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Various Phenotypes and Treatment Strategies for Heart Failure Among a Contemporary Cohort of Egyptian Patients

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Abstract

Background: Heart failure (HF) is a clinical syndrome characterized by structural and functional cardiac abnormalities. It is classified into three main phenotypes: HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF).

Objective: To evaluate the various phenotypes and treatment strategies for HF among a contemporary cohort of Egyptian patients.

Patients and Methods: This cross-sectional, multi-center study was conducted on 510 HF patients at Al Nasr Hospital in Port Said over 12 months. Patients were grouped based on ejection fraction: HFrEF (43.2%), HFmrEF (23.3%), and HFpEF (33.5%). Data on demographics, comorbidities, medications, and non-pharmacological treatments were collected

Results: Males were predominant in HFrEF (78.6%) while HFpEF was more common among females (35.1%, $P < 0.01$). Prior HF hospitalization was highest in HFrEF (89.5%, $P < 0.001$). HFrEF patients had lower eGFR (78 ±26 ml/min, $P = 0.003$), higher use of beta-blockers ($P < 0.001$) and angiotensin receptor neprilysin inhibitor (ARNI) (49.5%, $P < 0.001$), and more frequent revascularization. Sodium-glucose cotransporter 2 (SGLT2) inhibitors were underutilized due to cost ($P < 0.001$).

Conclusion: HFrEF is more prevalent in males, while HFpEF is more common in females and associated with higher systolic blood pressure (SBP) and left ventricular hypertrophy (LVH). The significant underutilization of SGLT2 inhibitors and ARNI highlights the need for improved accessibility to advanced HF therapies in Egypt. Tailored management strategies are essential for optimizing care based on HF phenotypes.

Keywords: Heart Failure; Phenotypes; Treatment Strategies; Egyptian Cohort, Ejection Fraction; SGLT2 Inhibitors.

INTRODUCTION

Heart failure (HF) is universally defined as a clinical syndrome with symptoms and/or signs caused by structural or functional cardiac abnormalities, supported by elevated natriuretic peptide levels or evidence of congestion. It is classified into HF with reduced ejection fraction (HFrEF) (LVEF ≤ 40%), HF with mildly reduced ejection fraction (HFmrEF) (LVEF 41-49%), HF with preserved ejection fraction (HFpEF) (LVEF ≥ 50%), and HF with improved ejection fraction [1].

HFpEF involves structural and cellular changes, such as cardiomyocyte hypertrophy, fibrosis, and inflammation, leading to impaired relaxation of the left ventricle [2]. In contrast, HFrEF is marked by substantial cardiomyocyte loss from conditions like myocardial infarction or myocarditis, resulting in systolic dysfunction and inability of the left ventricle to contract effectively [3].

HF can manifest as left-sided or right-sided, depending on the affected heart structures. Left HF is typically due to LV, mitral valve, or aortic valve dysfunction, while right HF is often caused by pulmonary hypertension or right ventricular issues. Left-sided HF is a common cause of right HF, and the two can occur concurrently [4].

Globally, HF affects an estimated 64.3 million people. In developed countries, it impacts 1% to 2% of the adult population [5]. In Egypt, cardiovascular disease has been the leading cause of premature death since the 1990s, accounting for 46.2% of all mortality in 2017.

The increasing aging population and improved survival from coronary events have contributed to the growing public health burden of HF [6].

The leading global causes of HF include ischemic heart disease (26.5%), hypertensive heart disease (26.2%), and chronic obstructive pulmonary disease (23.4%), among other conditions like cardiomyopathies and valvular diseases [7].

This study aimed to evaluate various phenotypes and treatment strategies for HF among a contemporary cohort of Egyptian patients.

PATIENTS AND METHODS

Study Design and Participants:

This was a cross-sectional, multi-center, observational study (prevalence survey) was carried out on 510 Egyptian HF patients either outpatients with HF or those admitted for acute, pre-existing, or new-onset HF at Al Nasr Hospital in Port Said over a period of 12 months (from the first of November 2022 to the end of October 2023).

Inclusion and Exclusion Criteria:

Inclusion criteria were patients aged >18 years and of both genders, all outpatients with chronic HF at the participating centers, patients admitted to participating centers complaining of new-onset HF (patients may present with rapid onset or progressively escalating symptoms and/or signs of HF that are associated with adverse outcomes, requiring urgent evaluation and treatment [8]), patients admitted to

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participating centers complaining of acute decompensated HF (The clinical presentation of symptoms and signs of congestion and poor organ perfusion due to HF requiring urgent therapy). Patients had a subacute evolution of their symptoms and signs resulting from cardiac and vascular dysfunction due to a variety of etiologies and triggers resulting in decompensated hemodynamics [9], patients with peri partum cardiomyopathy, and post COVID 19 cardiomyopathy. While patients aged < 18 years were excluded from the study.

Patients grouping:

Patients were divided into 3 groups according to ejection fraction; group 1: 220 (43.2%) with HFrEF, group 2: 119 (23.3%) with HFmrEF), and group 3: 171 (33.5%) with HFpEF.

METHODS

The researcher met with each patient to explain the study's objectives and procedures, obtaining informed consent before reviewing their medical files. The researcher also explained the questionnaire, which was completed during the meeting. Data collection involved a structured interview, observation, and review of patients' files.

