

Exploring Factors Influencing Medication Compliance in Saudi Rheumatoid Arthritis Patients: A Nationwide Cross-Sectional Survey – Results from the COPARA Study

Mohammed A Omair¹, Maha M Alshehri², Nouf A Altokhais², Ghada A Aljanobi³, Maha I El Dessougi⁴, Amal AlHarthi⁴, Maha A Omair⁵, Suzan M Attar⁶, Sami M Bahlas⁶, Abdullah S Alfurayj⁷, Mansour S Alazmi⁸, Alhussain M Asiri⁹, Mohammed M AlOmair⁹, Lobna Al Juffali¹⁰, Haya M Almalag¹⁰

¹Rheumatology Unit, Department of Medicine, King Saud University, Riyadh, Saudi Arabia; ²College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; ³Rheumatology Unit, Department of Medicine, Qatif Central Hospital, Qatif, Saudi Arabia; ⁴Rheumatology Unit, Department of Medicine, Security Forces Hospital, Riyadh, Saudi Arabia; ⁵Department of Statistics and Operations Research, College of Science, King Saud University, Riyadh, Saudi Arabia; ⁶Rheumatology Unit, Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; ⁷Rheumatology Unit, Department of Medicine, Buraidah Central Hospital, Buraidah, Saudi Arabia; ⁸Rheumatology Unit, Department of Medicine, Prince Mohammed Medical City, Sakaka-Aljouf, Saudi Arabia; ⁹Rheumatology Unit, Department of Medicine, Aseer Central Hospital, Abha, Saudi Arabia; ¹⁰Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Correspondence: Mohammed A Omair, Rheumatology Unit, Department of Medicine, King Saud University, Riyadh, Saudi Arabia, Tel +966505270513, Email momair@ksu.edu.sa

Purpose: Compliance is essential to achieve treatment goals in rheumatoid arthritis (RA) patients. The current study evaluated compliance and related factors in a large and diverse population.

Patients and Methods: Patients with RA who received active treatment were invited to participate in an online survey. The Arabic versions of the 5-Item Compliance Questionnaire for Rheumatology (ACQR-5) and the RA Impact of Disease (RAID) were used to measure compliance and disability, respectively. The patients were sub-grouped based on background disease-modifying anti-rheumatic drugs (DMARDs). Variables associated with high compliance were selected for the logistic regression analysis.

Results: A total of 1241 patients completed the survey and were included in the final analysis. Of those, 1055 (85%) were females with a mean ($\pm$ SD) age and disease duration of 47.14 ± 13.71 and 8.77 ± 7.43 years, respectively. The mean RAID was 4.4 ± 2.58 , with 980 (79%) having an unacceptable level state. Patients with an unacceptable RAID level had a lower compliance rate (78.8% vs 85.8%, $p = 0.001$). Demographics associated with high compliance were female sex and increased age, with reported odds ratios of 1.018 (95% CI: 1.007–1.028) and 1.464 (95% CI: 1.016–2.108), respectively. Compliance was similar between patients on Janus kinase inhibitors or biological DMARDs (88.14% vs 80.83%, $p = 0.17$), between monotherapy, double therapy, or triple therapy recipients (80% vs 82.23% vs 81.32%, $p = 0.665$), and between patients receiving injectable and oral therapy (77.32% vs 81.14%, $p = 0.246$).

Conclusion: A high compliance level was observed in this population, with patient demographics influencing compliance rather than the medication type or route of administration. Interventional studies should focus on the of high-risk patients identified in this study.

Keywords: rheumatoid arthritis, compliance, Saudi Arabia

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that burdens patients' lives.¹ Outcomes of RA management have improved in the last two decades owing to early diagnosis, the introduction of highly effective therapies, and the adoption of a Treat To Target strategy.² Treatment options include conventional synthetic Disease-Modifying Anti-rheumatic Drugs (csDMARDs), target synthetic DMARDs (tsDMARDs), and biological DMARDs (bDMARDs).³ Similar to other chronic

