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ORIGINAL ARTICLE

Prevalence of comorbidities and their associations with health-related quality of life and healthcare expenditures in patients with rheumatoid arthritis

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Abstract

Introduction/objectives Rheumatoid arthritis (RA) is known to be associated with an increased risk of comorbidities, premature mortality, and disability. We investigated the prevalence of comorbidities in RA compared with non-RA controls and the effect of comorbidities on health-related quality of life (HRQoL) and total healthcare expenditures.

Methods Adult RA patients and age-, sex-matched individuals without RA (non-RA controls) were identified from the Medical Expenditure Panel Survey 2010–2015 data. Twenty comorbidities were investigated including cardiovascular, psychological, respiratory, and musculoskeletal conditions. The Short Form-12 physical and mental component summary scores for HRQoL and total healthcare expenditures (2015 US dollars) were summarized based on the number of comorbidities as well as the type of comorbidities. Outcomes were further investigated using multivariable regression analyses.

Results A total of 2925 patients with RA and 14,625 non-RA controls were included. Approximately 60.4% of RA and 37.2% of non-RA controls had ≥ 3 comorbidities, and 23.5% of RA and 12.0% of non-RA controls had ≥ 5 comorbidities. The prevalence of comorbidities in RA was higher across different types of comorbidities compared with non-RA controls. The most prevalent comorbidities in RA were cardiovascular diseases (79.0%) followed by respiratory conditions (34.4%). Having ≥ 5 comorbidities in RA was significantly associated with lower SF-12 physical and mental scores and increase in healthcare expenditures compared with RA without any comorbidity ($23,214 ($19,941–$26,119) for ≥ 5 comorbidities vs. $11,137 ($7610–$14,396) for no comorbidity).

Conclusion A substantial number of patients with RA had multiple comorbidities. The comorbidities in RA were associated with poor HRQoL and higher healthcare expenditures.

Key Points

- *The prevalence of comorbidities was significantly higher in RA compared to age- and sex-matched non-RA controls.*
- *RA itself was associated with lower mental and physical health-related quality of life and increase in healthcare expenditures.*
- *A higher number of comorbidities in RA were associated with poorer mental and physical health-related quality of life and increase in healthcare expenditures.*
- *Specific comorbidities such as respiratory conditions and psychological disorders were associated with both health-related quality of life and economic burden in RA.*

Keywords Comorbidity · Economics · Health-related quality of life · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory, autoimmune disorder of idiopathic origin which presents as joint swelling and tenderness [1]. Over time, bone and joint damage caused by RA can lead to physical impairment and disability. In 2010, it was estimated that 1.5 million adults in the USA were affected by RA [2],

and in 2015, it was estimated that 24.5 million adults were affected by RA globally [3].

Over the last 15 years, the treatment of RA has been revolutionized by the development of new disease-modifying antirheumatic drugs (DMARDs) [4]. With these newer treatment options, most patients can be treated effectively, and bone and cartilage destruction can largely be prevented. Instead, it has been recognized that RA is a systemic condition and other disease manifestations may still be present even with the prevention of joint damage [5]. Although the extent varies, studies have been reported that RA is associated with a higher risk of developing comorbidities [6–13] and premature mortality [14, 15]. Inflammation seems to play a role in developing other comorbidities in RA [16]; however, the effect of these comorbidities or the comorbidity management strategies have not been widely studied.

The health-related quality of life (HRQoL) and economic burden can be largely affected by various comorbidities in patients with RA. It has been shown that patients with RA score consistently lower in both physical and mental components when compared with healthy controls, potentially due to the chronic pain and disability caused by RA [17, 18]. When compared with several other chronic conditions, including congestive heart failure, myocardial infarction, and type 2 diabetes, patients with RA scored worse in both physical and mental scores [19]. Economic burden of RA itself is substantial; it has been estimated that the medical cost of RA care was $22.3 billion per year [20], and the societal cost of treating RA was $39.2 billion [21] in the USA. The potential additive impact of comorbidities on HRQoL and economic burden in RA has been a subject of several studies [22], but most of the studies focus on a single specific comorbid condition (e.g., depression) rather than overall comorbidities in patients with RA.

It is inevitable for clinicians to manage multiple chronic conditions simultaneously in patients with RA. Undoubtedly, more studies are needed to better understand comorbidities in patients with RA. Understanding the burden of comorbidities in RA will provide important insights into the disease management strategies. The objectives of this study were (1) to estimate the prevalence of comorbidities in patients with RA compared to age-, sex-matched non-RA controls, and (2) to assess the association between the number and types of comorbidities and disease burden (HRQoL and total healthcare expenditures) in patients with RA and age-, sex-matched non-RA controls from a nationally representative sample in the USA.

