Clinical features and complications of advanced heart failure: single center follow up

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List of abbreviations

ACEi	angiotensin converting enzyme inhibitors
ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ADH	antidiuretic hormone
AF	atrial fibrillation
AHF	acute heart failure
ARBs	angiotensin receptor blockers
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CBC	complete blood count
CXR	chest x-ray
DVT	deep vein thrombosis
ECG	electrocardiography
EF	ejection fraction
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LA	left atrium
LFTs	liver function tests
LV	left ventricle
LVEF	left ventricular ejection fraction
NT pro-BNP	N-terminal pro-BNP
NYHA	New York Heart Association
PE	pulmonary embolism
RAAS	renin-angiotensin-aldosterone system
SNS	sympathetic nervous system
TTE	transthoracic echocardiography

Table of Contents

Summary

Clinical features and complications of advanced heart failure: single center follow up

Introduction Heart failure is a complex clinical syndrome that develops when adequate cardiac output cannot be maintained and can be accompanied by elevated intracardiac pressures. Advanced heart failure is a common cause of admission to hospital, and one with significant morbidity and mortality.

Objective The aim of the present study was to better understand the presentation and clinical features of advanced heart failure patients, as well as provide perspective on complications and mortality rate.

Methods This study was a prospective cohort study of patients presenting to the Emergency Department of Sisters of Charity University Hospital Centre, Zagreb, Croatia between February 23rd 2018 and March 29th 2019 for primary reason of presentation for acute heart failure.

Results The key clinical features that patients presented with were those of pulmonary congestion with dyspnea being present in 89.7% of all patients, and decreased exercise tolerance in 91.4%. The most common complications were cardiac arrhythmias (63.5%) and impaired kidney function (60.3%). Patients had an average three, six and twelve-month mortality rate of 23.9%, 34.8% and 43.5% respectively.

Conclusion Identifying the presenting clinical features and complications of advanced heart failure may help reduce its mortality, which is fairly high. Mortality rates are greater in HFpEF group of patients, suggesting these patients may need closer observation and management.

Sažetak

Kliničke prezentacije i komplikacije uznapredovale srčane dekompenzacije: jednocentrično prospektivno istraživanje

Uvod Zatajenje srca je složen klinički sindrom koji se razvija kada se ne može održavati adekvatan srčani rad te može biti praćen povišenim intrakardijalnim pritiscima. Uznapredovala srčana dekompenzaciha česti je uzročnik hospitalizacije sa značajnim morbiditetom i mortalitetom.

Cilj Cilj ovoga rada je bolje razumijevanje prezentacije i kliničkih značajki bolesnika s uznapredovalom srčanom insuficijencijom, kao i pružanje perspektive o komplikacijama i stopi smrtnosti.

Metode Ovo istraživanje bilo je prospektivno kohortno istraživanje bolesnika liječenih u Kliničkom bolničkom centru Sestre milosrdnice između 23.02.2018. I 29.03.2019 radi akutnog zatajenja srca.

Rezultati Glavne kliničke značajke bolesnika bile plućni edem (dispneja bila je prisutna u 89.7% bolesnika) i smanjena tolerancija napora (91.4%). Najčešće komplikacije su bile srčane aritmije (63.5%) i oštećenje bubrežne funkcije (60.3%). Prosječan tri-, šest- i dvanaest-mjesečni mortalitet bio je 23.9%, 34.8% i 43.5%.

Zaključak Prepoznavanje postojećih kliničkih značajki i komplikacija uznapredovalog zatajenja srca može pomoći u smanjenju smrtnosti, koja je prilično visoka. Stope smrtnosti veće su u skupini bolesnika sa sačuvanom ejekcijskom frakcijom, što sugerira da ovi bolesnici treba pažljivije promatranje i obradu.

