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Antiviral Use and Health Care Use Among US Patients With Rheumatoid Arthritis and Influenza in Three Influenza Seasons, 2016-2019

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Objective. Patients with rheumatoid arthritis (RA) are vulnerable to severe complications of influenza. We assessed whether health care resource use (HRU) and costs differed between patients with RA and influenza who received antiviral medication compared with matched patients with RA and influenza not receiving antiviral therapy.

Methods. This was a retrospective US health insurance claims analysis over three influenza seasons (each October to April) in 2016-2019. Adults with RA and a subsequent diagnosis of influenza were included. Treated patients (receiving antiviral influenza treatment within 2 days of diagnosis) and untreated patients were propensity score matched using baseline covariates. HRU and costs were assessed for inpatient, emergency department (ED), and outpatient visits and compared between cohorts using χ^2 tests and *t* tests.

Results. After matching, 2638 treated and 1319 untreated patients were included. For treated versus untreated patients, the mean number of all-cause outpatient visits was 0.96 versus 1.21 during 14 days of follow-up ($P < 0.001$) and 1.94 versus 2.24 over 28 days ($P = 0.001$), respectively. Over 28 days, the mean number of all-cause ED visits was lower among treated (0.23) than untreated (0.30) patients ($P = 0.042$). The mean number of respiratory-related outpatient visits was significantly lower for treated versus untreated patients, and mean costs for these visits were $17.89 versus $35.27 over 14 days ($P < 0.001$) and $28.92 versus $48.77 over 28 days ($P < 0.001$) for treated versus untreated patients, respectively.

Conclusion. Our findings demonstrate that prompt antiviral treatment after influenza diagnosis may reduce HRU and costs in patients with RA.

INTRODUCTION

Seasonal influenza has historically posed a large burden on the health care system (1,2). The 2017-2018 influenza season was especially severe. In 2017, approximately 55 million cases of lower respiratory tract infections worldwide were attributed to influenza; these cases resulted in 9.5 million hospitalizations and almost 1.5 million deaths (3).

Patients with certain chronic diseases are especially vulnerable to developing severe complications related to influenza (4). In particular, patients with rheumatoid arthritis (RA), a chronic autoimmune disease affecting joints and other tissues throughout the body, were found to have a 2.75-fold higher risk of serious complications from influenza compared with patients without RA (5). The increased susceptibility to infection in patients with RA is linked to both immunological abnormalities that may impair anti-infective responses and the immunosuppressive effects of therapies such as glucocorticoids, disease-modifying antirheumatic drugs, and biologic agents (6,7).

Vaccination is an important public health strategy to reduce the incidence and complications of seasonal influenza, including in patients with autoimmune inflammatory rheumatic diseases (8). In addition to vaccination, The Infectious Diseases Society of America recommends considering antiviral treatment with neuraminidase inhibitors for outpatients with documented or suspected influenza who have severe or progressive illness, are at

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high risk of complications, are pregnant, or are younger than 2 or older than 65 years of age (9). In an earlier retrospective claims analysis, use of antiviral influenza treatment was found to reduce health care resource use (HRU) and costs among patients diagnosed with influenza (10). Nonetheless, the impact of antiviral treatment in patients with RA is still unknown.

We conducted a retrospective cohort study to assess whether patients with RA who are diagnosed with influenza and receive antiviral medication incur lower HRU and costs compared with matched patients with RA and influenza who do not receive antiviral therapy.

MATERIALS AND METHODS

We conducted a retrospective claims analysis by influenza season (October to April of the following year). Our study used deidentified data and was exempt from institutional review board review. Our research was compliant with the Health Insurance Portability and Accountability Act.

Data source. Data for this study were extracted from IBM MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (MDCR) databases (IBM Watson Health). The CCAE database includes data for several million employees, spouses, and dependents in the United States with employer-sponsored private health insurance. The MDCR database includes data for retirees with Medicare supplemental insurance paid by employers and includes Medicare-covered and employer-paid expenses. The medical claims files capture inpatient and outpatient care, use of facilities and services, and payment information. Patients' outpatient prescription drug (pharmacy) claims are also available.

Study cohorts. The study cohorts included patients with RA, identified as those with one inpatient or two or more outpatient claims for RA (*International Classification of Diseases, Ninth Revision* [ICD-9] code 714.0, 714.1, or 714.2; *International Classification of Diseases, 10th Revision* [ICD-10] codes M05.0-M05.9, M06.0, M06.8, or M06.9) on separate dates at least 30 days apart. Patients with RA were selected within a 2-year time period for each influenza season: the year prior and up to the end of the influenza season. For example, for the 2016-2017 influenza season (which spans October 2016 to April 2017), patients who met the RA inclusion criteria from October 2015 to April 2017 were included in the analysis for that season.