Patients and methods

Data source

The data were pooled from the Medical Expenditure Panel Survey-Household Component (MEPS-HC), a nationally representative survey of the US civilian, non-institutionalized population [23]. The MEPS-HC uses the National Health Interview Survey conducted by the National Center for Health Statistics as its sampling frame. Through a series of five interviews over the course of 2 years, using computer-assisted personal interviews, the MEPS-HC collects detailed data on demographic characteristics, health conditions, health status, access to care, satisfaction with care, health insurance coverage, income, employment, and healthcare expenditures at the person and household level [23]. The medical conditions and procedures reported by the MEPS-HC respondent were recorded by the interviewer as verbatim text, which was then coded by professional coders to International Classification of Diseases, Ninth Revision (ICD-9) codes and Clinical Classification System (CCS) codes [23].

Study population

Patients with RA were identified from the 2010–2015 MEPS-HC medical condition files, using the ICD-9 code of 714.xx or the CCS code of 202. Patients were required to have at least two or more diagnosis codes from the medical condition files or have one or more diagnosis code with a DMARD prescription [24]. Patients < 18 years of age were excluded. Non-RA controls were identified among the adults without any RA diagnoses and were matched to the RA patients based on the survey year, age, and sex in a ratio of 1:5.

Comorbidity

Twenty different chronic conditions were identified using ICD-9 codes or CCS codes suggested by the United States Department of Health and Human Services Office of the Assistant Secretary of Health for research regarding multiple chronic conditions [25]. The patient-centered holistic approach was used to investigate comorbidities in this study; instead of focusing on all specific side effects or conditions associated with RA, we investigated a broader range of chronic conditions frequently reported in multiple chronic condition research. The outcomes were investigated based on the number of comorbidities (no comorbidity, 1–2 comorbidities, 3–4 comorbidities, and ≥ 5 comorbidities) as well as the clinical type of comorbidities (cardiovascular diseases, psychological disorders, diabetes/chronic kidney diseases (CKD), respiratory condition, musculoskeletal disorder, cancer, hepatitis/HIV). The definition and clinical type of each comorbidity is shown in Appendix 1.

Outcomes

Health-related quality of life The Short Form-12 (SF-12) [26] scale was used to report HRQoL in RA and age-, sex-matched non-RA controls. The SF-12 is a self-reported survey tool

used to measure health status, and responses are summarized into two categories: physical component summary (PCS) and mental component summary (MCS). [26] The SF-12 PCS and MCS scores range from 0 to 100, where zero means poorest health status and 100 the highest health status [26]. The weighted mean (SE) SF-12 PCS and MCS scores were estimated for patients with RA and non-RA controls by the number and types of different comorbidities. The adjusted SF-12 PCS and MCS scores by the number of comorbidities were estimated and the differences in SF-12 PCS and MCS scores were compared for those without comorbidities and between RA and non-RA controls with the specific type of comorbidity.

Healthcare expenditures Total direct healthcare costs were estimated including the treatment of RA and other comorbidities. The MEPS-HC collects all direct healthcare-related expenditures. The total healthcare expenditures included in this study were pharmacy, office visits, emergency department, inpatient, hospital outpatient, zero-night stay hospital use, home health care, dental care, vision aids, other medical equipment, and service-related costs. All cost estimates from 2010 and 2015 MEPS database were inflated to 2015 US dollars ($) using the Consumer Price Index [27].

Statistical analysis

Baseline characteristics were evaluated using descriptive statistics. Survey sampling weights were applied in all the analyses to adjust for non-response bias and oversampling of the survey design. We utilized an independent t test and Rao–Scott χ^2 test for differences in SF-12 PCS and MCS scores, as well as for healthcare costs based on the number and types of comorbidities among patients with RA and age-, sex-matched non-RA controls. The weighted mean (SE) SF-12 PCS and MCS scores and healthcare costs were estimated for RA and non-RA controls considering survey weights and strata. The differences in RA and non-RA controls, as well as groups with the specific comorbidity and without the comorbidity were reported. For the number of comorbidities, the patients with 1–2 comorbidities, 3–4 comorbidities, and ≥ 5 comorbidities were compared with the patients without any comorbidity.

