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Journal

ACR Open Rheumatology, 2(12)

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Publication Date

2020-12-01

DOI

10.1002/acr2.11200

Peer reviewed

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Trends in Hospitalization Rates, Major Causes of Hospitalization, and In-Hospital Mortality in Rheumatoid Arthritis in the United States From 2000 to 2014

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Objective. To evaluate national trends in hospitalizations and in-hospital mortality in rheumatoid arthritis (RA).

Methods. National Inpatient Sample from 2000-2014 and United States Census data were used to study temporal trends in adult RA hospitalizations, reasons for hospitalizations, and in-hospital mortality.

Results. The data represented 183 983 hospitalizations with a primary diagnosis of RA. The annual rates of hospitalization for the primary diagnosis of RA decreased from 76.54 admissions per 1 million in 2000 to 29.96 per 1 million in 2014 (P trend < 0.0001). The hospital mortality rate declined from 0.70% to 0.41% (P trend < 0.0001) in this group. With a primary or nonprimary diagnosis of RA, the mortality rate ranged between 1.95 and 2.87 (P trend 0.08). For a nonprimary diagnosis of RA, we noted that the proportion of hospitalizations with a diagnosis of myocardial infarction (6.4% in 2000 to 4.6% in 2014; P < 0.001) significantly decreased, but the absolute number of hospitalizations significantly increased. In contrast, the proportion and the absolute number of hospitalizations with any diagnosis of sepsis, congestive heart failure, lung disease, and urinary tract infection increased significantly. We also noted a significant increase in the actual rate and proportions for hospitalizations for hip and knee arthroplasty. Among in-hospital deaths when RA was a nonprimary diagnosis, the most common primary diagnosis was pneumonia (12.5 %) in 2000, whereas sepsis accounted for the most deaths in 2014 (31.4%).

Conclusion. We observed that hospitalization rates and in-hospital mortality rates in patients with RA have changed significantly over the past 15 years.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic joint disease characterized by inflammation of the synovial membrane (1) that affects approximately 0.6% of the United States (US) general population (2). In addition to its debilitating effect on joints, RA is also a systemic disease with several far-reaching consequences resulting from chronic inflammation. As a result, patients with RA may have several associated comorbidities, including accelerated atherosclerosis and an increased risk for cardiovascular disease. In addition, treatments used for RA, such as disease-modifying antirheumatic drugs, biologics, nonsteroidal anti-inflammatory drugs, and corticosteroids, themselves carry risks not limited to infections and exacerbation of moderate to severe heart failure (tumor

necrosis factor inhibitors). Thus, patients with RA are potentially at an increased risk of inpatient hospitalizations (3), serious infections (4), major cardiovascular events (5), and mortality (6,7). There is a lack of studies evaluating the trends in the rates and causes of RA-related hospitalizations and in-hospital mortality in the US.

Several reports that have analyzed trends in RA outcomes have focused on mortality and survival trends and have been conducted in outpatient observational cohorts (6,8-11). Jinno et al (12) evaluated the trends in certain infections as the cause of hospitalizations and mortality in RA, whereas Young et al evaluated the trends in arthroplasties performed on patients with RA (13,14). None of these studies examined whether there have been major shifts in the reasons for hospitalizations and in-hospital mortality in contemporary patients with RA relative to prior years.

In the recent decades, there has been a revolutionary improvement in the treatment of RA because of introduction of several biological treatments. With the recent increase in the availability of targeted RA therapies, early and more timely control of RA has translated into improved patient joint-related outcomes (15). Based on the expected reduction in systemic inflammation and overall better disease control, we hypothesized that hospitalization rates in RA as well as in-hospital mortality rates in RA would be on the decline. Thus, the objective of our study was to evaluate recent US national trends regarding RA-related hospitalizations and in-hospital mortality using a national database.

PATIENTS AND METHODS

Data source. We used the National Inpatient Sample (NIS) database, one of the Healthcare Cost and Utilization Project (HCUP) databases. This is the largest available all-payer database of inpatient hospitalizations managed under the HCUP of the Agency for Healthcare Research and Quality (AHRQ) (16). It contains discharge records from over 7 million hospital visits (unweighted), which are representative of discharges from a random 20% stratified sample of US hospitals. The NIS provides a useful representation of national US statistics and includes deidentified information on patient demographics, admission status, primary and second discharge diagnosis, and procedures. A maximum of 25 discharge diagnoses and 15 procedures are available on the NIS record for each patient. We adhered to the research practices as recommended by the AHRQ for the use of the NIS. Because these publicly available data are deidentified, our study was exempt from institutional review board approval requirements.

