Cross-sectional Study

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Risk factors of mortality among heart failure patients in Jordan: the Jordanian Heart Failure Registry (JoHFR)

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Background: Heart failure is one of the most common medical burdens facing the healthcare system worldwide. Based on our knowledge, only two heart failure registries have been conducted in the Middle East. Therefore, we decided to conduct this heart failure registry to investigate the follow-up results of patients with both acute and chronic heart failure in Jordan.

Methods: This study is a prospective observational multicenter national registry encompassing 21 health institutes in Jordan, comprising university hospitals, private hospitals, and private clinics. The criteria of inclusion were patients visiting the cardiology clinic or inpatients who were admitted due to acute decompensated HF. The primary outcome was 30-day mortality.

Results: The total number of enrolled patients in the study was 2128, with a total number of deaths during the follow-up of 204. Multivariate analysis demonstrated that smoking (odds ratio [OR] = 3.214; 1.005–5139), positive family history of premature coronary artery disease (OR = 2.686; 1.504–4.798), insulin (OR = 2.300; 1.356–3.899), hyponatremia at presentation (OR = 7.058; 1.698–29.342) and increased left ventricular diameter (OR = 1.009; 1.002–1.016) were significantly associated with higher odds of mortality.

Conclusion: Smoking, positive family history of premature coronary artery disease, insulin use, hyponatremia on presentation, and increased left ventricular diameter were associated with patients' mortality. Physicians should monitor these factors among patients to identify patients who are at higher risk of detrimental outcomes.

Keywords: heart failure, Jordan, mortality, registry

Introduction

Heart failure (HF) is described as a diverse syndrome that arises from structural or functional abnormalities[1]. It is considered a significant cause of morbidity and mortality worldwide and has one of the highest rates of hospital readmission[2,3]. Patients with HF often have several comorbidities, many of which are recognized as risk factors[4]. Evidence suggests that among the numerous known risk factors for HF, hypertension, coronary artery disease (CAD), and diabetes are most commonly associated with its development[4–6].

HIGHLIGHTS

- The data about HF in the Middle East is scarce.
- This article focused on the predictors of HF mortality.
- We found that smoking, positive family history of premature coronary artery disease, insulin, hyponatremia at presentation, and increased left ventricular diameter were associated with mortality.
- Out findings should guide clinicians regarding the factors associated with HF mortality.

HF is a major global health challenge, affecting more than 64 million people worldwide as of January 2023[7,8]. This progressive condition leads to significant morbidity and mortality, impacting multiple organ systems, including the respiratory[9], renal[10], gastrointestinal, and hepatic systems[11]. According to the EuroHeart Failure Survey, 90-day mortality rates were 12% for heart failure with reduced ejection fraction (HFrEF) and 10% for heart failure with preserved ejection fraction (HFpEF). In the nationwide Swedish Heart Failure Registry, which included patients with HF based on clinician judgment, mortality rates at 30 days, 1 year, and 3 years were lower in HFrEF at 2.8%, 15.4%, and 28.1%, compared to HFpEF at 2.9%, 17.4%, and 32.1%[12].

Both the Saudi Heart Failure Registry and the Egyptian cohort have reported that CAD is the leading cause of HF. This is

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attributed to the high prevalence of CAD in the region and the earlier age at which it presents, raising concerns about the greater prevalence of CAD risk factors in the region[13–15]. Evidence suggests that HFpEF is mainly a result of hypertension, while HFrEF is associated with multiple risk factors, with CAD being a significant contributor[16–18].

Considering the scarcity of the data about HF in the region and no previous registries were done in Jordan despite the importance of the differences in the genetic and demographic backgrounds, we have conducted the Jordanian Heart Failure Registry (JoHFR) to assess the risk factors associated with worse outcomes and mortality among patients with HF.

Methods

Study design and setting

This study is part of a national multicenter registry to study the characteristics and outcomes of Heart Failure patients in Jordan (JoHFR). The data for this study were sourced from Jordan's national HF registry. The characteristics of the JoHF registry and our study protocol were registered at clinicaltrials.gov (NCT04829591). In summary, it is a prospective cross-sectional observational multicenter national registry encompassing 21 health institutes in Jordan, comprising university hospitals, private hospitals, and private clinics. In our study, we employed a convenience sampling method. After reaching out to over 20 health institutes and clinics in Jordan and obtaining their consent, all patients admitted or visiting these clinics during the recruitment period, which spanned from 1 July 2021 to 1 July 2022, were included. The sampling was convenient in methods based on patients' availability, accessibility, and willingness to participate. The study was conducted in accordance with the Strengthening the Reporting of Cohort, Cross-sectional, and Case-Control Studies in Surgery[19]. Institutional review board (IRB) approvals were attained from all participating institutions. Patients were informed of their participation in an HF registry and were given the choice to reject participation. Participants' privacy and confidentiality were retained.

Inclusion and exclusion criteria

Patients included in the study had a confirmed diagnosis of HF, evidenced by two-dimensional echocardiographic findings. The inclusion criteria focused on patients with LVEF of less than 40% (HFrEF), and those with LVEF of 50% or more (HFpEF). Patients diagnosed with HFpEF should also meet the criteria for left ventricular diastolic dysfunction, which included typical clinical symptoms of HF (e.g. dyspnea, fatigue, and fluid retention), echocardiographic evidence of diastolic dysfunction (e.g. abnormal left ventricular filling pressures), and elevated natriuretic peptide levels. Exclusion criteria included patients with incomplete echocardiographic data, individuals under 18 years of age, those unable to provide informed consent, and patients unable to adhere to follow-up requirements.

