The use of the 4 pillars of HF management and the factors associated with it: results from the Jordanian Heart Failure Registry (JoHFR)

Peer review

The authors addressed an important question, especially in the presence of limited data about it in the Middle East. However, major revision is needed for a smooth and easy read.

General comments

1. Writing style refinement. There is unnecessary wording.
2. Results presentation does not flow well and outcome results are missing.

Main issue

The inclusion of HFpEF patients, i.e., except for SGLT2i, 4-pillar HF medications or quadruple therapy are not indicated in HFpEF, unless there is other compelling indication, due to the absence of positive evidence on prognosis.

Other points that may have impact the results

- Was there any documented reason that prevented the patients from receiving HF medications such as renal function, low blood pressure, etc. This is not clear or not discussed in the discussion section in terms of the collected data.
- It was mentioned that the patients were followed for 1 year, why hospitalization was not reported only the 30-day mortality? Hospitalization is one of the main outcomes that should be planned in HF research.
- A trivial point, why the medications doses were not collected?

I have more comments on the text for clarity.

Suggestion

STROBE check list for relevant study type gives direction to reporting observational studies. This may help to respond to the comments would be helpful and give a focused approach (Checklists - STROBE (strobe-statement.org))

Abstract

Background: Heart failure (HF) is a complex cardiovascular disease. Effective management typically involves four main medications: angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs), beta-blockers (BBs), angiotensin receptor-neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs), along with sodium-glucose co-transporter-2 inhibitors (SGLT2). This study assessed the prevalence and associated factors of these four pillars of HF management in Jordan.

Methods: Data from the Jordanian HF registry (JoHFR) was analyzed, encompassing records ~~from~~ ~~2151~~ of HF patients treated in various cardiology centers from 2021 to 2023. The study included both chronic and acute HF cases, with a focus on the combined usage of the four-pillar medications and the factors influencing this usage.

Results: The medical records of 2151 heart failure patients who were admitted to cardiovascular centers throughout Jordan were collected. Of these, only 0.6% received the complete four-pillar treatment for heart failure. Beta-blockers were the most frequently used medication, prescribed to 74% of patients, while SGLT2 inhibitors were the least common, used by only 9%. Notably, patients with diabetes were more likely to be on the four-pillar regimen (P-value = 0.016). Additionally, patients with a glomerular filtration rate (GFR) below 60 and an HbA1c level above 6% were consistently treated with this comprehensive approach (P-values = 0.044 and 0.066, respectively). The analysis revealed no significant difference in mortality rates between the patient groups (P-value = 0.475).

Conclusion: The low utilization of the four pillars of HF treatment in Jordan suggests a need for enhanced collaborative efforts to improve physician awareness and address issues such as medication costs and availability. Targeted governmental initiatives could also help address these challenges and improve adherence to these essential medications.

Keywords Heart Failure · Guidelines · Pillars · Cardiovascular Disease in Jordan

Commented [RK1]: The only abbreviation for the medications that was used in the abstract is SGLT2i so why to mention them?

Commented [RK2]: Kindly, refine and make it consistent with the objective stated in the manuscript.

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Commented [RK5]: Be consistent with the terms used. Above the term “cardiology” not “cardiovascular” centers was used.

Commented [RK6]: Usually the result section begins with general information such as age, sex, general characteristics. Then comes more focused results then the main outcome. Here the results section start was with the main point!

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Introduction

Heart failure (HF) is a complicated and debilitating disease of the cardiovascular system characterized by the inability of the heart to function normally and to pump blood properly and adequately, leading to impairment of cardiac input [1, 2]. As one of the major causes of morbidity and mortality, HF places a significant burden on health systems worldwide, including those in Jordan. (3) Where the prevalence of HF is on the rise, the importance of in-depth checking and inspection of the current guideline-directed medical therapy (~~GDMT~~) is essential, adding to it how adherent the physicians and the system are to it, which is fateful towards improving and identifying factors associated with compliance [3]. The main intervention for successfully treating heart failure is pharmacological [1]. The drugs used worldwide in the management and treatment of HF are angiotensin-converting enzyme inhibitors (ACEi), beta-blockers (BBs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter-2 inhibitors (SGLT2) [1], for HF with reduced ejection fraction (HFrEF), ACEi, ARNI, BBs, and SGLT2 are the main disease-modifying treatments for improving symptoms, reducing hospital admissions, and increasing survival [4,5]. However, only SGLT-2 improved mortality among patients with HF with preserved ejection fraction (HFpEF) [6].

