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Research Article

Exploring the Impact of Medication Regimen Complexity on Health-Related Quality of Life in Patients with Multimorbidity

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Background. Patients with multiple chronic conditions often have complex medication regimes which negatively impact their health-related quality of life (HRQoL), and there is limited evidence on this topic, particularly from the resource limiting set-up. Hence, this study is aimed at assessing the impact of medication regimen complexity on HRQoL in patients with multiple chronic conditions at a university hospital in Ethiopia. *Method*. A cross-sectional study was conducted on adult patients who had at least two long-term diseases and were already receiving medical therapy for the relevant disorders. The validated 65-item Medication Regimen Complexity Index (MRCI) and the EuroQol-5-Dimensions-5-Levels (EQ-5D-5L) instruments were used to assess MRC and HRQoL, respectively. The Welch test for unequal variance and Fisher's exact test were used to assess the impact of different variables on HRQoL. *Results*. The study surveyed 416 participants, with a 98.3% response rate, the majority of whom were female ($n = 267$, 64.2%) and had two chronic conditions ($n = 215$, 51.7%). About 46.4% of patients were taking five or more medications, with a significantly higher proportion at the high regimen complexity level ($P = 0.001$). The average MRCI score was 9.73 ± 3.38, indicating a high level of complexity. Patients with high MRCI scores reported more problems in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. There was a negative correlation between the MRCI score and HRQoL as measured by the EQ-5D-Index ($r = -0.175$; $P < 0.001$) and the EuroQol-Visual Analogue Scale score ($r = -0.151$; $P = 0.002$). In addition, there was a statistically significant difference in the mean EQ-5D-Index ($P = 0.001$) and EQ-VAS scores ($P = 0.001$) across low, medium, and high MRCI levels. *Conclusion*. Medication regimen complexity was prevalent among patients with multimorbidity and was associated with a decrease in HRQoL. Therefore, interventions addressing medication-related issues should be a priority to improve the well-being of patients with multiple chronic conditions.

1. Introduction

Multimorbidity refers to the coexistence of two or more long-term diseases in an individual [1, 2]. Its prevalence has risen in recent years [1, 2], with evidence in developed countries indicating that more than 40% of the population has at least one chronic disease, with around 25% having more than one [2]. Interestingly, recent evidence suggests that high levels of multimorbidity are present in low- and middle-income countries (LMICs) [3]. The empirical studies available indicate that multimorbidity is particularly prevalent among elderly individuals, who are often considered the largest users of the healthcare system [4, 5]. The prevalence of multimorbidity can vary greatly depending on various factors, such as setting/location, data sources, and sample characteristics such as age, gender, and socioeconomic class [6–8]. For example, a study of primary care patients in the Netherlands found that the prevalence of three chronic conditions increased by 60% from 1985 to 2005, and the prevalence of four or more conditions

increased by 300% [8]. A more recent study in the United States found that 23% of participants had multimorbidity [9].

Multimorbidity has a variety of negative impacts on health and well-being. Studies have shown that individuals with multimorbidity have a shorter life expectancy [10], are more likely to be admitted to the hospital, have longer hospital stays [11], and tend to see a greater number of healthcare providers in a given year [11]. In addition, multimorbidity can greatly affect an individual's overall well-being, HRQoL, and ability to function [12]. Reduced physical functioning due to multimorbidity can also contribute to the development of depression and other mental health issues, further exacerbating the challenges of managing multiple chronic conditions [13]. Managing multiple medications, often prescribed for different chronic conditions, can be difficult for individuals with multimorbidity [14], leading to a complex medication regimen, poor adherence to treatment, and decreased HRQoL [5, 15, 16].

