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Research Article

Evaluation of Cardiorenal Metabolic Syndrome in Patients with Heart Failure with Preserved Ejection Fraction. How Aware Are We?

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Aim: Despite the prevalence of cardiorenal metabolic diseases (CRMD) in heart failure with preserved ejection fraction (HFpEF) patients and their significant complications, they are thought to be under-recognized and under-screened. In our study, we aimed to evaluate patients with HFpEF who were followed up in our internal medicine clinic.

Methods: Our retrospective and cross-sectional study included 348 patients with HFpEF. Patients were evaluated according to laboratory, demographic, clinical, electrocardiographic and ultrasonographic findings.

Results: Of the patients, 37.95% had diabetes mellitus, 23.3% had chronic kidney disease, 70.1% had hypertension and 59.2% had metabolic dysfunction-associated steatotic liver disease. The mean NT-proBNP level was 360.7 ± 13.7.

Conclusion: We recommend that HFpEF, which is associated with increased cardiovascular mortality and morbidity in patients with CRMD, should be screened clinically and with NT-proBNP and evaluated with transthoracic echocardiography if necessary.

Keywords: CRMD, Diabetes mellitus, HFpEF, Hypertension, MASLD

1. INTRODUCTION

Heart failure (HF) is a major public health problem, affecting millions of adults worldwide. According to the definition of heart failure with preserved ejection fraction (HFpEF) by the European Society of Cardiology (ESC), HFpEF is present in individuals with symptoms and signs of heart failure, structural and/or functional cardiac abnormalities, and/or elevated natriuretic peptides (NPs), and a left ventricular ejection fraction (LVEF) of at least 50%.[1]

HFpEF accounts for more than half of all HF cases and is the most common form of HF in patients over 65 years of age. Its incidence and

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prevalence increase as the population ages and the prevalence of metabolic disorders such as obesity, diabetes mellitus (DM) and hypertension (HT) increases.[2,3] HFpEF is associated with high morbidity and mortality. Although cardiovascular mortality is lower in HFpEF compared to low ejection fraction HF (HFrEF), recurrent hospitalizations are frequent and quality of life is poor. Patients with HFpEF have similarly high rates of recurrent hospitalizations as patients with HFrEF. The risk of death in patients with HFpEF increases with increasing comorbidity burden.[4,5]

HFpEF is frequently associated with metabolic comorbidities. More than 80% of patients are overweight or obese, approximately 20-40% have diabetes and more than 40% have hyperlipidemia.[6] Cardiorenal metabolic diseases (CRMD) such as coronary artery disease (CAD), chronic kidney disease (CKD) and DM are the leading and pathophysiologically interrelated causes of death and disability worldwide. CRMD frequently coexist in individuals with HFpEF.[7]

The approach to HF has changed significantly in recent years. Despite the high prevalence of HFpEF and its increasing frequency in the elderly population, it has now become an important healthcare problem due to a marked lack of evidence-based prognostic treatments.[8] There are currently very few effective treatments for HFpEF. Most of the treatments approved for HFrEF have been shown to be ineffective for HFpEF. This suggests that there are important differences in the basic pathophysiology and therapeutic targets in HFpEF compared to HFrEF. Our understanding and awareness of this highly prevalent disease needs to be improved.[9]

Despite the prevalence and significant complications of CRMD in patients with HFpEF, it is thought that it is often overlooked, under-recognized and under-screened in clinical practice. By increasing the awareness of clinicians about the risk and clinical importance of patients with HFpEF, early diagnosis and timely intervention, the disease can be reversed. In our study, we aimed to evaluate patients with HFpEF who were followed up in our internal medicine clinic.

2. MATERIAL AND METHOD

2.1. Study population and laboratory measurements

Our retrospective and cross-sectional study included 348 patients with HFpEF whose medical history and previous examinations did not constitute an obstacle to their inclusion in the study. HFpEF was defined according to the 2021 ESC HF guidelines. Our study included symptomatic adults with HFpEF, clinical evidence of HF and confirmed LVEF≥50% on transthoracic echocardiography (TTE).[1] In patients with HFrEF, acute coronary syndrome, malignancies, pregnant women were excluded from the study. Patients between 01.01.2024 and 31.12.2024 were included in the study. Patients followed up in the inpatient and outpatient departments of the internal medicine clinic were included in the study. Diabetes diagnosis was made according to ADA guidelines, hypertension diagnosis according to ESC guidelines, and chronic kidney disease diagnosis according to KDIGO guidelines.[10] The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. Adana City Training and Research Hospital Ethics Committee approved the study with decision number 318 dated 02.01.2025. After 5 minutes of rest, in a dim and quiet environment, blood pressure measurements were taken from both arms using a suitable cuff and pulses were monitored. Anthropometric body weight measurements were performed. Height was measured with the feet bare and together, leaning perpendicular to the height measurement ruler. BMI was calculated as body weight (kg) divided by the square of height in meters (BMI=kg/m2). Laboratory procedures of the study were performed in the Biochemistry Laboratory of Health Sciences University Adana Training and Research Hospital. Venous blood was drawn from the antecubital vein after at least 8 hours of overnight fasting from the patients and the control group during routine controls. Laboratory measurements of participants were measured using automated laboratory methods (Abbott Aeroset, Minneapolis, MN) and appropriate commercial kits (Abbott). The FIB-4

