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Research Article

# Comorbidity profile of patients with heart failure with reduced, mid-range and preserved ejection fraction

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**Abstract.** Heart failure is a major cause of morbidity and mortality worldwide and a major public health problem. The number and severity of associated comorbidities in the setting of heart failure represent important prediction tools in heart failure prognosis. Most common studied comorbidities in heart failure patients are represented by obesity, diabetes mellitus, anemia, iron deficiency, chronic kidney diseases and respiratory diseases (chronic obstructive pulmonary disease) which associate a different prognostic and therapeutic management according to heart failure type, highlighting that a good management of these comorbidities might have a significant impact on therapy response, functional capacity and quality of life in patients diagnosed with heart failure. The aim of our clinical study is to evaluate the profile of associated non-cardiac comorbidities in patients diagnosed with heart failure with reduced, mid-range and preserved ejection fraction. The most common non-cardiac comorbidities in our study were diabetes, chronic kidney disease and obesity. With exception of diabetes and chronic kidney disease, which had the highest prevalence in HFrEF, most comorbidities were more frequent in HFpEF, whereas the comorbidities prevalence in HFmrEF was consistently in between HFpEF and HFrEF.

**Key Words:** heart failure, comorbidities, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction



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## Introduction

Heart failure (HF) is a major public health problem, representing the leading cause of hospital admission in patients over 65 years old. HF might be considered the end stage disease of associated comorbidities with high impact on quality of life (Azad et al 2014; Bielecka-Dabrowa et al 2017; Guo et al 2016; Iorio et al 2018; Kayvanpour et al 2015; Kloosterman et al 2020; Mentz et al 2014; Nayak et al 2020; Oktay et al 2013; Roth et al 2020). Most common studied non cardiovascular comorbidities in HF patients are represented by obesity, diabetes mellitus (T2DM), anemia, iron deficiency, chronic kidney diseases (CKD), respiratory diseases, chronic obstructive pulmonary disease (COPD), cognitive dysfunction and depression (Ahmeti et al 2017; Alosco et al 2014; Chong et al 2015; Comin-Colet et al 2020; Correale et al 2021; Drozd et al 2021; Kurz et al 2020; Laiteerapong et al 2019; Lam et al 2018; Lawson et al 2018; Li et al 2021; Mentz et al 2014; Michalska-Kasiczak et al 2018; Sirbu et al 2018; von Haehling et al 2017). The number and severity of associated comorbidities in heart failure might be considered an important prediction tool in HF clinical outcome (Faselis et al 2021; Gulea et al 2021; Khan et al 2020; Lawson et al 2018; Mentz et al 2013; Naito et al 2020; Rushton et al 2015; Rusinaru et al 2014; Vedin et al 2017; Zafrir et al 2018).

HF prevalence in developed countries is estimated at 11.8% in patients aged 65 years and over, underlining the importance of prevention strategies in cardiology, the prevention of associated comorbidities and the right management of comorbidities in order to decrease HF incidence, healthcare costs and improve

quality of life of patients diagnosed with HF (Comin-Colet et al 2020; Groenewegen et al 2020; Heidenreich et al 2020; Lawson et al 2018; McDonagh et al 2021b; Rushton et al 2015; Ziaeian et al 2016).

The aim of our clinical study was to evaluate the profile of associated non-cardiac comorbidities in patients diagnosed with different types of heart failure and the impact of associated comorbidities in HF highlighting the importance of comorbidities management in these cardiologic patients. Our study is a preliminary evaluation for therapeutic management of different types of HF and therapeutic strategies according to comorbidity profile of patients diagnosed with HF.

## Materials and methods

The study was observational, cross-sectional and analytical. The current study included 126 patients diagnosed with heart failure admitted in the Departments of Cardiology from "Niculae Stăncioiu" Heart Institute, Clinical Rehabilitation Hospital and Municipal Clinical Hospital of Cluj-Napoca, Romania, between November 2017 and March 2019. The inclusion criteria for our study were: patients aged at least 18 years old diagnosed with symptomatic heart failure of New York Heart Association (NYHA) functional classes II to IV, high NTpro-BNP values (over 300 pg/ml in an acute setting and over 125pg/ml in a non-acute setting). Our study excluded patients diagnosed with congenital heart disease, primary pulmonary hypertension, secondary arterial hypertension, pericardial disease, sepsis, malignancies, recent coronary bypass surgery and severe valvular heart disease. Written consent was obtained from each participant after information on study design and confirmation of protection and integrity of personal and clinical data of included patients. The study was approved by the Ethical Committee of "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania, following the rules and principles of the Helsinki Declaration. Clinical data of these patients were collected by our questionnaires, physical examination and medical evaluation: age, body mass index (BMI), comorbidities, smoking status, ejection fraction (EF).