Patient selection. We identified all adults ages 18 years or older who had an Internaltion Classification of Diseases, ninth revision (ICD-9), discharge code for RA (714.0 or 714.2) in any diagnosis position (Supplemental Table 1). In our study, we limited our search and excluded some codes (such as 714.1 and 714.4) that have been used in other similar studies of RA. Code 714.1 is the code used to describe Felty syndrome in RA. This is

a rare manifestation, seen in less than 1% of patients with RA (17) and is unlikely to make a meaningful contribution to our study. In our study, cases identified by 714.1 constituted 0.77% of total RA admissions (range 0.52-1.2% for any year) and were thus excluded from further analysis. Similarly, code 714.4 is used to identify chronic postrheumatic arthropathy, also known as Jaccoud arthropathy. This is a clinical condition with characteristic reversible joint deformities secondary to noninflammatory, nonerosive, and fibrotic processes in the joints and may not be associated with a true diagnosis of RA (18). Given the small contribution of these codes and the likely small impact on our overall analyses, we decided to exclude these codes from our final analyses.

To capture only RA-related admissions, we excluded patients with concomitant diagnoses of juvenile chronic polyarthritis (714.30-714.32), systemic lupus erythematosus (710.0), antiphospholipid syndrome (289.81), ankylosing spondylitis (720.0), and psoriatic arthropathy (696.0). In addition to diagnoses, we extracted information about each hospitalization, such as patient age, sex, race, payer (eg, Medicare, Medicaid, private insurance, uninsured, and others), length of stay, and in-hospital death.

Identifying the causes of hospitalization. When evaluating causes of hospitalizations and in-hospital mortality in patients with RA, a search was done for each hospitalization for which RA was the nonprimary diagnosis. Primary diagnoses among patients with a nonprimary diagnosis of RA were categorized using the AHRQ Clinical Classification Software, which collapses more than 16000 ICD-9-Clinical Modification diagnosis codes into more than 200 clinically relevant categories (19). We limited our search to evaluating some of the major causes of admission (myocardial infarction, pneumonia, sepsis, urinary tract infection [UTI], congestive heart failure, cerebrovascular disease, any cancer, chronic obstructive pulmonary disease [COPD]/bronchiectasis/asthma, hip arthroplasty, knee arthroplasty, and prosthetic joint infection) in patients with RA and evaluated their trends as causes of admission and mortality over time.

Statistical analysis. We used weights to estimate trends in the US in the number of hospital admissions with a primary diagnosis of RA by year. Between 1988 and 2011, the NIS included 100% of the discharges from a 20% representative sample of US hospitals. Beginning in 2012, the NIS sampling design changed to include a 20% national patient-level sample across all HCUP hospitals (19). Our analysis of hospitalization trends accounted for the change in sampling design in 2012 as recommended by HCUP while incorporating standard errors for estimates that accounted for the complex sample design (19). We used population estimates from the US Census American Community Survey for each year to calculate the number of admissions with RA as the primary diagnosis per 1 million residents. The proportion of hospitalizations for each condition among all hospitalizations

Table 1. Demographics, trends, mortality, and length of stay of hospitalization with a primary diagnosis of rheumatoid arthritis from 2000 to 2014

