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ORIGINAL ARTICLE

DESCRIBING ADULT HEART FAILURE PATIENTS – ASSESSMENT OF REAL-LIFE DATA IN TWO SITES

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Abstract. Background. *There is a lack of local clinical epidemiological data describing the different heart failure (HF) phenotypes in Bulgaria.* ***Objective:*** *Our goal was to describe the demographic and clinical characteristics of patients with HF in two cardiological hospitals. The primary objective was to describe the demographic and clinical characteristics of patients with HF in two cardiological hospitals. The secondary objective was to further specify the profile of chronic HF patients by describing HF phenotype and the current treatment patterns of hospitalized patients. Primary and secondary outcome measures corresponding to the objectives were descriptive in nature.* ***Methods.*** *This was a retrospective non-interventional study based on secondary anonymous pooled database analyses on management of patients with HF. The retrospective data was provided by Sqilline's Danny Platform® – analytics AI (Artificial Intelligence) platform for real-world data.* ***Results.*** *The total number of patients with heart failure as main diagnosis or as comorbidity, or heart failure patients, treated on outpatient basis was 1313 (8%) as of 31th of March, 2019. The number of patients with heart failure as main diagnosis in the inpatient care was 413. The mean age of the patients was 69.77 years and more than 50% of hospitalized patients were males. Ejection fraction was available in 352 HF patients in the inpatient care as follows: 40-49% in 48 patients, less than 40% in 67 patients and more than 50% in 240 patients. The most frequently observed comorbidity in hospitalized patients with two or more comorbidities (66.1%) was as follows: hypertensive heart disease with heart failure (78.0%), atrial fibrillation and flutter (42.1%).* ***Conclusions.*** *We succeeded in describing the demographic and clinical characteristics of 413 HF patients in Bulgaria. Digitalization in healthcare is an unmet need which should be addressed on a broad societal scale requiring all stakeholders to be involved.*

Key words: *cardiology, treatment, heart failure, artificial intelligence*

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Abbreviations

AI: artificial intelligence
ATC: anatomical therapeutic chemical
BNP: brain natriuretic peptide
Ca: calcium
COPD: chronic obstructive pulmonary disease
CKD: chronic kidney disease
eGFR: estimated glomerular filtration rate
EHR: electronic health record
ESC: European Society of Cardiology
HbA1: glycated haemoglobin
HF: heart failure
HfrEF: heart failure with reduced ejection fraction
HfpEF: heart failure with preserved ejection fraction
ICD: international classification of diseases
LVEF: left-ventricular ejection fraction
LVSD: left ventricular systolic dysfunction
NLP: natural language processing
NYHA: New York Heart Association
NT-proBNP: N-terminal pro–B-type natriuretic peptide
T2DM: Type 2 diabetes mellitus

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome that has a significant impact on public health, leading to high rates of hospitalizations and mortality [1]. The global population is expected to see a continued increase in the number of HF patients in the coming decades due to factors such as an aging population, a high prevalence of leading risk factors (such as hypertension, diabetes, dyslipidemia, and obesity), and improved survival rates after acute myocardial infarction. Despite recent advancements in the management of this condition, the prognosis for HF patients remains poor.

Bulgaria is one of the countries with the highest risk of cardiovascular diseases, ranking among the most underprivileged nations along with Russia, Ukraine, Belarus, and other former Soviet republics in Eastern Europe, as well as the former Yugoslav republics [2]. Currently, Bulgaria lacks accurate statistics on the number of HF patients. However, if we extrapolate the global prevalence of HF to the Bulgarian population, it can be estimated that around 140,000 Bulgarians suffer from HF.

HF is the second leading cause of death in Bulgaria, following cerebrovascular diseases. It is also the primary cause of hospitalization for patients over 65 years old. The mortality rate for heart failure in Bulgaria is increasing, particularly among younger individuals, with nearly 20.2% of all deaths in 2017 attributed to heart failure [3]. In recent years, there has been a noticeable rise in hospitalizations for both heart failure and cerebrovascular disease. Within the first month after initial hospitalization, approximately 25% of patients are re-hospitalized due to heart failure, followed by 40% within the third month, and the remaining within six months.

Many patients experience re-hospitalizations due to exacerbated concomitant diseases such as diabetes, renal failure, and anemia. These not only worsen the medical prognosis but also impose significant financial burden on the healthcare system. Various co-morbidities and pathophysiological processes can contribute to different types of heart failure [4, 5]. In recent decades, there has been a shift in the profile of patients with heart failure, with a lower prevalence of left ventricular systolic dysfunction (LVSD) and a higher occurrence of heart failure with preserved ejection fraction (HFpEF), possibly due to concomitant risk factors [6].

The impact of current treatment patterns in daily clinical practice can be assessed and compared with the latest European Society of Cardiology (ESC) Guidelines for HF at the time of the study. To achieve these goals, the use of real-world data is crucial. By utilizing available secondary data linked to clinical information, gaps in understanding the profile of HF patients can be filled. Improved patient monitoring will lead to better survival rates, reduced hospitalizations, and improved quality of life.

At the time of the analysis discussed here, the Bulgarian Society of Cardiologists had adopted the 2016 ESC „Guidelines for the diagnosis and treatment of acute and chronic heart failure." According to these guidelines, the left-ventricular ejection fraction (LVEF) cut-of f limits for classifying heart failure were as follows: HfrEF (HF with reduced ejection fraction < 40%), HFmrEF (HF with midrange ejection fraction of 40-49%), and HfpEF (HF with preserved ejection fraction ≥ 50%).

