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Research Article

Analyzing Short and Medium-Term Morbidity and Mortality in Patients with Heart Failure and Borderline Ejection Fraction (EF: 40-49%).

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Abstract:

Introduction: Heart failure with moderately impaired ejection fraction (HFmEF) has garnered increasing attention in recent years. However, understanding this new phenotype, particularly concerning morbidity and mortality, remains limited.

Materials and Methods: A prospective, observational, and single-center study spanning 26 months was conducted on 204 patients with HFmEF selected from 447 patients with chronic heart failure (CHF) categorized based on their left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF) if LVEF ≤ 40% (n = 173) and HF with preserved ejection fraction (HFpEF) if LVEF ≥ 50% (n = 70). This study included a detailed evaluation of factors precipitating cardiovascular (CV) death and rehospitalizations in patients with HFmEF.

Results: After a mean follow-up of 431 days in the HFmEF patient group, our results indicated that CV mortality at six months was 2.5%, and at one year, it was 5.9%. Prognostic factors for survival included chronic kidney disease, blood glucose level > 1.4g/l, presence of moderate to severe secondary mitral insufficiency, sphericity index < 1.7, elevated pulmonary vascular resistance, and resistance to diuretic treatment. HF rehospitalization rates at 6 and 12 months were 2.5% and 8.3%, respectively. Predictive factors for HF rehospitalizations included diabetes, hemoglobin level < 13g/dl, left atrial volume > 34 ml/m^{3-}, mitral S-wave < 0.05cm/s, non-improvement of global longitudinal strain, and resistance to diuretic treatment.

Conclusion: This category of HF remains underrecognized and neglected by practitioners, and its prognosis is formidable, especially in the presence of adverse prognostic factors.

Key words: Slightly impaired ejection fraction. Cardiovascular mortality. Rehospitalizations for heart failure. Predictive factors.

Introduction

Heart failure (HF) is a major public health issue affecting approximately 64 million patients worldwide [1]. It remains the leading cause of hospitalization among adults over the age of 65, imposing a considerable socio-economic burden due to healthcare resource utilization [2]. The 2021 guidelines from the European Society of Cardiology (ESC) classify HF patients into reduced ejection fraction (HFrEF), mildly reduced or midrange ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) [3]. However, prior. Data from various countries and regions have indicated heterogeneous long-term prognoses for these three HF phenotypes. Several cohort studies have demonstrated that patients with HFpEF and HFmrEF have a significantly better prognosis than those with HFrEF [4].

In contrast, a study from the United States and a Korean HF registry indicated similar mortality across the spectrum of left ventricular ejection fraction (LVEF) [5,6]. Finnish and Spanish cohort studies observed a significantly worse outcome in patients with HFpEF [7,8]. Furthermore, there is a lack of data comparing mortality and rehospitalizations at one year among patients with HFpEF, HFmrEF, and HFrEF in Algeria. We hypothesize that patients with HFmrEF constitute a distinct population from those with preserved or reduced ejection fraction. Therefore, the objective of this study was to analyze short-term (6 months) and medium-term (one year) cardiovascular morbidity and mortality in patients with HF of all types (HFpEF, HFrEF, and HFmrEF) and identify predictive factors for mortality and cardiovascular rehospitalizations in the group of patients with HFmrEF.

Materials and Methods

Study Sample

In this prospective observational study, we conducted a prognostic assessment of patients with heart failure (HF) who were under observation at the Regional Military University Hospital of Oran. We consecutively recruited patients between November 2019 and January 2023, diagnosing HF following the guidelines set forth by the European Society of Cardiology (ESC) [9]. Baseline demographic, clinical, and echocardiographic data were collected. Patients were categorized into three groups according to the new ESC guidelines for HF diagnosis and treatment: HFrEF if LVEF ≤ 40%, HFmrEF if LVEF: 41-49%, and HFpEF if LVEF ≥ 50% [29]. Data on LVEF at one year were also collected when

available. Inclusion criteria included adult patients (≥18 years) with recent HF (less than 12 months) diagnosed based on Framingham criteria for HF study [10], regardless of etiology.