Demographic and clinical characteristics:

Data collected included age, gender, residency, education, BMI, HF history, comorbidities, smoking, alcohol or drug use, and previous cardiovascular events. BMI was classified per WHO guidelines into underweight (18.5 kg / m^2), normal weight (18.5-24.9 kg / m^2), overweight (25-29.9 kg / m^2), obesity class I (30-34.9 kg / m^2), and obesity class II/III (≥35 kg/m^2) [10]. The use of HF medications, including ACE inhibitors, ARBs, ARNI, beta-blockers, MRAs, SGLT2 inhibitors, diuretics, ivabradine, antiplatelets, and anticoagulants, was also recorded.

Full clinical examination:

With particular emphasis on the pulse and blood pressure of the patients, as well as auscultation of the back to elicit the presence of any clinically detectable pulmonary venous congestion, auscultation of the heart for the presence of third heart sounds, or audible murmurs.

Laboratory investigations:

Baseline hemoglobin, creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium, random blood glucose, and high-sensitivity troponin (hsTroponin).

Radiological workup:

Abnormal findings from ECG, chest X-ray, echocardiography, and coronary angiography were recorded, detailing specific abnormalities and revascularization procedures. ECG was performed using a 12-lead system, and echocardiography using the Vevo imaging system to calculate ejection fraction (EF) and assess regional wall motion abnormalities (RWMA). The modified Simpson method, recommended by the American Society of Echocardiography, was used to measure LVEF by tracing the endocardial border in both apical four-chamber and two-chamber views, dividing the LV cavity into disks for volume calculation [11].

Non-Pharmacological and Device-Based Therapies:

Data on pacemaker implantation, CRT, ICD placement, patient health education, and rehabilitation scheduling were collected.

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Benha University (Approval number: MS 11-12-2022). All patients provided written informed consents prior to their enrolment. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data management and analysis were conducted using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality and summarized as means with standard deviations or median with ranges. Categorical data were presented as numbers and percentages. One-way ANOVA or Kruskal-Wallis tests were used to compare quantitative variables, with post-hoc Bonferroni adjustments for significant results. Post-hoc test with Kruskal-Wallis test were used. Categorical data were compared using Chi-square or Fisher's exact test, with P values below 0.05 considered significant.

RESULTS

Baseline clinical characteristics according to HF status

Significant differences were found in gender distribution, with a higher prevalence of males in the HFrEF group (78.6%) and females in the HFpEF group (35.1%). A history of HF and of HF hospitalization was most common in the HFrEF group followed by the HFmrEF and HFpEF groups. Systolic blood pressure was higher in HFpEF patients than in HFrEF and HFmrEF patients. Prior myocardial infarction/acute coronary syndrome (MI/ACS) and percutaneous coronary intervention (PCI) were more common in HFrEF and HFmrEF groups than in HFpEF. Peripheral arterial disease was more prevalent in HFrEF (57.3%) compared to HFmrEF and HFpEF. Other variables did not show significant differences across the groups **(Table 1)**.

Table 1: Baseline clinical characteristics of the studied patients according to HF status

		HFrEF (n = 220)	HFmrEF (n = 119)	HFpEF (n = 171)	Total	P-value
Patient's age (years)	Mean ±SD	61 ±11	63 ±10	60 ±11	61 ±11	0.085
Gender						
Males	n (%)	173 (78.6)	84 (70.6)	111 (64.9)	368 (72.2)	**0.01***
Females	n (%)	47 (21.4)	35 (29.4)	60 (35.1)	142 (27.8)	
Residency area						
Urban	n (%)	95 (43.2)	41 (34.5)	47 (27.5)	183 (35.9)	**0.005***
Rural	n (%)	125 (56.8)	78 (65.5)	124 (72.5)	327 (64.1)	
Patients educational level						
Illiterate	n (%)	7 (3.2)	7 (5.9)	5 (2.9)	19 (3.7)	0.112
School	n (%)	91 (41.4)	62 (52.1)	66 (38.6)	219 (42.9)	
College	n (%)	121 (55)	50 (42)	100 (58.5)	271 (53.1)	
Master or PhD	n (%)	1 (0.5)	0 (0)	0 (0)	1 (0.2)	
BMI (kg/m^2)	Mean ±SD	27.5 ±3.9	28.5 ±5.3	27.8 ±3.9	27.8 ±4.3	0.103
History of HF	n (%)	195 (88.6)	89 (74.8)	107 (62.6)	391 (76.7)	**<0.001***
History of HF hospitalization	n (%)	197 (89.5)	95 (79.8)	113 (66.1)	405 (79.4)	**<0.001***
Heart rate (bpm)	Mean ±SD	81 ±12	80 ±10	83 ±14	81 ±12	0.108
SBP (mmHg)	Mean ±SD	123 ±19	130 ±19	135 ±17	129 ±19	**<0.001***
DBP (mmHg)	Mean ±SD	76 ±12	80 ±10	83 ±10	79 ±11	**<0.001***
Primary etiology						
Dilated cardiomyopathy	n (%)	37 (16.8)	2 (1.7)	4 (2.3)	43 (8.4)	**<0.001***
HTN	n (%)	0 (0)	0 (0)	16 (9.4)	16 (3.1)	
IHD (documented by coronary angiography)	n (%)	119 (54.1)	82 (68.9)	102 (59.6)	303 (59.4)	
IHD (not documented by coronary angiography)	n (%)	37 (16.8)	13 (10.9)	14 (8.2)	64 (12.5)	
Tachycardia-induced cardiomyopathy	n (%)	0 (0)	1 (0.8)	1 (0.6)	2 (0.4)	
Valvular heart disease	n (%)	23 (10.5)	19 (16)	33 (19.3)	75 (14.7)	
Others	n (%)	4 (1.8)	2 (1.7)	1 (0.6)	7 (1.4)	
If primary etiology is valvular, please specify						
Aortic	n (%)	6 (26.1)	6 (31.6)	8 (24.2)	20 (26.7)	0.668
Mitral	n (%)	15 (65.2)	12 (63.2)	19 (57.6)	46 (61.3)	
Tricuspid	n (%)	2 (8.7)	1 (5.3)	6 (18.2)	9 (12)	
Smoking history	n (%)	120 (54.5)	66 (55.5)	81 (47.4)	267 (52.4)	0.274
AF history	n (%)	33 (15)	15 (12.6)	27 (15.8)	75 (14.7)	0.743
DM history	n (%)	107 (48.6)	47 (39.5)	67 (39.2)	221 (43.3)	0.109
Alcohol or other illicit drug use	n (%)	3 (1.4)	0 (0)	2 (1.2)	5 (1)	0.623
Prior MI/ACS	n (%)	67 (30.5)	62 (52.1)	72 (42.1)	201 (39.4)	**<0.001***
Prior PCI	n (%)	100 (45.5)	76 (63.9)	95 (55.6)	271 (53.1)	**0.004***
Prior CABG	n (%)	19 (8.6)	14 (11.8)	2 (1.2)	35 (6.9)	**<0.001***
Prior stroke/TIA	n (%)	10 (4.5)	5 (4.2)	2 (1.2)	17 (3.3)	0.152
Prior CKD	n (%)	22 (10)	9 (7.6)	10 (5.8)	41 (8)	0.318
Prior COPD	n (%)	68 (30.9)	36 (30.3)	41 (24)	145 (28.4)	0.283
Prior peripheral arterial disease	n (%)	126 (57.3)	53 (44.5)	70 (40.9)	249 (48.8)	**0.003***
Prior sleep apnea	n (%)	185 (84.1)	90 (75.6)	137 (80.1)	412 (80.8)	0.162
Prior device therapy for HF	n (%)	9 (4.1)	3 (2.5)	5 (2.9)	17 (3.3)	0.696
If yes for prior device therapy for HF, please specify						
CRT-D	n (%)	5 (55.6)	1 (33.3)	0 (0)	6 (35.3)	**0.030***
ICD	n (%)	3 (33.3)	1 (33.3)	0 (0)	4 (23.5)	
Pacemaker	n (%)	1 (11.1)	1 (33.3)	5 (100)	7 (41.2)	