Patients with influenza were identified among those with RA. To be considered as having influenza, patients were required to have an outpatient or emergency department (ED) visit with influenza (ICD-9 code 487 or 488; ICD-10 codes J09-J11) as a primary diagnosis between October 1 and April 30 (influenza season). The index influenza diagnosis date (index date) was the first influenza diagnosis date within each influenza season.

Additional inclusion criteria were age of 18 years or older, continuous enrollment in a health plan for 12 months before (baseline period) and 1 month after index influenza diagnosis date, and one or more diagnoses for RA during the baseline period (to ensure the patient was diagnosed with RA before contracting influenza). An individual patient with RA could appear in the analyses in one or more of the flu seasons.

Patients who met any of the following criteria were excluded from the analysis: those who received antiviral influenza treatment any time in the 1-month period before the index influenza diagnosis date, treated patients who were hospitalized between the date of their index influenza diagnosis and the date they filled their antiviral treatment prescription, and untreated patients who were hospitalized between the date of their index influenza diagnosis and up to 2 days after. Patients with treatment before the index date were excluded to remove prophylactic treatment with antiviral medication from the analysis. Hospitalized patients at index were excluded to avoid misclassification of treated and untreated patients in a setting where antiviral treatment might not be captured in health care claims.

Patients were divided into two cohorts: the treated and untreated cohorts. The treated cohort included patients who received a prescription for antiviral influenza treatment (oseltamivir, baloxavir, rimantadine, or peramivir) within 2 days of an outpatient or ED visit at which they received their influenza diagnosis, and the index treatment had less than 10 days' supply of medication (this criterion was intended to exclude prophylactic treatment). Patients were considered untreated if they did not receive antiviral influenza treatment within 30 days after the index influenza diagnosis date.

Treated and untreated patients were propensity score matched 2:1 (case: control), without replacement, using nearest neighbor matching. Propensity scores were based on covariates identified during the baseline period (see Statistical analysis).

Outcomes. HRU was assessed on the basis of inpatient, ED, and outpatient visits. The proportions of patients with inpatient, ED, or outpatient visits; the number of visits per patient; and the lengths of inpatient stays were captured. Costs associated with HRU were also quantified and adjusted to 2019 US dollars (11). All-cause and respiratory-related (ICD-9 codes 460-519 or ICD-10 codes J00-J99) HRU and costs were analyzed.

For treated patients, HRU and costs were assessed during the 14- and 28-day periods after the antiviral treatment fill date, not including the fill date itself. For untreated controls, HRU and costs were assessed during the 14 and 28 days after the proxy fill date, not including the proxy fill date itself. The proxy fill date was determined on the basis of the number of days from the index influenza diagnosis date to the first antiviral treatment of matched cases.

Statistical analysis. Covariates for propensity score matching were identified during the baseline period and included

Charlson comorbidity index (CCI) score, age at index date, sex, insurance plan type, geographic region of the United States, month and year of the index influenza diagnosis date, influenza diagnosis in the month before the start of the influenza season (yes or no), evidence of chronic lung disease during the baseline period, evidence of RA therapy (biologic or nonbiologic disease-modifying antirheumatic drug or oral steroids; see Supplementary Methods), and evidence of pre–index date HRU (at least one inpatient, ED, or outpatient visit at baseline; yes or no). Influenza vaccination status was not considered in the calculation of propensity scores because this information was not readily available in claims.

Descriptive statistics, including percentages, means, and standard deviations, were calculated. HRU and costs observed in the treated and untreated cohorts were compared using χ^2 tests (for comparison of proportions) and *t* tests (for comparison of means). Corrections for multiple comparisons were not performed.

RESULTS

Study population. Over the study period, a total of 568,228 patients with a diagnosis of RA were identified (Figure 1). Of these, 7743 (1.4%) patients were diagnosed with