Preface

Introduction to Heart Failure

Heart failure (HF) is a complex clinical syndrome that develops when adequate cardiac output cannot be maintained and can be accompanied by elevated intracardiac pressures. It results from structural and/or functional impairment of ventricular filling or ejection of blood, and is characterized by typical symptoms and signs.

Current HF definitions are restricted to stages when clinical symptoms are present, but structural or functional cardiac abnormalities, which are precursors of HF, can be apparent in an asymptomatic patient. Finding an underlying cardiac cause is essential to establishing the HF diagnosis. Usually it is a myocardial abnormality, but can also be due to an abnormality of the valve, pericardium, endocardium, heart rhythm or conduction (Ponikowski et al., 2016).

Historically, most HF patients were differentiated either as having systolic HF or diastolic HF (Federmann & Hess, 1994). Current terminology of HF divides patients according to left ventricular ejection fraction (LVEF). Patients with reduced ejection fraction (EF) are termed to have HF with reduced ejection fraction (HFrEF), and typically have LVEF < 40%. Those with LVEF ≥ 50% have HF with preserved ejection fraction (HFpEF). The new ESC guidelines (Ponikowski et al., 2016) recognize a previous 'grey area' of patients with LVEF in the range of 40-49%, that are now defined as having HF with mid-range EF (HFmrEF). Patients with HFpEF normally do not present with dilated left ventricle (LV), but have increased LV wall thickness, and possibly increased left atrium (LA), which would be a sign of increased filling pressures. These patients used to be defined as having diastolic HF, but have now been found to have subtle systolic function abnormalities (Pfeffer, Shah, & Borlaug, 2019). Patients with HFrEF were defined as having systolic HF, but also have a diastolic dysfunction. HFmrEF and HFpEF patients must have elevated natriuretic peptides and either relevant structural heart disease or diastolic dysfunction besides the appropriate EF measurements and clinical symptoms and signs.

In relation to the time course of HF, patients can be defined as having asymptomatic LV systolic dysfunction if they have never developed typical symptoms or signs of HF but are found to have reduced LVEF. New-onset or '*de novo*' HF patients can present with an acute heart failure (AHF) with sudden onset of symptoms or in a subacute fashion with symptoms gradually worsening over weeks or months. Chronic HF patients have had HF diagnosis for longer time, and can be stable when their symptoms are controlled, or can become 'decompensated' when symptoms start to worsen. Decompensated HF can also present as an AHF.

New York Heart Association (NYHA) functional classification is used to describe patients based on the severity of their symptoms and exercise intolerance. Symptom severity does not correlate well with measures of LV function, but has clear relationship to survival (Tripoliti, Papadopoulos, Karanasiou, Naka, & Fotiadis, 2017). The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification stages HF according to structural changes and symptoms. The correlation between the two classification systems is outlined in Table 1.

According to ESC 2018 guidelines (Crespo-Leiro et al., 2018) on advanced heart failure: "Advanced heart failure encompasses patients who remain severely symptomatic despite optimal guideline-directed management regardless of left ventricular ejection fraction (LVEF), including patients with advanced heart failure who remain ambulatory but are essentially New York Heart Association (NYHA) class IV."

Advanced heart failure is established independently of EF, and depends on patient's symptoms, prognostic markers, presence of end-organ damage, and goals for therapy. Unplanned outpatient hospital visits and hospitalizations due to worsening of symptoms should be included in diagnosis of advanced heart failure, as well as recurrent malignant arrhythmias (Crespo-Leiro et al., 2018).

Table 1 NYHA and ACCF/AHA heart failure classifications. Adapted from ESC 2018 guidelines on advanced heart failure (Crespo-Leiro et al., 2018).

