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Impact of Comorbidity Burden on Treatment Patterns and Disease Activity in Rheumatoid Arthritis: Insights from the Kuwait Registry for Rheumatic Diseases (KRRD)

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Abstract

Background: Rheumatoid arthritis (RA) frequently coexists with comorbidities that influence disease management and outcomes. This study evaluates how comorbidity burden affects disease activity and treatment patterns in RA patients within the Kuwait Registry for Rheumatic Diseases (KRRD). **Research Design and Methods:** This retrospective cohort study analyzed data from 2012-2025. Adults with RA were divided into two groups: low comorbidity (<3 conditions) and high comorbidity (≥3 conditions). Demographics, comorbidities, prescribed disease-modifying antirheumatic drugs (DMARDs), and changes in Disease Activity Score-28 (DAS28) from baseline to last follow-up were compared. **Results:** Among 1318 patients, 179 (13.6%) had ≥3 comor-

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bidities. These patients were older (average 60.7 vs. 48.3 years), predominantly female (84.4% vs. 71.5%), with longer disease duration (7.5 vs. 4.2 years). The overall distribution of treatment regimens differed significantly between the groups ($p < 0.001$), with biologic therapies (monotherapy or combined) being prescribed more frequently to patients in the high comorbidity burden group. Both groups achieved significant DAS28 reductions (0.73 and 0.82), but high comorbidity burden group had higher residual disease activity (mean DAS28 2.63 vs. 2.41). **Conclusion:** A higher comorbidity burden in RA correlates with increased disease activity and a tendency toward more intensive biologic and combination treatments. Integrated management of RA and comorbidities is crucial for improving long-term outcomes.

Keywords

Rheumatoid Arthritis, Kuwait Registry, Comorbidity Burden, Disease Activity, Biologics

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease characterized by progressive joint destruction and extra-articular involvement, including the eyes, lungs, and nervous system, ultimately contributing to premature mortality [1]. Beyond its direct disease burden, RA is frequently accompanied by multiple comorbid conditions such as cardiovascular disease, diabetes, osteoporosis, malignancy, and depression [2]-[4]. The multinational COMORA study, which enrolled nearly 4000 patients, underscored this high burden, reporting depression in 15%, cardiovascular disease in 6%, and solid malignancy in 4.5% of patients [2].

Comorbidities profoundly influence the clinical course of RA by exacerbating systemic inflammation, limiting therapeutic options, and reducing adherence [5]. They are also increasingly recognized as a central component of the difficult-to-treat (D2T) RA phenotype. The EULAR "points to consider" for D2T RA highlight that comorbidities may both amplify inflammatory activity and confound disease activity assessment, ultimately worsening quality of life and survival [6]. Large registries, including CORRONA and IORRA, have demonstrated that patients with higher comorbidity counts exhibit lower rates of Disease Activity Score-28 (DAS28) remission, poorer physical function, and reduced persistence on biologic therapies [7] [8]. Collectively, these findings suggest that comorbidity burden, rather than age alone, is a critical modifier of treatment response and prognosis [9] [10].

Therapeutic decision-making is also shaped by comorbid conditions. Studies from COMORA and other international cohorts show that each additional chronic disease can decrease the likelihood of biologic DMARD use, while prescriptions for conventional DMARDs remain unchanged or increase [3] [10]. This therapeutic conservatism, often reflecting safety concerns or drug contraindications, contributes to suboptimal control and higher discontinuation rates among patients with multiple comorbidities [9].

Data from Middle Eastern populations remain limited, with few studies reporting the prevalence of comorbidities among RA patients [11]-[14]. While these studies generally reflect trends observed internationally, they provide a limited evaluation of how the comorbidity burden affects disease activity and treatment patterns in the region. To address this gap, we analyzed data from the Kuwait Registry for Rheumatic Diseases (KRRD) to evaluate the impact of comorbidity burden on disease activity and DMARD utilization among adults with RA. The findings aim to provide region-specific insight into how comorbidities influence clinical outcomes and prescribing behavior, supporting more individualized management strategies for this patient population.

2. Methods

2.1. Study Design

This retrospective cohort study utilized data from the KRRD, a national multicenter registry encompassing all governmental hospitals in Kuwait. The registry prospectively collects standardized data every 3 - 4 months on demographics, comorbidities, laboratory parameters (including Erythrocyte Sedimentation Rate [ESR] and C-reactive Protein [CRP]), disease activity (DAS28 score), and treatment.

2.2. Comorbidity Ascertainment and Threshold

Comorbidities recorded in the KRRD at the time of patient enrollment were extracted from the registry-based comorbidity dataset and analyzed as a count variable. The included conditions were coronary artery disease, diabetes mellitus, hypertension, hyperlipidemia, asthma, osteoarthritis, osteoporosis, thyroid disease, hemoglobinopathy, hepatitis B virus infection, hepatitis C virus infection, peptic ulcer disease, and interstitial lung disease. For longitudinal analyses, comorbidity status was not updated during follow-up.