To further adjust for confounding factors, multivariable linear regression model was used for HRQoL analysis. Covariates were sex, age, race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black, others), region (Northeast, Midwest, South, West), education (lower than high school, high school, college or more), marital status, income level (poor/negative, near poor, low income, middle income, high income), and RA disease duration. For cost analysis, a generalized linear regression model (gamma distribution, log link) was used to calculate the adjusted mean healthcare expenditures along with bootstrapped confidence intervals. The differences in adjusted mean of SF-12 PCS, MCS, and healthcare expenditures by number of comorbidities were investigated. All analyses considered sampling strata and weights in this survey design. The analysis was conducted using SAS 9.4 and STATA 15. A p value of ≤ 0.05 considered statistically significant.

Results

The study identified 2925 patients with RA and 14,625 age- and sex-matched non-RA controls. Mean (SE) age of the study sample was 60.4 (0.2) years and mean (SE) years since diagnosis of RA was 19.3 (0.7). Among the patients with RA, 9.2% patients did not report any defined comorbidities, 30.4% had one to two comorbidities, 36.9% had three to four comorbidities, and 23.5% had five or more comorbidities. Among the age-, sex-matched non-RA controls, 26.3% did not report any comorbidities, and 12.0% had five or more comorbidities. Mean (SE) number of comorbidities were 3.1 (0.1) for RA and 2.1 (0.02) for non-RA controls.

Table 1 shows the baseline characteristics of RA and non-RA controls. Different socioeconomic status was observed between patients with RA and non-RA controls. A higher proportion of RA patients were non-Hispanic Black compared with non-RA controls (16.3% vs. 10.3%), a higher proportion of RA patients had public insurance only compared with non-RA controls (41.6% vs. 25.5%), and a higher proportion of RA patients reported poor income compared with non-RA controls (19.4% vs. 11.1%). The perceived health status of RA was poor compared with non-RA controls; 61.9% of the RA patients reported fair/poor health whereas 27.3% of the non-RA controls reported fair/poor health.

The prevalence of comorbidities was higher in RA patients compared with the age-, sex-matched non-RA controls across different types of comorbidities (Fig. 1). The frequency of cardiovascular diseases, respiratory disorders, psychological disorders, diabetes/CKD, cancer, and hepatitis/HIV were all higher in RA compared with non-RA controls. The prevalence of each comorbid condition in RA and non-RA controls is shown in Appendix 1.

Table 2 presents weighted mean (SE) of HRQoL scores and total healthcare expenditures in RA and non-RA controls by the number of comorbidities. Patients with RA had significantly lower mean SF-12 PCS and MCS scores and higher mean healthcare expenditures compared with non-RA controls. For those who had no other comorbidities, the mean (SE) SF-12 PCS scores were lower by 10.0 (0.7) and the mean (SE) total healthcare expenditures were higher by $8849 ($2031) in patients with RA compared with non-RA controls. The mean SF-12 PCS and MCS scores were progressively lower and the mean expenditures were higher as the number of comorbidities increases in both RA and non-RA controls.

Table 1 Patient characteristics in rheumatoid arthritis (RA) and age-, sex-matched non-RA controls

	Age-, sex-matched non-RA ($N = 14,625$)	RA ($N = 2925$)	p value
Mean (SE) age	60.4 (0.2)	60.3 (0.5)	< 0.0001
Age category			
Age 18–45	14.2%	14.5%	< 0.0001
Age 45–64	45.4%	44.7%	
Age ≥ 65	40.4%	40.9%	
Female sex	69.5%	67.1%	0.1472
Race/ethnicity			
Hispanic	11.1%	12.0%	< 0.0001
Non-Hispanic white only	71.7%	65.2%	
Non-Hispanic black only	10.3%	16.3%	
Others	6.9%	6.5%	
Marital status			< 0.0001
Married	52.1%	45.6%	
Others	47.9%	54.4%	
Education			< 0.0001
Lower than high school	13.8%	23.0%	
High school	32.1%	34.3%	
College or more	54.2%	42.7%	
Region			0.0424
Northeast	18.8%	15.2%	
Midwest	21.4%	21.1%	
South	36.6%	41.4%	
West	21.5%	20.8%	
Unknown	1.6%	1.4%	
Perceived health			< 0.0001
Excellent/very good	36.1%	11.3%	
Good	36.1%	26.5%	
Fair/poor	27.3%	61.9%	
Insurance			< 0.0001
Any private	65.7%	51.2%	
Public only	25.5%	41.6%	
Uninsured	8.8%	7.2%	
Income			< 0.0001
Poor/negative	11.1%	19.4%	
Near poor	4.4%	7.8%	
Low income	14.2%	17.1%	
Middle income	28.2%	26.9%	
High income	42.1%	28.8%	
Mean (SE) number of comorbidities	2.1 (0.02)	3.1 (0.1)	< 0.0001
Mean (SE) Elixhauser score	1.1 (0.1)	1.8 (0.2)	< 0.0001
Number of comorbidities			< 0.0001
0	26.3%	9.2%	
1–2	36.5%	30.4%	
3–4	25.2%	36.9%	
≥ 5	12.0%	23.5%	
Mean (SE) duration of RA	–	19.3 (0.7)	–