In Bulgaria, there are no national registries to document the profile of HF patients. There is a lack of available information regarding Bulgarian patients with HF and their current treatment patterns. Effective healthcare management can only be achieved through robust analysis, including digitalization, of available data and the follow-up of patients' prognosis and disease progression in real-world settings.

Primary objective

To describe the demographic and clinical characteristics of patients with HF in two cardiological hospitals: ACIBADEM City Clinic – Sofia and City Clinic Sv. Georgi – Montana, situated in different and remote regions of Bulgaria. Both hospitals are analyzing their data in real-world setting using the same AI platform (DANY platform).

Key outcome measures

The outcome measures corresponding to the objectives are descriptive in nature and included: a) demographics (age: average, the highest and the lowest; gender, education if available) within the three HF phenotypes according to LVEF (%); b) frequency of major accompanying diseases of interest in patients – comorbidity burden: type 2 diabetes mellitus (T2DM), arterial hypertension, coronary artery disease, atrial fibrillation, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity, anemia, dyslipidaemia; c) clinical events (retrospectively over the past 12 months, if available):

- frequency of hospitalizations and re-hospitalizations of patients within the three HF phenotypes;
- vital signs (blood pressure, heart rate, heart rythm);
- laboratory tests: blood creatinine with estimated eGFR, BNP, NT-proBNP, sodium, potassium, HbA1c, blood glucose, urea.

Secondary objectives

Secondary objectives aimed to further specify the profile of chronic HF patients by:

- HF phenotype (as per distribution in clinic) – % patients with: preserved ejection fraction (≥ 50%); mid-range ejection fraction (40-49%) and reduced ejection fraction (< 40%); distribution of patients according to New York Heart Association (NYHA) classification.
- describing the current treatment patterns of hospitalized HF patients including the proportion of patients treated according to the ESC treatment guidelines. It should be noted that the therapy was not evaluated in dynamics but analysis was based on two index evaluation moments: upon admission to the hospital and upon hospital discharge (if available).

Variables measured in this study included secondary use of aggregated analyses of anonymized patients' information, co-morbidities, drug therapies, disease measures, physical parameters.

All patients' data in the here discussed database were aggregated and anonymized, therefore patients' consent was not required. The study was approved during Ethics Committee's session on December 4th, 2019 by the Ethics Committee of Medical Research at Acibadem CityClinic Cardiovascular center, Sofia.

Study design

This retrospective non-interventional study was conducted using a secondary anonymous pooled database from two cardiological hospitals to analyze the management of patients with heart failure. Sqilline's Danny Platform is a Big Data healthcare solution that integrates a vast amount of real-world data from various hospital sources, including EHRs and lab tests. Utilizing proprietary machine learning and NLP algorithms, Danny Platform extracts structured and unstructured healthcare data, preprocesses and normalizes it to ensure high data quality. The software offers comprehensive searches, in-depth analyses, predictions, and treatment solutions.

The proprietary data processing pipeline of Danny Platform includes several steps such as data acquisition, processing (data mapping and harmonization), AI-enabled data extraction and curation, manual curation, validation (including handling missing data and normalizing categorical/numerical data), custom logics for data validation and aggregation, and various analyses including sophisticated filters, statistical summaries, survival outcome measure analyses, and cohort eligibility analysis. The platform allows domain experts to enhance and augment the knowledge within the system, thereby improving the quality of the machine learning models.

It is important to note that the clinical decision to prescribe any of the drugs included in the study was made in the past as part of routine clinical practice, separate from any consideration of participation in this study. Patients received standard medical treatment during the study period, without additional laboratory tests or medical procedures.

The clinical data used in this study were pre-recorded by physicians during clinical consultations. Therefore, no additional clinical data were recorded specifically for the purpose of this study. As a non-interventional retrospective study, there was no requirement for a specific therapy protocol, diagnostic/therapeutic procedure, or visit schedule. Due to the study design, no additional visits were expected to be performed.

The available data used in this study was originally generated and collected for reporting purposes to the National Healthcare Insurance Fund and other government agencies. Our study is based on secondary data analysis, utilizing the data described above. Once imported into Sqilline's Danny Platform, some data transformation is performed, but no extra data is added.

Study population

The study population included adult patients with a documented diagnosis of HF, defined by ICD (International Classification of diseases) I50 and further analyzed in subgroups during the identification period – from April 1st, 2018, to March 31, 2019. The first index event was the earliest available patient hospital record in the respective hospitals since April 1, 2018.

Key inclusion criteria

Patients included in the study were male and female patients, aged ≥ 18 years, and with documented diagnosis of chronic HF, defined by ICD I50 including: I50.0 Congestive heart failure; I50.1 Left ventricular failure; I50.9 Heart failure, unspecified.

Key exclusion criteria

Patients with HF aged < 18 years were excluded from the study.

MATERIALS AND METHODS

The original data source for this study was the health records from the respective hospitals, including both structured and unstructured free-text forms. Our data processing pipelines are specifically designed to be compatible with these systems, allowing for the extraction of important clinical variables and transforming them into structured data within the Danny Platform. We conducted checks to ensure data consistency, identify errors, and address missing values where applicable.

