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Hospitalized Infections in People With Osteoarthritis: A National US Study

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ABSTRACT. *Objective*. To study the incidence, time trends, and outcomes of serious infections in people with osteoarthritis (OA).

Methods. We used 1998–2016 US National Inpatient Sample (NIS) data. Using recommended weights, we examined the epidemiology of 5 types of serious infections requiring hospitalization in people with OA (opportunistic infections [OIs], skin and soft tissue infections [SSTIs], urinary tract infections [UTIs], pneumonia, and sepsis/bacteremia). We performed multivariable-adjusted logistic regression analyses to analyze factors associated with healthcare utilization (hospital charges, length of hospital stay, discharge to nonhome setting), and in-hospital mortality.

Results. Of all serious infection hospitalizations, 46,708,154 were without OA and 3,258,416 had OA. People with OA were 16.4 years older, more likely to be female (52% vs 65%), White (59% vs 70%), have a Deyo-Charlson Comorbidity Index (DCCI) ≥ 2 (42% vs 51%), receive Medicare (54% vs 80%), and less likely to receive care at an urban teaching hospital (45% vs 39%). Serious infection rates per 100,000 NIS hospitalizations increased from the study period of 1998–2000 to 2015–2016: OI (from 4.5 to 7.2); SSTI (from 48.4 to 145.9); UTI (from 8.4 to 104.6); pneumonia (from 164.0 to 224.3); and sepsis (from 39.4 to 436.3). In multivariable-adjusted analyses, older age, higher DCCI, sepsis, northeast region, urban hospital, and medium or large hospital bed size were significantly associated with higher healthcare utilization outcomes and in-hospital mortality; Medicaid insurance, non-White race, and female sex were significantly associated with higher healthcare utilization.

Conclusion. Serious infection rates have increased in people with OA. Association of demographic, clinic, and hospital variables with serious infection outcomes identifies potential targets for future interventions.

Key Indexing Terms: health services utilization, healthcare utilization, hospitalization, mortality, osteoarthritis, serious infections

Osteoarthritis (OA) is the most common of all joint disorders and is one of the leading causes of disability in the United States.[1] The prevalence of OA increases with age, such that 50% of individuals > 60 years have OA.[2] In the US, OA was the fourth leading cause for hospitalization in 2009.[3]

Serious infections in OA are an understudied area. The rate of serious infections in people with OA may be increased due to the association of OA with autoimmune rheumatic diseases (e.g., rheumatoid arthritis [RA], systemic lupus erythematosus [SLE]), reduced mobility in OA that is associated with a higher rate of urinary infections,[4] and increasing rates of prosthetic joint infections in people undergoing knee or hip arthroplasty for which OA is the cause in > 80% of the cases.[5] Most studies of hospitalized infections in OA are limited to people who

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underwent total knee or hip arthroplasty.[6,7] This is a subset of people with OA and those undergoing knee/hip arthroplasty are hospitalized for elective surgery (i.e., arthroplasty). In a study comparing RA to OA, 23% of people with RA vs 27% with OA or soft tissue rheumatism developed at least 1 infection.[8] However, this study was performed in 1986 (prebiologic era), infection diagnosis was based on patient interview, and the recall period was short, leading to a possibility of misclassification error including both underestimation and overestimation of the frequency of infections.[8] Therefore, our study objectives were to fill this knowledge gap by examining the healthcare utilization or inpatient mortality associated with serious infection hospitalizations in a nationally representative sample of people with OA.

Our specific aims were to (1) assess the rates of 5 serious infections requiring hospitalization in people with OA in the US and their time-trends; (2) estimate healthcare utilization and inpatient mortality associated with a serious infection hospitalization; and (3) analyze the factors associated with healthcare utilization and in-hospital mortality in people with OA hospitalized with a serious infection.

METHODS

Data source and study cohort selection. We performed a study of 5 common types of serious infections resulting in hospitalizations in people with OA in the US National Inpatient Sample (NIS) 1998–2016 sample. The NIS is a 20% stratified sample of discharge records from all participating community hospitals from all participating states in the US that includes all payers, including those without insurance.[9] Thus, it represents all hospitalizations in the US. The US NIS is a deidentified inpatient healthcare database that is publicly available. The institutional review board (IRB) at the University of Alabama at Birmingham (UAB) approved this study (UAB X120207004). All investigations were conducted in conformity with ethical principles of research. The IRB waived the need for informed consent for this database study.