Medication regimen complexity (MRC) refers to the various aspects of a patient's medication regimen, including the number of medications prescribed, their dosage forms, dosing frequencies, and usage instructions [17]. Many patients with long-term diseases are often prescribed multiple medications [18, 19], making it difficult for them to maintain the same level of commitment to managing their conditions over time [20]. As a result, patients with multimorbidity can experience a complicated medication regimen and reduced HRQoL. However, not all patients experience the burden of treatment in the same way. Those with multimorbidity are at a higher risk of experiencing MRC-related treatment burden [21]. Factors such as a patient's skills, cognitive and intellectual abilities, and social support can also affect their perception of MRC [21, 22]. In addition, mental illness, low health literacy, and limited overlap in the management of multiple conditions can further contribute to a higher treatment burden [21, 23].

Multimorbidity is becoming increasingly common in Ethiopia. A study conducted in the current study area found that 44.6% of patients with cardiovascular diseases also had multimorbidity [24]. This high prevalence can have a significant impact on patients' treatment burden and HRQoL. This is particularly concerning in Ethiopia, where health literacy rates are low [25], and studies have shown that individuals who struggle to understand their therapy are more likely to experience MRC [23]. Despite this, the relationship between MRC and HRQoL in patients with multimorbidity is not well understood. This lack of understanding is likely due to difficulties in accessing and enrolling these patients in research studies. Further research on this topic could lead to the development of interventions that improve health outcomes for this population. To the best of the authors' knowledge, there is limited literature on MRC and HRQoL in patients with multimorbidity in LMICs, particularly in Ethiopia. Therefore, the aim of this study was to assess MRC and investigate its impact on different dimensions of HRQoL, including mobility, self-care, usual activity, pain/discomfort, and anxiety/depression, among patients with multimorbidity in Ethiopia.

2. Materials and Methods

2.1. Study Design, Setting, and Participants. A cross-sectional study was conducted at the University of Gondar Comprehensive Specialized Hospital (UOGCSH) located in Gondar Town, Ethiopia. UOGCSH is one of the oldest referral hospitals in the northwest region of the country and receives referrals from a large population, nearly 17 million people [26]. The study population comprised patients who were aged 18 years or older, had been diagnosed with at least two long-term diseases, and were already on medical treatment for at least six months. However, patients who were in emergency conditions or had conditions that would prevent the administration of the study instruments, such as severe mental illnesses or dementia, were excluded from the study. The data were collected when patients came for routine check-ups or medication refills at the outpatient department of the hospital between May 2021 and July 2021.

2.2. Sample Size Determination. The sample size required for the present study was calculated using the formula for estimating a single population proportion [27]. In this formula, "n" represents the initial sample size, "Z" represents the desired level of confidence (95% confidence interval), "p" represents the estimated proportion of patients with the desired outcome within the study area, and "d" represents the level of precision (5%). As the proportion of patients with the desired outcome was not known a priori, a conservative estimate of 50% was used. Based on these assumptions, an initial sample size of 384 was calculated. To account for the potential nonresponse, a 10% nonresponse rate was added to the sample size, resulting in a final sample size of 423.

$$n = Z^2 p \frac{(1-p)}{d^2}. \tag{1}$$

Based on $Z = 1.96$, $P = 0.5$, and $d = 0.05$, $n = 384$.

$$N = n + \text{non} - \text{response}. \tag{2}$$

$N = 423$.

2.3. Data Collection Instruments and Procedure. To achieve the objectives of the present study, two validated instruments were utilized. The first instrument is the Medication Regimen Complexity Index (MRCI), which is a commonly used tool for evaluating the complexity of a medication regimen [28]. It is based on 65 items that take into consideration the dosage form, dosing frequency, and any additional instructions. For each patient, the MRCI score was determined by evaluating three different aspects of their medication regimen: dosage formulation, dosing frequency, and additional administration instructions. Each tablet or capsule dosage form that was administered once per day was given a weight of 1, and other dosage formulations and dosing frequencies were assigned increasing weights based on their difficulty of administration. Additional

administration instructions, such as "break or crush" or "take with food," were also taken into account and given increasing weight based on their level of difficulty. The MRCI score accounted for all prescription and over-the-counter medications for each patient and was interpreted as low MRC (≤4), medium MRC (5–8), or high MRC (>8) based on the final score [29–31]. The MRCI tool was translated and validated in Amharic language in a subset of multimorbid patients (diabetes patients) in Ethiopia [31].