score is calculated using the formula: (Age × AST) / [Platelet count × (ALT)^(1/2)]. Electrocardiographic findings of the patients, QRS and QTC were evaluated.

All patients underwent liver US screening using a high resolution USG device (Philips EPIQ 7), using a 1- to 5-MHz high-resolution convex probe (Philips Health Care, Bothell, WA). The liver US was performed after a minimum fasting of 8 hours initially with B-mode US in the gray scale, which was used to assess the liver dimensions and parenchymal echogenicity. Subjects were evaluated independently by two experienced radiologists. The diagnosis of MASLD was made based on the presence of fatty liver on ultrasound, as well as a diagnosis of type 2 diabetes, obesity, or at least two metabolic risk factors (increased waist circumference, dyslipidaemia, hypertension, insulin resistance, or metabolic syndrome findings).[11] Echocardiography measurements were performed by cardiologists with at least 10 years of experience using the ACUSON SC2000 PRIME (Siemens Medical Solutions USA) echocardiography device and 4V1c (Siemens Medical Solutions USA) probe.

2.2. Statistical analysis

All analyses were performed using the statistical software package SPSS 24.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess whether the distribution of continuous variables was normal. Continuous variables in group data were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. The κ coefficient was used to examine the interobserver and intraobserver variability of USG measurements. Statistical significance level was accepted as $p<0.05$.

3. RESULTS

The mean age of the patients was 70.3± 11.7 years. 57.8% of the patients were male. The mean body mass index (BMI) was 30.1± 3.09. 37.95% of the patients had DM, 23.3% had CKD, 70.1% had HT, 49.7% had atrial fibrillation (AF), 23.9% had CAD, 57.2% had hyperlipidemia, and 59.2% had metabolic associated fatty liver disease (MASLD). The mean NTproBNP was 360.7± 13.7 and Fib-4 index was 1.09± 0.25. All other data in the study group are shown in table 1.

Table 1.

Demographic, clinical, laboratory, ultrasonography and electrocardiography findings of patients with heart failure preserved ejection fraction

Variables	Patient with HFpEF (n=348)
Age (year)	70.3 ± 11.7
Gender (F/M, %)	57.8 / 42.2
Systolic blood pressure (mmHg)	138.6 ± 16.0
Diastolic blood pressure (mmHg)	87.4 ± 10.5
Body mass index (kg/m2)	30.1 ± 3.09
Basal heart rate (pulse/minute)	91.8 ± 10.3
Smoking, %	51.4
Diabetes mellitus, %	37.6
Chronic kidney disease, %	23.3
Hypertension, %	70.1
Atrial fibrilasyon, %	49.7
Coronary artery disease, %	23.9
Stroke, %	11.8
Chronic pulmonary obstructive disease, %	8.3
Peripheral artery disease, %	10.1
Hyperlipidemia, %	57.2
US-confirmed MASLD diagnosis, %	59.2
Fasting plasma glucose, mg/dL	118.1 ± 29.1
White blood cell (10^3/ µL)	8.59 ± 2.08
Hemoglobin (g/dL)	12.3 ± 2.31
Platelet (10^3/ µL)	288.5 ± 106.5
e-GFR (mL/min)	58.4 ± 20.1
Sodium (mmol/L)	137.2 ± 4.43
Potassium (mmol/L)	4.28 ± 0.35
Albumin (g/dL)	3.83 ± 0.22
Aspartate aminotransferase (u/L)	24.3 ± 10.4
Alanine aminotransferase (u/L)	30.2 ± 11.4
Triglycerides, mg/dL	154.5 ± 31.9
HDL cholesterol, mg/dL	43.0 ± 10.2
LDL cholesterol, mg/dL	135.1 ± 28.5
CRP (mg/L)	2.94 ± 1.39
NTproBNP (pg/mL)	360.7 ± 113.7
Fib-4 index	1.09 ± 0.25
QTc duration, ms	410.6 ± 26.2
QRS duration, ms	90.8 ± 8.74

