The Economic Burden of ACPA-Positive Status Among Patients with Rheumatoid Arthritis

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ABSTRACT

BACKGROUND: Anticitrullinated protein antibodies (ACPAs) are serological biomarkers associated with early, rapidly progressing rheumatoid arthritis (RA), including more severe disease and joint damage. ACPA testing has become a routine tool for RA diagnosis and prognosis. Furthermore, treatment efficacy has been shown to vary by ACPA-positive status. However, it is not clear if the economic burden of patients with RA varies by ACPA status.

OBJECTIVE: To determine if the economic burden of RA varies by patient ACPA status.

METHODS: IMS PharMetrics Plus health insurance claims and electronic medical record (EMR) data from 2010-2015 were used to identify patients with incident RA. Patients were aged ≥ 18 years, had ≥ 1 inpatient or ≥ 2 outpatient claims reporting an RA diagnosis code (ICD-9-CM code 714.0), and had an anticyclic citrullinated peptide (anti-CCP; a surrogate of ACPA) antibody test within 6 months of diagnosis. Incident patients were defined as those who had no claims with an RA diagnosis code in the 6 months before the first observed RA diagnosis. The primary outcome of interest was RA-related medical expenditures, defined as the sum of payer- and patient-paid amounts for all claims with an RA diagnosis code. Secondary outcomes included health care utilization metrics such as treatment with a disease-modifying antirheumatic drug (DMARD) and physician visits. Generalized linear regression models were used for each outcome, controlling for ACPA-positive status (defined as anti-CCP ≥ 20 AU/mL), age, sex, and Charlson Comorbidity Index score as explanatory variables.

RESULTS: Of 647,171 patients diagnosed with RA, 89,296 were incident cases, and 47% ($n=42,285$) had an anti-CCP test. After restricting this sample to patients with a linked EMR and reported anti-CCP test result, 859 remained, with 24.7% ($n=212$) being ACPA-positive. Compared with ACPA-negative patients, adjusted results showed that ACPA-positive patients were more likely to use either conventional (71.2% vs. 49.6%; $P<0.001$) or biologic (20.3% vs. 11.8%; $P<0.001$) DMARDs during the first year after diagnosis and had more physician visits (5.58 vs. 3.91 times per year; $P<0.001$). Annual RA-associated total expenditures were \$7,941 for ACPA-positive and \$5,243 for ACPA-negative patients ($\Delta=\$2,698$; $P=0.002$). RA-associated medical expenditures were \$4,380 for ACPA-positive and \$3,427 for ACPA-negative patients ($\Delta=\$954$; $P=0.168$), whereas DMARD expenditures were \$3,560 and \$1,817, respectively ($\Delta=\$1,743$; $P=0.001$).

CONCLUSIONS: RA-related economic burden is higher for patients who are ACPA-positive compared with those who are ACPA-negative. Providers may wish to inform patients diagnosed with ACPA-positive RA about the likely future disease and economic burden in hopes that both stakeholders can be more proactive in addressing them.

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What is already known about this subject

- Anticitrullinated protein antibodies (ACPAs) are established biomarkers for identifying early, rapidly progressing rheumatoid arthritis (RA).
- The efficacy of RA treatments varies depending on whether patients are ACPA-positive.

What this study adds

- This study is the first to measure the economic burden of patients with RA by ACPA status in the United States.
- RA-associated total expenditures were 51% higher among patients with the ACPA biomarker compared with those without the biomarker.

In the United States, 1.3 million people have rheumatoid arthritis (RA). RA patients incur \$19.3 billion in direct and indirect costs in the United States annually.¹⁻³ While there is a large number of treatments available for RA, patients often try multiple therapies before finding an optimal one, and the effectiveness of some therapies declines over time. Biomarkers such as anticitrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) can be used to better understand disease progression.^{4,5}

In particular, the ACPA serological biomarker of RA is being increasingly used to inform patient prognosis.^{6,7} As medicine has moved toward a more personalized treatment approach in recent years, published research has found that being ACPA-positive is an independent predictor of response for some biologic disease-modifying antirheumatic drugs (bDMARDs) more than others.^{8,9} DMARDs act on the immune system and block inflammation to slow the progression of RA; targeted DMARDs block pathways inside immune cells whereas bDMARDs are produced by living cells and work on immune proteins called cytokines.¹⁰ There is a wide range of published estimates for the percentage of patients with RA who are ACPA-positive, ranging from a low of 5% to as high as 91%.¹¹⁻¹³ ACPA status has crucial prognostic value for RA diagnosis and observation of RA progression, as it can be observed in serum samples earlier than RF.^{6,14} The RF biomarker, on the other hand, has not shown the same predictive power.^{8,15} However, both ACPA and RF are associated with more severe disease and joint damage.^{6,16}

FIGURE 1 Population Selection for the Incident Cohort

ACPA = anticitrullinated protein antibody; EMR = electronic medical record; RA = rheumatoid arthritis.