The second instrument utilized in the study is the EuroQol-5 Dimension (EQ-5D) instrument, a widely used generic and multiattribute tool that is employed to evaluate health status and inform decisions on resource allocation in healthcare [32]. With over three decades of experience and translations in over 170 languages [33], it is the most widely used measure of HRQoL. The EQ-5D-5L, a descriptive system of the EQ-5D, comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels, ranging from no problems to extreme problems, resulting in 3125 ($=5^5$) possible value sets that range from full health (11111) to extreme problems in all dimensions (55555). The EQ-5D-Index for Ethiopia was derived using the EQ-5D-5L value set [34]. In addition, the EQ-5D-5L includes the EuroQol-Visual Analogue Scale (EQ-VAS), which measures the patient's self-reported health on a vertical visual analogue scale, with endpoints labeled 100 "The best health you can imagine" and 0 "The worst health you can imagine." The EQ-VAS is a quantitative measure of health outcome that reflects the patient's personal judgment.

Data on the demographic and clinical characteristics of the patients, including age, gender, current diagnosis, number of multimorbidity, current medications, duration of illness, dosage formulation, frequency, route of administration, and other relevant clinical information, were collected by thoroughly reviewing the patients' medical records. The patient's HRQoL data were obtained through face-to-face interviews conducted by trained data collectors.

2.4. Outcome Measures. The outcome measures of this study include the MRCI score, the EuroQol-5 Dimension Index, the EQ-5D Visual Analogue Scale (EQ-VAS) score, and the EQ-5D dimensions.

2.5. Data Analysis. The study utilized descriptive statistics to summarize continuous and categorical variables, including the mean with standard deviation for continuous variables and frequency with proportion for categorical variables. The MRC score was categorized into three levels, low (score ≤4), medium (score 5–8), and high (score>8), for the purpose of comparing mean differences in the EQ-5D-Index and EQ-VAS score. The mean EQ-VAS score was calculated by averaging individual patient ratings on a scale of 0–100. To determine the significance of differences between the MRC categories, the study employed Welch's ANOVA test for unequal variance, followed by Games-Howell post hoc analysis to identify the specific groups responsible for any significant differences. For correlation analysis, the distribution of variables was examined for normality and linear relationship. All analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 26.0 software, with a 95% confidence interval and 5% precision.

2.6. Ethics Approval and Consent to Participate. Ethical clearance for the study was granted by the Ethical Review Committee of School of Pharmacy, University of Gondar. Prior to conducting the interviews, participants were provided with information regarding the background and purpose of the study. Participants who were able to read and write provided their informed consent by signing the consent form themselves. For those who were unable to read or write, the interviewer assisted them in providing their consent through thumbprinting. All information obtained through the interviews was kept confidential, and participant identifiers were not used.

3. Results

3.1. Sociodemographic and Clinical Characteristics. A total of 416 participants were included in the study, with a response rate of 98.3%. The participants' ages ranged from 18 to 92 years, with a mean age of 56.12 ± 13.75 years. The majority of the participants, 273 (65.6%), live in Gondar town. A significant proportion of the participants had either no formal education ($n = 117$, 28.1%) or primary school education ($n = 134$, 32.2%). At the time of the study, the majority of patients had been diagnosed with two long-term diseases 215 (51.7%) and they had a duration of illness of less than five years (n=240, 57.7%). In addition, nearly half of the patients, 193 (46.4%), were prescribed five or more drugs during the study period, with a statistically significant difference across the levels of MRC ($P < 0.001$). Overall, more than half of the patients, 238 (57.2%), had a high level of MRC (Table 1).

