ORIGINAL RESEARCH

Healthcare Costs of Not Achieving Remission in Patients with Rheumatoid Arthritis in the United States: A Retrospective Cohort Study

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ABSTRACT

Introduction: To compare all-cause and rheumatoid arthritis (RA)-related healthcare costs and resource use in patients with RA who do not achieve remission versus those who achieve remission, using clinical practice data.

Methods: Data were derived from Optum electronic health records linked to claims from commercial and Medicare Advantage health plans. Two cohorts were created: remission and non-remission. Remission was defined as Disease Activity Score 28-joint count with the C-reactive protein level or erythrocyte sedimentation rate (DAS28-CRP/ESR) < 2.6 or Routine Assessment of Patient Index Data 3 (RAPID3 ≤ 3.0). Outcomes were all-cause and RA-related costs and resource use during a 1-year follow-up period. A weighted generalized linear regression and negative binomial regression were used to estimate adjusted annual costs and resource use, respectively, controlling for confounding factors, including patient and socio-demographic characteristics.

Results: Data from 335 patients (remission: 125; non-remission: 210) were analyzed. Annual all-cause total costs were significantly less in the remission versus non-remission cohort ($30,427 vs. $38,645, respectively; cost ratio [CR] = 0.79; 95% CI 0.63, 0.99). All-cause resource use (mean number of visits) was less in the remission versus non-remission cohort: inpatient (0.23 vs. 0.63; visit ratio [VR] = 0.36; 95% CI 0.19, 0.70), emergency department (0.36 vs. 0.77; VR = 0.47; 95% CI 0.30, 0.74), and outpatient visits (20.7 vs. 28.5; VR = 0.73; 95% CI 0.62, 0.86). Annual RA-related total costs were similar in both cohorts; however, RA-related medical costs were numerically lower in the remission versus non-remission cohort ($8,594 vs. $10,002, respectively; CR = 0.86; 95% CI 0.59, 1.25). RA-related resource use was less in the remission versus non-remission cohort.

Conclusions: Significant economic burden was associated with patients who did not achieve remission compared with those who did achieve remission.

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Key Summary Points

Why carry out this study?

Rheumatoid arthritis (RA) is a chronic disease with substantial economic burden to patients and society

Guidelines recommend sustained remission of disease activity as a treatment goal for patients with RA

The economic benefit of achieving remission in a commercially insured RA population on healthcare services remains to be defined

What was learned from the study?

Significant economic burden was associated with patients who did not achieve remission compared with those who achieved remission

Higher costs in the non-remission cohort were driven mostly by non-RA-related outpatient visits, suggesting that tighter disease control may have beneficial effects beyond those related to RA

These findings may assist physicians and payers in making decisions regarding the management of patients with RA

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14292272.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease characterized by inflammation of multiple joints [1] affecting an estimated 1.3–1.4 million adults in the USA [2].

Without treatment, RA can lead to progressive joint damage resulting in disability and poor health-related quality of life [3–6]. The economic burden of RA to patients and society is substantial with annual costs related to hospital care, drug use, and work loss estimated to be 2–3 times higher in patients with RA compared with those without RA [7, 8].

Early therapy with disease-modifying antirheumatic drugs (DMARDs) can slow or prevent disease progression and limit disability [9–11]. Guidelines recommend sustained remission of disease activity as a treatment goal for patients with RA [12, 13]. Five different measures of disease activity are recognized by the American College of Rheumatology as preferred options to guide clinical practice decisions toward a target of clinical remission [14]. These include the Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 Joints with C-reactive protein level or erythrocyte sedimentation rate (DAS28-CRP/ESR), Routine Assessment of Patient Index Data 3 (RAPID3), Patient Activity Scale-II, and Simplified Disease Activity Index [14]. Each has its own strengths and limitations, while all are scientifically reliable for their intended use in routine clinical practice [14]. The goal of the treat-to-target approach is to stop disease progression, reduce joint damage, prevent functional disability, lower risk of cardiovascular disease, normalize participation in social and professional life, and maximize health-related quality of life using a tight control strategy [15–20]. Studies have shown that there is significantly greater improvement in clinical, functional, and patient-reported outcomes in patients with RA who achieve clinical remission compared with those who do not [20–24].

A number of drugs with different mechanisms of action are available to treat RA, including conventional synthetic DMARDs (e.g, methotrexate, sulfasalazine, and leflunomide), biologic DMARDs (e.g., tumor necrosis factor alpha inhibitors; interleukin [IL] 1, IL 6, and IL 6 receptor inhibitors, T-cell co-stimulation modulators, and agents that deplete B-cells), and targeted synthetic DMARDs (e.g., Janus kinase inhibitors) [25]. Despite the availability of these

treatments, only one-third of patients are known to achieve sustained remission [26, 27].