We identified 5 types of serious infections based on the presence of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes in the primary diagnosis position for hospitalization: (1) opportunistic infections (OIs; 010.xx–018.xx, 031.xx, 078.5, 075.xx, 053.xx, 112.4, 112.5, 112.81, 112.83, 130.xx, 136.3, 117.5, 027.0, 039.xx, 117.3, 114.xx, 115.xx, or 116.0); (2) skin and soft tissue infections (SSTIs; 040.0, 569.61, 681.xx, 682.xx, 785.4, 728.86, or 035.xx); (3) urinary tract infections (UTIs; 590.xx); (4) pneumonia (003.22, 481.0, 513.0, 480.xx, 482.xx, 483.xx, 485.xx, or 486.xx); and (5) sepsis/bacteremia (038.xx or 790.7).[10,11] These codes were valid, with positive predictive values (PPVs) of 70–100% in people with RA.[12] With the coding system change to ICD, 10th Revision, Clinical Modification (ICD-10-CM) in 2015 in the US, we used the ICD-10-CM codes for serious infections for the 2015–2016 data (Supplementary Table 1, available with the online version of this article). Composite infection was defined as any of the serious infections occurring as the primary diagnosis for hospitalization.

We identified OA based on the presence of ICD-9-CM or ICD-10-CM codes in a nonprimary (i.e., secondary) position during the index hospitalization, 715, M15, M16, M17, M18, or M19. A previous study showed a sensitivity of 55–57% and specificity of 75–100% and PPVs of 63–100% to using a diagnostic code approach for OA.[13,14]

Covariates. The covariates/confounders of interest included age, sex, race, serious infection type (OI, SSTI, UTI, pneumonia, and sepsis), median household income, insurance payer, hospital characteristics (region, location/teaching status, and bed size), and Deyo-Charlson Comorbidity Index (DCCI), a validated medical comorbidity measure that includes 17 comorbidities (where a higher score indicates more comorbidity load).[15]

Study outcomes. For descriptive analysis, we estimated the rate of hospitalization for each serious infection as the primary diagnosis, with OA listed in the nonprimary position (secondary position).

We examined in-hospital mortality and healthcare utilization as study outcomes for the remaining analyses. Healthcare utilization included the following: (1) total hospital charges above the median for each calendar year; (2) length of hospital stay above the median of 3 days; and (3) discharge to nonhome settings (rehabilitation or an inpatient facility).

This categorization using NIS medians for dichotomizing variables (> 3-day stay, > median hospital charge) was made on an *a priori* clinical decision to aid clinical interpretation of results of these outcomes. Additionally, both variables had a heavily right-skewed distribution, which made them most appropriate to be analyzed with logistic regression, to avoid undue influence of extreme values on linear regression.

Statistical analyses. We followed the survey analysis procedures that account for the weights, clusters, and strata as defined in NIS, including the modified weights with the change in sampling in 2012.[16] We used the "trend" discharge weights for 1993–2011 NIS files to minimize the effects of the redesign on estimated trends since our study period crossed the 1998 and 2012 data year. We used the trend weight (TRENDWT) in place of the original discharge weight (DISCWT) for years prior to 2012 to create national estimates for trend analysis that are consistent with the 2012 NIS data onward. The new trend weights are available for download on the Healthcare Cost and Utilization Project US website (www.hcup-us.ahrq.gov/db/nation/nis/trendwghts.jsp). We used the SAS procedures "surveyfreq," "surveymeans," and "surveylogistic" to perform this analysis.

We compared the summary statistics using chi-square or Student *t* test. We calculated incidence rates per 100,000 NIS claims and analyzed for trends over time using the Cochran–Armitage test. We used the SAS procedure "freq" to perform this analysis.

