Characteristics of patients with preserved, mildly reduced and reduced ejection fraction heart failure treated in Split

Ashraf, Hishaam

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UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

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Diploma Thesis

Academic year:

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Abbreviations

ACEi – Angiotensin-Converting Enzyme inhibitor

AHT – Arterial Hypertension

ARB – Angiotensin Receptor Blocker

ARNI - Angiotensin receptor neprilysin inhibitor

AF - Atrial Fibrillation

ESC – European Society of Cardiology

HF - Heart Failure

HFmrEF – Heart failure with mildly-reduced ejection fraction

HFpEF – Heart failure with preserved ejection fraction

HFrEF – Heart failure with a reduced ejection fraction

NYHA – New York Heart Association

RAAS - Renin-angiotensin-aldosterone system

1. INTRODUCTION

1.1 Definition of heart failure

Heart failure (HF) is a clinical-pathological syndrome characterized by failure of the heart to generate enough cardiac output (CO) to meet the peripheral tissues' minimum metabolic demands (1). As a result of either structural and/or functional cardiac defects, this syndrome is usually accompanied by characteristic symptoms (dyspnoea, oedema, and fatigue) and signs (increased jugular venous pressure, peripheral oedema, pulmonary rales, and oedema)(2).

There are a number of classification frameworks used to define HF and identify their distinct subsets. Of the classifications, HF classified according to Ejection Fraction (EF) of the left ventricle (LVEF) and the New York Heart Association (NYHA) classification, based on symptom severity are amongst the most commonly used today (3). Additionally, specific aetiologies and time of onset of HF are also used to classify HF with specific examples discussed later.

An excellent phenotypic marker used to define HF by assessing the efficiency of the ventricles is Ejection Fraction (EF). This is the fraction of end-diastolic volume (EDV) ejected per ventricular systole and can be calculated using the formula shown in Table 1. Clinically, the calculation of LVEF is calculated using two-dimensional echocardiography and is classified into three distinct phenotypes shown below (2).

Table 1. Classification of heart failure based on the ejection fraction (EF) and the formula for calculating EF (3).

Heart Failure Type	Ejection Fraction (EF) (%)
Heart failure with reduced ejection fraction (HFrEF)	≤40%
Heart failure with mildly-reduced ejection fraction (HFmrEF)	41%-49%
Heart failure with preserved ejection fraction (HFpEF)	≥ 50%
Formula for EF Calculation = EF $\frac{SV}{EDV}$	

Abbreviations: EF- Ejection Fraction, SV- Stroke Volume, EDV – End Diastolic Volume.

The NYHA classification on the other hand classifies patients into one of four categories according to their degree of symptoms at rest and with activity demonstrated below in Table 2 (4).

Table 2: NYHA classification of heart failure (4).

NYHA Class	Level of clinical impairment
Class I	▪ No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
Class II	▪ Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III	▪ Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20—100 m). Comfortable only at rest.
Class IV	▪ Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Abbreviations: NYHA -New York heart association.

HF defined according to its time of onset can be acute and chronic. Acute HF typically presents as rapid onset of new or worsening signs and symptoms of HF, usually requiring urgent intervention. Chronic HF however is typically gradual in onset and often coupled with multiple comorbidities (3).

The distinctions between the different classifications of HF emphasise the important differences in patient presentation, demographics, co-morbidities, and most importantly treatment response (2).

1.2 Epidemiology of heart failure

Heart failure is a worldwide pandemic with approximately 64.3 million people affected. The prevalence of HF in the developed world is estimated at 1% to 2% of the general adult population and varies considerably between countries and regions (5). In 2017, the highest prevalence rates of HF were observed in Central Europe, the Middle East and North Africa and ranged from 1133–1196 per 100,000 people. In comparison, lower rates were observed in Eastern Europe and Southeast Asia ranging from 498–595 per 100,000 people (6).

Prevalence according to EF has been demonstrated by various HF registries. In 2017, the European Society of Cardiology (ESC) Long-Term Registry found that 60% of HF patients had heart failure with reduced ejection fraction (HFrEF), 24% had heart failure with mildly-reduced ejection fraction (HFmrEF), and 16% had heart failure with reduced ejection fraction (HFpEF) (7). Similarly, in the Global Congestive Heart Failure (G-CHF) registry HFrEF was prevalent in 54% of the population, HFmrEF in 21%, and HFpEF in 24% (8).

Regarding the etiological distribution of HF, there is great variation between the developed and developing worlds. Studies have shown that ischemic heart disease is the leading cause of HF in the western world, primarily due to the transition in lifestyles over the past decades. Regions such as Africa on the contrary have hypertensive cardiac disease as its predominant aetiology of HF(9,10).

The 1-year mortality outcomes of HF globally was studied in the International Congestive Heart Failure (INTER-CHF) study, analysing 16 countries spanning Asia, Africa and South America. It showed the highest mortality after 1 year in Africa (34%), followed by India (23%), and Southeast Asia (15%) with the lowest in China (7%) (11).

In developed countries, HF incidence rates have plateaued in recent decades and have undergone significant decline. There is however a higher incidence of HF in individuals of lower socioeconomic status compared with those with high socioeconomic status (12).

Some of the most striking variations according to sex are seen in HF patients. Differences have been observed not only at the cellular level but also in certain "traditional" risk factors which have shown to confer a greater risk of development of HF in specific sexes. It has been shown that despite common risk factors, males have a predilection for developing HFrEF, whereas females predominate with HFpEF (13). Females, however, have a significantly lower incidence of HF compared to men in all age categories until more than 74 years at which point the risk becomes equal (14).

It is well known that cardiometabolic risk factors such as obesity and diabetes play a significant role in the genesis of HF. The Framingham Heart Study (FHS) reported obesity increased the relative risk of coronary artery disease (CAD), a major HF risk factor, in females by 64% as opposed to 46% in males (15). Females also appeared to have a poorer clinical outcome than men often presenting with increased symptom burden such as bronchitis-like symptoms, dyspnoea and overall poorer quality of life (13).

1.3 Aetiology

HF is caused by a combination of aetiologies that are not mutually exclusive. The majority of patients exhibit multi-morbidity which often shares a common set of risk factors which lead to the pathogenesis of HF. Aetiologies of HF can be best classified into three types as demonstrated in Table 3: predisposing, determining, and precipitating aetiologies.

Table 3: Aetiological factors for development of heart failure with clinical examples (17,18).