*Significant P-value; 1: Significantly different from HFrEF group; 2: Significantly different from HFmrEF group; 3: Significantly different from HFpEF group; HF HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; SD: Standard deviation; BMI: Body Mass Index; HF: Heart Failure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HTN: Hypertension; IHD: Ischemic Heart Disease; AF: Atrial Fibrillation; DM: Diabetes Mellitus; MI: Myocardial Infarction; ACS: Acute Coronary Syndrome; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting; TIA: Transient Ischemic Attack; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; CRT-D: Cardiac Resynchronization Therapy with Defibrillator.

Baseline laboratory characteristics according to HF status

Baseline hemoglobin and the estimated glomerular filtration rate (eGFR) levels were significantly lower in the HFrEF group compared to the HFmrEF and HFpEF groups. Other variables, such as baseline creatinine levels, sodium, potassium, and random blood glucose levels, did not show significant differences between the groups. Additionally, the presence of positive hsTroponin was not significantly different across the groups **(Table 2)**.

Table 2: Baseline laboratory characteristics of the studied patients according to HF status.

		HFrEF (n = 220)	HFmrEF (n = 119)	HFpEF (n = 171)	Total	P-value
Baseline hemoglobin (gm%)	Mean ±SD	12 ±1.3	12.2 ±1.1	12.6 ±1.5	12.3 ±1.3	**<0.001***
Baseline creatinine (mg/dl)	Median (range)	1 (0.6 - 5.5)	1 (0.6 - 2.7)	1 (0.5 - 10.4)	1 (0.5 – 10.4)	0.098
Baseline eGFR (ml/min)	Mean ±SD	78 ±16	84 ±21	87 ±28	82 ±27	**0.003***
Baseline sodium (mEq/L)	Mean ±SD	137 ±5	137 ±5	137 ±5	137 ±5	1.00
Baseline potassium (mEq/L)	Mean ±SD	4 ±0.4	4 ±0.4	4 ±0.4	4 ±0.4	1.00
Random blood glucose (mg/dl)	Mean ±SD	151 ±6	146 ±9	155 ±75	151 ±69	0.509
hsTroponin	n (%)	41 (18.6)	31 (26.1)	35 (20.5)	107 (21)	0.272

*Significant P-value; 1: Significantly different from HFrEF group; 2: Significantly different from HFmrEF group; 3: Significantly different from HFpEF group; HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; SD: Standard deviation; gm%: grams per deciliter; mg/dl: milligrams per deciliter; eGFR: estimated Glomerular Filtration Rate; mEq/L: milliequivalents per liter; hsTroponin: high-sensitivity Troponin.

Pharmacological therapy according to HF status

Significant differences were observed in the usage of ACE inhibitors, with captopril being more frequently prescribed in HFmrEF patients (25.2%) compared to HFrEF (20.9%) and HFpEF (23.4%). Similarly, the reason for not prescribing ACE inhibitors differed, with low blood pressure being more common in HFrEF (6.4%) compared to HFmrEF (3.2%) and HFpEF (2%). Angiotensin II receptor blockers (ARBs) also showed significant differences, with olmesartan usage being higher in HFpEF patients (1.2%) compared to HFrEF and HFmrEF groups (0%). ARNI was significantly prescribed in HFrEF patients (49.5%) compared to HFmrEF (10.1%) and HFpEF (1.8%) **(Table 3)**.