We performed multivariable-adjusted logistic regression analyses for each study outcome, adjusting for all covariates listed in the section above. Covariates included age, sex, race, serious infection type (OI, SSTI, UTI, pneumonia, and sepsis), median household income, insurance payer, hospital characteristics (region, location/teaching status, and bed size), and DCCI. We used the SAS procedure "surveylogistic" to perform this analysis. Sensitivity analyses adjusted the main model for calendar year. ORs and 95% CIs were calculated. We used SAS 9.3 (SAS Institute) for all analyses.

RESULTS

Characteristics and outcomes of people with vs without OA admitted with serious infection. Among people hospitalized with serious infections, there were 3,258,416 people with OA and 46,708,154 without OA in national estimates that used recommended weights. Compared to people with serious infections without OA, those with OA were 16.4 years older, more likely to be female (65% vs 52%), White (70% vs 59%), have DCCI ≥ 2 (51% vs 42%), receive Medicare (80% vs 54%), and less likely to receive care at an urban teaching hospital (39% vs 45%; Table 1). Compared to people with serious infections without OA, those with OA were more likely to be discharged to nonhome settings (35% vs 25%), less likely to die in-hospital (4.6% vs 6.3%), and as likely to have hospital charges above the median (57% vs 57%; Table 1).

Characteristics of people with each serious infection and OA. People with SSTI were 5–6 years younger than people with other serious infections (Supplementary Table 2, available with the online version of this article). Females constituted 64–82% and Whites constituted 65–72% of each serious infection cohort. In terms of hospitalization, Overall, 37–43% of people with serious

Table 1. Demographic characteristics of infection hospitalizations in people with vs without OA.

	Any Hospitalization in People With OA Diagnosis, n = 6,640,693[a]	Serious Infection Hospitalization in People Without OA, n = 46,708,154[a]	Serious Infection Hospitalization in People With OA, n = 3,258,416[a]
Age, yrs, mean (SE); median	73.0 (0.03); 74.8	58.7 (0.09); 63.7	75.1 (0.03); 77.1
Age category, yrs			
< 50 (%)	1,955,351 (6.08)	13,938,324 (30.07)	144,347 (4.45)
50–< 65	6,223,753 (19.35)	9,457,702 (20.40)	538,309 (16.61)
65–79	11,902,974 (37.01)	12,176,601 (26.27)	1,111,384 (34.29)
≥ 80	12,079,521 (37.56)	10,778,643 (23.25)	1,446,991 (44.65)
Sex			
Male	10,728,960 (33.36)	22,340,303 (48.22)	1,118,888 (34.53)
Female	21,428,319 (66.64)	23,984,951 (51.78)	2,121,736 (65.47)
Race			
White	21,389,350 (66.50)	27,497,186 (59.30)	2,261,686 (69.78)
Black	3,070,053 (9.55)	5,085,488 (10.97)	257,590 (7.95)
Hispanic	1,598,330 (4.97)	4,046,213 (8.73)	175,664 (5.42)
Other/missing	6,104,736 (18.98)	9,740,081 (21.01)	546,113 (16.85)
Deyo-Charlson Comorbidity Index			
0	7,796,316 (24.24)	15,010,295 (32.37)	673,534 (20.78)
1	8,207,134 (25.52)	12,024,008 (25.93)	913,367 (28.18)
≥ 2	16,160,294 (50.24)	19,339,287 (41.70)	1,654,313 (51.04)
Income category, percentile			
0–25th	8,318,330 (26.38)	12,090,341 (26.71)	889,336 (27.97)
> 25–50th	8,816,928 (27.96)	12,399,653 (27.40)	905,655 (28.48)
> 50–75th	7,663,994 (24.31)	10,862,479 (24.00)	755,089 (23.75)
> 75–100th	6,730,793 (21.35)	9,905,646 (21.89)	629,460 (19.80)
Insurance			
Private	5,069,319 (15.79)	10,578,781 (22.86)	378,109 (11.68)
Medicare	24,279,386 (75.61)	24,878,546 (53.77)	2,597,031 (80.24)
Medicaid	1,734,792 (5.40)	6,913,725 (14.94)	173,718 (5.37)
Other	603,564 (1.88)	1,455,988 (3.15)	46,523 (1.44)
Self	426,151 (1.33)	2,444,533 (5.28)	41,283 (1.28)
Hospital location/teaching			
Rural	5,291,083 (16.49)	6,481,258 (14.72)	551,438 (17.91)
Urban nonteaching	13,400,262 (41.77)	17,919,939 (40.70)	1,336,070 (43.40)
Urban teaching	13,386,218 (41.73)	19,630,903 (44.58)	1,190,903 (38.69)
Discharge status			
Rehabilitation or skilled nursing facility	9,170,864 (29.24)	10,594,684 (24.73)	1,072,873 (34.92)
Home	22,190,318 (70.76)	32,245,769 (75.27)	1,999,149 (65.08)
Length of stay in days			
≤ 3	14,857,065 (46.19)	19,001,734 (40.98)	1,119,995 (34.55)
> 3	17,306,680 (53.81)	27,371,856 (59.02)	2,121,219 (65.45)
Died during hospitalization	607,104 (1.89)	2,929,186 (6.32)	149,883 (4.63)
Length of stay in days, mean (SE); median	5.2 (0.01); 3.3	6.0 (0.01); 3.7	5.7 (0.01); 4.0
Total hospital charges, USD[b]			
≤ Median	12,430,982 (38.65)	19,750,315 (42.59)	1,405,007 (43.35)
> Median	19,732,763 (61.35)	26,623,275 (57.41)	1,836,207 (56.65)
Total hospital charges, USD, mean (SE); median	31,324 (166); 18,626	34,872 (169); 16,754	31,085 (180); 17,942
1998–2000	12,510 (160); 8360	11,709 (192); 8063	18,474 (343); 9629
2015–2016	49,808 (414); 31,983	54,383 (444); 28,862	45,242 (406); 27,977