Aetiology type	Examples	
Predisposing	▪ CAD, Congenital heart disease ▪ Diabetes, AHT	
Determining	**Cardiomyopathy**	▪ Dilated, ▪ Hypertrophic ▪ Restrictive
	Ventricular overload	▪ AHT, ▪ Aortic/Pulmonary stenosis, ▪ Pulmonary hypertension, ▪ Valvular insufficiency
	Altered ventricular filling	▪ Ventricular hypertrophy, ▪ Mitral/tricuspid stenosis, ▪ Cardiac tamponade
	Arrhythmias	▪ Bradycardia, ▪ Tachycardia,
Precipitating	**Cardiac**	▪ Arrhythmias, ▪ Ischemic cardiomyopathy, ▪ Negative inotrope drugs: beta-blockers, antiarrhythmics
	Extra-cardiac	▪ Infections, ▪ PE, ▪ Anaemia, ▪ Surgery

Abbreviations: AHT – Arterial hypertension, PE- Pulmonary embolism

1.3.1 Predisposing aetiologies of heart failure

Predisposing causes of HF refer primarily to the risk factors of HF development in a population of symptom-free people. These factors can include arterial hypertension (AHT), obesity, diabetes, smoking and even gender. The most important predisposing risk factor for the development of HF is AHT. According to the FHS, 91% of the HF cohort had previously been diagnosed with hypertension. Furthermore, when compared to normotensive individuals, both male and female hypertensive individuals had a 2- to 3-fold increased risk of developing HF, respectively (15,16). The risk of HF was also doubled in the population with mild AHT and increased four-fold when arterial pressure goes above 160/95 mm Hg. Furthermore, elevated systolic arterial pressure is associated with a two-fold increased risk of developing HF compared to elevated diastolic arterial pressure. AHT-induced left ventricular hypertrophy has shown a relative risk 17 times higher for HF development than the normal population. (17).

Obesity, diabetes, and arterial hypertension have all been linked to the development of heart failure over time, owing to myocardial metabolic and endothelial dysfunction, which leads to ventricular remodelling and eventual dysfunction. While the onset of hypertension or obesity preceded heart failure by an average of more than 10 years, heart failure has shown to occur more rapidly after coronary disease. For coronary disease, sudden cardiac events such as myocardial infarction may lead quickly to cardiac dysfunction and heart failure (18).

1.3.2 Determining aetiologies of heart failure

Determining causes of HF are factors that alter the regulating mechanisms of the ventricular function, heart rate and cardiac load.

Primary examples of those affecting ventricular function include cardiomyopathies, disorders of ventricular filling and cardiac overload disorders. The most common cardiomyopathy resulting in HF is hypertrophic cardiomyopathy (HCM). In most cases with a clear genetic origin, HCM is characterised by hypertrophy of the left ventricle often being a cause of sudden death, particularly in young athletes (17). The least common cardiomyopathy with a generally poor prognosis is restrictive cardiomyopathy characterised by diastolic dysfunction with a restrictive filling pattern on an echocardiogram (19).

Conditions that alter the cardiac load and lead to HF include AHT, valvular insufficiency or stenosis or cardiac tamponade. Common aetiologies that result in pressure overload-induced HF include stenosis of the aortic and pulmonary valves. Similarly, volume overload-induced HF is typically seen in valvular insufficiencies and extra-cardiac conditions resulting in hypervolemia.

Changes in heart rate can also result in, and be seen alongside, HF. Both bradyarrhythmia and tachyarrhythmias may be seen in different stages and types of heart failure (16).

1.3.3 Precipitating aetiologies of heart failure

Factors that produce decompensation in a stable patient with or without a previous diagnosis of HF or have an underlying structural heart defect are among the precipitating causes of HF. Causes are divided based on whether it is cardiac or non-cardiac in origin.

Cardiac causes include new-onset arrhythmias, ischemic cardiomyopathies, and the introduction of negative inotropic drugs such as beta-blockers and calcium-channel blockers. Extracardiac causes include infections, anaemias or history of pulmonary embolism or any surgeries (20).

1.4 Pathophysiology

The underlying pathophysiology of heart failure involves an interplay of hemodynamic, neurohormonal and structural changes. These changes are initially adaptive to maintain normal cardiac function. However, over time these changes become maladaptive resulting in HF.

In a healthy heart, the Frank-Starling curve describes a steep and positive relationship between the cardiac filling pressures (obtained from LVEDP or pulmonary capillary wedge pressure) and stroke volume/cardiac output. In HF, however, this relationship becomes right-shifted due to a greater filling pressure being required to achieve the same cardiac output. The curve also becomes flattened as the disease advances meaning any increases in left-heart filling pressure achieves minimal changes in stroke volume and cardiac output (Figure 1).

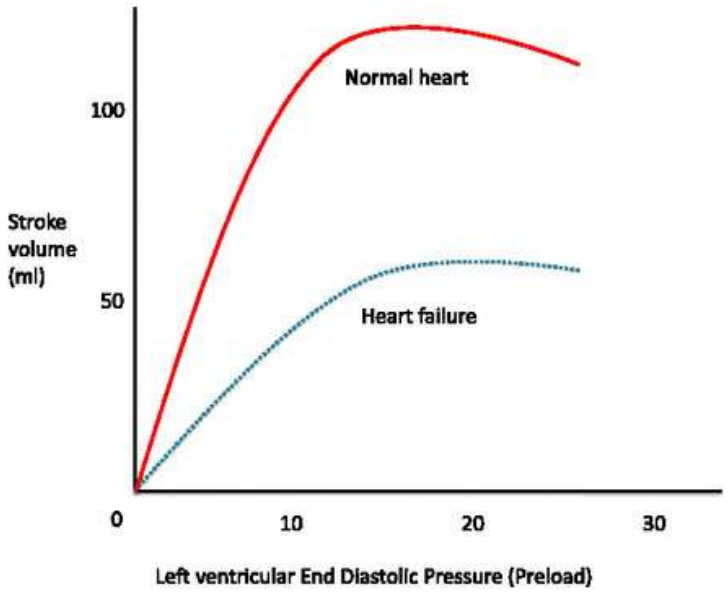

Figure 1. The Frank Starling curve in a normal heart and in heart failure.

Taken from: Hajouli S, Ludhwani D. Heart Failure And Ejection Fraction. StatPearls. 2020.

1.4.1 Neurohormonal Changes & Ventricular Remodelling

Patients with all types of HF (HFrEF, HFmrEF and HFpEF) have activation of the neurohumoral systems to maintain adequate perfusion of the essential organs. This involves interplay between the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) and the release of many vasoactive substances (21).

HF has been shown to lower the carotid baroreceptor responsiveness which results in enhanced SNS activity. This increased SNS activity exerts positive inotropic, chronotropic, and vasoconstrictive effects causing an increased afterload. Furthermore, RAAS activation in response to reduced renal perfusion from HF causes salt/water retention and angiotensin II-induced vasoconstriction to increase preload. These mechanisms over time, result in further stress on the ventricular wall, further deteriorating ventricular function often leading to decompensation. They also further induce unfavourable cardiac remodelling through mechanisms such as inflammation, apoptosis, fibrosis, and hypertrophy as depicted in figure 2 below (22).

