Hidden Cost of Rheumatoid Arthritis (RA): Estimating Cost of Comorbid Cardiovascular Disease and Depression Among Patients with RA

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ABSTRACT. ***Objective.*** To examine resource utilization and direct healthcare cost associated with comorbid cardiovascular disease (CVD) and depression among patients with prevalent rheumatoid arthritis (RA) based on analyses of retrospective healthcare claims data.

Methods. The index date was set as the first observed claim with an RA diagnosis. Patients were required to be ≥ 18 years of age, to have received RA-related treatment during the pre-index period, and to have 12-month pre- and post-index data. Based on pre-index utilization, patients were classified into 4 diagnosis groups: RA alone, RA + CVD, RA + depression, and RA + CVD + depression. Analyses focused on annual differences in costs between patients with RA alone and those with CVD and/or depression. A generalized linear model was applied to control for demographic and clinical characteristics and to estimate cohort-specific adjusted mean annual healthcare cost.

Results. Of 10,298 patients, 8,916 had RA alone (86.6%), 608 had RA + CVD (5.9%), 716 had RA + depression (7.0%), and 58 had RA + CVD + depression (0.5%). All patients with CVD and/or depression incurred significantly higher followup costs compared with patients with RA alone. Adjusted annual mean healthcare costs were highest for RA + CVD (US$14,145), followed by RA + CVD + depression ($13,513), RA + depression ($12,225), and RA alone ($11,404). Although patients with CVD and/or depression had a greater rate of RA-related hospitalization, adjusted RA-related healthcare costs did not reflect any statistically significant differences as compared to the RA-alone cohort.

Conclusion. A significant proportion (13.4%) of patients with prevalent RA have comorbid CVD and/or depression. The presence of these conditions significantly affects annual healthcare costs as well as specific RA-related utilization patterns. (First Release Feb 15 2009; J Rheumatol 2009; 36:743–52; doi:10.3899/ jrheum.080670)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is an inflammatory joint disease that affects 0.5%–1.0% of the population[1]. In addition to the joints, RA targets extraarticular sites such as the lungs, heart, and blood vessels[2]. In particular, cardiovascular disease (CVD) occurs earlier and at higher rates in patients with RA compared with the general population[3].

It has been suggested that the chronic inflammation observed in RA may play a critical role in the development and progression of atherosclerosis and CVD[4-6]. Inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor, and the extent of joint swelling and tenderness, are all associated with an increased risk of atherosclerosis[7]. In patients with RA, both ESR and CRP have been significantly correlated with accelerated progression of carotid intima-media thickness (a predictor of future CVD morbidity and mortality)[7].

RA is also associated with depression. Prevalence estimates range from 14% to 46%, largely because assessment methods vary widely. When uniform definitions for depression and standardized assessment tools are employed, prevalence is estimated to be 15%–20%, roughly 3.5 times that of the general population[8,9]. Available evidence indicates that RA-related depression arises out of complex interactions between clinical, demographic, and psychological factors[10]. The results of an 18-year longitudinal study to evaluate the influence of depression on mortality in patients with RA

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found that depressed patients had more comorbid conditions and increased RA disease activity compared with non-depressed patients[9].

The economic costs of RA are substantial and have likely been underestimated[11]. Numerous studies have been conducted to determine the direct costs of RA, but findings have varied widely and are difficult to compare across years[12,13]. However, the direct costs incurred by US patients with RA have been estimated to be 3–4 times those of patients without RA[11]; those patients with poor function and with comorbidities also have been found to incur substantially higher costs[14].

The introduction of biologic therapies such as tumor necrosis factor-α (TNF-α) inhibitors, interleukin 1 (IL-1) inhibitors, costimulation blockers, and anti-CD20 monoclonal antibody blockers[2] has significantly improved treatment for patients with RA. An important limitation of many evaluations of the economic burden of RA is that they did not take account of the costs of the newer biologic therapies[14].

Although previous studies have examined the burden of depression and/or CVD among patients with RA, few studies have accurately assessed the economic burden of RA since the introduction of biologic therapies[14], and no studies have evaluated the economic burden associated with varied manifestations of comorbid RA, CVD, and/or depression. Our study was designed to compare healthcare utilization among RA patients with and without cardiovascular and psychiatric comorbidities to determine the extent to which these comorbidities account for a higher rate of utilization and cost for comorbid patients, and whether utilization of RA-related services differs between comorbid and non-comorbid patients.

MATERIALS AND METHODS

Data source. Medical and pharmaceutical claims were obtained from the PharMetrics Patient-Centric Database for the period January 1, 2001, to December 31, 2005. At the time of the study, this retrospective database included fully adjudicated medical and pharmacy claims for 52 million patients from 92 health plans across the US. The database includes both inpatient and outpatient diagnoses [International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) format] and procedures [Current Procedural Terminology, 4th edition (CPT-4) and HCFA Common Procedural Coding System (HCPCS) formats], as well as prescription records. Both charged and paid amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables, plan characteristics, provider specialty, and patient enrollment dates. Records in the PharMetrics database are representative of the national commercially insured population on a variety of demographic measures including age, sex, geographic distribution, and plan type. The data are also longitudinal, with an average member enrollment time of 2 years.

Sample selection. Patients ≥ 18 years of age with a diagnosis of RA (ICD-9-CM 714.0, 714.89, 714.9, 714.8, 714) between January 1, 2002, and December 31, 2004, were eligible for inclusion. The date of the first observed claim with an RA diagnosis following a 12-month period of enrollment eligibility was deemed the "index date." All medical and pharmacy claims spanning the period January 1, 2001–December 31, 2005 were extracted for each eligible patient. A minimum pre-index period of 12 months and post-index followup of 12 months were required.