Values are n (%) unless indicated otherwise. [a] All the rates and frequencies are national level estimates based on the sampling weights as recommended by the US NIS. [b] Median total charges in US dollars were available for each calendar year and were as follows: 1998, $5775; 1999, $6060; 2000, $6723; 2001, $7504; 2002, $8601; 2003, $9732; 2004, $9918; 2005, $10,816; 2006, $12,078; 2007, $13,001; 2008, $13,983; 2009, $14,814; 2010, $15,560; 2011, $17,815; 2012, $19,654; 2013, $21,166; 2014, $22,343; 2015, $23,678; 2016, $25,261. NIS: National Inpatient Sample; OA: osteoarthritis; SE: standard error.

infection and OA were hospitalized in the southern US, 33–45% at an urban teaching hospital, and more than half at a hospital with a large bed size (Supplementary Table 2). In-hospital mortality ranged from 0.3 to 0.5% for UTI or SSTI to 9.9% for sepsis. We noted that 46% of sepsis patients and 25–33% with other serious infections were discharged to nonhome settings. Mean total hospital charges ranged from $21,036 for SSTI to $49,065 for sepsis.

Rate of serious infections in people with OA over time. The frequency of each serious infection increased in people with OA (Supplementary Table 3, available with the online version of this article). Rates of all serious infections increased in the general population over time except for pneumonia and OI (Supplementary Table 4). Rates of each of the serious infections per 100,000 NIS claims increased significantly in people with OA from 1998–2000 to 2015–2016 (increase): OI from 4.5 to 7.2 (1.6-fold); SSTI, 48.4 to 145.9 (3-fold); UTI, 8.4 to 104.6 (12.5-fold); pneumonia, 164.0 to 224.3 (1.4-fold); sepsis, 39.4 to 436.3 (11-fold); and composite infection, from 264.6 to 918.2 (3.5-fold; Supplementary Table 5; Figure 1; $P < 0.0001$ for each). We noted similar trends when using a different denominator of OA hospitalizations (OA as nonprimary diagnosis), except that OI and pneumonia rates declined over time; the overall rates of serious infection (composite) increased from 8.6% in 1998–2000 to 14.2% in 2015–2016 for OA hospitalizations with OA as nonprimary diagnosis (Supplementary Table 5; Figure 1). In general, unadjusted length of hospital stay and in-hospital mortality decreased, and total hospital charges increased for serious infections from 1998–2000 to 2015–2016 (Supplementary Table 6).

