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Rheumatoid Arthritis–Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs and Mortality

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ABSTRACT. Objective. Interstitial lung disease (ILD) is commonly associated with rheumatoid arthritis (RA) and can have significant morbidity and mortality. The objective of this study was to calculate the prevalence, incidence, healthcare costs, and mortality of RA-related ILD (RA-ILD) in the United States.

Methods. This retrospective cohort analysis used the Truven Health MarketScan Commercial and Medicare Supplemental health insurance databases from 2003 to 2014 and the Social Security Administration death database. Patients with RA-ILD were selected based on diagnoses on medical claims. Outcomes were 1-year prevalence and incidence of RA-ILD among the general enrollee population, all-cause and respiratory-related healthcare costs (2014 US\$), and all-cause survival for a subset of newly diagnosed patients with vital status information. This analysis was descriptive. No statistical testing was conducted.

Results. Prevalence of RA-ILD ranged from 3.2 to 6.0 cases per 100,000 people across the 10-year period and incidence ranged from 2.7 to 3.8 cases per 100,000 people. There were 750 incident patients with 5 years of followup data. Over that time, 72% had an inpatient admission and 76% had an emergency room visit. Mean total 5-year costs were US\$173,405 per patient (SD \$158,837). Annual per-patient costs were highest in years 1 and 5. At 5 years after first diagnosis in the data, 35.9% of patients had died.

Conclusion. Prevalence of RA-ILD increased over time. For patients who could be followed over a 5-year period, healthcare use and costs were somewhat stable over time, but were substantial. RA-ILD is associated with decreased survival. (J Rheumatol First Release December 15 2018; doi:10.3899/jrheum.171315)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
HEALTHCARE COSTS

INTERSTITIAL LUNG DISEASE
MORTALITY

Rheumatoid arthritis (RA) is a systemic inflammatory disorder marked by progressive destruction of joints, particularly the small joints of the wrists, hands, and feet, often resulting in significant disability¹. RA may cause a variety of extraarticular manifestations, including interstitial lung disease (RA-ILD), which typically manifests as diffuse parenchymal fibrosis^{1,2,3}. RA-ILD is a significant cause of

morbidity and mortality among patients with RA¹ and has economic implications. In the United States, the total excess societal costs attributable to RA, including direct healthcare costs, costs of quality-of-life deterioration, and costs of premature mortality, have been estimated to be US\$39.2 billion⁴. To our knowledge, the costs of RA-ILD specifically have not been described.

Differing case definitions and methods of case ascertainment have induced variability in estimates of the incidence and prevalence of RA-ILD. It is clear that large proportions of patients with RA (30–76%) have signs of ILD on imaging studies, but ILD is deemed clinically significant in a minority (around 5–10%) of them^{1,2,5,6}. Certain epidemiological studies suggest the incidence of RA-ILD has been relatively stable over time, but prevalence has increased^{7,8}. Most studies to date have focused on older data from small subsets of the population. In our study, we aimed to advance understanding of several aspects of RA-ILD by using large nationwide US claims databases to estimate the prevalence, incidence, healthcare costs, and mortality of RA-ILD.

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MATERIALS AND METHODS

Data sources. The Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplemental databases are US-based administrative claims databases. Each includes data on enrollment, inpatient and outpatient medical claims, and outpatient pharmacy claims for a convenience sample of enrollees and their dependents with either private insurance (through their employers or a health plan) or Medicare supplemental insurance (paid for by a current or former employer). The databases, with over 150 million covered lives from 2003 to 2014, cover all geographic regions of the country and include a variety of health plan types. The data were previously collected, statistically de-identified, and compliant with the Health Insurance Portability and Accountability Act of 1996; therefore, no Institutional Review Board approval was sought in accordance with the policy of Truven Health Analytics. A subset of individuals in the MarketScan data have the potential to be linked to the Social Security Administration Death Index (SSDI), because their Social Security numbers are transmitted as part of the MarketScan building process. These patients can be considered a denominator for mortality analyses. If one of these patients died and the death was reported to the Social Security Administration, the death date will be available in the SSDI.

Case definition for RA-ILD. Patients meeting ≥ 1 of the following criteria were identified as potential RA-ILD cases: (1) ≥ 2 claims with an International Classification of Diseases-9-Clinical Modification (ICD-9-CM) diagnosis code for pulmonary disease (fibrosis: ICD-9-CM 515, 516.3, 516.31; rheumatic lung disease: ICD-9-CM 714.81) on different days, with the second claim occurring within 12 months of the first plus ≥ 2 claims with a diagnosis of RA (ICD-9-CM 714.xx, excluding 714.3x and 714.4x) on different days in the 12 months before or after the first claim for pulmonary disease; or (2) ≥ 2 claims with a diagnosis of rheumatic lung disease (ICD-9-CM 714.81) on different days, with the second claim occurring within 12 months of the first based on a previously published algorithm². The date of the earliest claim in the identification period for pulmonary fibrosis or rheumatic lung disease was defined as the index date. We excluded patients with a claim with a diagnosis of another ILD [sarcoidosis (ICD-9-CM 135), hypersensitivity pneumonitis (ICD-9-CM 495.xx), pneumoconiosis (ICD-9-CM 500), asbestosis (ICD-9-CM 501), silicosis or talcosis (ICD-9-CM 502), berylliosis and other inorganic dusts (ICD-9-CM 503), unspecified pneumoconiosis (ICD-9-CM 505), or radiation fibrosis (ICD-9-CM 508.1)] in the 12 months following the index date. The remaining patients were considered prevalent cases of RA-ILD. This process was repeated for each year from 2004 through 2013.

Because the index date may not represent the date of initial diagnosis, we used an additional criterion to define incident RA-ILD cases: continuous enrollment for 6 months or more prior to the index date and with no claims that included diagnoses of pulmonary fibrosis or rheumatic lung disease (i.e., a “6-month clean period”).

To ensure all use and costs were recorded, we required that cases be continuously enrolled for 12 months after the index date when measuring patient demographic and clinical characteristics, healthcare use, and costs. Healthcare use and costs were also measured over a 5-year period for incident RA-ILD patients with 5 years of continuous enrollment after the index date. For the mortality analysis, there was no continuous enrollment requirement.

Prevalence and incidence estimates. Yearly prevalence and incidence estimates were calculated by dividing the number of prevalent or incident cases by the total number of MarketScan enrollees. For prevalence calculations, the denominator was the number of enrollees who were enrolled for ≥ 1 day in the year. For incidence calculations, the denominator was the number of enrollees who were enrolled for ≥ 1 day in the year and at least 6 months in the previous year. Denominators were not limited to patients with RA. Estimates are presented per 100,000 people, with 95% CI.