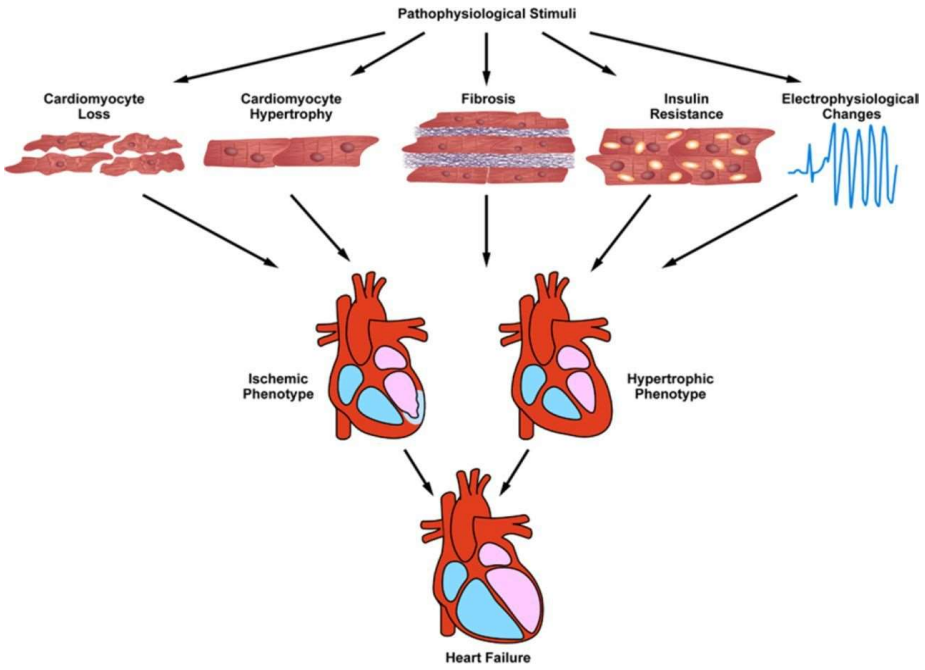

Figure 2: The cellular mechanisms within the cardiac myocyte of pathological ventricular remodelling.

Taken from: Burchfield JS, Xie M, Hill JA. Pathological Ventricular Remodeling. Circulation. 2013;

1.4.2 Pathophysiological findings in HFpEF and HFrEF

A thorough understanding of the underlying pathophysiology of HF, particularly HFrEF and HFpEF, is critical, as evidence-based therapy has shown to improve clinical symptoms and prognosis in HFrEF but not in HFpEF. Management for HFrEF, however, includes guideline-directed medical management, device-based therapies, and cardiac rehabilitation only.

Pathological findings in HFpEF typically show a thickened and stiff LV wall and a resulting high LV mass/end-diastolic volume ratio. Contrastingly, patients with HFrEF have an LV cavity that is often dilated with a normal or reduced LV mass/end-diastolic volume ratio (1). At the histological level, the cardiac myocyte diameter and the volume of myofibrils are higher in HFpEF than in HFrEF (23).

Both HFpEF and HFrEF have the same pathophysiological changes however the ventricular stiffness and altered relaxation results in concentric LV hypertrophy in HFpEF whereas eccentric LV hypertrophy is observed in HFrEF (24).

1.4.3 Pathophysiological findings in HFmrEF

The clear pathophysiological mechanisms for HFmrEF have not been thoroughly studied, however, several observations have been made. It has been observed that a subset of patients diagnosed with HFmrEF had previous HFpEF. This was suggestive that HFmrEF patients could be patients with HFpEF but with a deteriorating LV function. In contrast, however, it was also suggested that HFmrEF patients could be a group of HFrEF patients in which treatment has improved their EF (25).

1.4.4 High & Low Output Heart Failure

HF can be described based on its cardiac output as high or low output HF. High output heart failure (HOHF) is best described as heart failure with a resting cardiac output greater than 8 L/min or a cardiac index of greater than 4.0/min/m2 (26). Cardiac function, however, is normal with a significant decrease in systemic vascular resistance(27). HOHF is most often a consequence of an underlying disease process which can be characterised as either metabolic, myocardial or mechanical vascular in origin as described in Table 4 (26,28).

Table 4: Table demonstrating the underlying pathology and examples of metabolic, myocardial, and mechanical vascular high output heart failure (26,28).

Aetiology	Underlying pathology	Examples
Metabolic	▪ Metabolic diseases causing an increase in metabolic demand.	▪ Hyperthyroidism ▪ Myeloproliferative disease
Myocardial	▪ Diseases directly affecting myocardial tissue – Multifactorial pathophysiology	▪ Hyperthyroidism ▪ Sepsis ▪ Beriberi (Vitamin B6 Deficiency)
Mechanical Vascular	▪ Bypass of arterioles and capillary bed – increased flow to the venous circulation	▪ AV Fistula ▪ Liver cirrhosis associated AV shunts ▪ Obesity ▪ Carcinoid syndrome ▪ Paget's disease

Low output heart failure (LOHF) can be best described as resting cardiac output <4L/Min or a cardiac index < 2.0 L/min/m^2 and a systolic blood pressure [BP] < 90 mmHg. In LOHF, the heart is unable to generate enough pressure to push blood into the arterial tree. This can be due to several factors including cardiac contractility failure, an excess preload or afterload or arrhythmias (26).

1.5 Signs and symptoms

All patients with suspected HF should have a thorough history and physical examination, as a large part of establishing an accurate diagnosis is formed on clinical signs and symptoms. Initial assessment of patients should actively identify any potential risk factors to guide diagnosis.

Regardless of EF, the clinical symptoms of HF are almost uniform. Symptoms commonly manifest as dyspnoea, anasarca, orthopnoea, or fatigue and anorexia as a result of volume overload and reduced cardiac output respectively. Manifestations of volume overload in addition to those mentioned previously include increased jugular venous pressure (JVP), rales and pleural effusions seen on chest X-rays (29).

As HF advances, patients may experience diaphoresis, resting sinus tachycardia, and signs of peripheral vasoconstriction, such as pale and cool extremities, as the disease progresses (1).

1.6. Diagnosis

Diagnosis of HF is made by a combination of clinical parameters: Clinical symptoms and signs, laboratory tests, electrocardiogram (ECG) and imaging tests. Laboratory tests are used not only to establish any precipitating or predisposing factors for the development of heart failure but also for monitoring. Table 5 shows a list of common laboratory tests used in the diagnosis and management of HF.

Anaemia has been linked to higher severity of HF; hence a full blood count and hematinic screen are utilized to rule it out as a cause of the patient's symptoms. This also allows for monitoring effectiveness of anemia treatment: typically aiming for ferritin higher than 100ng/ml and transferrin saturation above 20% (30).

Kidney function and electrolytes are used to monitor kidney failure which may play a role in the development of exacerbation of HF. Certain HF drugs such as spironolactone, angiotensin-converting enzyme inhibitor (ACEi) or furosemide can cause electrolyte derangements and therefore require regular monitoring (31). Studies have shown that a high baseline BUN, even in absence of severe renal failure is a strong predictor of post-discharge mortality in HF patients (32).

Another important test used for HF diagnosis is ECG. This non-invasive test is necessary when assessing all suspected HF patients as it plays a role in determining the presence of heart failure and any possible aetiologies. Potential aetiologies which may be discovered include a history of a previous myocardial infarction suggesting CAD as a possible cause or even signs of LV hypertrophy induced by long-standing hypertension (33).