This is because ACPA and RF formation occurs prior to clinical manifestation of RA and irreversible joint damage.^{17,18}

Despite the relatively recent understanding of the importance of ACPA status on treatment response to specific medications,¹⁹ little is known about the differences in the economic burden of disease for ACPA-positive and ACPA-negative patients. While there has been substantial research into the health care resource utilization and costs of RA in general, the lack of specific data on ACPA status may result in a misunderstanding of the uniqueness of these subpopulations in terms of burden and unmet need. Further, ACPA status may be particularly relevant for patients who have an early, rapidly advancing form of RA.¹⁵ Recent studies from phase 3b clinical trials have shown benefit of some biologic DMARDs in this specific population.²⁰⁻²²

As understanding of the importance of ACPA status on treatment response to specific medications, particularly as a component of defining the early, rapidly progressing RA patient, is fairly recent,²³ little is known about the differences in burden of disease for ACPA-positive and ACPA-negative patients. This study measured the difference in economic cost burden between patients with RA who were ACPA-positive compared with those who were ACPA-negative using a health insurance claims database linked to an electronic medical record (EMR).

Methods

Study Design

This study is an observational, retrospective cohort study that measured differences in the economic burden of RA between patients with newly diagnosed (i.e., incident) cases of RA who are ACPA-positive compared with those who are not. We used health insurance claims data linked to EMR data containing laboratory results. After conducting sensitivity analysis differentiating ACPA as strongly or weakly positive, we defined patients as ACPA-positive if their anticyclic citrullinated peptide (anti-CCP) test result was ≥ 20 AU/mL.²⁴

Data Source

We used 5 years (2010-2015) of IMS PharMetrics Plus data for this study. The aggregated IMS PharMetrics Plus database is composed of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage in 2013 represent 40 million active lives. The PharMetrics Plus data have diverse representation of geography, employers, payers, providers, and therapy areas. Patients in the majority of 3-digit ZIP codes and in every metropolitan statistical area of the United States are represented, with coverage of data from 90% of U.S. hospitals and 80% of all U.S. doctors and representation from 85% of the

TABLE 1 Descriptive Statistics by ACPA Status^a

	ACPA-Negative (n = 647)	ACPA-Positive (n = 212)	P Value	Total (N = 859)
Age group, years n (%)			0.384	
18-34	72 (11.1)	18 (8.5)		90 (10.5)
35-44	116 (17.9)	31 (14.6)		147 (17.1)
45-54	172 (26.6)	69 (32.5)		241 (28.1)
55-64	210 (32.5)	70 (33.0)		280 (32.6)
65+	77 (11.9)	24 (11.3)		101 (11.8)
Male, n (%)	153 (23.6)	66 (31.1)	0.030	219 (25.4)
CCI score, n (%)			0.266	
0	442 (68.3)	157 (74.1)		599 (69.7)
1	126 (19.5)	32 (15.1)		158 (18.4)
2	55 (8.5)	13 (6.1)		68 (7.9)
≥3	24 (3.7)	10 (4.7)		34 (4.0)
Region, n (%)			<0.001	
East	196 (30.3)	97 (45.8)		293 (34.1)
Midwest	81 (12.5)	39 (18.4)		120 (14.0)
South	279 (43.1)	60 (28.3)		339 (39.5)
West	91 (14.1)	16 (7.5)		107 (12.5)

^aACPA-positive = anti-CCP ≥ 20 AU/mL.

ACPA = anticitrullinated protein antibody; CCI = Charlson Comorbidity Index.

Fortune 100 companies. IMS PharMetrics Plus data have been used in previous RA studies.^{25,26}

To obtain ACPA status, the PharMetrics Plus dataset was linked to available ambulatory EMR records. The EMR data contained laboratory results that were used to measure ACPA and RF from a patient's anti-CCP and RF tests, respectively.

Study Population

Our dataset contained 647,171 distinct patients with an RA diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 714.0). We matched the RA cohort selected based on the PharMetrics Plus health plan claims database using the deidentified patient number with the IMS ambulatory EMR database. EMR-linked patients with valid ACPA test results were selected to be included in the analytical sample.