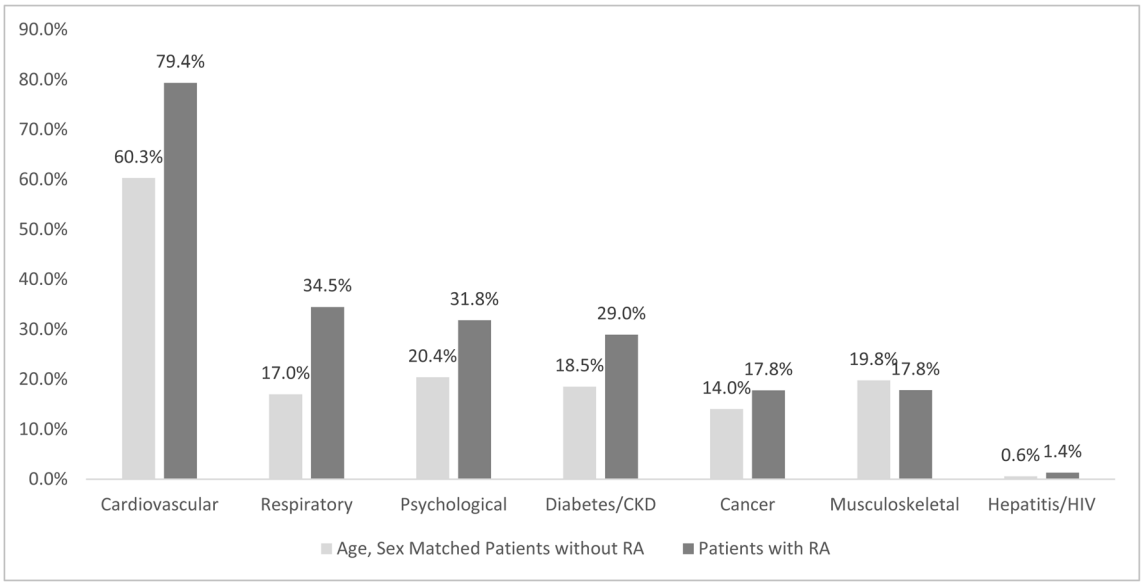

Fig. 1 Higher prevalence of comorbidities in rheumatoid arthritis (RA) compared with age- and sex-matched non-RA controls

The mean (SE) SF-12 PCS scores of RA patients with ≥ 5 comorbidities were 27.7 (0.8) which was statistically significantly lower than the mean of RA patients with no comorbidity (37.0 (1.7), $p < 0.001$) and lower than the mean of non-RA controls with ≥ 5 comorbidities (32.5 (0.5), $p < 0.001$). The similar trends were observed for SF-12 MCS scores and healthcare expenditures. The differences in SF-12 MCS scores between RA and non-RA became larger when patients had more comorbidities.

After adjusting for confounding factors, having ≥ 5 comorbidities were significantly associated with lower SF-12 PCS and MCS scores compared with no comorbidity in patients with RA. In addition, having ≥ 3 comorbidities were significantly associated with higher total healthcare expenditures compared with no comorbidity. Figures 2 and 3 show the adjusted mean (95% bootstrapped CI) of SF-12 PCS and MCS scores as well as healthcare expenditures by the number of comorbidities. The adjusted

Table 2 Weighted mean (SE) for SF-12 health-related quality of life scores and total healthcare expenditures by number of comorbidities in rheumatoid arthritis (RA) and age-, sex-matched non-RA controls

