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ORIGINAL RESEARCH

The Association Between Medication Adherence and Health-Related Quality of Life in Patients with COPD: A Cross-Sectional Study

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Purpose: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition with debilitating manifestations that adversely affect patients' health-related quality of life (HRQoL). The clinical course is complicated by patients' low medication adherence level. Low adherence and poor HRQoL are linked to unfavorable disease outcomes. Although many factors affect adherence and HRQoL in COPD, the impact of adherence on HRQoL remain controversial. This study aimed to measure medication adherence and its impact on HRQoL in patients with COPD.

Patients and Methods: This cross-sectional observational study included patients with COPD from two health centers in Riyadh, Saudi Arabia. Patients were identified using the medical database and only those fulfilling the GOLD 2020 criteria for COPD diagnosis were recruited. Data were collected via phone interviews and included sociodemographic information, the level of medication adherence assessed using the 5-item Medication Adherence Report Scale (MARS-5), and the HRQoL measured using the St. George Respiratory Questionnaire for COPD (SGRQ-C). Simple and multiple-regression analysis was used to study the factors affecting both parameters and the relation between adherence and HRQoL.

Results: The mean MARS-5 score was 21.17± 4.8 (mean ± SD) with only 56.4% of patients with COPD reporting high adherence to their medications. The average total SGRQ score was 51.35 ± 23.82 indicating low HRQoL. Using multiple-regression analysis, comorbidity and intermediate disease duration were associated with lower adherence, while older age, female gender, polypharmacy, and concomitant hypertension predicted lower HRQoL. Moreover, higher adherence to medications was associated with higher overall HRQoL in patients with COPD.

Conclusion: Patients with COPD have low medication adherence and low HRQoL. Several patient-, disease-, and therapy-related factors were shown to affect both outcomes; however, higher adherence to medication per se was associated with higher HRQoL in patients with COPD.

Keywords: pulmonary disease, chronic obstructive, MARS-5, SGRQ, medication adherence, quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogenous chronic lung condition characterized by progressive airflow limitation that is not fully reversible.[1,2] It lies among the top three causes of death worldwide with an estimated global prevalence at 10.3%.[2,3] In Saudi Arabia, the prevalence of COPD was reported to be between 2.4% and 4.2%.[4,5] However, using the Global Burden of Disease (GBD) 2019 dataset, Alqahtani reported an alarming increase of 49% in

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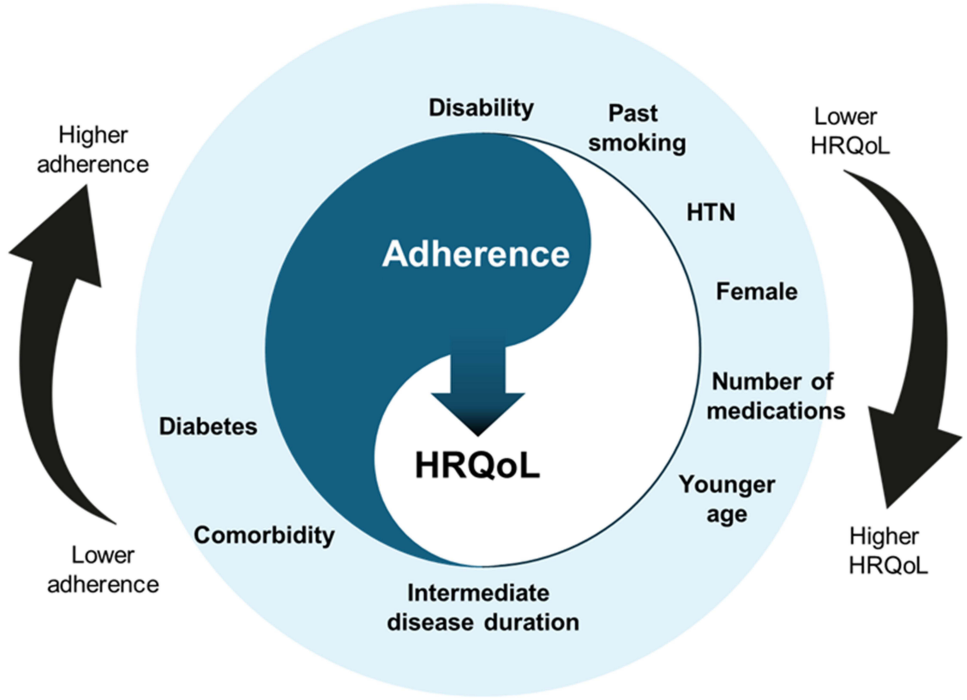
Graphical Abstract



age-standardized COPD prevalence in Saudi Arabia from 1990 to 2019.[6] This change along with the expansion in aging population and the increase in tobacco use among women means that COPD will soon become a pressing health issue.[7,8]

Despite its irreversible and progressive nature, COPD is both preventable and treatable.[1] Proper management has been shown to relieve patient's symptoms,[9] reduce exacerbations and hospitalizations,[10,11] improve patient's overall health status and reduce the risk of death.[10,12] Successful management relies heavily on patients' adherence to their therapeutic plan.[13] Unfortunately, adherence to long-term therapy in chronic diseases is generally low averaging around 50%,[14] and was reported to be even lower for pulmonary disease.[15] The rate of adherence in COPD varies greatly from country to country with poor adherence being reported in 46% to 80% of patients with COPD.[12,16–20]

The growing burden of chronic diseases caused a shift in disease management outlook with more emphasis on improving patients' health-related quality of life (HRQoL). HRQoL describes the patient's own perceptions of the impact of disease and treatment on their general well-being and day-to-day physical, psychological and social activities.[21,22] The presence of chronic diseases worsens the HRQoL of patients,[23,24] and COPD is among those with the greatest negative impact on patients' HRQoL.[25–27] Poor HRQoL and low medication adherence in COPD have both been linked to increased COPD exacerbations,[10,28] greater risk of hospital readmission,[10,29,30] and higher mortality.[10,28,31–33]

Several factors influence medication adherence and HRQoL in COPD patients. Identifying these factors can help guide healthcare efforts towards improving both. Moreover, adherence itself has been reported to affect patients' HRQoL,[12,34–36] however, the impact of adherence on HRQoL remains controversial.[21] The aim of the current study was to (1) assess the level of medication adherence and HRQoL in patients with COPD, (2) identify the factors affecting them, and (3) examine the relationship between medication adherence and HRQoL in patients with COPD.

