Majalah Farmaseutik
ISSN-e: 2614-0064 | ISSN-p: 1410-590x
Volume 20(4), 437-446

Complexity of Treatment Regimens and Patient Adherence in Individuals with Heart Failure in Yemen: A cross Sectional Study

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Submitted: 11-06-2024 *Revised: 19-06-2024* *Accepted: 20-06-2024*

ABSTRACT

Various studies have consistently found that increased complexity in medication regimens leads to poorer adherence. Recognizing the growing global prevalence of heart failure and the specific challenges it presents, especially in low-resource settings, this study aims to investigate the influence of complexity of treatment regimens on adherence levels among Individuals with heart failure in Yemen. Through a cross-sectional observational study conducted at three major hospitals in Sana'a, structured questionnaires were employed to assess self-reported medication adherence and regimen complexity. The findings reveal a significant negative association between higher regimen complexity and adherence with regression coefficient (B = -0.150; P value 0.020). Moreover, socioeconomic factors such as income (B = 2.753; P value 0.000) and employment status (B = -1.380; P value 0.006) were found to exert considerable influence on adherence levels. This study underscores the imperative for simplified medication regimens and improved patient education to enhance adherence rates among heart failure patients in developing nations.
Keywords: Heart failure; Medication adherence; Medication regimen complexity; Yemen

INTRODUCTION

Heart failure (HF) manifests as a clinical syndrome arising from diverse functional and structural abnormalities. Traditionally, it involves the heart's inability to pump or fill with blood effectively, often due to conditions like ventricular dilation or myocardial infarction. The heart may compensate by activating neurohormonal pathways and increasing ventricular pressures to sustain output. Despite varied causes, measuring left ventricular ejection fraction (LVEF) is crucial for diagnosis, prognosis, and guiding treatment in heart failure (Khan et al., 2022; Lund et al., 2022; Savarese et al., 2022). Rehospitalization rates for HF across seven Middle Eastern countries, including Yemen, were 18% at 3 months and 40% at 12 months. Cumulative mortality rates were 13% at 3 months and 20% at 12 months (Hassan, 2015).

Effective management of HF hinges on several factors, with medication adherence being critical for controlling the condition. Despite heart failure often being incurable, it can be effectively controlled through consistent medication usage (Bernell & Howard, 2016). However, adherence rates vary widely, patients with chronic diseases were found to be higher in developed countries at 50%, while they were less than 50% in developing countries (Sabaté & World Health Organization, 2003). A lack of adherence is linked to negative consequences such as increased hospital readmissions and higher mortality rates (Wu et al., 2008), influenced by a complex interplay of factors across five domains: patient characteristics, socioeconomic elements, healthcare system components, therapy-related factors (eg, prescription of complex regimens), and factors specific to the medical condition itself (Kardas et al., 2013).

Patients with HF typically manage complex medication regimens, often using between 2 and 9 different prescription drugs each day, leading to a total of approximately 10.1 doses, excluding any over-the-counter (OTC) medications or alternative and complementary treatments (Cobretti et al., 2017; Hajjar et al., 2007). Due to the chronic progression of heart failure, complex medication regimens are often essential for effective management. The necessity for such regimens is frequently linked to the presence of additional chronic conditions among these patients, which require sustained medication use. Consequently, managing heart failure becomes increasingly intricate as multiple medications are needed to address these health challenges (Masoudi & Krumholz, 2003).

Polypharmacy significantly heightens the likelihood of medication non-adherence and is just one aspect of the complexity of a medication regimen. Other factors adding to this complexity include the various attributes of the prescribed regimen, such as the number of dosage forms, dosing frequencies, and specific instructions for taking the medication (Beezer et al., 2022; Choudhry et al., 2011). Complexity in medication regimens has been linked to several negative health outcomes. These include increased rates of medication nonadherence, adverse reactions to drugs, incorrect prescriptions, hospitalizations, interactions between drugs, elevated healthcare costs, a reduction in quality of life, deterioration in functional status, and higher mortality rates (Fröhlich et al., 2010; Hajjar et al., 2007; Schoonover et al., 2014). A systematic review conducted by Pantuzza et al. (2017) found that a more complex medication regimen tends to result in lower adherence to pharmacotherapy. The review, which included fifty-four studies, indicated that most studies observed a negative correlation between regimen complexity and adherence, although a few studies pointed out that under specific conditions, complexity could enhance adherence (Pantuzza et al., 2017).