All patients enrolled in the registry were followed up for 30 days since the admission or visit onset. To reduce missed follow-ups, we utilized two follow-up options. If the patients stayed at the hospital for the whole follow up period, the follow up data were collected from the medical records while if the patients were discharged earlier, we contacted the patients with to collect the relevant data. We did not have any missed follow up in this study.

Data collection

A team of trained medical students and residents conducted data collection. An online form, based on similar forms used by other HF registries, was utilized to record the data. The form included various variables, such as patients' demographics and baseline comorbidities, which were grouped by sex, age (<40, 40–49, 50–59, 60–69, ≥70), and body mass index, categorized into normal (18.5–25), overweight (25–30), and obese (>30).

Upon presentation, data on systolic and diastolic blood pressure were collected, along with several laboratory investigations, including the following:

- Cholesterol: normal (<200 mg/dL) and high (>200 mg/dL)
- Low-density lipoprotein (LDL): normal (<130 mg/dL) and high (>130 mg/dL)
- High-density lipoprotein (HDL): normal (>40 mg/dL) and low (<40 mg/dL)
- Triglycerides: normal and high (>150 mg/dL)
- B-type natriuretic peptide (BNP): normal (<100 mg/dL) and high (>100 mg/dL)
- Sodium: hyponatremia (<136 mg/dL), normal (136–145 mg/dL), and hypernatremia (>145 mg/dL)
- Potassium: hypokalemia (<3.5 mg/dL), normal (3.5–5.5 mg/dL), and hyperkalemia (>5 mg/dL)
- Hemoglobin: <10 mg/dL and ≥10 mg/dL
- Blood urea nitrogen: normal (<20 mg/dL) and high (>20 mg/dL)
- Creatinine: normal (<115 μmol/L) and high (>115 μmol/L)

Echocardiographic measurements taken within 90 days prior to admission, including ejection fraction, left atrial diameter, and left ventricular diameter, were also recorded. Additionally, data on patients' baseline medications, as well as any new management and medications administered upon admission were collected.

The primary dependent variable is 30-day mortality among HF patients, which serves as the outcome of interest. The study examined various independent risk factors to determine their impact on patient mortality. These risk factors included age, sex, smoking status, patient comorbidities such as hypertension, CAD, and diabetes, HF types, the used medications like beta-blockers and angiotensin-converting enzyme inhibitors, echocardiographic measures, and laboratory investigations.

Data analysis

Sample size was calculated based on a 95% confidence interval (95% CI), 5% of type 1 error, and 80% power. We used the most recent national statistic on HF prevalence in Jordan to determine or population of interest size (N = 100 000). The data were entered using Microsoft Office Excel 2019 and then imported and analyzed using IBM SPSS v.25 software. The patients' demographics, comorbidities, laboratory investigations, and echocardiographic measures were compared according to outcome using t-test and Chi-square for continuous and categorical variables, respectively. A P-value <0.050 was considered statistically significant. Multivariate regression analysis for the variables significantly associated with the 30-day mortality was carried out to adjust for confounding variables. Results were expressed as an odds ratio (OR) and 95% CI. Moreover, the significant variables

in the univariate analysis and all their combination possibilities were evaluated using recursive feature elimination (RFE) to establish the best variables/combinations that can predict mortality. RFE generates the number of combinations that are associated with the lowest root mean squared error (RMSE) (highest performance) as well as the order of the variables in importance. The best possible combinations were evaluated using receiver operator characteristics (ROC).

Results

The study population was predominantly male (58%). The age distribution showed a significant proportion of patients aged 70 or older (45.5%), followed by those aged 60–69 (26.3%), 50–59 (16.5%), 40–49 (7.2%), and less than 40 years (4.4%). Smoking was prevalent among 31.3% of patients, while alcohol consumption was relatively rare (0.6%). Obesity was identified in 36.6% of the cohort. Positive family history of premature atherosclerotic cardiovascular disease (ASCVD) was reported by 5.3% of patients, while 23% had a personal history of premature ASCVD.

Differences in demographics, comorbidities, and laboratory investigations according to patient outcomes

The total number of enrolled patients in the study was 2128, with a total number of deaths during the follow-up of 204. Univariate analysis showed that patients with chronic HF had a higher rate of mortality compared to their counterparts (*P*-value = 0.049). In addition, age was significantly associated with mortality, as the age group ≥70 years had the highest rate of mortality compared to other age groups (58.5%). Smokers had a higher rate of mortality compared to non-smokers (*P*-value = 0.031). In addition, patients with dyslipidemia and patients with a positive family history of CAD had a higher percentage of mortality (*P*-value = 0.044, 0.000). Patients with a history of structural heart disease had a significantly higher rate of mortality compared to their counterparts (*P*-value = 0.008). Additionally, patients with a higher number of admissions in the last 6 months had higher rates of mortality (*P*-value = 0.002). Furthermore, patients with low HDL had higher rates of mortality compared to their counterparts (*P*-value = 0.002). Patients with hyponatremia, hyperkalemia, anemia, low glomerular filtration rate (GFR), and high creatinine also had higher rates of mortality (*P*-value <0.001). Patients who died had significantly higher mean left ventricular diameter (23.77 ± 24.10) compared to their counterparts (15.67 ± 25.02) (*P*-value = 0.001) (Table 1).