Data Collection Procedure

We retrieved data from patient records within the hospital. We collected demographic information, including age, sex, and race, alongside clinical data such as cardiovascular mortality and rehospitalizations for heart failure (HF). Echocardiographic data encompassed parameters such as left ventricular ejection fraction (LVEF), left ventricular diastolic volume (LVDV), left ventricular systolic volume (LVSV), global longitudinal strain (GLS), left atrial volume index (LAVi), right atrial surface (RAS), left ventricular sphericity index, pulmonary vascular resistances (PVR), indexed left ventricular mass (LVMi), presence of diastolic dysfunction, the distance between E-wave and interventricular septum (E-wave-IVS distance), pulmonary artery systolic pressures (PASP), and quantification of secondary mitral insufficiency (SMI).

Assessments of diastolic dysfunction followed the 2016 recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EASCVI) [11]. These assessments were based on measurements related to mitral inflow, tissue Doppler on the septum and lateral wall, pulmonary vein flow, and tricuspid velocity. Notably, all echocardiographic reports in our department undergo approval by two experienced cardiologists specializing in echocardiography.

Regarding cardiovascular risk factors, we defined diagnostic criteria for diabetes, hypertension, and dyslipidemias based on specific values of glycemia, blood pressure, and cholesterol, following the recommendations of the World Health Organization (WHO) [12], the American Diabetes Association (ADA) [13], and the French Haute Autorité de Santé (HAS) [14]. These criteria include plasma venous glycemia ≥ 2 g/L (11.1 mmol/L) and/or glycosylated hemoglobin A1C (HbA1C) ≥ 6.5% (48 mmol/mol) by standardized measurement and/or plasma venous glycemia ≥ 2 g/L (11.1 mmol/L) 2 hours after an oral load of 75 g glucose, blood pressure values ≥ 130/80 mm Hg, as well as specific levels of total cholesterol, triglycerides, HDL-C, and LDL-C to assess cardiovascular risk. Blood samples for these tests are collected after a 12-hour fast.

Follow-up

All patients were regularly followed up. Those who did not attend the clinical appointment were contacted by phone. The primary evaluation criterion was cardiovascular mortality during the 12-month follow-up period. Specifically, deaths and their causes were recorded and verified by reviewing relevant medical documents. In contrast, if not documented, any additional necessary information was obtained by contacting one of the physicians or the patient's relatives. Cardiovascular death was considered if it resulted from hypertension, sudden death, acute myocardial infarction, stroke, cardiovascular intervention, or other cardiovascular causes. Secondary evaluation criteria were defined as hospitalization for HF and major adverse cardiovascular events (MACE). Hospitalization for HF was defined as any new hospitalization with a primary diagnosis of HF. MACEs are composite events of myocardial infarction, stroke, or other peripheral arterial complications identified locally and recorded on the study case report forms.

Statistical Analysis

All collected data were entered into a computer and analyzed using IBM SPSS 24.0 software (IBM Corporation, New York, USA). Categorical variables were expressed as frequency and percentage, while quantitative variables were presented as mean, standard deviation (SD), and median ranks. The chi-square independence test was performed to explore the association of LVEF categories with various demographic and clinical factors. Kaplan-Meier survival curves were constructed for cardiovascular mortality, rehospitalizations for HF, and MACEs, while log-rank tests were used to compare the unadjusted survival curves of the three groups. Univariate and multivariate Cox proportional hazard regressions were performed to identify the association of predictive factors for cardiovascular mortality and rehospitalizations for HF in the group of patients with HFmrEF during one year of follow-up. All variables were tested in univariate analysis. Variables that reached a P value < 0.10 in univariate models or were considered clinically relevant to the outcomes were introduced into the multivariate analysis. All statistical tests were two-tailed, and statistical significance was defined by P values < 0.05 for all statistical analyses. In Cox regression and logistic regression models, hazard ratios (HR) and odds ratios (OR) with 95% confidence intervals (CI) were calculated, respectively.

Results

Among the 447 patients in the study, 45.6% had HFmrEF, 38.7% had HFrEF, and only 15.7% had HFpEF. HFmrEF was the most common form in men (48.2%) and women (40%). The mean age of the cohort was 60 ± 14 years, ranging from 20 to 80 years. There was a clear male predominance with a sex ratio of 2.2

Follow-up

The average follow-up duration was 431.25 days, with a standard deviation of 148.8 days, ranging from 59 to 1233 days. Most patients were followed for at least 12 months, with an average of 3 to 4 consultations. Clinical Improvement: Over 70% of patients showed clinical improvement, particularly regarding the New York Heart Association (NYHA) class. This improvement was more pronounced in patients initially diagnosed with HFmrEF and HFpEF than those with reduced ejection fraction.