Each comorbidity was captured as a binary variable and aggregated as a cumulative count to reflect overall comorbidity burden. The objective was to determine a clinically meaningful threshold associated with differences in RA disease activity, measured by DAS28. Exploratory analyses identified an inflection point at ≥3 comorbidities, where the prevalence of active disease (DAS28 ≥ 3.2) increased substantially compared with patients with fewer comorbidities. Accordingly, patients were categorized into two strata: low comorbidity burden (<3 comorbidities) and high comorbidity burden (≥3 comorbidities).

This threshold is consistent with the approach proposed by Calvo-Gutiérrez *et al.* using the BIOBADASER registry [5]. Established indices such as the Charlson Comorbidity Index (CCI), Rheumatic Disease Comorbidity Index (RDCI), and Modified Morbidity Index (MMI) were not applied, as they require detailed information on disease severity or control, which was not available in the registry [4] [15]-[18].

2.3. Study Period and Ethical Approval

The analysis included data from January 2012 through August 2025. Ethical approval was issued by the Joint Committee for the Protection of Human Subjects in the research of the Health Sciences (HSC) and the Kuwait Institute for Medical Specialization (KIMS) (2012/VDR/JC/882). All procedures complied with ethical standards of the institutional and national research committees, as well as the 1964 Helsinki Declaration and its amendments. Informed consent was obtained at enrollment, and all data were anonymized before analysis. The KRRD provided anonymized patient data, ensuring no personally identifiable information was used during the study.

2.4. Eligibility and Exclusion Criteria

Eligible patients were adults (≥18 years) who fulfilled the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for RA [19]. Exclusion criteria included follow-up duration of less than 12 months, absence of documented DAS28 at either the first or last visit or missing key data on comorbidities or treatment information.

2.5. Outcomes

The primary outcome was the change in RA disease activity between the first and last recorded visits, comparing patients across comorbidity strata. Disease activity was measured using the DAS28 (DAS-28 scores of ≤3.2 indicate low disease activity; >3.2 represent high disease activity). Because follow-up duration varied among patients, analyses focused on the absolute change in DAS28 rather than a fixed time interval. This approach was chosen to measure the cumulative improvement over the entire available observation period for each patient, which aligns with the study's objective of comparing overall outcomes rather than modeling the rate of change over time.

The secondary outcome was to characterize treatment patterns according to comorbidity status at baseline and at the last visit. Treatments were categorized as conventional DMARDs (methotrexate, sulfasalazine, leflunomide, hydroxychloroquine), biologic DMARDs (infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, certolizumab, golimumab), or targeted synthetic DMARDs (tofacitinib, baricitinib, upadacitinib), and further subcategorized as monotherapy or combination therapy. Changes in treatment distribution between baseline and last visit were also analyzed to explore longitudinal prescribing patterns in relation to comorbidity burden.

2.6. Statistical Analysis

All statistical analyses were conducted using JAMOVI (version 2.5.7.0). Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables as frequencies (percentages). Baseline demographic and clinical characteristics were compared using a univariate Linear Model (ANOVA) for continuous variables and Pearson's Chi-squared test for categorical variables. Comorbidity distributions and treatment patterns, including DMARD use at baseline and at the last recorded visit, were compared using Pearson's Chi-squared test. Within-group changes in disease activity were assessed using paired Student's t-tests, comparing DAS28 scores between the first and last recorded visits. Further analyses of DAS28 scores included adjustment for clinical and demographic factors such as age, sex, smoking status, BMI, disease duration, and seropositivity (positive rheumatoid factor [RF] or anti-cyclic citrullinated peptide [anti-CCP] antibodies, or both). All tests were two-sided, with a significance level set at $p < 0.05$. Results are reported with 95% confidence intervals (CI) and effect sizes (Cohen's d), in addition to p-values.

3. Results

3.1. Patient Characteristics

Out of 2467 patients enrolled in the registry, 1149 (46.6%) were excluded. The primary reasons for exclusion, in accordance with our pre-specified criteria, were a follow-up duration of less than 12 months, the absence of a documented DAS28 score at either the first or last visit or missing key data on comorbidities or treatment. A total of 1318 patients with RA were included in the final analysis, of whom 179 (13.6%) had a high comorbidity burden (≥3 comorbidities), and 1139 (86.4%) had fewer than three comorbidities (**Table 1**). Patients with higher comorbidity burden were significantly older at baseline (mean ± SD = 60.7 ± 9.4 years vs 48.3 ± 11.1 years, $p < 0.001$) and had an older age at diagnosis (52.7 ± 11.6 years vs 43.8 ± 11.3 years, $p < 0.001$). The mean body mass index (BMI) was also significantly higher among those with high comorbidity burden (30.9 ± 6.1 vs 28.9 ± 5.7, $p < 0.001$). They also exhibited a longer disease duration (7.5 ± 9.0 years vs 4.2 ± 5.9 years, $p < 0.001$) and were more frequently female (84.4% vs 71.5%, $p < 0.001$). The mean follow-up duration was 5.1 ± 3.4 years and did not differ significantly between the low and high comorbidity burden groups. The mean ESR was modestly higher among those with the high comorbidity burden (38.1 ± 25.7 mm/hr vs 32.7 ± 22.8 mm/hr, $p = 0.006$), while CRP levels, although elevated, did not differ significantly between groups (12.7 ± 18.4 mg/L vs 11.6 ± 16.7 mg/L, $p = 0.472$). Smoking history, antinuclear antibody (ANA) positivity, and seropositivity rates (positive RF or anti-CCP, or both) were comparable between the two groups (p = 0.343, 0.141, and 0.864, respectively). Patients with high comorbidity burden had slightly higher mean DAS28 scores (3.45 ± 1.33 vs 3.14 ± 1.33, $p = 0.005$), suggesting marginally greater baseline disease activity.