Differences in medications use according to patients outcomes

Patients who were not on aldosterone antagonists had higher rates of mortality (87.1% vs. 12.9%) (*P*-value = 0.006). Moreover, patients who were on sodium-glucose transfer inhibitors had lower rates of mortality compared to their counterparts (*P*-value = 0.036). Patients on ACE inhibitors, ARNIs, and lipid-lowering agents had also significantly lower rates of mortality. Patients on digoxin and nitrate had significantly lower rates of mortality compared to their counterparts (*P*-value = 0.040, 0.039). Moreover, patients on insulin had higher rates of mortality, while patients on sulfonylurea had lower rates of mortality

Table 1

Differences in demographics, comorbidities, and laboratory investigations according to patient outcomes.

Variable	Survived (*n* = 1924)	Died (*n* = 204)	*P*-value
Heart failure			
Acute	543 (28.4)	70 (35.0)	0.049*
Chronic	1372 (71.6)	130 (65.0)	
Gender			
Male	1126 (58.5)	109 (53.4)	0.161
Female	798 (41.5)	95 (46.6)	
Age			
<40	79 (4.4)	8 (4.3)	0.004*
40–49	135 (7.5)	7 (3.7)	
50–59	304 (16.9)	23 (12.2)	
60–69	482 (26.9)	40 (21.3)	
≥70	795 (44.3)	110 (58.5)	
Hypertension			
Yes	1452 (80.3)	163 (84.9)	0.122
No	357 (19.7)	29 (15.1)	
Body mass index			
Normal	294 (26.2)	35 (30.4)	0.593
Overweight	418 (37.2)	39 (33.9)	
Obese	411 (36.6)	41 (35.7)	
Diabetes			
Yes	1249 (68.9)	139 (72.0)	0.365
No	565 (31.1)	54 (28.0)	
Smoking			
Yes	580 (32.1)	47 (24.5)	0.031*
No	1229 (67.9)	145 (75.5)	
Alcohol			
Yes	12 (0.7)	0 (0.0)	0.258
No	1797 (99.3)	192 (100.0)	
Dyslipidemia			
Yes	1060 (58.6)	98 (51.0)	0.044*
No	749 (41.4)	94 (49.0)	
Obesity			
Yes	151 (8.3)	10 (5.2)	0.128
No	1658 (91.7)	182 (94.8)	
Positive family history of ASCVD			
Yes	86 (4.8)	21 (10.9)	0.000*
No	1723 (95.2)	171 (89.1)	
History of atherosclerotic cardiovascular disease			
Yes	1130 (80.0)	151 (85.3)	0.091
No	283 (20.0)	26 (14.7)	
History of arrhythmias			
Yes	440 (31.1)	60 (33.9)	0.456
No	973 (68.9)	117 (66.1)	
History of implanted cardiac device			
Yes	57 (4.0)	7 (4.0)	0.960
No	1356 (96.0)	170 (96.0)	
History of structural heart disease			
Yes	80 (5.7)	19 10.7)	0.008*
No	1333 (94.3)	158 (89.3)	
No. of admissions in past 6 months/office visits for HF			
0	768 (41.0)	86 (42.6)	0.002*
1	376 (20.1)	37 (18.3)	
2	152 (8.1)	11 (5.4)	
>2	216 (11.5)	41 (20.3)	
Cholesterol			
Normal	629 (85.2)	52 (92.9)	0.115
High (>200)	109 (14.8)	4 (7.1)	
Low density lipoprotein			
Normal	648 (86.9)	56 (94.9)	0.072
High (>130)	98 (13.1)	3 (5.1)	

(*Continued*)

Table 1

(Continued).

Variable	Survived (*n* = 1924)	Died (*n* = 204)	*P*-value
High density lipoprotein			
Normal	213 (29.2)	6 (10.2)	0.002*
Low (<40)	517 (70.8)	53 (89.8)	
Triglycerides			
Normal	465 (63.1)	39 (65.0)	0.768
High (>150)	272 (36.9)	21 (35.0)	
Barium natriuretic peptide			
Normal	21 (3.3)	3 (3.5)	0.894
High	624 (96.7)	82 (96.5)	
NT-ProBNP			
Normal	30 (9.9)	0 (0.0)	0.099
High	274 (90.1)	25 (100.0)	
Sodium			
<136	519 (28.5)	88 (44.4)	0.000*
136–145	1263 (69.2)	78 (39.4)	
>145	42 (2.3)	32 (16.2)	
Potassium			
<3.5	97 (5.3)	11 (5.6)	0.000*
3.5–5	1524 (83.7)	123 (62.1)	
>5	199 (10.9)	64 (32.3)	
Hemoglobin			
≥10	1477 (85.5)	115 (64.2)	0.000*
<10	250 (14.5)	64 (35.8)	
eGFR			
≥60	351 (61.0)	22 (29.3)	0.000*
<60	224 (39.0)	53 (70.7)	
BUN			
Normal	392 (24.0)	47 (25.4)	0.667
>20	1243 (76.0)	138 (74.6)	
HBA1c			
Normal	292 (35.8)	28 (35.9)	0.990
>6	523 (64.2)	50 (64.1)	
Echocardiography			
≥50	505 (29.8)	48 (28.9)	0.813
<50	1190 (70.2)	118 (71.1)	
Creatinine			
Normal	1064 (60.7)	56 (28.4)	0.000*
>115	688 (39.3)	141 (71.6)	
Systolic blood pressure at presentation			
Normal	1101 (91.8)	138 (95.2)	0.149
High	99 (8.3)	7 (4.8)	
Diastolic blood pressure at presentation			
Normal	1343 (94.0)	146 (94.2)	0.916
High	86 (6.0)	9 (5.8)	
Ejection fraction	39.09 ± 12.64	38.03 ± 13.46	0.958
Left ventricular diameter	15.67 ± 25.02	23.77 ± 24.10	0.001*
Left atrial diameter	25.26 ± 19.72	26.62 ± 19.76	0.434