For this report, we queried and extracted the patients within the defined scope from the analytics platform. The results were exported and further reviewed to generate this report. All data within the defined scope is accessible in each user account on the platform. We present the results in bar charts for statistical summaries, highlighting substantial data categories whenever possible. To facilitate interpretation, we also provide the corresponding data values in tabular form.

Statistical analysis

In the data processing, we utilized descriptive statistics and graphic analysis to derive statistical characteristics. Demographic indicators were presented using statistical characteristics such as the number (absolute frequency) and percentage (relative frequency). Laboratory test data was summarized using measures of central tendency (mean, median, and mode) as well as measures of statistical dispersion (standard deviation and standard error of mean). One-dimensional frequency distributions of disease data, coded using ICD10, were presented using absolute frequency and relative frequency. To visually represent the results, we used pie and bar charts, which provide a graphical representation of the data.

RESULTS

Baseline characteristics

Both hospitals covered the following population with cardiovascular disease (with or without HF) on inpatient and/or outpatient basis: 1002 in MHAT City Clinic "Sv. Georgi" – Montana and 15491 in UMHAT Acibadem City Clinic – Sofia. In total, the number of patients was 16448. There were patients who visited both hospitals and some patients were treated on both inpatient and outpatient basis, but only once included in the Total sum.

From this, the number of patients treated on inpatient basis was 1002* in MHAT City Clinic "Sv. Georgi – Montana, and 3899 in UMHAT Acibadem City Clinic – Sofia. In total, the number of inpatient care patients was 4866. The most frequently diagnosed cardiovascular diseases in outpatient care were the following: hypertensive heart disease without heart failure (ICD I11.9, number of patients: 2906 [18.8%]), essential (primary) hypertension (ICD I10, number of patients: 2488 [16.1%]), other forms of angina pectoris (ICD I20.8, number of patients: 2352 [15.2%]), and atrial fibrillation and flutter (ICD, I48, number of patients:1417 [9.2%]). The most frequently diagnosed cardiovascular diseases in hospitalized patients were other forms of angina pectoris (ICD I20.8, number of patients: 1253 [25.8%]), unstable angina (ICD I20.0, number of patients: 749 [15.4%]), embolism and thrombosis of arteries of the lower extremities (ICD I74.3, number of patients: 486 [10.0%]), atrial fibrillation and flutter (ICD I48, number of patients: 420 [8.6%]), and congestive heart failure (ICD I50.0, number of patients: 365 [7.5%]).

In hospitalized patients who were diagnosed with heart failure as main diagnosis (N = 413), the main comorbidities were the following: hypertensive heart disease (ICD I11.0, number of patients: 352 [85.2%]), atrial fibrillation and flutter (ICD I48, number of patients: 115 [27.8%]), mitral valve insufficiency (ICD I34.0, number of patients: 67 [16.2%], nonrheumatic tricuspid valve insufficiency (ICD I36.1, number of patients: 41 [9.9%]), and non-insulin-dependent diabetes mellitus without complications (ICD E11.9, number of patients: 33 [8.0%]) (Table 1).

Table 1. ICD-10 Code, inpatient care, comorbidities of patients diagnosed with heart failure as main diagnosis.

CD-10 code	ICD10 Term	Number of patients	% (N = 413)
I11.0	Hypertensive heart disease with (congestive) heart failure	352	85.2
I48	Atrial fibrillation and flutter	115	27.8
I34.0	Mitral (valve) insufficiency	67	16.2
I36.1	Nonrheumatic tricuspid (valve) insufficiency	41	9.9
E11.9	Non-insulin-dependent diabetes mellitus without complications	33	8
I35.1	Aortic (valve) insufficiency	18	4.4
I42.0	Dilated cardiomyopathy	18	4.4
I27.0	Primary pulmonary hypertension	17	4.1
E78.4	Other hyperlipidaemia	17	4.1
I11.9	Hypertensive heart disease without (congestive) heart failure	16	3.9

Note: * MHAT City Clinic "Sv. Georgi" – Montana has no outpatient care unit. Some patients have visited both hospitals and were reported to both but only once included in the total sum. Henceforth, the analysis is based only on available data on hospitalized patients

The total number of hospitalized patients with heart failure as main diagnosis or as comorbidity, or heart failure patients, treated on outpatient basis was 1313. In the inpatient care the number of hospitalized patients with heart failure as main diagnosis was 413. The mean age of the patients with heart failure as main diagnosis was 69.77 years (at the time of hospitalization) and most of the patients belonged to 70-84 years age groups (Figure 1). More than 50% of the hospitalized patients were males (n: 227) (Table 2).