Number of comorbidities	Age-, sex-matched non-RA ($N = 14,625$)	RA ($N = 2925$)	Differences between RA and non-RA (non-RA − RA)
SF-12 Physical Component Score			
None	47.2 (0.4)	37.0 (1.7)	10.0 (1.7)***
1–2	43.7 (0.4)***	36.1 (0.9)	7.6 (0.9)***
3–4	39.0 (0.4)***	31.7 (0.9)**	7.3 (1.0)***
5 or more comorbidities	32.5 (0.5)***	27.7 (0.8)***	4.8 (1.0)***
SF-12 Mental Component Score			
None	47.5 (0.4)	46.3 (1.6)	1.3 (1.6)
1–2	46.9 (0.4)	45.5 (0.9)	1.5 (0.9)
3–4	46.5 (0.4)*	43.0 (1.0)*	3.5 (1.1)**
5 or more comorbidities	43.8 (0.6)***	40.1 (1.0)***	3.6 (1.1)**
Healthcare expenditure (2015 USD)			
None	$2222 ($117)	$11,107 ($2033)	− $8849 ($2031)***
1–2	$5623 ($255)***	$11,893 ($870)	− $6270 ($921)***
3–4	$10,641 ($452)***	$15,624 ($1147)**	− $4983 ($1183)***
5 or more comorbidities	$19,980 ($1194)***	$24,660 ($2098)***	− $4680 ($2383)

Statistical significance in age-, sex-matched non-RA and RA columns were from the comparison with the "none" comorbidity category

*$p < 0.05$; **$p < 0.01$, ***$p < 0.001$

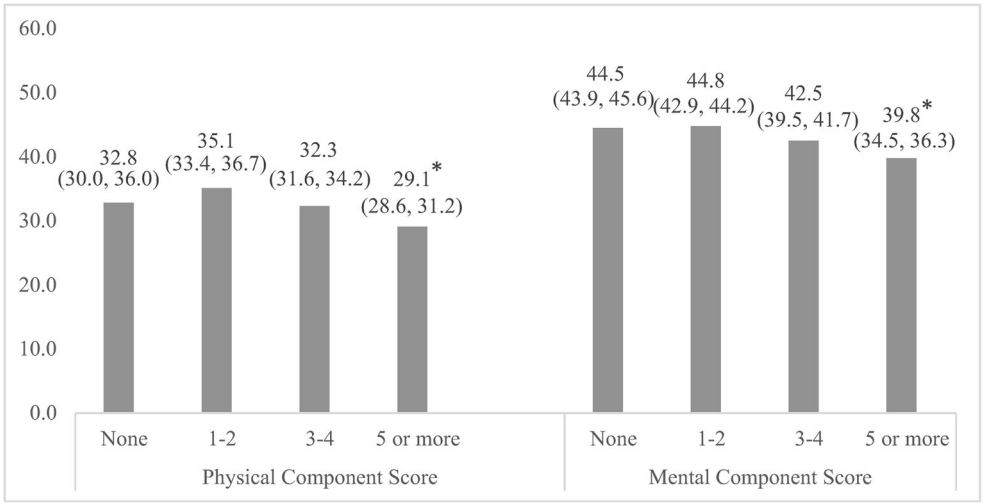

Fig. 2 Adjusted mean (95% bootstrapped CI) of SF-12 physical and mental component scores for rheumatoid arthritis (RA) patients by different number of comorbidities

mean (95% bootstrapped CI) SF-12 MCS scores were 44.5 (43.9–45.6) for no comorbidity and 39.8 (34.5–36.3) for ≥5 comorbidities; the mean SF-12 PCS scores were 32.8 (30.0–36.0) for no comorbidity and 29.1 (28.6–31.2) for ≥5 comorbidities; and the mean healthcare expenditures were $11,137 ($7610–$14,396) for no comorbidity, $13,696 ($12,431–$15,609) for 3–4 comorbidities, and $23,214 ($19,941–$26,119) for ≥5 comorbidities.

The weighted mean (SE) of SF-12 PCS and MCS scores and total healthcare expenditures are shown in Table 3. In patients with RA, respiratory conditions and psychological disorders were associated with physical and mental scores as well as economic burden. RA patients with these conditions consistently had lower SF-12 PCS, MCS, and higher healthcare expenditures compared with patients without respiratory or psychological comorbidities. Having diabetes/CKD in RA patients was associated with lower physical scores, whereas having hepatitis/HIV was associated with lower mental component scores. Diabetes/CKD, musculoskeletal disorder, and cancer in RA patients were associated with higher healthcare expenditures. These associations were somewhat different from findings in non-RA controls. The magnitude of differences in PCS scores, and in healthcare expenditures between patients with each type of comorbidity compared with no comorbidity was higher in non-RA controls than in RA. When we compared RA patients and non-RA controls with each type of comorbidity, the magnitude of differences in SF-12 PCS scores were similar throughout different types of comorbidities. The differences in SF-12 MCS scores between RA and non-RA controls were greater in patients with musculoskeletal disorder, cancer, and cardiovascular diseases, and the differences in healthcare expenditures between RA and non-RA controls were greater in musculoskeletal disorder, diabetes/CKD, and respiratory condition.