The benefit of achieving remission on healthcare services (e.g., hospitalizations, emergency department [ED] visits, and outpatient physician visits) remains to be defined. A few studies have evaluated the impact of remission on healthcare use and costs [24, 28, 29]. One study found significant economic benefits for the Canadian healthcare system in patients who required biological therapy with the greatest savings seen in those who achieved good disease control [29]. A retrospective study conducted in The Netherlands assessed clinical, functional, and cost outcomes in patients with early RA and found that achieving early remission was associated with lower disease activity and lower costs over a 5-year follow-up period [24]. Another study analyzed data from an elderly patient population in the US and found lower rates of hospitalizations, ED visits, and medical costs associated with remission [28].

It is important to examine the impact of RA on healthcare use and associated costs and determine cost drivers in a commercially insured patient population with RA. We hypothesized that achieving remission would be associated with lower healthcare costs compared with not achieving remission in a commercially insured population of patients with RA in the US. The objective of this study was to compare all-cause and RA-specific annual healthcare costs and health resource use in patients with RA who achieved remission with those who did not achieve remission.

METHODS

Study Design and Data Source

This was a retrospective cohort study evaluating the economic burden of not achieving remission in RA using data from Optum's de-identified Integrated Claims Clinical dataset in which electronic health records (EHR) were linked to healthcare claims from commercial and Medicare Advantage health plans in the US. The Optum EHR data (January 2007–March 2019)

were derived from multiple large health provider organizations in the US, representing > 140,000 providers, 7000 clinics, and 760 hospitals in all 50 states yielding study results that are generalizable to the RA population in the US.

This was a retrospective study using anonymous data; therefore, Ethics Committee approval was not required. However, the data were certified as de-identified by an independent statistical expert following the statistical de-identification rules of the Health Insurance Portability and Accountability Act (HIPPA) and managed according to customer data use agreements.

Study Population

Patients with RA in the integrated Optum EHR and claims database were identified using International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9-CM/ICD-10-CM) codes (714.0, 714.1, 714.2, 714.81, M05.x, M06.x). Inclusion criteria required that patients had at least two separate claims with an RA diagnosis on different days and at least one disease activity score (either DAS28-CRP/ESR or RAPID3) during the study period. Patients also had to have continuous insurance coverage for 6 months before and 1 year after the index date. Two cohorts were created: remission and non-remission (Fig. 1). In this study, achieving remission was defined as DAS28 < 2.6 or RAPID3 ≤ 3.0. In the remission cohort, the index date was defined as the first date remission was achieved. In the non-remission cohort (patients who never achieved remission during the whole study period), the index date was defined as the first date of DAS28 or RAPID3 measurement.

Outcomes

Outcomes were all-cause and RA-related total costs (medical and prescription), healthcare resource use (number of annual inpatient, ED, outpatient, and other visits), and number of prescriptions within 1 year of index date. Medical costs included inpatient, ED, outpatient,
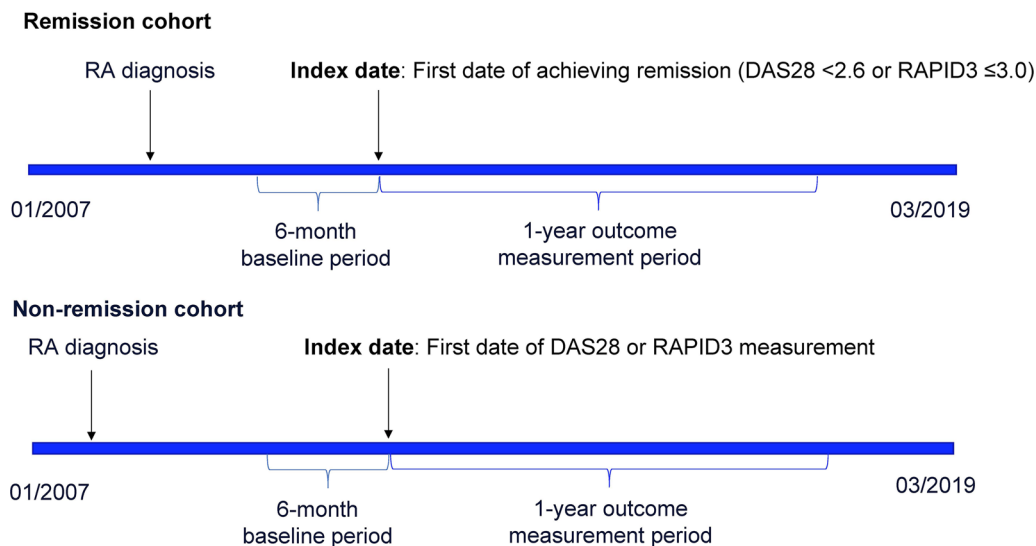
Remission cohort