Normally, ProBNP (pro-B-type natriuretic peptide) is secreted by cardiac myocytes in response to LV wall stretch from excess stress or volume. ProBNP, once released is cleaved into a biologically active B-type natriuretic peptide (BNP) and an inert N-terminal pro-BNP (NT-proBNP). Both circulating BNP and NT-proBNP levels are low in the healthy patients. However, in HF, their concentrations rise significantly helping to aid the diagnosis, predict clinical outcomes and monitor the effects of therapy (34). For the diagnosis of heart failure, BNP has been shown to have 70% sensitivity and 95% specificity, while NT-proBNP has 95% sensitivity and 85% specificity (35). Patients with HFpEF or obesity have been shown to have lower than expected BNP compared to HFrEF patients. Therefore multiple tests are used to confirm HF diagnosis (36).

Table 5: Recommended laboratory tests for the diagnosis of heart failure (2).

Laboratory test
Full blood count & Hematinic screen
Electrolytes – (Sodium, Calcium and Magnesium)
Kidney function (Serum creatinine, Urea
BNP/ NT-proBNP
Troponins
Liver function test
Thyroid function
Fasting glucose & HbA1C
Fasting lipid profile
Iron status (Ferritin and TSAT)

Abbreviations: BNP - B-type natriuretic peptide, HbA1C - glycated haemoglobin, NT-proBNP - N-terminal pro-B-type natriuretic peptide, TSAT – Transferrin saturation.

The most useful test for determining the diagnosis of HF and classifying it as HFrEF, HFmrEF or HFpEF is the transthoracic echocardiogram (TTE)(37). TTE allows for the accurate calculation of LV volumes and EF, as well as the assessment of parameters that aid in the identification of possible aetiologies. Confirmation of LV aneurysms, wall motion abnormalities of hypertrophic or dilated cardiomyopathies based on ventricular wall thickness, and mass findings are examples of this (38).

Table 6 shows how these described clinical tests are incorporated into ESC's 2016 criteria for making a HF diagnosis.

Table 6. European Society of Cardiology 2021 guidelines for diagnosis of heart failure.

Type of heart failure		**HFpEF**	**HFmrEF**	**HFrEF**
Criteria	1	Symptoms and/or signs *		
	2	LVEF < 50%	LVEF 40-49%	LVEF < 40%
	3	1. Increased concentration of natriuretic peptides[a] 2. At least one of the following criteria: a. Related structural heart disease (LVH or LAE) b. Diastolic dysfunction		

Abbreviations: HFrEF- heart failure with reduced ejection fraction, HFmrEF- heart failure with mildly-reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction, LVEF- left ventricular ejection fraction, LVH- Left ventricular hypertrophy, LAE – Left arial enlargement

* Symptoms may not be present in early heart failure or in patients treated with diuretics.

[a] BNP > 35 pg/ml and/or NT-pro-BNP >125pg/ml

1.7 Treatment & Management

Treatment and management options for HF are heavily aetiologically and pathophysiology guided and involve a combination of preventative strategies, medical, and surgical interventions. The key aim for management is to improve prognosis, reduce morbidity and mortality and appropriately manage the co-morbidities that contribute to the poor prognosis that is generally present with HF (39).

Medical management consists of those directed at symptomatic relief such as diuretics, nitrates, or digoxin. Drugs aimed at long-term management and reducing mortality include ACE-I, beta-blockers, ARBs, and sodium-glucose co-transporter 2 inhibitors (40).

1.7.1 Prevention

Preventative strategies for HF are recommended for all types of HF regardless of EF. It typically consists of dietary and lifestyle modifications. All patients are recommended a nutritional consultation with aims such as sodium restriction to <5 g/d in all adults or cases of hyponatremia fluid restriction to 2 L/day is enforced (41).

Patients are also counselled on self-care, controlling AHT, diabetes and discontinuing smoking and alcohol intake. Patients are also encouraged to partake in aerobic exercise training as it has shown to reverse LV remodelling in clinically stable patients (42).

1.7.2 Medical management of HFrEF

For management of HFrEF, a triad of an ACEi/angiotensin receptor neprilysin inhibitor (ARNI), a beta-blocker, and a mineralocorticoid receptor antagonist (MRA) is strongly recommended unless contraindicated or poorly tolerated.

In addition to this triad, dapagliflozin or empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor is often added to standard care for all patients, irrespective of the presence of diabetes. The EMPEROR-Reduced trial which studied empagliflozin in HF patients found that it was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo. Furthermore, they found a slower progressive decline in kidney function in patients with chronic HF and HFrEF (43).

As described earlier, one of the main pathophysiology's of HF is enhanced SNS activity which over time leads to cardiac decompensation. Utilising beta-blockers blocks the enhanced SNS activity in the heart thereby improving symptoms, and survival and increasing LVEF, especially in chronic HF (44).

ACEi is among the first-line therapies for HFrEF. ACE inhibitors inhibit the activity of ACE thereby preventing the formation of angiotensin II from angiotensin I, resulting in diuresis, natriuresis and a decrease in arterial blood pressure and thus afterload (45).

Multiple clinical trials have demonstrated improved survival and decreased hospitalization in patients with chronic symptomatic HFrEF treated with ACEi. Multiple clinical trials have shown that ACEi treatment improves survival and decreases hospitalization in patients with chronic symptomatic HFrEF (1). Furthermore, current 2021 ESC guidelines recommend that every patient with HFrEF receives an ACEI regardless of symptoms and if there are no contraindications. If patients are intolerant, ARBs are the recommended alternative. However, this group of medications have not shown significant evidence to reduce mortality in HFrEF patients (40).

1.7.3 Medical management of HFmrEF

Treatment of HFmrEF is similar to the other types of HF in that diuretics are used to reduce the cardiac overload and congestion often seen in HF. Unlike HFrEF and HFpEF, there have been no significant controlled trials on patients with HFmrEF to allow for a strong evidence-based recommendation of medical therapies. The 2021 ESC guidelines, however, have recommended ACE-I, beta-blockers, ARBs, and MRAs as treatment options to reduce the risk of HF hospitalization and death (40).

1.7.4 Medical management of HFpEF

Due to the vast majority of HFpEF patients having co-morbidities like AHT and CAD, patients at the time of diagnosis are already being treated with ACEi, beta-blockers or MRA's resulting in a lack of studies of these potential disease-modifying drugs. This was seen in the PARAGON study where over 86% of patients were on ARB/ACEi, 80% were on beta-blockers and over 20% were on MRA's (46).

Although beta-blockers are commonly used, they should only be used to treat co-existing conditions (e.g., atrial fibrillation or post-Myocardial infarction). This is because the negative chronotropic effects on a heart with a relatively fixed stroke volume and diastolic dysfunction increase the risk of HF exacerbation (47).

1.7.5 Device and non-surgical management

Device and non-surgical management include the use of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT). These options are considered when ACEi/ARB and beta-blockers have failed for a minimum of three months and EF is $\leq$ 35%.