3.2. Baseline Comorbidities

Cardiometabolic conditions were common in the high comorbidity burden group, including diabetes mellitus (64.8% vs 12.8%, $p < 0.001$), hypertension (78.8% vs 12.5%, $p < 0.001$), hyperlipidemia (49.2% vs 7.8%, $p < 0.001$), and coronary artery disease (16.8% vs 0.5%, $p < 0.001$) (**Table 2**). Non-cardiometabolic comorbidities were also more prevalent in the high comorbidity burden group, including asthma (38.5% vs 5.9%, p < 0.001), osteoarthritis (21.5% vs 3.2%, p < 0.001), osteoporosis (22.3% vs 0.4%, p < 0.001), and thyroid disease (25.0% vs 9.6%, p < 0.001). Less frequent conditions such as hemoglobinopathies (4.5% vs 0.7%, p < 0.001), hepatitis B (2.2% vs 0.1%, p < 0.001), hepatitis C (2.2% vs 0.4%, p = 0.003), peptic ulcer disease (10.1% vs 1.0%, p < 0.001), and interstitial lung disease (3.4% vs 0.4%, p < 0.001) were also significantly higher among those with multiple comorbidities.

Table 1. Baseline characteristics of rheumatoid arthritis patients stratified by comorbidity burden (<3 vs ≥3).

Characteristics/comorbidities	<3 (N = 1139)	≥3 (N = 179)	Total (N = 1318)	p-value
Age				
Mean (SD)	48.3 (11.1)	60.7 (9.4)	50.0 (11.7)	**<0.001**[1]
Age at diagnosis				
Mean (SD)	43.8 (11.3)	52.7 (11.6)	45.0 (11.8)	**<0.001**[1]
Gender				
Female	814.0 (71.5%)	151.0 (84.4%)	965.0 (73.2%)	**< 0.001**[2]
Male	325.0 (28.5%)	28.0 (15.6%)	353.0 (26.8%)	
BMI (kg/m²)				
Mean (SD)	28.9 (5.7)	30.9 (6.1)	29.2 (5.8)	**<0.001**[1]
Disease duration				
Mean (SD)	4.2 (5.9)	7.5 (9.0)	4.6 (6.5)	**<0.001**[1]
Smoking history				
Smokers	80.0 (10.4%)	7.0 (6.3%)	87.0 (9.9%)	0.343[2]
ESR (mm/hr)				
Mean (SD)	32.7 (22.8)	38.1 (25.7)	33.4 (23.3)	**0.006**[1]
CRP (mg/L)				
Mean (SD)	11.6 (16.7)	12.7 (18.4)	11.7 (16.9)	0.472[1]
ANA				
Mean (SD)	289.0 (33.0%)	36.0 (26.7%)	325.0 (32.2%)	0.141[1]
Seropositive status				
Seropositive	934.0 (88.2%)	143.0 (87.7%)	1077.0 (88.1%)	0.864[1]
DAS28				
Mean (SD)	3.1 (1.3)	3.4 (1.3)	3.2 (1.3)	**0.005**[1]

[1]linear model ANOVA for continuous variables, and [2]Pearson's Chi-squared test for categorical variables. SD, standard deviation; BMI, body mass index; (kg/m²), kilograms per square meter; ESR: erythrocyte sedimentation rate; mm/hr: millimeters per hour; CRP: C-reactive protein; mg/L, milligrams per liter; ANA, antinuclear antibody; Seropositive, positive for rheumatoid factor or anti-CCP antibodies or both; DAS28, disease activity score 28.

Table 2. Baseline comorbidities in rheumatoid arthritis patients stratified by comorbidity burden (<3 vs ≥3).