<table>
<tr><th colspan="2">NYHA functional classification</th><th colspan="2">ACCF/AHA Stages of HF</th></tr>
<tr><td>none</td><td></td><td>A</td><td>At high risk for HF but without structural heart disease or symptoms of HF.</td></tr>
<tr><td>I</td><td>No limitations of physical activity. Ordinary physical activity does not cause symptoms of HF.</td><td>B</td><td>Structural heart disease but without signs or symptoms of HF.</td></tr>
<tr><td>II</td><td>Slight limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in symptoms of HF.</td><td rowspan="3">C</td><td rowspan="3">Structural heart disease with prior or current symptoms of HF.</td></tr>
<tr><td>III</td><td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.</td></tr>
<tr><td>IV</td><td>Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td></tr>
<tr><td colspan="2"></td><td>D</td><td>Refractory HF requiring specialized interventions.</td></tr>
</table>

Pathophysiology

In heart failure, cardiac output fails to meet body's circulatory demand, and is most commonly caused by a ventricular dysfunction. This can be either due to a poor systolic contraction, where there is an underlying myocardial disease, or diastolic

dysfunction due to abnormal ventricular relaxation, as is the case in left ventricular hypertrophy (Jackson, Gibbs, Davies, & Lip, 2000). Reduced cardiac output leads to the activation of sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS). When ventricular function is impaired, activation of these two systems leads to a vicious cycle with further decrease in cardiac output, and continuous activation of SNS and RAAS, exacerbated by an increase in peripheral vascular resistance. RAAS is responsible for vasoconstriction and sodium and water retention, which contribute to increased afterload and preload, respectively. Activated SNS results in increased myocardial contractility and heart rate and peripheral vasoconstriction, which initially helps sustain sufficient cardiac output. However, prolonged activation of SNS can cause apoptosis of cardiac myocytes, cardiac hypertrophy and focal myocardial necrosis (Hartupee & Mann, 2017). Increased left and right atrial pressures cause pulmonary and peripheral edema, respectively, which are exacerbated by sodium and water retention.

Signs & Symptoms

Patients with heart failure normally present with non-specific signs and symptoms that can be due to a number of other conditions. However, there are a number of signs and symptoms that are more typical of heart failure, this is summarized in Table 2.

Table 2 Typical signs and symptoms of heart failure. Adapted from 2018 ESC guidelines on advanced heart failure (Crespo-Leiro et al., 2018).

Signs	Symptoms
Typical	Typical
Jugular veins distention Protodiastolic gallop (S3) Laterally displaced apical impulse	Dyspnea Orthopnea Paroxysmal nocturnal dyspnea Worsening of usual physical activity Fatigue
Less typical	Less typical
Rales on lung auscultation Pleural effusion Hepatomegaly Ascites Peripheral edema Tachycardia Irregular pulse Cheyne Stokes respiration Cold extremities	Loss of appetite Oliguria Body weight rise (>2kg/week) Syncope Palpitations Dizziness

Investigations

Apart from routinely performed tests – complete blood count (CBC), blood urea nitrogen (BUN) and creatinine, glucose, serum electrolytes, liver function tests (LFTs), and coagulation profile – heart failure patients normally have their chest x-ray (CXR) taken, receive electrocardiography (ECG) and transthoracic echocardiography (TTE) (Davies, Gibbs, & Lip, 2000).

In suspected HF patients, B-type natriuretic peptide (BNP) or its precursor N terminal pro-BNP (NT pro-BNP) are measured. If the value is normal and the patient is not treated for HF or other cardiac disease, it excludes cardiac disease. High values are suggestive of HF (Katritsis, 2016).

CXR can show pulmonary venous congestion or edema in an acute setting, and an enlarged heart shadow in a non-acute setting.

ECG may show ventricular hypertrophy, atrial enlargement, previous or active ischemia, and arrhythmias. Absence of any ECG abnormality has a high negative predictive value for the diagnosis of HF (Katritsis, 2016).

Transthoracic echocardiography is the method of choice when it comes to assessing systolic and diastolic function of the myocardium.

Complications

Advanced heart failure can lead to a myriad of complications. Some of the more frequent ones are:

Electrolyte abnormalities (hypokalemia, hyperkalemia, hyponatremia)

Hypokalemia could be the result of either treatment with potassium losing diuretics or hyperaldosteronism which occurs upon activation of renin-angiotensin system (RAAS).