RA diagnosis   **Index date**: First date of achieving remission (DAS28 <2.6 or RAPID3 ≤3.0)

01/2007   03/2019

6-month   1-year outcome
baseline period   measurement period

Non-remission cohort

RA diagnosis   **Index date**: First date of DAS28 or RAPID3 measurement

01/2007   03/2019

6-month   1-year outcome
baseline period   measurement period

Fig. 1 Study design. Patients were grouped into the remission cohort or non-remission cohort based on their remission status at the index date. Patients with DAS28 < 2.6 or RAPID3 ≤ 3.0 were defined as achieving remission, based on the American College of Rheumatology treatment guideline for RA [12]. *DAS28* Disease Activity Score 28, *RA* rheumatoid arthritis, *RAPID3* Routine Assessment of Patient Index Data 3

and other costs. Specifically, inpatient costs were costs associated with inpatient hospital, inpatient hospice, skilled nursing facility, inpatient psychiatry, and inpatient rehabilitation. Outpatient costs were costs associated with office/clinic visits, retail health clinics, urgent care, outpatient hospital, ambulatory surgical center, independent clinic, federally qualitied health center, community mental health center, non-residential substance abuse treatment facility, mass immunization center, outpatient rehabilitation facility, state or local public health office/clinic, and psychiatric facility-partial hospitalization. Other costs included costs associated with services at pharmacy, school, homeless shelter, home, assisted living facility, group home, mobile unit, temporary lodging, nursing facility, custodial care facility, ambulance-land, ambulance-air or water, intermediate care facility for mentally retarded, end-stage renal disease treatment facility, independent laboratory, other unlisted facility, and unknown place of service. RA-related costs were defined as healthcare cost claims that had an ICD-9-CM/ICD-10-CM code for RA. RA-related prescriptions included

conventional synthetic DMARDs, biologic DMARDs, targeted synthetic DMARDs, nonsteroidal anti-inflammatory drugs, and corticosteroids for the treatment of RA (Table S1).

Statistical Analyses

Baseline characteristics were described using mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Given that the remission cohort was likely to be different from the non-remission cohort in terms of demographics and health status factors that may affect healthcare costs and resource utilization, an inverse probability of treatment weighting (IPTW) approach was used to minimize confounding by patient characteristics and disease complexities between remission and non-remission cohorts. The weights were estimated from a multivariate logistic regression, adjusting for age, sex, race (Caucasian, African American vs. others), and comorbidities using the Elixhauser index [30] (ranging 0–28). Standardized mean differences for age, sex, race, and Elixhauser index before and after weighting were calculated. The

standardized mean difference for each variable was small ($\leq$ 0.2) after weighting [31] (Table S2). An IPTW weighted generalized linear regression and negative binomial regression were used to estimate adjusted annual direct costs and healthcare resource use, respectively. All costs were adjusted to 2019 US dollars based on Optum all payer data cost factors. Cost ratios (CR; mean expenditures in remission cohort divided by mean expenditures in the non-remission cohort) and inpatient, ED, and outpatient visit ratios (VR; mean number of visits in the remission cohort divided by mean number of visits in the non-remission cohort) with 95% confidence intervals (CI) were reported. All analyses were performed using SAS version 9.4 (SAS, Inc., Cary, NC, US).

Sensitivity Analysis

Some patients in the remission cohort may have DAS28/RAPID3 measurements within the year following the index date that change to non-remission status, which could result in a potential misclassification for the remission cohort. To minimize the influence of misclassification, a sensitivity analysis was performed, which excluded individuals from the remission cohort who had a non-remission record within 1 year following the index date, and healthcare costs in the remission and non-remission cohorts were recalculated.

RESULTS

Study Population

A total of 335 patients with RA (remission cohort: 125; non-remission cohort: 210) met the study inclusion criteria (Fig. 2). Age, sex, and race were similar in the remission and non-remission cohorts (Table 1). Patients in the remission cohort had a significantly lower Elixhauser comorbidity index score than those in the non-remission cohort (1.7 vs. 2.5; $P = 0.002$).