3.2. Long-Term Diseases and Their Treatment. According to the International Classification of Diseases (ICD), the majority of patients ($n = 388$, 93.3%) were diagnosed with circulatory system diseases. This was followed by endocrine system disease ($n = 220$, 52.9%) and respiratory system disease ($n = 57$, 13.7%). The complete list of chronic diseases and their associated medications are available in the supplement (Supplementary file). All patients diagnosed with endocrine ($n = 220$, 100%) and respiratory system diseases ($n = 57$, 100%), as well as almost all patients diagnosed with circulatory system diseases ($n = 379$, 97.7%), had either medium or high levels of MRC (Figure 1). The most commonly prescribed drug classes were cardiovascular ($n = 395$, 95.0%), followed by endocrine ($n = 210$, 50.5%) and analgesics and antipyretics ($n = 141$, 33.9%). Similarly, patients who were prescribed endocrine and cardiovascular drugs ($n = 386$, 97.7%) had either medium or high level of medication regimen complexity (Figure 2).

3.3. Medication Regimen Complexity and Health-Related Quality of Life. The overall mean MRCI score was 9.73 ± 3.38, indicating that the overall complexity of the medication

Table 1: Sociodemographic and clinical characteristics stratified by the level of medication regimen complexity.

Variable	Low complexity	Medium complexity	High complexity	*P* value
Sex *n* (%)				0.087
Female	5 (55.6%)	119 (70.4%)	143 (60.1%)	
Age, years (mean ± SD)	59.2 ± 13	55.8 ± 14	56.2 ± 14	
Educational status *n* (%)				0.132
No formal education	7 (77.8%)	48 (28.4%)	62 (26.1%)	
Primary school (Grades 1–8)	1 (11.2%)	56 (33.1%)	77 (32.4%)	
Secondary school (Grades 9-10)	1 (11.2%)	36 (21.3%)	50 (21.0%)	
College and above	0 (0.0%)	29 (17.2%)	49 (20.6%)	
Residence *n* (%)				0.901
Out of Gondar town	3 (33.3%)	56 (33.1%)	84 (35.3%)	
Gondar town	6 (66.7%)	113 (66.9%)	154 (64.7%)	
Payment status				0.229
Free of charge	4 (44.4%)	117 (69.2%)	153 (64.3%)	
Other*	5 (55.6%)	52 (30.8%)	85 (35.7%)	
Duration of illness (in years)				0.878
Less than five	5 (55.6%)	100 (59.2%)	135 (56.7%)	
Five to ten	3 (33.3%)	59 (34.9%)	86 (36.1%)	
Above ten	1 (11.2%)	10 (5.9%)	17 (7.1%)	
Number of drugs per patient				<0.001
Less than five	9 (100%)	125 (74.0%)	89 (37.4%)	
Five and above	0 (0.0%)	44 (26.0%)	149 (62.6%)	
Number of long-term conditions				0.187
Two	6 (66.7%)	98 (58.0%)	111 (46.6%)	
Three	3 (33.3%)	56 (33.1%)	99 (41.6%)	
Four and above	0 (0.0%)	15 (8.9%)	28 (11.8%)	

*Paid in full by the patient/family or by the employer or paid in part by the employer; SD: standard deviation. *P* values are generated from either chi-squared or Fisher's exact tests.