diseases, treatment compliance is essential to achieve the desired therapeutic goal.^{4,5} Methotrexate (MTX), the anchor drug in RA management, is usually started as a monotherapy orally or subcutaneously in moderate to severe RA patients. Its failure requires the addition of csDMARDs, bDMARDs, or tsDMARDs with a large variety of routes and frequencies of administration. However, this can negatively impact compliance with drugs administered daily compared to weekly or monthly injections. tsDMARDs such as the Janus Kinase Inhibitors (JAKi) tofacitinib, baricitinib, and upadacitinib are required to be consumed once daily compared to bDMARDs, with frequencies ranging from once weekly to once every six months. The ARCO (Study on Adherence of Rheumatoid Arthritis patients to SubCutaneous and Oral Drugs) study was multicenter, looking at compliance related to drug route of administration and frequency using a Medication Possession Ratio of $\geq 80\%$ as the cutoff level to define non-compliance. Interestingly, they found that patients on a monthly interval of administration had a better compliance level than patients on a weekly interval of administration (6.4% vs 17.4%, $p=0.034$).⁶ However, most studies published in the literature had sample sizes ranging from 100 to 400 patients, which could not have adequate statistical power to assess numerous factors.^{6–8} A large study included a mixed population of 3390 patients with RA, psoriatic arthritis, and ankylosing spondylitis. A higher odds ratio of compliance was observed in RA patients using Tumor Necrosis Factor inhibitors (TNFi) combined with csDMARDs (5.45; 3.35–8.87) and monotherapy (3.63, 1.72–7.69) compared to csDMARDs alone.⁹

Systematic assessment of compliance among Saudi patients with RA is challenging owing to the lack of validated tools in Arabic. The 19 and 5 item Compliance Questionnaire for Rheumatology (CQR) versions were only recently validated in the Arabic language.^{10,11} The current study aimed to establish compliance on large sample size and study the impact of patient-related factors, disease characteristics, medication frequency, and route administration.

Materials and Methods

Study Design

The Compliance and Patient Activation in Rheumatoid Arthritis (COPARA) study is a multicenter, nationwide, cross-sectional study that assessed compliance and patient activation. The first part of this study reports the compliance component. The study report was prepared in compliance the Strengthening the Reporting of Observational Studies in Epidemiology Checklist (STROBE Statement).¹²

Ethical Consideration

Ethics approval for this study was obtained from the Institutional Review Board (IRB) of King Saud University (KSU) in Riyadh, Saudi Arabia (IRB approval: E-19-4363). Electronic consent was obtained from all participants. All participants were informed about the purpose of the study, in accordance with the Declaration of Helsinki.

Setting

Participants were recruited from rheumatology clinics at multiple national centers in Saudi Arabia. The centers included Security Forces Hospital, Riyadh; King Khalid University Hospital, King Abdulaziz University Hospital, Jeddah; Prince Mohammed Medical City, Al-Jouf; Qatif Central Hospital, Qatif; Buraidah Central Hospital, Buraidah; Aseer Central Hospital, Abha; and the Charitable Association for Rheumatic Diseases database.

Participants

Consecutive patients aged ≥ 18 years diagnosed with RA were eligible for inclusion based on the American College of Rheumatology/European League Against Rheumatism classification criteria for ≥ 6 months.¹³ Patients in drug-free remission or rituximab monotherapy were excluded. Patient recruitment was performed between May and June 2021.

Confounding variables included patient-related factors such as age, sex, educational level, employment status, income, living status, smoking, comorbidities, and medications. In addition, patients were stratified into an oral group if they were receiving only oral DMARDs, and an injectable group if they were only on injectable DMARDs. The study's primary outcome was the level of compliance measured using the ACQR-5. The secondary outcome was to explore the

relationship between the ACQR-5 level and patient demographics, disease characteristics, medication use, and treatment strategy.

Instrument

The online survey was created using Google Forms, consisting of a series of questionnaires in Arabic, focused on sociodemographic information, health condition characteristics, and currently prescribed medications. Additionally, they included the A-CQR5 tool, which aims to measure the extent to which a RA patient adheres to treatments by choosing the degree of agreement to five statements, where the score ranges from (scored 1) “Definitely do not agree” to (scored 4) “Definitely agree”.¹⁴ The CQR5 was translated in a previous study.¹⁰ The last part was the Arabic version of the Rheumatoid Arthritis Impact of Disease (RAID), developed initially in English.¹⁵ The tool aimed to measure the impact of RA by answering seven questions on a scale of (0 to 10) where (0) “Did not cause me pain” and¹⁰ “Caused me severe pain.” Patients who accessed the questionnaire but did not complete all the items were excluded from the analysis.