One-Year Events

Cardiovascular Mortality

After analyzing cardiovascular mortality in the three groups, it was observed that short-term cardiovascular mortality was lower in the midrange group compared to the preserved group (4.3%). Furthermore, there was a significant difference between HFmrEF and HFrEF, with a mortality rate of 2.5% for HFmrEF and 7.5% for HFrEF (p = 0.02). However, this mortality rate increased to 5.9% after 12 months of follow-up, becoming similar to HFpEF patients (5.7%) but still lower than HFrEF patients (13.3%) (p = 0.01). See Figure 1.A.

Rehospitalizations for HF

No significant difference was observed in the short-term rehospitalization rate among the three HF categories (HFmrEF: 2.5% versus 2.9% for HFpEF and 2.3% for HFrEF). However, in the medium term, the rehospitalization rate in the midrange group was lower than in the other two categories (8.3% for HFmrEF versus 11.4% and 13.3% for HFpEF and HFrEF, respectively) without a significant difference between the three categories. See Figure 1.B

Major Adverse Cardiovascular Events (MACEs)

The MACE rate was significantly higher in the midrange group

compared to the other two groups (HFmrEF: 3.9% versus 2.9% and 0.6% for HFpEF and HFrEF, respectively, P = 0.03) in the short term; however, there was no significant difference between the three categories after a 12-month follow-up. See Figure 1.C.

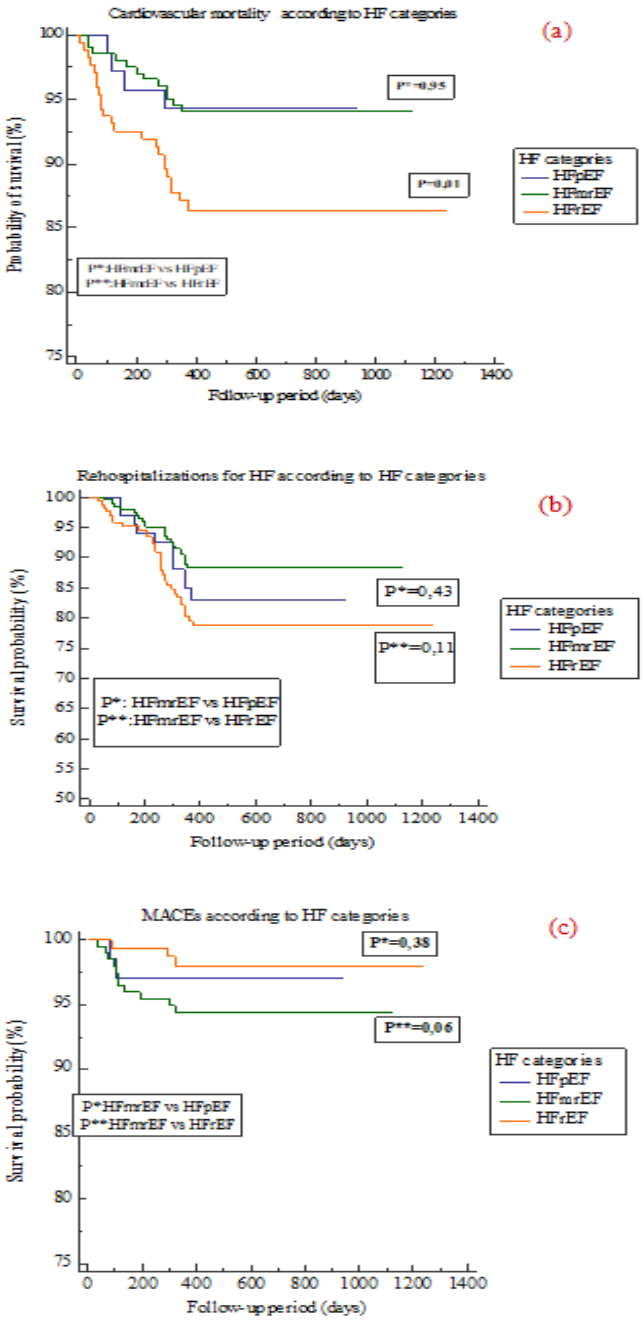

Figure 1: Kaplan-Meier Survival Analysis in the Three HF Categories Based on Follow-up Period for A. Cardiovascular Mortality, B. Rehospitalizations for HF Exacerbation, C. Major Adverse Cardiovascular Events (MACEs).