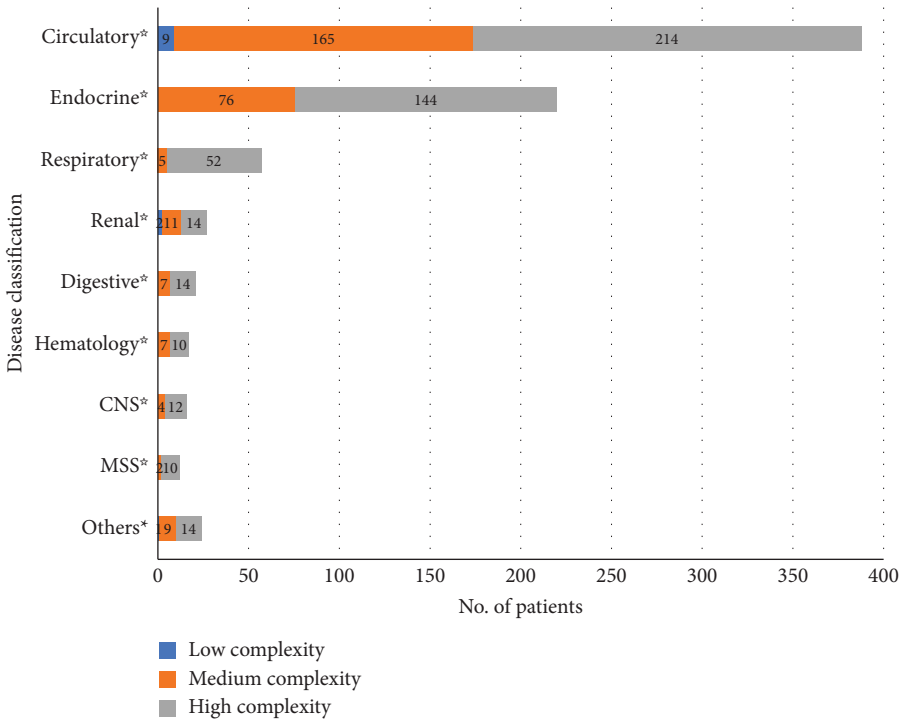

Figure 1: Long-term diseases stratified by the level of medication regimen complexity ($n = 416$). *Diseases of the eye and adnexa, diseases of the skin and subcutaneous tissue, neoplasms, mental and behavioral disorders, and nutritional and electrolyte disorders; ☆disease of the indicated systems; CNS: central nervous system; MSS: musculoskeletal system.