The prescription of beta-blockers showed significant differences, with bisoprolol being the most commonly prescribed across all groups. MRAs, particularly spironolactone, were more frequently used in HFrEF patients (61.8%) compared to HFmrEF (52.9%) and HFpEF (27.5%). The use of SGLT2 inhibitors, particularly dapagliflozin, also demonstrated significant variability, being more frequently prescribed in HFrEF (22.7%) than in HFpEF (4.7%). Significant differences were found in the prescription of oral diuretics and ivabradine, with furosemide usage higher in HFrEF (7.7%) compared to HFmrEF (5%) and HFpEF (0.6%). While antiplatelet usage approached significance, insulin prescription and COPD treatments did not show significant differences between the groups. Apixaban was more frequently prescribed in HFpEF patients (70.4%) compared to HFrEF (55.9%) and HFmrEF (63.2%), while warfarin was higher in HFmrEF patients (36.8%) **(Table 3)**.

Table 3: Pharmacological therapy according to HF status.

		HFrEF (n = 220)	HFmrEF (n = 119)	HFpEF (n = 171)		P-value
Is patient on ACEIs						
Captopril	n (%)	46 (20.9)	30 (25.2)	40 (23.4)	116 (22.7)	NA
Enalapril	n (%)	8 (3.6)	14 (11.8)	24 (14)	46 (9)	
Others	n (%)	0 (0)	1 (0.8)	0 (0)	1 (0.2)	
Perindopril	n (%)	1 (0.5)	0 (0)	0 (0)	1 (0.2)	
Ramipril	n (%)	24 (10.9)	43 (36.1)	58 (33.9)	125 (24.5)	
No	n (%)	141 (64.1)	31 (26.1)	49 (28.7)	221 (43.3)	
If no ACEIs, specify cause						
Low BP	n (%)	9 (6.4)	1 (3.2)	1 (2)	11 (5)	**0.005***
Not tolerated	n (%)	4 (2.8)	1 (3.2)	9 (18.4)	14 (6.3)	
Patient on other RAAS inhibitor	n (%)	124 (87.9)	27 (87.1)	35 (71.4)	186 (84.2)	
Physician preference not to prescribe	n (%)	0 (0)	0 (0)	1 (2)	1 (0.5)	
Renal impairment	n (%)	4 (2.8)	2 (6.5)	3 (6.1)	9 (4.1)	
Is patient on ARBs?						
Candesartan	n (%)	1 (0.5)	1 (0.8)	3 (1.8)	5 (1)	**0.031***
Losartan	n (%)	0 (0)	4 (3.4)	5 (2.9)	9 (1.8)	
No	n (%)	194 (88.2)	93 (78.2)	133 (77.8)	2 (0.4)	
Olmesartan	n (%)	0 (0)	0 (0)	2 (1.2)	74 (14.5)	
Valsartan	n (%)	25 (11.4)	21 (17.6)	28 (16.4)	420 (82.4)	
If no ARBs, specify cause						
Low BP	n (%)	10 (5.2)	1 (1.1)	1 (0.8)	12 (2.9)	0.172
Not tolerated	n (%)	11 (5.7)	3 (3.2)	9 (6.8)	23 (5.5)	
Patient on other RAAS inhibitor	n (%)	169 (87.1)	87 (93.5)	118 (88.7)	374 (89)	
Physician preference not to pre	n (%)	0 (0)	0 (0)	2 (1.5)	2 (0.5)	
Renal impairment	n (%)	4 (2.1)	2 (2.2)	3 (2.3)	9 (2.1)	
Is patient on ARNI	n (%)	109 (49.5)	12 (10.1)	3 (1.8)	124 (24.3)	**<0.001***
If yes for ARNI on discharge, please specify the dose						
100 mg BID	n (%)	55 (50.5)	5 (41.7)	1 (33.3)	61 (49.2)	0.055
200 mg BID	n (%)	25 (22.9)	0 (0)	0 (0)	25 (20.2)	
50 mg BID	n (%)	29 (26.6)	7 (58.3)	2 (66.7)	38 (30.6)	
If no for ARNI, specify cause						
Cost issues	n (%)	6 (5.4)	3 (2.8)	1 (0.6)	10 (2.6)	**0.022***
Patient did not receive any RAAS inhibition	n (%)	11 (9.9)	6 (5.6)	7 (4.2)	24 (6.2)	
Patient on other ACEIs or ARBs	n (%)	93 (83.8)	98 (91.6)	152 (90.5)	343 (88.9)	
Physician preference not to prescribe ARNI	n (%)	0 (0)	0 (0)	1 (0.6)	1 (0.3)	
The patient did not hear about ARNI before	n (%)	1 (0.9)	0 (0)	7 (4.2)	8 (2.1)	
Is patient on beta blockers?						
Bisoprolol	n (%)	125 (56.8)	62 (52.1)	96 (56.1)	283 (55.5)	0.902
Carvedilol	n (%)	33 (15)	22 (18.5)	21 (12.3)	76 (14.9)	
Metoprolol	n (%)	45 (20.5)	26 (21.8)	37 (21.6)	108 (21.2)	
No	n (%)	15 (6.8)	8 (6.7)	16 (9.4)	4 (0.8)	
Others	n (%)	2 (0.9)	1 (0.8)	1 (0.6)	39 (7.6)	
If no for beta blockers, specify cause						
Low BP	n (%)	11 (73.3)	4 (50)	2 (12.5)	17 (43.6)	**0.006***
Low heart rate	n (%)	2 (13.3)	4 (50)	6 (37.5)	12 (30.8)	
Patient still having hypervolemia	n (%)	2 (13.3)	0 (0)	3 (18.8)	5 (12.8)	
Physician preference not to prescribe	n (%)	0 (0)	0 (0)	5 (31.3)	5 (12.8)	
Is patient on MRAs?						
Eplerenone	n (%)	66 (30)	34 (28.6)	29 (17)	129 (25.3)	**<0.001***
Spironolactone	n (%)	136 (61.8)	63 (52.9)	47 (27.5)	135 (26.5)	
No	n (%)	18 (8.2)	22 (18.5)	95 (55.6)	246 (48.2)	
If no for MRAs, specify cause						
Hyperkalemia	n (%)	1 (5.6)	1 (4.5)	2 (2.1)	4 (3)	**<0.001***
Low BP	n (%)	9 (50)	2 (9.1)	3 (3.2)	14 (10.4)	