Patient characteristics. Demographic characteristics were based on enrollment information. Clinical characteristics were based on medical and pharmacy claims during the 12-month period after the index date. RA

severity was measured using the Claims-based Index for RA Severity algorithm⁹. We queried for several comorbid conditions; patients were considered to have a comorbidity if they had at least 1 claim with the relevant ICD-9-CM diagnosis code [or at least 2 outpatient pharmacy claims for pertinent medications for gastroesophageal reflux disease (GERD), dyslipidemia, or diabetes]. Medication use was based on the presence of at least 1 outpatient medical or outpatient pharmacy claim with the relevant medication code, and diagnostic testing was based on at least 1 medical claim with the relevant procedure code.

Healthcare use and costs. All-cause and respiratory-related healthcare use and costs (the patient-paid and insurer-paid amount on claims) included inpatient admissions, emergency room visits, outpatient office visits, other outpatient services (including laboratory and radiology testing, medication infusions, etc.), and outpatient pharmacy claims in the 12 months following the index date. An inpatient admission was considered respiratory-related if the primary diagnosis was ICD-9-CM 460.xx–519.xx^{10,11}. An emergency room visit, outpatient office visit, or other outpatient service was considered respiratory-related if any of the diagnoses on the claim were ICD-9-CM 460.xx–519.xx. Respiratory-related medications included (1) antibiotics billed through outpatient medical and prescription claims if the claim occurred within 15 days of a diagnosis of acute upper respiratory infection or pneumonia, and (2) medications classified as “Respiratory Therapy Agents” in First Data Bank drug database¹² billed through outpatient pharmacy claims. The average costs per patient per year are presented in 2014 US dollars. Yearly costs over a 5-year followup period were calculated for patients with incident RA-ILD who had followup that was sufficient to enable evaluation of trends in costs over time.

All-cause survival. For the subset of patients who could potentially be linked to the SSDI, survival was measured. For incident cases who died, survival was calculated as time from index date to death. Incident cases without a date of death were censored at the end of continuous enrollment or the end of the study period.

Analysis. Descriptive statistics were generated for demographic and clinical characteristics, and healthcare use and costs. Means and medians are presented for healthcare costs because of skewness. A Kaplan-Meier plot was generated to describe survival for the subset of patients linked to the death data. Analyses were conducted with SAS version 9.4 (SAS Inc.).

RESULTS

Prevalence and incidence estimates. Between 2004 and 2013, the number of patients meeting the inclusion criteria ranged from 892 patients to 3232 patients per year. Yearly prevalence estimates ranged from 3.2 (95% CI 3.0–3.4) to 6.0 (95% CI 5.7–6.2) RA-ILD cases per 100,000 people (Figure 1). Yearly incidence rates ranged from 2.7 (95% CI 2.5–2.9) to 3.8 (95% CI 3.5–4.0) per 100,000 people. From 2004 to 2013, incidence appeared relatively stable while prevalence increased. Among enrollees who maintained 12 months of continuous enrollment after the index date, the raw numbers of prevalent RA-ILD cases ranged from 648 to 1775 patients per study year.

Patient characteristics. The range of mean ages for cases was 64–66 years and most patients were female (66.0%–70.1% across study years; Table 1). Comorbidities were common. Of those evaluated in this study, the most common were hypertension, GERD, dyslipidemia, coronary artery disease, and diabetes. Acute bronchitis/pneumonia was also common during the 12-month followup, present in roughly one-third of patients with RA-ILD. About 80% of patients had a claim

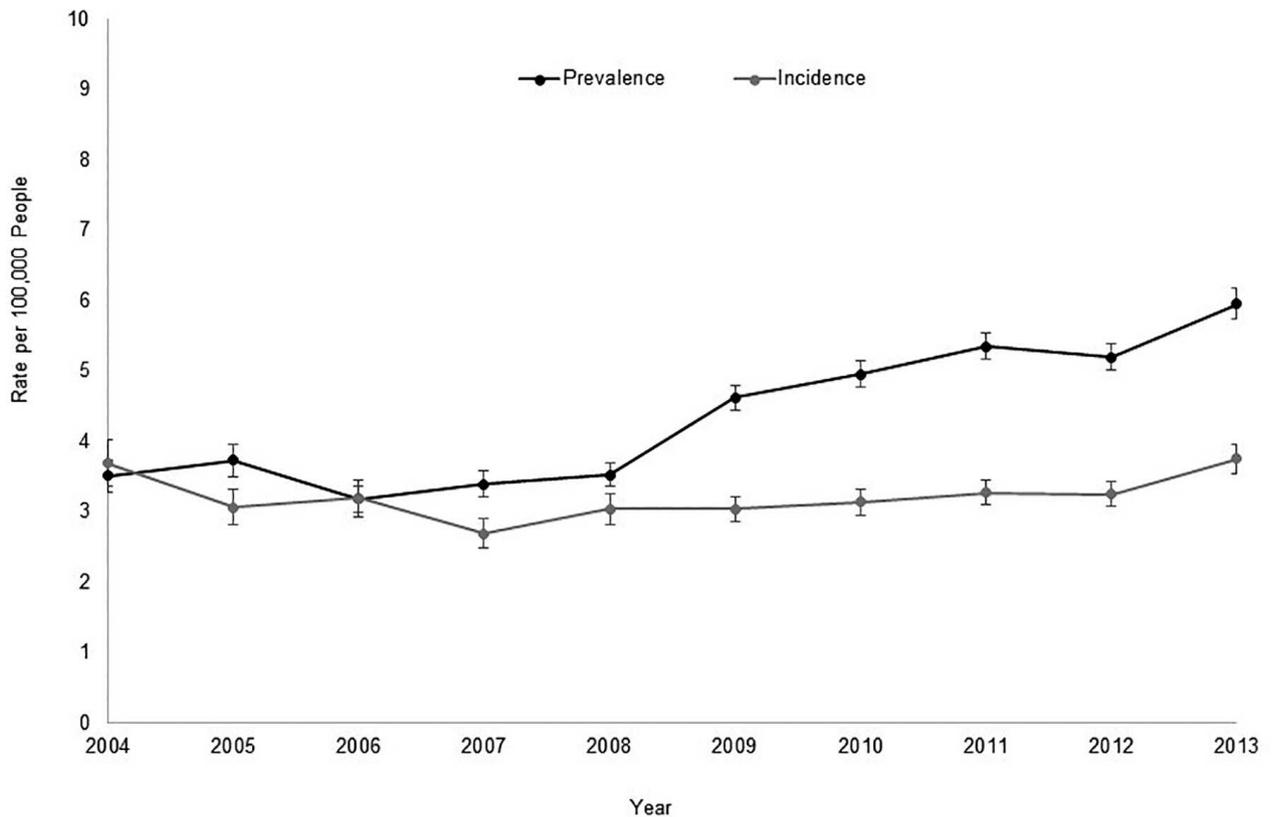


Figure 1. Prevalence and incidence of RA-ILD per 100,000 people with 95% CI from 2004 to 2013. RA-ILD: rheumatoid arthritis–related interstitial lung disease.