Materials and Methods

Patient Recruitment

This is a cross-sectional study conducted between September 2020 and June 2022. Adult patients with COPD were recruited from two hospitals, King Saud University Medical City (KSUMC) and King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia. Patients were initially identified by reviewing the medical database at both hospitals, then only those fulfilling the GOLD 2020 criteria for COPD diagnosis were included, namely, the demonstration of persistent airflow limitation using a post-bronchodilator FEV1/FVC < 0.70 in a patient with typical symptoms such as dyspnea, sputum production and shortness of breath.[37] Inclusion criteria included (1) an established diagnosis of COPD for at least 1 year, (2) the prescription of at least one COPD maintenance medication within the 6 months before joining the study. Maintenance medications included: inhaled corticosteroids (ICSs), long-acting beta2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) alone or in combination. Exclusion criteria were limited to inability to understand the questionnaires. Patients eligible for inclusion were contacted by members of the research team and data was collected via phone interviews after acquiring patients' verbal consent for participation in the study.

Sample size was calculated using the equation n=Z2pq/d2, where (Z) was set at 1.96 which corresponds to a 95% of confidence interval, (p) is the proportion of adherence among COPD (36%), (q) is 1-p and with a precision of ± 5% (d). The estimated sample size was found to be 355. Assuming that non-response rate would be 20%, the total number of participants required would be 424.

Data Collection Tools

Three data sets were collected, (i) sociodemographic characteristics such as age, gender, and educational level along with medication and disease-related information such as disease duration, number of regular medications, comorbidities, and smoking habits. (ii) the HRQoL of patients with COPD using the St. George Respiratory Questionnaire for COPD (SGRC-C),[38] and (iii) the level of medication adherence using the Medication Adherence Report Scale-5 (MARS-5, ©Professor Robert Horne).[39]

HRQoL

HRQoL was measured using the SGRQ-C questionnaire. This is a disease-specific validated questionnaire developed to measure quality of life and health impairment in COPD patients.[38] It is a shorter version of the original SGRQ questionnaire.[40] A validated Arabic translation of the SGRQ-C is available and permission to use both English and Arabic versions of the SGRQ-C was obtained from the original authors. The questionnaire is composed of 40 items divided between two parts, the first assesses the patient's perception of their symptoms constituting the symptom component of the questionnaire. While the second assesses disturbances to daily physical activity and psycho-social function, representing the activity and impact components, respectively.[40,41] Each item has a specific weight. Scores were calculated following the instructions provided by the original authors. Briefly, component scores were calculated by summing up item weights of positive responses within each component. While the total score is generated by summing the item weights of all positive responses. SGRQ-C scores were then converted to SGRQ scores according to the original authors' instructions. Scores are expressed as percentages of overall impairment with higher scores indicating lower HRQoL.[41] It is worth noting that, in the current study, one item was missing from the activity component which according to the developers can tolerate a maximum of three missing items. The data was managed according to guidelines provided by original authors in their manual (https://www.sgul.ac.uk/research/research-operations/research-administration/st-georges-respiratory-questionnaire/docs/sgrq-c-manual-april-2012.pdf) for handling missing items.

Medication Adherence

Medication adherence was measured using the MARS-5 scale. This is a generic self-reported measure of adherence that evaluates intentional and unintentional non-adherent behavior. It consists of 5 questions scored on a 5-point Likert scale (always = 1 to never = 5).[39] The first statement addresses non-intentional nonadherence, whereas the remaining 4

statements address intentional nonadherence behavior. Scores range from 5 to 25, with higher scores indicating higher self-reported adherence. The scale is valid and shows good reliability (Cronbach's alpha ranged from 0.67 to 0.89).[39]

MARS-5 Translation

Permission for use and translation of the English version of MARS-5 was obtained from its developers (©Professor Robert Horne). Forward translation of the scale into Arabic language was done by four bilingual authors independently. The translations were combined into one single Arabic translation that was checked linguistically by an Arabic language expert. Backtranslation was done by a bilingual independent reviewer. Both the Arabic translation and backtranslation were sent to the developers (©Professor Robert Horne) for review and authorization. Approval and permission to use the Arabic translation was obtained from the original author. The Arabic translation was piloted on a group of adult patients visiting the primary care clinics at KSUMC with similar demographic characteristics to the intended study population (n=20) to check for consistency, validity, and reliability.