Comorbidities	<3 (N = 1139)	≥3 (N = 179)	Total (N = 1318)	p-value
CAD	6 (0.5%)	30 (16.8%)	36 (2.7%)	**<0.001**[1]
DM	146 (12.8%)	116 (64.8%)	262 (19.9%)	**<0.001**[1]
Hypertension	142 (12.5%)	141 (78.8%)	283 (21.5%)	**<0.001**[1]
Hyperlipidemia	89 (7.8%)	88 (49.2%)	177 (13.4%)	**<0.001**[1]
Asthma	67 (5.9%)	69 (38.5%)	136 (10.3%)	**<0.001**[1]
OA	30 (3.2%)	79 (21.5%)	109 (8.4%)	**<0.001**[1]
Osteoporosis	4 (0.4%)	82 (22.3%)	86 (6.6%)	**<0.001**[1]
Thyroid disease	90 (9.6%)	92 (25.0%)	182 (13.9%)	**<0.001**[1]
Haemoglobinopathy	8 (0.7%)	8 (4.5%)	16 (1.2%)	**<0.001**[1]
HBV	1 (0.1%)	4 (2.2%)	5 (0.4%)	**<0.001**[1]
HCV	4 (0.4%)	4 (2.2%)	8 (0.6%)	**0.003**[1]
PUD	11 (1.0%)	18 (10.1%)	29 (2.2%)	**<0.001**[1]
ILD	5 (0.4%)	6 (3.4%)	11 (0.8%)	**<0.001**[1]

[1]linear model ANOVA for continuous variables. All between-group differences were statistically significant (p < 0.05, Pearson's Chi-squared test). CAD, coronary artery disease; DM, diabetes; OA, osteoarthritis; HBV, hepatitis B; HCV, hepatitis C; PUD, peptic ulcer disease; ILD, interstitial lung disease.

3.3. Prescribed Medications and Treatment Regimens at Baseline

Methotrexate was the most frequently prescribed conventional DMARD (cDMARD) in both groups, used by 33.0% of patients with the high comorbidity burden group and 26.9% of those with the low comorbidity burden group (p = 0.090). Use of other cDMARDs, including sulfasalazine (15.6% vs 14.0%, p = 0.549), leflunomide (5.6% vs 6.7%, p = 0.584), and hydroxychloroquine (21.8% vs 18.2%, p = 0.249), did not differ significantly between groups. Among biologic DMARDs (bDMARDs), adalimumab (15.6% vs 7.4%, p < 0.001), etanercept (11.7% vs 4.4%, p < 0.001), rituximab (5.0% vs 1.6%, p = 0.002), and infliximab (6.7% vs 3.1%, p = 0.015) were prescribed significantly more often in patients with the high comorbidity burden. The use of other biologics such as abatacept, tocilizumab, certolizumab, and golimumab was infrequent and comparable between groups. Prescription rates of targeted synthetic DMARDs (tsDMARDs) remained very low overall, with tofacitinib (1.1% vs 0.6%), baricitinib (0% vs 0.3%), and upadacitinib (0.6% vs 0.1%) showing no significant intergroup differences.

At baseline, cDMARD monotherapy was the most common treatment, used by 52.7% of patients with the low comorbidity burden and 41.3% of those with the high comorbidity burden (p < 0.001) (Table 3). In contrast, bDMARD monotherapy was significantly more frequent among patients with the higher comorbidity burden (19.0% vs 11.1%, p < 0.001). Combination therapy with cDMARDs and bDMARDs was also more prevalent in the high-comorbidity burden group (30.7% vs 17.3%, p < 0.001). While tsDMARD monotherapy was infrequent overall, its use was slightly more common among patients with a high comorbidity burden (1.7% vs 0.6%, p < 0.001). Combinations of cDMARDs with tsDMARDs were rare (0% vs 0.5%, p < 0.001). Surprisingly, a greater proportion of patients with the low comorbidity burden were not receiving any DMARD therapy at baseline (17.8% vs 7.3%, p < 0.001).

Table 3. Treatment distribution by comorbidity burden at baseline and last follow-up.

Treatment type	<3 (N = 1139)	≥3 (N = 179)	Total (N = 1318)	p-value
		Baseline		
Mono cDMARDS	600 (52.7%)	74 (41.3%)	674 (51.1%)	<0.001[1]
Mono bDMARDS	126 (11.1%)	34 (19.0%)	160 (12.1%)	<0.001[1]
Mono tsDMARDS	7 (0.6%)	3 (1.7%)	10 (0.8%)	<0.001[1]
Combination cDMARDS and bDMARDS	197 (17.3%)	55 (30.7%)	252 (19.1%)	<0.001[1]
Combination cDMARDS and tsDMARDS	6 (0.5%)	0 (0.0%)	6 (0.5%)	<0.001[1]
None	203 (17.8%)	13 (7.3%)	216 (16.4%)	<0.001[1]
		Last follow-up visit		
Mono cDMARDS	573 (50.3%)	56 (31.3%)	629 (47.7%)	<0.001[1]
Mono bDMARDS	192 (16.9%)	44 (24.6%)	236 (17.9%)	<0.001[1]
Mono tsDMARDS	47 (4.1%)	5 (2.8%)	52 (3.9%)	<0.001[1]
Combination cDMARDS and bDMARDS	281 (24.7%)	68 (38.0%)	349 (26.5%)	<0.001[1]
Combination cDMARDS and tsDMARDS	21 (1.8%)	5 (2.8%)	26 (2.0%)	<0.001[1]
None	25 (2.2%)	1 (0.6%)	26 (2.0%)	<0.001[1]

All comparisons were assessed using Pearson's Chi-squared test ([1]). cDMARDs, conventional disease modifying antirheumatic drugs; bDMARDs, biologic disease modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs. [1]A single Pearson's Chi-squared test was used to assess the overall association between comorbidity burden and the distribution of treatment regimens across all six categories. The overall test was statistically significant (p < 0.001) at both baseline and the last follow-up visit.