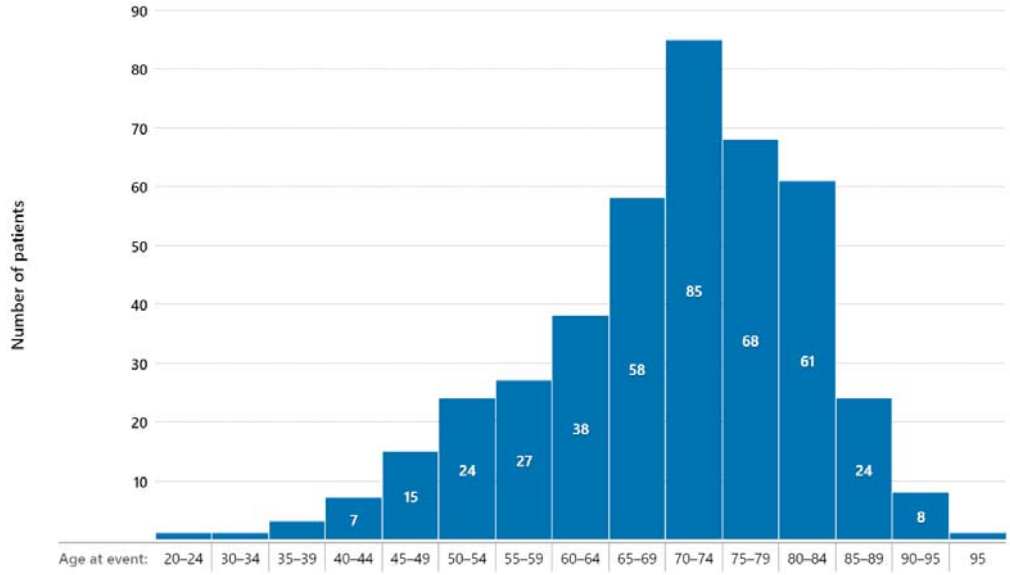

Fig. 1. Age group in years in hospitalized patients with heart failure as main diagnosis

Table 2. Number of males and females in hospitalized patients with heart failure as main diagnosis

Gender	Female	Male
Number of patients	186	227
%	45.0%	55.0%

Primary objectives

Demographics by ejection fraction range

Most of the patients were in the 60-89 years age groups independent of the ejection fraction range and gender. The overall prevalence rate of heart failure was similar in both sexes, however men have had a higher incidence of heart failure with reduced ejection fraction < 40%, since women tend to be older when diagnosed with heart failure and more often have had preserved ejection fraction > 50%, which is in line with what is already known about the global disease epidemiology (Table 3).

The mean heart rate was the highest in patients with ejection fraction 40-49% and the lowest in patients with > 50% ejection fraction (Table 4).

Table 4. Heart rate by ejection fraction range

Inpatient care heart rate (bpm) by ejection fraction range	<40%	40-49%	> 50%
Mean	85.50	87.14	80.64
Standard Deviation of the Mean	20.60	25.34	19.62
Standard Error of the Mean	2.75	3.86	1.37
Number of patients	56	43	206
Median	81.50	84.00	78.00
Mode	78.00	84.00	78.00

Table 3. Demographics by ejection fraction range

Ejection fraction range	Gender	Age	Number of patients
< 40%	F	50–59	1
		60–69	3
		70–79	7
		80–89	8
	M	40–49	4
		50–59	10
		60–69	11
		70–79	15
		80–89	11
40-49%	F	60–69	4
		70–79	9
		80–89	9
	M	40–49	1
		50–59	3
		60–69	5
		70–79	9
		80–89	6
		90–95	2
> 50%	F	30–39	1
		40–49	4
		50–59	14
		60–69	26
		70–79	57
		80–89	24
		90–95	4
	M	30–39	2
		40–49	9
		50–59	18
		60–69	28
		70–79	35
		80–89	20
		90–95	2

Laboratory by ejection fraction range

Only available data in medical records are subject of here described retrospective analyses.

The creatinine (μmol/L) level was the highest in patients with ejection fraction 40-49% and the lowest in patients with more than 50% ejection fraction (Table 5).

Table 5. Creatinine (μmol/L) level by ejection fraction range

Creatinine level (μmol/L) by ejection fraction range	< 40%	40-49%	> 50%
Mean	134.59	182.29	111.69
Standard Deviation of the Mean	63.33	168.82	41.90
Standard Error of the Mean	12.19	45.12	6.25
Number of patients	27	14	45
Median	111.00	127.00	99.00
Mode	91.50	182.29	88.00

The mean value of NT-proBNP was 3748.2 pg/ml in patients with ejection fraction range more than 50%. These mean values were higher in patients with ejection fraction range 40-49% (14240.17 pg/ml), and those who had ejection fraction range less than 40% (15159.65 pg/ml) (Table 6).

Table 6. NT-proBNP (pg/ml) level by ejection fraction range

NT-proBNP level (pg/ml) by ejection fraction range	< 40%	40-49%	> 50%
Mean	15159.65	14240.17	3748.20
Standard Deviation of the Mean	12650.70	11399.85	5606.19
Standard Error of the Mean	2828.78	3290.85	947.62
Number of patients	20	12	35
Median	9665.50	9327.50	1709.00
Mode	35000.00	14240.17	3748.20

The HbA1c (%) was the highest in patients with preserved ejection fraction (6.84%) and the lowest in patients with mid-range ejection fraction (5.90%). The mean HbA1c was 6.40% in the patients with reduced ejection fraction (Table 7).

The urea (mmol/l) was the highest in patients with mid-range ejection fraction (13.84 mmol/l) and the lowest in patients with preserved ejection fraction (9.05 mmol/l) (Table 8).