Ethical Considerations

The study was approved by King Saud University (KSU) Institutional Review Board (IRB) with ethical approval no. (E-20-5200) as well as the IRB of Second Health Cluster, King Fahad Medical City with ethical approval no. (E-20-706E). Due to the COVID-19 lockdown and precautionary measures that were implemented at the time of study conduction, initial IRB approval was amended to allow for verbal consent acquisition and data collection via phone interviews. The amendment was approved by KSU IRB (Ref. No. 20/0893/IRB). Patients eligible for inclusion were contacted by phone by members of the research team and the study was explained. An informed verbal consent was obtained from those who agreed to participate in the study and was documented electronically on the data collection sheet. All data collected was kept confidential. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using SPSS 29.0 version statistical software. Mean and standard deviation were used to describe quantitative variables, while frequencies were used for categorical variables. The impact of each independent variable on the level of medication adherence (MARS-5) and HRQoL (SGRQ) was explored using simple linear regression. For HRQoL, the analysis was run on the whole sample (n=424), while for medication adherence it was run on the subgroup of patients that were taking regular medication (n=376) since adherence cannot be accurately assessed in those not receiving regular medication. To delineate the combined effects of the various variables on each outcome variable, ie MARS-5 and SGRQ scores, multiple linear regression (MLR) was conducted. Predictors included in the MLR models are the independent variables that showed significant impact ($p \leq 0.05$) on each of the outcome variables or had a p-value ≤ 0.1. When MARS-5 score was included as one of the predictors in the multiple linear regression model, the analysis was run on the group of patients receiving regular medications (n=376). B coefficients and 95% confidence intervals (CI) were used to report the statistical significance and precision of results. A p-value of <0.05 was considered significance.

Results

Validation of the Arabic Translation of MARS-5

Face validity was checked by conducting mini interviews with adult patients visiting the KSUMC primary care clinic that shared similar sociodemographic characteristics to the study population. The piloting showed questionnaire items to be clear and understandable with no language ambiguities. Internal consistency was checked, and the Arabic translation was found reliable with Cronbach's alpha = 0.89. Test–retest reliability of MARS-5 was evaluated using a two-way mixed-effects model.[42] This was done by administering the scale twice to the same group of participants (n = 31) with a 2-week interval. The intraclass correlation coefficient (ICC) was 0.884 (95% CI: 0.752, 0.945), indicating excellent test–retest reliability.

Sociodemographic, Medication, and Disease-Related Characteristics of Study Population

A total of 424 patients with COPD were included in the study with a mean age of (65.3 ±13.8, m±SD) years. The majority were males (65%) and have received formal education up to school level (70.3%). Almost a third of enrolled patients were past smokers, while current smokers constituted (30.2%). The remainder were non-smokers with only 8% being passive smokers (Table 1). Gender differences in smoking status were noted (Supplementary Figure 1). The

Table 1 Sociodemographic, Medication, and Disease-Related Characteristics of COPD Patients (n=424)

Variable	N (%)
Age (mean ±SD)	65.3 (±13.8)
Gender	
Male	276 (65.1)
Female	148 (34.9)
Educational level	
School education (intermediate or high)	298 (70.3)
University education or higher	126 (29.7)
Smoking status	
Current smoker	128 (30.2)
Past smoker	136 (32.1)
Passive smoker	34 (8.0)
Non-smoker	126 (29.7)
Presence of comorbid condition/s	
Yes	338 (79.7)
No	86 (20.3)
Types of comorbid conditions	
Diabetes	237 (55.9)
Hypertension	261 (61.6)
Cardiovascular disease	163 (38.4)
Presence of disability[a]	
Yes	86 (20.3)
No	338 (79.7)
Patients receiving regular medications	
Yes	376 (88.7)
No	48 (11.3)
Number of medications (mean ±SD)	2.4 (±1.2)
Disease duration	
≤ 2 years	70 (16.5)
3 years	59 (13.9)
4 years	75 (17.7)
5 years	72 (17)
≥ 6 years	148 (34.9)

Notes: [a]Disability was defined as any perceived limitation to mobility by the patient him/herself.

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majority of male patients with COPD were either current (44.6%) or past smokers (42.4%) while most female patients with COPD were non-smokers (64.9%). Passive smokers constituted 2.2% and 18.2% of male and female patients with COPD, respectively.

A considerable number of patients (79.7%) reported having a comorbid condition. Approximately third (34.9%) have had COPD for 6 years or more, with the majority (88.7%) receiving regular medications. Most patients reported no disability (79.7%) (Table 1).

Medication Adherence in Patients with COPD

Level of Medication Adherence

Given that medication adherence cannot be accurately assessed in patients not receiving regular medications (n=48), the level of medication adherence was analyzed only in those reporting regular use (n=376). The average total MARS-5 score was 21.57 ± 4.34 (m ± SD) reflecting the overall level of medication adherence (Table 2). Although the MARS-5

Table 2 The Level of Medication Adherence in COPD Patients Taking Their Medication Regularly and Its Correlation[a] with Sociodemographic, Medication, and Disease-Related Characteristics (n=376)[b]

Variable	Descriptive Statistics		Total MARS-5[c] Score			
	N	Mean ± SD *OR* (%)	Mean ± SD	R^2	B Coefficient (95% CI)	*p*-value
Age (m+SD)	376	65.57 ± 13.88	21.57 ± 4.34	0.011	0.032 (0.001, 0.064)	0.046
Gender (%)						
Female	132	35.1%	21.42 ± 4.36	0.001	−0.231 (−1.153, 0.692)	0.623
Male	244	64.9%	21.65 ± 4.33		Ref	
Education level (%)						
University education and higher	109	29%	21.18 ± 4.54	0.003	−0.539 (−1.508, 0.430)	0.275
School education	267	71%	21.72 ± 4.25		Ref	
Smoking status (%)						
Current smoker	105	27.9%	20.87 ± 4.93	0.027	−0.546 (−1.688, 0.597)	0.348
Past smoker	125	33.2%	22.52 ± 3.26		1.108 (0.014, 2.201)	0.047
Passive smoker	32	8.5%	20.69 ± 5.68		−0.725 (−2.414, 0.965)	0.399
Non-smoker	114	30.3%	21.41 ± 4.22		Ref	
Presence of comorbid condition/s (%)						
Yes	308	81.9%	21.38 ± 4.44	0.009	−1.050 (−2.189, 0.089)	0.071
No	68	18.1%	22.43 ± 3.76		Ref	
Presence of diabetes (%)						
Yes	213	56.6%	21.08 ± 4.69	0.016	−1.112 (−1.993, −0.230)	0.014
No	163	43.4%	22.20 ± 3.75		Ref	
Presence of hypertension (%)						
Yes	235	62.5%	21.43 ± 4.54	0.002	−0.365 (−1.273, 0.544)	0.431
No	141	37.5%	21.79 ± 3.98		Ref	

(*Continued*)

Table 2 (Continued).