All-Cause Healthcare Resource Use

Compared with the non-remission cohort, a lower percentage of patients in the remission cohort had at least one inpatient visit (13.6% vs. 26.2%) or ED visit (22.4% vs. 39.5%) for any reason. The mean number of all-cause inpatient visits was 64% lower in the remission cohort than in the non-remission cohort (0.23 vs. 0.63, respectively; VR = 0.36; 95% CI 0.19, 0.70). Mean ED visits were 53% lower in the remission cohort compared with the non-remission cohort (0.36 vs. 0.77, respectively; VR = 0.47; 95% CI 0.30, 0.74). Most patients (> 99%) in both cohorts had an outpatient visit for any reason. The mean number of all-cause outpatient visits was 27% lower in the remission cohort than in the non-remission cohort (20.7 vs. 28.5, respectively; VR = 0.73; 95% CI 0.62, 0.86). Other medical visits and the number of prescriptions were also lower in the remission cohort compared with the non-remission cohort (Table 2).

RA-Related Healthcare Resource Use

A lower percentage of patients in the remission cohort than in the non-remission cohort had an RA-related inpatient visit (10.4% vs. 16.7%) or RA-related ED visit (4.0% vs. 8.6%). Mean inpatient visits were 33% lower in the remission cohort than in the non-remission cohort (0.15 vs. 0.22; VR = 0.67; 95% CI 0.35, 1.30). Mean ED visits were 69% lower in the remission cohort compared with the non-remission cohort (0.04 vs. 0.13, respectively; VR = 0.31; 95% CI 0.10, 0.95). Compared with the non-remission cohort, the mean number of RA prescriptions (Table 2) in the remission cohort was 12% greater (8.25 vs. 7.36; VR = 1.12; 95% CI 0.90, 1.40).

All-Cause Healthcare Costs

Annual all-cause total costs in the remission cohort were significantly less than in the non-remission cohort ($30,427 vs. $38,645, respectively; CR = 0.79; 95% CI 0.63, 0.99). All-cause medical costs were 32% lower in the remission
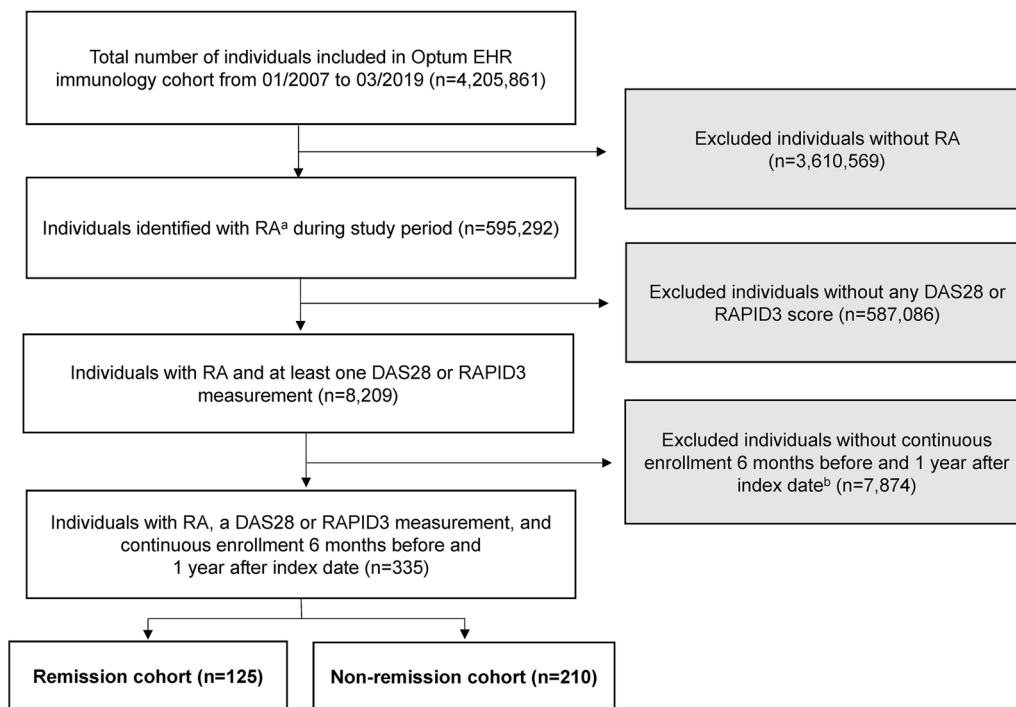
Fig. 2 Selection of study population. [a]Defined as ≥ 2 International Classification of Diseases-9/10-Clinical Modification diagnosis codes (ICD-9-CM/ICD-10-CM: 714.0, 714.1, 714.2, 714.81, M05x, M06x) on different days. [b]Based on the first date of achieving remission for the remission group and first DAS28 or RAPID3 score for the non-remission group, respectively. *DAS28* Disease Activity Score 28, *EHR* electronic health record, *RA* rheumatoid arthritis, *RAPID3* Routine Assessment of Patient Index Data 3