The ESC 2016 guidelines recommend an ICD as a form of primary prevention in symptomatic HF (NYHA II-III) with an LVEF ≤ 35% despite ≥ three months of guideline-directed medical therapy in cases of ischemic cardiomyopathy or non-ischemic dilated cardiomyopathy (2).

CRT is recommended by the ESC 2016 guidelines in cases of symptomatic HF with a sinus rhythm. They also state that an LVEF of 35% despite guideline-directed medical therapy is required, as well as a left bundle branch block with a QRS duration of 150 Ms (48).

2. OBJECTIVES

This study has the following aims:

1. Identify common comorbidities in selected groups of heart failure patients,
2. Determine the prognostic value of laboratory findings,
3. Determine differences in drug therapy used in patients with preserved ejection, mildly reduced, and reduced ejection fraction heart failure,

Hypothesis:

1. The most common comorbidities of patients with heart failure will be arterial hypertension, coronary artery disease and atrial fibrillation.
2. The medical management of HFmrEF is more similar to HFpEF than HFrEF.

3. MATERIALS & METHODS

3.1 Study type and subjects

This study is a retrospective observational study based on data obtained from the Croatian registry for patients with heart failure. The study included patients hospitalized for symptoms of heart failure in the Republic of Croatia between the period of 2005 to 2010. In line with the 2016 guidelines from ESC, patients were divided based on their LVEF. There were a total of 869 patients in our database of which, 322 had HFpEF, 150 patients had HFmrEF and 397 had HFrEF. Patients without ejection fraction data and patients who had passed away during hospitalization were excluded from the study.

3.2 Methods & data analysis

The data was obtained from the Croatian Heart Failure Registry and entered into Microsoft Excel 2016 format for extraction. Authorization for the use of registry data at the request of the head of the working group of research “Registry of patients with heart failure (HFIII)" Assist. Prof Duška Glavaš, MD, PhD was adopted by the Ethics Committee of the University Hospital of Split, by decision 2181-147-01/06/M.S.-18-2.

The database contained various data points on patients including patient demographics, values of various laboratory tests and imaging findings used in the diagnosis of HF. Additionally, ultrasound findings, concomitant diseases, comorbidities, and patient discharge medications were also obtained.

Statistical analysis was performed in Microsoft Excel, 2016 (Microsoft Inc, USA) and GraphPad Prism inc, (Version 9.0). A One-way ANOVA test was used to perform analysis and determine any statistical differences. Categorical variables were presented as whole numbers and percentages (%). Quantitative variables were presented as mean values, standard deviations and the statistical significance was set at $P< 0.05$.

4. RESULTS

Figure 3 shows a bar chart depicting the gender distribution of patients according to HF type. Males appeared to have a higher prevalence of HFrEF and HFmrEF, with 68% and 55%, respectively, of affected patients. Females, on the other hand, appeared to have a higher prevalence of HFpEF than males, with 55% affected.

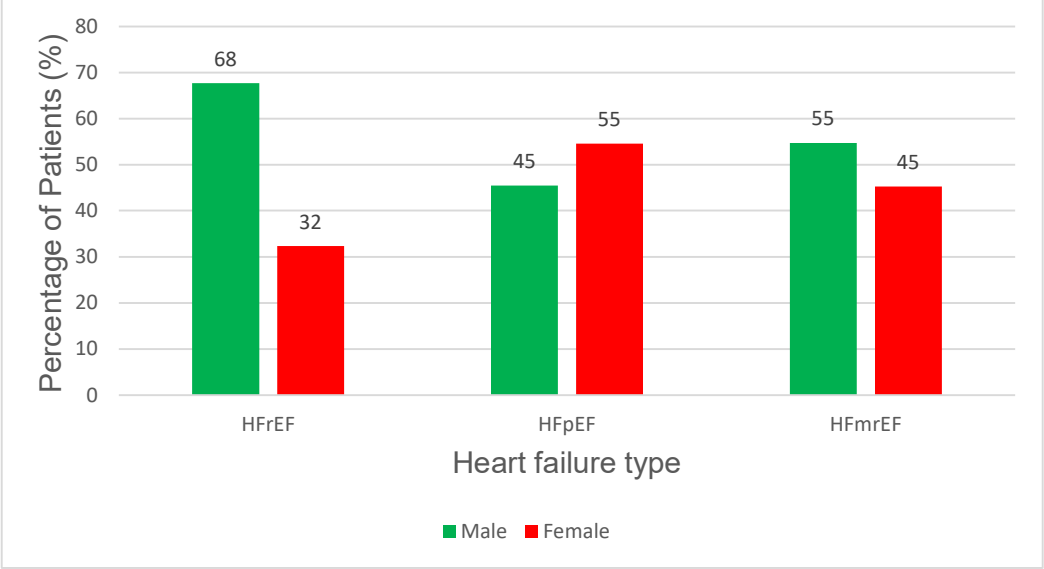

Figure 3. The distribution of patients treated with HFrEF, HFpEF and HFmrEF according to gender.

Abbreviations: HFrEF- Heart failure with reduced ejection fraction, HFmrEF – Heart failure with mildly-reduced ejection fraction, HFpEF- heart failure with

Figure 4 shows a bar chart depicting the average age of patients based on the type of heart failure they have. Patients with HFpEF had the highest average age of the three types, with 73 years and a standard deviation of 9.7. The average age in the HFmrEF group was 72 years, with a standard deviation of 10.8. Finally, patients with HFrEF had the lowest average age of 68 years, with a standard deviation of 12.5.

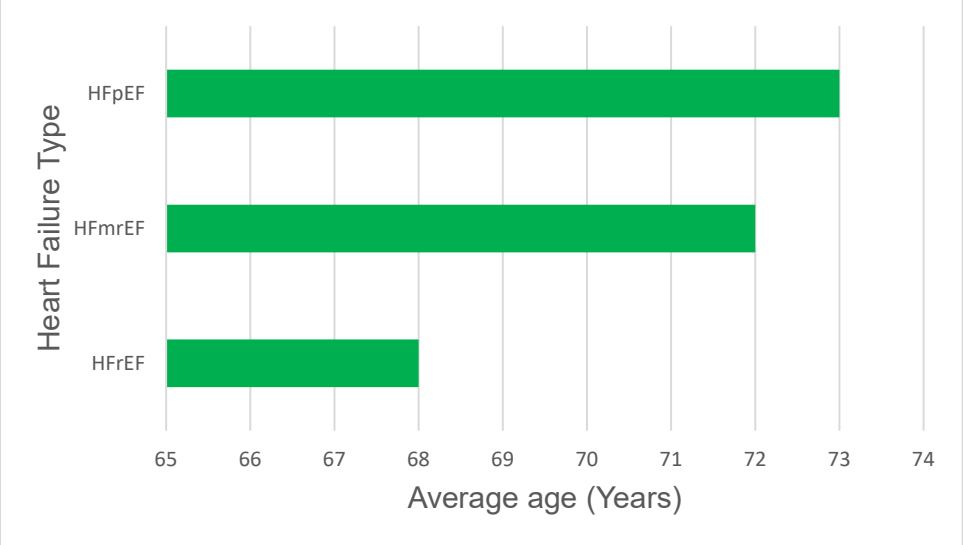

Figure 4. Bar chart showing the average age of heart failure patients based on Ejection Fraction (EF).