Variable	Descriptive Statistics		Total MARS-5[c] Score			
	N	Mean ± SD *OR* (%)	Mean ± SD	R^2	B Coefficient (95% CI)	*p*-value
Presence of cardiovascular disease (%)						
Yes	145	38.6%	21.84 ± 4.2	0.003	0.447 (−0.456, 1.351)	0.331
No	231	61.4%	21.39 ± 4.42		Ref	
Presence of disability (%)						
Yes	78	20.7%	23.04 ± 3.31	0.030	1.857 (0.788, 2.927)	<0.001
No	298	79.3%	21.18 ± 4.5		Ref	
Disease duration (%)						
≤ 2 years	63	16.8%	21.86 ± 4.07	0.034	−0.624 (−1.913, 0.665)	0.342
3 years	54	14.4%	21.00 ± 4.98		−1.481 (−2.841, −0.121)	0.033
4 years	65	17.3%	21.00 ± 4.63		−1.481 (−2.756, −0.206)	0.023
5 years	61	16.2%	20.38 ± 4.42		−2.104 (−3.407, −0.801)	0.002
≥ 6 years	133	35.4%	22.48 ± 3.82		Ref	
Number of medications (m±SD)	376	2.44 ± 1.18	21.57 ± 4.34	0.014	0.441 (0.068, 0.813)	0.020

Notes: [a]The relationship between MARS-5 (the outcome variable) and each independent variable was assessed using simple linear regression. A *p*-value of < 0.05 was considered significant. [b] The group of COPD patients that are not on regular medications (n=48) were excluded from all analysis involving the level of medication adherence, since it cannot be accurately assessed under such circumstances. [c] Medication Adherence Report Scale-5 (MARS-5) is a 5-item self-administered questionnaire that measures medication adherence. Each item is scored on a 5-point Likert scale (never = 5, rarely = 4, sometimes = 3, often = 2, and always =1). Total score is calculated by summing the score of the 5 items. The higher the score the higher the adherence.

scale was designed to be used as a continuous scale, its results were dichotomized into "high" and "low" adherence to enable comparison with other investigators and to identify the extent of low adherence in our population. A cutoff was set at the median value which has been previously used by Chan et al to dichotomize the scale.[39] The median MARS-5 score in the current study was 23, and as such patients with a total MARS-5 score ≥ 23 were considered to have "high" adherence, and those with a total MARS-5 score <23 were considered to have "low" adherence. Using this cutoff, high adherence was reported by 56.4% of patients with COPD while 43.6% reported "low adherence".

Factors Affecting Medication Adherence

Using simple linear regression, several factors were identified to be significantly associated with high adherence including, older age, past smoking, and the presence of disability (Table 2). On the other hand, patients with concomitant diabetes displayed a significantly lower adherence level when compared to those without diabetes (Table 2). With regards to disease duration, patients with intermediate disease duration (3–5 years) had a significantly lower medication adherence compared to those who have had the disease for 6 years or more (Table 2).

The combined effect of the various variables on the level of medication adherence was assessed using multiple-regression analysis showing that the presence of comorbidities, and disease durations ranging between 3 and 5 years were independently associated with lower medication adherence. While the presence of disability was independently associated with higher adherence level when compared to patients without disability (Figure 1).

HRQoL in Patients with COPD

The average total SGRQ score was found to be 51.35 ± 23.82 (m±SD) (Table 3). The highest average score was reported in the activity component (60.46 ± 27.67, m±SD), reflecting disturbances to daily physical activity. This was followed by the symptom (53.37 ± 22.83, m±SD), and the impact components (45.76 ± 25.97, m±SD), reflecting frequency of respiratory symptoms, and disturbances to psycho-social function, respectively (Supplementary Table 1 and 2).