To identify a population with prevalent RA, patients were required to have a diagnosis of RA and to have undergone treatment with selected RA-related therapies prior to the index date; this included having been prescribed at least one disease-modifying antirheumatic (DMARD; e.g., methotrexate, hydroxychloroquine, sulfasalazine) or biologic (e.g., etanercept, infliximab, anakinra) drug during the pre-index period. Patients whose insurance coverage did not include retail pharmacy, or whose health plans did not have mental health coverage or did not report prescription-days supplied and quantity dispensed, were excluded. Patients ≥ 65 years of age whose insurance coverage was not "Medicare Risk" also were excluded (as full utilization and cost data were not available for older patients with traditional Medicare or alternative payers).

Patients identified as eligible for inclusion in the analysis were evaluated for a medical claim or pharmacy claim indicative of depression. Depression was defined as a diagnosis of major depressive disorder (ICD-9-CM 296.2x, 296.3x, 296.82, 296.90), dysthymic disorder (ICD-9-CM 300.4), depressive disorder NOS (ICD-9-CM 311), or depressive mood (brief or prolonged; ICD-9-CM 309, 309.1) plus evidence of antidepressant intake during the pre-index period. Antidepressants included selective serotonin reuptake inhibitors (SSRI), selective serotonin/norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOI). Similarly, existing CVD was identified during the pre-index period. Diagnosis was based on a medical or facility claim including a diagnosis of CVD, myocardial infarction, angina pectoris, stroke, revascularization procedure, or angioplasty (ICD-9-CM 410.XX-414.XX, 436.XX; see Appendix A for CPT-4 procedure list). Patients who did not have evidence of depression or CVD in the pre-index period but who were diagnosed with CVD or depression in the post-index period were excluded.

Following this identification, patients were classified into 4 mutually exclusive diagnosis groups: patients with RA without comorbid depression or CVD (RA alone); patients with RA plus comorbid depression but not CVD (RA + depression); patients with RA plus comorbid CVD but not depression (RA + CVD); and patients with RA, comorbid CVD, and depression (RA + CVD + depression). Figure 1 depicts final patient selection and classification.

Measures. Measures of interest in this study included demographic and clinical characteristics, resource utilization, and direct medical cost (i.e., health plan payments for services rendered) for 12 months for the 4 cohorts. Patient demographics (age, sex, plan type, physician specialty, geographic region) were assessed from the index date claims. Pre-index (12-month period prior to the index date) healthcare costs were also assessed. Pre-index resource utilization measures consisted of number of physician visits, medications received, and evidence of hospitalization. Clinical characteristics were derived from data obtained on the index date or in the pre-index period and included evidence of CVD or depression, comorbidities (e.g., migraine, Crohn's disease, diabetes, hypertension, cancer; see Appendix B for a complete list and codes), as well as the number of comorbidities per patient. In addition, the baseline comorbidity profile was defined for each patient using the Charlson Comorbidity Index[15].

All instances of resource utilization were categorized as RA-related, CV-related, depression-related, or other-related care. Categorizations were based on diagnosis codes, procedure codes, and medications indicative of the conditions of interest. For outpatient claims with diagnoses for multiple conditions, the following hierarchy was applied to attribute claims to only one category: RA-related, CV-related, depression-related, and other-related care. Hospitalizations were classified based on the diagnoses listed on the discharge claim; if RA, CVD, or depression were listed as the primary diagnosis, the hospitalization was assigned to that condition. If none of these conditions was indicated as primary discharge codes, the second, third, and fourth codes were examined for evidence of RA, CVD, or depression-related hospitalization.

