatment, physicians have treated HFmrEF like HFrEF in real-world studies.[8,32] However, HFmrEF needs evidence-based treatment recommendations within its subgroups.[7]

In a retrospective study conducted in the black race in 2016, mortality due to all causes in HFmrEF was significantly lower compared to HFrEF.[33] In the OPTIMIZE-HF study, in-hospital mortality was evaluated and found significantly higher in the HFrEF group.[34] Curable predictors such as ischemic etiology, impaired renal function tests, and non-compliance with diet were found, which made a significant difference between the groups.[17,34] In a one-year observational study by Litian et al., HmrHF was found to be superior to HFrEF in both mortality and cardiovascular mortality.[35] In the same study, age and gender effects on mortality were evaluated, and no

significant results were reported.[35] A meta-analysis performed in 100,000 patients reported that the cardiovascular mortality of the HFmrEF group was lower than that of the HFrEF group.[25] The life expectancy from the first diagnosis to death was longer in patients with HFmrEF than patients with HFrEF. In the light of these informations, heart failure is a complicated clinical syndrome, not just stroke volume deficiency.

LIMITATIONS

The main limitation in our study are being single-centered and retrospective. The sample size were small and the number of descriptive markers were not abundant. All results of study does not generalize to all patients with HF. Also, we could not classify the patients according to their etiology. Finally, although our clinic is a respected clinic in the field of HF, the errors in the data entries cannot be completely ignored since the data sources are taken from the computer environment.

CONCLUSION

All the facts about HF are important for our country and the world. Patients with heart failure who are divided into HFrEF and HFmrEF groups with LVEF values below 50% according to the European Society of Cardiology (ESC) guidelines, were also different in our study. In the single-center retrospective analysis, we found that patients with HFrEF had a shorter life expectancy than patients with HFmrEF. Extensive and continued research is needed to understand how HF patients recover. In these researches, many descriptive factors should be examined in patients with heart failure.

Informing

Due to the presence of the name of the journal editor's among the authors, the assessment process of the study was conducted by the guest editor.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Birhan Yılmaz, Ferhat Dindaş;* ***Design:*** *Ferhat Dindaş, Okan Onur Turgut;* ***Control/Supervision:*** *Okan Onur Turgut, Mehmet Birhan Yılmaz;* ***Data Collection and/or Processing:*** *Ferhat Dindaş;* ***Analysis and/or Interpretation:*** *Okan Onur Turgut, Mehmet Birhan Yılmaz;* ***Literature Review:*** *Okan Onur Turgut, Ferhat Dindaş;* ***Writing the Article:*** *Ferhat Dindaş, Okan Onur Turgut, Mehmet Birhan Yılmaz;* ***Critical Review:*** *Okan Onur Turgut, Mehmet Birhan Yılmaz;* ***Knee Specialist, Language Editing:*** *Dilşad Bakır.*

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