Statistical Analysis

Data were cross-tabulated, coded, entered, and statistically analyzed using the IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA). A unique study number was assigned to each patient to ensure patient confidentiality. Descriptive statistics of confounding variables were expressed as means and standard deviations for continuous variables and numbers and percentages for categorical variables. Univariate and multivariate analyses of the factors affecting CQR as dependent variables were performed. The odds ratio (OR) of being highly compliant with regard to demographic characteristics and medication classes is displayed. In addition, the adjusted OR of being highly compliant in medication classes was noted, considering significant confounders in the univariate analysis.

Results

Patients' Demographics

A total of 1356 patients were invited, with 1241 completing the survey and being included in the final analysis, generating a response rate of 91%. Of those, 1055 (85%) were women with a mean ($\pm$ SD) age of 47.14 ± 13.71 years. Most of the patients were from the central region (46.8%), followed by the western and southern regions (21.8% and 11%, respectively) of Saudi Arabia. The level of education was variable, with 162 (13.1%) being illiterate and 798 (64.3%) completing high school or higher education. The majority were unemployed (71.4%), with a monthly income of <3000 SAR in 53% of participants. Two or more comorbidities were reported in 395 (31.9%) patients. Hypertension and diabetes mellitus (DM) were the most common comorbidities, affecting 20.2% and 17.2% of patients, respectively.

Disease Characteristics and Background Medications

The mean disease duration was 8.77 ± 7.43 years. The mean RAID was 4.4 ± 2.58 , with 980 (79%) having an unacceptable level state. Most patients were treated with ≥ 2 agents. csDMARDs and prednisolone were being used in 938 (75.6%) and 318 (25.6%) patients, respectively. TNFi was the most frequently identified bDMARD (30.5%), followed by non-TNFi (24.4%) and JAKi (4.8%).

Compliance Level and Associated Factors

High compliance was observed in 996 patients (80.25%). Patients with higher postgraduate education and working status were more likely to have low compliance ($p=0.05$ and 0.008 , respectively). The region of residence affected adherence ($p<0.001$), with the northern and southern regions scoring the highest (93.2% and 83.2%, respectively) in terms of compliance, followed by the western and central regions (79.7% and 78.1%, respectively). The eastern region scored the lowest (74.2%) (Figure 1). Having DM and osteoporosis were associated with higher compliance ($p=0.008$ and 0.045 , respectively). Using csDMARDs, oral medication, and abatacept treatment were associated with higher compliance. The mean RAID was similar between patients classified as high and low compliant (4.4 ± 2.64 vs 4.41 ± 2.32 , $p=0.939$); however, patients with an unacceptable level of disease impact had a lower compliance level (78.8% vs 85.8%,