cohort than in the non-remission cohort ($17,846 vs. $26,391; CR = 0.68; 95% CI 0.52, 0.88; Table 3, Fig. 3). Furthermore, among all-cause medical costs, outpatient visit costs were 39% lower in the remission than in the non-remission cohort ($10,498 vs. $17,235; CR = 0.61; 95% CI 0.47, 0.79).

Annual RA-related total costs were similar in both cohorts (Table 3, Fig. 4); however, RA-related medical costs were numerically lower in the remission versus non-remission cohort ($8594 vs. $10,002, respectively; CR = 0.86; 95% CI 0.59, 1.25). RA-related costs were driven primarily by outpatient visits in both cohorts.

Results of a sensitivity analysis examining annual all-cause and RA-related healthcare costs excluding patients in the remission group with a non-remission status within 1 year following the index date are provided in Table S3. Generally, the results of the sensitivity analysis were similar to the main analysis. Regarding all-cause total costs, the CR in the main analysis of 0.79 (95% CI 0.63, 0.99) was comparable to that of the sensitivity analysis (0.80 [95% CI 0.62, 1.04]). Similar results were observed for RA-related total costs with a CR of 1.00 (95% CI 0.72, 1.39) in the main analysis compared with 1.06 (95% CI 0.73, 1.54) in the sensitivity analysis.

DISCUSSION

To our knowledge, this is the first study to examine the direct cost impact of achieving remission in a commercially insured patient population in the US. We estimated all-cause and RA-specific annual healthcare costs in patients with RA who achieved remission compared with patients who did not achieve remission. We found that annual all-cause total costs were significantly lower in the remission cohort compared with the non-remission

Table 1 Baseline characteristics of remission and non-remission cohort

Characteristic	Remission (*n* = 125)	Non-remission (*n* = 210)	*P* value
Age (years), mean ± SD	67.1 ± 10.7	68.6 ± 11.2	0.21
Female, *n* (%)	89 (71.2)	161 (76.7)	0.27
Race, *n* (%)			0.20
Caucasian	113 (90.4)	182 (86.7)	
African American	5 (4.0)	19 (9.0)	
Other/unknown	7 (5.6)	9 (4.3)	
Geographic region[a], *n* (%)			0.17
Southeast	1 (0.9)	2 (1.0)	
Midwest	110 (92.4)	171 (84.3)	
West	3 (2.5)	8 (3.9)	
South	5 (4.2)	22 (10.8)	
Immunomodulator-naïve[b], *n* (%)	99 (79.2)	182 (86.7)	0.07
Elixhauser comorbidity index[c], mean ± SD	1.7 ± 1.7	2.5 ± 2.4	0.002
Baseline healthcare costs ($), mean ± SD	11,562 ± 14,342	15,270 ± 20,304	0.07

Baseline was defined as 6 months before index date

SD standard deviation

[a] Percentage of missing data for remission group and non-remission group was 4.8% and 3.3%, respectively

[b] Included abatacept, adalimumab, anakinra, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib

[c] Range 0–28

cohort, which further underscores the importance of targeting remission as the treatment goal in RA and treating patients to achieve that goal. Furthermore, evidence from the present study suggests that treating patients to remission reduces not only outpatient visit costs, which are common among patients with RA, but also overall annual all-cause and RA-related total costs.