for either oral or intravenous glucocorticoids. Computed tomography (CT) scans and radiographs were common in the 12-month followup. Around 10% of patients had a lung biopsy during that time.

Healthcare use and costs. For each year of query, more than one-third of cases had an inpatient admission or emergency room visit in the 12 months after the index date (Table 2). Across all study years, the average yearly all-cause healthcare costs ranged from \$40,941 (SD \$55,682) to \$51,849 (SD \$77,125). The median all-cause healthcare costs ranged from \$28,021 [interquartile range (IQR) \$13,314–\$49,879] to \$31,914 (IQR \$13,563–\$56,180). Based on the average costs, the main cost drivers were inpatient admissions (range of mean costs: \$12,224–\$18,471; range of median costs: \$0–\$0), other outpatient services (mean: \$15,758–\$20,008; median: \$7892–\$10,563), and outpatient pharmacy (mean: \$10,563–\$12,775; median: \$4768–\$7890). Median all-cause inpatient costs among patients who had at least 1 inpatient admission ranged from \$30,541 to \$47,615. Each year, 13.6–19.5% of cases had a respiratory-related hospitalization, and 13.7%–19.4% had a respiratory-related emergency room visit. Average yearly respiratory-related costs ranged from \$8944 (SD \$21,021) to \$14,008 (SD \$65,346) and accounted for 18.5%–29.4% of total all-cause costs. Median yearly

respiratory-related costs ranged from \$2828 (IQR \$1022–\$7844) to \$3502 (IQR \$1198–\$8574).

Longitudinal RA-ILD cohort. There were 750 incident RA-ILD cases followed for 5 years. Over 5 years, 71.6% of patients had an all-cause inpatient admission and 76.0% had an all-cause emergency room visit (Supplementary Tables 1 and 2, available with the online version of this article). Average total all-cause 5-year costs were \$173,405 (SD \$158,837) per patient and median all-cause 5-year costs were \$132,929 (IQR \$76,555–\$211,141). The average total respiratory-related 5-year costs were \$24,133 (SD \$42,942) and the median was \$11,613 (IQR \$3680–\$26,539). Mean annual per-patient costs were greatest in years 1 and 5 (Figure 2A–2B). That was true of the medians for all-cause costs as well. Median respiratory-related costs were highest in years 1 and 2 and then were lower but stable. Similar to 12-month costs, the main cost drivers of the mean costs in the 5-year followup analysis were inpatient admissions, other outpatient services, and outpatient pharmacy claims.

All-cause survival. Of the 6313 incident RA-ILD patients, 3142 (49.8%) could potentially be linked to the SSDI. Of those patients, a death date was present for 834 patients. At 5 years after first diagnosis, 35.9% of patients had died. Median survival was 7.8 years (95% CI 7.1–8.3; Figure 3).

Table 1. Demographic and clinical characteristics of patients with RA-ILD from 2004 to 2013.

	Year									
	2004, n = 648	2005, n = 676	2006, n = 738	2007, n = 857	2008, n = 1085	2009, n = 1346	2010, n = 1549	2011, n = 1775	2012, n = 1596	2013, n = 1575
Demographics										
Mean age, yrs	65.7 ± 11.8	65.2 ± 12.0	64.7 ± 12.2	64.7 ± 12.5	63.9 ± 12.3	64.5 ± 12.3	65.2 ± 12.4	64.6 ± 12.4	65.5 ± 12.6	65.1 ± 12.8
Female	434 (67.0)	446 (66.0)	512 (69.4)	588 (68.6)	739 (68.1)	923 (68.6)	1078 (69.6)	1235 (69.6)	1119 (70.1)	1096 (69.6)
Clinical characteristics										
Mean RA severity score ^a	4.0 ± 1.5	4.0 ± 1.5	4.1 ± 1.5	4.3 ± 1.6	4.4 ± 1.6	4.4 ± 1.6	4.3 ± 1.6	4.3 ± 1.6	4.2 ± 1.6	4.3 ± 1.6
Comorbidities										
PH	30 (4.6)	42 (6.2)	46 (6.2)	65 (7.6)	68 (6.3)	92 (6.8)	121 (7.8)	140 (7.9)	109 (6.8)	95 (6.0)
CAD	167 (25.8)	160 (23.7)	157 (21.3)	199 (23.2)	262 (24.1)	340 (25.3)	381 (24.6)	439 (24.7)	391 (24.5)	387 (24.6)
Hypertension	277 (42.7)	288 (42.6)	337 (45.7)	351 (41.0)	538 (49.6)	755 (56.1)	855 (55.2)	1037 (58.4)	956 (59.9)	961 (61.0)
Obesity	9 (1.4)	9 (1.3)	11 (1.5)	14 (1.6)	40 (3.7)	75 (5.6)	103 (6.6)	122 (6.9)	131 (8.2)	158 (10.0)
Sleep apnea	0 (0)	17 (2.5)	37 (5.0)	75 (8.8)	129 (11.9)	180 (13.4)	234 (15.1)	294 (16.6)	246 (15.4)	262 (16.6)
GERD	299 (46.1)	356 (52.7)	375 (50.8)	442 (51.6)	587 (54.1)	727 (54.0)	759 (49.0)	948 (53.4)	820 (51.4)	822 (52.2)
Dyslipidemia	225 (34.7)	237 (35.1)	256 (34.7)	344 (40.1)	476 (43.9)	651 (48.4)	759 (49.0)	902 (50.8)	820 (51.4)	825 (52.4)
Diabetes	138 (21.3)	152 (22.5)	155 (21.0)	189 (22.1)	258 (23.8)	337 (25.0)	390 (25.2)	466 (26.3)	395 (24.7)	382 (24.3)
Emphysema	32 (4.9)	40 (5.9)	39 (5.3)	37 (4.3)	55 (5.1)	94 (7.0)	105 (6.8)	110 (6.2)	115 (7.2)	104 (6.6)
Chronic bronchitis	98 (15.1)	123 (18.2)	114 (15.4)	127 (14.8)	174 (16.0)	254 (18.9)	259 (16.7)	297 (16.7)	249 (15.6)	234 (14.9)
Acute bronchitis/ pneumonia	226 (34.9)	244 (36.1)	248 (33.6)	297 (34.7)	364 (33.5)	517 (38.4)	587 (37.9)	634 (35.7)	574 (36.0)	592 (37.6)
Tobacco use disorder	10 (1.5)	12 (1.8)	22 (3.0)	38 (4.4)	44 (4.1)	93 (6.9)	94 (6.1)	134 (7.5)	99 (6.2)	129 (8.2)
Medications										
Use of glucocorticoids (oral or intravenous)	529 (81.6)	560 (82.8)	599 (81.2)	684 (79.8)	866 (79.8)	1085 (80.6)	1252 (80.8)	1438 (81.0)	1288 (80.7)	1281 (81.3)
Use of azathioprine	93 (14.4)	90 (13.3)	104 (14.1)	127 (14.8)	165 (15.2)	202 (15.0)	223 (14.4)	238 (13.4)	203 (12.7)	208 (13.2)
Use of supplemental oxygen	237 (36.6)	245 (36.2)	285 (38.6)	299 (34.9)	416 (38.3)	503 (37.4)	629 (40.6)	713 (40.2)	612 (38.3)	593 (37.7)
Procedures										
Chest CT scan	378 (58.3)	400 (59.2)	421 (57.0)	496 (57.9)	626 (57.7)	733 (54.5)	785 (50.7)	917 (51.7)	799 (50.1)	792 (50.3)
Chest radiograph	519 (80.1)	519 (76.8)	565 (76.6)	629 (73.4)	775 (71.4)	990 (73.6)	1120 (72.3)	1321 (74.4)	1122 (70.3)	1084 (68.8)
Lung biopsy	80 (12.3)	86 (12.7)	77 (10.4)	100 (11.7)	113 (10.4)	128 (9.5)	140 (9.0)	139 (7.8)	110 (6.9)	148 (9.4)