Abbreviations: HFrEF- Heart failure with reduced ejection fraction, HFmrEF – Heart failure with mildly-reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction.

The most common comorbidity in patients with HF was coronary artery disease (CAD), which was seen in 77% of HFpEF and HFrEF patients and, 85% of HFmrEF patients. Similarly, the second most common comorbidity in all three groups of HF patients was arterial hypertension, which was found in 68% of HFpEF and HFmrEF patients and 49% of HFrEF patients. Atrial fibrillation was the third most common co-morbidity found in HFmrEF and HFpEF patients, affecting 57% and 55% of patients, respectively. However, in HFrEF patients, this appeared to be pulmonary hypertension, which was found in 48% of the patients.

The fourth most common comorbidity was pulmonary hypertension for HFmrEF and HFpEF affecting 38% and 40% of patients respectively. In HFrEF, however, this was the third most frequent comorbidity. Kidney failure and Diabetes Mellitus were two of the least common comorbidities observed in all types of HF.

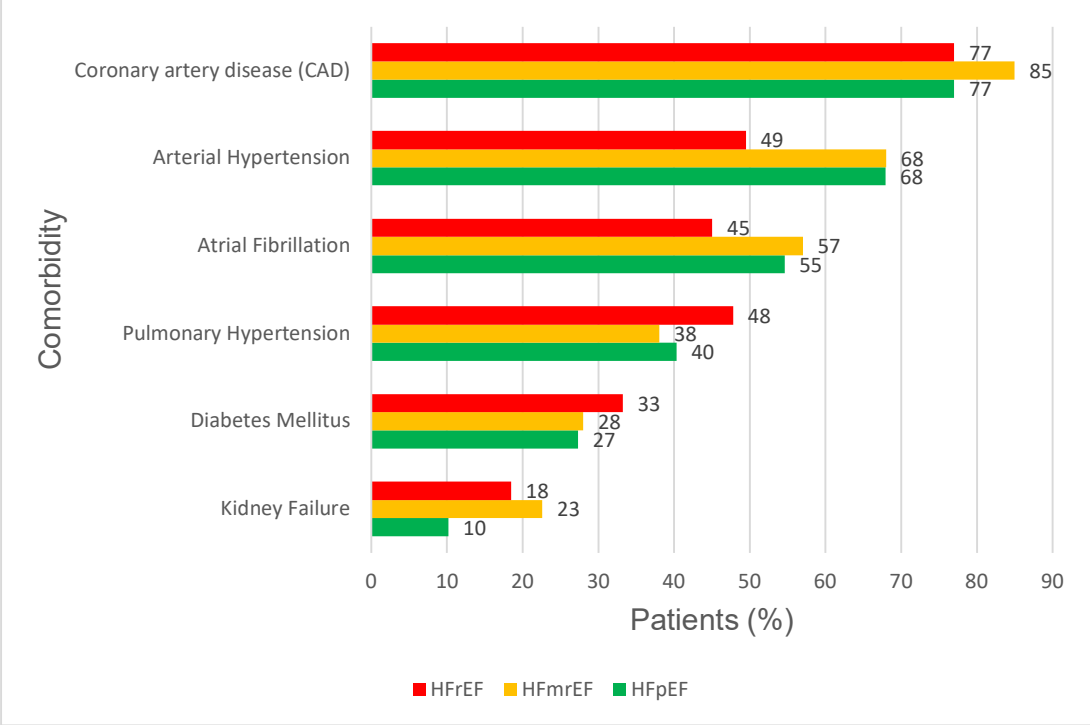

Figure 5. Bar chart showing the proportion of individual comorbidities in patients treated for heart failure with preserved ejection fraction (HFpEF), mildly-reduced ejection fraction (HFmrEF) and reduced ejection fraction (HFrEF).

Abbreviations: HFrEF- Heart failure with reduced ejection fraction, HFmrEF – Heart failure with mildly-reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction.

Table 7 shows the frequency of relevant clinical findings, as well as the average values of selected laboratory and imaging tests. Patients with HFpEF had a statistically significant higher average systolic and diastolic blood pressures compared to HFmrEF and HFrEF of 140mmHg (*P* =<0.001) and 28.9mmHg *(P*=0.029), respectively. These patients also had the highest percentage of coexisting valvular disease (50.4%).

HFrEF patients had a statistically significant higher average haemoglobin level of 132.5g/L (*P*=0.017) than HFpEF patients, who had the lowest average haemoglobin level of 127.7g/L. Furthermore, triglyceride levels and the percentage of patients with coexisting valvular heart disease were the lowest at 1.5 mmol/L (*P*=0.004) and 44.3%, respectively. HFmrEF patients showed to have the highest average creatinine value of 128.3 μmol/L (*P*=0.003) compared to the lowest seen in HFpEF.

Table 7. Table showing the basic characteristics of patients on admission

Parameters	HFpEF (N=322)	HFmrEF (N= 150)	HFrEF (N= 397)	*P* *
Systolic pressure (mmHg)	140±27.4	137.6±24.1	128.6±24.1	<0.001
Diastolic pressure (mmHg)	82.9±14.2	82.0±12.9	80.2±13.7	0.029
Heart rate (beats per minute)	89.7±29.7	90.3±29.0	93.9±30.0	0.138
Ejection fraction (%)	59.4±8.2	45.1±2.5	31.0±7.1	<0.001
Hemoglobin (g/L)	127.7±23.6	131.9±20.2	132.5±19.7	0.017
Glucose (mmol/L)	8.4±3.9	8.8±4.1	8.6±4.1	0.583
Sodium (mmol/L)	138.9±4.1	138.9±4.5	137.7±4.6	<0.001
Potassium (mmol/L)	4.2±0.8	4.2±0.6	4.2±0.6	0.368
Creatinine (µmol/L)	108±51.2	128.3±103.8	122±62.5	0.003
Total cholesterol (mmol/L)	4.7±1.3	4.8±1.3	4.5±1.4	0.031
Triglycerides (mmol/L)	1.7±1.0	1.7±0.8	1.5±0.8	0.004
LVEDD [a] (mm)	62.9±9.9	63.8±10	56.5±12.1	<0.001
Left atrium (mm)	47.7±10	50.1±8.2	49.1±9.5	0.024
NYHA Stage III (N)	26% (67/259)	27% (35/130)	47% (153/329)	NA
NYHA Stage IV (N)	17%(43/259)	9%(12/130)	22% (74/329)	NA
Valvular heart disease (%)	50.4%	47.5%	44.3%	NA

Data are presented as mean ± standard deviation or as number (%)

* One-way ANOVA

a Left ventricular end-diastolic diameter

Table 8 depicts the percentage of patients who received commonly prescribed HF medications based on their HF type. Diuretics were the most common medications prescribed: found in 78.2%, 70.4% and 81.6% of HFpEF, HFmrEF and HFrEF patients, respectively. The second most commonly prescribed medications were: ACEi found in 63.2% and 60.5% of HFmrEF and HFpEF patients, respectively.