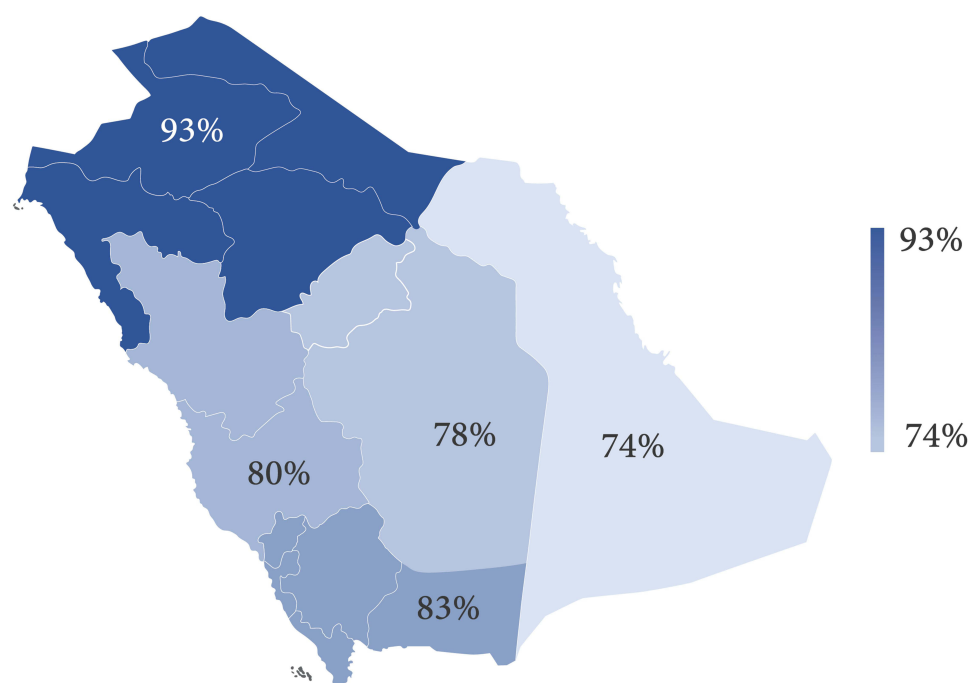


Figure 1 Compliance level stratified by region. Total population = 1241.

$p=0.001$) (Table 1). Demographics associated with high compliance were female sex and increased age, with reported OR of 1.018 (95% CI: 1.007–1.028) and 1.464 (95% CI: 1.016–2.108), respectively. In addition, the northern region, having an acceptable RAID, positive diabetes, osteoporosis, and presence of two or more comorbidities were associated with a high compliance status. Higher education with a university degree [OR 0.595 (95% CI: 0.368–0.962)] or postgraduate degree [OR 0.669 (95% CI: 0.479–0.900)] was inversely correlated with compliance. Participants receiving abatacept (OR 3.903), with the use of background csDMARDs (odds ratio 1.413), and any oral medication (OR: 1.437) were more likely to be compliant, even after adjusting for confounders (Table 2). Subgroup analysis did not show a statistically significant difference between patients on JAKi or bDMARDs (88.14% vs 80.83%, $p=0.17$) (Figure 2), between monotherapy, double, or triple therapy (80% vs 82.23% vs 81.32%, $p=0.665$) (Figure 3), or between patients receiving injectable and oral therapy (77.32% vs 81.14%, $p=0.246$) (Figure 4).

Discussion

Advancements in RA treatment have led to better control of disease activity, improved quality of life, and reduced disability. In addition, studies on RA have reported adherence or compliance to treatment plans with variable results based on the population studied, medication assessed, and tool used.^{4,5,16} Viller et al reported one of the first prospective studies on compliance over three years. This large multicenter study recruited 556 patients from Norway, France, and the Netherlands. They noted consistent behavior in 429 patients (77.2%). Of these patients, 35.7% were consistently compliant. Older age, female sex, decreased disability, more personal knowledge of RA, and better relationships with healthcare professionals were associated with compliant behavior.¹⁷ Other studies have assessed compliance with specific medications. For example, MTX is administered orally and subcutaneously at weekly doses. Curtis et al performed a systematic review assessing adherence to MTX with results ranging between 50–94% at year one and dropping to 25–79% at year 5.⁵ Another systematic review assessing adherence to adalimumab, etanercept, and infliximab found high methodological variability that generated a wide-ranging adherence between 32.0% and 90.9%.⁴

In our study, compliance was primarily affected by patient-related factors. Being older, living in rural areas, having a low socioeconomic status, and being unemployed were associated with better compliance. Similarly, Park et al found that older age and the ability to cope with the disease were associated with higher adherence. In contrast, living a busy

Table I Baseline Demographics and Comorbidities Stratified by Compliance Score High or Low with p-value of Difference