Despite ongoing advancements in pharmaceuticals and shifts in demographic and epidemiological trends, marked by an aging populace and the increasing occurrence of chronic illnesses, a unanimous understanding regarding the link between regimen intricacy and medication adherence has yet to be established (Advinha et al., 2014). This lack of agreement persists despite numerous studies, underscoring the necessity of exploring this association as pharmacotherapies become increasingly complex (Ferreira et al., 2015; Stange et al., 2013). Moreover, most research on this topic has been limited to specific populations or has focused only on certain aspects that may influence the complexity of medication regimens (Claxton et al., 2001; Ferreira et al., 2015). Notably, there are few studies that evaluate the impact of complexity of treatment regimens on adherence to treatments for heart failure, especially in developing countries (Abdelbary et al., 2023). To date, no data have been collected on how the complexity of medication regimens affects medication adherence among heart failure patients in Yemen. Therefore, this research aims investigate the influence of complexity of treatment regimens on adherence levels among Individuals with heart failure in Yemen.

METHODS

Research design, Location, and duration

An observational cross-sectional study, based in hospital settings, was carried out starting from December 19, 2023, to February 17, 2024, with heart failure patients visiting cardiac clinics in Sana'a, the capital of Yemen. The study took place in three major hospitals: *Hospital General Modern Thawra*, a governmental facility, and two private hospitals, *University of Science & Technology Hospital* and *Azal Hospital*. Utilizing self-reported survey for data collection was chosen for its practicality in efficiently gathering data from patients with limited time during hospital visits.

The criteria for participant inclusion and exclusion

All adults aged 18 years or older who have been diagnosed with heart failure and are actively receiving medication therapy were included in the study. They must have had at least one follow-up appointment over the last six months, ensuring they were not evaluated at their initial consultation. Participants were required to have the capacity to provide informed consent. The exclusion criteria included individuals with cognitive impairments or other conditions that affect self-report measures, such as severe language barriers or significant communication disorders. Pregnant patients were also excluded from the study because Pregnant women often have additional comorbidities such as dyslipidemia, diabetes, and hypertension, which can significantly alter their treatment regimens. These comorbidities require tailored medication plans that can differ greatly from those of non-pregnant patients with heart failure.

Sample Size and Sampling Approach

Convenience sampling was used to select participants due to its practicality in a hospital setting, where patients are readily available and likely to consent. This method allowed for the efficient and cost-effective recruitment of participants during their scheduled clinic appointments,

held from 08:00 AM to 02:00 PM in the outpatient department. It also accommodated the variable daily attendance of heart failure patients, which could fluctuate due to changes in appointment times or absences.

The sample size was calculated using the formula below, which is designed to estimate the correlation between variables with a 95% confidence level. The formula incorporates a correlation coefficient (a midpoint r = 0.24) based on findings from prior research by (Ma et al., 2020):

$$\boldsymbol{n = \left[\frac{Z_{a/2} + Z_B}{0.5 \ln[(1+r)/(1-r)]}\right]^2 + 3}$$

Where $\boldsymbol{Z_{a/2}}$ = 1.96 (standard normal distribution corresponding to the significance level) and $\boldsymbol{Z_B}$ = 0.842 (the critical value corresponding to the desired statistical power). The initial calculation suggested a minimum sample size of 134 patients.

Data collection procedure and methods

The research predominantly utilized structured questionnaires (paper-based questionnaires) as the main tool for data collection. These questionnaires were divided into several sections, each targeting different aspects: sociodemographic details, medication adherence, and the specific medications currently being used by the patients. The sociodemographic section gathered information such as gender, age, marital status, level of education, income level, employment status, and the duration since the diagnosis of heart failure.

