

Comparative Analysis of Heart Failure with Preserved Vs Reduced Ejection Fraction: Patient Characteristics, Outcomes, Mortality Prediction, and Machine Learning Model Development in the JoHFR

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Background: Heart failure (HF) is a global health challenge affecting millions, with significant variations in patient characteristics and outcomes based on ejection fraction. This study aimed to differentiate between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) with respect to patient characteristics, risk factors, comorbidities, and clinical outcomes, incorporating advanced machine learning models for mortality prediction.

Methodology: The study included 1861 HF patients from 21 centers in Jordan, categorized into HFrEF (EF <40%) and HFpEF (EF ≥ 50%) groups. Data were collected from 2021 to 2023, and machine learning models were employed for mortality prediction.

Results: Among the participants, 29.7% had HFpEF and 70.3% HFrEF. Significant differences were noted in demographics and comorbidities, with a higher prevalence of males, younger age, smoking, and familial history of premature ASCVD in the HFrEF group. HFpEF patients were typically older, with higher rates of diabetes, hypertension, and obesity. Machine learning analysis, mainly using the Random Forest Classifier, demonstrated significant predictive capability for mortality with an accuracy of 0.9002 and an AUC of 0.7556. Other models, including Logistic Regression, SVM, and XGBoost, also showed promising results. Length of hospital stay, need for mechanical ventilation, and number of hospital admissions were the top predictors of mortality in our study.

Conclusion: The study underscores the heterogeneity in patient profiles between HFrEF and HFpEF. Integrating machine learning models offers valuable insights into mortality risk prediction in HF patients, highlighting the potential of advanced analytics in improving patient care and outcomes.

Keywords: Heart failure, mortality prediction, machine learning, patient outcomes, Jordan heart failure registry

Introduction

Heart failure (HF) is a significant global health burden, affecting over 64 million people worldwide as of January 2023.^{1,2} This condition is progressive and can lead to severe morbidity and mortality, impacting various bodily systems, including the respiratory,³ renal,⁴ gastrointestinal (GI), and hepatic systems.⁵ The etiology of heart failure is diverse, encompassing specific causes such as congenital heart diseases and cardiomyopathies, as well as multifactorial origins that accelerate cardiovascular aging.⁶ Coronary artery disease is a prominent risk factor, influenced by a range of underlying conditions.⁷ Ultimately, these etiologies disrupt structural, cellular, neurohormonal, and molecular functions essential for maintaining

cardiac physiological homeostasis.⁸ This disruption impairs blood flow through the vascular system, leading to clinical signs and symptoms of HF, including water overload and inadequate perfusion.⁹

A critical measure in heart failure diagnosis is the Left Ventricular Ejection Fraction (LVEF), which assesses the systolic function of the left ventricle via two-dimensional echocardiography. Normal LVEF readings range from 53% to 75%, with values below 53% considered abnormal.^{10,11} LVEF is pivotal in differentiating heart failure types: heart failure with reduced ejection fraction (HFrEF) is characterized by an LVEF of less than 40%, heart failure with mid-range ejection fraction (HFmrEF) is characterized by an LVEF between 40% and 49%, and heart failure with preserved ejection fraction (HFpEF) is defined by an LVEF of 50% or more, accompanied by signs of cardiac dysfunction such as reduced LV filling, elevated filling pressures, and increased natriuretic peptide levels.¹² These heart failure types, although sharing many risk factors and comorbidities, differ in their responses to systemic inflammation and cardiac remodeling,¹³ necessitating divergent management strategies. HFpEF predominantly affects older, female, obese patients and is associated with higher comorbidity rates. Despite current therapeutic options primarily alleviating symptoms, they have limited impact on halting disease progression or reducing mortality rates, although SGLT2 inhibitors have been shown to decrease heart failure hospitalizations.¹⁴ This study aims to conduct a comprehensive analysis of factors influencing HFrEF, HFmrEF, and HFpEF, including patient characteristics, risk factors, and comorbidities, and their impact on morbidity and mortality outcomes. Additionally, the study seeks to utilize machine learning models to predict mortality in heart failure patients, thereby introducing an innovative dimension to understanding and managing this complex condition.