One blood sample (2ml EDTA) was collected for each patient for evaluation of total cholesterol, low-density lipoprotein, high density cholesterol, triglycerides, fasting plasma glucose, urea, serum creatinine, NT-proBNP. We performed 2D echocardiography to all patients using an Epiq7 (Phillips) or Affiniti 50 (Phillips) or Arietta 60 (Hitachi) machine. Standard parasternal and apical views were performed to assess LV dimensions. We performed the measurements of the left ventricle and its wall from a parasternal long-axis view at the level of the mitral valve leaflet tips perpendicular to the LV long axis using two-dimensional sections. Left ventricular ejection fraction (LVEF) was measured using Simpson biplane formula.

**Study definitions**

Heart failure with reduced ejection fraction (HFrEF): EF ≤40%

Heart failure with preserved EF (HFpEF): EF ≥ to 50%

Heart failure with mid-range EF (HFmrEF) when EF = 41%-49% (McDonagh et al 2021a)

Coronary artery disease was defined in our study in the presence of 50% stenosis of the left main or proximal left descending artery and 70% of the rest epicardial coronaries documented in angiography.

Obesity was defined as a body mass index above or equal to 30 kg/m2, thyroid dysfunction included hypo- and hyperthyroid disease, chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m2, anaemia was defined as a haemoglobin below 12 g/dL in woman and below 13 g/dL in men, measured at baseline, liver disease included nonalcoholic fatty liver disease, alcoholic liver disease and chronic viral hepatitis.

Data analysis was performed using R 4.0.1. Categorical variables were represented as absolute value (percent). Contingency tables were analyzed using Fisher's test. Normality of the distribution was assessed using Shapiro-Wilk test and histogram visualization. Variables that presented a normal distribution were represented as mean +/- standard deviation, whereas non-normally distributed variables were represented as median (quartile 1, quartile 3). Differences between two non-normally distributed groups were assessed using Mann-Whitney-Wilcoxon rank sum test. Differences between two normally distributed groups were assessed using the t-test. Differences between more than two non-normally distributed groups were assessed using the Kruskall-Wallis test. Differences between more than two normally distributed groups were assessed using ANOVA. A non-linear correlation between two variables was assessed using Spearman's test. A p value under 0.05 was considered statistically significant.

## Results

In the present study were included a total of 126 patients diagnosed with heart failure with cohort characteristics and differences between HFrEF, HFmrEF and HFpEF being summarised in Table 1.

The prevalence of the three types of HF was as follows: 58 (46.03%) diagnosed with HFrEF, 40 (31,75%) with HFpEF and 28 (22.22%) with HFmrEF.

Patients diagnosed with HFpEF were mostly of female gender (72.5%).

In all three groups, most patients were in functional class NYHA II (59, 46.83%) and NYHA III. (53, 42.06%).

Arterial hypertension (80.2%) was the most frequent cardiovascular comorbidity in our study and type II diabetes (T2DM) (48.4%) the most frequent non-cardiac comorbidity.

We observed a significant difference in the prevalence of arterial hypertension (42 (72,4%) vs. 20(71,4%) vs. 39(97.5%); p=0.01), atrial fibrillation (12 (20,7%) vs. 5 (17.9%) vs. 17 (42.5%); p=0.032), CAD (49 (84.5%) vs. 23 (82.15) vs 10 (25%); p<0.0001), obesity (9(15.5%) versus 10(35.7%) vs. 19(47.5%), p<0.01) and thyroid dysfunction (1(1.7%) vs. 1(3.6%) vs. 11(27.5%); p<0.001) between the 3 groups of HF.

Arterial hypertension manifested predominantly in the group of patients diagnosed with HFrEF with a 72.4% (42) prevalence and atrial fibrillation in the HFpEF group (42.5%, 17).

There was a significant difference (p<0.0001) for NT-proBNP levels between HF groups with a median of 5734 (2257, 9211) pg/ml for HFrEF, 3050 (1806, 7320) pg/ml for HFmEF and 1135 (891, 2440) pg/ml for HFpEF.