Predictive Factors for One-Year Events

Predictive Factors in Univariate Analysis

In a univariate analysis with a significance threshold of 10%, 32 significant variables were identified and categorized into five main groups:

- Epidemiological: Higher mortality risk in males (p = 0.02), individuals aged 65 to 72 years (p = 0.03), and those with a history of hypertension (p = 0.05) and chronic kidney disease (p < 10^-3).
- Clinical: Presence of paroxysmal nocturnal dyspnea (p < 10^-3).
- Electrocardiography: Atrial fibrillation (AF) (p < 10^-3) and QRS duration ≥ 0.08s (p = 0.003) were associated with reduced survival.
- Biochemical: Blood glucose > 1.4g/l (p = 0.02), hemoglobin < 13g/dl (p = 0.07), sodium level ≤ 136mmol/l (p = 0.002), creatinine clearance ≤ 60ml/min (p < 10^-3) were linked to decreased survival. However, NTproBNP levels showed no significant difference in survival at a threshold of 2600pg/ml (p = 0.51).
- Echocardiography: Left atrial volume index (LAVi) ≥ 34 ml/m^2 (p = 0.02), right atrial surface area (SOD) > 18 cm^2 (0.006), left ventricular mass index (MVGi) ≥ 170 g/m^2 (0.02), pulmonary artery systolic pressure (PAPS) > 35 mm Hg (p < 10^-3), E/vp ratio > 2.5 (p = 0.05), maximum velocity of the mitral S wave ≤ 0.05 cm/s (p = 0.001), tricuspid S wave velocity ≤ 9 cm/s (p = 0.003), sphericity index ≤ 1.7 (p = 0.04), pulmonary vascular resistance (RVP) > 0.2 dynes/sec/cm^3 (p = 0.001), restrictive filling pattern (p = 0.03), moderate to severe mitral regurgitation (p = 0.003), and E-SIV distance > 1.1 cm (p = 0.08).
- Therapeutic: Lower survival in patients requiring high doses of diuretics (p = 0.002) and those on anticoagulants (p = 0.03).
- Evolutionary: Improvement in NYHA class (p = 0.001), heart rate (HR) < 70 bpm under beta-blockers (0.05), decrease in filling pressures (p = 0.05) and PAPS (p = 0.06), increase in left ventricular ejection fraction (p = 0.002), global longitudinal strain (GLS) (p = 0.001), and cardiac output (p = 0.002) were associated with better survival.

Predictive Model for Cardiovascular Mortality

Using multivariate analysis with a significance threshold of 5%, six factors were selected to constitute the final predictive model: chronic kidney disease (CKD) (OR: 39, p < 10^-3), blood glucose > 1.4g/l (OR: 4.2, p: 0.02), presence of moderate to severe secondary mitral regurgitation (MR) (OR: 38.3, p = 0.001), sphericity index < 1.7 (OR: 4.9, p = 0.03), elevated pulmonary vascular resistance (RVP) (OR: 11.3, p < 10^-3), and resistance to diuretic treatment (OR: 16.6, p = 0.03). See Table 1.

The ROC curve analysis revealed that this model has a good discriminatory ability for mortality in HFmrEF patients, with a C-statistic (area under the ROC curve) of 0.901. The model exhibited a sensitivity of 91% and specificity of 95%. See Figure 2.

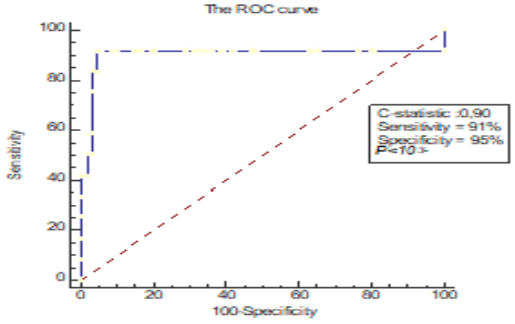

Figure 2: Receiver Operating Characteristic (ROC) Curve Analysis of the Predictive Model for One-Year Mortality in HFmrEF Patients.