Patients were also classified according to the presence of specific

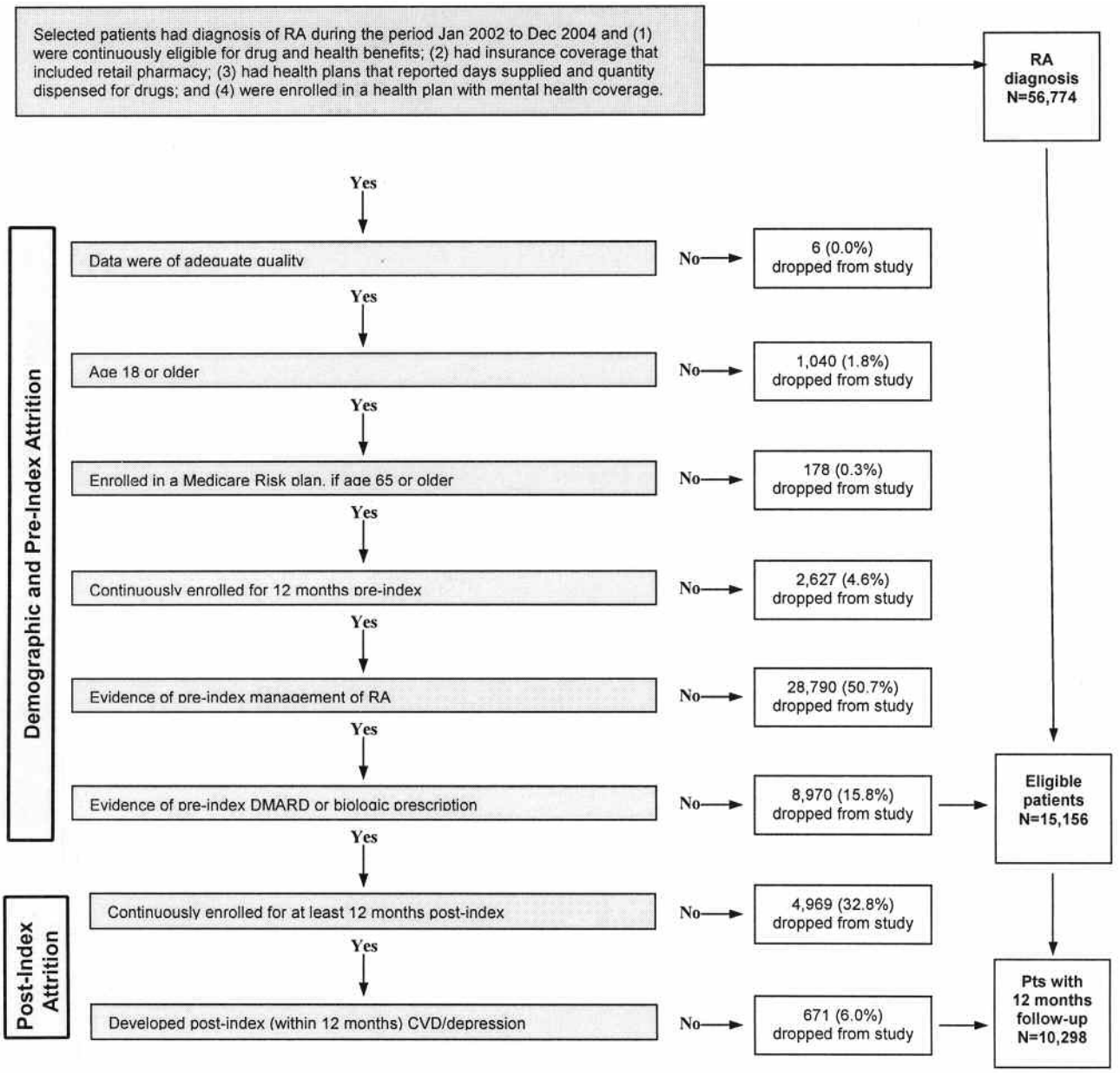

Figure 1. RA sample selection and attrition.

RA-related severity covariates (adapted from Setoguchi, *et al*[16]). These included RA-related surgery, inflammation markers, tendon injections, arthrocentesis, extraarticular manifestations, difficulty walking, and joint pain (see Appendix C for ICD-9 codes). All measures were stratified by cohort group.

Analyses. Utilization and direct medical costs were calculated for the 12-month followup period. All costs were expressed in 2006 US dollars and were adjusted as necessary using the medical care component of the US Consumer Price Index (unpublished data, US Bureau of Labor Statistics, 2007). Initial significance testing was conducted using the chi-square test for categorical variables and the t test or Wilcoxon rank-sum test for continuous variables. All analyses were conducted using Statistical Analysis Software (SAS®), version 8.2.

In addition to unadjusted comparisons, generalized linear models (GLM) with a log-link function[17] were conducted to examine differences in RA-related and total costs between the diagnosis groups, using a gamma distribution for cost-skewed data. Covariates in the RA-related and total cost models included sex and age (18–34, 35–44, 45–54, 55–64, and 65+ years); presence of comorbidities (RA alone, RA + CVD, RA + depression, or RA + CVD + depression); health plan type, payer type; non-RA comorbidities diagnosed in the pre-index period (e.g., migraine, Crohn's disease, diabetes, hypertension, cancer), pre-index utilization of medications associated with RA treatment (e.g., biologics, DMARD, cyclooxygenase-2 inhibitors), pre-index RA-related surgery; inflammation markers, tendon injections, arthrocentesis, extraarticular manifestations, difficulty walking, or joint pain; pre-index evidence of hospitalization; and an interaction term of pre-index utilization of biologic therapy with the diagnosis group. The resulting Pearson chi-square statistic (2.3092) indicated a good model fit for the total-cost model. Annual total costs and RA-related adjusted costs were calculated for each cohort along with 95% confidence intervals.

RESULTS

Patient population. A total of 56,774 patients were initially identified with an RA diagnosis during the study timeframe. Following sample attrition because of selection criteria, a total of 10,298 patients were available for analysis (Figure 1). Of this sample, 8,916 patients had RA alone (86.6% of sample), 608 RA + CVD (5.9%), 716 RA + depression (7.0%), and 58 RA + CVD + depression (0.5%). Patient age by cohort group varied (Table 1), patients with RA + CVD tending to be older than those with RA alone (mean age 58.7 vs 50.9 yrs, respectively; $p < 0.001$), while patients with RA + depression were somewhat younger (49.6 yrs; $p < 0.001$). The proportion of men with RA + CVD (45%) was higher than the proportion of men in any other cohort (range 12%–23%).

Observed annual pre-index utilization and comorbidity. Table 2 shows selected 12-month pre-index utilization patterns and relevant comorbidities within the study sample. Compared with patients with RA alone (21.9%), patients with any combination of CVD and/or depression were more likely to have undergone arthrocentesis (RA + CVD, 28.0%, $p < 0.001$; RA + depression, 26.7%, $p < 0.001$; RA + CVD + depression, 34.5%, $p = 0.021$). In general, rates of RA-related surgery were similar across cohorts, with the exception of patients with RA + CVD + depression, who experienced a significantly higher rate of surgery compared with patients with RA alone (17.2% vs 4.9%; $p < 0.001$).

Patients with RA + CVD and/or depression were significantly ($p < 0.05$) more likely to have systemic lupus erythematosus, diabetes, hypertension, hyperlipidemia, asthma or respiratory disease, including chronic obstructive pulmonary disease and pneumonia/influenza, osteoarthritis, cancer, and congestive heart failure during the pre-index period compared with patients with RA alone. Patients with depression (with or without CVD) were also significantly ($p < 0.05$) more likely to have ankylosing spondylitis,

Table 1. Demographic characteristics of study sample, by cohort.