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P Trend
Hospitalizations (total = 183983), n	15 424	15 846	16 298	13 866	15 040	14 167	13 142	12 510	11 938	10 766	10 395	9951	9055	8235	7350	
Age																
Mean (SD), yr	62.7 (30.7)	62.7 (31.1)	62.1 (31.6)	61.8 (30.9)	62.2 (30.9)	63 (30.1)	62.2 (30.9)	62.6 (30.8)	62.3 (29.7)	62 (31.5)	61.6 (31.8)	61.8 (31.1)	62.3 (31.8)	62.1 (32.5)	61.9 (32.3)	
<65 years old, %	50.66	50.65	51.91	54.08	52.47	51.03	53.72	53.58	55.15	53.67	54.52	54.24	52.73	51.85	53.33	
≥65 years old, %	49.34	49.35	48.09	45.92	47.53	48.97	46.28	46.42	44.85	46.33	45.48	45.76	47.27	48.15	46.67	
Sex, %																
Female	78.19	78.49	78.43	78.44	79.84	78.77	79.42	78.14	77.61	78.21	77.32	77.58	76.81	76.5	77.89	
Male	21.81	21.51	21.57	21.56	20.16	21.23	20.58	21.86	22.39	21.79	22.68	22.42	23.19	23.5	22.11	
Race/ethnicity, %[a]																
White	56.86	75.62	73.13	69.37	71.11	70.33	65.9	69.44	70.44	65.95	65.72	65.16	65.06	63.87	61.45	
Nonwhite	19.37	24.38	26.87	30.63	28.89	29.67	34.1	30.56	29.56	34.05	34.28	34.84	34.94	36.13	38.55	
Primary payer, %																
Medicare	58.25	58.06	58.14	57.28	57.54	58.77	55.94	56.12	53.04	54.76	52.62	56.75	58.21	55.08	54.84	
Medicaid	7.07	6.79	6.86	7.78	7.76	8.48	9.21	9.09	7.99	8.31	9.69	9.68	7.3	10.1	10.91	
Private	30.49	31.57	31.84	31.24	31.16	28.46	30.29	29.39	32.63	31.1	31.57	28.24	28.41	27.63	29.47	
Other	4.18	3.59	3.16	3.71	3.54	4.29	4.56	5.4	6.34	5.83	6.13	5.33	6.08	7.18	4.77	
Hospitalization rate (per 1 million persons)	76.54	77.32	78.30	65.94	70.68	65.82	58.25	54.94	51.87	46.30	44.19	41.86	37.68	33.94	29.96	<0.0001
<65 years old	46.39	46.75	48.46	42.51	44.20	40.04	37.47	35.29	34.40	29.93	29.10	27.49	24.22	21.57	19.68	<0.0001
≥65 years old	229.90	235.13	233.51	187.85	208.62	199.83	163.52	153.63	138.01	126.30	116.88	110.02	99.25	88.78	74.23	<0.0001
Female	114.94	116.65	118.18	99.76	108.93	100.22	90.01	83.61	78.43	70.57	66.36	63.13	56.30	50.53	45.40	<0.0001
Male	34.83	34.67	35.16	29.52	29.56	28.95	24.67	24.68	23.86	20.72	20.66	19.32	17.99	16.41	13.63	<0.0001
Median length of stay, days	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	

[a] The total does not equal 100% since race/ethnicity data were unavailable in certain states during certain years.

with a nonprimary diagnosis of RA was calculated by dividing the number of hospitalizations due to the specified condition (eg, sepsis) with any nonprimary diagnosis of RA by the number of any hospitalizations with a nonprimary diagnosis of RA. Deaths in the hospital were identified using the discharge disposition code, and principal diagnoses among patients who died were also examined. The proportion of in-hospital mortality from a specified cause was calculated by dividing the number of deaths from the specific cause in patients with a primary or secondary diagnosis of RA by the patients with a primary or secondary diagnosis of RA. Additionally, we examined reasons for admission and in-hospital mortality among patients admitted with a nonprimary diagnosis of RA. For the trend analysis, a simple linear regression model was employed. A P value of less than 0.05 was set to be significant. All analyses were performed using software SAS version 9.4 (SAS Institute).

RESULTS

Demographic characteristics of RA hospitalizations. Between 2000 and 2014, there were 5 636 171 hospitalizations with a discharge diagnosis of RA in a primary or secondary position. As shown in Table 1, there were 183 983 hospitalizations in the study period with RA as the primary diagnosis for admission. The mean age of all patients hospitalized for RA remained largely stable over the years and was 62.7 in 2000 and 61.9 years in 2014. The proportion of RA hospitalizations for patients aged less than 65 years steadily increased, from 50.6 in 2000 to 53.3 in 2014. The distribution of sex remained stable, with roughly 78% of patients being female. The majority of the patients were white, and this proportion increased over the defined period. The most common payer was Medicare in 2000 (58.3%) but that showed a slight decline and was 54.8% in 2014. On the other hand, the proportion of Medicaid-covered admissions increased slightly over this period from 7.1% in 2000 to 10.9% in 2014.

Trends in hospitalization rates, length of stay, and in-hospital mortality. The annual rates of hospitalization with a primary diagnosis of RA decreased by approximately 60% over the study period, from 76.5 admissions per 1 million US persons in 2000 to 29.9 per 1 million US persons in 2014 (P < 0.0001 for trend) (Table 1). This trend persisted among subgroups by age and sex (P < 0.0001 for all) (Table 1). The median length of hospital stay (3 days) did not significantly vary during this period.