HDL: high density lipoprotein, LDL: low density lipoprotein, CRP: c reaktif protein, Fib-4: fibrosis-4, USG: ultrasonography, DM: diabetes mellitus, HFpEF: heart failure preserved ejection fraction, QTc: corrected QT

4. DISCUSSION

The main findings of our study are that patients diagnosed with HFpEF have a high prevalence of diseases called CRMD, mainly HT, MASLD, DM, CKD, hyperlipidemia. These findings indicate that HFpEF screening should be performed in patients with CRMD in outpatient clinics. While these patient groups are analyzed in detail for their own diseases in outpatient clinic examinations, they should also be screened for HFpEF clinically and with NT-proBNP and appropriate patients should be evaluated with TTE.

The total number of people with HFpEF continues to increase due to a the increasing prevalence of conditions that contribute to the pathophysiology. Growing and aging population and of HFpEF, such as obesity, HT and DM in high-income countries, it is estimated that approximately 50% of known HF patients have HFpEF. The number of prospective, population-based studies using natriuretic peptides and detailed echocardiography to assess the true prevalence of HFpEF is insufficient. It is possible that the prevalence of HFpEF is much higher than currently indicated. A meta-analysis of echocardiographic screening studies in the general population reported an 11.8% prevalence of overall HF in people aged 65 years and older in high-income countries. More than three-quarters of these cases are HFpEF.[12] Epidemiologic data show that the prevalence of HFpEF is increasing more frequently than HFrEF. These data make HFpEF the most common type of HF.[13]

Epidemiologic characteristics of HFpEF show an increasing prevalence with advancing age, female gender, and metabolic and inflammatory conditions that contribute to myocardial stiffness or comorbidities such as atrial fibrillation and valvular disease that worsen functional abnormality.[14] HFpEF is more common in women. In a study, HFpEF was found in 67% of cases in women with HF, whereas 42% of men with HF were shown to have HFpEF.[15] In our study, 57.8% of the patient group was female and the mean age was 70.3± 11.7 years. These data may suggest that gender may play a pathophysiologic role in this condition. The higher prevalence of HFpEF in women than men may be partly related to obesity and diabetes. Obesity is more common in women than men, and the association between obesity and incident HFpEF is greater in women. The fact that women have a longer life expectancy and develop comorbidities with advancing age may also explain why the prevalence of HFpEF increases with age and is higher in women. Low socioeconomic status is associated with a 62% higher risk of HF, including HFpEF.[16] In our study, we did not classify patients according to socioeconomic status. This may be related to the higher prevalence of negative behavioral risk factors such as physical inactivityin low socioeconomic societies, poor diet, smoking and medication nonadherence.

Cardiovascular and non-cardiovascular comorbidities are highly prevalent in patients with HFpEF and contribute significantly to the burden of morbidity and mortality in this population. The precise pathophysiologic mechanisms driving HF progression in HFpEF are still poorly understood. Current studies indicate that comorbidities such as obesity, HT, DM, chronic obstructive pulmonary disease and CKD contribute to a systemic proinflammatory state that increases endothelial dysfunction and HF progression. Since comorbidities disease progression may accelerate and contribute to functional intolerance in patients with HFpEF, systematic assessment and treatment of these comorbidities should be a fundamental treatment strategy.[17,18] Most patients with HFpEF have a history of HT. Lowering systolic blood pressure in patients with hypertension significantly and consistently reduces the incidence of HF. Uncontrolled HT may accelerate HF progression by exacerbating diastolic dysfunction, left ventricular hypertrophy, endothelial dysfunction and myocardial fibrosis.[18] In our study, the rate of HT in the patient group was 70.1%. In the PATENT-2 study conducted in Türkiye in 2012, the prevalence of HT was 30%. Above the age of 50 years, this rate reaches 50%.[19] Considering the increasing prevalence of hypertension in Turkey

and the high rate of HT in patients with HFpEF in our study as in other studies, we think that the awareness of internal medicine specialists on this issue should be increased.