		Low Compliance	High Compliance	Total	p value
Age , mean (standard deviation)	Years	44.53 (13.20)	47.79 (13.77)	47.14 (13.7)	<0.001*
Gender , n (%)	Male	47 (25.3)	139 (74.7)	186 (15.0)	0.040*
	Female	198 (18.8)	857 (81.2)	1055 (85.0)	
Educational level , n (%)	No education	24 (14.8)	138 (85.2)	162 (13.1)	0.050*
	Elementary School	27 (15.9)	143 (84.1)	170 (13.7)	
	Intermediate School	25 (22.5)	86 (77.5)	111 (8.9)	
	High School	38 (16.5)	193 (83.5)	231 (18.6)	
	University or Diploma	116 (22.6)	397 (77.4)	513 (41.3)	
	Postgraduate	15 (27.8)	39 (72.2)	54 (4.4)	
Employment status , n (%)	Not Working	158 (17.8)	728 (82.2)	886 (71.4)	0.008*
	Working	87 (24.5)	268 (75.5)	355 (28.6)	
Income , n (%)	<3000 Saudi Riyals	117 (17.8)	541 (82.2)	658 (53.0)	0.175
	3000–10,000 Saudi Riyals	71 (20.3)	279 (79.7)	350 (28.2)	
	10,000–20,000 Saudi Riyals	49 (24.6)	150 (75.4)	199 (16.0)	
	>20,000 Saudi Riyals	8 (23.5)	26 (76.5)	34 (2.7)	
Living status , n (%)	Alone	4 (3.2)	39 (79.4)	43 (3.5)	0.080
	With Family	241 (17.9)	957 (77.5)	1198 (96.5)	
Smoking status , n (%)	No	215 (19.1)	910 (80.9)	1125 (90.7)	0.084
	Yes	16 (21.9)	57 (78.1)	73 (5.9)	
	Former smoker	14 (32.6)	29 (67.4)	43 (3.5)	
Residency Region , n (%)	Central Region	127 (21.9)	454 (78.1)	581 (46.8)	<0.001*
	Western Region	55 (20.3)	216 (79.7)	271 (21.8)	
	Eastern Region	31 (25.8)	89 (74.2)	120 (9.7)	
	Southern Region	23 (16.8)	114 (83.2)	137 (11.0)	
	Northern Region	9 (6.8)	123 (93.2)	132 (10.6)	
Start of symptoms , mean (SD)	Years	10.37 (7.56)	10.46 (8.05)	10.44 (7.95)	0.874
Diagnosis , mean (SD)	Years	8.53 (7.04)	8.83 (7.52)	8.77 (7.43)	0.577
Rheumatoid Arthritis Impact of Disease score-RAID , median (interquartile range)	Score	4.53 (3.96–4.83)	4.68 (4.43–4.86)	4.64 (4.42–4.80)	0.995

(Continued)

Table I (Continued).

		Low Compliance	High Compliance	Total	p value
RAID interpretation, n (%)	Unacceptable	208 (21.2)	772 (78.8)	980 (79.0)	0.001*
	Acceptable	37 (14.2)	224 (85.8)	261 (21.0)	
Hypertension, n (%)	Yes	44 (17.5)	207 (82.5)	251 (20.2)	0.324
Diabetes, n (%)	Yes	28 (13.1)	185 (86.9)	213 (17.2)	0.008*
Thyroid Diseases, n (%)	Yes	30 (15.1)	169 (84.9)	199 (16.0)	0.071
Osteoporosis, n (%)	Yes	22 (13.8)	137 (86.2)	159 (12.8)	0.045*
Increase lipid panel, n (%)	Yes	21 (16.8)	104 (83.2)	125 (10.1)	0.384
Asthma, n (%)	Yes	23 (20.9)	87 (79.1)	110 (8.9)	0.747
Heart Diseases, n (%)	Yes	11 (17.7)	51 (82.3)	62 (5.0)	0.685
Depression, n (%)	Yes	13 (30.2)	30 (69.8)	43 (3.5)	0.079
Fibromyalgia, n (%)	Yes	10 (33.3)	20 (66.7)	30 (2.4)	0.058
Cancers, n (%)	Yes	3 (30.0)	7 (70.0)	10 (0.8)	0.413
Viral hepatitis, n (%)	Yes	3 (37.5)	7 (62.5)	10 (0.6)	0.424
Other, n (%)	Yes	136 (20.9)	514 (79.1)	650 (52.4)	0.273
Comorbidities, n (%)	0–1	183 (21.7)	662 (78.3)	845 (68.1)	0.014*
	≥2	62 (15.7)	333 (84.3)	395 (31.9)	

Notes: *Significant at a significance level of <0.05; significant values are in bold case.