Table 7. HbA1c (%) level by ejection fraction range

HbA1c level (%) by ejection fraction range	< 40%	40-49%	> 50%
Mean	6.40	5.90	6.84
Standard Deviation of the Mean	1.18	0.42	1.43
Standard Error of the Mean	0.53	0.30	0.45
Number of patients	5	2	10
Median	5.90	5.90	6.15
Mode	6.40	5.90	6.10

Table 8. Urea (mmol/l) level by ejection fraction range

Urea level (mmol/l) by ejection fraction range	< 40%	40-49%	> 50%
Mean	12.18	13.84	9.05
Standard Deviation of the Mean	7.53	6.90	4.51
Standard Error of the Mean	1.45	1.85	0.67
Number of patients	27	14	45
Median	9.50	13.10	7.50
Mode	20.80	13.84	6.40

Comorbidities by ejection fraction range (ejection fraction <40%)

The most frequently observed comorbidity in hospitalized patients with heart failure as main diagnosis and ejection fraction below 40%, were: hypertensive heart disease with heart failure (ICD I11.0, number of patients: 47 [70.1%]), atrial fibrillation and flutter (ICD-I48, number of patients: 19 [28.4%] (Table 9).

Table 9. Comorbidities in patients with HF with ejection fraction range < 40%

ICD-10 code	ICD-10 Term	Number of patients	% (N = 67)
I11.0	Hypertensive heart disease with (congestive) heart failure	47	70.1
I48	Atrial fibrillation and flutter	19	28.4
I11.9	Hypertensive heart disease without (congestive) heart failure	6	9.0
E11.9	Non-insulin-dependent diabetes mellitus without complications	6	9.0
I25.2	Old myocardial infarction	3	4.5
I21.0	Acute transmural myocardial infarction of anterior wall	2	3.0
E11.4	Non-insulin-dependent diabetes mellitus with neurological complications	2	3.0
J44.8	Other specified chronic obstructive pulmonary disease	2	3.0
I20.0	Unstable angina	1	1.5
N18.0	Chronic kidney disease	1	1.5

Comorbidities by ejection fraction range (ejection fraction 40-49%)

The most frequently observed comorbidity in hospitalized patients with heart failure as main diagnosis and ejection fraction between 40 and 49%, were the following: hypertensive heart disease with heart failure (ICD I11.0, number of patients: 40 [83.3%]), atrial fibrillation and flutter (ICD I48, number of patients: 17 [35.4%]) (Table 10).

Comorbidities by ejection fraction range (ejection fraction > 50%)

The most frequently observed comorbidity in hospitalized patients with heart failure as main diagnosis and ejection fraction > 50%, were the following: hypertensive heart disease with heart failure (ICD I11.0, number of patients: 228 [95.0%]), atrial fibrillation and flutter (ICD I48, number of patients: 61 [25.4%]) (Table 11).

Number of heart failure patients in inpatient care with two or more comorbidities

The most frequently observed comorbidity in hospitalized patients with two or more comorbidities were the following: hypertensive heart disease with heart failure (ICD I11.0, number of patients: 213 [78.0%]), and atrial fibrillation and flutter (ICD I48, number of patients: 115 [42.1%]) (Table 12).

The patients with two or more comorbidities presented here are 273, which is 66.1% of all 413 inpatient care patients with heart failure as main diagnosis (Table 12).

Table 10. Comorbidities in patients with HF with ejection fraction range 40-49%

ICD-10 code	ICD-10 Term	Number of patients	% (N = 48)
I11.0	Hypertensive heart disease with (congestive) heart failure	40	83.3
I48	Atrial fibrillation and flutter	17	35.4
I11.9	Hypertensive heart disease without (congestive) heart failure	2	4.2
N18.9	Chronic kidney disease, unspecified	2	4.2
E11.9	Non-insulin-dependent diabetes mellitus without complications	2	4.2
J44.8	Other specified chronic obstructive pulmonary disease	2	4.2
I25.2	Old myocardial infarction	1	2.1
E11.5	Non-insulin-dependent diabetes mellitus with peripheral circulatory complications	1	2.1
I20.8	Other forms of angina pectoris	1	2.1
E11.4	Non-insulin-dependent diabetes mellitus with neurological complications	1	2.1

Table 11. Comorbidities in patients with HF with ejection fraction range > 50%

ICD-10 code	ICD10 Term	Number of patients	% (N = 240)
I11.0	Hypertensive heart disease with (congestive) heart failure	228	95.0
I48	Atrial fibrillation and flutter	61	25.4
E11.9	Non-insulin-dependent diabetes mellitus without complications complications	14	5.8
N18.9	Chronic kidney disease, unspecified	11	4.6
J44.8	Other specified chronic obstructive pulmonary disease	7	2.9
I11.9	Hypertensive heart disease without (congestive) heart failure	5	2.1
E11.4	Non-insulin-dependent diabetes mellitus with neurological complications	4	1.7
I20.8	Other forms of angina pectoris	3	1.3
D50.0	Iron deficiency anaemia secondary to blood loss (chronic)	2	0.8
I25.2	Old myocardial infarction	2	0.8

Table 12. Number of heart failure patients, inpatient care, with two or more comorbidities*

ICD-10 code	ICD10 Term	Number of patients	% (N = 273)
I11.0	Hypertensive heart disease with (congestive) heart failure	213	78.0
I48	Atrial fibrillation and flutter	115	42.1
I34.0	Mitral (valve) insufficiency	67	24.5
I36.1	Nonrheumatic tricuspid (valve) insufficiency	41	15.0
E11.9	Non-insulin-dependent diabetes mellitus without complications complications	33	12.1
I35.1	Aortic (valve) insufficiency	18	6.6
E78.4	Other hyperlipidaemia	17	6.2
I42.0	Dilated cardiomyopathy	17	6.2
I27.0	Primary pulmonary hypertension	17	6.2
I11.9	Hypertensive heart disease without (congestive) heart failure	16	5.9

*Each comorbidity is listed in a separate row.