Data are presented as mean ± SD or n (%). ^a Measured using the CIRAS algorithm. CAD: coronary artery disease; GERD: gastroesophageal reflux disease; RA-ILD: rheumatoid arthritis-related interstitial lung disease; PH: pulmonary hypertension; CT: computed tomography; CIRAS: Claims-based Index for RA Severity.

After 10 years, the number of patients at risk was small (n = 33) and therefore, the curve was truncated at that point.

DISCUSSION

In this real-world, claims-based analysis, we found that the prevalence of RA-ILD ranged from 3.2 to 6.0 per 100,000 people, and the incidence ranged from 2.7 to 3.8 per 100,000 people. Over time, prevalence rates appeared to be slowly increasing while incidence rates were relatively stable. The increased prevalence suggests increased duration of RA-ILD (i.e., improved survival of patients with condition). If the estimate is accurate, it could be that newer therapies for RA-ILD are more effective than past therapies, or that, perhaps due to increased disease awareness (e.g., from the increased use of chest CT) beginning prior to the study period, there has been a trend in patients being diagnosed with the disease earlier in its course. Our data do not allow more in-depth evaluation of this issue, and it merits further analysis.

We found that patients with RA-ILD were also commonly diagnosed with GERD, dyslipidemia, acute bronchitis/

pneumonia, systemic hypertension, and coronary artery disease. They incurred annual healthcare costs of about \$30,000–\$50,000. The costs of inpatient admissions, outpatient services other than office visits, and outpatient pharmacy were the main cost drivers. On average, over the first 5 years after diagnosis, incident cases incurred nearly \$175,000 in healthcare costs and 50% of cases incurred ≥ \$130,000. This research adds to the body of literature on the epidemiology of RA-ILD and provides a foundation of data revealing the burden of RA-ILD on the US healthcare system. To our knowledge, this is the first study to describe the incidence and prevalence of RA-ILD among the general population and to estimate costs among US patients with RA-ILD.

Although the primary manifestation of RA is inflammatory polyarthritis, lung involvement is frequent and associated with substantial morbidity and mortality. The most common clinically significant lung manifestation of RA is ILD^{1,2,3}. While the exact mechanism by which ILD occurs in patients with RA is unclear, high levels of circulating autoantibodies, particularly rheumatoid factor and anticyclic

Table 2. All-cause and respiratory-related use and costs (2014 US\$) over 12 months from 2004 to 2013.