Table 1: Predictive Factors for One-Year Mortality in HFmrEF Patients. Multivariate Analysis by Logistic Regression (n=204).

Factors	$HR_{adjusted}$	95% confidence interval	P value
CKD			
No	1		
Yes	39,65	7,33-214,41	$<10^{3-}$
Blood glucose (g/l)			
=1,4	1		
>1,4	4,20	1,19-14,82	0,02
RVP (dynes /sec/$cm^{3)}$			
=0,2	1		
>0,2	11,39	2,76-46,98	0,001
Sphericity index			
>1,7	1		
=1,7	4,94	1,16-21,07	0,03
Moderate to severe MR			
No	1		
Yes	38,36	4,28-343,48	0,001
Resistance to diuretic treatment			
No	1		
Yes	13,67	1,21-154,35	0,03

Predictive Model for Rehospitalizations

Through a multivariate analysis with a significance threshold of 5%, six factors were identified to form the final predictive model: diabetes (OR: 5.46), hemoglobin level < 13g/dl (OR: 5.25, p=0.03), left atrial volume index (LAVi) ≥ 34 ml/m^3 (OR: 3.79, p=0.02), mitral S wave velocity < 0.05 cm/s (OR: 2.73, p=0.03), lack of improvement in global longitudinal strain (GLS) (OR: 8.67, p < 10^-3), and resistance to diuretic treatment (OR: 10.75, p=0.003). The ROC curve analysis demonstrated a robust ability to discriminate rehospitalizations in HFmrEF patients with a C-statistic (area under the curve "AUC") of 0.84, a sensitivity of 77%, and a specificity of 89%. See Table 2 and Figure 3.

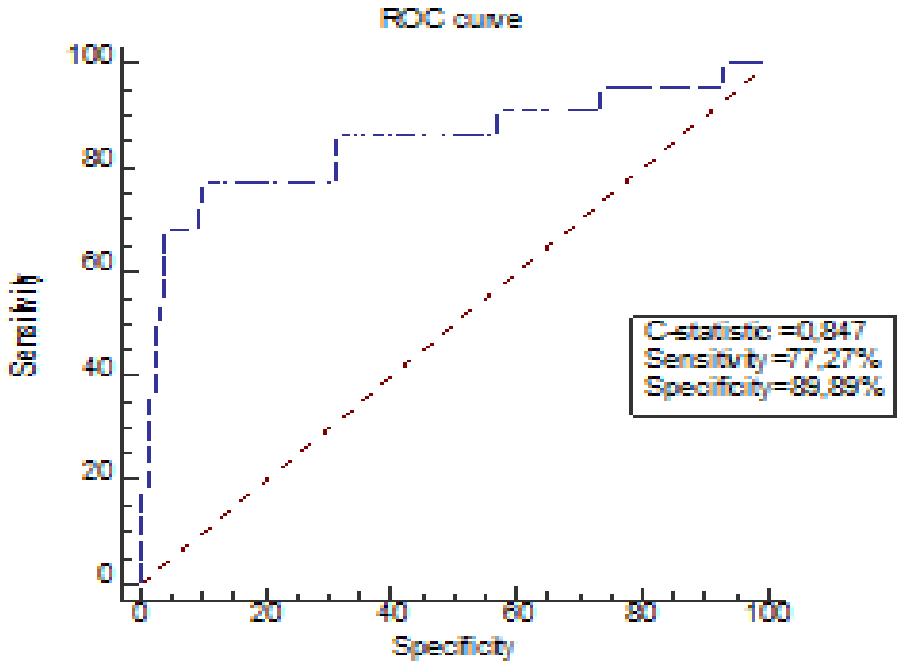

Figure 3: Receiver Operating Characteristic (ROC) Curve Analysis of the Predictive Model for One-Year Rehospitalizations in Patients with HFmrEF.

Table 2: Predictive Factors for One-Year Rehospitalizations in HFmrEF Patients. Multivariate Analysis Logistic Regression (n=204).