In a separate analysis of patients with RA in any position (Table 2), we noted that the annual rates of hospitalization with a primary or secondary RA diagnosis per 1 million US residents increased by 36.4%. There was a significant trend towards an increasing number of hospitalizations when RA was either a primary or nonprimary diagnosis. Moreover, the proportion of all RA hospitalizations with RA as the primary diagnosis decreased from 5.9% in 2000 to 1.5% in 2014.

The annual hospital mortality rate declined from 0.7% in 2000 to 0.4% in 2014 (P < 0.0001 for trend) among patients admitted with a primary diagnosis of RA. Among patients with either a primary or nonprimary diagnosis of RA, the mortality rate ranged between 1.95 and 2.87 during the same period (P = 0.08 for trend) (Table 3).

Principal reasons for hospitalization and in-hospital mortality among patients with RA. We then identified hospitalizations in which RA was listed as a nonprimary diagnosis and evaluated trends in selected diagnoses that are common reasons for admissions. Over the 15 years, we noted that the proportion of hospitalizations with a diagnosis of myocardial infarction (6.4% in 2000 to 4.6% in 2014; P < 0.001) significantly decreased, but the absolute number of hospitalizations significantly increased (15813 to 21768) (Table 4). In contrast, the proportion and the absolute number of hospitalizations with a diagnosis of sepsis, congestive heart failure, lung disease, and UTI increased significantly (P for trend < 0.0001) with an accompanying decrease in the proportion of pneumonia (6.% to 4.3%) between 2000 and 2014. We also noted a significant increase in the actual number and proportions for hospitalizations for hip and knee arthroplasty.

Among the deaths that occurred in-hospital when RA was listed as a nonprimary diagnosis, the most common principal diagnosis was pneumonia (12.5 %) in 2000, whereas sepsis accounted for the most deaths in 2014 (31.4%) (Figure 1). Most of the evaluated principal causes of death showed a decreasing trend since 2000 except for sepsis (P < 0.0001 for trend) and hospitalizations for hip (P = 0.78) and knee arthroplasty (P = 0.2), which revealed a contrasting nonsignificant increase.

DISCUSSION

Our results, based on a nationally representative contemporary inpatient data, provide evidence that hospitalization patterns of patients with RA in the US have significantly changed over 15 years. The in-hospital mortality rate has declined 30% over the study period. In keeping with the peak age of onset of RA in the fifth and sixth decades (20), hospitalization rates remained largely stable, with the mean age being 62.7 (±30.7) in 2000 and 61.9 (±32.3) years in 2014, likely related to comorbid illnesses and the effects of systemic inflammation that occurs secondary to ongoing RA disease activity. Women had higher hospitalization rates compared with men, which is consistent with the sex differences in the prevalence of the disease. Overall our findings affirm the results of other population studies (21,22) that have demonstrated an improvement rate in mortality and hospitalizations of patients with RA over a similar period.

Chronic inflammation, the use of glucocorticoids, and oxidative stress have all been shown to contribute to accelerated atherosclerosis in RA. It has been reported that the risk of myocardial infarction (MI) in patients with RA is comparable with that in patients with diabetes mellitus, according to results from a large

Table 2. Trend in hospitalization rates in patients with rheumatoid arthritis (primary or nonprimary reason for admission) from 2000 to 2014

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
All RA hospitalizations (primary and nonprimary)	262 502	278 321	289 950	302 918	316 523	332 169	347 784	359 252	400 068	415 681	430 450	478 123	471 020	470 840	480 570	5 636 171
Primary diagnosis of RA	15 424	15 846	16 298	13 866	15 040	14 167	13 142	12 510	11 938	10 766	10 395	9951	9055	8235	7350	183 983
Nonprimary diagnosis of RA	247 078	262 475	273 652	289 052	301 483	318 002	334 642	346 742	388 130	404 915	420 055	468 172	461 965	462 605	473 220	5 452 188
US census	201 524 907	204 943 608	208 144 701	210 291 625	212 798 888	215 251 252	225 613 367	227 708 235	230 169 098	232 534 305	235 217 323	237 741 224	240 281 843	242 627 222	245 365 242	
Hospitalization rate (per million); RA in any position/ total census population	1226	1280.7	1314.7	1374.5	1416.8	1477.3	1483.2	1522.7	1686.3	1741.3	1785.8	1969.2	1922.6	1906.7	1928.6	Change in rate between 2014 and 2000 = 0.3642

RA, rheumatoid arthritis; US, United States.