3.4. Prescribed Medications and Treatment Regimens at Last Follow-Up

At the last follow-up visit, methotrexate remained the most frequently prescribed cDMARD, utilized by 59.7% of patients overall, with a significantly higher prevalence in the low comorbidity group (61.0% vs 51.4%, p = 0.015). The use of other cDMARDs, including sulfasalazine (14.7.% vs 11.7.0%, p = 0.28), leflunomide (12.3% vs 10.6%, p = 0.52), and hydroxychloroquine (32%vs 27.4%, p = 0.21), did not differ significantly between groups.

Regarding bDMARDs, rituximab was significantly more frequently prescribed in patients with high comorbidity burden (21.2% vs. 12.2%, $p < 0.001$). Similarly, abatacept (5.6% vs. 1.8%, $p = 0.002$) and tocilizumab (13.4% vs. 6.9%, $p = 0.003$) exhibited increased utilization within this subgroup. In contrast, the prescription rates of other biologics, including adalimumab, etanercept, certolizumab, and golimumab, were comparable across groups. tsDMARDs such as tofacitinib, baricitinib, and upadacitinib remained infrequently used across both groups, with no statistically significant differences observed.

At the last recorded visit, cDMARD monotherapy remained the most frequently prescribed regimen, but was significantly more common among patients with low comorbidity burden (50.3% vs 31.3%, $p < 0.001$) (Table 3). In contrast, bDMARD monotherapy was more prevalent in the high-comorbidity burden group (24.6% vs 16.9%, $p < 0.001$). Combination therapy with cDMARDs and bDMARDs was also more common among patients with the high comorbidity burden (38.0% vs 24.7%, $p < 0.001$). tsDMARD monotherapy remained infrequent, though slightly higher in the low-burden group (4.1% vs 2.8%, $p < 0.001$). Combinations of cDMARDs with tsDMARDs were rare in both strata (1.8% vs 2.8%, $p < 0.001$). At follow-up, 2.2% of patients with low comorbidity burden and 0.6% of those with high comorbidity burden were not receiving any DMARD therapy ($p < 0.001$). However, the registry did not specify the reasons for treatment discontinuation in these patients.

3.5. Changes in Disease Activity over Time

Across the cohort, disease activity improved significantly from baseline to the last follow-up visit, regardless of comorbidity burden (Table 4, **Appendix** Table A1, Figure 1 and Figure 2). Among patients with the low comorbidity burden, the mean DAS28 score decreased by 0.73 ± 0.05 ($p < 0.001$; Cohen's d = 0.42), while those with high comorbidity burden showed a mean reduction of 0.82 ± 0.12 ($p < 0.001$; Cohen's d = 0.49). Despite these improvements, patients with higher comorbidity burden maintained slightly higher disease activity at follow-up (DAS28 2.6 vs. 2.4). The regression analyses (Figure 3) revealed no significant associations between the change in DAS28 and various clinical and demographic factors, such as age at time of enrollment, age at diagnosis, disease duration, BMI, gender, smoking status, or seropositive status, in both groups (all $p > 0.05$).

Table 4. Disease activity and comorbidity status analysis at first and last follow-up visit.

	Comorbidity status	Mean	Median	SD	Minimum	Maximum
First-DAS28	Less than 3	3.14	2.98	1.33	0.000	7.33
	3 and more	3.45	3.35	1.33	0.513	7.04
Last-DAS28	Less than 3	2.41	2.28	1.31	0.00	6.90
	3 and mor	2.63	2.43	1.28	0.00	6.44

DAS28, disease activity score 28; SD, standard deviation.