Factors	$HR_{adjusted}$	95% confidence interval	*P value*
Diabetes			
Yes	1	1,93-15,42	0,001
No	5,46		
Hemoglobin (g/dl)			
>13	1		
=13	5,25	1,16-23,68	0,03
LAVi (ml/m^3)			
=34	1	1,21-11,87	0,02
>34	3,79		
Mitral S wave velocity (cm/s)			
>0,05	1	1,05-7,09	0,03
=0,05	2,73		
Improvement in GLS			
Yes			
No	1	3,33-22,55	$<10^{3-}$
	8,67		
Resistance to diuretic treatment			
Non	1	2,28-50,75	0,003
Oui	10,75		

Discussion

The prevalence of HFmrEF varies across prior studies, with figures comparable to HFpEF and less frequent than HFrEF [15-24]. Our study yielded different results, indicating a prevalence of 45.6% for HFmrEF, diverging from previous registries. Geographical variations, diverse study populations, and methodological disparities may account for these differences. Our study specifically targeted the midrange category, recruiting initially from an interventional department primarily composed of coronary patients, thus influencing our sample.

One-Year Events

Cardiovascular Mortality

In our investigation, one-year cardiovascular mortality in HFmrEF patients was noted to be lower than in HFrEF patients but similar to the HFpEF group. These observations align with several studies, including meta-analyses by Raja [25] and MAGGIC [26], analysis of the Chinese Heart Failure Registry [27], the APOLLON trial [28], and the CHART-2 study [29].

Heart Failure Rehospitalizations

Our study's conclusions align with prior observations, indicating a similar risk of readmission for heart failure across the three studied groups. These findings correspond to various research endeavors, such as the Multicenter Registry in Spain [30], the Chinese Heart Failure Registry [27], the Middle East Multinational Registry [31], ALTAIE's meta-analysis [32], and the TIME-HF study [20].

Predictive Factors for One-Year Cardiovascular Mortality

In our study, females with HFmrEF exhibited significantly higher survival than males, consistent with existing data. Simultaneously, we observed higher cardiovascular mortality in patients aged 65 to 72 compared to younger counterparts. These observations corroborate findings from numerous previous studies such as CHARM [33], MAGGIC [34], BHAMBANI's meta-analysis [35], and CHART-2[29].

Comorbidities were a focus of our study. We noted that atrial fibrillation (AF) served as an indicator of one-year mortality in HFmrEF patients, confirming similar findings in studies like the Swedish Heart Failure Registry [36] and ESC HF meta-analyses [37]. Additionally, chronic kidney disease (CKD) showed a significant impact on one-year mortality [38-42], aligning with several prior studies and meta-analyses. Finally, our study highlighted that anemia could predict one-year mortality, consistent with findings from the Japanese Heart Failure Registry [40] and similar studies [39,40]. Results regarding the impact of diabetes are divergent. Some clinical trials have not shown the benefits of strict glycemic control [43], while others suggested that adequate management could reduce the risk of mortality in HF patients [44]. Studies like CHARM [33], SOLVD [45], and ALLHAT [46] reported increased hospitalizations and deaths in these patients. However, in our study, diabetes was not directly linked to prognosis. Nevertheless, elevated blood glucose levels above 1.4 g/dl were significantly associated with decreased patient survival. Dysglycemia may influence HF development by causing functional, biochemical, and morphological alterations in the cardiac muscle, known as diabetic cardiomyopathy, impacting fibrosis, calcium management, microcirculation impairment, and coronary reserve [47,48].

Analyzing HFmrEF etiologies, our study did not reveal a major impact of ischemic etiology on prognosis ($p = 0.09$). These findings align with some studies [49] but contradict others [29] [38,50]. This could be attributed to our patient group's

composition, primarily consisting of individuals with coronary issues, potentially introducing selection bias to our study results.

Clinical aspects deserve special attention: In contrast to various studies [9,38], our analysis did not confirm the significant impact of an advanced NYHA stage (III or IV) at baseline on mortality ($p = 0.24$). However, Kaplan-Meier survival curve analysis indicated that the presence of paroxysmal nocturnal dyspnea could play a role in mid-term cardiovascular death predictions ($p < 0.001$).

Concerning electrical indices: To our knowledge, no previous research explored the prognostic aspect of these electrical indicators in HFmrEF patients. In our study, Kaplan-Meier survival analysis indicated that a QRS duration exceeding 0.08 ms was a parameter demonstrating prognostic impact, with a significance level of 0.002.