Table 3. Trends in mortality among those with primary and nonprimary diagnosis of RA

|	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P Trend
Deaths during hospitalization with RA as primary diagnosis only, n	108	65	65	45	58	61	53	23	43	14	23	39	0	10	30	<0.0001
Hospitalization mortality rate, %	0.7	0.41	0.4	0.33	0.38	0.43	0.4	0.19	0.36	0.13	0.22	0.39	0	0.12	0.41	
Deaths during hospitalization with RA as primary or nonprimary diagnosis, n	7539	7494	7522	7760	6970	6751	7398	7021	8704	9744	9441	10 632	11 085	11 130	11 415	0.08
Hospitalization mortality rate, %	2.87	2.69	2.59	2.56	2.2	2.03	2.13	1.95	2.17	2.34	2.19	2.22	2.35	2.36	2.37	

RA, rheumatoid arthritis.

Table 4. Trends in hospitalizations for select diagnoses among patients admitted with a nonprimary diagnosis of RA from 2000 to 2014

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P Value
Hospitalizations with any secondary code of RA, n	247 078	262 475	273 652	289 052	301 483	318 002	334 642	346 742	388 130	404 915	420 055	468 172	461 965	462 605	473 220	
All RA hospitalizations	262 502	278 321	289 950	302 918	316 523	332 169	347 784	359 252	400 068	415 681	430 450	478 123	471 020	470 840	480 570	
Hospitalizations due to major diseases with any secondary code of RA, n																
Cerebrovascular disease	17 048	17 061	17 514	17 921	18 692	19 716	20 413	22 191	25 228	27 534	28 144	33 708	32 800	32 845	33 125	<0.0001
Congestive heart failure	38 050	39 634	41 048	46 826	48 539	50 880	53 543	54 092	60 548	69 645	71 409	84 739	85 464	86 507	93 224	<0.0001
Myocardial	15 813	14 699	14 777	15 031	14 471	14 310	15 394	14 910	16 301	17 411	16 802	18 727	20 326	20 355	21 768	<0.0001
COPD/bronchiectasis/asthma	56 828	60 369	64 308	71 974	75 974	84 271	91 357	96 048	108 676	120 665	126 017	146 070	147 829	148 959	156 636	<0.0001
Hip arthroplasty	8895	9449	10 125	9250	10 853	11 448	12 716	13 870	15 137	17 816	19 323	22 940	22 636	22 205	23 661	<0.0001
Knee arthroplasty	12 107	12 861	13 409	13 874	15 677	16 536	18 071	20 805	23 288	27 129	30 244	36 517	34 647	35 621	39 277	<0.0001
Pneumonia	14 825	14 961	15 872	17 921	15 979	19 398	18 071	18 031	19 407	20 246	20 583	22 472	22 174	21 742	20 348	<0.0001
Prosthetic Joint Infection	1730	2100	2463	2312	2412	2544	3012	2774	3105	3239	3780	3745	3696	3701	4259	<0.0001
Sepsis	4694	5250	5473	6359	6934	7950	9035	10 402	13 973	17 411	19 743	25 281	28 180	32 845	37 384	<0.0001
UTI	20 755	22 573	24 081	26 593	29 545	31 800	35 137	37 795	45 799	50 209	53 347	62 267	60 055	59 676	60 099	<0.0001
Proportion of hospitalizations, %																
Cerebrovascular disease	6.9	6.5	6.4	6.2	6.2	6.2	6.1	6.4	6.5	6.8	6.7	7.2	7.1	7.1	7	0.0115
Congestive Heart failure	15.4	15.1	15	16.2	16.1	16	16	15.6	15.6	17.2	17	18.1	18.5	18.7	19.7	<0.0001
Myocardial	6.4	5.6	5.4	5.2	4.8	4.5	4.6	4.3	4.2	4.3	4	4	4.4	4.4	4.6	0.0005
COPD/Bronchiectasis/Asthma	23	23	23.5	24.9	25.2	26.5	27.3	27.7	28	29.8	30	31.2	32	32.2	33.1	<0.0001
Hip arthroplasty	3.6	3.6	3.7	3.2	3.6	3.6	3.8	4	3.9	4.4	4.6	4.9	4.9	4.8	5	<0.0001
Knee arthroplasty	4.9	4.9	4.9	4.8	5.2	5.2	5.4	6	6	6.7	7.2	7.8	7.5	7.7	8.3	<0.0001
Pneumonia	6	5.7	5.8	6.2	5.3	6.1	5.4	5.2	5	5	4.9	4.8	4.8	4.7	4.3	<0.0001
Prosthetic Joint Infection	0.7	0.8	0.9	0.8	0.8	0.8	0.9	0.8	0.8	0.8	0.9	0.8	0.8	0.8	0.9	0.2554
Sepsis	1.9	2	2	2.2	2.3	2.5	2.7	3	3.6	4.3	4.7	5.4	6.1	7.1	7.9	<0.0001
UTI	8.4	8.6	8.8	9.2	9.8	10	10.5	10.9	11.8	12.4	12.7	13.3	13	12.9	12.7	<0.0001