	Year									
	2004, n = 648	2005, n = 676	2006, n = 738	2007, n = 857	2008, n = 1085	2009, n = 1346	2010, n = 1549	2011, n = 1775	2012, n = 1596	2013, n = 1575
All-cause										
Inpatient admission	274 (42.3)	293 (43.3)	280 (37.9)	343 (40.0)	427 (39.4)	570 (42.3)	588 (38.0)	657 (37.0)	569 (35.7)	557 (35.4)
Mean costs, all patients	\$18,471 ± \$72,588	\$16,281 ± \$66,328	\$12,566 ± \$39,193	\$12,224 ± \$40,376	\$16,596 ± \$107,150	\$17,207 ± \$60,702	\$14,286 ± \$49,317	\$17,624 ± \$58,275	\$15,407 ± \$48,002	\$15,826 ± \$56,978
Median costs, all patients (IQR)	\$0 (\$0, \$13,356)	\$0 (\$0, \$12,977)	\$0 (\$0, \$8025)	\$0 (\$0, \$10,710)	\$0 (\$0, \$11,102)	\$0 (\$0, \$13,661)	\$0 (\$0, \$10,790)	\$0 (\$0, \$13,407)	\$0 (\$0, \$12,709)	\$0 (\$0, \$12,052)
Mean costs, patients with admission	\$43,684 ± \$106,686	\$37,564 ± \$96,787	\$33,120 ± \$58,091	\$30,541 ± \$59,324	\$42,169 ± \$167,732	\$40,634 ± \$88,071	\$37,634 ± \$74,388	\$47,615 ± \$88,053	\$43,214 ± \$72,571	\$44,751 ± \$88,847
Median costs, patients with admission (IQR)	\$16,754 (\$7166, \$42,636)	\$14,865 (\$7370, \$34,061)	\$16,633 (\$6336, \$35,480)	\$15,541 (\$8164, \$29,675)	\$16,234 (\$8333, \$35,332)	\$16,673 (\$8715, \$38,487)	\$16,256 (\$8112, \$37,473)	\$21,023 (\$10,832, \$44,440)	\$21,266 (\$11,357, \$43,829)	\$19,565 (\$10,893, \$41,241)
Emergency room visit	271 (41.8)	292 (43.2)	298 (40.4)	344 (40.1)	442 (40.7)	564 (41.9)	654 (42.2)	760 (42.8)	657 (41.2)	626 (39.7)
Mean costs, all patients	\$518 ± \$1500	\$453 ± \$1446	\$451 ± \$1493	\$357 ± \$945	\$434 ± \$1124	\$526 ± \$1726	\$527 ± \$1275	\$739 ± \$2121	\$687 ± \$2165	\$873 ± \$4313
Median costs, all patients (IQR)	\$0 (\$0, \$397)	\$0 (\$0, \$428)	\$0 (\$0, \$358)	\$0 (\$0, \$351)	\$0 (\$0, \$395)	\$0 (\$0, \$425)	\$0 (\$0, \$498)	\$0 (\$0, \$618)	\$0 (\$0, \$518)	\$0 (\$0, \$529)
Outpatient office visit	643 (99.2)	669 (99.0)	736 (99.7)	855 (99.8)	1079 (99.4)	1341 (99.6)	1542 (99.5)	1770 (99.7)	1589 (99.6)	1562 (99.2)
Mean costs, all patients	\$1604 ± \$1128	\$1954 ± \$1313	\$1897 ± \$1213	\$2038 ± \$1469	\$2085 ± \$1485	\$2092 ± \$1514	\$2067 ± \$1492	\$2091 ± \$1407	\$2060 ± \$1464	\$2005 ± \$1356
Median costs, all patients (IQR)	\$1501 (\$826, \$2263)	\$1695 (\$1069, \$2520)	\$1651 (\$1122, \$2400)	\$1779 (\$1208, \$2538)	\$1760 (\$1206, \$2620)	\$1796 (\$1197, \$2514)	\$1764 (\$1176, \$2617)	\$1782 (\$1170, \$2686)	\$1787 (\$1143, \$2628)	\$1714 (\$1158, \$2540)
Other outpatient service	648 (100)	676 (100)	738 (100)	857 (100)	1084 (99.9)	1346 (100)	1547 (99.9)	1775 (100)	1595 (99.9)	1575 (100)
Mean costs, all patients	\$16,487 ± \$25,471	\$16,477 ± \$20,958	\$15,935 ± \$21,290	\$15,738 ± \$24,968	\$17,951 ± \$28,311	\$18,081 ± \$27,799	\$18,847 ± \$32,346	\$20,008 ± \$30,042	\$18,753 ± \$30,327	\$19,499 ± \$31,829
Median costs, all patients (IQR)	\$8481 (\$4002, \$18,366)	\$9517 (\$4626, \$20,395)	\$7892 (\$3832, \$19,047)	\$8584 (\$3795, \$17,689)	\$9203 (\$4430, \$21,127)	\$9978 (\$4621, \$21,753)	\$9417 (\$4298, \$22,430)	\$10,563 (\$4559, \$23,822)	\$9398 (\$3964, \$22,806)	\$8870 (\$3520, \$23,540)
Pharmacy claim	638 (98.5)	667 (98.7)	717 (97.2)	833 (97.2)	1057 (97.4)	1304 (96.9)	1504 (97.1)	1726 (97.2)	1566 (98.1)	1537 (97.6)
Mean costs, all patients	\$10,635 ± \$12,481	\$12,726 ± \$16,457	\$10,917 ± \$12,521	\$10,563 ± \$11,986	\$11,026 ± \$14,374	\$10,568 ± \$16,085	\$10,567 ± \$16,130	\$11,387 ± \$17,460	\$11,487 ± \$18,321	\$12,775 ± \$23,364
Median costs, all patients (IQR)	\$6994 (\$2972, \$13,495)	\$7890 (\$3934, \$17,369)	\$6602 (\$3049, \$14,198)	\$6144 (\$2647, \$14,231)	\$5961 (\$2425, \$14,078)	\$5166 (\$2022, \$13,465)	\$4962 (\$1908, \$13,537)	\$5004 (\$1792, \$14,500)	\$4768 (\$1817, \$14,136)	\$5015 (\$1700, \$15,292)
Mean total costs, all patients	\$47,716 ± \$83,858	\$47,891 ± \$85,916	\$41,766 ± \$54,073	\$40,941 ± \$55,682	\$48,091 ± \$115,687	\$48,473 ± \$74,617	\$46,294 ± \$67,893	\$51,849 ± \$77,125	\$48,392 ± \$67,602	\$50,979 ± \$77,696
Median total costs, all patients (IQR)	\$28,141 (\$14,009, \$49,095)	\$31,109 (\$16,997, \$51,860)	\$28,021 (\$13,314, \$49,879)	\$28,698 (\$14,279, \$47,450)	\$30,502 (\$14,574, \$50,967)	\$30,507 (\$15,234, \$53,373)	\$29,236 (\$13,610, \$54,014)	\$31,491 (\$14,892, \$56,922)	\$30,911 (\$14,265, \$55,703)	\$31,914 (\$13,563, \$56,180)
Respiratory-related										
Inpatient admission	124 (19.1)	132 (19.5)	122 (16.5)	156 (18.2)	187 (17.2)	229 (17.0)	233 (15.0)	283 (15.9)	217 (13.6)	227 (14.4)
Mean costs, all patients	\$9041 ± \$63,256	\$5119 ± \$21,336	\$4491 ± \$21,144	\$5138 ± \$26,023	\$5456 ± \$41,582	\$5029 ± \$33,307	\$4804 ± \$35,706	\$5279 ± \$25,094	\$3699 ± \$16,509	\$5513 ± \$39,015
Median costs, all patients (IQR)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)
Mean costs, patients with admission	\$47,247 ± \$138,664	\$26,216 ± \$42,288	\$27,168 ± \$45,847	\$28,224 ± \$55,533	\$31,657 ± \$96,141	\$30,615 ± \$75,914	\$31,940 ± \$87,387	\$33,110 ± \$55,106	\$27,206 ± \$37,014	\$38,248 ± \$96,662
Median costs, patients with admission (IQR)	\$18,277 (\$9221, \$36,143)	\$12,708 (\$7072, \$26,266)	\$12,564 (\$7400, \$30,154)	\$12,475 (\$7843, \$24,119)	\$13,867 (\$8195, \$24,736)	\$13,735 (\$8315, \$27,205)	\$13,507 (\$7832, \$28,706)	\$15,785 (\$8340, \$32,769)	\$15,292 (\$9572, \$30,189)	\$13,688 (\$8887, \$25,265)
Emergency room visit	100 (15.4)	101 (14.9)	106 (14.4)	117 (13.7)	157 (14.5)	229 (17.0)	286 (18.5)	319 (18.0)	310 (19.4)	273 (17.3)
Mean costs, all patients	\$135 ± \$871	\$85 ± \$328	\$86 ± \$360	\$79 ± \$386	\$112 ± \$548	\$108 ± \$406	\$132 ± \$534	\$182 ± \$812	\$163 ± \$666	\$187 ± \$952
Median costs, all patients (IQR)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)
Outpatient office visit	577 (89.0)	602 (89.1)	677 (91.7)	793 (92.5)	1014 (93.5)	1271 (94.4)	1436 (92.7)	1657 (93.4)	1485 (93.0)	1473 (93.5)
Mean costs, all patients	\$369 ± \$376	\$431 ± \$406	\$436 ± \$393	\$487 ± \$452	\$506 ± \$447	\$547 ± \$526	\$571 ± \$586	\$588 ± \$615	\$573 ± \$566	\$598 ± \$547
Median costs, all patients (IQR)	\$258 (\$76, \$559)	\$331 (\$147, \$574)	\$358 (\$162, \$577)	\$366 (\$181, \$649)	\$391 (\$202, \$685)	\$400 (\$209, \$709)	\$419 (\$217, \$747)	\$425 (\$216, \$779)	\$421 (\$219, \$740)	\$461 (\$238, \$789)
Other outpatient services	622 (96.0)	638 (94.4)	700 (94.9)	810 (94.5)	1023 (94.3)	1275 (94.7)	1473 (95.1)	1685 (94.9)	1497 (93.8)	1486 (94.3)
Mean costs, all patients	\$3508 ± \$6113	\$3485 ± \$6226	\$3394 ± \$7330	\$3191 ± \$6571	\$3254 ± \$6277	\$3849 ± \$9414	\$3832 ± \$8158	\$3918 ± \$7854	\$3644 ± \$8920	\$3890 ± \$9764