life negatively impacted adherence.¹⁸ In the post hoc analysis of the Spanish ARCO study by Marras et al, they found that educational level did not impact compliance measured by CQR, but working status comparing currently working vs others was associated with lower compliance, almost reaching a statistical difference (27.8% vs, 16.7% $p=0.062$).¹⁹ Also, a French study has not identified education level or working status as significant factors affecting compliance.⁷ In contrast to all the previously reported findings, Mena-Vazquez et al have shown better compliance in RA patients with a university degree ($p=0.039$).⁸

We hypothesized that existing oral medications and combination therapy would negatively impact compliance. The findings of this study suggest that background therapy does not significantly affect compliance levels. These findings confirm that using JAKi does not negatively impact compliance in general. However, we suggest that these findings should be cautiously interpreted. Choosing the most suitable therapy requires incorporating variables such as patient engagement, comorbidities, pregnancy planning, health coverage, and utilization. The study did not include any disease activity measure because of its nature as a multicenter survey. RAID is a validated tool¹⁵ that functions well as patient-reported outcomes and correlates with disease activity score (DAS28).^{20,21} The finding that patients with an unacceptable RAID state had a lower compliance level could be explained by the fact that lower compliance leads to higher disease activity, causing a lower RAID. Finally, the observed high compliance level could be due to the ACQR-5 properties, which could be overestimated compared to previous studies using other tools.^{4,5,16} In a previous study conducted during the COVID-19 pandemic, we observed a similar level of compliance using the Medication Adherence Rating Scale in 637 patients (85.8%) with different rheumatic diseases, with 42.7% of them having RA.²²

Table 2 Binary Logistic Regression of Demographics and Medication with the Resulting Odds Ratio of Being Highly Compliant

	Odds Ratio	95% Confidence Intervals	p value
Age	1.018	1.007 – 1.028	0.001*
Female	1.464	1.016 – 2.108	0.041*
Elementary School/Read and Write	0.921	0.507 – 1.674	0.787
Intermediate School	0.598	0.321 – 1.114	0.105
High School	0.883	0.507 – 1.540	0.662
University or Diploma	0.595	0.368 – 0.962	0.034*
Postgraduate	0.452	0.216 – 0.944	0.035*
Working	0.669	0.497 – 0.900	0.008*
3000–10,000	0.850	0.612 – 1.180	0.275
10,000–20,000	0.662	0.453 – 0.968	0.005*
>20,000	0.703	0.310 – 1.591	0.418
Western Region	1.099	0.770 – 1.567	0.604
Eastern Region	0.803	0.510 – 1.264	0.343
Southern Region	1.387	0.850 – 2.262	0.191
Northern Region	3.823	1.889 – 7.736	<0.001*
Acceptable RAID	1.631	1.115 – 2.385	0.012*
Diabetic	1.768	1.156 – 2.703	0.009*
Osteoporotic	1.617	1.007 – 2.596	0.047*
Two or more comorbidities	1.485	1.082 – 2.038	0.014*
Medication class	Unadjusted odds ratio	95% Confidence Intervals	p value
Conventional synthetic DMARDs	1.413	1.036 – 1.929	0.029*
Oral	1.437	1.055 – 1.956	0.021*
Injectable	1.126	0.849 – 1.494	0.408
Monotherapy	0.970	0.733 – 1.283	0.831
Double	1.217	0.903 – 1.640	0.196
Triple	1.077	0.648 – 1.789	0.775
Medication class	Adjusted[£] odds ratio	95% Confidence Intervals	p value
csDMARDs	1.427	1.030 – 1.976	0.032*
Oral	1.459	1.055 – 2.018	0.022*
Injectable	1.172	0.874 – 1.573	0.289
Monotherapy	0.927	0.692 – 1.243	0.614
Double	1.269	0.933 – 1.728	0.129
Triple	1.123	0.665 – 1.896	0.664

Notes: *Significant according to a significance level of <0.05; significant values are in bold case; £ Adjusted for age, sex, educational level, employment status, residence region, diabetes, osteoporosis, and comorbidities.

Abbreviations: RAID, Rheumatoid Arthritis Impact of Disease; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; JAKi, Janus kinase inhibitors.