COPD, chronic obstructive pulmonary disease; RA, rheumatoid arthritis; UTI, urinary tract infection.
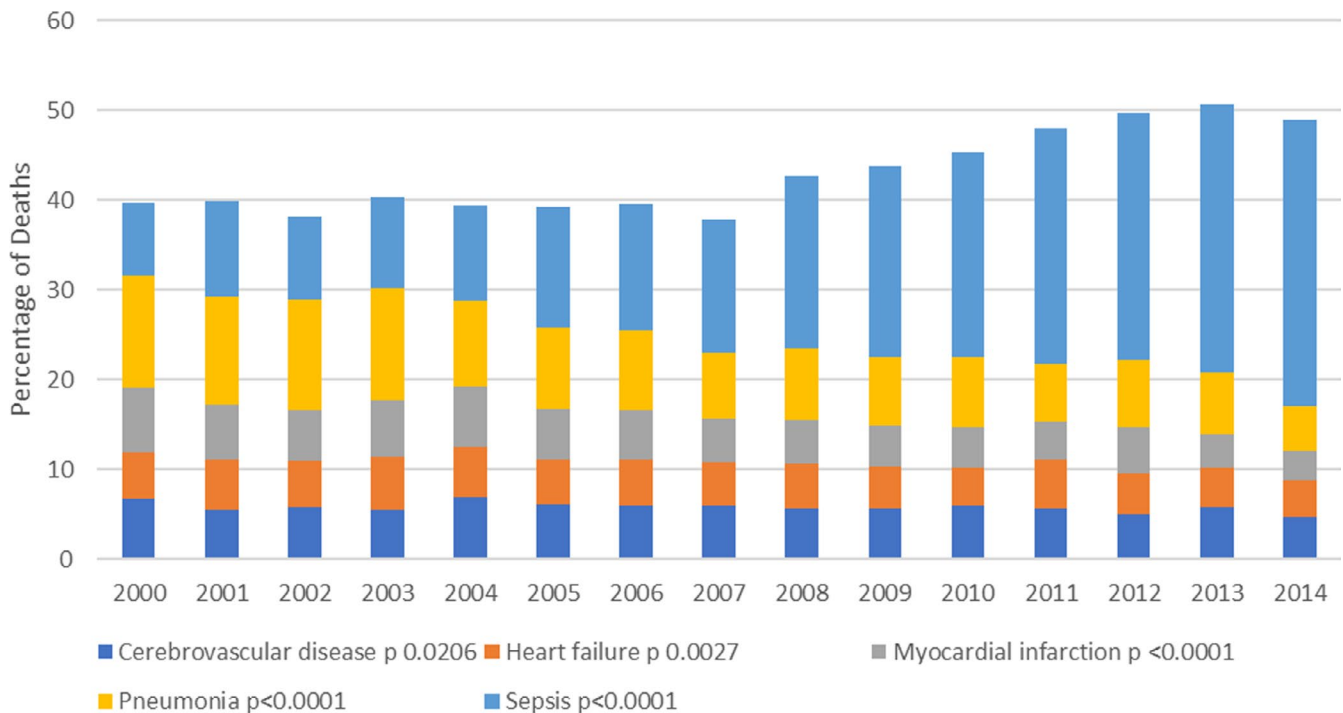
Figure 1. Trends in major causes of mortality among patients admitted with a nonprimary diagnosis of rheumatoid arthritis (RA) from 2000 to 2014.