		HFrEF (n = 220)	HFmrEF (n = 119)	HFpEF (n = 171)		P-value
Physician preference not to prescribe MRA (for HFpEF/HFmrEF cases only)	n (%)	0 (0)	16 (72.7)	89 (93.7)	105 (77.8)	
Renal impairment	n (%)	8 (44.4)	3 (13.6)	1 (1.1)	12 (8.9)	
Is patient on SGLT2i?						
Dapagliflozin	n (%)	50 (22.7)	23 (19.3)	8 (4.7)	81 (15.9)	**<0.001***
Empagliflozin	n (%)	49 (22.3)	18 (15.1)	12 (7)	79 (15.5)	
Others	n (%)	0 (0)	0 (0)	2 (1.2)	348 (68.2)	
No	n (%)	121 (55)	78 (65.5)	149 (87.1)	2 (0.4)	
If no for SGLT2i, specify cause						
Cost issues	n (%)	66 (54.5)	46 (59)	58 (38.9)	170 (48.9)	**<0.001***
Dehydration	n (%)	13 (10.7)	3 (3.8)	2 (1.3)	18 (5.2)	
High patient's frailty	n (%)	1 (0.8)	0 (0)	2 (1.3)	3 (0.9)	
Low eGFR	n (%)	3 (2.5)	1 (1.3)	2 (1.3)	6 (1.7)	
The patient did not hear about SGLT2i before	n (%)	38 (31.4)	28 (35.9)	85 (57)	151 (43.4)	
Is patient on oral diuretics?						
Furosemide	n (%)	17 (7.7)	6 (5)	1 (0.6)	24 (4.7)	**<0.001***
Others	n (%)	0 (0)	1 (0.8)	0 (0)	1 (0.2)	
Torasemide	n (%)	73 (33.2)	27 (22.7)	29 (17)	129 (25.3)	
No	n (%)	130 (59.1)	85 (71.4)	141 (82.5)	356 (69.8)	
Is patient on ivabradine?	n (%)	30 (13.6)	17 (14.3)	1 (0.6)	48 (9.4)	**<0.001***
Is patient on antiplatelets?	n (%)	177 (80.5)	99 (83.2)	124 (72.5)	400 (78.4)	0.059
Is patient on oral anticoagulants?	n (%)	34 (15.5)	19 (16)	27 (15.8)	80 (15.7)	0.991
If yes for oral anticoagulants, please specify						
Apixaban	n (%)	19 (55.9)	12 (63.2)	19 (70.4)	50 (62.5)	0.747
Rivaroxaban	n (%)	2 (5.9)	0 (0)	1 (3.7)	3 (3.8)	
Warfarin	n (%)	13 (38.2)	7 (36.8)	7 (25.9)	27 (33.8)	
Is patient on amiodarone?	n (%)	12 (5.5)	8 (6.7)	12 (7)	32 (6.3)	0.797
Is patient on digitalis?	n (%)	25 (11.4)	21 (17.6)	12 (7)	58 (11.4)	**0.02***
Is patient insulin?	n (%)	83 (37.7)	36 (30.3)	50 (29.2)	169 (33.1)	0.156
Is patient on oral anti-DM?						
Glitazones	n (%)	4 (1.8)	1 (0.8)	4 (2.3)	9 (1.8)	0.776
Metformin	n (%)	43 (19.5)	23 (19.3)	34 (19.9)	100 (19.6)	
Others	n (%)	27 (12.3)	19 (16)	21 (12.3)	67 (13.1)	
Sulphonylurea	n (%)	8 (3.6)	1 (0.8)	3 (1.8)	12 (2.4)	
No	n (%)	138 (62.7)	75 (63)	109 (63.7)	322 (63.1)	
Is patient on any treatment of COPD?						
Beta2 agonists	n (%)	22 (10)	8 (6.7)	9 (5.3)	39 (7.6)	0.14
Corticosteroids	n (%)	34 (15.5)	22 (18.5)	19 (11.1)	75 (14.7)	
No	n (%)	164 (74.5)	89 (74.8)	143 (83.6)	396 (77.6)	

*Significant P-value; HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; ACEIs: Angiotensin-Converting Enzyme Inhibitors; ARBs: Angiotensin II Receptor Blockers; ARNI: Angiotensin Receptor Neprilysin Inhibitor; BID: Twice Daily; RAAS: Renin-Angiotensin-Aldosterone System; HR: Heart Rate; MRAs: Mineralocorticoid Receptor Antagonists; SGLT2i: Sodium-Glucose Cotransporter 2 inhibitors; AF: Atrial Fibrillation; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease.