The primary objective of this article is to assess and identify the utilization of HF medications and the potential variation in clinical practice and explore the factors influencing guideline adherence among healthcare professionals in Jordan. Ultimately, the results will inform healthcare providers, policymakers, and other relevant stakeholders of the current state of HF management in the country, facilitating the implementation of strategies aimed at optimizing patient care, reducing morbidity and mortality rates, and improving overall health outcomes for individuals living with HF in Jordan.

Methods

Setting, Design, and Population

This is a national heart failure registry in Jordan. Detailed methodology information is found in the study protocol registration [7]. In brief, medical records from heart failure patients who reviewed cardiology medical centers across Jordan from 2021 to 2023 were collected and studied. The study population includes patients who were seen in outpatient clinics for chronic HF and patients who were admitted through the ER for either new-onset HF or an acute on-top-of-chronic exacerbation attack. A total of 21 centers were involved in the study, including private centers, teaching and nonteaching hospitals, and public secondary and tertiary university hospitals. This is a prospective study in which patients were followed up to 1 year after the first medical record was collected. Patients under the age of 18 were excluded from the study. According to Jordanian research data collection guidelines, each site's principal investigator was responsible for getting an institutional review board (IRB) approval from their institution. The IRB of the Specialty Hospital approved the conductance of this research (approval number: 5/1T/104826). Patients were informed of the conduct of a heart failure registry and given the

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Commented [RK13]: This sentence with this reference is not appropriate to describe the methodology! In addition, the reference is for a registry with another objective!

Commented [RK14]: What does this mean?

Commented [RK15]: You have to be clear in using terms. Is this a prospective "study" or "registry" as stated at the beginning? Also in the discussion section, it is stated that the registry continued for two years. Why this popped up in the discussion section. Does this mean that it is still running to recruit patients? Please, add concise proper description of the study design in the methods section.
It seems a multicenter study rather than a registry! In addition, there are two comparison groups so this is a cohort study.
A patient registry is a long-term, open-ended data collection system that uses observational methods to collect data on a patient population. In a registry, there is no question of 'what intervention is to be performed?'.

A registry study or a clinical study seeks to answer a specific research question and parameters such as duration, patient population, data to be collected (and analysis to be performed) are defined (and constrained) by a study-specific protocol.

option to reject their data entry. A written informed consent was obtained from all the participants. All patients' data were dealt with anonymously.

Data Collection

An online Google form was distributed among the data collection team. This form was based on similar forms made by other heart failure registries. In summary, the form had several sections, including demographic characteristics of the patients, baseline co-morbidities, baseline laboratory investigations, and what drugs the patients were on.

This form was filled out after hospital discharor ge outpatient clinic visits. It was then shared into a database managed by this research's administrative and analytic team. Heart failure with reduced ejection fraction is defined by an echocardiogram ejection fraction <50% ; meanwhile, heart failure with preserved ejection fraction (HFpEF) is diagnosed by an echocardiogram ejection fraction >50% with diastolic dysfunction. Lipid profiles were abnormal if one or more of the following were positive:

total cholesterol was ≥200 mg/dL, LDL >130 mg/dL was high, triglycerides >150 mg/dL, or HDL levels were <40. Elevated BNP and NT-ProBNP were ≥100 pg/L and ≥125 pg/L, respectively. The normal sodium (Na) range is 136 to 145 mmol/L. Meanwhile, the normal potassium (K) range was 3.5-5 mmol/L; any result that exceeded or fell outside this range is considered abnormal. Anemia was defined when hemoglobin levels (Hg) were less than 10 g/dL. Kidney function tests were abnormal when urea levels were >20 mmol/L, creatinine was >115 micromoles\L, and eGFR was <60 ml/min/1.73 m^2. Lastly, HBA1c levels above 6% were considered abnormally high. The 30-day mortality, need for mechanical ventilation, and length of hospital stay were collected for the patients admitted to the hospital.