Secondary objectives

Distribution of patients according to NYHA

Heart failure classification by NYHA class was unknown in 398 patients. The number of patients with moderate (NYHA class II) and severe HF (NYHA class III or IV) were 2 and 16, respectively (Table 13).

Table 13. Number of heart failure patients, inpatient care, per NYHA class

NYHA classification	II	III	IV	N/A
Number of patients	2	8	8	398
% (N = 413)	0.00%	0.02%	0.02%	0.96%

Distribution of patients according to heart failure phenotypes

Ejection fraction was available in 355 patients with heart failure as main diagnosis in the inpatient care: the ejection fraction range was: 40-49% in 48 patients, less than 40% in 67 patients and more than 50% in 240 patients (Table14).

Table 14. Number of heart failure patients, inpatient care, per ejection fraction range

Ejection fraction range	< 40%	40-49%	> 50%	TOTAL
Number of patients	67	48	240	355
%	19.0%	13.6%	68.2%	100%

Distribution of applied therapies

We focused on and examined the main therapies administered (at admission and prescribed after discharge) in hospitalized patients with heart failure as main diagnosis and ejection fraction < 40%. We present only drugs with ATC (Anatomical Therapeutic Chemical) level 2 codes of: C03, C07, C08, C09.

The most frequently used drugs prescribed at discharge for use at home were furosemide (n: 22), bisoprolol (n: 21) and spironolactone (n: 13). There were a total of 32 patients with home therapy mentioned in the documentation (Table 15).

Table 15. Hospitalized patients with heart failure as main diagnosis, ejection fraction below 40%, therapy prescribed at discharge*

ATC Level 2	ATC Level 3	Number of patients	% (N = 67)
C03: Diuretics	C03C: High-ceiling diuretics	32	47.8
	C03D: Potassium-sparing agents	18	26.9
C07: Beta blocking agents	C07A: Beta blocking agents	30	44.8
C08: Calcium channel blockers	C08C: Selective calcium channel blockers with mainly vascular effects	4	6.0
C09: Agents acting on the renin-angiotensin system	C09A: Ace inhibitors, plain	7	10.4
	C09B: Ace inhibitors, combinations	2	3.0
	C09C: Angiotensin ii receptor blockers (arbs), plain	1	1.5
	C09D: Angiotensin ii receptor blockers (arbs), combinations	4	6.0

* A patient may have more than one prescribed drug. There are patients with no therapy prescribed at discharge, mentioned (included in the denominator).

As admission therapy the most frequently applied drugs were furosemide (n: 36), bisoprolol (n: 30), and spironolactone (n: 24). Admission therapy was mentioned in the documentation of a total of 56 patients (Table 16).

Change in ejection fraction range between first and second hospitalization

Table 16. Hospitalized patients with heart failure as main diagnosis, ejection fraction below 40%, admission therapy drug*

ATC Level 2	ATC Level 3	Number of patients	% (N = 67)
C03: Diuretics	C03A: Low-ceiling diuretics, thiazides	1	1.5
	C03C: High-ceiling diuretics	48	71.6
	C03D: Potassium-sparing agents	30	44.8
	C03E: Diuretics and potassium-sparing agents in combination	2	3.0
C07: Beta blocking agents	C07A: Beta blocking agents	44	65.7
C08: Calcium channel blockers	C08C: Selective calcium channel blockers with mainly vascular effects	10	14.9
C09: Agents acting on the renin-angiotensin system	C09A: Ace inhibitors, plain	19	28.4
	C09B: Ace inhibitors, combinations	2	3.0
	C09C: Angiotensin ii receptor blockers (arbs), plain	7	10.4
	C09D: Angiotensin ii receptor blockers (arbs), combinations	7	10.4

* A patient may have more than one prescribed drug. There are patients with no admission therapy mentioned (included in the denominator)

Table 17. Change in ejection fraction range between first and second hospitalization*

Ejection fraction range 1st hospitalization	Ejection fraction range 2nd hospitalization	Number of patients
40-49%	40-49%	22
	< 40%	7
	> 50%	10
< 40%	40-49%	8
	< 40%	41
	> 50%	2
> 50%	40-49%	12
	< 40%	4
	> 50%	76
	N/A	2
N/A	> 50%	2
	N/A	1

* First hospitalization in patients with heart failure as main diagnosis or comorbidity. The second has any diagnosis for cardiovascular disease.