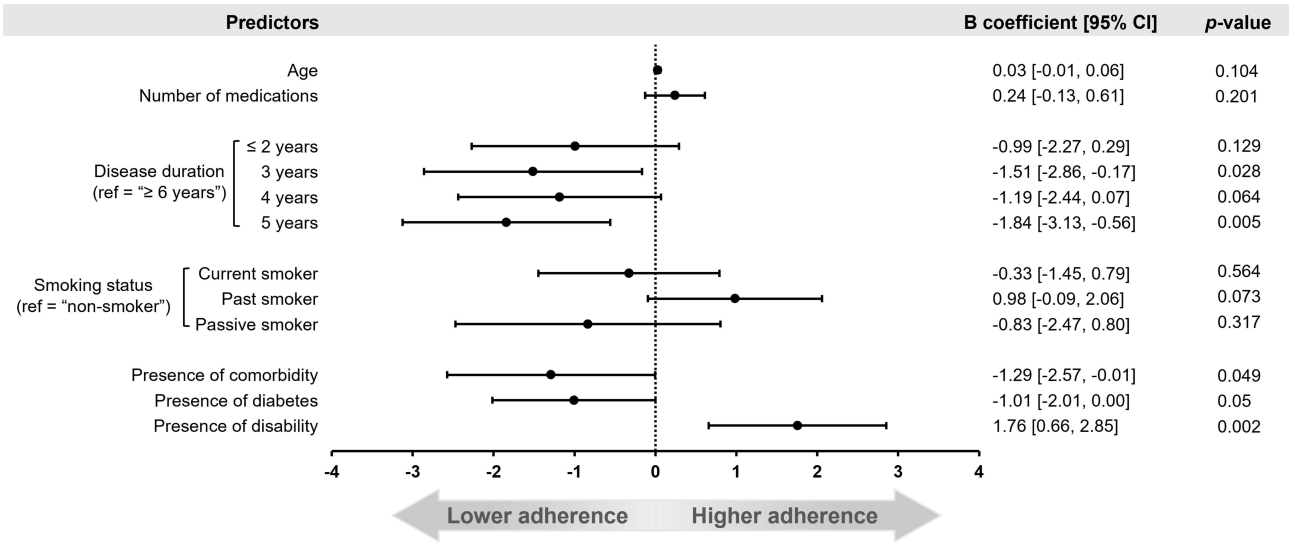

Figure 1 Multivariable analysis of predictors of medication adherence in patients with COPD receiving regular medications. The analysis was done using multiple linear regression and was conducted on the group of patients receiving regular medications (n=376). The regression model explained 9.4% of the variation seen in the level of medication adherence in patients with COPD, $R^2_{adjusted}$= 0.094, *F* (12, 363) = 4.254, p-value = <0.001. A *p*-value of < 0.05 was considered significant. Higher MARS-5 scores indicated higher adherence.

Factors Affecting the HRQoL

Simple linear regression analysis revealed that older age, being female, past smoking, presence of comorbidities and disability, as well as higher number of medications were all associated with a significant increase in the patients' total SGRQ score, indicating lower overall HRQoL (Table 3). A comparable effect on all three SGRQ components was

Table 3 The HRQoL[a] in COPD Patients and Its Correlation[b] with Sociodemographic, Medication, and Disease-Related Characteristics (n=424)

Variable	Total SGRQ Score			
	Mean ± SD	R^2	B Coefficient (95% CI)	*p*-value
Overall	51.35 ± 23.82	-	-	-
Age (m+SD)	51.35 ± 23.82	0.138	0.642 (0.489, 0.796)	<0.001
Gender (%)				
Female	54.58 ± 23.22	0.010	4.968 (0.217, 9.720)	0.040
Male	49.62 ± 23.99		Ref	
Education level (%)				
University education and higher	52.99 ± 25.33	0.002	2.332 (−2.644, 7.307)	0.358
School education	50.66 ± 23.16		Ref	
Smoking status (%)				
Current smoker	44.36 ± 24.66	0.047	−7.004 (−12.761, -1.248)	0.017
Past smoker	57.25 ± 20.81		5.889 (0.217, 11.561)	0.042
Passive smoker	54.03 ± 23.89		2.671 (−6.194, 11.535)	0.554
Non-smoker	51.36 ± 24.35		Ref	

(*Continued*)

Table 3 (Continued).

Variable	Total SGRQ Score			
	Mean ± SD	R^2	B Coefficient (95% CI)	*p*-value
Presence of comorbid condition/s (%)				
Yes	55.53 ± 22.50	0.122	20.625 (15.320, 25.931)	<0.001
No	34.91 ± 21.73		Ref	
Presence of diabetes (%)				
Yes	57.29 ± 22.22	0.079	13.470 (9.070, 17.870)	<0.001
No	43.82 ± 23.70		Ref	
Presence of hypertension (%)				
Yes	58.20 ± 22.12	0.133	17.815 (13.457, 22.172)	<0.001
No	40.38 ± 22.35		Ref	
Presence of cardiovascular disease (%)				
Yes	60.52 ± 21.38	0.093	14.890 (10.433, 19.347)	<0.001
No	45.63 ± 23.50		Ref	
Presence of disability (%)				
Yes	67.68 ± 16.08	0.120	20.490 (15.179, 25.800)	<0.001
No	47.19 ± 23.69		Ref	
Disease duration (%)				
≤ 2 years	52.61 ± 23.82	0.025	−3.207 (−9.945, 3.531)	0.350
3 years	49.18 ± 24.44		−6.635 (−13.787, 0.516)	0.069
4 years	47.34 ± 22.22		−8.485 (−15.068, -1.901)	0.012
5 years	46.89 ± 24.55		−8.928 (−15.602, -2.254)	0.009
≥ 6 years	55.82 ± 23.45		Ref	
Taking regular medications				
Yes	52.75 ± 23.32	0.027	12.329 (5.243, 19.416)	<0.001
No	40.42 ± 25.09		Ref	
Number of medications (m±SD)	51.35 ± 23.82	0.077	5.582 (3.738, 7.425)	<0.001

Notes: [a]The HRQoL was measured using the disease-specific SGRQ-C questionnaire. The score shown in the table is the total SGRQ scores. Total SGRQ scores are expressed as percentages of overall impairment with higher scores indicating lower HRQoL. [b]The correlation between total SGRQ score (the outcome variable) and each independent variable was assessed using simple linear regression. A *p*-value of < 0.05 was considered significant.

observed for older age, presence of comorbidities and disability, and higher number of medications (Supplementary Table 1 and 2). Female COPD patients displayed higher SGRQ component scores compared to their male counterparts; however, the difference was significant only for the impact component (Supplementary Table 2).

With regards to disease duration, the highest total and component SGRQ scores were reported in patients who had the disease for 6 years or more (Table 3 and Supplementary Table 1 and 2). Compared to this group, patients with COPD

disease durations ranging between 3 and 5 years showed a significantly lower total and activity SGRQ scores (Table 3 and Supplementary Table 1).

Compared to non-smokers, current smokers had a significantly higher overall HRQoL which was mainly pronounced in the activity and impact components. On the other hand, past smokers showed lower overall HRQoL affecting mainly the activity component (Table 3 and Supplementary Table 1 and 2).