Beta-blockers were the third most commonly prescribed medications in all three HF groups, with 94 (54%) in HFpEF patients, 51 (65%) in HFmrEF patients, and 161 (65%) in HFrEF patients.

Table 8: Overview of most commonly prescribed medications in heart failure management.

Drugs	HFpEF (N=322)	HFmrEF (N=150)	HFrEF (N=397)
Diuretics	78% (N=158/202)	70% (N=69/98)	82% (N=231/283)
ACEi	63% (N=115/182)	60% (N=49/81)	44% (N=152/349)
ARB	28% (N=7/57)	5% (N=7/141)	8% (N=24/300)
Aldosterone antagonists	19% (N=28/145)	10% (N=13/67)	37% (N=83/227)
Beta Blockers	54% (N=94/175)	65% (N=51/79)	65% (N=161/249)
Digoxin	27% (N=75/276)	49% (N=35/71)	43% N=105/243)
Calcium channel blockers	27% (N=38/140)	25% (N=15/60)	18% (N=38/206)
Oral hypoglycemics	12% (N=29/233)	26% (N=16/62)	25% (N=48/193)
Hypolipemic	30% (N=43/146)	35% (N= 23/66)	35% (N=77/219)

Data is presented as a % of adjusted patient numbers.

Abbreviations: ACE inhibitors- Angiotensin converting enzyme inhibitor, ARB- Angiotensin receptor blocker

4. **DISCUSSION**

This study included 869 patients, 322 of whom had HFpEF, 150 had HFmrEF, and 397 had HFrEF. One of the primary objectives of this study was to compare common risk factors and commonly prescribed medications used in their treatment, as well as examine the prognostic value of certain laboratory or imaging tests used in HF diagnosis.

As many studies have shown, despite the similar risk factors seen in the development of HF, males overall have a predilection for developing HFrEF whereas females predominate with HFpEF, a finding that was confirmed in this study with over 68% and 55% of male and female patients being affected, respectively(14).

The average age of HF was found to be the highest in HFpEF and HFmrEF and lowest in HFrEF of patients at 73, 72 and 68 years, respectively. Although the average age seems to be higher than the other HF types, younger HFpEF patients still display similar adverse cardiac remodelling compared to their older counterparts. Furthermore, obesity has been suggested to be a major cause of HFpEF development at an earlier age (49).

CAD was the most common comorbidity found in all groups with a prevalence of 77% in HFpEF and HFrEF and the highest in HFmrEF (85%). In the TIME-CHF study, CAD was prevalent in 58.2%, 56.5% and 31.3% of HFrEF, HFmrEF and HFpEF, respectively (50). Furthermore, in a study of the Swedish Heart Failure registry assessing baseline CAD in 42,987 patients, 52%, 61% and 60% of HFpEF, HFmrEF and HFrEF patients had CAD. They also discovered that prevalent CAD was linked to an increased risk of CAD events and all other outcomes across all EF categories, with the exception of all-cause mortality in HFpEF(51). This suggested that HFmrEF patients were more likely to deteriorate towards HFrEF rather than to HFpEF over time.

AHT was found to be the second most common comorbidity throughout all three groups of HF, evident in 68% of HFpEF and HFmrEF patients and 49% of HFrEF patients. This was consistent with many studies including the FHS in which 91% of the HF cohort had an earlier AHT diagnosis.

Over 55% of HFpEF patients had been diagnosed with atrial fibrillation (AF) on admission. A positive history has been proved to be a strong risk factor for the development of new-onset HFpEF(52). As HFpEF is the least commonly occurring HF and the type with the poorest evidence-based treatment guidelines, closer observation, or screening of AF patients, especially females for HFpEF could prove preventative.

On admission, HFpEF patients had the lowest statistically significant average hemoglobin level (127.7g/L) compared to HFrEF and HFmrEF patients, who had 131.9g/L and 135.5g/L, respectively (P= 0.017). Iron deficiency, which can exist without anemia, is found in up to 55% of chronic HF patients and up to 80% of AHF patients. Although the exact cause of iron deficiency in HF is unknown, it could be the result of a combination of increased loss, poor absorption or intake, and/or impaired metabolism caused by chronic HF-induced inflammation (53). Iron deficiency anaemia (IDA) is a widely known precipitating cause of HF and in severe cases, a primary cause of high output HF. Furthermore, it has been associated with a higher HF severity and poorer clinical outcomes, independent of hemoglobin levels in all types of HF. Therefore, the ESC recommends full hematinic blood tests including ferritin and TSAT during diagnosis and screening for HF(54).

Given that diuretics reduce congestion and thus improve symptoms in all forms of heart failure, it was not surprising that they were the most prescribed medications in all three groups of patients. Diuretics were prescribed to 78% of patients suffering from HFpEF, 70% in HFmrEF and 82% in HFrEF. These values are in line with the current literature (55).

In this study, fewer patients with HFpEF received beta-blockers compared to HFmrEF and HFrEF, this was consistent with studies and guidelines proving them as ineffective in the management of HFpEF and only recommended for patients with a co-existing condition requiring them (2).

The use of calcium channel blockers was higher in the HFpEF and HFmrEF group of patients, compared to HFrEF which may be due to the higher prevalence of hypertension in the HFpEF group and the fact that these agents have shown to exacerbate HF in HFrEF due to their negative inotropic effects (56).

ACEi were one of the first classes of drugs shown to reduce morbidity and mortality in patients with HFrEF and are recommended in all patients unless contraindicated or not tolerated. This study, however, found that there was fewer percentage of patients prescribed ACEi in HFrEF compared to HFmrEF and HFpEF. This was inconsistent with the current literature and was most likely due to either a reduction in sample size available for this drug, skewing and misinterpreting the results, or to the guidelines in place at the time of the study not having sufficient evidence for its disease-modifying effects. A similar problem was seen in the finding for the prescription of ARBs. However, the percentage of patients prescribed ARBs

in the management of HFrEF is generally expected to be low as they are recommended as a second-line agent for patients who cannot tolerate ACE-I or ARNIs (40).

These results for the most common comorbidities supported our initial hypothesis that CAD, AHT, and AF were the most common comorbidities in HF patients. We also observed consistency in the treatment of HFmrEF, which was more similar to HFpEF than HFrEF, as evidenced by the increased use of ACEi and calcium channel blockers in these patients.

This retrospective study did have several limitations. Various data points were emitted from patients without adequate reasoning, resulting in a smaller data set being used to determine information such as averages or percentages. This difference in sample size could have skewed and misrepresented certain findings, this was especially prevalent for the data regarding medications and for prevalence of kidney failure and diabetes. This study showed them to be the least common comorbidities observed in all types of HF. This finding was contraradictory to current literature whose proves them to be very common risk factors for HF development (15,42).