Hyperkalemia might result from different set of drugs used for treatment of HF, such as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) or aldosterone antagonist. All these are more severe in the setting of renal failure (Leier, Dei Cas, & Metra, 1994).

Hyponatremia can occur due to increased antidiuretic hormone (ADH) release, as body's response to reduced cardiac output and systemic blood pressure. It can also be caused by diuretic therapy or cell membrane ion pump failure. It is thought to be poor prognostic sign.

Cardiac arrhythmias (atrial fibrillation occurs in 20% of HF patients)

Arrhythmias result from electrolyte misbalance, structural changes of the heart, or sympathetic activation which has pro-arrhythmogenic effects (Masarone et al., 2017). Atrial fibrillation (AF) is said to have prevalence of 5% in NHYA I patients and 25-50% in NHYA III/IV patients (Katritsis, 2016). Ventricular arrhythmias are associated with a worse prognosis in HF patients.

End-organ damage (renal failure and impaired hepatic synthetic function)

Low cardiac output leads to poor perfusion which in combination with diuretic use ACEi or ARBs can result in renal failure. Poor perfusion can also affect the liver, especially in combination with venous congestion due to right sided heart failure, which can clinically present as mild jaundice and deranged liver function tests (LFTs). Due

to hepatic involvement, synthesis of clotting factors can be reduced, and anticoagulation can also prove to be difficult to control.

Thromboembolism

Low cardiac output and immobility can cause deep vein thrombosis (DVT) and pulmonary embolism (PE) with a relative risk of 1.18 in acute heart failure patients (Ng, Tsai, Khatri, Barakat, & Elkayam, 2010), while patients with concurrent AF or atrial flutter can have systemic emboli, predisposing patients to stroke.

Sudden death

Sudden death in heart failure patients mainly occurs due to ventricular arrhythmias, electromechanical dissociation or asystole as a consequence of pump failure (Saour, Smith, & Yancy, 2017).

Hypothesis

The main hypotheses of this study are:

- Complications in advanced HF patients are very common, and that there may be blood and imaging results obtained in the emergency department before admission that are predictive of complications and mortality
- HF patients with reduced ejection fraction should have higher 1-year mortality rate.
- Ejection fraction has been shown to affect presentations differently and this study will compare how advanced HF patients with reduced EF present compare to patients with mid-range and preserved EF, as well as whether there is a difference in 1-year mortality rate between these groups.

Objectives

The aim is to better understand the presentation and clinical features of advanced HF patients, as well as provide perspective on complications and mortality rate.

Methods

This study was a prospective cohort study of patients presenting to the Emergency Department of Sisters of Charity University Hospital Centre, Zagreb, Croatia between February 23rd 2018 and March 29th 2019 for primary reason of presentation of acute heart failure. Patients were subsequently admitted to the hospital and treated according to European Society of Cardiology guidelines, as well as local guidelines by the Croatian Society of Cardiology.

Study setting

The study was conducted in Sisters of Charity University Hospital Centre, Zagreb, Croatia, a tertiary centre located within the metropolitan area of Zagreb, Croatia. The hospital is a teaching hospital for the University of Zagreb School of Medicine. Further, the hospital serves as a catchment for the local area, as it offers intensive cardiology treatment and supports required in advanced heart failure patients, such as continuous inotropic infusions, mechanical circulatory support and surgical treatments.

Participants

The study population comprised of 58 adult heart failure patients who were consecutively managed by the emergency and cardiology team form the arrival to the emergency department to discharge from the hospital, or death in case of inpatient death outcome. The physiological aetiology and causes of trauma differ significantly between children and adults and are investigated and treated under separate protocols; therefore, heart failure patients < 18 were not included in the study.