Radiological workup according to HF status

Abnormal ECG findings were significantly different among the groups, with 94.1% of HFrEF, 90.8% of HFmrEF, and 97.7% of HFpEF patients showing abnormalities. LVH was notably more common in HFpEF patients (12.6%) compared to HFrEF (7.7%) and HFmrEF (9.3%). Pathological Q waves were more frequent in HFmrEF patients (23.1%) than in HFrEF (14%) and HFpEF (18.6%) patients. Echocardiographic findings also showed significant differences, with LVH present in 37.4% of HFpEF patients compared to 17.3% in HFrEF and 20.2% in HFmrEF. Additionally, LA diameter and LVEDD were significantly larger in HFrEF patients compared to the other groups **(Table 4)**. Moderate-to-severe mitral regurgitation (MR) and tricuspid regurgitation (TR) did not show significant differences between groups. Coronary angiography findings were borderline significant, with abnormalities observed in 89.8% of HFrEF, 93.3% of HFmrEF, and 87.8% of HFpEF patients. Revascularization attempts, including CABG and PCI, were significantly less common in HFpEF patients (0%) compared to HFrEF (12.2%) and HFmrEF (10.7%). Three-vessel disease was more frequent in HFrEF patients (26%) compared to HFmrEF (20.2%) and HFpEF (13%). **(Table 4)**.

Table 4: Radiological workup according to HF status.

		HFrEF (n = 220)	HFmrEF (n = 119)	HFpEF (n = 171)	Total	P-value
Abnormal ECG	n (%)	207 (94.1)	108 (90.8)	167 (97.7)	482 (94.5)	**0.037***
If abnormal, "major" ECG finding is						
AF	n (%)	16 (7.7)	9 (8.3)	16 (9.6)	41 (8.5)	**<0.001***
LBBB	n (%)	44 (21.3)	9 (8.3)	3 (1.8)	56 (11.6)	
LVH	n (%)	16 (7.7)	10 (9.3)	21 (12.6)	47 (9.8)	
Paced rhythm	n (%)	6 (2.9)	3 (2.8)	5 (3)	14 (2.9)	
Pathological Q waves	n (%)	29 (14)	25 (23.1)	31 (18.6)	85 (17.6)	
RBBB	n (%)	3 (1.4)	2 (1.9)	4 (2.4)	9 (1.9)	
Other abnormality	n (%)	93 (44.9)	50 (46.3)	87 (52.1)	230 (47.7)	
CXR performed	n (%)	160 (72.7)	64 (53.8)	97 (56.7)	321 (62.9)	**<0.001***
If yes for CXR, was it						
Abnormal	n (%)	152 (95)	56 (87.5)	66 (68)	274 (85.4)	**<0.001***
Normal	n (%)	8 (5)	8 (12.5)	31 (32)	47 (14.6)	
If CXR was abnormal, what "major" abnormality was						
Alveolar edema	n (%)	14 (9.2)	8 (14.3)	9 (13.6)	31 (11.3)	0.479
Cardiomegaly	n (%)	99 (65.1)	32 (57.1)	45 (68.2)	176 (64.2)	
Pleural effusion	n (%)	39 (25.7)	16 (28.6)	12 (18.2)	67 (24.5)	
LVH in echo	n (%)	38 (17.3)	24 (20.2)	64 (37.4)	126 (24.7)	**<0.001***
LA diameter in echo (in cm)	Mean ±SD	4.5 ±0.8	4 ±0.6	3.8 ±0.5	4.1 ±0.7	**<0.001***
LVEDD in echo (in cm)	Mean ±SD	5.9 ±0.9	5.7 ±0.9	5.6 ±0.9	5.7 ±0.9	**0.004***
Moderate-to-severe MR in echo	n (%)	54 (24.5)	33 (27.7)	47 (27.5)	134 (26.3)	0.741
More than moderate MS in echo	n (%)	5 (2.3)	2 (1.7)	10 (5.8)	17 (3.3)	0.077
Moderate-to-severe AR in echo	n (%)	11 (5)	5 (4.2)	13 (7.6)	29 (5.7)	0.396
Moderate-to severe AS in echo	n (%)	10 (4.5)	4 (3.4)	12 (7)	26 (5.1)	0.336
Moderate-to severe TR in echo	n (%)	128 (58.2)	64 (53.8)	96 (56.1)	288 (56.5)	0.734
ePASP in echo (mmHg)	Mean ±SD	44 ±13	41 ±12	43 ±14	43 ±13	0.208
Coronary angiography done	n (%)	137 (62.3)	90 (75.6)	123 (71.9)	350 (68.6)	**0.021***
If yes for coronary angiography, was it						
Abnormal	n (%)	123 (89.8)	84 (93.3)	108 (87.8)	315 (90)	0.411
Normal	n (%)	14 (10.2)	6 (6.7)	15 (12.2)	35 (10)	
If coronary angiography was abnormal, was it						
Left main disease	n (%)	0 (0)	0 (0)	1 (0.9)	1 (0.3)	**0.023***
Single vessel disease	n (%)	60 (48.8)	47 (56)	75 (69.4)	182 (57.8)	
Three vessel disease	n (%)	32 (26)	17 (20.2)	14 (13)	63 (20)	
Two vessel disease	n (%)	31 (25.2)	20 (23.8)	18 (16.7)	69 (21.9)	
If coronary angiography was abnormal, was revascularization attempted						
No	n (%)	11 (8.9)	4 (4.8)	14 (13)	29 (9.2)	**0.002***
Yes, by GABG	n (%)	15 (12.2)	9 (10.7)	0 (0)	24 (7.6)	
Yes, by PCI	n (%)	97 (78.9)	71 (84.5)	94 (87)	262 (83.2)	