In figure 1 is represented the distribution of non-cardiac comorbidities according to the HF type.

Table 1. Summary of clinical cases introduced in study

| Study variables | All HF patients in our study (N=126) | HFrEF ($n_1$=58) | HFmrEF ($n_2$=28) | HFpEF ($n_3$=40) | P |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| **Age** | 69 (66, 75) | 68 (63, 74) | 70 (68, 75) | 71 (68, 77) | 0.074 |
| **Female gender** | 49 (38.89%) | 10 (17.24%) | 10 (55.56%) | 29 (72.5%) | <0.001 |
| **Clinical parameters** | | | | | |
| **NYHA class** | | | | | |
| **II** | 59 (46.83%) | 20 (34.38%) | 15 (53.57%) | 24 (60%) | |
| **III** | 53 (42.06%) | 27 (46.55%) | 11 (39.29%) | 15 (37.5%) | 0.035 |
| **IV** | 14 (11.11%) | 11 (18.97%) | 2 (7.14%) | 1 (2.50%) | |
| **EF (%)** | 40 (32, 50) | 31 (27, 35) | 43 (40, 45) | 54 (50, 60) | <0.001 |
| **Cardiovascular comorbidities** | | | | | |
| **CAD** | 82 (65.1%) | 49 (84.5%) | 23(82.1%) | 10 (25%) | <0.001 |
| **AF** | 34 (26.9%) | 12 (20.7%) | 5 (17.9%) | 17 (42.5%) | 0.032 |
| **Hypertension** | 101 (80.2%) | 42 (72.4%) | 20 (71.4%) | 39 (97.5%) | <0.01 |
| **Noncardiac comorbidities** | | | | | |
| **COPD** | 18 (14.3%) | 10 (17.2%) | 2 (7.1%) | 6 (15.0%) | 0.543 |
| **Obesity** | 38 (30.2%) | 9 (15.5%) | 10 (35.7%) | 19 (47.5%) | <0.01 |
| **Liver disease** | 5 (3.9%) | 1 (1.7%) | 1 (3.6%) | 3 (7.5%) | 0.303 |
| **Thyroid disfunction** | 13 (10.3%) | 1 (1.7%) | 1 (3.6%) | 11 (27.5%) | <0.001 |
| **Stroke** | 16 (12.7%) | 5 (8.6%) | 4 (14.3%) | 7 (17.5%) | 0.397 |
| **PAD** | 23 (18.3%) | 9 (15.5%) | 4 (14.3%) | 10 (25.0%) | 0.418 |
| **CKD** | 44 (34.9%) | 19 (32.8%) | 10 (35.7%) | 15 (37.5%) | 0.886 |
| **T2DM** | 61 (48.4%) | 26 (44.8%) | 14 (50.0%) | 21 (52.5%) | 0.759 |
| **Anemia** | 15 (11.9%) | 6 (10.3%) | 3 (10.7%) | 6 (15.0%) | 0.774 |
| **Therapeutic protocol** | | | | | |
| **ARB or ACE inhibitor** | 102 (81.0%) | 45 (77.6%) | 23 (82.1%) | 34 (85.0%) | 0.672 |
| **Beta-blockers** | 105 (83.3%) | 51 (87.9%) | 24 (85.7%) | 30 (75.0%) | 0.223 |
| **MRA** | 88 (69.8%) | 50 (86.2%) | 16 (57.1%) | 22 (55.0%) | <0.001 |
| **Neprilysin inhibitor** | 16(12.69%) | 13(22.41%) | 3(10.71%) | 0 (0%) | <0.01 |
| **Nitrates** | 44(34.92%) | 19 (32.8%) | 13 (46.4%) | 12 (30.0%) | 0.344 |
| **Ivabradine** | 2(1.58%) | 1 (1.7%) | 1 (3.6%) | 0 (0%) | 0.495 |

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; MRA= Mineralocorticoid receptor antagonist; EF = left ventricular ejection fraction; CAD= coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PAD = peripheral arterial disease; AF= atrial fibrillation; T2DM= type 2 diabetes mellitus

Most common non-cardiac comorbidities in our cohort were diabetes, CKD and obesity. An ascending distribution of comorbidities' prevalence from HFrEF to HFpEF with HFmrEF in between was found in CKD, diabetes, obesity, anemia, stroke, liver and thyroid disease.