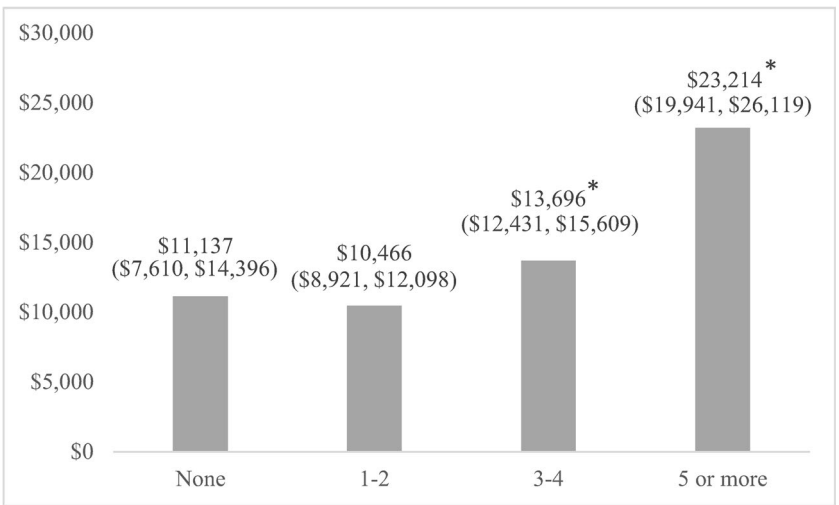

Fig. 3 Adjusted mean (95% bootstrapped CI) of healthcare expenditures for rheumatoid arthritis (RA) patients by different number of comorbidities

Table 3 Weighted mean (SE) for SF-12 health-related quality of life scores and total healthcare expenditures by type of comorbidities in rheumatoid arthritis (RA) and age-, sex-matched non-RA controls