Data from observational studies suggest that approximately 30% to 40% of patients with HFpEF have DM. Recent data from randomized trials suggest that prediabetes may be present in approximately one-third of patients without diabetes and insulin resistance in three-quarters of patients with HFpEF.[13,20] The rate of DM was 37.6% in our study. DM causes diabetic cardiomyopathy by causing changes in the myocardium independent of classical risk factors such as CAD, HT and valvular heart disease. Patients with DM have an increased risk of HF. HFpEF accounts for about half of the incidence of HF in DM. LVEF ≥50% and is characterized by exercise intolerance as the chief complaint. Due to the increased prevalence of HFpEF in patients with DM, it is recommended that NT-proBNP should be checked once a year in the follow-up of these patients.[21]

More than 80% of patients with HFpEF are overweight or obese. Compared with non-obese patients, obese HFpEF patients more right ventricular dysfunction, higher filling pressures and more congestion.[22] In our study, the BMI ratio of the patients was 30.1± 3.09. Because of the close association of obesity with all cardiovascular diseases and its increasing prevalence worldwide, all patients with a BMI of 30 and above who present to the internal medicine outpatient clinic should be evaluated for HFpEF. CKD increases the risk of developing HFpEF and may directly accelerate adverse cardiac remodelling (e.g. left ventricular hypertrophy, inflammation and myocardial fibrosis) and sodium/fluid retention, which contribute to the pathogenesis of HF. Patients with CKD tend to have more advanced symptoms, more impaired cardiac structure, fibrosis, and higher cardiac biomarker levels reflecting oxidative stress compared to those without CKD. A low estimated glomerular filtration rate and higher urinary albumin excretion are associated with an increased risk of developing HFpEF. This condition is also associated with an increased risk of adverse outcomes, including the severity of CKD, cardiovascular death, and hospitalisation due to HF. Lower estimated glomerular filtration rate and higher urinary albumin excretion are associated with a higher risk of developing HFpEF. It is also the severity of CKD and including cardiovascular death and hospitalization for HF associated with the risk of adverse outcomes.[23] In our study, 23.3% of patients had a diagnosis of CKD. Because of the increased frequency of HFpEF and cardiovascular events in patients with CKD, patients should definitely be evaluated in this respect.

Recent data have shown that approximately one third of the general adult population is affected by MASLD, making it one of the most common non-communicable diseases. Metabolic dysfunction is an important factor linking HFpEF and MASLD. MASLD triggers chronic inflammation and oxidative stress, leading to myocardial hypertrophy and stiffness. Up to 50% of patients with HFpEF are diagnosed with MASLD and this prevalence is much higher than in patients with HFrEF. This important association suggests that the pathophysiologic processes of HFpEF and MASLD are deeply intertwined, primarily through metabolic and inflammatory pathways.[24] In our study, the rate of MASLD in patients was 59.2%. The prevalence of MASLD is increasing worldwide, especially in DM patients. However, awareness of HFpEF in DM, which is one of the more well-known diseases, is low as well as awareness of MASLD screening. We think that it is important not to evaluate these diseases, which have similar physiopathologic processes, separately, but to screen for other conditions in patients with one of these diseases and to take a holistic approach. Our findings show that AF is highly prevalent in patients with HFpEF. The AF prevalence identified in our study is similar to the rates reported in previous studies. Large multicentre studies have reported AF prevalence rates ranging from 30% to 45%.[25] In our study, the AF rate was found to be 49.7%, which once again confirms the strong association between HFpEF and AF.

HFpEF refers to a cardiometabolic syndrome with multiple comorbidities and

accounts for more than 50% of all heart failure cases. Unlike HFrEF, HFpEF is strongly associated with metabolic disorders such as obesity, DM, HT and MASLD. Prevention and proper treatment of other risk factors such as HT, DM and obesity have been associated with lower risk or incident HF. Prevention of HT, obesity, DM and MASLD can significantly prolong survival, reduce heart failure-related morbidity and reduce the impact of heart failure on public health. CRMD is a set of clinical problems that is characterized by the interrelationships between obesity, DM, HT, CKD and cardiovascular disease. The CRMD approach is of increasing interest and these diseases are the most common patient groups encountered by internal medicine specialists. In the approach of DM, HT, obesity, HT and MASLD, which are diseases with similar physiopathologic processes and whose frequency is increasing day by day, patients should be evaluated and screened for HFpEF with NT-proBNP, clinical and, if necessary, TTE.

Our study had some limitations. Our study was single centered. Further studies with a larger number of patients and multicenter studies are needed. We did not classify the patients according to their medications, disease duration and TTE findings. We evaluated only HFpEF patients. New studies including HFrEF patients can be planned. Follow-up studies related to our study can be performed. Other limitations include its retrospective cross-sectional, the small number of parameters, and the fact that relationships are not statistically evaluated.

5. CONCLUSION

Given the increasing prevalence of CRMD, screening and awareness of HFpEF, which has a high prevalence in patients with CRMD, should be increased. We recommend clinical and NT-proBNP screening for HFpEF, which is associated with increased cardiovascular mortality and morbidity in patients with CRMD, and evaluation with TTE if necessary.

Article Information Form

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The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

Adana City Training and Research Hospital Ethics Committee approved the study with decision number 318 dated 02.01.2025.

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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