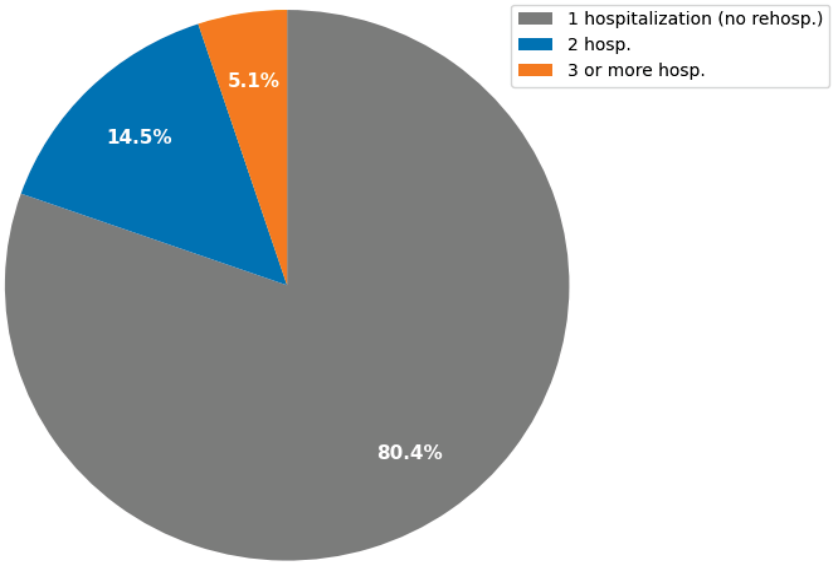

Fig. 2. Rehospitalizations in inpatient care patients with HF as main diagnosis – from April 1st, 2018 to March 31, 2019

KEY RESULTS

A total of 1002 patients at MHAT City Clinic "Sv. Georgi" – Montana, Bulgaria, and 15491 patients at UMBAL Acibadem City Clinic – Sofia, Bulgaria contributed data for this study. The number of patients on an inpatient basis was 1002 at MBAL and 3899 at UMHAT clinic, respectively.

The mean age of the participants was 69.77 years, and the majority belonged to the age group of 70-84 years (Figure 1). More than 50% of the hospitalized patients were males (n: 227) (Table 2).

The ejection fraction was measured in 352 patients. Among them, the ejection fraction ranged from 40 to 49% in 48 patients (mid-range ejection fraction), less than 40% in 67 patients (reduced ejection fraction), and more than 50% (preserved ejection fraction) in 240 patients (Table 14). Regardless of ejection fraction range or gender, most patients were aged 60-89 years (Figure 1).

The number of patients with moderate (NYHA class II) and severe HF (NYHA class III-IV) were 2 and 16, respectively. Heart failure classification by NYHA class was unknown in 398 patients (Table 13). The most prevalent comorbidities were hypertension, atrial fibrillation, and diabetes mellitus type 2, regardless of the ejection fraction (Tables 9, 10, 11).

The creatinine level (μmol/L) was the highest in patients with mid-range ejection fraction and the lowest in patients with preserved ejection fraction (Table 5). The mean value of NT-proBNP was 3748.2 pg/ml in patients with preserved ejection fraction (Table 6). It was higher in patients with mid-range ejection fraction (14240.17 pg/ml) and in those with reduced ejection fraction (15159.65 pg/ml) (Table 6). The HbA1c (%) was highest in patients with preserved ejection fraction (6.84%) and lowest in patients with mid-range ejection fraction (5.90%) (Table 7). The mean of HbA1c was 6.40% in patients with reduced ejection fraction (Table 7). The urea level (mmol/l) was the highest in patients with mid-range ejection fraction (13.84 mmol/l) and the lowest in patients with preserved ejection fraction (9.05 mmol/l) (Table 8).

Changes in ejection fraction range were observed between the first and the second hospitalizations. Out of the patients with mid-range ejection fraction at the first hospitalization (n = 39), 7 patients deteriorated to the reduced ejection fraction group, and 10 patients improved to the preserved ejection fraction group at the time of the second hospitalization (Table 17). From the patients with reduced ejection fraction at the first hospitalization (n = 51), only 10 patients showed improvement in their ejection fraction status (Table 17). Finally, out of the patients with preserved ejection fraction at the first hospitalization (n=94), the ejection fraction status of 76 patients remained unchanged (Table 17).

The most used drugs for home therapy in hospitalized patients with reduced ejection fraction were furosemide (n: 22), bisoprolol (n: 21), and spironolactone (n: 13) (Table 15). The most frequently used drugs as admission therapy were furosemide (n: 36), bisoprolol (n: 30), and spironolactone (n: 24) (Table 16).

During the identification period from April 1st, 2018 to March 31, 2019, a total of 81 out of 413 patients had at least 2 or more hospitalizations, and 21 patients had at least 3 or more hospitalizations (Figure 2).

DISCUSSION

The primary and secondary objectives in this study were to describe the demographic and clinical characteristics of heart failure patients in two Bulgarian cardiological hospitals. Heart failure was categorized by the left ventricular ejection fraction according to the European Society of Cardiology guidelines which separate patients with HF to either reduced ejection fraction range (< 40%), mid-range ejection fraction range (41-49%), or preserved ejection fraction range (≥ 50%). The pattern of demographic variables was like other observational studies, however the proportion of patients with preserved ejection fraction was higher in this study [8].

The most prevalent comorbidities in our study were hypertension, atrial fibrillation, and type 2 diabetes mellitus in all subgroups. This ranking of comorbidities is comparable to a Swedish cohort study [9].