Comorbidity	Age-, sex-matched non-RA ($N = 14,625$)			RA ($N = 2925$)			RA vs. non-RA with comorbidity
	Without comorbidity (A)	With comorbidity (B)	Differences (A) − (B)	Without comorbidity (C)	With comorbidity (D)	Differences (C) − (D)	Differences (B) − (D)
SF-12 Physical Component Score							
Cardiovascular disease	45.8 (0.4)	39.6 (0.3)	6.2 (0.4)***	35.6 (1.2)	31.8 (0.6)	3.8 (1.3)**	7.8 (0.7)***
Diabetes/CKD	43.5 (0.3)	35.9 (0.5)	7.6 (0.5)***	33.6 (0.6)	30.3 (0.9)	3.3 (0.9)***	5.6 (1.0)***
Psychological disorder	43.1 (0.3)	37.9 (0.5)	5.2 (0.5)***	33.3 (0.6)	31.1 (0.8)	2.2 (0.9)*	6.9 (0.9)***
Respiratory condition	42.9 (0.3)	37.9 (0.5)	5.1 (0.5)***	33.9 (0.7)	30.1 (0.8)	3.8 (1.0)***	7.7 (1.0)***
Musculoskeletal disorder	43.2 (0.3)	37.5 (0.4)	5.7 (0.5)***	32.9 (0.6)	31.5 (1.0)	1.4 (1.1)	6.1 (1.1)***
Cancer	42.5 (0.3)	39.4 (0.6)	3.1 (0.6)***	33.0 (0.6)	30.9 (1.4)	2.2 (1.5)	8.5 (1.5)***
Hepatitis/HIV	42.1 (0.2)	41.1 (1.7)	1.0 (1.7)	32.6 (0.6)	32.3 (2.2)	0.3 (2.3)	8.8 (2.7)**
SF-12 Mental Component Score							
Cardiovascular disease	46.5 (0.3)	46.7 (0.3)	− 0.1 (0.4)	43.6 (1.3)	43.3 (0.6)	0.4 (1.5)	3.4 (0.7)***
Diabetes/CKD	47.0 (0.3)	45.0 (0.5)	2.0 (0.5)***	43.6 (0.7)	42.8 (0.9)	0.8 (1.1)	2.2 (1.1)
Psychological disorder	48.1 (0.3)	40.3 (0.5)	7.8 (0.6)***	45.9 (0.6)	37.8 (0.8)	8.1 (0.9)***	2.5 (0.9)**
Respiratory condition	46.9 (0.3)	44.9 (0.5)	2.0 (0.5)***	44.3 (0.6)	41.6 (1.0)	2.6 (1.1)*	3.3 (1.1)**
Musculoskeletal disorder	46.5 (0.3)	47.2 (0.4)	− 0.7 (0.5)	43.3 (0.6)	43.7 (1.0)	− 0.3 (1.2)	3.6 (1.0)***
Cancer	46.5 (0.3)	47.2 (0.6)	− 0.7 (0.3)	43.6 (0.6)	42.3 (1.8)	1.3 (1.8)	4.9 (1.8)**
Hepatitis/HIV	46.6 (0.2)	43.7 (1.6)	2.9 (1.6)	43.5 (0.6)	36.9 (3.2)	6.6 (3.2)*	6.8 (3.5)
Healthcare expenditure (2015 USD)							
Cardiovascular Disease	$3788 ($210)	$10,336 ($317)	− $6548 ($388)***	$13,994 ($1606)	$16,772 ($817)	− $2778 ($1832)	− $6437 ($846)***
Diabetes/CKD	$6514 ($230)	$12,928 ($547)	− $6414 ($598)***	$14,463 ($745)	$20,441 ($1503)	− $5978 ($1627)***	− $7513 ($1605)***
Psychological disorder	$6339 ($205)	$13,335 ($655)	− $6997 ($684)***	$14,532 ($810)	$19,765 ($1462)	− $5232 ($1692)**	− $6429 ($1565)***
Respiratory condition	$6659 ($196)	$12,902 ($880)	− $6242 ($922)***	$14,149 ($792)	$20,077 ($1602)	− $5928 ($1860)**	− $7175 ($1820)***
Musculoskeletal disorder	$6525 ($222)	$12,468 ($552)	− $5943 ($604)***	$14,788 ($727)	$22,611 ($1994)	− $7823 ($2092)***	− $10,143 ($2096)***
Cancer	$6636 ($171)	$14,532 ($1013)	− $7896 ($1031)***	$15,155 ($770)	$20,995 ($1981)	− $5839 ($2181)**	− $6463 ($2339)**
Hepatitis/HIV	$7593 ($203)	$25,286 ($8299)	− $17,693 ($8309)*	$16,037 ($714)	$27,401 ($7501)	− $11,363 ($7490)	− $2114 ($11,319)

*$p < 0.05$; **$p < 0.01$, ***$p < 0.001$

Discussion

This study showed that patients with RA have a higher number of comorbidities compared with patients without RA but having same age and sex. Over 90% of RA patients had at least one comorbidity, two thirds of RA patients had three or more comorbidities, and one in four RA patients had five or more comorbidities. The estimated prevalence of comorbidities varies based on the study population, settings, and definition of comorbidities in different studies. It should be noted that this study investigated the prevalence of comorbidities in patients with RA in a nationally representative US sample including patients with long-standing RA. The average years since RA diagnosis were 19 years in this study, and this may be the reason why this study shows a higher prevalence of comorbidities than other studies which investigated early inflammatory stage of RA [28].

Almost all comorbidities we have investigated were consistently higher in patients with RA compared with the age-, sex-matched non-RA controls. Prevalence of cardiovascular diseases was higher in patients with RA compared with the general population which is consistent with other studies [8, 29]. Respiratory conditions were over two times more common in patients with RA than in non-RA controls; these findings also confirm previous reports [9, 29]. Furthermore, patients with RA were found to have a higher prevalence of depression [7, 10, 29] and a higher prevalence of diabetes, CKD, and malignancies [11, 29] when compared to non-RA, which is again consistent with other studies. A higher prevalence of alcohol/drug abuse was found in RA compared with non-RA, which may need further investigation in other studies. Contrary to other studies [30], arthritis other than RA or osteoporosis was lower in RA compared with non-RA. This may be due to the potential misclassification; the definition of RA or other arthritis was based on survey responses. Patients might not be able to distinguish RA from similar conditions such as osteoarthritis and osteoporosis.