## Discussions

We studied nine non-cardiac comorbidities (anemia, CKD, diabetes mellitus, COPD, obesity, liver and thyroid disease, peripheral arterial disease, stroke) in patients diagnosed with heart failure with reduced, mid-range and preserved ejection fraction. The most common non-cardiac comorbidities in our cohort were diabetes, chronic kidney disease and obesity. With exception of diabetes and chronic kidney disease which had the highest prevalence in HFrEF, most comorbidities were more frequent in HfpEF.

The prevalence of diabetes in our study was 48.4%, which is higher than in other studies ranging from 22% to 45% (Ather et al 2012; Kristensen et al 2016; Mentz et al 2014; Streng et al 2018). In our clinical study the prevalence of diabetes was 52.5% in HFpEF, 50% in HFmrEF and 44.8% in HFrEF. According to previous reported data, the prevalence of diabetes in medical records, observational data and clinical trials was estimated at 27-40% in HFrEF and 30-45% in HFpEF patients (J. G. Cleland et al 2003; Ergatoudes et al 2019; Fonarow et al 2007; Khan et al 2020; Mentz et al 2014; Yancy et al 2006). A

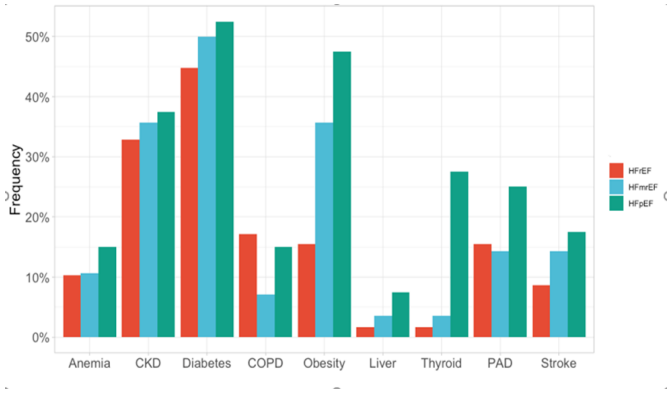


Figure 1. Non-cardiac comorbidities distribution according to HF type.
HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with midrange ejection fraction; HFpEF = heart failure with preserved ejection fraction; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; PAD = peripheral arterial disease.

possible hypothesis of the higher prevalence of T2DM in our cohort might be the contributing cardiovascular risk factors like arterial hypertension which has a high prevalence in our cohort, the continuous increasing prevalence over time of T2DM and the socio-economic status.

The association of diabetes, chronic kidney disease and anemia are independently corelated to increased mortality and HF hospitalization rate (Cleland et al 2003).

The pathogenesis of diabetic cardiomyopathy is complex and includes different associated pathways: RAAS activation, abnormal calcium metabolism, increased oxidative stress, mitochondrial dysfunction, free fatty acids disturbance, cardiac lipo-toxicity, accumulation of advanced glycation end-products (Alonso et al 2018; Aneja et al 2008; Pappachan et al 2013).

In our study chronic kidney disease was diagnosed in 34.9% patients, with no significant differences between HF types. The prevalence of renal dysfunction is similar with other studies, where data indicate a range between 28% to 55% (Damman et al 2014; Streng et al 2018; van Deursen, Damman, et al 2014; van Deursen, Urso, et al 2014).

According to current clinical data, more than 40% of HF patients have associated CKD and the relationship between CKD and HF worsens their clinical outcome. Accurate evaluation of the pathophysiology between the two diseases and appropriate therapeutic management is necessary in order to improve the prognosis of patients with HF and CKD, underlining the importance of guidelines and best clinical practice models from cardiology and nephrology professional societies and the importance of personalized future therapies (Ahmed et al 2008; Lunney et al 2020; Romero-Gonzalez et al 2020; Segall et al 2014; Shiba et al 2011).

Renal dysfunction is an independent predictor of poor clinical outcome and increased mortality in HF patients (Bock et al 2010; Dries et al 2000; Heywood et al 2007; Hillege et al 2006). The relation between HF and renal dysfunction is bidirectional and can by described by the "cardiorenal syndrome". CKD can exacerbate HF by fluid, salt and uremic toxins retention, anemia, RAAS and sympathetic nervous system activation, meanwhile HF can determine or worsen renal dysfunction by inflammation, atherosclerosis, reduced renal perfusion and increased venous pressure (Damman et al 2011; Mentz et al 2014).