Medication complexity

The Medication Regimen Complexity Index (MRCI), a validated scoring system that comprises 65 items to assess the complexity of a patient's medication regimen (George et al., 2004). This system includes an evaluation of the number of medications, the variety of dosage forms, dosing frequencies, and specific administration instructions, including food-related restrictions. The MRCI is categorized into three sections: Section A, with 32 items for dosage forms; Section B, with 23 items for dosing frequency; and Section C, with 10 items for additional instructions. The complexity of a regimen is quantified by summing the scores from all three sections, where a higher total score indicates greater complexity. The tool has also been successfully adapted into Arabic, maintaining strong interrater and test-retest reliability (Aksoy et al., 2023; George et al., 2004; Hirsch et al., 2014; Mansur et al., 2012).

Medication adherence

The *Medication Adherence Report Scale* (MARS-5) was employed to measure medication adherence. It consists of five items that evaluate behaviors like forgetting doses, altering dosages, and skipping medications, with responses rated on a 5-point Likert scale. Widely validated, MARS-5 has demonstrated reliability and validity in various global contexts, including Arabic-speaking regions. In the current study, the scale demonstrated internal consistency with a Cronbach's Alpha of 0.856, underscoring its utility in measuring medication adherence. This aligns with findings from studies in countries such as Jordan, Iran, Germany, and Ethiopia, which have confirmed its consistency and correlational validity with medication adherence rates (Al-Qerem et al., 2022; Irshaidat et al., 2023; Lin et al., 2018; Mahler et al., 2010; Seid et al., 2023).

Data entry and statistical analysis

Data was entered into IBM SPSS V.20 and initially checked for completeness. Descriptive statistics summarized categorical variables in terms of counts and percentages, while continuous variables were represented using means with standard deviations or medians with interquartile ranges for skewed data. Medication adherence, measured by MARS-5, was analyzed using median and interquartile range. Relationships between adherence and variables were examined through Mann Whitney tests for categorical variables and Spearman's Correlation for continuous ones. Significant predictors of adherence were identified via multiple linear regression. Statistical significance of $p < 0.25$ was applied for univariate analyses, and $p < 0.05$ for multivariate analyses, with variables not meeting the 0.25 threshold excluded from the final model.

Ethical consideration

Approval for this study was obtained from the Ethics Committees of AL-Nasser University and AL-Thawra Hospital, with reference codes NU-REC-M2302 and NO 5-2023. All participants provided informed consent after being fully informed about the study's objectives, benefits, potential risks, and procedures. They were also assured of their right to withdraw at any point without facing any consequences. Data was anonymized and securely stored to safeguard participant confidentiality and ensure research integrity.

RESULTS AND DISCUSSION

Sociodemographic and health-related characteristics

The study analyzed 250 heart failure patients who meet the criteria of inclusion, with 65.2% being men and a mean age of 51.08 (±11.47) years. Most participants (72.8%) were educated, and the median number of prescribed medications was six. The majority (69.6%) had been diagnosed with heart failure for years. About a half (53.6%) of the participants earned under 100,000 Yemeni Rial per month (less than $200). Further demographic details are provided in