Although current guidelines recommend treating patients with RA to target with the ultimate goal of achieving clinical remission [12, 13], there is a lack of clarity around a single universal definition of remission. Several measures are recommended for assessing disease activity in routine clinical care [14], which may result in variable response rates of remission depending on the measure used to assess the outcome and the data source examined. To be comprehensive, we used RAPID3 and DAS28 to define remission in this study. The most recorded disease measure in the EHR system was RAPID3; however, the overall percentage of patients reporting RAPID3 was low (0.25%). Implementation of RAPID3 assessment in clinical practice and recording the results in EHR systems may help to track treatment goals. Since, RAPID3 is completely patient reported, measures that include physician assessments such as CDAI and CDAI-based remission definitions may also be considered. To achieve clinical remission, disease activity and use of appropriate therapies need to be monitored on a regular basis during routine clinical care. Because RA is a life-long disease, multiple successive therapies may be needed to achieve and

Table 2 All-cause and RA-related annual healthcare resource use per patient

Resource, mean (95% CI)	Remission cohort (*n* = 125)	Non-remission cohort (*n* = 210)	Visit ratio (95% CI)
All cause			
Inpatient[a] visits	0.23 (0.13, 0.40)	0.63 (0.45, 0.89)	0.36 (0.19, 0.70)
ED visits	0.36 (0.25, 0.53)	0.77 (0.61, 0.98)	0.47 (0.30, 0.74)
Outpatient[b] visits	20.73 (18.19, 23.60)	28.46 (25.80, 31.40)	0.73 (0.62, 0.86)
Other[c] visits	4.85 (4.05, 5.85)	7.03 (6.15, 8.03)	0.69 (0.55, 0.87)
Prescriptions	42.46 (37.70, 47.82)	58.86 (53.77, 64.43)	0.72 (0.62, 0.84)
RA related			
Inpatient[a] visits	0.15 (0.09, 0.26)	0.22 (0.15, 0.31)	0.67 (0.35, 1.30)
ED visits	0.04 (0.01, 0.11)	0.13 (0.08, 0.21)	0.31 (0.10, 0.95)
Outpatient[b] visits	5.37 (4.46, 6.46)	7.41 (6.46, 8.51)	0.72 (0.58, 0.91)
Other[c] visits	1.55 (1.25, 1.93)	1.29 (1.08, 1.54)	1.20 (0.91, 1.59)
Prescriptions	8.25 (6.92, 9.84)	7.36 (6.42, 8.43)	1.12 (0.90, 1.40)

CI confidence interval, *ED* emergency department, *RA* rheumatoid arthritis

[a] Inpatient visits included the inpatient hospital, inpatient hospice, skilled nursing facility, inpatient psychiatry, and inpatient rehabilitation

[b] Outpatient visits included visits to office/clinic, retail health clinics, urgent care, outpatient hospital, ambulatory surgical center, independent clinic, federally qualified health center, community mental health center, non-residential substance abuse treatment facility, mass immunization center, outpatient rehabilitation facility, state or local public health office/-clinic, and psychiatric facility-partial hospitalization

[c] Other included services at pharmacy, school, homeless shelter, home, assisted living facility, group home, mobile unit, temporary lodging, nursing facility, custodial care facility, ambulance-land, ambulance-air or water, intermediate care facility for mentally retarded, end-stage renal disease treatment facility, independent laboratory, other unlisted facility, and unknown place of service

maintain remission. Although the best clinical outcome for patients with RA is clinical remission, current guidelines indicate that low disease activity, which implies the presence of a low level of inflammation, is an acceptable alternative as it is recognized that remission may not be achievable in all patients with RA [12, 13]. However, it should be noted that patients who are able to achieve remission have better physical function, greater work productivity, and higher health-related quality of life compared with those with low disease activity [20, 32, 33]. If patients with low, moderate, or high disease activity do not begin treatment early, are not regularly monitored, and therapy is not adjusted based on disease assessments, then patients will not be able to achieve

remission. As shown in our study, a state of non-remission can have a substantial economic burden.

In the present study, annual all-cause medical costs were 32% lower in the remission cohort than in the non-remission cohort. Our results are consistent with those reported in a Medicare population in the US [28]. In the Medicare population, a decrease in annual medical costs of 45% was observed in patients in remission compared with those with high disease activity, and a decrease of 37% was shown for patients in remission compared with those with moderate disease activity [28]. An analysis of Canadian healthcare service costs [29] associated with achieving remission reported reductions in annual overall total costs in