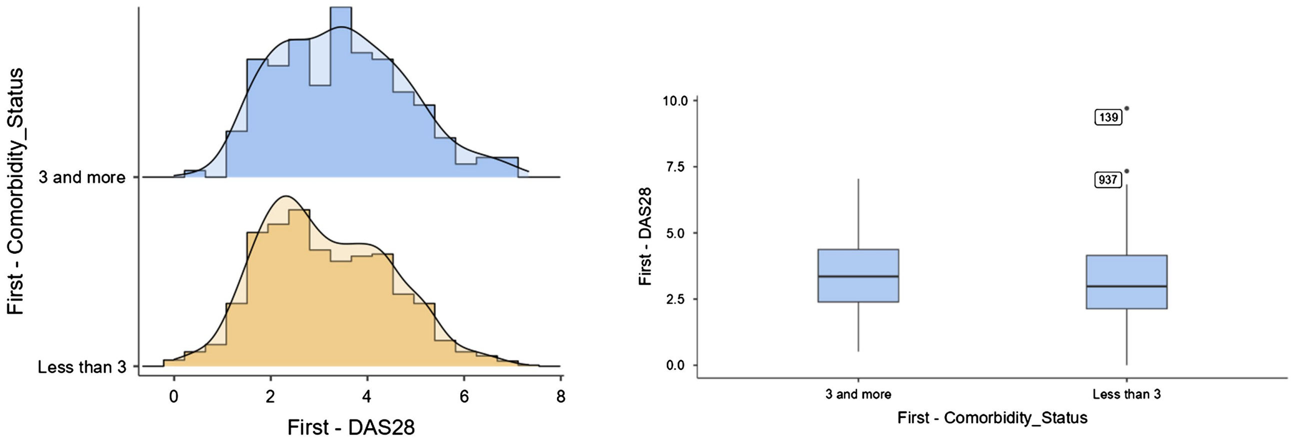

Figure 1. Baseline disease activity according to comorbidity burden. DAS28: Disease Activity Score 28. At the first visit, patients with ≥3 comorbidities had a higher mean DAS28 (3.45, median 3.35; range 0.51 - 7.04) compared with those with <3 comorbidities (mean 3.14, median 2.98; range 0.00 - 7.33). Histograms with density overlays (left) illustrate the distribution of DAS28 values in each group, while boxplots (right) depict medians, interquartile ranges, and outliers. These visualizations indicate a slightly higher baseline disease activity in patients with greater comorbidity burden, though with overlapping distributions.

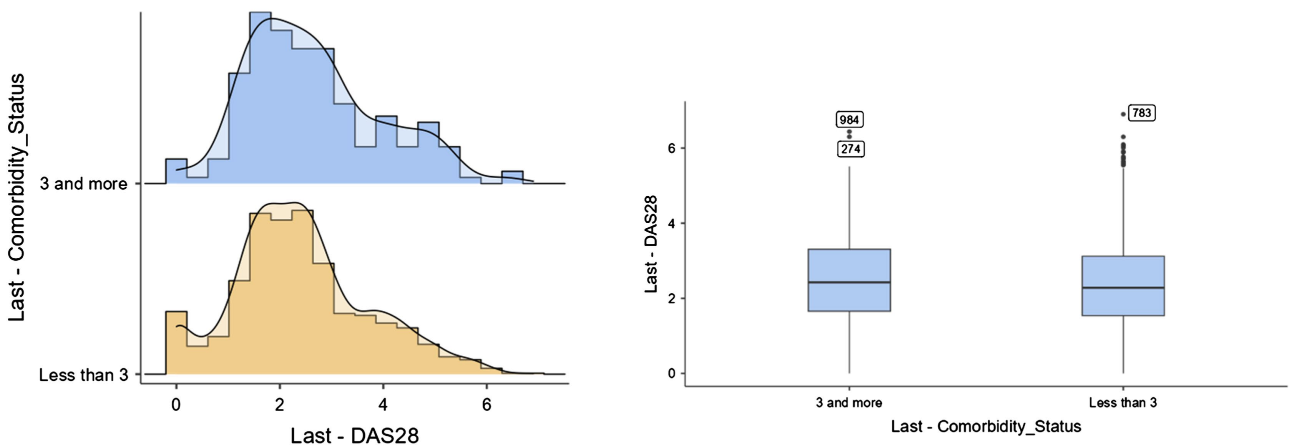

Figure 2. Disease activity at last visit according to comorbidity burden. DAS28: Disease Activity Score 28. At the last follow-up, patients with ≥3 comorbidities had a mean DAS28 of 2.63 (median 2.43; range 0.00 - 6.44), compared with 2.41 (median 2.28; range 0.00 - 6.90) in those with <3 comorbidities. Histograms with density overlays (left) display the distribution of DAS28 values across groups, while boxplots (right) show medians, interquartile ranges, and outliers. Both groups demonstrated overall reductions in disease activity compared to baseline, with distributions largely overlapping at the last visit.

4. Discussion

4.1. Summary of Findings

In this national RA registry, 13.6% of patients exhibited a high comorbidity burden (≥3 comorbidities). Patients in this group were significantly older, more often female, and had longer disease duration. Cardiometabolic comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease, were substantially more prevalent, but non-cardiometabolic conditions such as asthma, osteoarthritis, osteoporosis, thyroid disease, and interstitial lung disease were also significantly increased in this subgroup. Patients with higher comorbidity burden were more frequently treated with bDMARDs and combination regimens, while cDMARDs and tsDMARDs use was similar across groups. This pattern may also reflect treatment escalation in patients with more active or treatment-refractory disease. Both groups achieved significant improvement in DAS28 scores (mean change 0.73 vs 0.82; $p < 0.001$). However, patients with higher comorbidity burden remained at a higher disease activity, suggesting that comorbidity burden may limit the extent of disease control achievable through intensified DMARD therapy alone.