Multivariable-adjusted correlates of healthcare utilization and mortality for serious infections in OA. In multivariable-adjusted analyses, we found that older age, higher DCCI, sepsis, Medicare payer, northeast region, urban teaching or nonteaching hospital, and medium or large hospital bed size were each associated with higher healthcare utilization outcomes and in-hospital mortality (Table 2). For example, compared to age < 50 years, those ≥ 80 years had a higher OR of discharge to a care facility (OR 6.48, 95% CI 6.20–6.78), length of hospital stay > median (OR 1.40, 95% CI 1.36–1.44), and in-hospital mortality (OR 6.06, 95% CI 5.32–6.90; Table 2). Compared to a DCCI of 0, a score ≥ 2 was associated with a higher OR of discharge to care

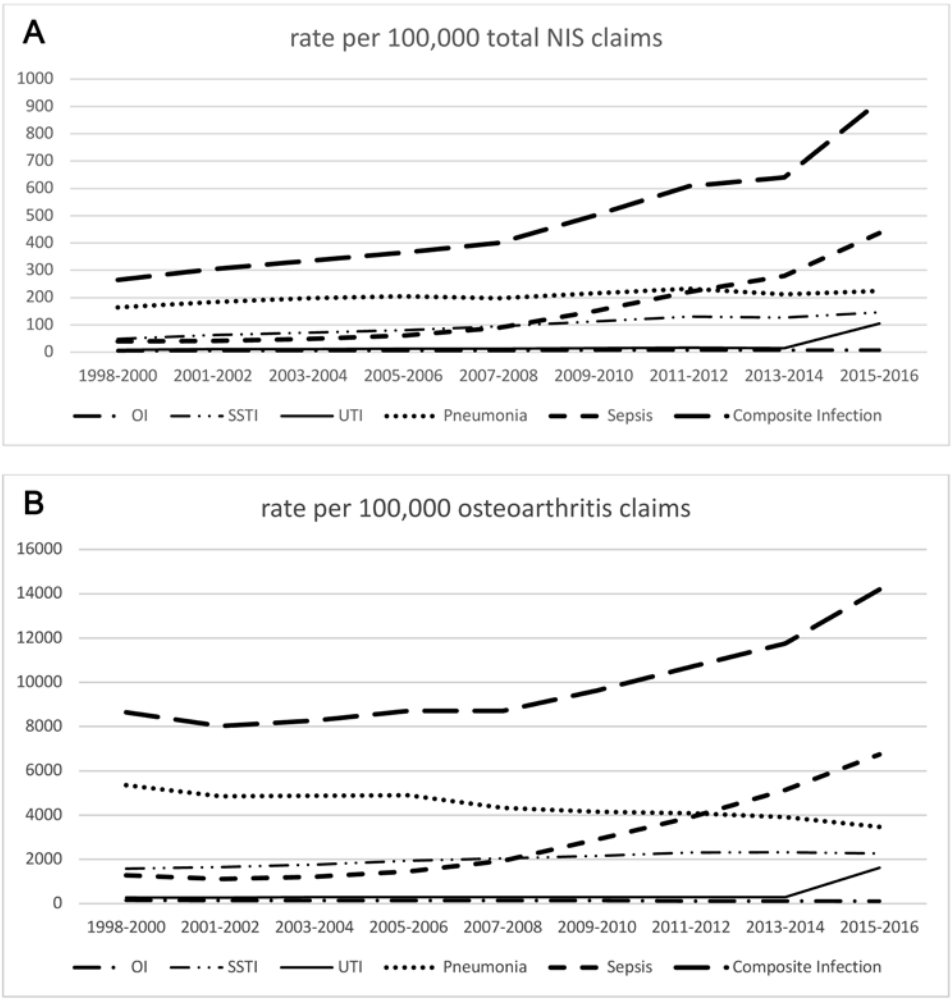

Figure 1. (A) Rate of hospitalized infection in people with OA per 100,000 total NIS claims, and (B) per 100,000 overall OA claims. The Y-axis shows rate per 100,000 hospitalization claims. The denominator for (A) is all NIS claims, and for (B) claims with OA as a nonprimary (or secondary) diagnosis. The top line in each graph represents the composite infection, a sum of all 5 types of infection. The study cohort had a primary diagnosis of one of the hospitalized infections of interest. NIS: National Inpatient Sample; OA: osteoarthritis; OI: opportunistic infection; SSTI: skin and soft tissue infection; UTI: urinary tract infection.