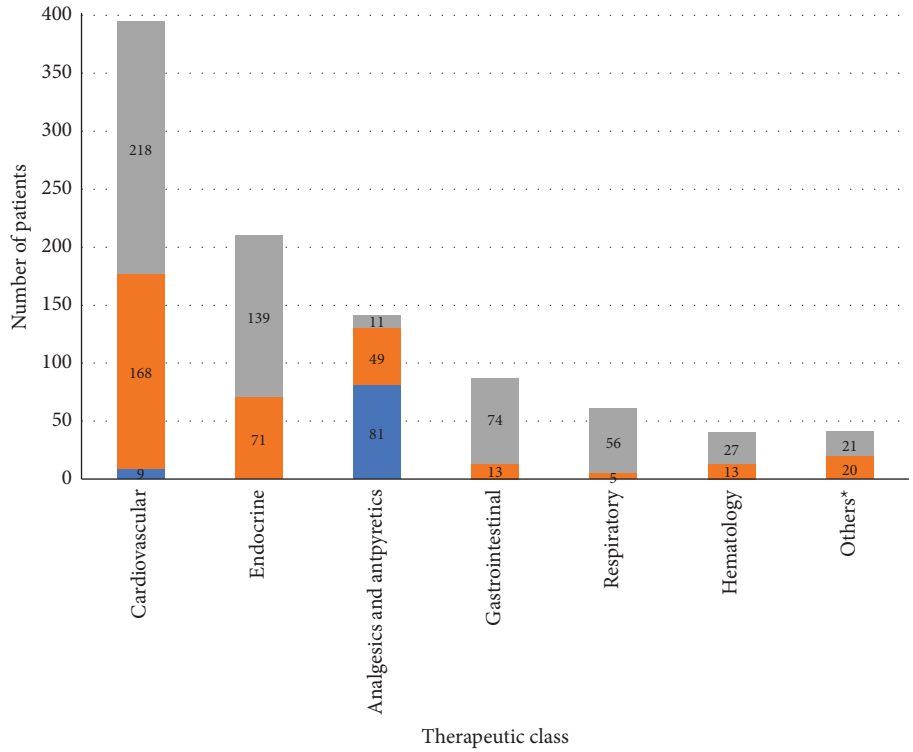

FIGURE 2: Prescribed medications stratified by the level of medication regimen complexity ($n = 975$). *Antimicrobial agents, drugs acting on the central nervous and musculoskeletal systems, and supplements (vitamins and minerals).

regimen was high. Pain/discomfort and anxiety/depression problems were highly prevalent in these patients, with only 7.5% and 9.6% reporting no problems in these domains, respectively. Among patients who reported having at least some problems with pain/discomfort and anxiety/depression on the EQ-5D-5L, the majority had level 2 and level 3 problems. The majority of patients also reported problems with self-care (52.6%) and usual activities (72.8%), while most patients (53.8%) reported no mobility problems (Figure 3).

Overall, patients with high regimen complexity reported "severe" and "unable/extreme" levels more frequently than the other groups. There was a statistically significant weak negative correlation between the MRCI score and the mean EQ-5D-5L index ($r = -0.175$; $P < 0.001$), as well as between the MRCI score and the EQ-VAS score ($r = -0.151$; $P = 0.002$). There was also a statistically significant difference in the mean EQ-5D-5L index ($P = 0.001$) and EQ-VAS score ($P = 0.001$) across MRC levels (Table 2).

4. Discussion

This study looked at the relationship between MRC and HRQoL in patients with multiple long-term diseases in a low-income environment. Complexity in medication regimens is an increasingly recognized concept that can have a negative impact on patient outcomes. The study used the MRCI to evaluate regimen complexity, and the authors note that this is the first study to connect MRCI and HRQoL in this study population. Previous research has found that polypharmacy, or the use of multiple medications, is associated with HRQoL [35–37]. However, the authors note that medication count alone is not an adequate measure of complexity, as it does not take into account other factors such as dosage forms, dosing frequency, and usage instructions [28, 38]. Patients may, for example, use tablets, creams, or patches, each with its own set of dosing instructions [38]. In addition, the medication count may not include over-the-counter (OTC) medications, which can also contribute to complexity in some individuals [28]. The study highlights the importance of considering complexity in medication regimens when evaluating patients with multiple chronic diseases and the negative impact it can have on their HRQoL.

The present study assessed MRC using a validated measuring instrument called the MRCI, which is a 65-item instrument that can be computed using data from the patient's medical record. The level of complexity is determined by factors such as the number of medications, dosage frequency, additional instructions, and dosage forms [28]. The MRCI instrument has various potential clinical applications for patients with multimorbidity [38], but more research is needed. One potential clinical intervention is simplifying patients' regimens, such as switching from a twice-daily drug regimen to a once-daily drug regimen [38]. However, it is unclear if lowering regimen complexity improves clinically important health outcomes, such as adherence, readmission, and hospitalization [38]. In addition, the MRCI does not take into account the financial burden associated with drugs, which is a significant concern for patients with