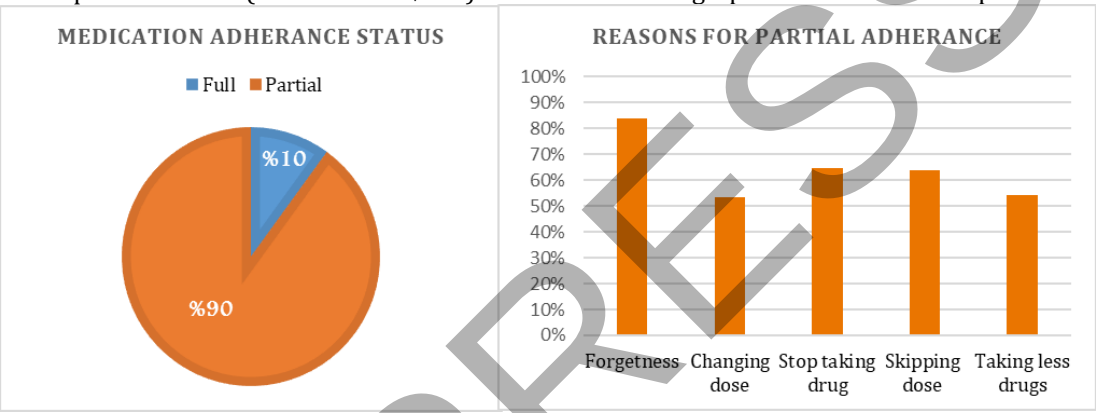

Figure 1. medication adherence status and reason for partial adherence

Table.

Medication Adherence

The study revealed moderate self-reported medication adherence among heart failure patients, with a median MARS-5 score of 19.0 and an interquartile range of 16-23. Only about 10% (25 individuals) reported full adherence, while the majority, 90% (225 individuals), showed partial adherence. The most common reason for partial adherence was forgetfulness, affecting 84% of patients. Other reasons included stopping medication temporarily (64.8%), skipping doses (64%), taking less than prescribed (54.4%), and altering dosages without medical advice (53.6%). Figure 1.

Medication Complexity

The Medication Regimen Complexity Index (MRCI) analysis, detailed in Table , assesses the complexity of participants' medication schedules, focusing on dosage forms (MRCI-A), dosing frequency (MRCI-B), and additional instructions (MRCI-C). The dosage forms had minimal variability, with a mean of 1.16 (SD=0.54), while dosing frequency showed a broad spectrum of schedules, evidenced by a mean of 6.538 (SD=1.909). Additional instructions further highlighted the regimen's complexity, with a mean of 6.068 (SD=1.83). Overall, the total MRCI score averaged at 13.75 (SD=3.789), underscoring the diverse and multifaceted nature of medication regimens that patients must navigate.

Uni- and multivariate analysis of factors associated with heart failure medication adherence:

Univariate analysis identified significant associations between medication adherence and factors such as employment status, marital status, monthly income, duration of illness, and

medication regimen complexity (Table). Subsequent multiple linear regression highlighted the significance ($p<0.05$) of three predictors effecting adherence: employment status, income, and regimen complexity. The regression model showed that being unemployed (B = -1.380) and increased regimen complexity (B = -0.150) negatively affected adherence, whereas higher income (B = 2.753) positively influenced adherence.

This study confirms that age does not significantly impact medication adherence among heart failure patients in the Middle East, consistent with broader findings across the region, including studies by (Amininasab et al., 2018; Lin et al., 2020), which reported no significant age-related differences in adherence. However, some regional variations do exist; for instance, (Jarrah et al., 2023), observed that younger patients in Jordan exhibited higher adherence, whereas (Shojaee et al., 2023), noted lower adherence among older patients in Iran. Despite some regional discrepancies suggesting gender disparities, we find that gender does not significantly influence medication adherence, as evidenced by multiple studies (Al-Zaazaai et al., 2019; Jarab et al., 2023; Moaddab et al., 2023; Raffaa et al., 2020). However, notable exceptions from Iran, involving 487 patients, indicate a gender disparity, with females showing lower adherence than males (Rezaei et al., 2022; Sadeghiazar et al., 2022).