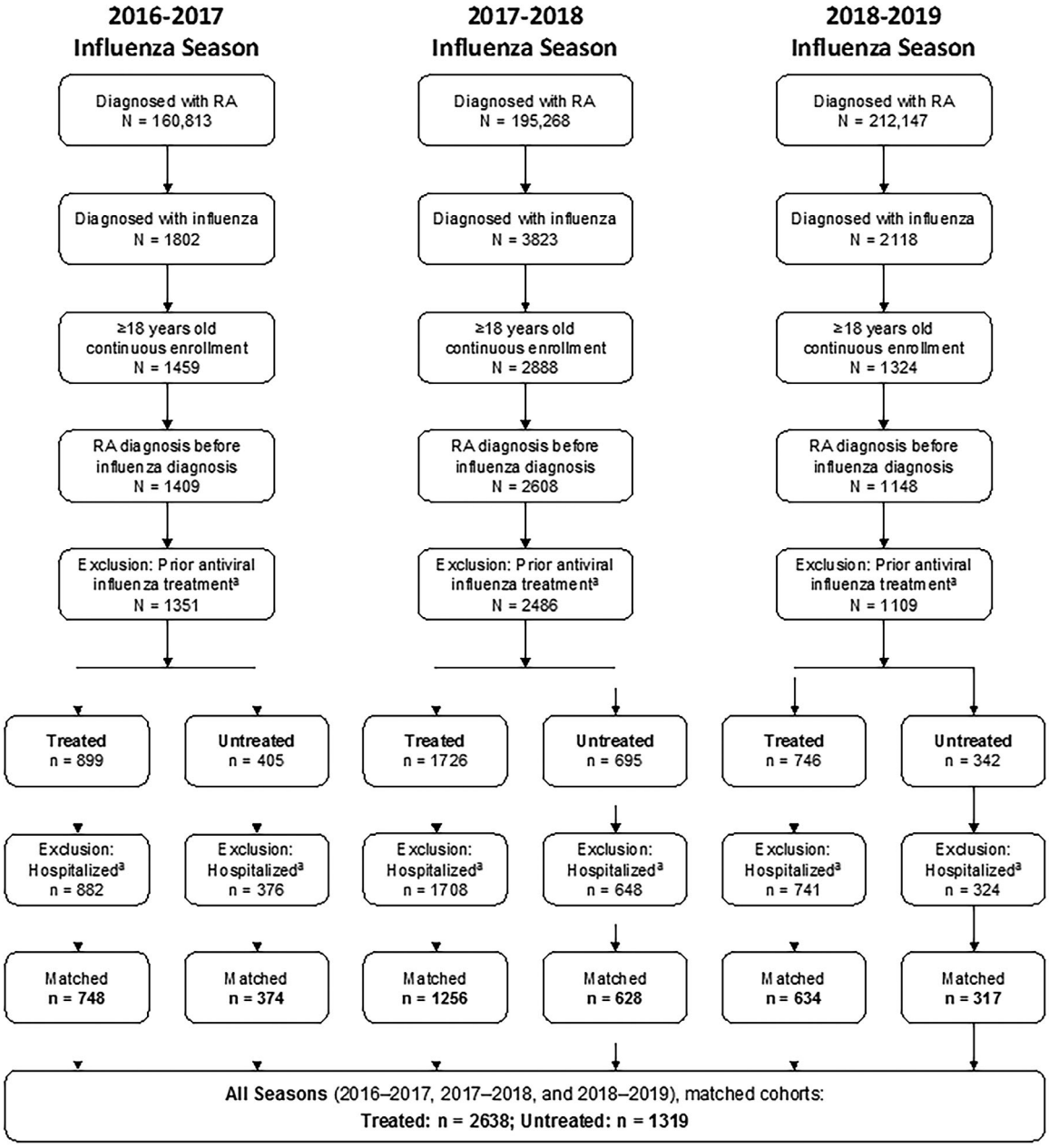

Figure 1. Study population. Matched cohorts of patients with rheumatoid arthritis (RA) and influenza who were treated with antiviral therapy or untreated during the 2016-2017, 2017-2018, and 2018-2019 influenza seasons. [a]n shown is after application of exclusion criteria.

influenza in an outpatient or ED setting during one of three influenza seasons (2016-2017, 2017-2018, or 2018-2019), 5671 of these patients met additional inclusion criteria (≥18 years old, continuous enrollment), 5165 patients had an RA diagnosis during the baseline period, and 4946 patients had not received antiviral influenza treatment (ie, prophylactic treatment) in the month before the influenza diagnosis.

Of the remaining 4946 patients with RA and influenza, 3371 (68.2%) patients received acute antiviral influenza treatment within 2 days of diagnosis (treated patients), 3331 of these patients were not hospitalized before filling the treatment prescription, and 2638 patients remained in the sample after propensity score matching. Of 1442 (29.2%) patients with RA and influenza who did not receive antiviral influenza treatment within 30 days after diagnosis (untreated patients), 1348 were not hospitalized within 2 days of the diagnosis date, and 1319 remained in the sample after matching (Figure 1).

For patients in the matched treated and untreated cohorts, respectively, across all influenza seasons, the mean (SD) patient age was 53.3 (11.9) and 54.0 (13.0) years, 82.1% and 82.4% of patients were female, 58.0% and 57.4% had a preferred provider organization plan, and the mean (SD) CCI score was 2.09 (1.63) and 2.28 (1.98); all patients had outpatient visits during the baseline period, 40.0% and 43.7% had ED visits, and 12.4% and 15.2% had inpatient visits (Table 1).