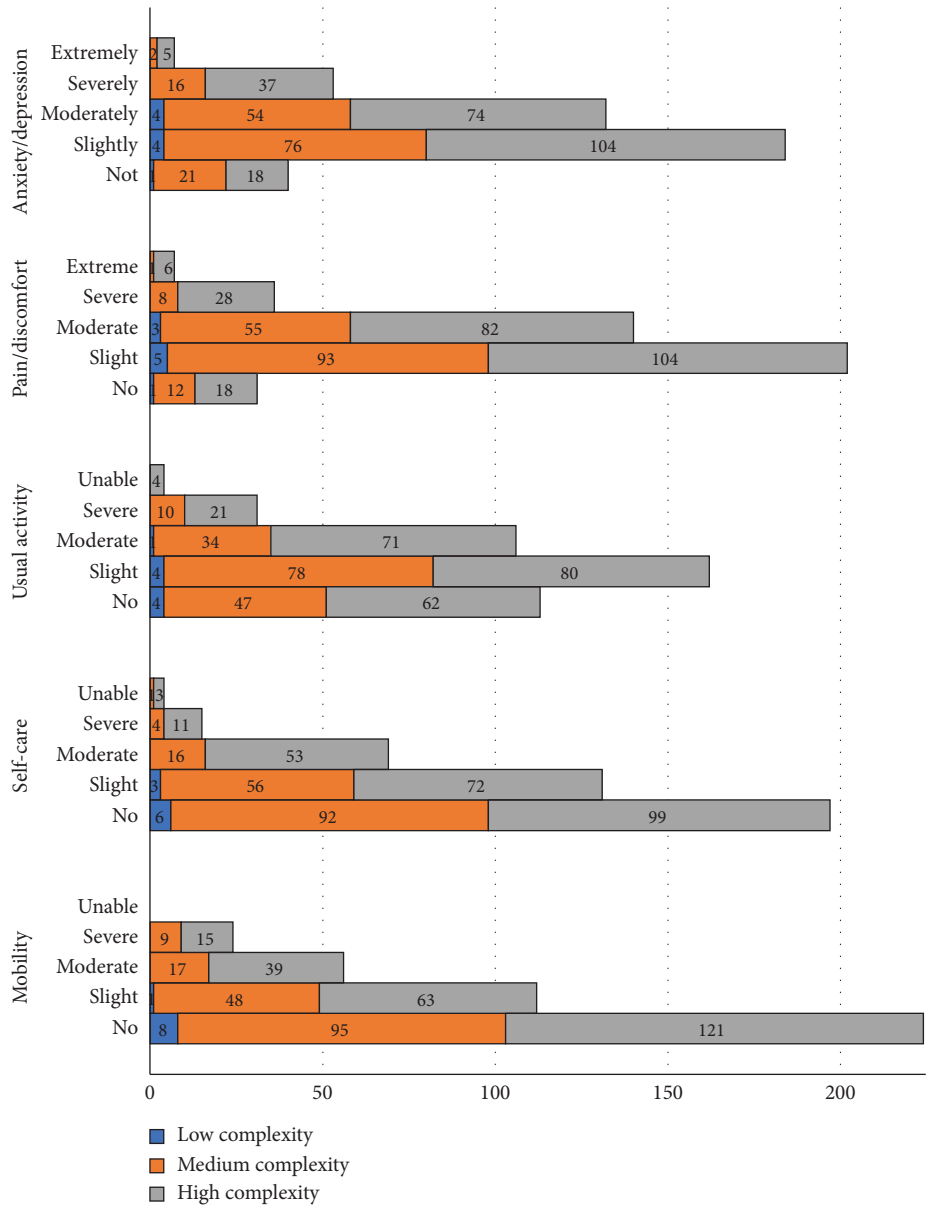

Figure 3: EQ-5D dimensions stratified by the level of medication regimen complexity ($n = 416$).

multimorbidity and limited income, particularly in low-income settings [13].

The study findings indicate that the majority (57.2%) of patients with multimorbidity had a high treatment regimen complexity. The mean MRCI score, which is a measure of complexity, was considerably higher than that reported in a previous study from Spain (9.7 versus 6.9) [39]. This difference in regimen complexity can be explained in part by the higher number of long-term conditions (2 or more versus 1) and the average number of prescribed medications (5 versus 3) in the current study population. Other studies from Australia [38] and the World Health Organization [40] also suggest that patients with multimorbidity tend to have more complex management regimens and polypharmacy and that the complexity of a medication regimen is usually correlated with the number of prescriptions.