Table 3 Annual all-cause and RA-related healthcare costs per patient

Cost ($), mean (95% CI)	Remission cohort (*n* = 125)	Non-remission cohort (*n* = 210)	Cost ratio (95% CI)
All cause	**30,427 (25,403, 36,445)**	**38,645 (33,704, 44,312)**	**0.79 (0.63, 0.99)**
Medical	17,846 (14,504, 21,960)	26,391 (22,560, 30,877)	0.68 (0.52, 0.88)
Inpatient[a]	4157 (2247, 7691)	5399 (3436, 8484)	0.77 (0.36, 1.66)
ED	866 (552, 1359)	1833 (1372, 2450)	0.47 (0.28, 0.81)
Outpatient[b]	10,498 (8559, 12,878)	17,235 (14,792, 20,083)	0.61 (0.47, 0.79)
Other[c]	2325 (1731, 3122)	1924 (1529, 2422)	1.21 (0.83, 1.76)
Prescription	12,581 (10,098, 15,674)	12,254 (10,344, 14,516)	1.03 (0.78, 1.36)
RA related	**17,546 (13,565, 22,679)**	**17,515 (14,369, 21,351)**	**1.00 (0.72, 1.39)**
Medical	8594 (6396, 11,548)	10,002 (7993, 12,517)	0.86 (0.59, 1.25)
Inpatient[a]	2329 (1176, 4612)	2975 (1810, 4890)	0.78 (0.34, 1.82)
ED	141 (47, 426)	434 (233, 810)	0.33 (0.09, 1.16)
Outpatient[b]	4407 (3241, 5992)	5821 (4622, 7331)	0.76 (0.52, 1.11)
Other[c]	1717 (1083, 2724)	722 (528, 1128)	2.22 (1.22, 4.04)
Prescription	8952 (6584, 12,171)	7513 (5909, 9553)	1.19 (0.81, 1.76)

CI confidence interval, *ED* emergency department, *RA* rheumatoid arthritis

[a] Inpatient costs included costs associated with inpatient hospital, inpatient hospice, skilled nursing facility, inpatient psychiatry, and inpatient rehabilitation

[b] Outpatient costs included costs associated with office/clinic visits, retail health clinics, urgent care, outpatient hospital, ambulatory surgical center, independent clinic, federally qualitied health center, community mental health center, non-residential substance abuse treatment facility, mass immunization center, outpatient rehabilitation facility, state or local public health office/clinic, and psychiatric facility-partial hospitalization

[c] Other costs included costs associated with services at pharmacy, school, homeless shelter, home, assisted living facility, group home, mobile unit, temporary lodging, nursing facility, custodial care facility, ambulance-land, ambulance-air or water, intermediate care facility for mentally retarded, end-stage renal disease treatment facility, independent laboratory, other unlisted facility, and unknown place of service

patients who achieved remission compared with those not able to achieve remission, which agrees with our finding in a commercially insured population in the US. Thus, our finding that non-remission in RA is associated with higher medical costs in a commercial market-based healthcare system in the US is reinforced by a similar finding in a single-payer healthcare system in Canada. These results may assist physicians and payers in making decisions regarding the treatment and management of patients with RA.