Characteristic	RA Alone, n = 8,916	RA + CVD, n = 608	p*	RA + Depression, n = 716	p*	RA + CVD + Depression, n = 58	p*
Age, yrs							
Mean	50.9	58.7	< 0.001	49.6	< 0.001	53.0	
SD	9.8	9.6		9.8		9.3	
Median	52	58		51		53.5	
Minimum	18	32		18		25	
Maximum	97	97		95		79	
Sex, n (%)							
Male	2056 (23)	272 (45)	< 0.001	86 (12)	< 0.001	11 (19)	0.460
US geographic region, n (%)							
Northeast	2047 (23)	157 (26)	0.003	124 (17)	0.003	11 (19)	0.741
Midwest	3681 (41)	215 (35)		337 (47)		28 (48)	
South	2469 (28)	198 (33)		166 (23)		15 (26)	
West	719 (8)	38 (6)		89 (12)		4 (7)	
Plan type, n (%)							
Consumer-directed healthcare product	2 (0)	0 (0)	0.018	0 (0)	0.018	0 (0)	0.570
Health maintenance organization (HMO)	2972 (33)	194 (32)		285 (40)		24 (41)	
Indemnity plan	709 (8)	71 (12)		57 (8)		2 (3)	
Point of service (POS)	1003 (11)	79 (13)		76 (11)		4 (7)	
Preferred provider organization (PPO)	4190 (47)	262 (43)		294 (41)		28 (48)	
Unknown	40 (0)	2 (0)		4 (1)		0 (0)	
Payer type, n (%)							
Commercial plan	8095 (91)	474 (78)	< 0.001	638 (89)	< 0.001	44 (76)	< 0.001
Medicaid	132 (1)	13 (2)		35 (5)		4 (7)	
Medicare risk	420 (5)	104 (17)		29 (4)		8 (14)	
Self-insured	245 (3)	16 (3)		11 (2)		2 (3)	
Unknown	24 (0)	1 (0)		3 (0)		0 (0)	
Physician specialty, n (%)							
PCP (family/general practice)	603 (7)	50 (8)	< 0.001	72 (10)	< 0.001	5 (9)	0.197
Internal medicine	764 (9)	56 (9)		76 (11)		6 (10)	
Rheumatology	5993 (67)	370 (61)		431 (60)		33 (57)	
Cardiology	106 (1)	24 (4)		9 (1)		2 (3)	
Orthopedics/orthopedic surgery	129 (1)	10 (2)		13 (2)		2 (3)	
Psychiatry/psychology	1 (0)	1 (0)		2 (0)		0 (0)	
Other	1172 (13)	83 (14)		103 (14)		10 (17)	
Unknown	148 (2)	14 (2)		10 (1)		0 (0)	

* Reference group is RA Alone.

Table 2. 12-month pre-index comorbidities and utilization of study sample, by cohort. Data are percentages, except where indicated.

Characteristic	RA Alone, n = 8,916	RA + CVD, n = 608	p*	RA + Depression, n = 716	p*	RA + CVD + Depression, n = 58	p*
No. of comorbidities, mean (SD)	1.3 (1.3)	2.8 (1.5)	< 0.001	1.9 (1.6)	< 0.001	3.9 (1.9)	< 0.001
Comorbidities							
Crohn's	0.8	0.7	0.730	0.8	0.878	3.4	0.023
Ankylosing spondylitis	1.0	1.3	0.397	2.1	0.004	6.9	< 0.001
SLE	3.1	4.9	0.012	5.0	0.004	8.6	0.015
Psoriasis	1.6	1.6	0.869	2.0	0.414	1.7	0.919
Fibromyalgia	6.8	8.4	0.143	16.9	< 0.001	27.6	< 0.001
Diabetes	9.0	24.0	< 0.001	11.0	0.067	27.6	< 0.001
Hypertension	27.1	66.1	< 0.001	31.8	0.006	65.5	< 0.001
Hyperlipidemia	19.9	61.2	< 0.001	24.0	0.008	62.1	< 0.001
Asthma and COPD	11.1	22.5	< 0.001	20.0	< 0.001	37.9	< 0.001
Osteoporosis	11.9	14.3	0.072	11.7	0.922	20.7	0.038
Osteoarthritis	23.4	35.5	< 0.001	28.5	0.002	48.3	< 0.001
Pneumonia/influenza	3.5	10.2	< 0.001	7.1	< 0.001	13.8	< 0.001
Epilepsy	0.3	0.5	0.524	0.7	0.122	5.2	< 0.001
Cancer	5.7	10.0	< 0.001	6.7	0.272	13.8	0.008
Respiratory disease	1.0	2.8	< 0.001	1.0	0.935	8.6	< 0.001
Migraine	2.4	2.6	0.746	8.1	< 0.001	10.3	< 0.001
CHF	0.7	13.3	< 0.001	2.1	< 0.001	19.0	< 0.001
Generalized anxiety disorder	0.4	0.7	0.270	5.0	< 0.001	5.2	< 0.001
Panic disorder	0.2	0.3	0.603	2.0	< 0.001	1.7	0.018
Evidence of hospitalization	7.9	34.9	< 0.001	18.6	< 0.001	60.3	< 0.001
RA-related severity covariates							
RA-related surgery	4.9	6.3	0.155	8.4	< 0.001	17.2	< 0.001
Inflammation markers	57.1	55.9	0.555	61.3	0.030	56.9	0.97
Tendon injections	5.4	7.6	0.026	7.1	0.057	5.2	0.932
Arthrocentesis (small/intermediate/major)	21.9	28.0	< 0.001	26.7	0.003	34.5	0.021
Extraarticular manifestations	3.2	4.3	0.157	5.9	< 0.001	6.9	0.115
Difficulty walking	0.1	0.5	0.005	0.0	0.423	0.0	0.819
Pain in joint	0.7	1.2	0.200	1.0	0.389	1.7	0.35
NSAID	39.0	29.1	< 0.001	40.4	0.479	36.2	0.662
COX-2 inhibitors	24.2	23.4	0.650	25.8	0.317	27.6	0.545
Narcotic analgesics	44.7	58.9	< 0.001	67.6	< 0.001	74.1	< 0.001
Corticosteroids	64.4	71.4	< 0.001	70.8	< 0.001	86.2	< 0.001
MTX	73.7	67.9	0.002	75.4	0.314	58.6	0.009
Cytotoxic DMARD	3.5	5.4	0.016	2.7	0.216	13.8	< 0.001
Noncytotoxic DMARD	22.4	21.1	0.430	23.3	0.582	24.1	0.756
Etanercept	20.9	19.4	0.386	20.3	0.689	25.9	0.353
Adalimumab	4.9	3.9	0.305	4.7	0.887	6.9	0.475
Infliximab	11.9	14.6	0.041	13.7	0.147	17.2	0.206
Anakinra	1.0	1.3	0.488	1.1	0.805	3.4	0.069
Charlson Comorbidity Index, mean (SD)	1.4 (0.9)	2.6 (1.8)	< 0.001	1.7 (1.2)	< 0.001	3.3 (2.1)	< 0.001
Total pre-index cost of care, mean (SD) US$	11,091 (14,082)	24,667 (29,358)	< 0.001	16,313 (17,315)	< 0.001	38,094 (40,578)	< 0.001

* Reference group is RA Alone. CVD: cardiovascular disease, SLE: systemic lupus erythematosus, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, MTX: methotrexate, DMARD: disease modifying antirheumatic drug.

fibromyalgia, migraine, generalized anxiety disorder, and panic disorder as compared to patients with RA alone.