BUN, bilirubin urea nitrogen; eGFR, estimated glomerular filtration rate; HBA1c, glycated hemoglobin; NT-ProBNP, N-terminal pro b-type natriuretic peptide.
**P*-value <0.050.

(*P*-value = 0.013) compared to their counterparts (*P*-value <0.001) (Table 2).

Multivariate regression analysis for the factors associated with mortality

Multivariate regression analysis demonstrated that smoking was significantly associated with higher odds of mortality (OR = 3.214; 95% CI: 1.005–5.139). In addition, patients who had a positive family history of premature CAD had significantly higher odds of mortality (OR = 2.686; 95% CI: 1.504–4.798). Insulin treatment was significantly associated

Table 2

Differences in medications use according to patients outcomes

Variable	Survived (*n* = 1924)	Died (*n* = 204)	*P*-value
Aldosterone antagonists			
Yes	394 (21.5)	24 (12.9)	0.006*
No	1438 (78.5)	162 (87.1)	
Beta blockers			
Yes	1240 (67.7)	120 (64.5)	0.380
No	592 (32.3)	66 (35.5)	
SGLT2 inhibitors			
Yes	82 (9.6)	3 (3.2)	0.036*
No	768 (90.4)	92 (96.8)	
ACE inhibitors			
Yes	342 (18.7)	23 (12.4)	0.033*
No	1490 (81.3)	163 (87.6)	
AR blockers			
Yes	460 (25.1)	48 (25.8)	0.835
No	1372 (74.9)	138 (74.2)	
ARNI			
Yes	206 (11.2)	11 (5.9)	0.025*
No	1626 (88.8)	175 (94.1)	
Calcium channel blockers			
Yes	356 (19.4)	32 (17.2)	0.463
No	1476 (80.6)	154 (82.8)	
Loop diuretics			
Yes	944 (51.5)	97 (52.2)	0.871
No	888 (48.5)	89 (47.8)	
Thiazide diuretics			
Yes	203 (11.1)	13 (7.0)	0.085
No	1629 (88.9)	173 (93.0)	
Lipid lowering agent			
Yes	1203 (65.7)	145 (78.0)	0.001*
No	629 (34.3)	41 (22.0)	
Aspirin			
Yes	1101 (60.1)	106 (57.0)	0.410
No	731 (39.9)	80 (43.0)	
Antiplatelet agents other than aspirin			
Yes	318 (17.4)	23 (12.4)	0.083
No	1514 (82.6)	163 (87.6)	
Digoxin			
Yes	105 (5.7)	4 (2.2)	0.040*
No	1727 (94.3)	182 (97.8)	
Nitrate			
Yes	172 (9.4)	9 (4.8)	0.039*
No	1660 (90.6)	177 (95.2)	
Metformin			
Yes	386 (45.4)	42 (44.2)	0.823
No	464 (54.6)	53 (55.8)	
Dipeptidyl peptidase-4 inhibitors			
Yes	135 (15.9)	12 (12.6)	0.407
No	715 (84.1)	83 (87.4)	
Insulin			
Yes	418 (49.2)	70 (73.7)	0.000*
No	432 (50.8)	25 (26.3)	
Sulfonylurea			
Yes	135 (15.9)	6 (6.3)	0.013*
No	715 (84.1)	89 (93.7)	

ACE, angiotensin converting enzyme; AR, angiotensin receptor; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2, sodium glucose transporter 2.
**P*-value <0.050.