*Significant P-value; HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; GABG: Coronary Artery Bypass Grafting; PCI: Percutaneous Coronary Intervention; ECG: Electrocardiogram; CXR: Chest X-ray; LVH: Left Ventricular Hypertrophy; LA: Left Atrium; LVEDD: Left Ventricular End Diastolic Dimension; MR: Mitral Regurgitation; MS: Mitral Stenosis; AR: Aortic Regurgitation; AS: Aortic Stenosis; TR: Tricuspid Regurgitation; ePASP: Estimated Pulmonary Arterial Systolic Pressure.

Non-pharmacological and device-based therapies according to HF status

Significant differences were observed in the scheduling of rehabilitation, with 5.5% of HFrEF patients, 19.3% of HFmrEF patients, and 11.7% of HFpEF patients scheduled for rehabilitation. Other variables, such as pacemaker implantation, CRT, ICD, and patient health education, did not show significant differences between the groups **(Table 5)**.

Table 5: Non-pharmacological and device-based therapies according to HF status.

		HFrEF (n = 220)	HFmrEF (n = 119)	HFpEF (n = 171)	Total	P-value
Pacemaker implantation done	n (%)	5 (2.3)	3 (2.5)	6 (3.5)	14 (2.7)	0.748
CRT (D/P) done	n (%)	5 (2.3)	2 (1.7)	0 (0)	7 (1.4)	0.129
ICD done?	n (%)	4 (1.8)	1 (0.8)	0 (0)	5 (1)	0.206
Patient health education given	n (%)	219 (99.5)	116 (97.5)	171 (100)	506 (99.2)	0.054
Patient scheduled for rehabilitation	n (%)	12 (5.5)	23 (19.3)	20 (11.7)	55 (10.8)	**<0.001***

HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; CRT: Cardiac Resynchronization Therapy; D: Defibrillator; P: Pacemaker; ICD: Implantable Cardioverter Defibrillator.

DISCUSSION

HF is a prevalent and growing global health challenge, particularly in Egypt, where cardiovascular disease remains the leading cause of death. So, we aimed to evaluate the various phenotypes and treatment strategies for HF among a contemporary cohort of Egyptian patients.

In our study, HFrEF was more common in males, with frequent hospitalizations and a strong ischemic component, including higher rates of prior MI/ACS and peripheral arterial disease. HFpEF was more common in females, associated with higher systolic blood pressure and hypertension as a primary cause.

Our findings align with those of **Bendary *et al.*,** who reported that 77% of patients had HFrEF (LVEF ≤ 40%), 9.8% had HFmrEF (LVEF 41-49%), and 13.3% had HFpEF (LVEF ≥ 50%). Females predominated in HFpEF, while males dominated HFrEF and HFmrEF (P < 0.001). HFpEF and HFmrEF patients had higher BMIs and significant differences in cardiovascular risk factors and comorbidities, such as ACS/MI, AF, anemia, and uncontrolled hypertension, compared to HFrEF patients [12].

Badran *et al.* also reported HFrEF as the most common type (61.9%) compared to HFpEF (38.1%) (P < 0.001). HFpEF patients had more hypertension and UA/NSTEMI, while HFrEF patients had more STEMI and ACS. Hypertensive heart disease was more common in HFpEF, whereas ACS was a major cause in HFrEF [13]. **Linde *et al.*** found that HFpEF patients were older, more frequently female, and had a higher burden of comorbidities, including atrial fibrillation and hypertension, compared to HFrEF patients [14].

In the present study, HFrEF patients had lower hemoglobin, higher creatinine, and significantly lower eGFR, indicating more severe anemia and renal impairment. HFmrEF had the highest prevalence of positive hsTroponin, suggesting ongoing myocardial injury.

Consistently, **Savarese *et al.*** conducted a study to assess role of anemia in HF across the ejection fraction spectrum and found that anemia was more prevalent in HFpEF than in HFmrEF and HFrEF in a nation-wide registry. However, anemia was linked to an increased risk of death across all EF types, with a higher risk of death or hospitalization in HFpEF and HFmrEF compared to HFrEF [15].

Elevated troponin levels indicate myocardial injury, which is more pronounced in HFmrEF due to the combined effects of systolic and diastolic dysfunction. HFmrEF patients often have underlying ischemic heart disease, contributing to ongoing myocardial damage and higher troponin levels [16]. In contrast, HFpEF is primarily associated with diastolic dysfunction and less myocardial injury, explaining the decreased troponin levels in this group [17].

In our study, ACEI usage varied significantly, with captopril more commonly prescribed in HFmrEF. Low blood pressure was a more frequent reason for not prescribing ACEIs in HFmrEF compared to HFrEF and HFpEF.

These findings are consistent with the European Society of Cardiology (ESC) guidelines, which strongly recommend ACEIs for HFrEF due to their proven mortality and morbidity benefits [18]. Studies such as those by **Swedberg *et al.*** have demonstrated the efficacy of ACEIs in improving outcomes for patients with reduced ejection fraction [19].