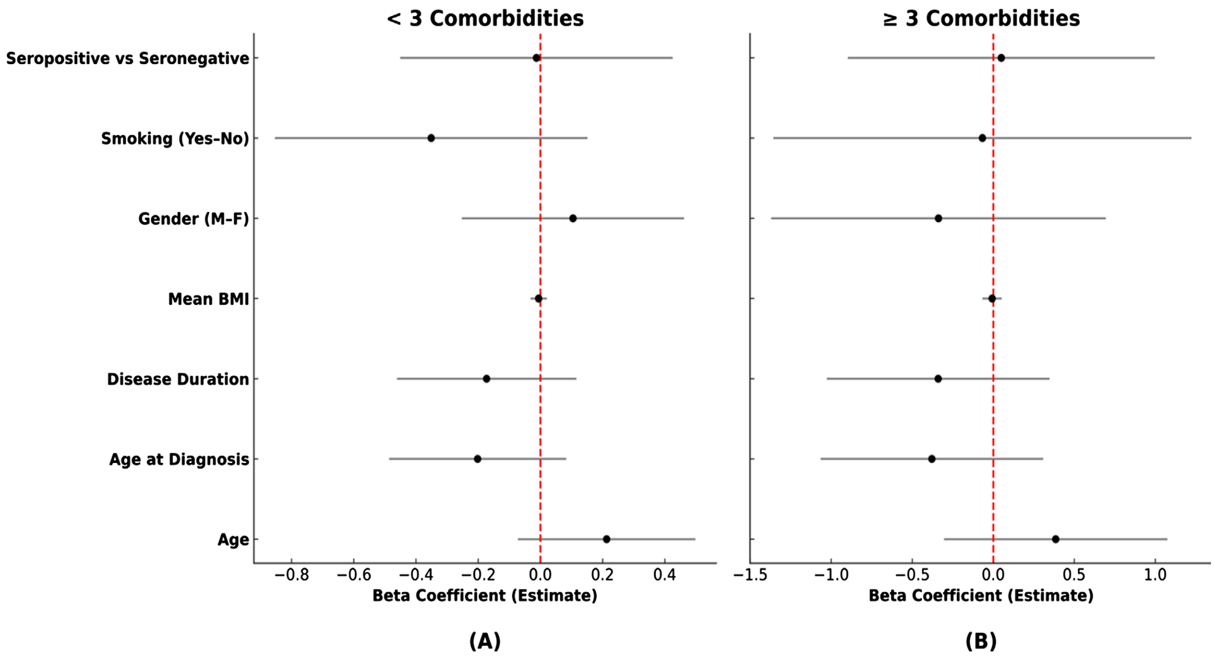

Figure 3. Forest plots showing the association between clinical and demographic factors and DAS28 change, stratified by comorbidity burden. Panel (A) shows patients with Low comorbidity burden, and panel (B) shows patients with high comorbidity burden. Each point represents the beta coefficient, and horizontal lines indicate 95% confidence intervals from linear regression models. The red dashed vertical line represents the null effect. No statistically significant associations with DAS28 change over one year were observed. BMI, body mass index; M-F, male-female; Seropositive, positive for rheumatoid factor or anti-CCP antibodies or both; seronegative, rheumatoid factor and anti-CCP are negative.

4.2. Inflammatory Markers and Comorbidity

In our cohort, CRP did not differ between high- and low-comorbidity burden groups, despite reports linking higher CRP with common comorbidities in RA [20]. Although ESR was marginally higher in patients with multiple comorbidities, this small difference highlights the need to interpret disease activity markers cautiously, given their confounding influence and linear relationship with comorbidities [3]. Notably, acute-phase reactants often diverge from clinical activity: in the CORRONA registry, only 16% of patients with active RA had both ESR and CRP elevated, whereas 58% had neither [21]. Taken together, these data indicate that ESR and CRP reflect different aspects of inflammation and are influenced by factors beyond RA activity (e.g., age, anemia, fibrinogen for ESR; short-lived IL-6-driven signal and treatment/adiposity effects for CRP); therefore, neither should be used in isolation to infer RA disease activity [22]-[25].

4.3. Comparison with Previous Studies

Our results are consistent with prior work showing that comorbidity burden can limit treatment response in RA [6]-[8]. Notably, in the Canadian Early Arthritis Cohort, Fatima *et al*. reported that higher RDCI scores predicted slower improvement despite biologic use [26]. Together, these studies align with our observation that comorbidity burden may constrain treatment outcomes once RA is established.

Furthermore, Corrao *et al*. emphasized that RA patients are at a markedly increased risk of cardiovascular diseases, including myocardial infarction and heart failure, with cardiovascular disease accounting for up to 40% of RA-related deaths [27]. In our registry, patients with high comorbidity burden exhibited notably high rates of diabetes (64.8%), hypertension (78.8%), and hyperlipidemia (49.2%). These findings underscore the need for comprehensive care beyond immunosuppressive treatments, including thorough screening and personalized therapeutic interventions to address the diverse health risks faced by RA patients.