In 2021, the ACC (American College of Cardiology) and the AHA (American Heart Association) gave SGLT2 inhibitors a class 1 indication for treating HFrEF and a class IIa indication for both mildly reduced EF (41-49%) and HF with preserved EF (≥50%). These recommendations made SGLT2 inhibitors one of the main four pillars of treating heart failure. Accordingly, the main 4 pillars of treating HF are BB, ACEI/ARBs, ARNI, and SGLT2. Therefore, the outcome of interest in this study was the prevalence of using the main 4 pillars in Jordan. In addition, we aimed to investigate the factors associated with the use of these 4 pillars.

Data Analysis

The data was 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 using 4 pillars of HF using T-test and Chi-square for continuous and categorical variables, respectively. A p-value <0.050 was considered statistically significant.

Results

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Commented [RK19]: How important to use this space for regular lab values? Especially that the table included data for normal and high values!

Commented [RK20]: Unit?

Commented [RK21]: Is this for all patients or for those who were admitted to hospital like LOS and MV?

Commented [RK22]: Why the aim or objective is re-mentioned here!!

Commented [RK23]: Can also consider how to describe the data, i.e., mean (SD)/median (IQR) and proportion (%) for continuous and categorical data.

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Characteristics of the included patients

The medical records of 2115 heart failure patients who were admitted to cardiovascular centers throughout Jordan were collected. Males comprised 1235 (58.0%) (~~1235/2115~~) of the included patients.

Moreover, number (71.0%) of patients had chronic HF, whereas the rest, 29.0%, had acute HF. A percentage of 70.3% of patients had heart failure with reduced ejection fraction (HFrEF). whereas, 29.7% had heart failure with preserved ejection fraction (HFpEF). Patients who were on the 4 pillars of HF (the pillars are SGLT2 inhibitors, ARNI, B-blockers, and MRA) were 0.6% of all study samples. Figure 1 describes the use of each of the 4 pillars in HF management. The most commonly used medication was beta-blockers (74%), while the least commonly used were ARNI (10%) and SGLT2 inhibitors (9%). Figure 2 shows the percentage of usage of the 4 pillars among the included patients. Furthermore, 69.2% of pts had diabetes, whereas 80.7% had hypertension. The percentage of smoking and alcohol among the included patients was 31.3% and 0.6%, respectively.

Comparison of the Characteristics of the Patients According to the Use of the HF-4 Pillars

Table 1 summarizes the factors studied between two distinct patient groups: those on the four-pillar regimen for heart failure (HF) management and those not on this regimen. A pronounced discrepancy was observed in the prevalence of diabetes between these groups. Remarkably, all patients with diabetes were treated with the four-pillar regimen (P-value = 0.016), underscoring a targeted approach for this subset of the population. This association is further visualized in Figure 3, which delineates the proportional use of each of the four pillars across patients with and without diabetes, demonstrating a higher utilization rate among diabetic individuals. Furthermore, every patient prescribed SGLT2 inhibitors had a concurrent diagnosis of diabetes.

The employment of the four-pillar treatment strategy was also evaluated across different types of heart failure. Figure 4 highlights a greater percentage of patients with heart failure with reduced ejection fraction (HFrEF) receiving all four medications in contrast to those with heart failure with preserved ejection fraction (HFpEF), suggesting a trend towards more aggressive treatment protocols in HFrEF. ~~However,~~ the analysis indicated no significant distinction in the use of the four pillars when comparing patients with acute HF to those with chronic HF, nor was there a significant difference in the adoption of this regimen between genders, or across the variables of hypertension ~~(HTN)~~, smoking, alcohol use, dyslipidemia, obesity, or family history of atherosclerotic cardiovascular disease (~~ASCVD~~) or premature death.