Patients receiving regular medications displayed higher total, activity, and impact SGRQ scores when compared to patients not taking medications regularly. Moreover, a significant increase in total and component SGRQ scores was observed as the number of prescribed medications increase (Table 3 and Supplementary Table 1 and 2).

Impact of Medication Adherence on HRQoL

Univariate analysis showed that an increase of one unit in the total MARS-5 score predicts a statistically significant decrease in SGRQ symptom score by 0.801 (β = −0.801, CI = −1.322 to −0.280; p=0.003) indicating an improvement in respiratory symptoms (Table 4).

To account for confounders, a multivariate analysis was undertaken including adherence as a predictor for HRQoL. The model explained 36% of the variation seen in the total SGRQ score in COPD patients receiving regular medications [$R^2_{Adjusted}$ = 0.360, F (16, 359) = 14.186, $p < 0.001$] (Figure 2). Older age, increasing number of medications, past smoking, being female, as well as the presence of hypertension and disability independently predicted lower overall HRQoL in patients with COPD. On the other hand, an increase in MARS-5 score, indicating higher medication adherence, independently predicted higher overall HRQoL in patients with COPD (β = −0.88, CI = −1.35 to −0.41, $p < 0.001$) (Figure 2).

Comparable results were seen with component SGRQ scores with older age, number of medications, past smoking, and presence of hypertension predicting more respiratory symptoms and more disturbance to physical activity and psycho-social functions. Female gender was associated with higher activity component score, while the presence of diabetes and cardiovascular disease (CVS) was associated with higher symptom component score. The presence of disability was associated with higher activity and impact component scores (Supplementary Figures 1, 2, and 3). With regards to medication adherence, higher MARS-5 score, predicted a significant decrease in both symptom and impact

Table 4 Univariate Analysis of the Relationship Between Medication Adherence in Patients with COPD Receiving Regular Medication and Their HRQoL (n=376)[a]

MARS-5 total score 21.57 ± 4.34 (mean ± SD)	**Total SGRQ score**			
	Mean ± SD	**R^2**	**B coefficient (95% CI)**	***p*-value**
	52.75 ± 23.32	0.003	−0.297 (−0.843, 0.249)	0.286
	Symptom SGRQ score			
	Mean ± SD	**R^2**	**B coefficient (95% CI)**	***p*-value**
	53.92 ± 22.49	0.024	−0.801 (−1.322, −0.280)	0.003
	Activity SGRQ score			
	Mean ± SD	**R^2**	**B coefficient (95% CI)**	***p*-value**
	62.22 ± 27.16	0.003	0.367 (−0.269, 1.002)	0.257
	Impact SGRQ score			
	Mean ± SD	**R^2**	**B coefficient (95% CI)**	***p*-value**
	47.20 ± 25.45	0.008	−0.510 (−1.104, 0.084)	0.092

Notes: [a]Analysis was done using simple linear regression with total MARS-5 score as the predictor and each SGRQ score as the dependent variable separately. Given that medication adherence cannot be accurately assessed in patients not receiving regular medications, this group was excluded from the analysis (n=48). A p-value of < 0.05 was considered significant.

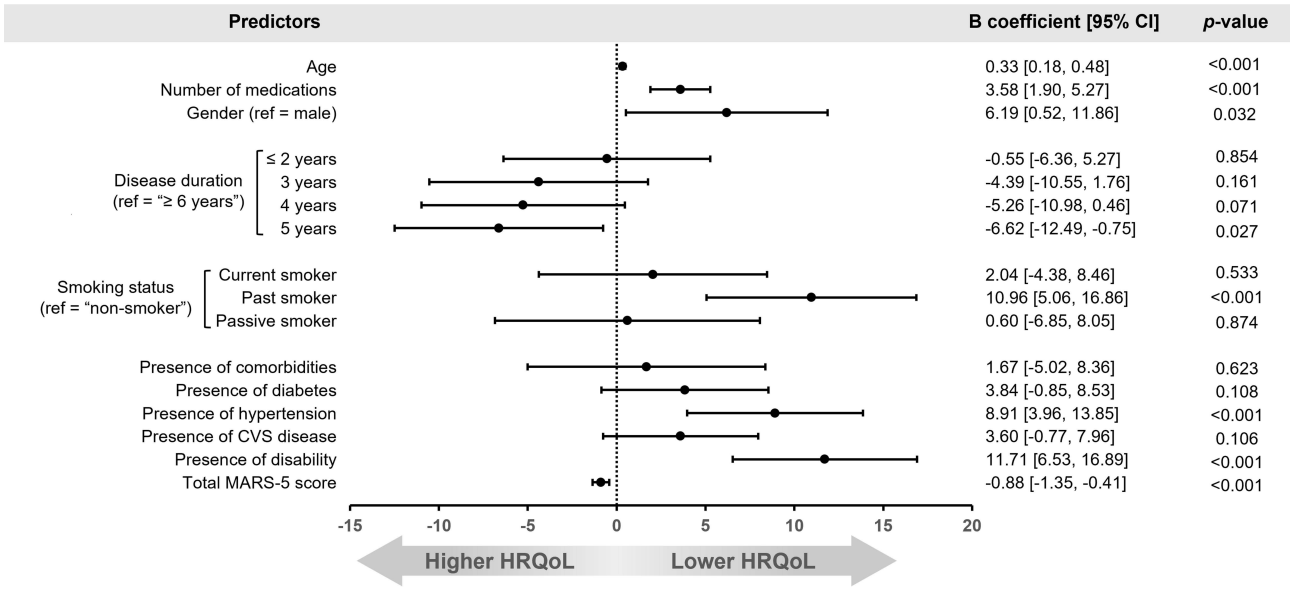

Figure 2 Multivariable analysis of predictors of HRQoL in patients with COPD receiving regular medications. Multiple linear regression was used to predict the HRQoL (outcome variable) in patients with COPD receiving regular medications given the above predictors. The model included Mars-5 total score as one of the predictors and as such it was analyzed on the group of patients on regular medications (n=376). The regression model explained 36% of the variation seen in total SGRQ scores in patients with COPD, $R^2_{adjusted}$ = 0.360, F (16, 359) = 14.186, p-value = <0.001. A p-value of < 0.05 was considered significant. Higher SGRQ scores indicate lower HRQoL.