Obesity is a risk factor and a direct cause of HF development (Artham et al 2009; Carbone et al 2019; Kenchaiah et al 2002; Powell-Wiley et al 2021).

Obesity is an independent risk factor for cardiovascular diseases and HF development. "Obesity paradox" describes a particular situation, where patients with heart failure and overweight but without major metabolic derangements, have a better prognosis, highlighting the limitations of BMI for cardiometabolic risk stratification and describing the "fat but fit" phenomenon. In conclusion, the metabolic syndrome might represent a better prognostic tool of cardiovascular risk than BMI alone (Ebong et al 2014; Elagizi et al 2018; Lavie et al 2016; Massie 2002).

The obesity paradox was confirmed in HFrEF and HFpEF (Carbone et al 2019; Moreira et al 2020; Nagarajan et al 2016; Padwal et al 2014; Tadic et al 2019). The pathophysiological mechanism underlying this condition is not completely elucidated. A possible explanation might be the presence of lean mass, which might contribute to a higher cardiorespiratory fitness (Bonney et al 2018; Carbone et al 2019; Kamil-Rosenberg et al 2020) or the adiponectin hypothesis, where an increased BMI correlates higher adiponectin levels and a lower mortality rate (Atzmon et al 2008; Cohen et al 2011; Frankenberg et al 2017; Tadic et al 2019).

The diagnosis of HFpEF can be hampered by low concentrations of natriuretic peptides in obese patients or the BNP deficiency phenotype (Ponikowski et al 2016; Streng et al 2017). An inverse relationship between BMI and NT-proBNP levels was observed in obese patients diagnosed with HF, cardiovascular (CV) or non-CV disorders (Christensen et al 2013; Clerico et al 2012; Daniels et al 2006; Huang et al 2016; Lee et al 2021; Madamanchi et al 2014; Ndumele et al 2016; Zheng et al 2014). A clear consensus regarding the pathophysiological mechanism underlying this relationship is not clarified yet. A reduced expression of BNP caused by lipid accumulation in obese patients might be an explanation. Triglycerides are stored in the heart causing apoptosis. BNP determines adipocyte lipolysis and a reduced release of free fatty acids (Bartels et al 2010; Kintscher et al 2020; Kloosterman et al 2020; Nair 2020; Ponikowski et al 2015; Streng et al 2017; Yang et al 2020).

In our study 30.2% of HF patients associated obesity. The highest incidence is found in patients diagnosed with HFpEF. Our results are similar with other clinical studies (Carbone et al 2020; Haass et al 2011; Kirkman et al 2020; Oktay et al 2013; Owan et al 2006; Sundaram et al 2021).

The prevalence of each associated morbidity in HFmrEF was in between HFrEF and HFpEF, showing similar results with other clinical studies (Streng et al 2018).

Nauta J et al suggested that HFmrEF is more similar to HFrEF than HFpEF regarding the prevalence of ischaemic aetiology, which is more frequent in both HFmrEF and HFrEF compared to HFpEF (Nauta et al 2017).In our study coronary artery disease is more frequent associated in patients diagnosed with HFrEF (84.5%) and HFmrEF (82.1%) compared to HFpEF (25%).

Arterial hypertension is an important risk factor in developing HFpEF. Left ventricular hypertrophy and LV diastolic dysfunction are the main determinants in HFpEF development (Bello et al 2020; Cilia et al 2019; Gong et al 2018; Heinzel et al 2015; Obokata et al 2020; Tadic et al 2019; Tadic et al 2018).

In large studies arterial hypertension had a prevalence of over 70% in HFpEF. In our study arterial hypertension had a prevalence of 97.5% in HFpEF, highlighting the importance of a right management of arterial hypertension as strategy in the management of heart failure patients, but also in decreasing the incidence of HF (Andersson et al 2014; Tadic et al 2018; Yoon et al 2019).

Atrial fibrillation and HF coexist frequently, influencing each other progression and its association increases the risk of stroke, dementia, hospitalization and all-cause mortality (Gopinathannair et al 2021; Gorenek et al 2020; Hindricks et al 2021; Kotecha et al 2016; Mulder et al 2021; Wang et al 2021).