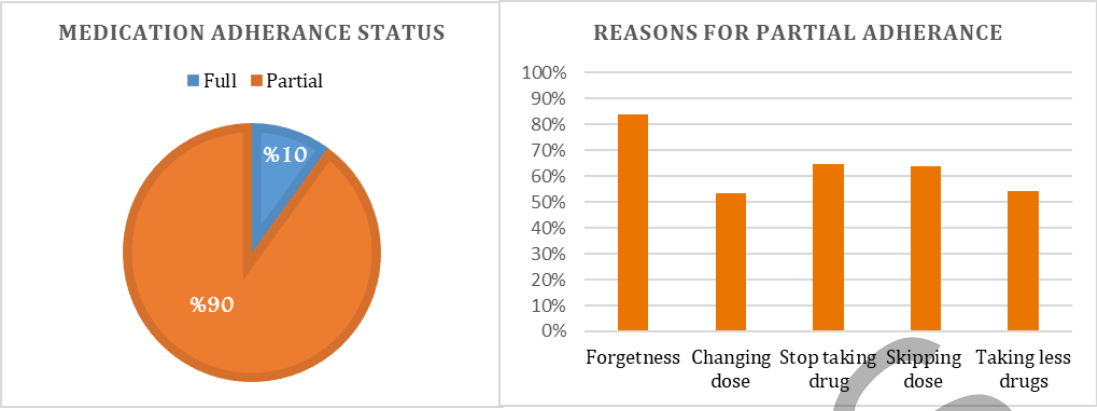

Figure 1. medication adherence status and reason for partial adherence

Table I. Sociodemographic and health-related characteristics

Descriptive and health-related statistics	Frequency (%)
Gender	
Male	163 (65.2)
Female	87 (34.8)
Age, mean (SD)	51.08 (11.47)
Education Level	
Illiterate	68 (27.2)
School	107 (42.8)
High education	75 (30.0)
Marital Status	
Single	15 (6.0)
Married	221 (88.4)
Divorced	4 (1.6)
Widowed	10 (4)
Employment status	
***Employed*:**	**106 (42.4)**
Government & non-government	54 (21.6)
Self-employed	52 (20.8)
Unemployed:	**144 (57.6)**
Student	7 (2.8)
Housewife	65 (26.0)
Unable to work	72 (28.8)
Monthly income	
< 100,000 YR[1]	134 (53.6)
100,000 - 200,000 YR	76 (30.4)
> 200,000	40 (16.0)
Time when diagnosed with heart failure	
> 6 months to < 1 year	86 (34.4)
1 to 3 years	88 (35.2)
> 3 years	76 (30.4)
Number of medications, median (IQR)	6 (5-7)

[1]Yemeni Rial

Moreover, this study founds no significant impact of marital status on medication adherence, contrasting with some regional studies suggesting that married individuals exhibit higher adherence. Notably, two studies reported that married patients, or those not living alone, had better adherence, attributing this to greater social support (Jarrah et al., 2023; Raffaa et al., 2020). However, our

Table II. Descriptive statistics for the Medication Regimen Complexity Index

Medication Regimen Complexity Index	**Mean**	**SD**
Dosage forms (MRCI-A)	1.16	0.54
Dosing frequency (MRCI-B)	6.538	1.909
Additional instructions (MRCI-C)	6.068	1.838
Medication Regimen Complexity Index	**13.75**	**3.789**

Table III. Uni- and multivariate analysis of factors associated with heart failure medication adherence

Description Variable		**Heart failure medication adherence**			
		Univariate analysis		**Multivariate analysis**	
			P value	**B**	**P value**
Age		-0.048 [C]	0.453[a]		
Gender	Male Female		0.458[b]		
Education Status	Illiterate Educated		0.667[b]		
Marital Status	Married Single		0.055[b]	-0.967	0.212
Employment	Unemployed Employed		0.001[b]	-1.380	0.006*
Income	< 200,000 YR > 200,000 YR		0.000[b]	2.753	0.000*
Diagnosed Time (years)	< 3 > 3		0.088[b]	0.351	0.525
Number of Medications		0.068 [C]	0.278[a]		
Medication regimen complexity		-0.089 [C]	0.161	-0.150	0.020*

Note: [a]Spearman's Correlation; [b]Mann Whitney test; [c]Correlation coefficient

findings align with other studies, which did not find a significant correlation between marital status and adherence (Jarab et al., 2023; Sadeghiazar et al., 2022). Notably, this study affirms that income significantly predicts medication adherence. Research from Iran and Jordan shows higher incomes correlate with better adherence (Jarrah et al., 2023; Sadeghiazar et al., 2022), although a Saudi study found the opposite, possibly due to influences like the Wasfaty platform (Raffaa et al., 2020). However, not all findings align; some studies report no significant income-adherence correlation (Amininasab et al., 2018; Jarab et al., 2023). Similarly, employment status negatively impacts adherence with unemployment being linked to lower adherence. Employment often negatively affects adherence, as busy work schedules compete with health routines (Okuboyejo, 2014; Raffaa et al., 2020). Yet, in some contexts, employment supports better adherence, as seen in studies from Iraq and Korea (Malih Radhi et al., 2023; Park et al., 2013), suggesting that these relationships can vary by region and health condition.