Methodology

Study Design, Setting, and Data Collection

The data for this study were sourced from the national heart failure registry of Jordan. The characteristics of the JoHF registry and our study protocol were registered at clinicaltrials.gov (NCT04829591). This study adhered to ethical guidelines and standards outlined in the Declaration of Helsinki. Ethical approval was obtained from the Research Committee of the Faculty of Medicine and the Institutional Review Board at the Specialty Hospital, with a waiver of patient consent due to the non-interventional nature of the study and the routine registration of outcomes in heart failure patients. The IRB approval number is (5/1/T/104826). Medical records of heart failure patients from 2020 to 2023 across 21 centers in Jordan were collected and analyzed. The primary inclusion criterion was a documented diagnosis of heart failure by echocardiography, regardless of whether the diagnosis was made in the emergency room for acute HF or in a clinical setting for chronic HF. Data collection encompassed patient characteristics, past medical history, drug and social history, and the diagnosis, presentation, and progression of heart failure. Data collection was conducted by a medically trained team using an online Google form.

Inclusion and Exclusion Criteria

Patients included in the study had a confirmed diagnosis of heart failure, evidenced by echocardiographic findings. The inclusion criteria focused on patients with an LVEF less than 40% (HFrEF), and those with an LVEF of 50% or more (HFpEF). Patients diagnosed with HFpEF met the criteria for left ventricular diastolic dysfunction, which included typical clinical symptoms of heart failure (eg, dyspnea, fatigue, and fluid retention), echocardiographic evidence of diastolic dysfunction (eg, abnormal left ventricular filling pressures), and elevated natriuretic peptide levels. Exclusion criteria included patients with incomplete echocardiographic data, those diagnosed with acute coronary syndromes within three months prior to the study, and patients with significant valvular heart disease requiring surgical intervention.

Outcomes of Interest

The study examined the impact of different heart failure types on overall patient outcomes. The primary outcomes included the need for mechanical ventilation during hospitalization, the number of hospital admissions within a year following the initial heart failure presentation, and mortality rates.

Follow-Up and Treatment Information

The study did not specify the length of follow-up for patients. Information on pharmacological and non-pharmacologic treatments administered to the patients, such as medications and lifestyle interventions, was not provided. This information is essential for understanding variations in patient management and their potential impact on outcomes.

Statistical Analysis

Data were entered into Microsoft Office Excel 2019 and analyzed using IBM SPSS v.25 software. Baseline characteristics, comorbidities, and clinical outcomes were compared using *T*-tests for continuous variables and Chi-square tests for categorical variables, with a *p*-value < 0.050 indicating statistical significance. Normality of data distribution was assessed using the Shapiro–Wilk test. For normally distributed variables, descriptive statistics were presented as mean and standard deviation, while median and interquartile range were used for non-normally distributed variables. Categorical variables were summarized as frequencies and percentages. To address missing data, multiple imputations were performed using the “mice” package in R, generating five imputed datasets through Predictive Mean Matching (PMM). Post-imputation, statistical analyses were conducted on each dataset, and results were pooled to provide final estimates, ensuring robust handling of missing data and enhancing the reliability of findings.

Machine Learning Analysis

A machine learning-based approach was employed to predict mortality. Numerical columns underwent median imputation for missing values, while categorical columns were imputed with the most frequent value. All numerical data were standardized using a StandardScaler to ensure feature comparability. Recursive Feature Elimination with Cross-Validation (RFECV) was applied using a RandomForestClassifier to identify the most relevant features. The dataset was split into training, validation, and test sets, with 40% allocated for the combined validation and test sets. To address class imbalance, the training set was resampled using the SMOTEENN technique, a combination of Synthetic Minority Over-sampling (SMOTE) and Edited Nearest Neighbors (ENN) algorithms.

A grid search with fivefold cross-validation was conducted to tune hyperparameters for the models. The study evaluated four machine learning models: Random Forest Classifier (RFC), Logistic Regression (LR), Support Vector Machine (SVM), and Extreme Gradient Boosting (XGBoost). The models' effectiveness was assessed using accuracy, precision, recall, F1 score, and the Area Under the ROC Curve (AUC). SHapley Additive exPlanations (SHAP) values were employed to interpret the contribution of each feature to the models' predictions, providing insights into the factors driving mortality risk predictions.