Inclusion Criteria

-Patients with a primary presentation for acute heart failure in the Emergency Department of Sisters of Charity Hospital centre Zagreb
-Patients with a confirmed diagnosis of acute heart failure according to the Framingham criteria (as shown below)
-Patients older than 18 years of age

Framingham criteria

Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria:
· Paroxysmal nocturnal dyspnea · Neck vein distention · Rales · Radiographic cardiomegaly (increasing heart size on chest radiography) · Acute pulmonary edema · S3 gallop · Increased central venous pressure (>16 cm H2O at right atrium) · Hepatojugular reflux · Weight loss > 4.5 kg in 5 days in response to treatment

Minor criteria:
· Bilateral ankle edema · Nocturnal cough · Dyspnea on ordinary exertion · Hepatomegaly · Pleural effusion · Decrease in vital capacity by one third from maximum recorded · Tachycardia (heart rate>120 beats/min.)

Minor criteria are acceptable only if they cannot be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome).

The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure (McKee, Castelli, McNamara, & Kannel, 1971).

Exclusion Criteria

On presentation to the ED department, patients were excluded from the study if
-Undergoing dialysis and/or with renal insufficiency (creatinine 400umol/L)
-Liver cirrhosis Stage B or C
-Acute or chronic inflammatory disease
-Patients that have been treated due to severe trauma or had surgery in the last 30 days
-Patients currently undergoing chemotherapy or having emergency transfer to a different hospital
-Patients with unusual aetiology of heart failure (amyloidosis, sarcoidosis, operated congenital heart defects)
-Patients that have expected shorter life expectancy (metastatic carcinoma)
-Patients that refuse to participate in the study

<u>On admission to hospital, patients were subsequently excluded if:</u>

-During their hospitalisation, the patient developed another acute condition unrelated to heart failure (e.g. pneumonia, pancreatitis, acute viral or toxic hepatitis)
-Patients that, after further diagnostic evaluation had heart failure diagnosis excluded

Outcome measures

Patients remained hospitalised until clinically necessary, and were discharged upon clinical improvement, transferred to another hospital if further treatment was necessary or until their death if it occurred during the course of treatment.
After the inclusion in the study, patients were followed up for a year to track mortality rate.

Results

Demographics

Table 3 Age and gender distribution of patients included in the study.

Age group	% Female	% Male
< 50	33	67
50 – 59	0	0
60 – 69	20	80
70 – 79	43	57
> 80	71	29
All	47	53

Overall, the divide between male and female population of patient cohort is fairly equal. However, we can observe that there is a difference in age distribution. The younger age groups, under 50 years of age and 60-69 years have higher male proportion, 67 and 80 percent respectively, while the oldest age group has a higher female proportion with 71 percent of the age group over 80 years being female.

Symptoms

Table 4 Presenting symptoms of patients included in the study.

Symptoms	% of all patients	% of HFrEF	% of HFmrEF	% of HFpEF
Dyspnea	89.7	79.0	100.0	95.2
Orthopnea	80.7	68.4	90.9	85.7
Paroxysmal nocturnal dyspnea	47.4	31.6	72.7	47.6
Loss of appetite	40.4	57.9	45.5	23.8
Fatigue	89.5	94.7	72.7	90.5
Oliguria	24.6	21.1	18.2	33.3
Body weight rise	19.6	27.8	0.0	19.1
Worsening of usual physical activity	91.4	94.7	83.3	90.5
Syncope	3.4	0.0	0.0	9.5

The most frequent symptoms in patients presenting to the ED were dyspnea, fatigue, and worsening of the usual physical activity, that were present in 89.7, 89.5 and 91.4 percent of all patients, respectively. Worsening of usual physical activity was the most evenly distributed among the three groups of patients (HFrEF, HFmrEF, HFpEF), while dyspnea and fatigue ranged from 79.0-100.0 and 72.7-94.7 percent respectively. Orthopnea was present in 80.7 percent of patients overall, and ranging from 68.4 percent in HFrEF patients to 90.9 percent in HFmrEF patients, with HFpEF patients presenting with it in 85.7 percent of cases.