A lower proportion of patients (7.9%) with RA alone had a hospitalization stay in the 12 months prior to their index date compared with the other cohorts (RA + CVD, 34.9%; RA + depression, 18.6%; RA + CVD + depression, 60.3%; all $p < 0.001$). As expected, patients with RA + depression, RA + CVD, and RA + CVD + depression showed progressively higher Charlson Index scores (1.7, 2.6, and 3.3, respectively; all $p < 0.001$) compared with patients with RA alone (1.4).

Observed annual post-index utilization and comorbidity. Table 3 presents selected 12-month post-index patient resource utilization measures. Patients with RA + CVD, RA + depression, and RA + CVD + depression filled substantially more prescriptions in the 12 months following their index diagnosis (mean number of claims 69.2, 71.3, and 114.3, respectively) compared with patients with RA alone

Table 3. Annual total post-index resource utilization of study sample, by cohort. Data are mean number (SD), except where indicated.

Characteristic	RA Alone, n = 8,916 Mean (SD)	RA + CVD, n = 608 Mean (SD)	p*	RA + Depression, n = 716 Mean (SD)	p*	RA + CVD + Depression, n = 58 Mean (SD)	p*
Medications							
NSAID	2.07 (3.57)	1.52 (3.03)	< 0.001	1.94 (3.37)	0.866	0.74 (1.60)	0.025
COX-2 inhibitors	1.25 (2.98)	1.05 (2.57)	0.153	1.28 (2.83)	0.185	1.16 (3.08)	0.603
Narcotic analgesics	2.65 (5.66)	4.60 (11.51)	< 0.001	6.07 (9.27)	< 0.001	12.59 (13.60)	< 0.001
Corticosteroids	3.31 (4.53)	3.87 (4.77)	< 0.001	3.91 (5.22)	< 0.001	4.34 (4.61)	0.007
MTX	5.10 (5.77)	4.70 (5.59)	0.023	4.79 (5.78)	0.138	3.31 (4.28)	0.006
Cytotoxic DMARD	0.22 (1.47)	0.25 (1.46)	0.056	0.18 (1.13)	0.647	0.84 (2.57)	< 0.001
Noncytotoxic DMARD	1.31 (3.32)	1.07 (2.97)	0.186	1.22 (3.02)	0.908	1.26 (3.30)	0.719
Etanercept	1.77 (4.08)	1.55 (3.46)	0.528	1.43 (3.27)	0.289	2.36 (4.20)	0.214
Adalimumab	0.50 (2.08)	0.38 (1.84)	0.077	0.51 (2.06)	0.787	0.34 (1.25)	0.923
Infliximab	0.98 (4.92)	0.95 (2.48)	0.249	1.06 (4.34)	0.429	1.12 (2.64)	0.232
Anakinra	0.05 (0.65)	0.04 (0.49)	0.853	0.04 (0.42)	0.638	0.07 (0.41)	0.083
CV-related medications	5.43 (10.05)	18.57 (17.13)	< 0.001	6.62 (10.73)	< 0.001	20.78 (17.29)	< 0.001
Depression-related medications	1.45 (3.77)	2.37 (5.03)	< 0.001	8.71 (7.40)	< 0.001	11.95 (7.67)	< 0.001
Other medications	20.69 (19.93)	28.32 (28.14)	< 0.001	33.58 (27.02)	< 0.001	53.48 (35.15)	< 0.001
Total medication utilization	46.79 (34.42)	69.24 (49.95)	< 0.001	71.34 (44.77)	< 0.001	114.34 (62.30)	< 0.001
Outpatient							
Emergency room	0.13 (0.44)	0.33 (1.15)	< 0.001	0.35 (0.90)	< 0.001	0.76 (0.93)	< 0.001
Management	16.68 (19.90)	23.81 (22.48)	< 0.001	28.44 (36.46)	< 0.001	42.02 (34.40)	< 0.001
CABG/angioplasty/PTCA	0.00 (0.02)	0.02 (0.18)	< 0.001	0.00 (0.04)	0.022	0.00 (0.00)	0.937
RA-related surgery	0.11 (0.81)	0.08 (0.65)	0.566	0.17 (0.93)	0.025	0.29 (1.23)	0.038
Inflammation markers	2.76 (3.98)	2.88 (4.36)	0.734	3.09 (4.52)	0.032	2.86 (5.73)	0.316
Tendon injections	0.09 (0.46)	0.19 (1.12)	< 0.001	0.18 (0.73)	< 0.001	0.12 (0.38)	0.125
Arthrocentesis	0.54 (1.60)	0.83 (2.52)	< 0.001	0.73 (1.78)	< 0.001	0.90 (1.96)	0.12
Lab/radiology	28.33 (24.55)	38.26 (39.65)	< 0.001	35.41 (28.91)	< 0.001	46.66 (35.77)	< 0.001
Other outpatient ancillary	17.07 (21.56)	31.43 (36.48)	< 0.001	26.19 (40.74)	< 0.001	37.36 (35.55)	< 0.001
Inpatient							
Hospitalizations	0.14 (0.54)	0.43 (0.91)	< 0.001	0.32 (0.93)	< 0.001	0.84 (1.21)	< 0.001
Days in hospital	0.85 (5.10)	2.92 (11.29)	< 0.001	2.13 (12.49)	< 0.001	7.36 (18.13)	< 0.001
Evidence of hospitalization, n (%)							
All hospitalizations	875 (9.8%)	163 (26.8%)	< 0.001	130 (18.2%)	< 0.001	26 (44.8%)	< 0.001
RA-related hospitalizations	483 (5.4%)	57 (9.4%)	< 0.001	66 (9.2%)	< 0.001	9 (15.5%)	< 0.001
CV-related hospitalizations	0 (0.0)	51 (8.4%)	< 0.001	3 (0.4%)	< 0.001	7 (12.1%)	< 0.001
Depression-related hospitalizations	2 (0.0%)	1 (0.2%)	0.056	17 (2.4%)	0.056	2 (3.4%)	< 0.001

* Reference group is RA Alone. CVD: cardiovascular disease, CABG: coronary artery bypass graft, PTCA: percutaneous transluminal coronary angioplasty.