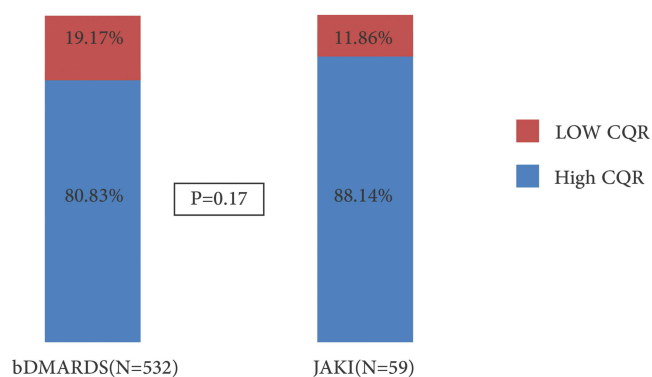


Figure 2 Comparison between the high compliance levels of patients with bDMARDS and JAKi.

Abbreviations: CQR, Compliance Questionnaire for Rheumatology; bDMARDS, biological disease anti-rheumatic drugs; JAKi, Janus kinase inhibitor.

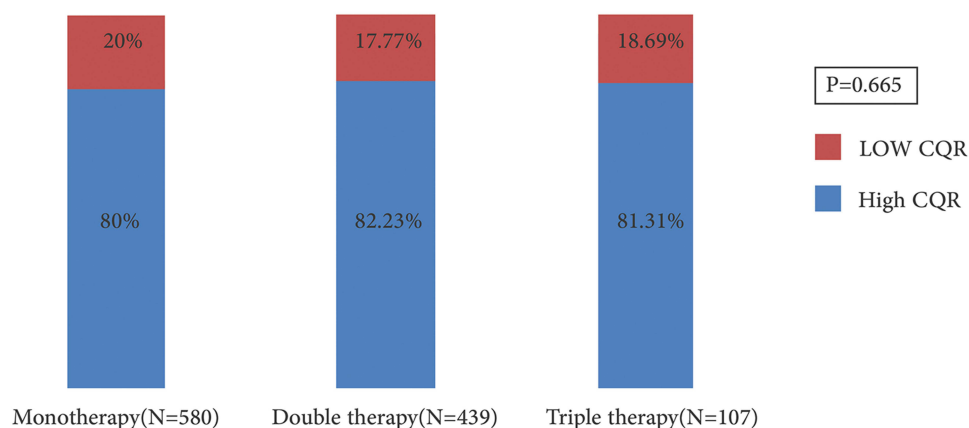


Figure 3 Comparison between compliance levels of patients receiving monotherapy, double therapy, and triple therapy.

Abbreviation: CQR, Compliance Questionnaire for Rheumatology.

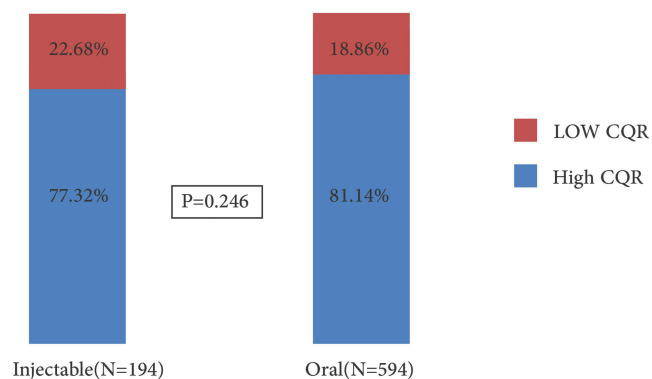


Figure 4 Comparison between the level of compliance in patients using injectable and oral therapies.

The strengths of this study include its large sample size and adequate representation of Saudi Arabia's regions. However, the study was limited by its cross-sectional design, the use of a subjective measure of compliance, and the fact that the assessment did not include factors such as seropositivity and disease activity.

Conclusion

In conclusion, to the best of our knowledge, the current study is so far the largest to assess compliance in RA in the Middle East. Improvements in clinical projects and interventional studies can be used to describe patients' characteristics in the current study to identify high-risk patients.

Data Sharing Statement

Data are available through a request directed to the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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