Table 3

Multivariate regression analysis for the factors associated with mortality

Variable	Response	AOR (95% CI)	*P*-value
Age	<40	Reference	Reference
	40–49	0.603 (0.146–2.498)	0.486
	50–59	0.729 (0.217–2.454)	0.610
	60–69	1.045 (0.329–3.317)	0.940
	≥70	1.411 (0.460–4.326)	0.547
Smoking	Yes	3.214 (1.005–5.139)	0.046*
Dyslipidemia	Yes	0.723 (0.505–1.037)	0.078
Positive family history of premature coronary disease	Yes	2.686 (1.504–4.798)	0.001*
History of structural heart disease	Yes	1.502 (0.730–3.091)	0.269
Number of hospital admission in the past 6 months	0	Reference	Reference
	1	0.838 (0.508–1.382)	0.488
	2	0.685 (0.325–1.445)	0.321
	>2	1.468 (0.880–2.449)	0.142
Aldosterone antagonists	Yes	0.579 (0.287–1.170)	0.128
SGLT2 inhibitors	Yes	0.436 (0.131–1.455)	0.177
ACE inhibitors	Yes	0.678 (0.323–1.425)	0.306
AR blockers	Yes	1.036 (0.626–1.713)	0.891
Lipid lowering agent	Yes	0.836 (0.490–1.429)	0.513
Digoxin	Yes	0.390 (0.092–1.659)	0.202
Nitrate	Yes	0.727 (0.321–1.647)	0.445
Insulin	Yes	2.300 (1.356–3.899)	0.002*
Sulfonylurea	Yes	0.586 (0.236–1.457)	0.250
Low high-density lipoprotein	1.609 (0.566–4.577)		0.372
Hyponatremia	0.483 (0.205–1.139)		0.096
Hypernatremia	7.058 (1.698–29.342)		0.007*
Hypokalemia	0.900 (0.135–5.994)		0.913
Hyperkalemia	2.262 (0.286–17.909)		0.439
Anemia	0.428 (0.167–1.096)		0.077
GFR <60	0.974 (0.275–3.448)		0.968
High creatinine	2.317 (0.635–8.460)		0.203
Left ventricular diameter (mm)	1.009 (1.002–1.016)		0.018*

ACE, angiotensin converting enzyme; AOR, adjusted odds ratio; AR, angiotensin receptor; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2, sodium glucose transporter 2.
*P-value <0.05.

with higher odds of mortality compared to their counterparts (OR = 2.300; 95% CI: 1.356–3.899). Hyponatremia was significantly associated with higher odds of mortality (OR = 7.058; 95% CI: 1.698–29.342). Increased left ventricular diameter was also associated with higher odds of mortality (OR = 1.009; 95% CI: 1.002–1.016) (Table 3). Figure 1 demonstrates the results of the multivariate regression analysis.

RFE results

The RFE demonstrated that the number of combinations that had the lowest RMSE was two variables (Fig. 2). Sodium and creatinine had the highest two importance (Fig. 3). Combining these two variables resulted in an area under the curve (AUC) of 0.81 with 95% CI of 0.71–0.91.

Discussion

This is the first national multicenter HF registry to be conducted in Jordan. This large-scale registry was conducted to represent different healthcare sectors in Jordan, such as university hospitals, the Ministry of Health, Military hospitals, and private hospitals. We identified several distinctive findings regarding prognostic and mortality-associated factors in HF patients across the country. Regarding demographics, age, smoking history, chronic HF, previous history of dyslipidemia, structural heart disease, and family history of HF were associated with increased HF mortality. However, certain medications, such as ACEI, aldosterone antagonists, ARNIs, statins, sulfonylureas, SGLT-2 inhibitors, digoxin, and nitrates, were associated with lower mortality in HF patients; others, like insulin, were associated with higher mortality. Furthermore, laboratory indices, including low HDL, hyponatremia, hyperkalemia, anemia, low GFR, elevated creatinine, and left ventricular hypertrophy were associated with higher mortality in HF patients. However, only smoking, a positive family history of premature CAD, hyponatremia, treatment with insulin, and high left ventricular diameter remained statistically significant in the multivariate regression models. RFE models demonstrated that best two predictors of mortality were combining sodium and creatinine.

Our registry demonstrated that HF mortality is correlated with age, where similar results were mentioned by Gerber *et al*, and Sciomer *et al*[20,21]. This is explained by various factors: (a) age-related hemodynamic and structural changes in the heart; (b) the accumulation of multiple comorbidities with age such as hypertension, diabetes, atrial fibrillation, and atherosclerosis[22]. In addition, smoking and structural heart disease were significantly associated with a worse prognosis in HF patients. A study by Kondo *et al*[23] in Japan demonstrated that oxidative stress and endothelial injury, which release inflammatory cytokines and reactive oxygen species, lead to cardiac remodeling and dysfunction.

Similarly, our registry points out that a history of HF and HF-related hospital admissions were associated with an increase in mortality. This was previously investigated in a study done by Lassus *et al*[24]. Furthermore, our study showed evidence that a family history of premature CAD correlates with an increase in morbidity and mortality in HF patients. Previous studies explain this with the collective accumulation of polygenetic and environmental risk factors predisposing individuals to HF[25,26]. Moreover, patients with dyslipidemia and low HDL had higher mortality in this registry. This is justified in the literature through the biological pathophysiology of lipoprotein (a) as it enters the endothelial barrier and promotes foam cell and smooth muscle cell proliferation, leading to atherosclerosis, which in turn increases the risk for HF[27,28]. The low levels of HDL hinder the cardiac muscles from their cardioprotective action, thus leading to more pro-fibrotic, pro-inflammatory, and pro-oxidative effects, which in turn lead to a worse HF prognosis[29,30].