(46.8; $p < 0.001$ for all). In terms of specific medications prescribed, patients with CVD and/or depression were significantly more likely to receive narcotic analgesics, corticosteroids, CV-related medications, depression-related medications, and other medications. Mean numbers of RA-related medications were somewhat higher among patients with RA + depression (22.4) and RA + CVD + depression (28.1) as compared with RA alone (19.2) or RA + CVD (20.0).

Patients with RA and comorbid CVD and/or depression generally had higher rates of inpatient and outpatient medical resource use compared with patients with RA alone. Rates of emergency room utilization, laboratory testing/radiology procedures, and general management encounters were all significantly higher in dual- or multiple-diagnosis patients. Patients with CVD and/or depression experienced higher overall hospitalization rates (RA + CVD, 26.8%; RA + depression, 18.2%; RA + CVD + depression, 44.8%) compared with patients with RA alone (9.8%; all $p < 0.001$). Further, patients with RA and CVD and/or depression were more likely than patients with RA alone to be hospitalized for both RA- and CVD/depression-related reasons; these patients were also more likely to require longer hospital stays (calculated as days in hospital/utilization rate — RA alone, 6.0 days; RA + CVD, 6.8 days; RA + depression, 6.7 days; RA + CVD + depression, 8.7 days).

Unadjusted annual costs. Compared with patients with RA alone, patients with RA and depression, CVD, or CVD + depression experienced significantly and progressively higher overall annual unadjusted healthcare costs (data not shown) — $14,257 for RA alone versus $21,410, $24,444, and $35,246, respectively ($p < 0.001$ for all), as well as significantly higher costs for all assessed subcategories (medication, outpatient and inpatient care). Patients with depression had significantly elevated RA-specific total healthcare

costs (RA alone, $9,322; RA + depression, $9,940, p = 0.014; RA + CVD + depression, $12,318, p = 0.012), while patients with CVD alone did not have significantly different RA-specific costs (RA + CVD, $10,891; p = 0.225). RA-related inpatient costs were significantly higher for patients with CVD and/or depression compared with patients with RA alone.

Multivariate adjusted annual costs. In our multivariate analyses, we initially adjusted for sex, age, health plan type, payer type, non-RA comorbidities diagnosed in the pre-index period, pre-index utilization of medications associated with RA treatment, pre-index RA-related surgery, inflammation markers, tendon injections, arthrocentesis, extra-articular manifestations, difficulty walking or joint pain, and pre-index evidence of hospitalization. We found that an important predictor of total direct healthcare costs was prior use of a biologic and added an interaction term of pre-index utilization of biologic therapy with the diagnosis group. When the interaction term "prior biologic use" was added to the model, the differences in total annual costs were significant between the cohort groups as compared with patients with RA alone, suggesting that prior biologic exposure is a proxy for RA severity within the diagnosis groups with associated comorbidities. Comparison between total cost models with and without interaction of pre-index biologic use with the cohort indicators led us to accept the model with interaction, since this model had a better model fit (Pearson chi-square statistic 2.3092). The model including the interaction term is the model presented here.

The adjusted 12-month mean total overall costs and RA-related healthcare costs by cohort are shown in Figures 2 and 3, respectively. Patients with RA + CVD had the highest annual mean overall healthcare expenditures ($14,145; p < 0.001 vs RA alone), followed by patients with RA + CVD + depression ($13,513; p = 0.023), RA + depression ($12,225; p = 0.017), and patients with RA alone ($11,404). Adjusted mean RA-related healthcare costs ranged from roughly $6,100 to $6,700 annually and did not reflect any statistically significant differences between the cohort groups.

DISCUSSION

Findings from this retrospective claims-based study suggest that overall healthcare utilization in the year following RA diagnosis is substantially higher for patients with comorbid CVD and/or depression. Compared with patients with RA alone, annual adjusted healthcare costs were $2,741 higher for patients with RA + CVD, $821 for patients with RA + depression, and $2,109 for patients with RA + CVD + depression.

A diagnosis of CVD was associated with increased resource utilization. The proportion of patients with RA +