Table 2. Multivariable-adjusted correlates of healthcare utilization and mortality for serious infections in OA in a national US sample.[a]

	Hospital Charges > Median	Discharge to Care Facility	Length of Hospital Stay > Median	In-hospital Mortality
	Adjusted OR (95% CI)			
Age category, yrs				
< 50	Ref	Ref	Ref	Ref
50–< 65	**1.04 (1.01–1.07)**	**1.66 (1.59–1.74)**	**1.17 (1.14–1.20)**	**1.89 (1.66–2.16)**
65–79	1.01 (0.98–1.04)	**2.71 (2.59–2.83)**	**1.25 (1.22–1.29)**	**3.16 (2.78–3.60)**
≥ 80	0.94 (0.92–0.97)	**6.48 (6.20–6.78)**	**1.40 (1.36–1.44)**	**6.06 (5.32–6.90)**
Sex				
Male	Ref	Ref	Ref	Ref
Female	**1.02 (1.01–1.03)**	**1 .18 (1.16–1.19)**	**1.11 (1.09–1.12)**	1.01 (0.99–1.04)
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	**1.17 (1.15–1.19)**	**1.10 (1.08–1.13)**	**1.17 (1.15–1.20)**	1.03 (0.98–1.07)
Hispanic	**1.71 (1.67–1.76)**	**0.73 (0.71–0.75)**	**1.08 (1.06–1.11)**	**0.92 (0.87–0.97)**
Other/missing	0.98 (0.97–0.99)	**0.88 (0.87–0.89)**	1.02 (1.00–1.03)	1.02 (0.98–1.06)
Deyo-Charlson Comorbidity Index				
0	Ref	Ref	Ref	Ref
1	**1.27 (1.25–1.29)**	**1.10 (1.08–1.11)**	**1.24 (1.22–1.26)**	**1.15 (1.11–1.20)**
≥ 2	**1.53 (1.51–1.55)**	**1.38 (1.36–1.40)**	**1.53 (1.51–1.55)**	**1.65 (1.59–1.71)**
Income category, percentile				
0–25th	**0.94 (0.92–0.96)**	1.00 (0.98–1.02)	**1.03 (1.01–1.04)**	0.97 (0.93–1.01)
25–50th	**0.92 (0.91–0.94)**	0.99 (0.97–1.01)	**1.04 (1.02–1.06)**	0.97 (0.94–1.01)
50–75th	**0.93 (0.92–0.95)**	1.01 (0.99–1.02)	1.01 (0.99–1.02)	**0.94 (0.90–0.97)**
75–100th	Ref	Ref	Ref	Ref
Primary infection diagnosis				
Sepsis	Ref	Ref	Ref	Ref
OI	**0.86 (0.82–0.90)**	**0.48 (0.45–0.50)**	**0.92 (0.87–0.96)**	**0.32 (0.28–0.36)**
SSTI	**0.42 (0.42–0.43)**	**0.44 (0.44–0.45)**	**0.64 (0.63–0.65)**	**0.04 (0.03–0.04)**
UTI	**0.37 (0.36–0.38)**	**0.48 (0.46–0.49)**	**0.36 (0.36–0.37)**	**0.05 (0.04–0.06)**
Pneumonia	**0.70 (0.70–0.71)**	**0.48 (0.48–0.49)**	**0.73 (0.72–0.74)**	**0.31 (0.30–0.32)**
Insurance payer				
Medicare	**1.19 (1.17–1.22)**	**1.79 (1.75–1.83)**	**1.25 (1.22–1.27)**	**0.89 (0.85–0.94)**
Medicaid	**1.29 (1.25–1.32)**	**1.55 (1.49–1.60)**	**1.23 (1.20–1.27)**	0.96 (0.88–1.04)
Other	**1.13 (1.08–1.18)**	**1.28 (1.21–1.36)**	1.05 (1.00–1.09)	**1.63 (1.47–1.81)**
Private	Ref	Ref	Ref	Ref
Self	**1.15 (1.09–1.21)**	**0.72 (0.66–0.78)**	1.01 (0.97–1.06)	**1.18 (1.02–1.37)**
Hospital region				
Northeast	Ref	Ref	Ref	Ref
Midwest	**0.74 (0.73–0.76)**	0.99 (0.97–1.01)	**0.76 (0.75–0.78)**	**0.85 (0.82–0.89)**
South	**0.88 (0.87–0.90)**	**0.76 (0.74–0.77)**	**0.84 (0.83–0.85)**	**0.94 (0.90–0.97)**
West	**1.09 (1.07–1.11)**	**0.74 (0.73–0.76)**	**0.61 (0.60–0.62)**	**0.93 (0.89–0.97)**
Hospital location/teaching				
Rural	Ref	Ref	Ref	Ref
Urban nonteaching	**2.36 (2.32–2.40)**	0.99 (0.97–1.01)	**1.27 (1.25–1.30)**	**1.06 (1.02–1.10)**
Urban teaching	**2.02 (1.99–2.05)**	**0.88 (0.87–0.90)**	**1.14 (1.12–1.16)**	**1.06 (1.02–1.10)**
Hospital bed size				
Small	Ref	Ref	Ref	Ref
Medium	**1.37 (1.35–1.39)**	0.97 (0.95–0.99)	**1.16 (1.14–1.18)**	**1.07 (1.03–1.11)**
Large	**1.82 (1.79–1.85)**	**0.91 (0.90–0.93)**	**1.31 (1.29–1.33)**	**1.17 (1.13–1.22)**