In our study, the use of ARBs differed significantly among HF patients. This variation can be attributed to the intolerance of some patients to ACEIs, necessitating the use of ARBs as an alternative. The preferential use of different ARBs in specific HF subtypes may also be influenced by physician familiarity and regional prescribing practices [20].

In our study, the use of ARNI was more common in HFrEF (49.5%) compared to HFmrEF (10.1%) and HFpEF (1.8%). This significant difference is likely due to the strong evidence supporting the benefits of ARNI in reducing cardiovascular mortality and HF hospitalization in HFrEF patients, as demonstrated in the PARADIGM-HF trial [20]. The lower adoption in HFmrEF and HFpEF reflects the emerging and less robust evidence base for these subtypes or this may be attributed to cost issues as found in our study in which we found the primary reason for not prescribing ARNI was cost-related reasons despite its proven efficacy.

Our study reported that beta-blockers, particularly bisoprolol, were more frequently used in HFrEF (56.8%) compared to HFmrEF (52.1%) and

HFpEF (56.1%). This is aligned with current guidelines, which recommend beta-blockers for all patients (if not contraindicated by the decreased blood pressure) with HFrEF to improve survival and reduce hospitalizations [18].

In our study, prescription patterns varied significantly by HF type. Spironolactone was most used in HFrEF, but hyperkalemia limited its use. SGLT2 inhibitors were more common in HFrEF and HFmrEF, with cost being a barrier in HFmrEF. Diuretic use was lower in HFpEF, reflecting less fluid overload. Antiplatelet and insulin use was higher in HFrEF and HFmrEF, linked to ischemic heart disease and diabetes. Apixaban was more common in HFpEF, focusing on stroke prevention, while warfarin was more used in HFmrEF, reflecting older practices.

Medication variations among HF groups reflect differences in disease pathology and guidelines. Research shows that HF medications are tailored to each subtype, considering distinct pathophysiological mechanisms and patient profiles [21-23].

Badran *et al.* found no disparity in the prescription rates of ACE inhibitors/ARBs, beta-blockers, and MRAs between patients with HFrEF and those with HFpEF as prescribed by coronary care unit (CCU) physicians [13]. Conversely, **Linde *et al.*** reported that ACE inhibitors were more commonly prescribed in HFrEF (67%) and HFmrEF (61%), while ARBs were more common in HFpEF. MRA prescription rates were similar across all HF types. Beta-blockers were used more frequently in HFrEF, and ARNI was rarely prescribed, with only 2% of HFrEF and HFmrEF patients receiving it, and none in HFpEF [14].

Radiological workup showed significant differences across HF subtypes. Abnormal ECG findings and LVH were most frequent in HFpEF, while pathological Q waves were more common in HFmrEF. Echocardiography revealed higher LVH in HFpEF, with larger LA diameters and LVEDD in HFrEF, indicating more severe remodeling. Moderate-to-severe MR was slightly more common in HFmrEF, and TR was most prevalent in HFrEF. These findings highlight distinct structural and electrical changes in each HF subtype, emphasizing the need for tailored diagnostic and management strategies.

Linde *et al.* reported a higher prevalence of AF in HFpEF (43%) and HFmrEF (34%) compared to HFrEF (29%). HFpEF patients had smaller LV end-diastolic and systolic diameters and volumes than HFrEF. Mitral regurgitation grade ≥ 2 was significantly lower in HFpEF (8%) and HFmrEF (10%) compared to HFrEF (27%) ($P < 0.001$) [14].

Coronary angiography showed abnormalities across all HF groups, with 93.3% in HFmrEF, 89.8% in HFrEF, and 87.8% in HFpEF. Single-vessel disease was most common in HFpEF patients (69.4%), while three-vessel disease was more prevalent in HFrEF patients (26%). Revascularization procedures, such as CABG and PCI, were frequently performed without significant differences among groups, but revascularization attempts were less common in HFpEF patients (0%) compared to HFrEF (12.2%) and HFmrEF (10.7%).

This aligns with the study conducted by **Trevisan *et al.*** to assess prevalence and characteristics of CAD in HF and revealed that 64% of HF patients had significant coronary stenosis, with a global CAD prevalence of 80%. CAD prevalence was similar for HFpEF and HFmrEF. Significant stenosis in the left main coronary artery occurred in 6.5% of cases, and 39% had two- or three-vessel disease. Complete revascularization was achieved in 36% of patients with significant stenosis and 23% of HFpEF/HFmrEF patients [24].

Based on the findings of this study, it is evident that the adherence to ESC guidelines for managing HF in our cohort is promising but has areas for improvement. Pharmacological adherence is strong, with high usage rates of ACE inhibitors, beta-blockers, MRAs, and SGLT2 inhibitors, aligning with ESC recommendations. ARNI usage in HFrEF patients was also notable, reflecting proper guideline-directed medical therapy (GDMT). However, device-based therapies like CRT and ICD were significantly underutilized across all HF subtypes, indicating a gap in guideline adherence, likely due to socioeconomic and access-related barriers.

This study had some limitations including the cross-sectional design that limits findings to associations rather than establishing causality, and the absence of long-term follow-up data preventing evaluating the impact of treatments on outcomes over time. Additionally, reliance on patient interviews may introduce recall bias or inaccuracies in self-reported data.

CONCLUSIONS

HFrEF is more prevalent in males, while HFpEF is more common in females and associated with higher SBP and LVH. The significant underutilization of SGLT2 inhibitors and ARNI highlights the need for improved accessibility to advanced HF therapies in Egypt. Tailored management strategies are essential for optimizing care based on HF phenotypes.

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