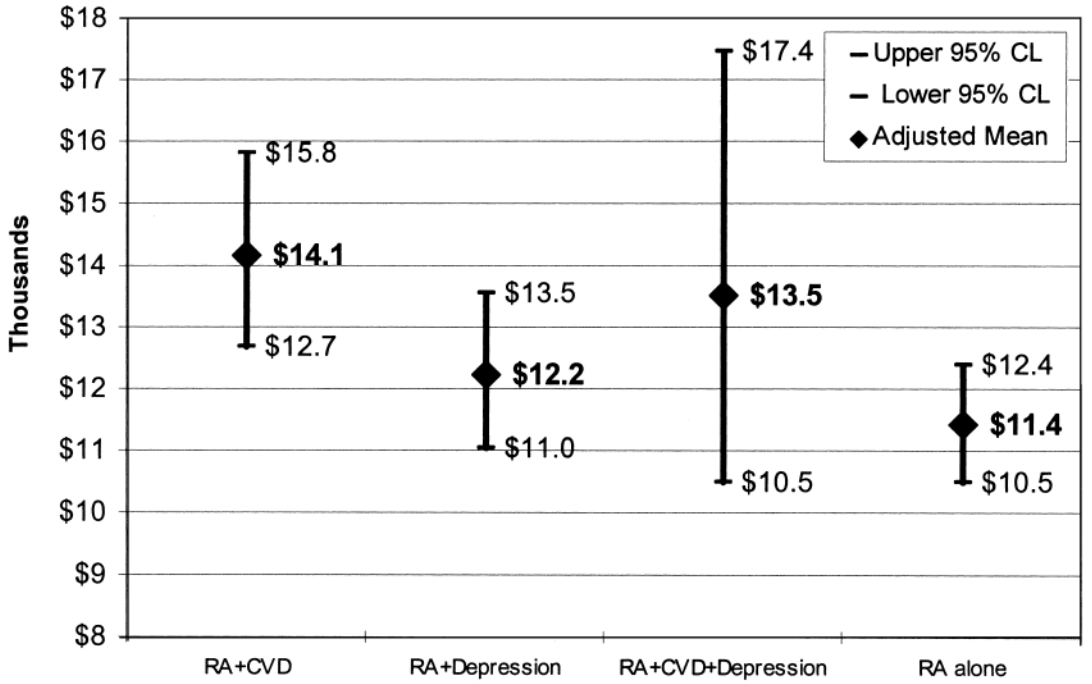

Figure 2. Adjusted 12-month mean total healthcare costs, by cohort. All adjusted mean estimates as compared to RA-alone group were significant (p < 0.05). Covariates included sex, age (18–34, 35–44, 45–54, 55–64, and 65+ yrs); health plan type; payer type; non-RA comorbidities diagnosed in the pre-index period; pre-index utilization of medications associated with RA treatment; pre-index RA-related surgery, inflammation markers, tendon injections, arthrocentesis, extraarticular manifestations, difficulty walking, or joint pain; pre-index evidence of hospitalization; and an interaction term of pre-index utilization of biologic therapy with the diagnosis group.

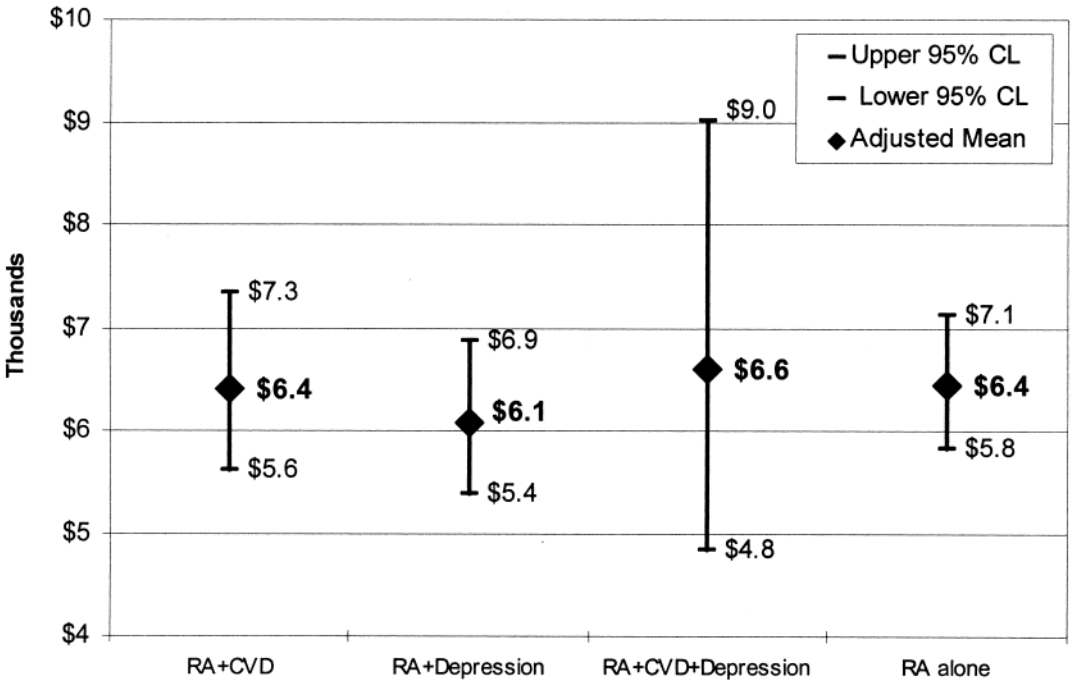

Figure 3. Adjusted 12-month mean RA-related healthcare costs, by cohort. No significant ($p < 0.05$) differences were found between RA-alone cohort and each of the other cohorts. Covariates included sex, age (18–34, 35–44, 45–54, 55–64, and 65+ yrs); health plan type; payer type; non-RA comorbidities diagnosed in the pre-index period; pre-index utilization of medications associated with RA treatment; pre-index RA-related surgery, inflammation markers, tendon injections, arthrocentesis, extraarticular manifestations, difficulty walking, or joint pain; pre-index evidence of hospitalization; and an interaction term of pre-index utilization of biologic therapy with the diagnosis group.

CVD with any hospitalization was more than twice that of patients with RA alone (26.8% vs 9.8%), while almost half (44.8%) of patients with depressive disorder in addition to CVD required a hospital stay. The presence of these comorbidities also significantly affected the duration of time spent in the hospital. The mean length of hospitalization stay was 2–3 days longer for patients with RA + CVD + depression compared with the other diagnosis groups.

We found that patients with comorbid depression had higher resource utilization, particularly emergency room visits, management visits, and hospitalizations, as compared with patients with RA alone. These results support existing data, which indicate that comorbid depression in RA is associated with increased use of health services and pain medication[1]. Specific physiologic pathways remain unclear, yet 2 large longitudinal studies have demonstrated an association between high levels of CRP and depression[18,19]. Additionally, the therapeutic administration of cytokines, including TNF-α, in animal and human studies has been shown to induce symptoms of depression[1,20].

Although patients' overall healthcare costs increased with the presence of comorbidities, particularly CVD, overall adjusted costs specific to RA were not significantly elevated when compared with patients with RA alone. For example, patients with comorbid CVD and/or depression utilized more medications (and as a result, incurred increased pharmacy costs); however, RA-related medication use among the 4 cohorts did not differ substantially. Similarly, patients with the comorbidities of interest incurred significantly higher outpatient and inpatient costs, but the additive burden of these costs was not RA-related.