The study findings of higher prevalence of many different types of comorbidities in patients with RA suggest that clinicians who manage RA should be aware that these patients are at a higher risk for comorbidities, and the RA comorbidity management strategies such as screening for risk factors, prevention, and treatment of comorbidities should be further developed [31, 32]. Although current clinical guidelines emphasize regular screenings of specific comorbidities such as CVD risk factors (e.g., Systematic Coronary Risk Evaluation calculator) [32] or cancer screening [31], further clinical guidelines may be needed for other comorbidities such as depression or respiratory conditions in RA. Moreover, future studies to investigate the treatment response or treatment strategies to better manage these comorbidities in RA patients may be necessary. A systematic review suggested that the use of TNF-alpha antagonists was associated with decreased risk of CVD [33], and similar studies may be able to answer whether specific therapies for specific comorbidities are particularly beneficial.

This study showed that RA patients had a substantial disease burden associated with their comorbidities on their HRQoL. RA itself had a significant impact on physical component of HRQoL, and moreover, additional comorbidities further burden the patients. These comorbidities were also associated with lower mental component of HRQoL. Overall, an increased number of comorbidities was associated with poor HRQoL in RA. Also, there were specific types of comorbidities associated with poorer HRQoL in RA. Respiratory and hepatitis/HIV conditions were associated with poor mental component of HRQoL and CVD, diabetes/CKD, and respiratory conditions were associated with poor physical component of HRQoL. These findings suggest that RA patients with specific types of comorbidities may need special attention in both their mental and physical health status.

This study also suggests that for the RA patients with a higher number of comorbidities (five or more), the total healthcare expenditures are almost two times higher when compared with the RA patients without comorbidity or with the RA patients with 1 or 2 comorbidities. Currently, very few studies exist on the relationship between total healthcare expenditures and comorbidities in RA. These results may be consistent with Han et al.'s study, which showed that as the number of comorbidities increased, patients with RA spent more time hospitalized and accrued more medical charges [22]. These study findings may be useful for clinicians, payers, or policy-makers for developing clinical programs in RA patients; specific care plans or treatment strategies should be discussed in patients with a higher number of comorbidities, which may include nurse- or pharmacist-led interventions suggested by other studies [34]. Our study findings suggest further studies to elucidate the optimal management of comorbidities in RA patients are warranted, and that future RA practice guidelines may need to put a greater emphasis on managing comorbidities. Also, collaborative and patient-centered care models may be useful for these complex RA patients to improve HRQoL and reduce healthcare costs [35]. Moreover, these findings may be helpful in investigating comparative effectiveness or safety of therapies or serve as baseline population data understanding patient-reported outcomes and healthcare expenditures in patients with RA with/without comorbidities.

This study has limitations which cannot be avoided by the nature of the study design. This is a cross-sectional study investigating the association between comorbidities and HRQoL or healthcare expenditures. This study was not aimed at investigating a casual inference of comorbidity on outcome; therefore, the study results should be interpreted with caution. Measurement errors and response bias may be present in this study due to the nature of survey data analysis. Patients'

unawareness of RA condition or potential misclassification with other types of arthritis is possible. The RA disease activity such as the Disease Activity Score 28 or the Health Assessment Questionnaire score was not available in this dataset which limits the interpretation of our findings. It is possible that RA disease activity may have affected HRQoL rather than comorbidities in patients with RA.

Despite these limitations, this study has several strengths. First, the study provides a more comprehensive view of multiple chronic conditions that patients with RA may have rather than focusing on a specific comorbidity of RA. This study performed holistic investigations of comorbidity in patients with RA compared with non-RA; therefore, to our knowledge, this is one of the first few studies looking at the association between the number of multiple chronic conditions and outcomes in RA and non-RA controls. In addition, different aspects of comorbidity burden were investigated from the total healthcare expenditures and mental and physical HRQoL in RA compared with non-RA. Lastly, this study investigated a nationally representative sample using patients with RA and age-, sex-matched non-RA controls. The prevalence of comorbidities can be considered as a national prevalence of conditions in patients with RA and non-RA controls.

In conclusion, this study found that a substantial number of patients with RA had multiple comorbidities compared with non-RA controls. The higher number of comorbidities in RA was associated with poorer HRQoL and higher healthcare expenditures. Specific comorbidities such as respiratory conditions and psychological disorders associated with both HRQoL and economic burden may need further attention in comorbidity management in RA.

Compliance with ethical standards The manuscript does not contain clinical studies or patient data. This study analyzed the publicly available data sets, and the data available to the public are not individually identifiable.

Disclosures None.

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