SGRQ component scores indicating lower symptom frequency and less disturbance to psycho-social function (Supplementary Figures 1 and 3).

Discussion

The first aim of the current study was to assess the level of medication adherence and HRQoL in patients with COPD and identify the factors affecting each. Only 56.4% of patients in the current study reported high adherence to their medication, while the average total SGRQ score was(51.35 ± 23.82 m ± SD) indicating low overall HRQoL. Multimorbidity, disability, and intermediate disease duration were found to be significantly associated with lower medication adherence. While older age, female gender, higher number of prescribed medications, past smoking, hypertension, and disability were linked to lower HRQoL. Lastly, we attempted to delineate the relationship between medication adherence and HRQoL in patients with COPD and found that higher medication adherence was associated with higher HRQoL.

Patients' adherence to medications is a challenge facing physicians treating chronic respiratory conditions.[14,43] The average medication adherence level in the current study was 21.57±4.34 (m±SD), which is lower than that reported by other investigators.[19,44] In those studies, COPD patients had a higher average age compared to the current population.[19,44] The positive impact of increasing age on adherence shown by many studies including the current may partially explain the observed difference.[12,16] However, this is not the first report of lower adherence in Saudi COPD patients.[12] In the multicenter ADCARE study conducted between Saudi Arabia and Turkey, Kokturk et al reported lower adherence in Saudi patients with COPD compared to their Turkish counterparts (4.6±2.4 vs 6.2±1.8 [m±SD], respectively).[12]

Approximately 56% of patients with COPD were classified as "highly adherent" in the current study. This figure is in line with those reported by the WHO for chronic conditions and those reported by other investigators for COPD,[14,18,45] but higher than that reported by George et al and Kokturk et al.[12,19] Comparison with other studies is hampered by differences in adherence assessment method and lack of agreement on cut points to stratify continuous scales such as MARS-5. George et al reported that 38% of Australian patients with COPD are highly adherent; however, they used a more stringent cutoff of 25 to dichotomize their MARS-5 scale which could explain the lower proportion of highly adherent patients.[19] More patients reported high adherence in the current study compared to Saudi patients with COPD enrolled by Kokturk et al which may be attributed to differences in measurement tool.[12,46] Regardless of how it may

compare to other studies, the finding that 43.6% of COPD patients reported low adherence in the current study is unsettling and warrants deeper understanding of the factors leading to such poor adherence.

Medication nonadherence is multifactorial being influenced by patient-, disease-, medication-, health system-, and socioeconomic-related factors as well as the presence of informal caregivers.[13,14,47] Using multivariable analysis, several factors were found to be associated with lower adherence including intermediate disease durations, presence of diabetes, and comorbidities, while the presence of disability was associated with higher adherence level. The negative impact of comorbidities on adherence is worrisome given that most patients with COPD have comorbidities. Eighty percent of patients in the current study were shown to have at least one comorbid condition with diabetes being reported in approximately 56% of patients. Multimorbidity in COPD is well documented[48] and does not come as a surprise in view of the older age, natural history of the disease, underlying chronic inflammatory state, and shared risk factors with other comorbid conditions.[49–51] Comorbidities complicate the treatment regimen making it difficult for patients to navigate their medication plan and increase forgetfulness. Moreover, treatment of multimorbidity in COPD is challenging especially that some medications used to treat COPD may negatively impact the course of concomitant diseases and vice versa.[50,52]

Living with a chronic respiratory condition poses a physical and psychological strain on patients due to the progressive limitation it imposes on patients' day-to-day activities, negatively impacting their HRQoL.[53,54] Unfortunately, patients with COPD score the lowest in overall health and quality of life compared to those with other chronic conditions.[24,27] The mean total SGRQ of 51.4 ± 23.8 (m±SD) reported in the current study lies within the range reported by other investigators for patients with COPD.[18,29,55,56] The disease appeared to affect the "activity" component the most followed by "symptom" and the "impact" components. A similar order was observed by Horvat et al, whereas both Xu et al and Osman et al reported the worst score for the symptom component.[18,29,57] The fact that the activity component displayed the worst score in the current study is not surprising given that approximately 80% of COPD patients had comorbidities with more than third suffering from cardiovascular disease limiting patients' activity.

Identifying the factors affecting patients' overall HRQoL is of great importance. Using multiple-regression analysis, older age, female gender, polypharmacy, past smoking, presence of hypertension and disability emerged as independent predictors for lower HRQoL in patients with COPD. In the clinical setting, these factors commonly occur simultaneously with one feeding into the other. As patients with COPD get older, their chances of developing disease-related/unrelated complications/comorbidities increase and with it the number of prescribed medications. Such complexity highlights the importance of a shared multi-professional team approach when managing patients with COPD aiming to optimize management plans and limit polypharmacy.[47]

Female patients are more prone to the detrimental effects of COPD compared to their male counterparts. This is evidenced by the lower overall HRQoL reported in female patients in the current study with the greatest effect on the activity component. Similar findings were reported by other investigators that showed higher SGRQ scores with more activity limitations and greater disease impact in women with COPD compared to men, despite comparable symptomatology and airflow limitation.[29,58,59] The tendency for COPD to adversely affect the HRQoL of female patients more than male is worrisome, especially that most women in the current study were non-smokers. The occurrence of COPD in non-smoking females in the current study could not be attributed to exposure to biomass fuel since their use in Saudi households amounts to only 5.21% across the kingdom.[60] Neither can incense (Bakhour) burning account for it since its use is limited to brief social occasions and data implicating its use in COPD development were inconclusive.[61–63] However, it may be attributed to underreporting of cigarette use which is well-documented in female patients.[64–66] Additionally, several investigators highlighted biologic and physiologic differences between males and females in their susceptibility to the injurious effects of smoke.[67–69] This, along with passive smoking and the higher frequency and intensity of dust and sandstorms recorded in recent years[70–72] may also contribute to the occurrence of COPD in non-smoking females.