The prevalence of AF varied between studies:19-48% in HFpEF and 17-44% in HFrEF patients (Eapen et al 2014; Olsson et al 2006; Santhanakrishnan et al 2016).

The prevalence of atrial fibrillation in our study is within the above mentioned ranges for HFpEF/HFrEF, showing the highest prevalence of atrial fibrillation in patients diagnosed with HFpEF (42.5%), followed by HFrEF (20.7%) and HFmrEF (17.9%).

A higher prevalence of atrial fibrillation was observed in the Swedish Heart Failure registry: 65%, 60%, and 53% in HFpEF, HFmrEF, and HFrEF, which included a more contemporary generalizable population, but the prevalences between studies are difficult to compare because of the different settings (Sartipy et al 2017).

Current standardized therapeutic protocols used in clinical practice for patients diagnosed with HF correlates a low rate of therapy response and must be adapted to associated comorbidities and therapeutic dosage must be carefully selected by clinical adapted survey and/or pharmacogenomic tests in order to improve therapy response and clinical outcome of these patients (Fonarow et al 2010; Greene et al 2018; Khan et al 2020; Mottet et al 2016; Oni-Orisan et al 2014).

In our study 81% patients followed a therapy with ACE inhibitors or Angiotensin receptor blocker (ARB), 83.3% had a BB therapy, 69.8% a Mineralocorticoid receptor antagonist (MRA) and 12.7% a Neprylisin inhibitor.

ACE inhibitors, Angiotensin receptor-neprilysin inhibitor, BB, MRA and Sodium-glucose co-transporter 2 inhibitors reduce mortality and morbidity in HFrEF (McDonagh et al 2021a).

In patients diagnosed with HFpEF, medical treatment failed to improve substantially clinical outcomes, highlighting the importance of the therapeutic management of comorbidities in improving therapy response and clinical outcome of these patients. HFpEF therapy is challenging and requires a good management of associated comorbidities and pharmacogenomic testing in order to improve therapy response and clinical outcome of these patients (J. G. Cleland et al 2006; Cresci et al 2019; Fu et al 2016; Krittanawong et al 2017; Massie et al 2008; Yusuf et al 2003). Standard therapeutic guideline applied in HFpEF patients is correlated with poor therapy response (McDonagh et al 2021a; Schlapfer-Pessina et al 2015; Shear 2019). Despite the evidence, more than 86% of patients are treated with ACE inhibitors/ARBs, 80% with BB and over 24% on MRA in HFpEF according to PARAGON trial (Solomon et al 2019).

Our study shows similar results regarding treatment with ACE-I/ARBs (85%), BB (75%) and a higher percentage of MRA treatment (55%) in HFpEF patients.

In our study we had a small number of patients treated with Neprilysin inhibitors because of cost issues at that time regarding this therapy. The selection criteria for Neprilysin inhibitor treatment in our study was predominantly based on PARADIGM-HF trial, choosing patients with EF ≤40% or appropriate to 40% (McMurray et al 2014).

More recent data suggest that a selected population of patients may benefit from Neprilysin inhibitors in patients diagnosed HFmrEF/HFpEF. This might be applied in HF patients with EF 45-57% and especially in women diagnosed with HF (McMurray et al 2020; Wintrich et al 2020).

A good management of associated comorbidities in HF patients will be effective for both the HFrEF and HFpEF populations and will significantly improve functional capacity, therapy response, quality of life and survival rates in HF patients (Chong et al 2015; Del Buono et al 2019; Lawson et al 2018; Oktay et al 2015; Upadhya et al 2017).

Some of the common studied comorbidities associated in HF patients like depression, dementia, cognitive disorders, malignancies and obstructive sleep apnea were excluded from our study because of incomplete data from our medical registry, these comorbidities were surely evaluated in therapeutic approach of HF patients, but existing data were insufficient for an accurate analysis for comorbidity profile in different studied HF types.

## Conclusion

We studied nine non-cardiac comorbidities (anemia, CKD, diabetes mellitus, COPD, obesity, liver and thyroid diseases, PAD, stroke) in a mixed group patients diagnosed with heart failure. The most common comorbidities in our cohort were diabetes, chronic kidney disease and obesity. With exception of diabetes and chronic kidney disease, which had the highest prevalence in HFrEF, most comorbidities were more frequent in HFpEF, whereas the prevalence in HFmrEF was consistently in between HFpEF and HFrEF.

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