Moreover, this registry showed the protective effects of HF medications on the progression of the disease. Anti-hypertensive medications such as ACE inhibitors, aldosterone antagonists, and ARNIs were significantly associated with an improved disease outcome. This is consistent with the latest recommended guidelines[31]. In a recent systematic review and meta-analysis, pharmacological therapy with ARNI, aldosterone antagonists, and SGLT-2 inhibitors was the most effective treatment for cardioprotection from all-cause deaths in HF patients[32]. Other associations of HF with glucose-lowering drugs, including sulfonylureas and SGLT-2 inhibitors, decreased patient

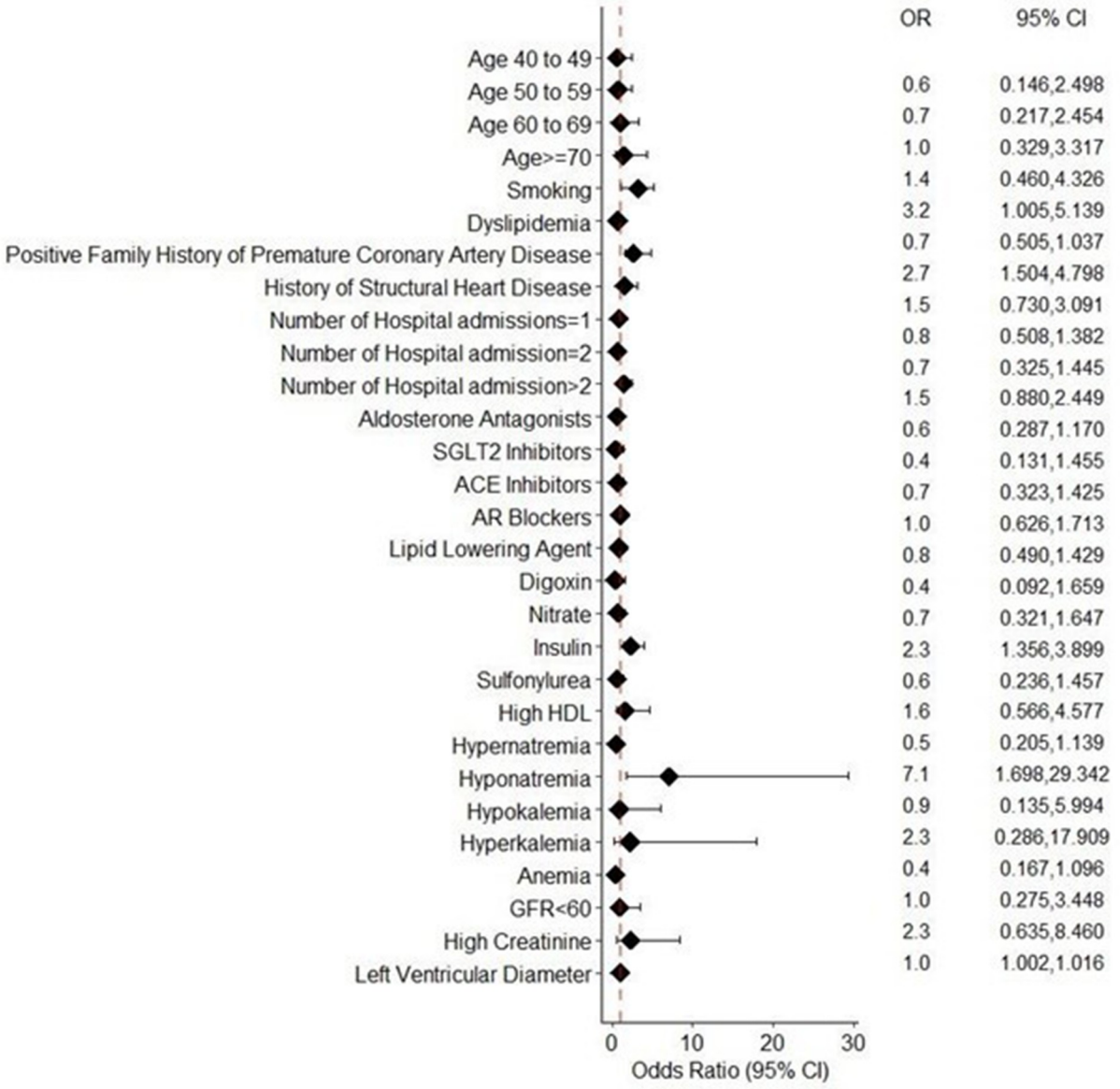

Figure 1. Factors associated with HF mortality.

mortality; however, patients on insulin had higher mortality rates. Previous studies demonstrated that insulin had a worse outcome in patients with HF, while there was no evidence that sulfonylureas had any effect on cardiac mortality[33,34].

Additionally, statin therapy has been shown to improve mortality rates in HF patients in this registry. A study conducted by Ovchinnikov *et al*[35] revealed that lipid-lowering agents, specifically statins, were associated with higher survival rates in HF patients. This can be explained through the reduction of CAD progression and the decrease in LDL levels leading to lower HF hospitalizations[36]. Nitrates have also been shown to decrease HF complications in our registry, which coincides with previous explanations since nitrates decrease cardiac preload and myocardial oxygen demand and improve coronary blood flow through vasodilation[37]. Moreover, our study showed that digoxin has been shown to improve HF mortality. This has been analyzed in the DIG trial, where it showed improved mortality in specific HF patients: patients with New York Heart Association functional classification III and IV, in addition to patients with EF <25% and/or cardiothoracic ratio >55%[38,39].