HRU. During 14 days of follow-up after initiation of antiviral treatment fill, most (>76%) treated and untreated patients had at least one all-cause HRU, and greater than 90% had at least one all-cause HRU during 28 days of follow-up (Table 2). During 28 days of follow-up, all-cause ED visits were less common among treated (6.5%) compared with untreated (8.8%) patients across all influenza seasons; this difference was statistically significant ($P = 0.012$). Inpatient visits occurred among ~2% of treated and untreated patients during 28 days of follow-up.

Patterns of all-cause HRU differed somewhat between influenza seasons. Over 14 days of follow-up in the 2016-2017

Table 1. Baseline demographic and clinical characteristics of matched cohorts

Characteristic	All seasons		2016-2017		2017-2018		2018-2019	
	Treated (n = 2638)	Untreated (n = 1319)	Treated (n = 748)	Untreated (n = 374)	Treated (n = 1256)	Untreated (n = 628)	Treated (n = 634)	Untreated (n = 317)
Index age, y, mean (SD)	53.3 (11.9)	54.0 (13.0)	54.1 (12.7)	54.9 (14.3)	53.5 (11.7)	53.7 (12.3)	52.3 (11.3)	53.4 (12.5)
Age distribution, y								
<65	2336 (88.6)	1130 (85.7)	629 (84.1)	305 (81.6)	1128 (89.8)	547 (87.1)	579 (91.3)	278 (87.7)
65-74	186 (7.1)	105 (8.0)	71 (9.5)	31 (8.3)	77 (6.1)	53 (8.4)	38 (6.0)	21 (6.6)
≥75	116 (4.4)	84 (6.4)	48 (6.4)	38 (10.2)	51 (4.1)	28 (4.5)	17 (2.7)	18 (5.7)
Female sex	2167 (82.1)	1087 (82.4)	621 (83.0)	309 (82.6)	1034 (82.3)	519 (82.6)	512 (80.8)	259 (81.7)
Region								
North Central	411 (15.6)	237 (18.0)	122 (16.3)	73 (19.5)	210 (16.7)	123 (19.6)	79 (12.5)	41 (12.9)
Northeast	487 (18.5)	266 (20.2)	119 (15.9)	73 (19.5)	225 (17.9)	116 (18.5)	143 (22.6)	77 (24.3)
South	1504 (57.0)	695 (52.7)	445 (59.5)	193 (51.6)	714 (56.8)	334 (53.2)	345 (54.4)	168 (53.0)
West	230 (8.7)	114 (8.6)	61 (8.2)	34 (9.1)	103 (8.2)	52 (8.3)	66 (10.4)	28 (8.8)
Unknown	6 (0.2)	7 (0.5)	1 (0.1)	1 (0.3)	4 (0.3)	3 (0.5)	1 (0.2)	3 (0.9)
Health plan type								
HMO	226 (8.6)	106 (8.0)	60 (8.0)	28 (7.5)	107 (8.5)	52 (8.3)	59 (9.3)	26 (8.2)
PPO	1531 (58.0)	757 (57.4)	430 (57.5)	212 (56.7)	716 (57.0)	351 (55.9)	385 (60.7)	194 (61.2)
Other	881 (33.4)	456 (34.6)	258 (34.5)	134 (35.8)	433 (34.5)	225 (35.8)	190 (30.0)	97 (30.6)
CCI score, mean (SD)	2.09 (1.63)	2.28 (1.98)	2.13 (1.73)	2.43 (2.19)	2.13 (1.66)	2.34 (2.02)	1.95 (1.44)	2.00 (1.55)
CCI score = 1	1322 (50.1)	615 (46.6)	369 (49.3)	168 (44.9)	617 (49.1)	282 (44.9)	336 (53.0)	165 (52.1)
CCI score = 2	644 (24.4)	325 (24.6)	190 (25.4)	87 (23.3)	296 (23.6)	155 (24.7)	158 (24.9)	83 (26.2)
CCI score = ≥3	672 (25.5)	379 (28.7)	189 (25.3)	119 (31.8)	343 (27.3)	191 (30.4)	140 (22.1)	69 (21.8)
Baseline CLD	773 (29.3)	402 (30.5)	234 (31.3)	123 (32.9)	377 (30.0)	199 (31.7)	162 (25.6)	80 (25.2)
Baseline use of RA therapy								
Biologic DMARD	1064 (40.3)	493 (37.4)	327 (43.7)	150 (40.1)	477 (38.0)	224 (35.7)	260 (41.0)	119 (37.5)
Nonbiologic DMARD	1714 (65.0)	797 (60.4)	500 (66.8)	221 (59.1)	808 (64.3)	384 (61.1)	406 (64.0)	192 (60.6)
Oral steroids	1757 (66.6)	866 (65.7)	503 (67.2)	242 (64.7)	820 (65.3)	403 (64.2)	434 (68.5)	221 (69.7)
HRU in previous 1 year[a]								
Inpatient	327 (12.4)	201 (15.2)	99 (13.2)	61 (16.3)	168 (13.4)	104 (16.6)	60 (9.5)	36 (11.4)
ED	1054 (40.0)	577 (43.7)	297 (39.7)	170 (45.5)	513 (40.8)	278 (44.3)	244 (38.5)	129 (40.7)
Outpatient	2638 (100)	1319 (100)	748 (100)	374 (100)	1256 (100)	628 (100)	634 (100)	317 (100)

Note: Data are presented for all influenza seasons combined (2016-2019) and individual influenza seasons (2016-2017, 2017-2018, 2018-2019) and expressed as n (%), except as noted.