Results

Demographics, Baseline Characteristics, and Comorbidities

The study enrolled 1861 individuals diagnosed with heart failure (HF), comprising 553 with HF with preserved ejection fraction (HFpEF) and 1308 with HF with reduced ejection fraction (HFrEF). [Table 1](#) highlights the differences in demographics, baseline characteristics, and comorbidities between patients with HFpEF and those with HFrEF. There was a significant variation in gender distribution between the two groups (*P*-value = <0.001); males constituted 66.3% of the HFrEF group while only constituting 43.6% of the HFpEF group. Moreover, significant differences were noted across age groups (*P*-value = <0.001); patients aged 70 or above formed the majority of the HFpEF group (59.8%), while those formed only 39.5% of patients with HFrEF. Patients aged less than 40 accounted for 5.6% of the HFrEF group, compared to only 0.9% in the HFpEF group. Comorbidities, namely diabetes mellitus (DM), hypertension (HTN), and obesity were significantly more prevalent in the HFpEF group compared to the HFrEF group: 73.7% vs 67.0% (*P*-value = 0.006), 88.9% vs 77.0% (*P*-value = <0.001), and 13.0% vs 6.6% (*P*-value = <0.001), respectively. In contrast, smoking exhibited a higher prevalence in the HFrEF group, with a rate of 36.2% compared to 22.1% in the HFpEF group (*P*-value = 0.000). Notably, dyslipidemia rates showed no significant difference between both groups. Furthermore, patients with HFrEF were more likely to have a familial history of premature atherosclerotic cardiovascular disease (ASCVD) compared to patients with HFpEF (6.8% vs 3.8%, *P*-value = 0.016). On the other hand, a history of arrhythmia was more prevalent in

Table 1 Demographics, Baseline Characteristics, and Comorbidities

Variable, n (%)		HFpEF (EF ≥ 50%)(n= 553**)	HFrEF (EF <40%)(n=1308**)	P-value
Gender	Male	240(43.6)	855(66.3)	<0.001*
	Female	311(56.4)	435(33.7)	
Age	<40	5(0.9)	71(5.6)	<0.001*
	40–49	21(4.0)	115(9.1)	
	50–59	51(9.7)	249(19.8)	
	60–69	135(25.6)	327(26.0)	
	≥70	316(59.8)	498(39.5)	
Diabetes	No	138(26.3)	402(33.0)	0.006*
	Yes	386(73.7)	815(67.0)	
Hypertension	No	58(11.1)	279(23.0)	<0.001*
	Yes	466(88.9)	933(77.0)	
Smoking	No	408(77.9)	773(63.8)	<0.001*
	Yes	116(22.1)	439(36.2)	
Alcohol	No	523(99.8)	1205(99.4)	0.275
	Yes	1(0.2)	7(0.6)	
Dyslipidemia	No	224(42.7)	496(40.9)	0.479
	Yes	300(57.3)	716(59.1)	
Obesity	No	456(87.0)	1132(93.4)	<0.001*
	Yes	68(13.0)	80(6.6)	
Positive family history of premature ASCVD	No	504(96.2)	1130(93.2)	0.016*
	Yes	20(3.8)	82(6.8)	
History of ASCVD	No	77(20.5)	195(19.5)	0.656
	Yes	298(79.5)	807(80.5)	
History of arrhythmias	No	305 (62.7)	809 (70.0)	0.008*
	Yes	242 (37.3)	488 (30.0)	
History of implanted devices	No	364(97.1)	961(95.9)	0.315
	Yes	11(2.9)	41(4.1)	
History of structural heart disease	No	356(94.9)	946(94.4)	0.704
	Yes	19(5.1)	56(5.6)	

Notes: * Statistical significance was determined with a p-value ≤ 0.05. ** Totals for some variables may not sum to the total group size due to missing values.

Abbreviations: HFpEF, heart failure with preserved ejection fraction; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; ASCVD, atherosclerotic cardiovascular disease.

patients with HFpEF compared to patients with HFrEF (37.3% vs 30.0%, P-value = 0.010). Rates of having ASCVD, implanted devices, and structural heart disease were not significantly different between both groups.