In this study, the complexity of patients' treatment regimens was evaluated using the MRCI. The scores ranged from 2 to 19, with 2.2% of patients' regimens classified as low complexity, 40.6% as medium complexity, and 57.2% as high complexity. The most important factor in determining complexity was the frequency of dosing, followed by the dosage form and additional instructions. Factors such as the number of drugs in the regimen, the number of doses per day, drug-drug, or drug-food interactions also contributed to complexity. The study found that patients with multiple chronic diseases, particularly those related to the circulatory, endocrine, and respiratory systems, had a medium to high level of regimen complexity. This highlights the importance of carefully reviewing and documenting medication use in these patients, as certain prescriptions for those conditions such as insulin, salbutamol inhaler, beclomethasone inhaler,

Table 2: EQ-5D-5L index and EQ-VAS score stratified by the level of medication regimen complexity.

MRC category	n	EQ-5D-5L index					EQ-VAS score				
		Mean ± SD	Welch F	P value	Games-Howell posthoc analysis: P value (95% CI)		Mean ± SD	Welch F	P value	Games-Howell posthoc analysis: P value (95% CI)	
					Low complexity	Medium complexity				Low complexity	Medium complexity
Low complexity	09	0.85 ± 0.08	8.71	0.001			81.67 ± 6.61	7.88	0.002		
Medium complexity	169	0.79 ± 0.14			0.229 (−0.03–0.14)		79.24 ± 10.87			0.575 (−3.99–8.85)	
High complexity	238	0.74 ± 0.15			0.003 (0.01–0.09)	0.017 (0.18–0.28)	75.30 ± 11.85			0.002 (1.29–6.63)	0.05 (−0.01–12.78)

CI: confidence interval; EQ-5D-5L: euroqol-five dimensions five-levels; EQ-VAS: euroqol-visual analogue scale MRC: medication regimen complexity; SD: standard deviation.

and propylthiouracil may significantly contribute to the overall complexity due to the increased frequency of medication administration, complicated dosage forms, and special instructions.

The current study also found a significant negative relationship between treatment regimen complexity and HRQoL, which is consistent with previous research that has used the MRCI as a measure of complexity [39]. This association suggests that as the complexity of treatment regimens increases, patients report lower HRQoL. This was reflected in the decrease in the mean EQ-5D-Index and EQ-VAS scores as treatment regimen complexity increased. Specifically, patients with high treatment regimen complexity reported more problems in all dimensions of the EQ-5D, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Overall, these findings highlight the importance of addressing medication-related issues in order to improve HRQoL for patients with multimorbidity.

This study is the first to investigate the relationship between treatment regimen complexity and HRQoL in Ethiopian patients with multiple chronic conditions. The study employed validated instruments and had a sufficient sample size, but it is limited by being conducted in a single setting and basing the MRCI on what was documented in the patient's medical records, which may have resulted in a weak correlation. Therefore, the findings should be interpreted with these limitations in mind.

5. Conclusion

This study found that MRC is prevalent among patients with multiple chronic conditions, with 57.2% of patients having high complexity. This complexity was found to be significantly associated with worse HRQoL. Patients with high complexity reported more problems in areas such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Therefore, chronic disease management programs should focus on assessing patients' medications and implementing strategies to simplify regimens, such as reducing dosing frequencies. Future studies are needed to determine the causal association between regimen complexity and HRQoL.

Data Availability

The materials and data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

BMG and ATK conceived the study, drafted and revised the study proposal, prepared data collection instruments, supervised data collection, performed data analysis and interpretation, drafted the manuscript, revised, and approved submission of the manuscript.

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Supplementary Materials

The supplementary file contains detailed tables presenting comprehensive information related to the long-term conditions investigated in this study. These tables outline the specific conditions studied and provide a comprehensive list of medications prescribed for the conditions. Furthermore, the supplementary file also includes an analysis of the comorbidity pattern observed among the study participants. (*Supplementary Materials*)

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