Abbreviations: CCI, Charlson comorbidity index; CLD, chronic lung disease; DMARD, disease-modifying antirheumatic drug; ED, emergency department; HMO, health maintenance organization; HRU, health care resource use; PPO, preferred provider organization; RA, rheumatoid arthritis.

[a]During the baseline period.

season, a smaller proportion of treated patients than untreated patients had all-cause inpatient stays (1.1% vs 3.5%, respectively; $P = 0.010$); a similar trend in 2018-2019 did not reach statistical significance, and an opposite trend was observed in 2017-2018. During 14 days of follow-up, a smaller proportion of treated than untreated patients had ED visits during each influenza season; these differences were not statistically significant (Table 2).

During each influenza season, a slightly higher proportion of treated versus untreated patients had all-cause HRU (any medical or pharmacy encounters) during 28 days of follow-up; this difference was statistically significant in 2017-2018 (92.8% vs 89.6%; $P = 0.023$). During the same 28-day period, numerically lower proportions of treated versus untreated patients had all-cause ED visits during each influenza season; similarly for inpatient stays, numerically lower proportions of patients with at least one inpatient stay were observed among treated versus untreated patients across influenza seasons.

Regarding respiratory-related HRU, across all influenza seasons, greater than 22% of treated and untreated patients had respiratory-related HRU during 14 days of follow-up; this was greater than 28% in each cohort during 28 days of follow-up (Table 2). During 28 days of follow-up, 2.9% of treated and 3.8% of untreated patients had respiratory-related ED visits, and 0.3% of treated and 0.7% of untreated patients had respiratory-related inpatient stays.

Similar to all-cause HRU, between-cohort differences for respiratory-related HRU varied somewhat across influenza seasons. In 2016-2017, a significantly lower proportion of treated (23.0%) versus untreated (29.1%) patients had respiratory-related HRU during 14 days of follow-up ($P = 0.030$); patterns differed in the other two influenza seasons. In all but one instance (respiratory-related ED visits over 14 days in 2018-2019), numerically lower proportions of treated versus untreated patients had respiratory-related inpatient and ED visits during each influenza season and during 14 or 28 days of follow-up (Table 2).

The mean number of outpatient visits per patient was consistently lower among treated patients compared with untreated patients (Table 3). For treated versus untreated patients, the mean (SD) number of all-cause outpatient visits was 0.96 (1.20) versus 1.21 (1.84) during 14 days of follow-up ($P < 0.001$) and 1.94 (2.10) versus 2.24 (2.91) during 28 days of follow-up ($P = 0.001$), respectively. During 28 days of follow-up, the mean (SD) number of all-cause ED visits was also lower among treated compared with untreated patients (0.23 [0.61] vs 0.30 [0.66], respectively; $P = 0.042$); a similar trend, without statistical significance, was observed during 14 days of follow-up.