Clinical Outcomes

Assessment of the clinical outcomes revealed no statistically significant differences between patients with HFpEF and those with HFrEF across the studied variables. (Table 2) The number of admissions or office visits for HF in the past 12 months was comparable for both groups. Additionally, rates of mechanical ventilation (4.6% vs 4.8%) and mortality (8.7% vs 9.0%) were nearly identical. The mean length of hospitalization was 6.5 days for HFpEF and 6 days for HFrEF.

Prediction of Death Using Machine Learning Models

We evaluated the performance of various machine learning models to predict mortality in patients with Heart Failure. The Random Forest Classifier (RFC) achieved an accuracy of 0.9002, with a precision of 0.50, a recall of 0.28, an F1 Score of 0.36, and an AUC of 0.7556. Logistic Regression showed an accuracy of 0.7332, a precision of 0.21, a recall of 0.63, an F1 Score of 0.32, and an AUC of 0.7722. The Support Vector Machine (SVM) model resulted in an accuracy of 0.7935, a precision of 0.23, recall of 0.44, an F1 Score of 0.30, and an AUC of 0.7375. Lastly, the XGBoost model demonstrated

Table 2 Clinical Outcomes

Variable, n (%)		HFpEF (EF ≥ 50%)(n= 553*)	HFrEF (EF <40%)(n=1308*)	P-value
Admissions in past 6 months	0	219(41.8)	497(39.1)	0.224
	1	114(21.8)	265(20.9)	
	2	35(6.7)	117(9.2)	
	>2	156 (29.7)	391 (30.7)	
Mechanical ventilation	No	335(95.4)	750(95.2)	0.847
	Yes	16(4.6)	38(4.8)	
Death	No	505(91.3)	1190(91.0)	0.813
	Yes	48(8.7)	118(9.0)	
Length of Hospitalization, mean ± SD		6.58 ± 6.86	6.05 ± 8.07	0.227

Notes:* Totals for some variables may not sum to the total group size due to missing values.

Abbreviations: HFpEF, heart failure with preserved ejection fraction; EF, ejection fraction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure.

an accuracy of 0.8979, with a precision of 0.48, a recall of 0.37, an F1 Score of 0.42, and an AUC of 0.7542. ROC curves for all models are shown in [Figure 1](#).

Model Interpretation and Feature Importance

The SHAP plot provides an intuitive understanding of the key features influencing the model's predictions, as seen in [Figure 2](#). It indicates that a longer Length of Hospital Stay, the requirement for Mechanical Ventilation, and a higher Number of Hospital Admissions for HF in the Past 6 Months are associated with a higher probability of the adverse