Danish cohort (23). In this study, we found that hospitalizations and mortality for MI in RA had significantly decreased between 2000 and 2014. This observed decrease in recent years is multifactorial and points toward the progress made with early diagnosis and management of RA, both of which likely contribute to optimal control of disease activity and thus confer a protective effect on these outcomes. This decrease is also consistent with other trends with decreasing hospitalizations for MI (24-26) noted nationwide; hence, it is unclear whether the treatment of RA has had a significant impact on MI hospitalizations. Bandhopadhyay et al (27) also studied trends in MI among RA hospitalizations. Our conclusions differ from their results (increasing trend of MI among patients with RA). Interestingly the authors did not explicitly define the methods adopted for their search; hence, we could not verify the reasons for the contrasting results. In addition, their inclusion and exclusion criteria differed from our study, possibly accounting for some of the observed differences in results.

Our results may have also been influenced by improved outpatient management of RA and its related comorbidities. The advent of shorter outpatient observation stays is rapidly replacing longer inpatient admissions and is also likely to have an impact on hospitalization rates. An observational study based on US administrative health insurance claims databases suggested that prevalence of RA ranged from 0.41% to 0.54% and steadily increased from 2004 to 2014 (28). This increase in prevalence may have contributed to an increased rate of hospitalizations for patients with RA.

Our analysis demonstrates that although the rate of hospitalizations for sepsis has increased over time, the admission for

pneumonia has decreased over a similar period. This observed decline is in contrast to studies in other populations that have reported that respiratory infections (especially bacterial pneumonia) (29-31)) are the most common hospitalized infection. Prior reports suggest that the increasing use of sepsis as a principal diagnosis and the changes in temporal trends in diagnostic coding may reflect higher reimbursement rates for diagnosis-related groups derived from principal sepsis codes than from infection-site codes (32). However, this may not entirely explain the increase in hospitalizations and mortality from sepsis noted in other studies, which suggests a true increase in the incidence of severity and mortality from sepsis (33,34) in recent years.

Several studies have reported a higher mortality risk in RA compared with the general population with standardized mortality rates (SMRs) ranging between 1.27 and 2.03 (35), except for one study from Sweden that reported an SMR of 0.87. These rates have had little variation in the last 50 years despite advances in diagnosis and therapy. Most studies (6,36) have continued to report increased mortality in patients with RA compared with the general population, but these have produced inconsistent results and have been conducted primarily in outpatient cohorts (37), not in the inpatient setting. A recent study (38) from Ontario, Canada, has reported a decrease in all-cause mortality for patients with RA compared with the general population. Ours is a comprehensive study to report inpatient hospitalization trends and mortality for patients with RA in the US.

The contribution of systemic inflammation and the subsequent proinflammatory state to the pathogenesis of COPD has

previously been well described (39). Our findings suggest a small insignificant increase in hospitalizations with a primary diagnosis of COPD and RA (P = 0.03 for trend). These were findings were corroborated in another NIS-based analysis conducted by Dhital et al (40) that reported improved mortality in patients with RA and COPD because of improved treatment strategies.

Our study has several strengths. First, we used a large inpatient US database to study RA-related hospitalizations and in-hospital mortality over multiple years. Over the last several decades, the management of RA has significantly evolved with the emergence of several new therapies and the continued emphasis on an earlier escalation of treatment. This has had a significant impact on comorbidities and outcomes observed in patients.

The major limitation of our study includes the use of ICD-9 codes for the identification of the RA cohort. However, large automated databases, such as health care utilization databases, have been widely used for epidemiological studies (41). Katz et al showed that the sensitivity and positive predictive value of physician claims for RA exceeded 80% (42). Because our study focused on the trends, our analyses were not adjusted for variables such as measures of disease severity, outpatient medication, or laboratory data for each encounter, as they are not available in the NIS database. Lastly, documentation might have missed RA as a code for all patients, as this may not have been an acute diagnosis to address during the hospitalization.

In conclusion, from 2000 to 2014, the proportion of hospitalizations and mortality among patients with RA appeared to decline, with a decrease in cardiovascular and cerebrovascular disease but a definite increase in sepsis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Iyer, Gao, Field, Curtis, Lynch, Vaughan-Sarrazin, Singh.
Acquisition of data. Gao, Vaughan-Sarrazin, Singh.
Analysis and interpretation of data. Gao, Vaughan-Sarrazin.

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