Paroxysmal nocturnal dyspnea and loss of appetite presented in less than half of all patients, paroxysmal nocturnal dyspnea raging from 31.6-72.7 in different groups and loss of appetite 23.8-57.9 percent.

Oliguria, body weight rise and syncope were all present in less than third of all patients.

Vital signs

Table 5 Vital signs of patients included in the study.

Vital signs	**% of all patients**	**% of HFrEF**	**% of HFmrEF**	**% of HFpEF**
Hypertension	40.4	21.1	58.3	47.6
Hypotension	0.0	0.0	0.0	0.0
Tachycardia	28.1	26.3	50.0	19.1
Bradycardia	3.5	0.0	0.0	4.8
Tachypnea	76.5	62.5	81.8	84.2

Of all vital signs, the most common among all patients was tachypnea, standing at 76.5 percent overall, with a range 62.5-84.2 percent between the groups. The second most common was hypertension, which was present in 40.4 percent overall, but was as low as 21.2 percent in HFrEF group of patients, and significantly higher in HFmrEF and HFpEF groups, standing at 58.3 and 47.6 percent, respectively. Tachycardia showed to have a different presentation amongst the groups as well, standing at 50.0 percent in HFmrEF group, and lower in HFrEF and HFpEF groups, at 26.3 and 19.1 percent, respectively. Bradycardia was only present in HFpEF group, at 4.8 percent of patients within the group, while hypotension was not present in any of the groups.

Clinical signs

Table 6 Clinical signs of patients included in the study.

Clinical signs	**% of all patients**	**% of HFrEF**	**% of HFmrEF**	**% of HFpEF**
Jugular vein distention	30.4	33.3	36.4	19.1
Protodiastolic gallop (S_3)	9.4	11.8	0.0	10.0
Rales (crackles) on lung auscultation	72.2	76.5	81.8	70.0
Pleural effusion	67.9	58.8	63.6	80.0
Liver enlargement	27.8	41.2	18.2	25.0
Ascites	16.7	17.7	9.1	10.0
Peripheral edema	64.3	72.2	36.4	66.7

The most common clinical sign present in AHF patients in the ED were rales on auscultation in 72.2 percent of patients, followed by pleural effusion and peripheral edema, at 67.9 and 64.3 percent, respectively. These signs were relatively equally present between different groups of patients, apart for the peripheral edema that had a significant drop in HFmrEF group to 36.4 percent.

Jugular vein distention, protodiastolic gallop, liver enlargement and ascites were all present in less than a third of all patients. Jugular vein distention was more prominent in HFrEF and HFmrEF groups, representing 33.3 and 36.4 percent respectively, with HFpEF only having 19.1 percent presence.

Complications

Table 7 Abnormal findings in patients included in the study.

Complications	**% of all patients**	**% of HFrEF**	**% of HFmrEF**	**% of HFpEF**
Cardiac arrhythmias	63.5	77.8	45.5	61.1
Hyponatremia	10.3	10.5	16.7	9.5
Hypokalemia	3.6	0.0	18.2	0.0
Hyperkalemia	18.2	21.2	18.2	21.1
High urea	87.9	89.5	91.7	81.0
High creatinine	60.3	68.4	91.7	66.7
Low albumin	26.0	29.4	9.1	27.8
High bilirubin	43.1	58.8	30.0	36.8
High AST	19.3	31.6	8.3	15.0
High ALT	10.3	10.5	8.3	14.3

Patient workup showed majority of them had elevated urea – 81.0 percent of patients in HFpEF group, 89.5 percent in HFrEF group and 91.7 percent in HFmrEF group. The second most common of complications were cardiac arrhythmias that were present in 63.5 percent of all patients, but comprised 77.8 percent in HFrEF group and only 45.5 percent in HFmrEF. Other common abnormalities were high creatinine, at 60.3 percent of all patients, and high bilirubin present in 43.1 percent of all patients. Electrolyte abnormalities, low albumin and high AST and ALT were present in less than a third of all patients.