Table 2. HRU up to follow-up days 14 and 28 in matched cohorts

	All seasons		2016-2017		2017-2018		2018-2019	
HRU	Treated (n = 2638)	Untreated (n = 1319)	Treated (n = 748)	Untreated (n = 374)	Treated (n = 1256)	Untreated (n = 628)	Treated (n = 634)	Untreated (n = 317)
All-cause HRU, 14-day follow-up, n (%)								
Any setting[a]	2044 (78.9)	1013 (76.8)	590 (78.9)	300 (80.2)	1009 (80.3)	482 (76.8)	482 (76.0)	242 (76.3)
Inpatient	35 (1.4)	24 (1.8)	8 (1.1)	13 (3.5)[b]	21 (1.7)	5 (0.8)	7 (1.1)	6 (1.9)
ED	126 (4.9)	80 (6.1)	44 (5.9)	24 (6.4)	63 (5.0)	41 (6.5)	20 (3.2)	16 (5.0)
Outpatient	1416 (54.7)	735 (56.5)	421 (56.3)	226 (60.4)	696 (55.4)	343 (54.6)	329 (51.9)	172 (54.3)
All-cause HRU, 28-day follow-up, n (%)								
Any setting	2386 (92.1)	1175 (90.3)	692 (92.5)	341 (91.2)	1166 (92.8)	563 (89.6)[b]	571 (90.1)	285 (89.9)
Inpatient	52 (2.0)	28 (2.2)	14 (1.9)	15 (4.0)	30 (2.4)	7 (1.1)	9 (1.4)	6 (1.9)
ED	168 (6.5)	114 (8.8)[b]	58 (7.8)	36 (9.6)	83 (6.6)	56 (8.9)	28 (4.4)	23 (7.3)
Outpatient	1915 (73.9)	967 (74.3)	567 (75.8)	287 (76.7)	923 (73.5)	460 (73.2)	461 (72.7)	229 (72.2)
Respiratory-related HRU, 14-day follow-up, n (%)								
Any setting	585 (22.6)	307 (23.6)	172 (23.0)	109 (29.1)[b]	296 (23.6)	130 (20.7)	131 (20.7)	70 (22.1)
Inpatient	6 (0.2)	9 (0.7)	2 (0.3)	4 (1.1)	4 (0.3)	3 (0.5)	0 (0)	2 (0.6)
ED	67 (2.6)	40 (3.1)	20 (2.7)	14 (3.7)	37 (2.9)	22 (3.5)	10 (1.6)	4 (1.3)
Outpatient	549 (21.2)	287 (22.1)	162 (21.7)	101 (27.0)	274 (21.8)	120 (19.1)	127 (20.0)	67 (21.1)
Respiratory-related HRU, 28-day follow-up, n (%)								
Any setting	736 (28.4)	382 (29.4)	221 (29.5)	126 (33.7)	354 (28.2)	169 (26.9)	178 (28.1)	90 (28.4)
Inpatient	8 (0.3)	9 (0.7)	3 (0.4)	4 (1.1)	5 (0.4)	3 (0.5)	0 (0)	2 (0.6)
ED	76 (2.9)	49 (3.8)	23 (3.1)	17 (4.5)	41 (3.3)	25 (4.0)	12 (1.9)	7 (2.2)
Outpatient	701 (27.1)	362 (27.8)	211 (28.2)	117 (31.3)	333 (26.5)	159 (25.3)	174 (27.4)	88 (27.8)

Note: Data are presented for all influenza seasons combined (2016-2019) and individual influenza seasons (2016-2017, 2017-2018, 2018-2019).
Abbreviations: ED, emergency department; HRU, health care resource use.
[a]Any setting includes medical and pharmacy encounters.
[b]$P < 0.05$ vs treated.

Table 3. Mean (SD) number of all-cause and respiratory-related visits and days of inpatient stays

All-cause and respiratory-related visits	14-day follow-up		28-day follow-up	
	Treated (n = 2638)	Untreated (n = 1319)	Treated (n = 2638)	Untreated (n = 1319)
All-cause, mean (SD)				
Inpatient stays, days	4.74 (4.63)	6.39 (7.28)	4.75 (5.54)	8.15 (10.82)
Inpatient visits, n	0.10 (0.32)	0.13 (0.35)	0.15 (0.38)	0.15 (0.39)
ED visits, n	0.16 (0.47)	0.19 (0.50)	0.23 (0.61)	0.30 (0.66)[a]
Outpatient visits, n	0.96 (1.20)	1.21 (1.84)[b]	1.94 (2.10)	2.24 (2.91)[c]
Respiratory-related, mean (SD)				
Inpatient stays, days	4.35 (2.35)	5.46 (8.01)	4.39 (2.63)	9.23 (14.57)
Inpatient visits, n	0.23 (0.44)	0.27 (0.45)	0.30 (0.48)	0.29 (0.50)
ED visits, n	0.18 (0.47)	0.17 (0.47)	0.21 (0.54)	0.21 (0.51)
Outpatient visits, n	0.28 (0.60)	0.47 (1.36)[b]	0.43 (0.87)	0.67 (1.94)[b]

Note: Data are presented up to follow-up days 14 and 28 in matched cohorts for all influenza seasons combined (2016-2019).
Abbreviation: ED, emergency department.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$ vs treated.

Similar to the findings for all-cause outpatient visits, the mean (SD) number of respiratory-related outpatient visits per patient for treated versus untreated patients was 0.28 (0.60) versus 0.47 (1.36) during 14 days of follow-up ($P < 0.001$) and 0.43 (0.87) versus 0.67 (1.94) during 28 days of follow-up ($P < 0.001$), respectively. The mean length of both all-cause and respiratory-related inpatient stays was consistently shorter for treated versus untreated patients, but these differences were not statistically significant (Table 3).

Costs. Among patients with RA and influenza, mean all-cause health care costs per patient during 28 days of follow-up were greater than $500 for inpatient stays and greater than $150 for outpatient visits in each treatment cohort (Figure 2A and C, respectively). Costs for all-cause inpatient and ED care were numerically lower for treated versus untreated patients during 14 and 28 days of follow-up (Figure 2A and B, respectively). Median (range) costs are shown in Supplementary Table 1.