Values in bold are statistically significant. [a] All the rates and frequencies are national level estimates based on the sampling weights as recommended by the US NIS. NIS: National Inpatient Sample; OA: osteoarthritis; OI: opportunistic infection; Ref: reference category; SSTI: skin and soft tissue infection; UTI: urinary tract infection.

facility (OR 1.38, 95% CI 1.36–1.40), length of hospital stay > median length (OR 1.53, 95% CI 1.51–1.55), and in-hospital mortality (OR 1.65, 95% CI 1.59–1.71; Table 2). Medicaid insurance payers, non-White race, and female sex were associated with higher healthcare utilization only (Table 2). Sensitivity analyses adjusted additionally for calendar year confirmed all findings with minimal/no attenuation of OR; calendar year was associated with significantly lower odds of hospital charges > median, length

of hospital stay > median, and in-hospital mortality, but was not associated with discharge disposition (Supplementary Table 7, available with the online version of this article).

DISCUSSION

We compared the characteristics of people with OA vs without OA in this national study of a large cohort of people with OA hospitalized with a primary diagnosis of a serious infection. We used NIS-recommended weights in obtaining national estimates and rates. In the cohort with serious infections and a secondary diagnosis of OA, we examined the epidemiology and outcomes of the 5 serious infections. We described the factors associated with healthcare utilization and in-hospital mortality. We made several observations that merit further discussion.

We found that compared to people with serious infections without OA, those with OA were 16.4 years older, had more medical comorbidities, and were more likely to be female, White, receive Medicare, and receive care at a rural hospital. Not surprisingly, those with OA were more likely to be discharged to nonhome settings than those without OA (35% vs 24%), which may be related to their older age and higher comorbidity, and Medicare's benefits for discharge to a rehabilitation/healthcare facility, especially after a knee or hip joint replacement, for which OA is the most common indication. People with OA and serious infections were less likely to die in hospital than those without OA (4.6% vs 6.3%).