Mortality rate

Table 8 Mortality rates of patients included in the study.

Mortality rate	% of all	% of HFrEF	% of HFmrEF	% of HFpEF
3 month	23.9	13.3	22.2	33.3
6 month	34.8	26.7	44.4	33.3
9 month	41.3	33.3	44.4	38.9
12 month	43.5	33.3	44.4	44.4

Three-month mortality rate was 23.9 percent for all patients, being the highest in HFpEF group where it is standing at 33.3 percent and the lowest in HFrEF group where it is 13.3 percent.

Six-month mortality rate leaped to 34.8 percent overall, being the highest in HFmrEF group at 44.4 percent, slightly lower for HFpEF group at 33.3 percent, and the lowest for HFrEF group at 26.7 percent.

Nine-month mortality rate stands at 41.3 percent overall, and remains the highest in in HFmrEF group at 44.4 percent, followed by HFpEF group with 38.9 percent, and remaining the lowest in HFrEF group at 33.3 percent.

Twelve-month mortality rate remained fairly close to nine-month, with 43.5 percent, only rising in the HFpEF group to 44.4 percent.

Discussion

Patients with advanced heart failure that presented to the ED and fulfilled the criteria to be included in the research were equally likely to be male or female. However, female patients were more likely to be in an older age group than their male counterparts. There was no clear peak age of incidence for hospitalisation for advanced heart failure, and therefore the clinician should suspect the diagnosis in all patients, consistent with global epidemiological data (Rudiger et al., 2005). It is important to discuss the clinical features that may indicate a diagnosis of advanced heart failure, for the clinician to be aware of the major potential complications during a patient's admission, and to have a realistic understanding of mortality rates and the influence of the type of heart failure on these rates. These three areas are discussed below.

Clinical features

Respiratory distress dominated the symptoms, vital signs and clinical signs of patients presenting to the ED with advanced heart failure, and this was consistent between all three groups of patients according to their ejection fraction. The most common presenting symptoms were those of pulmonary congestion (dyspnea, orthopnea, paroxysmal nocturnal dyspnea), as found in other studies (Gheorghiade, Filippatos, De Luca, & Burnett, 2006), and decreased physical tolerance (fatigue, worsening of usual physical activity). Similarly, the vital sign that was most commonly out of the normal references range was tachypnea. There were also just under half patients who had hypertension, which may have a causative effect on their heart failure or may exist as a co-morbidity (Mentz & Felker, 2013). Finally, the most common clinical signs were pleural effusion (a clinical sign that was correlated with consistent x-ray findings) and rales (crackles) on lung auscultation, further highlighting that pulmonary congestion and its effects accounted for the most prominent presenting clinical features of advanced heart failure. Pathophysiologically, pulmonary congestion reflects left heart failure, which occurs in all groups of HF patients according to their ejection fraction.
However, advanced heart failure patients may still present with signs and symptoms other than of pulmonary origin. Fatigue and worsening of normal physical activity are amongst the highest reported, but remain fairly non-specific. Peripheral edema is

reported in over half of all patients, reflecting right sided heart failure, that may be isolated or in conjunction with left side heart failure. Other possible signs of right side heart failure are jugular vein distention, liver enlargement and ascites which were present in less than a third of all patients. Due to low effective circulating blood volume causing water retention, patients may present with oliguria, body weight rise and tachycardia.

Complications

Heart failure can lead to a great range of complications, which themselves carry a significant risk of morbidity and mortality. In this study, complications were assessed from blood results and ECG findings on presentation to the ED.