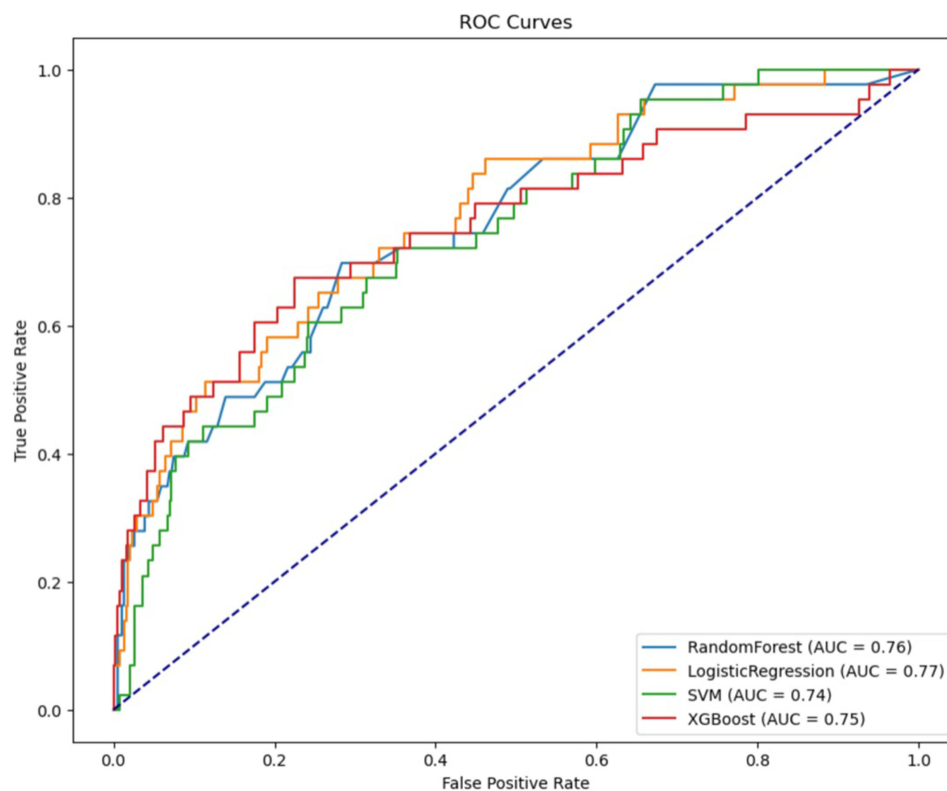


Figure 1 Receiver Operating Characteristic Curve (ROC) for all Machine Learning Models.