Consistent with the lower mean number of respiratory-related outpatient visits among treated versus untreated patients, costs of respiratory-related outpatient visits were also lower among treated patients (Figure 2C). Mean (SD) costs per patient for respiratory-related outpatient visits were $18 ($56) versus $35 ($134) during 14 days of follow-up ($P < 0.001$) and $29 ($87) versus $49 ($178) during 28 days of follow-up ($P < 0.001$) for treated versus untreated patients, respectively. The direction of between-cohort differences for respiratory-related inpatient and ED care varied (Figure 2A and B).

DISCUSSION

RA is a serious autoimmune condition, and patients with RA often receive immunosuppressive therapy; these patients are therefore at higher risk of developing complications from influenza infection (4), and antiviral treatment should be considered (9). In this study, we found that among 4946 patients with RA in this study who were diagnosed with influenza in 2016-2019, 3371 (68.2%) received antiviral influenza therapy. This finding indicates that although many US clinicians prescribe antiviral treatment for this vulnerable population, there is a considerable population of patients with RA who could benefit from antiviral therapy.

Among patients with RA in this study, HRU was high during the month after influenza diagnosis: greater than 90% of all patients had all-cause HRU in any care setting during 28 days of follow-up, which can be assumed to reflect, in part, routine care for the underlying disease. With few exceptions, patients treated with antiviral medication experienced lower HRU than untreated patients across the usage categories and influenza seasons studied. Mean numbers of all-cause and respiratory-related outpatient visits were significantly higher among untreated versus treated patients during 14 and 28 days of follow-up, and mean costs for respiratory-related outpatient visits were higher for untreated versus treated patients during both follow-up periods.

In addition, all-cause ED visits were significantly more common, and the mean number of all-cause ED visits was higher among untreated compared with treated patients during 28 days of follow-up. These findings demonstrate that treatment with antiviral therapy can lower the subsequent health care burden among patients with RA who are diagnosed with influenza. As a methodological note, our sample included more patients with influenza in the 2017-2018 season compared with the seasons before and after. This may reflect the severity of the 2017-2018 influenza season and contribute to variability in our data from year to year (12).

Our findings are consistent with previous studies that have found lower rates of complications, reduced HRU and costs, and fewer hospitalizations among patients with influenza who were treated with antiviral medication compared with untreated patients (10,13–15). Among patients with high-risk conditions, antiviral treatment was found in one study to reduce the risk of