Table 2. Continued.

	Year									
	2004, n = 648	2005, n = 676	2006, n = 738	2007, n = 857	2008, n = 1085	2009, n = 1346	2010, n = 1549	2011, n = 1775	2012, n = 1596	2013, n = 1575
Median costs, all patients (IQR)	\$1356 (\$413, \$4437)	\$1333 (\$390, \$4089)	\$1233 (\$417, \$3666)	\$1287 (\$382, \$3694)	\$1395 (\$427, \$3495)	\$1466 (\$392, \$3972)	\$1500 (\$368, \$4117)	\$1534 (\$404, \$4243)	\$1131 (\$309, \$3530)	\$1201 (\$339, \$3615)
Antibiotic claim ^a	140 (21.6)	133 (19.7)	140 (19.0)	159 (18.6)	221 (20.4)	292 (21.7)	325 (21.0)	383 (21.6)	351 (22.0)	333 (21.1)
Mean costs, all patients	\$141 ± \$1527	\$122 ± \$1927	\$65 ± \$539	\$50 ± \$374	\$130 ± \$2408	\$168 ± \$2645	\$57 ± \$367	\$74 ± \$650	\$47 ± \$393	\$20 ± \$129
Median costs, all patients (IQR)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)	\$0 (\$0, \$0)
Respiratory therapy pharmacy claim	445 (68.7)	488 (72.2)	515 (69.8)	591 (69.0)	714 (65.8)	889 (66.0)	987 (63.7)	1,112 (62.6)	1,025 (64.2)	977 (62.0)
Mean costs, all patients	\$814 ± \$1648	\$1005 ± \$2618	\$878 ± \$2361	\$767 ± \$1245	\$745 ± \$1345	\$793 ± \$1451	\$799 ± \$2067	\$762 ± \$1511	\$819 ± \$2071	\$732 ± \$1508
Median costs, all patients (IQR)	\$183 (\$0, \$1072)	\$252 (\$0, \$1203)	\$157 (\$0, \$1069)	\$177 (\$0, \$1027)	\$104 (\$0, \$894)	\$87 (\$0, \$908)	\$84 (\$0, \$861)	\$74 (\$0, \$776)	\$74 (\$0, \$813)	\$53 (\$0, \$660)
Mean total costs, all patients	\$14,008 ± \$65,346	\$10,247 ± \$24,716	\$9349 ± \$25,482	\$9712 ± \$29,980	\$10,204 ± \$43,826	\$10,674 ± \$36,642	\$10,195 ± \$38,290	\$10,802 ± \$28,513	\$8944 ± \$21,021	\$10,939 ± \$43,123
Median total costs, all patients (IQR)	\$3502 (\$1198, \$8574)	\$3450 (\$1225, \$9764)	\$2997 (\$1153, \$7505)	\$2906 (\$1222, \$7926)	\$2995 (\$1232, \$8055)	\$3358 (\$1153, \$8661)	\$3269 (\$1162, \$8151)	\$3191 (\$1202, \$9289)	\$2828 (\$1022, \$7844)	\$2921 (\$1074, \$8358)

Data are presented as mean ± SD or n (%) unless otherwise specified. ^a Billed through outpatient medical claims or pharmacy claims. IQR: interquartile range.

citruillated peptide^{1,13,14}, and cigarette smoking^{1,15,16,17,18} have been implicated as risk factors. Unfortunately, neither antibody status nor smoking history are available in the databases we used. Although the diagnosis of tobacco use disorder was queried, it is almost certainly undercoded. Surprisingly, we found that a majority of patients with RA-ILD were female. While RA is more common among women^{7,19,20}, results from other studies suggest the prevalence of RA-ILD is greater in men^{20,21}, or similar between sexes²². The difference in results between studies may stem from differences in the source populations. Overall, females make up just over half of the MarketScan database.