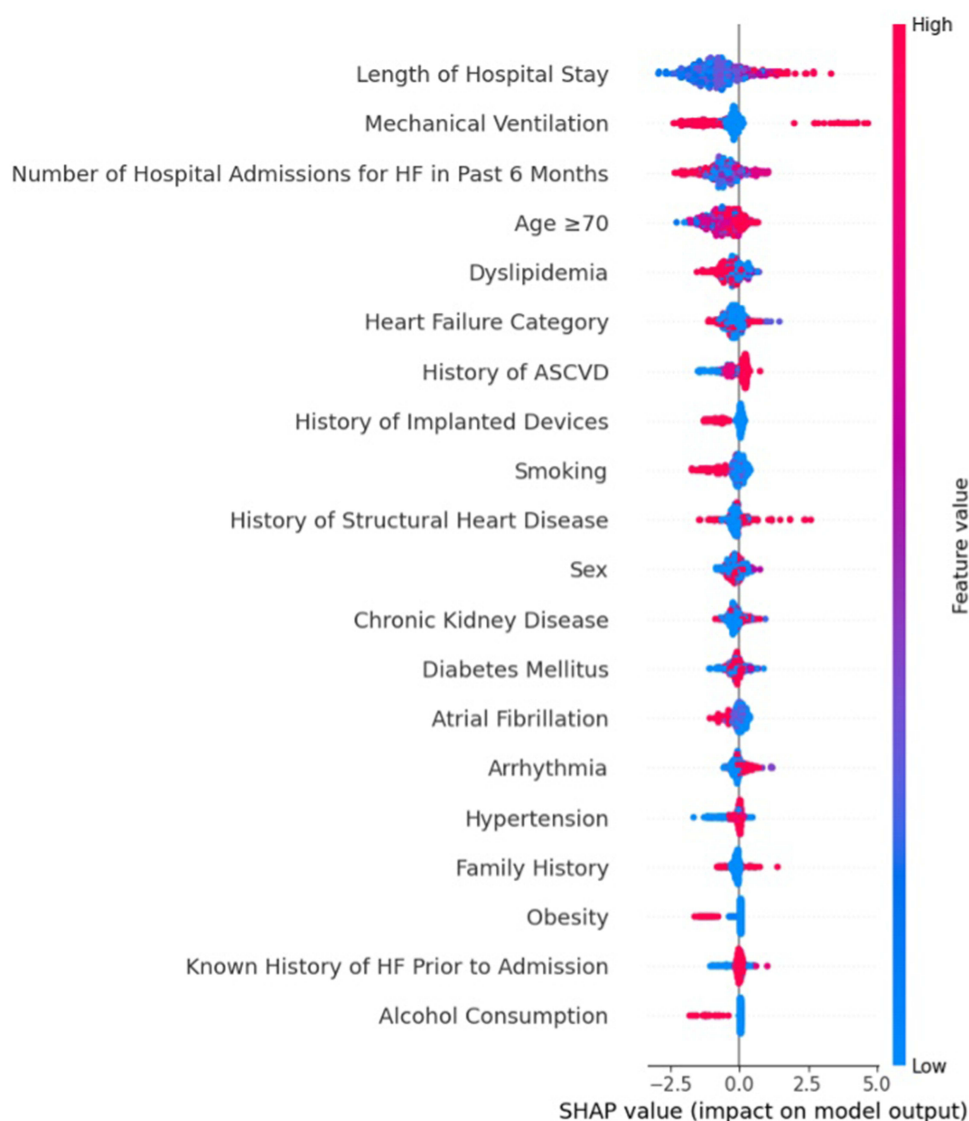


Figure 2 SHAP Summary Plot of Predictive Factors for Mortality in HFrEF and HFpEF Patients Using Machine Learning-Based Death Prediction Models. The features are listed on the y-axis in order of importance. The top feature has the most significant impact on the model's predictions. The x-axis represents the SHAP value. A positive SHAP value indicates that the feature increases the likelihood of the predicted outcome (in this case, mortality), while a negative SHAP value suggests a decrease in the likelihood. Each dot in the plot represents a SHAP value for an individual patient. The color represents the feature value (eg, red for high values and blue for low values).

outcome predicted for patients with heart failure (HF). These features, along with Age ≥ 70 and Dyslipidemia, stand out as the top risk factors according to the model's calculations. In contrast, Alcohol Consumption is shown to have the least influence on the predictions, with its SHAP values clustered around zero, indicating a neutral impact on the outcome. Additionally, the presence of chronic kidney disease, Diabetes Mellitus, and Atrial Fibrillation are observed to moderately influence the model's output, suggesting that these conditions contribute to the risk assessment in HF patients, albeit to a lesser extent than the top factors. The SHAP values also reveal that Sex, Smoking, and History of Implanted Devices have varied impacts on the model's predictions, with some instances increasing the likelihood of the adverse outcome and others decreasing it. This variability underscores the complex interplay of individual patient characteristics in determining health outcomes.

Discussion

Heart failure (HF) represents a growing health problem, with ejection fraction (EF) serving as a universal discriminator that classifies it into two main categories: HFpEF (Heart Failure with preserved Ejection Fraction) and HFrEF (Heart

Failure with reduced Ejection Fraction). The primary objective of this study was to explore and compare the distinct characteristics and clinical outcomes of individuals falling into the HFpEF and HFrEF categories. Out of the total 1861 individuals diagnosed with heart failure, 29.7% (553 individuals) were identified with HFpEF (EF \geq 50%), and 70.3% (1308 individuals) with HFrEF (EF $<$ 40%). The study revealed substantial differences in both gender distribution and age groups between HFrEF and HFpEF. Males constituted 66.3% of HFrEF compared to 43.6% in HFpEF; notably, our study found an association between ischemic causes and male gender, reinforcing the predominance of males in the HFrEF group. Furthermore, male gender is considered a significant predictor among the various factors associated with heart failure readmissions.¹ The higher proportion of females in HFpEF further supports the recognition of the female gender as a predictor for this phenotype.² Moreover, our analysis revealed significant age differences. Patients aged 70 or above were notably prevalent in the HFpEF group. Therefore, both female gender and older age are consistently associated with HFpEF, as observed in multiple registries, including Saudi (HEARTS), Egyptian, Framingham, JCARE-CARD, and GWTG-HF.^{1–8} Comorbidities such as hypertension (HTN), atrial fibrillation/flutter, and obesity exhibited a significantly higher prevalence in the HFpEF group compared to the HFrEF group in our study. Conversely, smoking was more prevalent in the HFrEF group. These findings align with the Results presented by Shah et al.⁵ In contrast to our study, Shah et al's results indicated that patients with HFrEF more frequently presented with a history of dyslipidemia, coronary artery disease, and prior myocardial infarction.^{5,15,16} However, our study revealed no significant difference in dyslipidemia or a history of atherosclerotic cardiovascular disease (ASCVD) rates between the HFpEF and HFrEF groups. Furthermore, a higher prevalence of diabetes mellitus (DM) was observed in the HFpEF group in our study. Considering the high association of comorbidities with HFpEF, addressing these comorbidities when indicated becomes essential. Indeed, further research is crucial to establish comprehensive guidelines that address the management and treatment of HFpEF.