Although emerging literature suggests that gender may influence RA disease activity and response to therapy, with female patients often experiencing poorer quality of life, higher disease activity, and reduced functional capacity [28], our data did not demonstrate a significant association between gender and disease activity in either group. Additionally, in contrast to prior evidence [29], overweight and obesity, defined according to World Health Organization criteria (BMI ≥ 25 kg/m^2), with mean BMI values ranging from 28.9 to 30.9 in our population, were not independent predictors of changes in DAS28 scores. Similarly, contrary to findings from international studies [30] [31], smoking status and seropositivity did not exhibit independent associations with disease activity measures within our cohort. Despite these differences from major global research, our findings underscore the importance of region-specific studies to better understand these relationships and develop tailored management approaches.

Future research should also include multivariable regression models to adjust for confounders and determine the independent predictive effect of comorbidity burden on disease activity outcomes.

4.4. Strengths and Limitations

Strengths of this study include its large sample size and standardized prospective data capture across all governmental hospitals in Kuwait, making it one of the few registry-based studies from the Middle East to evaluate comorbidity burden in RA patients. The inclusion of medication prescription patterns alongside disease activity provided a comprehensive view of both management and outcomes in real-world practice. The use of DAS28 further allowed consistent, longitudinal assessment of disease activity trajectories.

Several limitations should be acknowledged. The primary limitation is that comorbidities were recorded as binary variables without data on their severity or control measures (e.g., HbA1c, blood pressure), which may influence both prescribing behavior and outcomes. Additionally, certain comorbidities, such as depression and fibromyalgia, were not captured in the dataset, despite their potential to cause symptoms like pain and fatigue that may confound assessments of disease activity. While we primarily relied on DAS28 scores to evaluate the impact of comorbidities on disease activity, incorporating patient-reported outcomes, such as pain, physical function, fatigue, and sleep quality, in future studies would provide a more comprehensive understanding of the overall disease burden, particularly since these outcomes are underreported in our registry. Furthermore, as a robust statistical comparison between the included and excluded cohorts was not feasible due to the anonymized nature of the registry data, the potential for selection bias cannot be fully ruled out. Finally, as this study was designed as a descriptive evaluation of real-world treatment patterns, adjustment for confounding by indication was not undertaken. Differences in baseline disease activity, treatment-refractory status, or other unmeasured factors may have influenced therapeutic escalation and treatment selection. Accordingly, the observed treatment differences should be interpreted with caution, and causal inferences cannot be established. Given the registry-based design within a single healthcare system, the generalizability of these findings to other populations may be limited.

5. Conclusions

Our study emphasizes that comorbidity burden is a critical factor influencing treatment patterns and disease outcomes in RA. Patients with multiple comorbidities are more likely to receive biologic or combination therapy, yet tend to have higher residual disease activity. This indicates that antirheumatic therapy alone may not suffice to achieve optimal control in this subgroup. Implementing comprehensive treat-to-target strategies should include systematic screening and management of comorbidities such as diabetes, hypertension, and dyslipidemia, alongside the ongoing treatment of RA.

Future prospective studies with comprehensive data collection, including comorbidity control, severity, medication exposures, and long-term outcomes, are essential to refine risk stratification and optimize management strategies. Incorporating regional-specific and validated comorbidity indices will further enhance measurement precision. Ultimately, integrating structured management of comorbidities into RA treatment frameworks is crucial for improving outcomes in the RA population.

Authorship Contributions

All authors contributed equally to the conception and design of the work, the acquisition, analysis, and interpretation of data, as well as drafting and critically revising the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the study. The guarantor of the work takes full responsibility for the content, had access to all data, and made the decision to publish. Artificial intelligence (AI) assisted technologies were not used to generate the content of this manuscript. AI was employed solely to assist with editing for grammar and spelling mistakes in the final version.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Joint Committee for the Protection of Human Subjects in the research of the Kuwait Institute for Medical Specialization (KIMS) [Approval number: 2012/VDR/JC/882]. Ethical approval was obtained prior to data collection, and all procedures adhered to institutional and national guidelines.

Patient Consent

Written informed consent was obtained from all participants prior to enrollment, allowing the use of their clinical data for research purposes. All data were anonymized to protect patient privacy.

Permission to Reproduce Material

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

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Appendix

Table A1. Changes in disease activity for patients with low and high comorbidity burden.

Comorbidities	Comparison	Statistic	df	p-value		SE	Effect size
<3	First-Last DAS28	14.0	1138	<0.001	0.733	0.0522	0.416
≥3	First-Last DAS28	6.60	178	<0.001	0.816	0.124	0.494

DAS28: Disease Activity Score 28. DAS28 scores improved significantly from baseline to last visit in both groups. Among patients with <3 comorbidities, mean DAS28 decreased by 0.73 (SE 0.052, $p < 0.001$; Cohen's $d = 0.416$), indicating a moderate effect size. In patients with ≥3 comorbidities, mean DAS28 decreased by 0.82 (SE 0.124, $p < 0.001$; Cohen's $d = 0.494$), also corresponding to a moderate effect size. Differences were assessed using paired Student's t-tests.