For biological parameters, our study confirmed:

- Findings from the Japanese registry [40] confirm that sodium levels below 136 mmol/L are linked to an increased risk of mid-term cardiovascular mortality ($p = 0.002$).
- Conclusions from the MAGGIC meta-analysis [26] and recent studies in Spain [8] and Japan[18] indicate that a total cholesterol level > 2g/l was associated with mid-term cardiovascular mortality.
- Results from several studies [51-53] suggest that hemoglobin levels below 13 g/dl could predict the risk of death in HFmrEF patients ($p = 0.07$).
- Regarding natriuretic peptides, our study found no significant disparity in cardiovascular mortality in HFmrEF patients, whether the NT-proBNP threshold was 2600 pg/l or not. This observation aligns with other conclusions supported by several studies [54-55].

Our study highlighted that the presence of severe diastolic dysfunction is an indicator of mid-term mortality in HFmrEF patients, consistent with several previous studies [38,53,56]. Concerning other echocardiographic parameters, a previous study by Chen [57], involving 489 patients, explored the Echocardiographic Index of Heart Failure (EIHF) to assess the prognosis of HFmrEF patients. This index considers various cardiac aspects and was identified as an independent risk factor for adverse events at one year in these patients, with good mid-term predictive value. Our results confirmed the relevance of this index, revealing that right ventricular dysfunction, elevated pulmonary artery systolic pressure (PAPS), moderate to severe mitral regurgitation (MR), and left atrial size were predictive elements of mortality in HFmrEF patients. These findings also align with other studies [38,58-61]. Our study emphasized the potential importance of pulmonary vascular resistance (PVR) in prognostic evaluation, an aspect explored minimally until now. Among other parameters identified in our analysis, MVGi, mitral S wave velocity, sphericity index, and E-SIV distance were also associated with cardiovascular mortality in these patients. However, additional studies are necessary to confirm these results.

Examining treatment impact, evidence regarding their efficacy in the HFmrEF category remains limited. In our study, the prescription of renin-angiotensin-aldosterone system inhibitors did not have a notable effect on cardiovascular mortality ($p=0.53$), corresponding to findings in the CHART-2 study [29]. However, initiating beta-blocker treatment, aiming for a heart rate < 70 bpm, demonstrated benefits in mid-term prognosis regarding cardiovascular mortality. This result aligns with observations from Cleland's study [62] and data from the Swedish Heart Failure Registry [63]. This trend could be attributed to the similarity of our cohort, including a notable proportion of ischemic pathologies.

Limitations

This study has several limitations that need consideration in the analysis of results. The sample of patients with heart failure was restricted, potentially limiting the generalizability of the conclusions. The male predominance and predominant recruitment from a specialized service may introduce bias to the representativeness of the findings. Only some factors could influence the conclusions despite the adjustments made. Our study, conducted at a singular center, may need to fully capture the nuances of the broader population experiencing heart failure. Additionally, the short follow-up duration and low incidence of outcome criteria could constrain the statistical robustness of the conclusions. Future research with larger samples and extended follow-up periods will be necessary to validate these findings and assess their long-term implications.

Conclusions

This study represents the first comprehensive prospective analysis of similarities and differences among patients with HFpEF, HFmrEF, and HFrEF in Algeria. Given the scarcity of publications on this topic at the national and regional levels, it provides new and clinically significant data. As a single-center observational study, its strength lies in the uniformity of tests and diagnosis, ensuring clinical relevance in the results. Furthermore, the follow-up with repeated echocardiograms allowed the identification of changes in the patient's cardiac function over time, offering a unique perspective. In this study, we diligently documented mortality rates at six months and one year, allowing for a thorough survival analysis of Kaplan-Meier curves. The findings address gaps in understanding HFmrEF, offering valuable insights that can guide future clinical directions.

Ethics approval and consent to participate

All data collected in patient records were anonymous. Upon admission to the hospital, all patients signed a written informed consent indicating their acceptance of using their recorded data (anonymously and confidentially) for research purposes. All patients benefited from the same examination conditions and optimization according to the latest ESC 2021 recommendations [3]. The methodology for this study was obtained from the Ethics Committee of the University of Algiers, Faculty of Medicine.

Conflicts of Interest

None.

Acknowledgments

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