The clinical outcomes assessment revealed no statistically significant differences between patients with HFpEF and those with HFrEF across the studied variables in our study. The number of admissions or office visits for heart failure (HF) was comparable for both groups. Additionally, mechanical ventilation and mortality rates were nearly identical, with the mean length of hospitalization being 6.5 days for HFpEF and 6 days for HFrEF. These findings align with results from multiple other studies, including Shah et al's 5-year outcomes study based on the GWTG registry. In their study, risk-adjusted analyses demonstrated similar outcomes, indicating that mortality and rehospitalization were comparable for both HFrEF and HFpEF.⁵ These findings are consistent with results from the JCARE-CARD study, which indicated that HF patients with preserved ejection fraction (EF) had a mortality risk and re-hospitalization rates comparable to those with reduced EF.⁷ Interestingly, other studies have shown that mortality is lowest in patients with ejection fractions greater than or equal to 50%.⁸ Moreover, findings from another study revealed that among patients hospitalized with HF, those with HFpEF had slightly lower mortality and higher all-cause readmission risk than patients with HFrEF. However, the mortality differences did not persist after risk adjustment.⁶ Nevertheless, this does not undermine the fact that heart failure (HF), irrespective of ejection fraction (EF), significantly affects mortality, hospitalization, and admissions, making it a growing public health problem.^{15–21} Evidence suggests that among patients hospitalized with HF, individuals across the EF spectrum share a similarly poor survival. The study by Shah et al revealed that all patients, regardless of EF, experienced a remarkably high mortality rate at 5 years from the index.⁵ Other studies have indicated that patients with HFpEF are associated with a higher risk of all-cause mortality.

In contrast, patients with HFrEF were found to be related to a higher risk of cardiovascular mortality.⁹ In our study, the machine learning (ML) models, particularly the Random Forest Classifier, demonstrated significant predictive capability for mortality among heart failure (HF) patients. This aligns with Shin et al,²² who emphasized the potential of ML over conventional statistical models in predicting heart failure outcomes. Notably, our analysis identified key predictors such as length of hospital stay, need for mechanical ventilation, and number of hospital admissions, which are crucial in assessing patient risk. This is in line with the findings of Álvarez-García et al,²³ who highlighted the significance of hospital stay length and mechanical ventilation as predictors of mortality. This study has several limitations. The retrospective nature of the registry data may introduce selection and information biases. Detailed analyses of the causes leading to mechanical ventilation and management of comorbidities were not performed, which could affect the interpretation of these outcomes. Additionally, the national registry may not capture all variations in

practice patterns and patient populations. Moreover, we did not evaluate the prognostic role of the Charlson comorbidity index (CCI) and the CHA2DS2-Vasc score. Both indices are important for assessing the burden of comorbidity and thromboembolic risk in heart failure patients. Recent studies have demonstrated their prognostic significance in heart failure.^{21,24–26} Including these indices could provide additional insights and improve the prognostic evaluation of our patient cohort. This is an area for future research where we plan to incorporate these indices to enhance our understanding of heart failure outcomes. Additionally, our study did not include heart failure patients with mildly reduced ejection fraction (HFmrEF), defined as those with LVEF between 41% and 49%. HFmrEF represents a significant subgroup that may occur either as a recovery from HFrEF or a deterioration from HFpEF.²⁷ Future analyses should consider including HFmrEF patients to provide a more comprehensive understanding of heart failure phenotypes. Future research should focus on prospective studies to validate these findings and incorporate more detailed analyses of comorbidities and their management. Further exploration into the specific causes of critical outcomes like mechanical ventilation could enhance our understanding and improve patient care.

Conclusion

These findings emphasize the urgent need for comprehensive strategies to address heart failure and promptly treat HF, considering both preserved and reduced EF, to improve outcomes and enhance the overall well-being of individuals affected by HF. Our machine learning models provided a good tool for the identification of high-risk patients. However, the precision and recall of our models were not the highest due to class-imbalanced data. Future studies in the Middle East should implement such models on more extensive and more balanced datasets.

Disclosure

The authors report no conflicts of interest in this work.

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