Furthermore, as HFmrEF was introduced in the ESC 2016 guidelines, treatment options before this were limited to those studied for the management of HFpEF and HFmrEF. Hence patients should have been studied from 2016 onwards to highlight which treatments have often been employed for use in HFmrEF and analyse their effectiveness in reducing morbidity and mortality. This would further allow for a better understanding of all three HF types and what possible risk factors may play a role in the transition between certain HF types.

5. CONCLUSION

Based on the study results, we can conclude the following:

1. In the group of patients treated with heart failure with preserved ejection fraction, women predominated;
2. In patients treated with heart failure with mildly-reduced and reduced ejection fraction, men predominated;
3. The average age of patients was lowest in patients with reduced ejection fraction heart failure;
4. The most common comorbidity found in all types of heart failure was coronary artery disease followed by arterial hypertension;
5. Patients treated for heart failure with preserved ejection fraction had the lowest average haemoglobin levels;
6. The most common medication used upon admission in all groups of patients were diuretics;
7. Beta-blockers were prescribed more often to patients with preserved ejection fraction heart failure;
8. Angiotensin converting enzyme inhibitors and Calcium channel blockers were more commonly prescribed to patients with mildly-reduced and preserved ejection fraction heart failure.

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8. SUMMARY

Objectives: The aims and objectives of this study were to compare the baseline characteristics of patients treated for heart failure with reduced (HFrEF), mildly-reduced (HFmrEF) and preserved (HFpEF) ejection fraction according to data obtained from the Croatian registry for patients with heart failure.

Materials and Methods: This retrospective study included a total of 869 patients hospitalised with heart failure of which 322 had HFpEF, 150 had HFmrEF and 397 had HFrEF. All patient data was extracted from the Croatian registry for patients with heart failure and analyzed using Microsoft Excel and GraphPad Prism.

Results: Of the 322 patients who were treated for HFpEF, 55% were females. The average age of patients treated with HFrEF was 68 years whereas the average age in HFmrEF and HFpEF was 72 and 73 years respectively. The most common comorbidity in patients treated with HFpEF was coronary artery disease (77%), arterial hypertension (68%), and pulmonary hypertension (55%). The most common comorbidities in patients with HFmrEF were coronary artery disease (85%), arterial hypertension (68%), and atrial fibrillation (57%). The most common comorbidities in patients with HFrEF were coronary artery disease (77%), arterial hypertension (49%), and atrial fibrillation (45%). The most commonly prescribed medications in HFpEF were diuretics (78%), ACEi (63%), and beta-blockers (54%). The most commonly prescribed medication in HFmrEF were diuretics (70%), beta-blockers (65%), and ACEi (61%). The most commonly prescribed medication in HFrEF were diuretics (82%), Beta-blockers (65%), and ACEi (44%).

Conclusions: Patients treated for HFpEF were more likely to be women and more elderly. The most common among all heart failure groups were coronary artery disease and arterial hypertension. Regarding medical management, beta-blockers were more often prescribed to HFpEF patients whereas calcium channel blockers were more often prescribed to HFmrEF and HFpEF patients.

9. CROATIAN SUMMARY

Naslov: Karakteristike pacijenata s očuvanom, srednjom i smanjenom funkcijom rada srčane klijetke kod zatajenja srca liječenih u Splitu

Ciljevi: Ciljevi i zadatci ovog istraživanja bili su usporediti osnovne karakteristike bolesnika liječenih od zatajenja srca sa smanjenom, srednjom i očuvanom funkcijom rada srčane klijetke prema podatcima dobivenim iz hrvatskog registra za pacijente sa zatajenjem srca.

Materijali i metode: Ova retrospektivna studija uključivala je ukupno 869 pacijenata hospitaliziranih sa zatajenjem srca od kojih je 322 imalo HFpEF, 150 HFmrEF, a 397 HFrEF. Svi podatci o pacijentima izvađeni su iz hrvatskog registra za pacijente sa zatajenjem srca i analizirani s pomoću Microsoft Excela i GraphPad prizme.

Rezultati: Od 322 pacijenta liječena od HFpEF-a, 55 bile su žene. Prosječna dob bolesnika liječenih od HFrEF-a bila je 68 godina, dok je prosječna dob bolesnika liječenih od HFmrEF-a i HFpEF-a bila 72, odnosno 73 godine. Najčešći komorbiditet u bolesnika liječenih od HFpEF-a bila je bolest koronarnih arterija (77 %), arterijska hipertenzija (68 %) i plućna hipertenzija (55 %). Najčešći komorbiditeti u bolesnika s HFmrEF-om bili su bolest koronarnih arterija (85 %), arterijska hipertenzija (68 %) i fibrilacija atrija (57 %). Najčešći komorbiditeti kod bolesnika s HFrEF-om bili su bolest koronarnih arterija (77 %), arterijska hipertenzija (49 %) i fibrilacija atrija (45 %). Najčešće propisani lijekovi za HFpEF bili su diuretici (78 %), ACEi (63 %) i beta-blokatori (54 %). Najčešće propisani lijekovi protiv HFmrEF-a bili su diuretici (70 %), beta-blokatori (65 %) i ACEi (61 %). Najčešće propisani lijekovi za HFrEF bili su diuretici (82 %), beta-blokatori (65 %) i ACEi (44 %).

Zaključak: Pacijenti liječeni od HFpEF-a uglavnom su bile starije žene. Najčešća među svim skupinama zatajenja srca bila je bolest koronarnih arterija i arterijska hipertenzija. Kad je riječ o medicinskom liječenju, beta-blokatori češće su propisivani pacijentima s HFpEF-om, dok su blokatori kalcijevih kanala češće propisivani pacijentima s HFmrEF-om i HFpEF-om.

10. CURRICULUM VITAE

Personal Data

Name: Hishaam Ashraf

Date of Birth: 10th January 1994

Place of Birth: Bradford, England

Nationality: British

Email: hishaam1234@hotmail.co.uk

Education:

Medicine, MD, University of Split, School of Medicine Split, Croatia – 2016-2022

BSc (Hons) Biomedical Science, University of Lincoln, England – 2013-2016

4 A-levels, Woking College, Surrey, England - 2010-2013

8 GCSE, Fullbrook School, Surrey, England - 2005-2010

Languages:

English (Fluent)

Urdu (Fluent)

Croatian (basic)

Traineeships:

Jan 2022 – Feb 2022: Acute Medicine, Chelsea and Westminster Hospital, London, England

May 2020 – Emergency Medicine, Dubrovnik District General Hospital, Dubrovnik, Croatia

Jun 2015 – Trauma and Orthopaedic Surgery, Lincoln County Hospital, Lincoln, England

Extra-curricular activities

Director of University Affairs, International Students Association (ISA) – 2018-2020

Project lead for University of Split, Interdisciplinary Skills Competition 2020 - 2020

Course vice-representative – 2020-2021