A differential effect of smoking status on HRQoL was also detected. Past smokers displayed a significantly lower HRQoL while current smokers displayed a higher, albeit non-significant, HRQoL when compared to non-smokers. Although similar findings were described by Wijnhoven et al,[73] other investigators reported lower HRQoL in current smokers.[74,75] The difference in HRQoL observed in relation to smoking status may be attributed to differences in disease

severity which have not been addressed in the current study. Past smokers may have been prompted to quit smoking due to deterioration of their clinical condition, while the higher HRQoL observed in current smokers may be attributed to "healthy smoker" effect with current smokers having a less severe disease compared to past smokers.[73,74]

One of the major goals of the current study was to delineate the effect of medication adherence on patients' HRQoL. Although initial univariate analysis showed that higher adherence was significantly associated with lower symptom SGRQ score only, after correcting for confounders, higher adherence emerged as an independent predictor of better overall HRQoL as well as improved symptom and impact SGRQ components. Controversy surrounds the impact of adherence on HRQoL in patients with COPD. A similar positive association between adherence and HRQoL have been demonstrated by some investigators,[12,76] yet others reported either no relation[18,77,78] or, conversely, a negative association.[35,36] This does not come as a surprise given the complexity of the relationship.

Adherence and HRQoL are dynamic parameters that change in response to patient, disease, socioeconomic, and therapy-, and health system-related factors.[21,47,76] A complex bidirectional relationship exists between adherence and HRQoL.[21] Many factors that affect patients' adherence and HRQoL are shared, with contradictory deductions at times that are difficult to interpret in view of cause-and-effect due to the cross-sectional nature of the study. Nonetheless, an attempt to explain some of these seemingly contradictory associations can be informative as it may shed some light on certain behavioral patterns in patients with COPD. For example, it was shown that patients with disease durations ranging between 3 and 5 years have worse medication adherence yet were found to have better overall HRQoL. While patients with disabilities displayed worse HRQoL despite having better adherence. One possible explanation can be extracted by looking at the pattern of adherence across the different disease duration groups. High adherence was reported in the first two years following disease diagnosis, dropping in those with disease durations between 3 and 5 years to pick up again in patients who had the disease for 6 years or more. It could be speculated that the respiratory distress and symptomatology that prompt patients to seek medical advice are strong incentives promoting good adherence at the time of diagnosis. However, as patients' symptoms improve, their adherence wares off as they do not perceive the need for the medication.[17,35] Then, as the disease gradually worsens, patients are pressed to adhere to their treatment once again. A progressive drop in medication adherence over a period of 24 months has been documented in patients with COPD.[79] Most patient educational programs focus on newly diagnosed patients where adherence is naturally higher. While the above findings emphasize the importance of targeting patients in the intermediate stages of the disease where symptom control might offer a false sense of reassurance decreasing their adherence. In fact, patients with COPD that underwent a structured pharmacist-led program on medication adherence displayed better adherence after 24 months compared to the non-intervention control group.[79]

The presence of disability implies that patients are becoming less autonomous and more dependent on external help in their day-to-day activities. Although caregiver status was not assessed in the current study, the divergent effect of disability on adherence and HRQoL may be attributed to the involvement of a caregiver in patient care. The presence of informal caregivers has been shown to improve adherence to both medication and smoking cessation and to increase the odds of patients' participation in a pulmonary rehabilitation program.[80–82] Thus, in addition to dispersing patient educational programs, care should be taken to include informal caregivers in such programs.

Limitations

The study has several potential limitations. Firstly, the use of a self-reporting questionnaire to assess adherence may lead to overestimation and inaccuracy due to their susceptibility to social desirability and recall bias. Moreover, the cross-sectional nature of the study does not allow for cause-and-effect interpretation of results. The intriguing finding that female COPD patients were largely non-smokers warrants further exploration of the causes behind such an observation which is beyond the scope of the current study. Lastly, the analysis could have benefitted from stratification of patients according to disease severity and type of medication which would have clarified some of the associations observed, and such information should be taken into consideration in future studies.

Conclusions

In conclusion, patients with COPD were found to have low medication adherence and poor HRQoL. Factors associated with low adherence included comorbidity, intermediate disease duration, and diabetes while the presence of disability was linked to better medication adherence. Poor HRQoL was seen in relation to older age, female gender, polypharmacy, past smoking, hypertension, and disability while intermediate disease duration was linked to higher HRQoL. It thus appears that some factors display a dual effect on both adherence and HRQoL. This relationship is further complicated by the demonstration that medication adherence itself has a direct independent effect on the overall HRQoL with higher adherence being associated with higher HRQoL in patients with COPD. This multilayered complex relationship between medication adherence and HRQoL emphasizes the importance of adopting a more personalized and holistic approach in the management of patients with COPD aiming to optimize management plans, limit polypharmacy, and encourage adherence.

Abbreviations

COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life; MARS-5, 5-item Medication Adherence Report Scale; SGRQ-C, St. George Respiratory Questionnaire for COPD; GBD, Global Burden of Disease; SGRQ, George Respiratory Questionnaire.

Data Sharing Statement

Data supporting the results reported in the manuscript are available with the corresponding author and can be shared upon request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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