This study concludes that educational level and duration since diagnosis do not significantly impact medication adherence. Supporting this, (Jarab et al., 2023; Lin et al., 2020; Rezaei et al., 2022). However, other studies present a more nuanced view. For instance, many research found that higher educational levels enhance adherence due to better communication with healthcare providers and a deeper understanding of health information (Amininasab et al., 2018; Jarab et al., 2023; Jarrah et al., 2023). In contrast, studies like those by (Mohamad Yahaya et al., 2009; Raffaa et al., 2020) indicate that higher education does not improve adherence and sometimes lower educational levels correlate with better adherence due to a stronger trust in medical advice. Furthermore, while some data points to consistent adherence regardless of the duration since diagnosis, other findings suggest that newly

diagnosed patients may adhere more strictly to their medication regimes compared to those who have been managing the condition longer (Raffaa et al., 2020; Rezaei et al., 2022; Shojaee et al., 2023).

It is important to note that while patient-related factors do contribute to adherence, their effects are generally smaller compared to other factors that can be treated or changed. For instance, factors such as depression, practical and emotional support, income, and complexity of the regimen have been found to have more significant associations with adherence than patient demographics alone. These modifiable factors often have a greater impact on adherence and can be addressed through appropriate interventions and support strategies (DiMatteo, 2004b). For instance, age can correlate with adherence patterns, but this relationship varies across different age groups, with some older adults exhibiting better adherence while very old adults might face challenges due to comorbidities and cognitive decline (Leslie et al., 2019). Similarly, gender differences in adherence are typically minimal and often specific to particular patient populations, such as females being more adherent in pediatric settings (DiMatteo, 2004b). The mixed results regarding marital status and education further underscore the limited predictive power of these factors on adherence (Vik et al., 2004).

This study also found a negative impact of treatment complexity on medication adherence. Increased complexity in treatment regimens was associated with decreased adherence. This observation is consistent with findings in other health conditions. For example, (Tinoco et al., 2021) noted higher rates of non-adherence among coronary artery disease patients dealing with complex medication regimens, particularly those with concurrent conditions like diabetes mellitus and hypertension. Similarly, (Goldstein et al., 2017) reported a link between treatment complexity and reduced adherence among heart failure patients, especially those suffering from depressive symptoms, highlighting the compounded challenges faced by patients with mental health issues.

The study is notable for being the first to investigate the association of medication complexity on medication adherence among heart failure patients in Yemen, filling a crucial gap in research. It provides valuable insights into the challenges these patients face in adhering to their treatment regimens. However, it has limitations such as reliance on self-reported data due to the absence of electronic prescription systems in some hospitals, potentially affecting data accuracy. Additionally, the study's narrow geographic focus, cross-sectional design, and exclusion of important factors like adverse drug events and health insurance influence limit its generalizability. The use of convenience sampling and the small sample size introduce biases, while the exclusion of socio-demographic factors further limits the findings' robustness. Future research should employ more rigorous methods, explore a wider range of factors, and assess intervention effectiveness to improve medication adherence among heart failure patients.

CONCLUSION

This study provides clear evidence of how the complexity of medication regimen impacts adherence among heart failure patients in Yemen. Despite limitations like reliance on self-reported data, the findings strongly suggest that higher regimen complexity is linked to lower medication adherence. Additionally, socio-economic factors, particularly employment status and income levels, were found to significantly influence adherence to medication.

ACKNOWLEDGMENT

The author would like to thank the *Faculty of Pharmacy, Gadjah Mada University, Thawra Modern General Hospital, University of Science & Technology Hospital, Azal Hospital*, all research respondents, the clinical pharmacists, heart failure consultant doctors as well as all parties who have helped carry out this research in the hospitals.

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