In addition, in regard to HF and laboratory biomarkers that indicate the progression of the disease, our registry showed that electrolyte abnormalities, including hyponatremia and hyperkalemia, are poor prognostic factors for HF patients. Hyponatremia is a result of decreased cardiac output, renal hypoperfusion, and decreased baroreceptor stimulation. It can lead to plenty of complications in HF patients, like cerebral edema, if not treated[40]. Hyperkaliemia, on the other hand, is mainly generated by other comorbidities such as diabetes, or kidney disease or the use of diuretics such as RAAS inhibitors and aldosterone antagonists[41]. Hyperkalemia can produce arrhythmias in HF patients, which

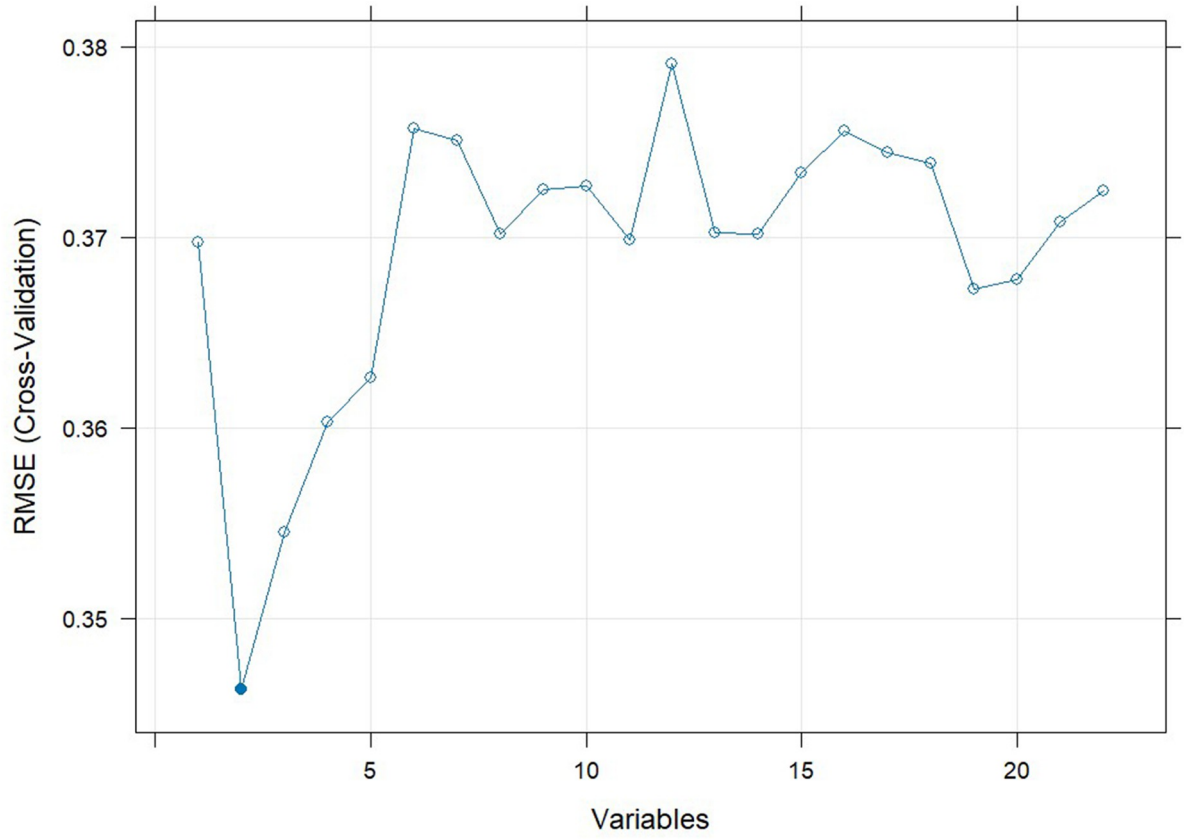

Figure 2. Recursive feature elimination analysis for predictors of mortality among patients with HF.

could be fatal[41,42]. Furthermore, our registry shows that low hemoglobin levels lead to increase in HF morbidity and mortality. This can be explained by tissue hypoxia responsible for the development of hemodynamic and nonhemodynamic compensatory mechanisms[43].

Finally, our registry revealed that elevated creatinine and decreased GFR are both linked to a decline in HF prognosis. Chronic kidney disease was shown to have a negative impact on cardiac function through decreased renal perfusion, fluid retention, irregularities in metabolism, anemia, uraemic toxins, and sympathetic hyperstimulation[44,45]. As for significant echocardiographic findings, increased left ventricular thickness was associated with increased mortality in HF. Previous studies showed that left ventricular remodeling in response to increased cardiac preload and afterload leads to myocardial fibrosis and dysfunction[46–48].

Although previous studies investigated the factors associated with mortality in HF. We add to the literature by providing data from a region where there is scarcity in data about HF. In addition, we have provided models that illustrated the most important clinical variables that can predict mortality.

However, several limitations should be acknowledged. Hospital enrolment was voluntary; hence, the study results are not representative of all hospitals in the country, especially that they were mostly tertiary care centers. Moreover, these hospitals might be more compliant with the international guidelines, this may shift our results towards patients with better outcomes. In addition, due to the observational design of the study, selection bias limits our results. Lastly, although we used regression analysis to adjust confounders, the possibility of confounding bias cannot be excluded.