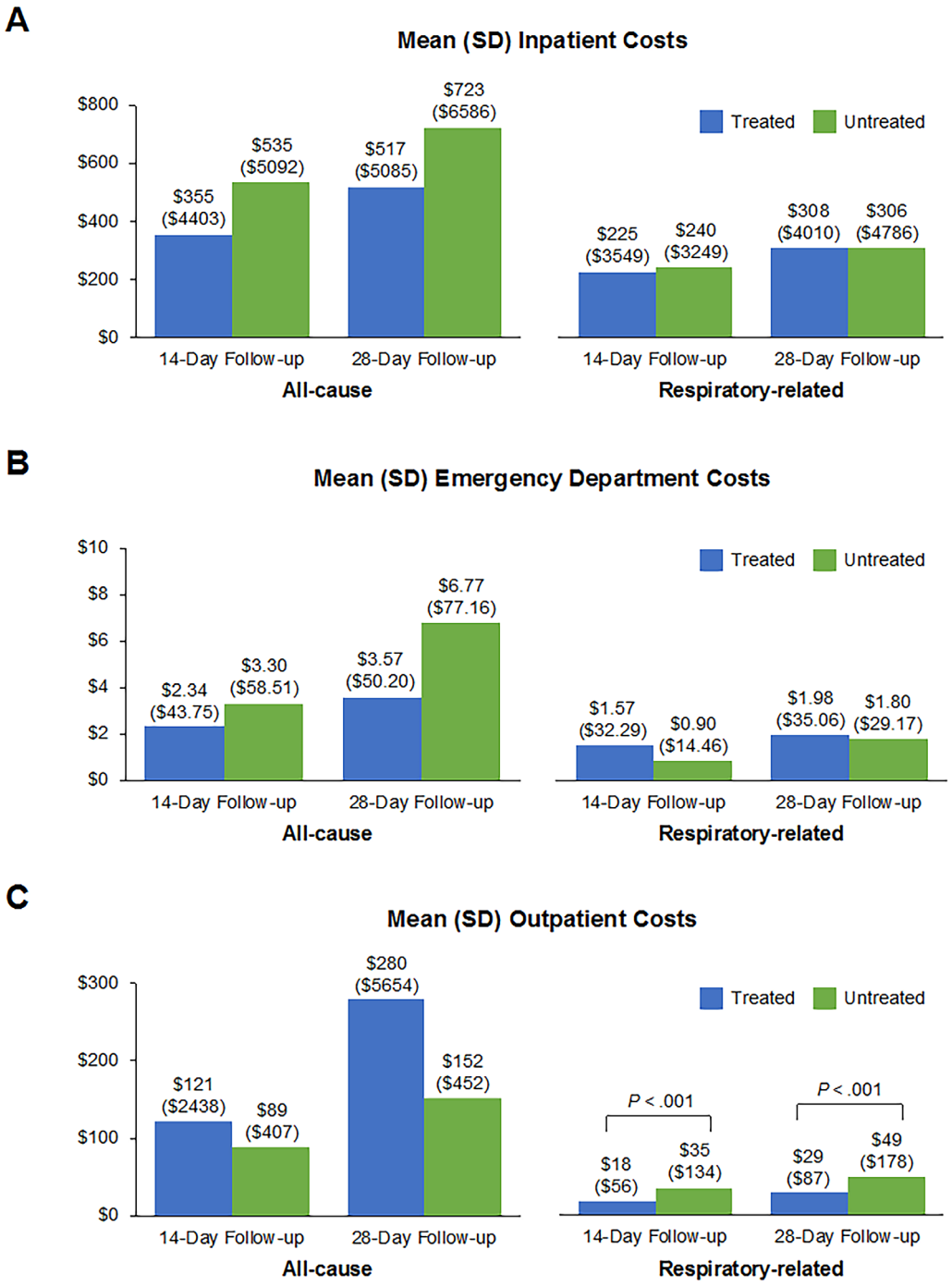

Figure 2. Mean (SD) costs for inpatient (**A**), emergency department (**B**), and outpatient (**C**) care up to follow-up days 14 and 28 in matched cohorts. Data are presented for all influenza seasons combined (2016-2019). Costs are reported in adjusted 2019 US dollars.

hospitalization by greater than 70% (16). Similarly, in a claims analysis of patients with diabetes and influenza, antiviral treatment reduced the risk of respiratory illness by 17% and the risk of hospitalization by 30% (17). Our findings of reduced HRU and costs among patients with RA and influenza thus add to a body of evidence on the benefits of antiviral treatment for high-risk patient populations.

As in any claims database analysis, diagnoses and HRU that were not submitted for health insurance reimbursement in the patient's record could not be identified. This can include diagnoses and treatments received outside the patient's participating provider network. Selection of patients with influenza based on diagnosis codes might have resulted in inclusion of patients who did not have laboratory-confirmed diagnoses. It is also possible that some

patients with RA might have had influenza but opted not to seek medical care; in these cases, the proportion of influenza cases among patients with RA might have been underestimated.

Because of limited clinical information available in claims databases, we were unable to adjust for influenza severity or influenza vaccination status in our analysis. A selection bias is possible wherein patients with less severe influenza did not receive treatment; their milder disease could appear as better outcome relative to the outcome of patients with more severe disease who were treated. Potential confounding may also be present because claims data did not capture variables, such as patient symptoms, income, and attitude toward medications or antivirals, that may have influenced receipt of antiviral treatment. Another important confounder is duration and/or severity of RA. Because of substantial attrition with more strict continuous enrollment criteria, to capture every patient from disease inception would have greatly reduced our sample size and biased our patient population to those with shorter durations of therapy. We therefore used the RA therapy variable (ie, biologic vs nonbiologic and disease-modifying antirheumatic drug vs steroids) to serve as a proxy for disease severity–correlated duration. Further, with claims data, it is difficult to follow patients over their entire course of disease and accurately differentiate established from early RA, thus leading us to use the proxy variable. Because of limited clinical information, other unmeasured confounders could have affected the results. We used the CCI to account for key comorbidities and also considered RA therapies in the propensity score matching.

Additionally, because outcomes were not assessed within 2 days of the proxy fill date for untreated patients, it was likely that there were unmeasured HRU and costs for untreated patients. For both of these reasons, these analyses may be considered a conservative estimate of the potential benefit from antiviral treatment. Also, because of the rarity of certain outcomes, such as hospitalization, our sample size had low statistical power to detect differences.

Additionally, corrections were not made for multiple comparisons, but these should be considered in the interpretation of the *P* values.

Lastly, our database analysis included individuals enrolled in commercial health plans and supplemental Medicare plans and may therefore not be representative of the entire US population.

In a large real-world sample of patients with RA and influenza infection diagnosed in an outpatient setting, antiviral treatment reduced the health care burden associated with outpatient and ED visits over 28 days of follow-up, reflecting the potential for antiviral treatment to reduce economic burden associated with management of influenza and its complications in this vulnerable patient population.

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. Dr. Seetasith 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.

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