There are limited recent cost data to compare to our results. However, the most comprehensive study, conducted by Michaud and colleagues in 2001, assessed age- and sex-adjusted mean total annual direct healthcare costs for RA patients at $9,519 per year[14]. At the time, these medical costs were found to be substantially higher than prior estimates; this was attributed to the recent introduction of biologic therapy. In our study, the reported mean total direct annual healthcare costs (in 2006 dollars) for patients with RA alone were $11,404 (adjusted). Since US national healthcare expenditures increased by 35% in the period between 2001 and 2005[21], the observed increases are indicative of a comparable burden of expense between these 2 studies.

This study is subject to some important limitations. First, the strict attrition process applied to subject selection (designed to include patients with prevalent RA and those with sufficient enrollment) may have led to a study sample that was not comparable to the overall RA population.

About 75% of patients in our study were female, which is consistent with existing research indicating that RA prevalence is 2- to 4-fold higher in women than in men[11]. The absolute rate of comorbid depression observed in the study was only 7.5%; this is lower than the 15% to 20% prevalence validated in previous reports[8,9]. However, the rules applied to define depression in this study may be more restrictive, since this study included only patients with both a diagnosis and antidepressant treatment in the one-year pre-index period. Further, this limitation would not appear to be related to the sample-selection process.

In addition, older patients (> 65 years of age) were limited to individuals covered under Medicare Risk (5.4% of study population). These patients may differ in certain respects from the overall US elderly population. That said, our findings should generalize well to the increasing percentage of Medicare beneficiaries enrolled in managed-care organizations (due to the implementation of the Medicare drug benefit). Also, because all study costs reported were from the payer perspective, additional expenses incurred by patients (such as co-pays, fees for services not covered by insurance) as well as intangible costs (such as indirect costs for caregiver expenses, lost productivity, and decreased quality of life)[22] could not be considered; therefore, cost underreporting may have occurred.

The possibility also exists that some patients may not have been allocated to the correct diagnosis cohort. For example, the use of CVD- and depression-related drugs was significantly elevated in all patients with either comorbidity, indicating the possibility of underdiagnosis or patient misallocation. It has been suggested that both depression and CVD (particularly among women) are underdiagnosed[23,24]. Underdiagnosis of depression and CVD may have narrowed the difference in annual costs between the RA-alone and RA-comorbidity cohorts. Possible misallocation within the comorbidity groups and the small number of patients with combined RA, CVD, and depression (n = 58) may explain the $600 higher average total adjusted costs for RA + CVD patients as compared with RA + CVD + depression patients. Finally, because it was only possible to control for differences observed using administrative claims data, the possibility exists that other factors influencing the diagnosis groups were not controlled for in the GLM analysis. Nevertheless, the persistence of a statistically significant effect of CVD and depression on overall healthcare cost following adjustment does indicate that a valid cost pattern has been identified in this study.

A significant portion of patients with active RA have comorbid CVD and/or depression (13.4%). Comorbid depression and cardiovascular events are associated with a significant increase not only in the annual total medical costs, but may also be associated with increases in RA-related utilization. The management of a patient with RA should include an awareness of these particular comorbidities, especially given the documented link between pain and depression and the chronic inflammation associated with RA, and the development and progression of atherosclerosis and CVD.

Appendix A: Cardiovascular Disease CPT codes

1. Coronary artery bypass graft/open angioplasty. 33140, 33141, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33520, 33521, 33522, 33523, 33525, 33528, 33530, 33532, 33533, 33534, 33535, 33536, 33570, 33572, 33575, S2204, S2205, S2206, S2207, S2208 , S2209
2. Angioplasty/arthrectomy. 35450, 35452, 35454, 35456, 35458, 35459, 35470, 35471, 35472, 35473, 35474, 35475, 35480, 35481, 35482, 35483, 35484, 35485 , 35490 , 35491, 35492, 35493 , 35494, 35495
3. Percutaneous transluminal coronary angioplasty. S2211, 92975, 92977, 92973, 92974, 92980, 92981, 92982, 92984, 92995, 92996, G0290, G0291, S2220

Appendix B: Comorbidity ICD-9 codes

Crohn's (555.xx), ankylosing spondylitis (720, 720.0), systemic lupus erythematosus (710.0x), psoriasis (696, 696.1, 696.8), fibromyalgia (729.1x), diabetes (250.xx), hypertension (401.xx, 402.xx, 403.xx, 404.xx), hyperlipidemia (272.xx), asthma and chronic obstructive pulmonary disease (490.xx–496.xx), osteoporosis (733.0x), osteoarthritis (715.xx), pneumonia/influenza (480.xx-487.xx), epilepsy (345.xx), cancer (140.xx–208.xx), respiratory disease (519.xx), migraine (346.xx), congestive heart failure (428.0), generalized anxiety disorder (300.02), panic disorder (300.01)

Appendix C: RA-related severity codes

1. RA-related surgery. CPT 22532, 22533, 22534, 22548, 22554, 22556, 22558, 22585, 22590, 22595, 22600, 22610, 22612, 22614, 22630, 22632, 22800, 22802, 22804, 22808, 22810, 22812, 23800, 23802, 24800, 24802, 25800, 25805, 25810, 25820, 25825, 25830, 26841, 26842, 26843, 26844, 26850, 26852, 26860, 26861, 26862, 26863, 27280, 27282, 27284, 27286, 27580, 27870, 27871, 28705, 28715, 28725, 28730, 28735, 28737, 28740, 28750, 28755, 28760, 29899
2. Tests ordered (inflammation markers). CPT 86430–86431, 85651–85652, 86140–86141
3. Joint aspirations/injections. CPT 20256, 20550–20553
4. Extraarticular manifestation. ICD-9 714.81, 782.2, 714.1, 710.2
5. Difficulty walking. ICD-9 719.7

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