Rehospitalization is a major issue for heart failure patients. In our study we found that the number of patients hospitalized at least 2 or more times during the one-year study period was 81 out of 413 (19.6%) and the number of those hospitalized at least 3 or more times was 21 (5.1%) (Figure 2). A recently published study found that 13% of patients had at least two readmissions during the study period. However, it should be noted that in this case the follow-up period was two years [10]. Another study reported that half of the re-hospitalized patients were found to have non-cardiovascular indications [11]. The Heart Failure Pilot Study after a one-year follow-up reported that 36.5% of patients were readmitted for cardiovascular reasons and 14.6% for non-cardiovascular reasons, and hospitalizations due to HF accounted for 56.4% of total hospitalizations [12]. The analysis of the present study did not provide detailed informa-

tion on either the cause for rehospitalization, or the outcome of the events.

Although the association between poor glycemic control in diabetes and heart failure is well-known, the relationship between HbA1c and left ventricular ejection fraction is unclear [13]. In our study the mean of HbA1c was less than 7% in all subgroups (Table 7). However, this result could not be interpreted as no detailed analysis was performed in the subgroup of patients diagnosed with type 2 diabetes mellitus.

We found an improvement in the ejection fraction between the first and the second hospitalization in almost half of the patients (n = 10) registered with a mid-range ejection fraction at the first hospitalization (Table 17). In parallel, a deterioration was observed in 17% of patients registered with a preserved ejection fraction at the first hospitalization (Table 17). In general, improvement implies a better outcome and deterioration implies a worse disease outcome for the patient [14]; however, we cannot confirm this statement due to missing outcome information.

The three subgroups of patients showed similar patterns of therapy at hospital admission and discharge (Tables 15, 16). In patients with preserved ejection fractions, the ratio of diuretic usage was slightly lower meanwhile administration of Ca channel blocker was higher. The reason for this observation may be that the treatment of HF patients with preserved ejection fractions differs from the management of those patients with mid-range and reduced ejection fraction.

In the present study, among patients hospitalized with heart failure with reduced ejection fraction, outpatient use of guideline-directed HF therapy was insufficient. Even after discharge the level of disease-modifying drug classes (beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, or mineralocorticoid receptor antagonists) remains low, but significantly improved compared to baseline (Table 15). This demonstrates hospitalizations are an opportunity for treatment optimization that should not be missed. A better understanding of post-discharge treatment patterns and early outpatient follow-up may inform intervention opportunities to improve clinical management of patients with HFrEF and effectively reduce the risk of death and rehospitalization in real -world clinical settings. Along with insufficient information in analyzed data base, further investigation is needed for non-adherence to guidelines, observed in local clinical practice.

Previous cohort and registry studies have showed that patients with HFmrEF have intermediate characteristics between those of HFrEF and HFpEF. Unlike HFrEF, for many years there have been no guideline-directed therapies in HFmrEF and HFpEF proven to have effect on the clinical status, functional capacity, and quality of life, or preventing hospitalizations and reducing mortality.

Even our study with all the limitations of data collected, showed that compared to HFrEF patients, hospitalizations in HFmrEF/HFpEF patients were likely to be non-cardiovascular. Therefore, screening for cardiovascular and non-cardiovascular comorbidities is crucial, and management should focus on interventions shown to improve symptoms, well-being, or outcomes related to specific comorbidities. In HFmrEF/HFpEF population analyzed, hospitalizations also resulted in greater use of therapy recommended for managing comorbidities compared to baseline.

LIMITATIONS

Since this analysis is based on the secondary use of aggregated data, there are numerous information gaps. Certain important information was either not collected or not available in the medical records. For example, the New York Heart Rate Association (NYHA) classification is the most widely used method for describing the impact of heart failure on patients' life. Although NYHA classification can be used to estimate rehospitalization or mortality in heart failure patients, we had only a limited number of NYHA-classified patients [7]. Another limitation of our study is the relatively small number of enrolled subjects in some of the categories. For example, when comparing the average creatinine levels between the different ejection fraction range groups, we observed that patients with mildly reduced ejection fraction had significantly higher average creatinine levels. This finding contradicts other epidemiological studies and may well be caused by the small number of subjects with available data in this group (14 vs. 27 and 45 in the other groups). As a result, important characteristics are not included in this analysis, even though they may have been filled in the hospital information system later or elsewhere but were missing from the data reported to the National Healthcare Insurance Fund as mentioned already. It is important to note that this is a secondary analysis that utilizes existing data and does not involve collecting additional data.

CONCLUSION

This retrospective study described the demographic and clinical characteristics of 413 HF patients in two cardiological hospitals in Bulgaria. To further specify the profile of chronic HF patients, we analized: HF

phenotype (as per distribution in clinic); distribution of patients according to NYHA classification; current treatment patterns of hospitalized HF patients including the proportion of patients treated according to the ESC treatment guidelines. These findings complement existing data from randomized trials and provide a comprehensive understanding of the research scientific questions. The value of conducting such studies is impeded by a gap linked to important parameters e.g., missing data in patients' records. Reasons for the information gap may vary, whether it be at the hospital level, the patients' level, or the level of organization/structure within the healthcare system. Despite the digital revolution and the shift towards outcome-based healthcare, patient care in Bulgaria has not yet been digitized. Digitalization creates a solid base for reliable analyses in service of national health polices and, most importantly, it improves patient safety and clinical outcomes through various mechanisms.

Despite the limitations, this study is valuable in analyzing standard clinical practice in Bulgaria and can serve as a foundation for better national strategies in healthcare.

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