Furthermore, renal function and glycemic control were pivotal in determining the use of the four pillars, as all patients who had GFR<60 or HbA1c>6 were found to be on the complete four-pillar treatment (P-value = 0.044, and 0.066, respectively). In contrast, no significant correlations were observed

Commented [RK26]: You defined HF abbreviation above. Try to be consistent. You should define abbreviations in abstract and then in the manuscript once!

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Commented [RK29]: I have a major issue here, i.e., including patients with HFpEF because the 4-pillar HF therapy is only applicable for HFrEF. Whereas, in HFpEF only SGLT2i are proven to improve outcomes. I am afraid that the results are not meaningful in this case!

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Commented [RK32]: Results section, should present the data as is without interpretations or commentary.

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Commented [RK35]: This is normal and does not add anything because there is no evidence to force the 4-pillar approach in HFpEF patients and imposing additional cost on patient for no evidence.

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Commented [RK37]: The inclusion of acute HF, especially the de novo acute HF can be acknowledged in the discussion section if you agree. I think compared to those with acute on top chronic HF, might have lower chance to be prescribed all the 4 pillars before discharge.

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173 between the use of the four-pillar therapy and other laboratory findings, such as lipid profiles, B-type
174 natriuretic peptide (BNP), N-terminal pro b-type natriuretic peptide (NT-proBNP), sodium, potassium,
175 hemoglobin, urea, and creatinine levels. Furthermore, the 30-mortality rate did not significantly differ
176 between the patient groups (P-value = 0.475).

This was mentioned above: The 30-day mortality, need for mechanical ventilation, and length of hospital stay were collected for the patients admitted to the hospital. This needs to be addressed clearly.

Discussion

178 This is the first large-scale national prospective multi-center registry to study heart failure patients in
179 Jordan that has continued enrolling patients for two years. Data regarding patient demographics,
180 medical history, clinical characteristics, prescribed medications, and follow-up visits is collected and
181 analyzed. The results of this study shed light on several important aspects related to the utilization of
182 medications for the treatment of heart failure (HF) in Jordan and the degree of adherence to current
183 guidelines. A notable observation is the low percentage of patients receiving the recommended
184 combination therapy consisting of beta-blockers, angiotensin receptor neprilysin inhibitors (ARNIs),
185 sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors), and mineralocorticoid receptor
186 antagonists (MRAs).
187 Our study revealed that only 0.6% of HF patients were prescribed this optimal combination therapy.

188 This low percentage of utilizing these medications can be attributed to several factors, including cost
189 and availability. SGLT2 inhibitors are relatively newer agents demonstrating substantial
190 cardiovascular benefits in HF patients. However, their higher acquisition costs compared to traditional
191 HF medications, coupled with their limited availability within healthcare facilities, may contribute to
192 the lower prescription rates. Cost-related factors and medication availability also play a crucial role in
193 the utilization of other HF medications. Patients with limited financial resources or inadequate health
194 insurance coverage may face barriers to accessing prescribed medications, leading to non-compliance
195 or suboptimal treatment.
196 Similarly, the availability of certain medications within healthcare facilities, particularly in resource-
197 limited settings, can influence prescription patterns. Addressing these barriers through policy
198 interventions, such as improved reimbursement systems or the inclusion of essential medications in
199 formularies, may help increase the utilization of guideline-recommended HF therapies. The suboptimal
200 usage of combined medications raises concerns about the potential impact on patient outcomes. Several
201 studies have demonstrated the significant benefits of these medications in improving survival, reducing

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hospitalizations, and enhancing quality of life in HF patients [8, 9]. Cardiovascular risk factors and co-morbidities, as well as cost and availability, are several patient-related factors that impact the selection and usage of HF medications.