An important strength of this study is that the EHR data used in the analysis was derived from all 50 states in the US representing > 140,000 providers, 7000 clinics, and 760 hospitals. Although the overall sample size in this study was small (350 patients), there was representation from patients across the US. Another strength of this study is that the EHRs were linked to claims data, which provided a means to estimate costs associated with clinical outcomes. Furthermore, this study evaluated healthcare costs of not achieving remission using commercial insurance data, which represents an important portion of the RA population. This study also describes the individual components (e.g., inpatient costs, outpatient
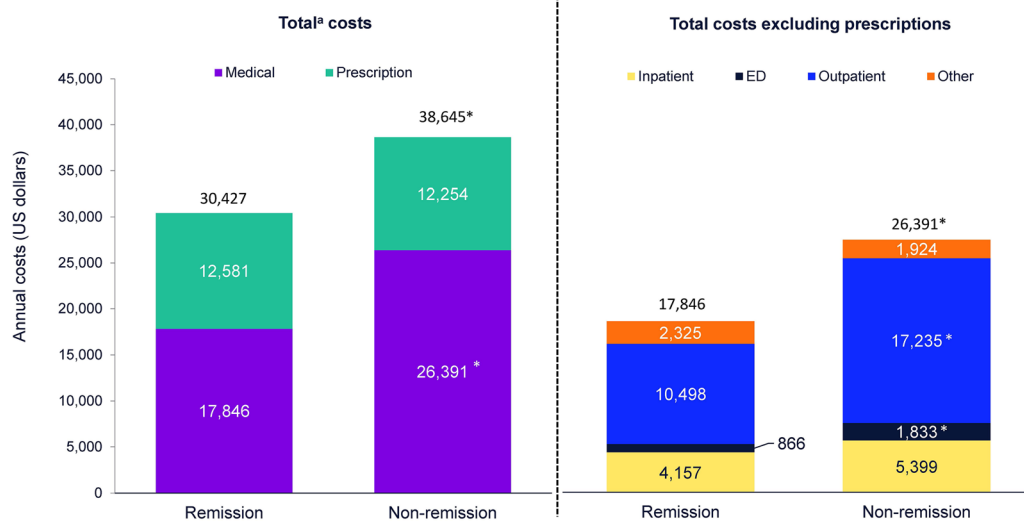
Fig. 3 Annual all-cause direct costs per patient. *Indicates a significant difference between remission and non-remission cohorts based on non-overlapping 95% confidence intervals. ^aTotal costs included costs associated with inpatient, ED, outpatient, and other visits (medical) and prescriptions. *ED* emergency department
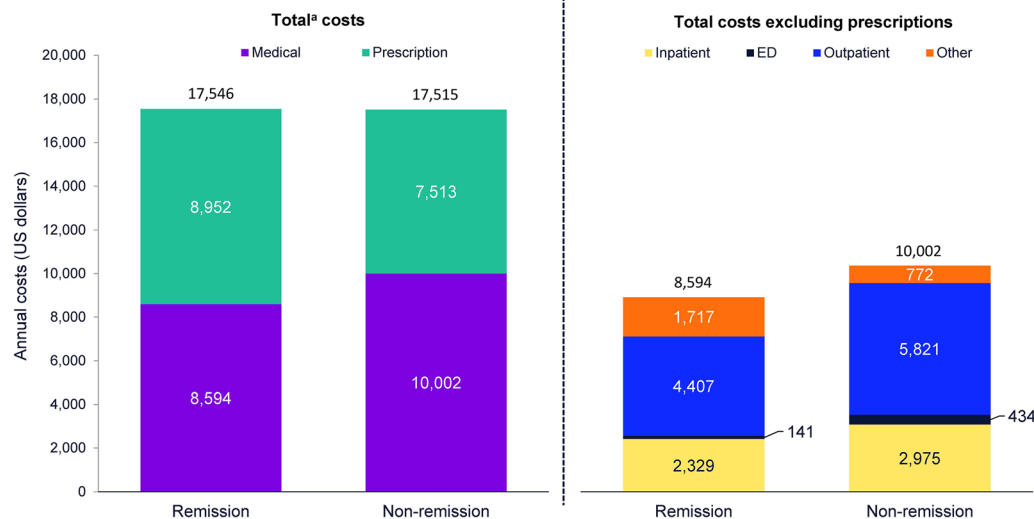

Fig. 4 Annual RA-related direct costs per patient. ^aTotal costs included costs associated with inpatient, ED, outpatient, and other visits (medical) and prescriptions. *ED* emergency department, *RA* rheumatoid arthritis

costs, prescription costs) that drive the cost differences between patients with RA who achieved remission and those who were not able to achieve remission. Despite these strengths, some limitations should be noted. The sample size was relatively small; hence, there may be uncertainty about the findings from the EHR and claims-linked data. Given the limited data available in the EHR data, we only included DAS28 and RAPID3 to define remission in this study. Another commonly used remission measurement, CDAI, was not included because of lack of data. Future studies may include CDAI or other remission measures.

DAS28 and RAPID3 (the remission definition) may not be measured routinely in clinical practice, in which case a misclassification of remission status may occur in this study. To address this limitation, we conducted a sensitivity analysis excluding those individuals with non-remission records within 1 year following the index date for the remission cohort. The results of this sensitivity analysis were generally similar to those obtained in the main analysis. Some comorbidities (e.g., obesity, dyslipidemia, diabetes, and cardiovascular diseases) may influence achievement of remission in RA and may have an impact on costs [34, 35]. To minimize confounding by disease complexities related to comorbidity between the remission and non-remission cohorts, an IPTW approach was used in the analysis. Weights were estimated from multivariate logistic regression, and differences in comorbidities between cohorts as determined by the Elixhauser index [30] were controlled using IPTW. Unmeasured confounding, an inherent limitation of any observational study, cannot be ruled out. Future studies with larger sample sizes are needed to replicate these findings. In addition, studies comparing work productivity among remission and non-remission RA populations are needed to understand the complete economic burden of not achieving remission in patients with RA.

CONCLUSIONS

In conclusion, significant economic burden was associated with patients who did not achieve remission compared with those who achieved remission. Although outpatient visits were the driver of medical costs in both groups studied in this analysis, the contribution of outpatient visits was greater among those who did not achieve remission. Higher costs in the non-remission cohort were driven mostly by non-RA related visits suggesting that tighter disease control may have effects beyond those related to RA.

ACKNOWLEDGEMENTS

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