In conclusion, this is the first HF registry in Jordan and the largest in the Middle East region. The 30-day mortality rate among our sample was 9.5%. This mortality rate is higher compared to registries conducted in Western countries. Smoking, a positive family history of premature CAD, hyponatremia, treatment with insulin, and high left ventricular diameter were independently associated with increased odds of 30-day mortality. The best two predictors of mortality were combining sodium and creatinine. This report highlights a gap between international guidelines in HF management and real-life practice in Jordan. As a result, we recommend a national initiative to collaborate with international programs to reduce this gap and, hence, improve patient outcomes.

Ethical approval

The institutional review board (IRB) at each participating center has reviewed and approved the conductance of this study. The IRB at the Specialty Hospital in Amman, Jordan on 29 March 2021 approved the conductance of this research. IRB approval number is 5/1/T/104826.

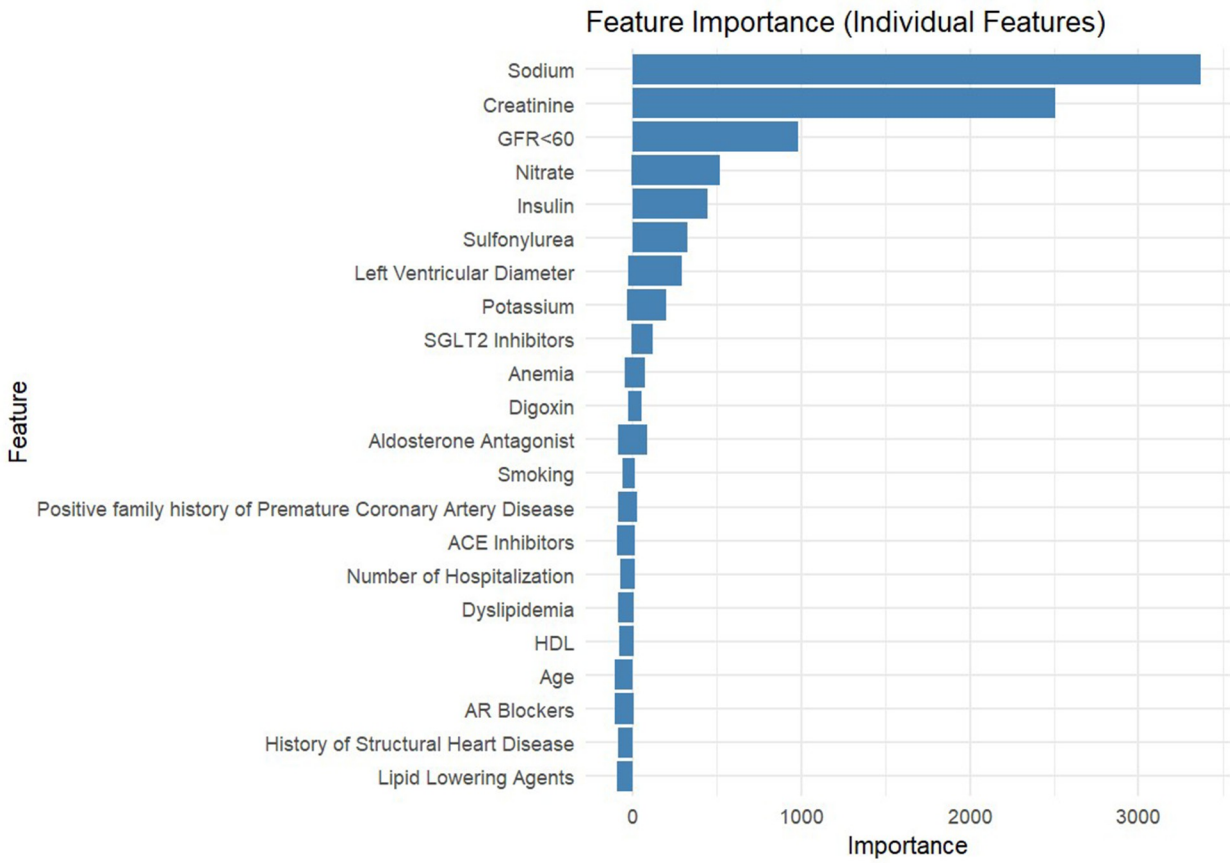

Figure 3. The order of the predictors in their importance of predicting mortality among patients with HF.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author's contribution

K.A.-B., H.A.Hantash, and M.I. were involved in conceptualization. A.T., F.A., Y.Y.O., H.A.Tawileh, S.A.-Q., M.Y.M., L.H., and T.A. were involved in data curation. A.T. was involved in formal analysis. K.A.-B., H.A.Hantash, A.A.-S., H.A., and M.I. were involved in investigation, methodology, project administration, and supervision. A.T., F.A., Y.Y.O., H.A.Tawileh, S.A.-Q., M.Y.M., L.H., and T.A. were involved in manuscript drafting. K.A.-B., H.A.Hantash, A.A.-S., H.A.Tawileh, and M.I. were involved in manuscript revision and editing.

Conflicts of interest disclosure

The authors declare that there are no conflicts of interest.

Research registration unique identifying number (UIN)

This registry was registered on Clinical Trials.gov (Identifying number: NCT04829591). Available online at https://clinicaltrials.gov/study/NCT04829591.

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Not applicable.

Data availability statement

Not applicable.

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