Heart failure can lead to end-organ damage. Impaired renal function, measured by elevated urea and creatinine were two of the most common complications seen in the patients. Pathophysiology of the two diseases, heart failure and kidney failure, can be caused by the same underlying disease process, ischemia or HF can lead to renal hypoperfusion and excess activation of the RAAS system impairing kidney function (Metra et al., 2012).

Impaired liver function is also not an uncommon complication in these patients. Although not a definitive indicator, a significant number of patients, 43.1%, had elevated bilirubin with a smaller proportion of patients having elevated AST and ALT and low albumin.

Another common complication is cardiac arrhythmias, which was present in over 60% of patients. Arrhythmias, which included all abnormal rhythms that were not in sinus, are associated with worsening of the disease and poor prognosis. Consequently, it is important to diagnose and treat arrhythmias to prevent morbidity and mortality from malignant arrhythmias- ventricular tachycardia, ventricular fibrillation (Gorenek Chair et al., 2020).

Electrolyte abnormalities, the cause of which is multifactorial and can be due to the disease process or as a result of treatment, were uncommon in the patients, but should be routinely monitored as treatment is initiated.

Mortality

There were two trends in mortality analysis. The first is that there is a consistent increase in mortality from three to nine months after hospital admission, after which the rate plateaus. Secondly, there is a difference in mortality based on ejection fraction of patients with mortality rates being slightly higher in HFpEF and lowest in HFrEF patients. This difference was not statistically significant (P=0.19) which could be due to small sample size of the study. Regardless, this second trend is in opposition to previously reported literature, including meta-analyses, which have suggested that patients with heart failure with reduced ejection fraction have worse mortality outcomes than those with mid-range or preserved ejection fraction (Vergaro et al., 2019) (Lam et al., 2018). However, this is mostly from outpatients sampled in the community. it is important to compare morbidity and mortality outcomes between these groups in hospitalised patients, which is the focus of this study in these hospitalised patients, consistent with other studies, there is no significant difference in mortality outcomes, with our study suggesting that in fact those with preserved ejection fraction may have higher mortality. The reasons for this may be multifactorial: less treatment options available for HFpEF, later presentations of those patients or other co-morbidities (Burkhoff, 2012).

Limitations

This study is a prospective cohort patient study, based on available data at the patient presentation, and consequently followed up for mortality rate for one year after admission. One limitation is that symptoms were taken from patient's report and can thus be influenced by patient's medical understanding and cognitive status.

Another limitation is that complications were inferred from laboratory results and whilst they may indicate certain complications, patients were not specifically assessed for those complications.

Finally, although we have mortality data one year after patient's initial presentation, we do not know whether their death was related to heart failure or other co-existing medical conditions.

Future directions

Future studies should more thoroughly investigate potential complications of advanced heart failure, as this would help elucidate the most significant considerations that a clinician has to make in managing heart failure patients both during their admission, as well as long-term to reduce mortality. It would also be helpful to follow patients for a longer period after their initial admission (e.g. five years), to get a more long-term perspective on the differences in mortality rates between heart failure patients with different ejection fractions.

Conclusions

Advanced heart failure is a common cause of admission to hospital, and one with significant morbidity and mortality. Recognising that patients commonly present with clinical features of pulmonary congestion and decreased physical tolerance will help guide swift and appropriate management. Further, recognising key complications – cardiac arrhythmias and impaired renal function – can help guide management of patients. Finally, it is important to note that patients had an average three, six and twelve-month mortality rate of 23.9%, 34.8% and 43.5% respectively, with patients with preserved ejection fraction possibly having higher mortality rates than those with reduced ejection fraction. In future studies, assessing complications more thoroughly and following patients for up to 5 years would be helpful.

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Biography

Ilona Arih was born in Ljubljana, Slovenia in 1994. She was raised in Ljubjana where she finished high school in 2013. She enrolled into Medical Studies in English at School of Medicine University of Zagreb. During her years at the university she enjoyed tutoring younger generations and engaging in sports. After graduating in 2020 she plans to complete her internship in Slovenia.