Our study highlights the significance of comorbid conditions such as diabetes mellitus (DM), ~~Haemoglobin A1C~~, and kidney function ~~measured by estimated glomerular filtration rate [GFR~~]. These factors are found to be significant in influencing medication choices and dosing strategies. In a long-term heart failure registry done by the European Society of Cardiology, the included patients with chronic HF were 31.9%, 37.7%, and 18.4 for DM, atrial fibrillation, and renal dysfunction, respectively [8]. HF itself is considered an insulin-resistant state and is associated with a significant risk for the future development of diabetes [8]. Higher HbA1C levels are associated with increased mortality, which is mainly multifactorial and may involve both direct and indirect effects of hyperglycemia. Adverse effects of hyperglycemia are potentially represented by endothelial dysfunction, high oxidative stress, increased protein kinase C activation, and potentially accelerated atherosclerosis [8]. In addition, the magnification of glycation end products (AGEs), resulting from chronic hyperglycemia, may lead to many detrimental processes such as increased myocardial stiffness and activation of the receptor for AGEs leads to upregulation of cellular signals and that results in cellular dysfunction [8] Also, elevated levels of HbA1C may be an indicator for a greater level of insulin resistance with the associated derangements of myocardial energy and cardiac metabolism utilization in the insulin resistant myocardium and increased activation of the sympathetic nervous system [8]. Finally, high HbA1C levels also may be reflective of poor compliance with medications, which in turn may be associated with poor outcomes, and that could clarify the considerable association between high HbA1C and the significant percentage of HF patients who were described in the 4 pillars [1]. In addition, 100% of the patients on SGLT2 inhibitors had diabetes. This highlights that SGLT2 is still being considered as a medication to control HbA1c and diabetes and not a main pillar of heart failure treatment as recommended by the international guidelines [4]. Similarly, impaired renal function, as indicated by decreased GFR, was also associated with the physiciansí adherence to prescribing the 4 pillars of HF, indicating that physicians are still cautious about the safety of these medications among patients with reduced GFR. Thus, we recommend conducting clinical trials investigating the safety of the 4 pillars of HF among HF patients with reduced GFR.

Several limitations should be acknowledged. Due to the observational design of this study, it is not possible to establish cause-and-effect relationships for many of the associations mentioned. Additionally, we cannot dismiss the potential impact of unmeasured confounding factors on the non-use of the 4 pillars of HF. The study included patients enrolled in the Jordanian Heart Failure Registry (JoHFR), so we cannot disregard the possibility of changes in the prescription practices following the termination of the enrolment in the JoHFR trial in 2023. Data about the specific types of BB, ARNI, ACEI, and SGLT2 used in the registry was unavailable in our dataset. The applicability of our findings to other countries relies on similarities in population characteristics, healthcare systems, and heart failure management. Finally, a significant limitation of this and other registry studies is the absence of longitudinal data and the ability to establish the timing of clinical variables, particularly prior measurements of serum potassium levels, which could have influenced decisions regarding the

Commented [RK43]: There is proper HF-related outcomes that are specific to HF patients in Jordan properly reported and presented in the study as this will be more convincing for local authority.

Commented [RK44]: Rephrase please because the study simply tells us that those with DM and renal impairment received more optimal medications. The subsequent discussion is hard to put in context. In addition ESC registry is reference 9 not 8.

The discussion and detailed comparison with other papers should be to compare and contrast the results of the present study and has been published.
In addition, there are several studies that have published on quadrable therapy in HF.

Commented [RK45]: Are you influencing the prescribed intervention during the follow-up? This is not relevant for registries! Otherwise needs rephrasing.

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242 initiation of therapy and medication usage.

Conclusion

243 In conclusion, we used the data from the JoHFR study, which is considered the largest HF registry in
244 the Middle East, to assess the prevalence of the four HF management pillars and investigate the factors
245 associated with it. Our analysis revealed that the use of the 4 pillars was very low. In addition, a history
246 of diabetes, as well as high HbA1c levels and reduced GFR, were significantly associated with
247 decreased prescription of the 4 medications. This highlights that there is still a large underuse of the 4
248 pillars of HF. National efforts are needed to collaborate with international HF associations to improve
249 the knowledge of physicians about the use of the 4 pillars of HF. Also, governmental initiatives should
250 focus on reducing the underuse of these medications by addressing high costs, low availability, and
251 poor insurance coverage.

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