Our findings of stable incidence and rising prevalence of RA-ILD corroborate results from other studies. Myasoedova and colleagues calculated the incidence of ILD among individuals with RA in Olmsted County, Minnesota, by reviewing medical records obtained through the Rochester Epidemiology Project⁷. They estimated a 10-year cumulative incidence of 6.6% from 1985 to 1994, and 5.0% from 1995 to 2007 among individuals with RA, with no significant difference in incidence between the 2 time periods⁷. Bartels and colleagues found that the prevalence of RA-related ILD or pleurisy increased from about 2% in 1985 to about 4% in 2006 in the inpatient setting among patients with RA⁸. The prevalence in the outpatient setting increased from 0.56% in 1997 to 0.98% in 2006⁸. The prevalence of other extra-articular manifestations declined over time⁸. The authors hypothesized that the increase in ILD/pleurisy was due, in part, to increased use of chest high-resolution CT scans⁸. Differences in incidence and prevalence estimates of RA-ILD between these and our study are caused by different denominators being used: in our study, the denominator was all people enrolled in MarketScan, and in the other studies, the denominator was patients with RA. When limiting our analysis to patients with RA (defined as ≥ 2 diagnoses), the proportion of patients with RA-ILD was < 2% from 2007 to 2013. In a study using death certificate data from the National Center for Health Statistics from 1988 to 2004, Olson and her co-investigators found that the prevalence of ILD among decedents with RA increased across time for men (7.5–9.8%) and women (4.7–6.8%); however, these results are not the same as prevalence estimates for RA-ILD².

ILD results in decreased lung function and is a leading cause of death among patients with RA, after cardiovascular disease^{1,23,24,25}. As demonstrated in other studies, we found RA-ILD to be a life-shortening disease: among patients with vital status information, 35.9% of RA-ILD patients had died by 5 years after index date, and median survival among all-comers for whom death data were available was 7.8 years. In comparison, at age 65 (the mean age of RA-ILD patients in this study), a person in the United States is expected to live another 19 years²⁶. Bongartz and colleagues followed 582 patients with RA over time and found that 46 developed probable or definite ILD²⁰. Median survival for patients with

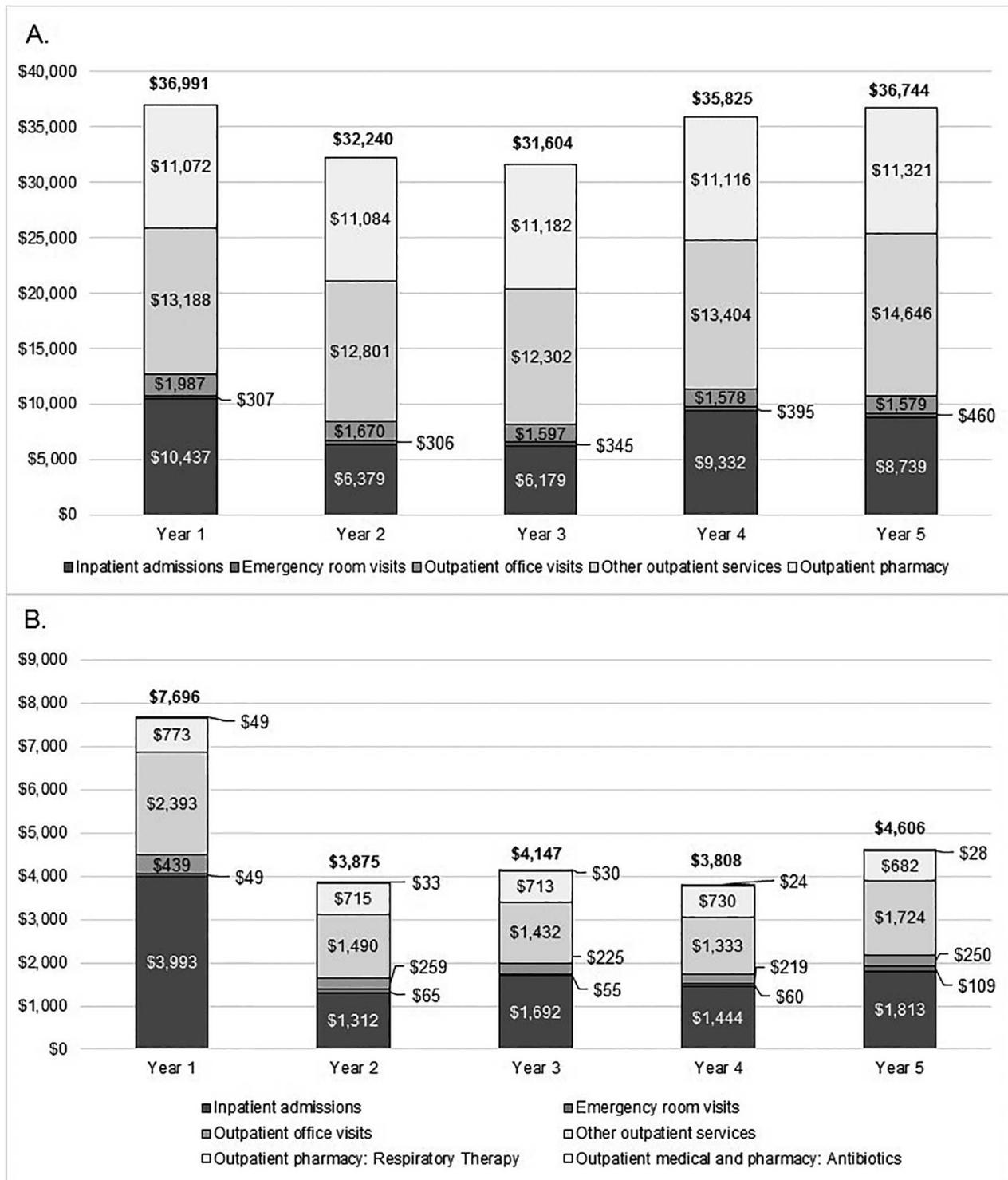


Figure 2. Mean (A) all-cause and (B) respiratory-related healthcare use and costs (2014 US\$) over a 5-year followup for incident RA-ILD patients. RA-ILD: rheumatoid arthritis–related interstitial lung disease.