The overall rates of serious infections (composite) in people with OA increased over the study period from 264 per 100,000 NIS hospitalizations in 1998 to 918 per 100,000 in 2016, a 3.5-fold rate increase, in contrast to a 1.7-fold increase in serious infection hospitalizations in the general NIS population over the same period. This higher rate of increase in serious infections in the OA cohort compared to that of the general NIS sample may be due to the differences in the 2 cohorts in age and comorbidity (i.e., people with OA were older and sicker compared to their counterparts). Some differences may be related to increasing rates of prosthetic infections in people undergoing knee or hip arthroplasty.[5] Increasing rates of use of biologics and glucocorticoids in other concomitant rheumatic conditions in OA, such as RA and SLE, may have contributed. In a study of the 1993–2003 NIS, hospitalizations for serious infections more than doubled in people with RA, mostly due to a 3-fold increase in sepsis rate, but SSTI, UTI, and OI rates decreased over time.[10] A similar increase in sepsis rate over time in OA may have also occurred, but it cannot explain the increases in other serious infections.

Relative increases in rates per 100,000 NIS hospitalizations of sepsis and UTIs of 11–12.5 fold exceeded those of pneumonia at 1.4-fold. Many of these time trends in each serious infection hospitalization were in parallel to those in the general NIS cohort, although the relative increases were higher in OA vs non-OA cohorts. These are important observations that can inform policymakers regarding the relative contribution of these serious infections to the overall morbidity burden of serious infection in the OA cohort in the US.

Our findings of the association of patient, comorbidity, and hospital variables with higher healthcare utilization outcomes and in-hospital mortality add to the current knowledge. We observed independent associations of older age, higher DCCI, sepsis, northeast region, Medicare insurance payer, urban teaching or nonteaching hospital, and medium or large hospital bed size with higher healthcare utilization outcomes and in-hospital mortality. Additionally, Medicaid insurance payer, non-White race, and female sex were associated with higher healthcare utilization only. This knowledge can help in better prognostication of healthcare utilization and mortality in people hospitalized with serious infections in OA that have these risk factors.

We found that the unadjusted length of hospital stay and in-hospital mortality decreased, and total hospital charges increased for serious infections from 1998–2000 to 2015–2016. These findings are in parallel with the similar time trends in the overall NIS sample.

Several study limitations must be considered when interpreting our findings. Misclassification bias was minimized by the use of valid codes for serious infection[10,11,12,17,18] and OA[13,14] with high PPVs, but is possible since we used the ICD codes. A separate validation of codes in the NIS is not possible, since no medical records, laboratory and imaging tests, and medications are available in the NIS. Misclassification might have biased our results toward the null. The absence of measures of disease severity and extent, and imaging tests in the NIS limits analyses of OA disease subgroups, which could provide valuable insight. These questions need to be examined in future studies that use other datasets providing these data. The unit of analysis in NIS is hospitalizations, not people. A greater increase in the rate of sepsis over time vs pneumonia and other serious infections may at least partially be due to upcoding pneumonia and other infections being coded as sepsis diagnosis in the more recent years.[19,20,21] We used a completed case sample for our multivariable-adjusted analyses and the exclusion of incomplete cases may have biased our results. However, of the almost 3.2 million eligible serious infection hospitalizations in people with RA, 93–98% were included in the multivariable-adjusted analyses, which minimizes this bias. We dichotomized hospital stay and charges, which may have limited our ability to detect changes; however, these allowed a more clinically meaningful interpretation of results and we noted several significant associations with our current approach.

Our study strengths include the use of the US national data, inclusion of several important confounders of healthcare utilization and mortality, and large sample size.

In conclusion, we found that people hospitalized with a primary diagnosis of a serious infection and a secondary diagnosis of OA differed in important ways from people hospitalized with serious infections, but without OA. We found that the rate of serious infections increased from 1998 to 2016 in people with OA. The rate of increase in each serious infection in people with OA varied across the serious infections, the lowest being for pneumonia and highest for UTI and sepsis. We found that over time, in people with OA and serious infection, the unadjusted length of hospital stay and in-hospital mortality decreased, and the total hospital charges increased. Several patient, comorbidity,

and hospital characteristics were associated with higher healthcare utilization and in-hospital mortality. Our study provides data for the serious infection hospitalization burden for people with OA. Several novel findings from our study can lead to the development and testing of interventions to improve outcomes of serious infection hospitalizations in OA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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