RA overall was 9.9 years, while median survival after ILD diagnosis was 2.6 years²⁰. Other investigators from tertiary referral centers have found similarly dismal survival rates after RA-ILD is diagnosed²⁷. Still other investigators have

found survival times that mirror our results²⁸. A prospective analysis reported that 5-year mortality for RA patients with ILD was 39.0%, and for patients with RA but no ILD was 18.2%²⁹. The longer median survival in our study is likely

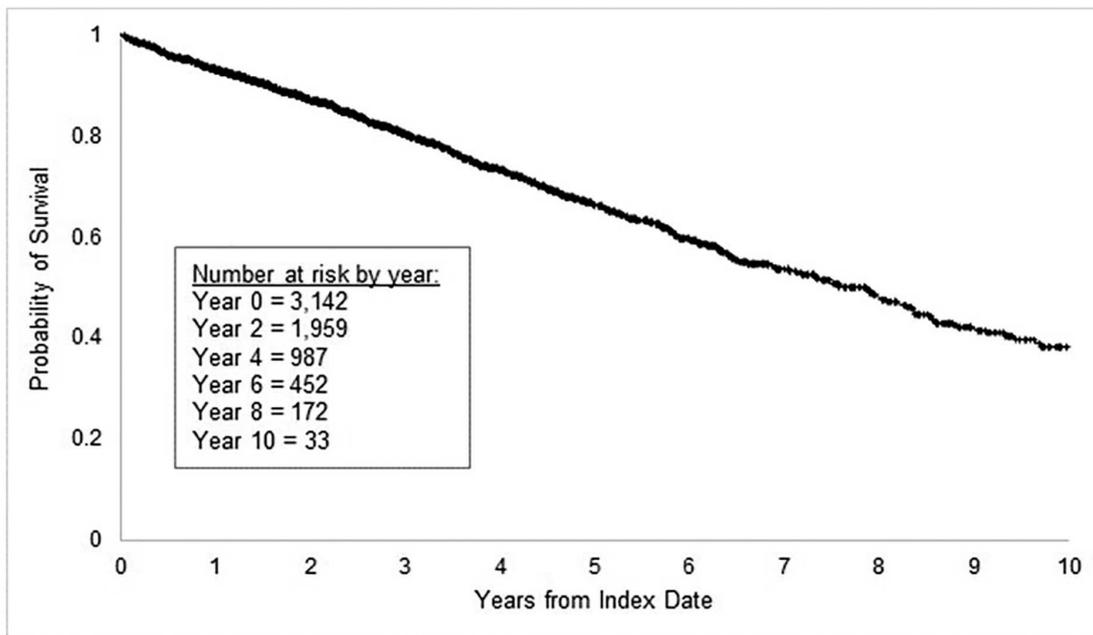


Figure 3. Kaplan-Meier plot of survival for incident RA-ILD patients. RA-ILD: rheumatoid arthritis–related interstitial lung disease.

because our patient population was healthier than others analyzed (inclusion in the database is linked to employment for most patients).

To our knowledge, this is the first study to describe costs among the subgroup of patients with RA-ILD. In an analysis of administrative claims from privately insured, Medicare beneficiaries, and Medicaid beneficiaries, investigators reported that patients with RA had greater annual healthcare costs than matched patients without RA⁴. Average annual direct medical costs, including out-of-pocket costs, were \$10,774 for privately insured patients with RA and \$13,374 for Medicare-insured RA patients, compared to \$5063 and \$5457 for matched controls in the 2 populations⁴. After weighting the population, the annual excess healthcare costs for patients with RA were \$8.4 billion in 2005 US dollars⁴. The direct healthcare costs incurred by patients with RA were substantially smaller than the average yearly costs of patients with RA-ILD measured in our analysis. Considering the US population in 2013³⁰, patients with RA-ILD incurred about \$970.5 million in total healthcare costs in 2013. Future analyses of RA-ILD costs should be conducted to compare costs of patients with RA who have ILD to those who do not.

Our study has limitations. As with any claims databases, the MarketScan Research Databases relied on administrative claims data for clinical detail. These data were subject to data entry error and diagnostic coding limitations. Because of the reliance on ICD-9-CM diagnoses on claims rather than more detailed clinical information included in medical records, misclassification of RA-ILD status may have occurred. Our case definition for RA-ILD required multiple diagnoses and may have resulted in true cases of RA-ILD being excluded,

leading to underestimates of prevalence. Because date of diagnosis was not available, previously diagnosed cases of RA-ILD may have been misclassified as incident cases. We attempted to reduce the likelihood of misclassification by requiring a 6-month clean period with no diagnoses of ILD. It is possible that prevalent cases who had no contact with the healthcare system over that 6-month period may have been misclassified as incident cases. Requiring a longer clean period would have limited the study's generalizability, by causing the selection of healthier enrollees. Likewise, without a definitive date of diagnosis, survival estimates may be inaccurate. Our estimates of prevalence and incidence may be influenced by continuous enrollment requirements³¹. Ideally, a study estimating incidence and prevalence would be conducted in a closed population, where individuals do not leave the population for reasons other than death. The MarketScan data involve an open population in which people enter and leave based on employment/enrollment, thus forcing us to use different denominators for prevalence and incidence estimates, and potentially inducing inaccuracies. Additionally, the MarketScan databases include only individuals with commercial or Medicare Supplemental Insurance. Individuals insured through Medicaid programs or uninsured individuals, who typically have lower socioeconomic status, were not analyzed. Our healthcare cost and survival results may not be generalizable to those populations who may have more severe disease. The 12-month costs for prevalent RA-ILD patients and the 5-year costs for incident patients were measured for patients with sufficient enrollment. This may have resulted in selection bias, with sicker patients and those who died being excluded from our

analyses. These patients may have had higher costs than patients who survived for 12 months or 5 years. Thus, costs should be viewed as low-end estimates, because they represent the healthcare costs for patients with RA-ILD who were healthy enough to survive. Information on the cause of death was not available, so there is no way to know whether deaths should be directly attributed to complications of ILD. Only a portion of the RA-ILD patients in MarketScan had the potential to be linked to the SSDI. Additionally, mortality may be underestimated because of the reduction of data included in the SSDI³². Reliable smoking history is not available in claims. Additionally, other potential factors affecting mortality such as pulmonary function and disease patterns on radiological or laboratory testing were not available in claims. The results of our analysis may not apply to patients with other types of coverage or with no health insurance.

We found the prevalence of RA-ILD has increased over the 10-year period from 2004 to 2013, while its incidence has remained fairly stable. RA-ILD leads to high healthcare use and costs, due in large part to inpatient admissions, outpatient services other than office visits, and outpatient pharmacy claims. RA-ILD shortens survival, even in a presumably healthier population than those evaluated at tertiary referral centers: within 5 years of index date, about one-third of RA-ILD patients with a potential linkage to SSDI died.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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