To be included in the analysis, patients were required to have ≥ 1 inpatient or ≥ 2 outpatient claims with an ICD-9-CM diagnosis code of 714.0, similarly to other claims-based RA analyses in the literature.²⁷ Patients were required to have ≥ 2 outpatient claims because these claims data may contain so-called “rule-out” diagnoses where the physician includes the diagnosis code for tests for a specific condition even when the patient does not have the condition.²⁸ Patients were also required to have an anti-CCP test within 6 months of diagnosis, be at least 18 years of age at the time they were diagnosed, and be continuously enrolled for at least 6 months after diagnosis in a health plan covering medical and pharmacy expenditures. Patients living outside of the United States were excluded from the study population.

To identify newly diagnosed patients, we followed a previous work²⁹ by requiring at least a 6-month “clean period” with no RA diagnosis before the first observed RA diagnosis in the data.

Key Variables of Interest

The primary outcome of interest was health care costs. Costs were defined as payments made by both payers and patients (i.e., out-of-pocket deductibles, coinsurance, and copayments) and were captured over a 12-month period following diagnosis. Costs measured included pharmacy and medical costs (e.g., inpatient, outpatient, emergency department [ED], physician visits). Both all-cause costs and RA-related costs were analyzed, with the latter defined from all medical claims carrying an ICD-9-CM diagnosis code for RA in any diagnosis position. All costs were expressed in 2015 constant dollars, adjusted using the medical care component of the Consumer Price Index.

The secondary outcome of interest was RA-related health care resource utilization. This included hospitalizations, ED visits, physician visits, and number of prescriptions. For the small proportion of patients who had a follow-up period less than 12 months, we annualized their health care costs and utilization to reflect an annual rate.

The key independent variable of interest was whether patients were ACPA-positive. ACPA-positive status was defined by anti-CCP test ≥ 20 AU/mL per American College of Rheumatology (ACR) guidelines.^{19,30} Additional independent variables included patient demographics (age, gender), region of residence, and patient health status (Charlson Comorbidity Index [CCI] score).

Statistical Analyses

For each outcome variable, descriptive statistics were tabulated through univariate analysis by ACPA status. The distributions of test results were also presented as means, medians, standard deviations, and ranges. Patient characteristics including age, gender, region, and other demographic and clinical variables (e.g., comorbidities) were summarized. In addition, Wilcoxon rank-sum tests were conducted to determine whether any differences in resource use or cost were statistically significant across these cohorts.

Health care costs were measured using the financial fields on administrative claims in the IMS PharMetrics Plus databases and include the gross covered payments for all health care services or products (i.e., the amount eligible for payment after applying pricing guidelines such as fee schedules and discounts but including deductibles, copayments, and coordination of benefits amounts). All costs were expressed in 2015 constant dollars, adjusted using the medical care component of the Consumer Price Index.³¹

Health care spending was compared using a regression analysis to control for observed differences between ACPA-positive and ACPA-negative patients. In our baseline approach, we used a generalized linear model (GLM) to adjust for confounders/

TABLE 2 Descriptive Analysis of Health Care Costs by ACPA Status, Baseline Analysis Using Incident Cohort^a

	RA-Associated Costs ^b			All-Cause Costs		
	ACPA-Negative n = 647	ACPA-Positive n = 212	Difference	ACPA-Negative n = 647	ACPA-Positive n = 212	Difference
Prescription drug costs	1,798 (5,807)	3,617 (7,961)	1,819 ^c	4,780 (10,287)	5,096 (8,621)	316
Medical costs	3,423 (8,677)	4,390 (8,768)	967	13,662 (23,148)	10,790 (16,497)	-2,872
Inpatient	1,670 (7,152)	1,324 (6,314)	-346	4,098 (14,388)	2,584 (9,518)	-1,514
Outpatient	1,754 (4,131)	3,066 (6,411)	1,312 ^d	9,565 (14,849)	8,206 (11,418)	-1,359
Doctor visit	545 (685)	754 (622)	209 ^c	2,530 (2,428)	2,042 (1,844)	-488 ^d
ED	101 (882)	68 (695)	-33	305 (1,307)	162 (851)	-143
Outpatient hospital	1,000 (3,924)	2,154 (6,407)	1,154 ^d	5,278 (13,364)	5,185 (10,419)	-93
Other outpatient	108 (460)	89 (295)	-19	1,451 (2,651)	818 (1,755)	-633 ^d
Total costs	5,222 (10,382)	8,007 (11,801)	2,785 ^d	18,442 (28,366)	15,886 (19,088)	-2,556

^aIncident cohort = 859; all values are shown as mean (SD) in 2015 U.S. dollars.

^bRA-associated prescription drug costs only include spending on DMARDs.

^cP < 0.01.

^dP < 0.05.

ACPA = anticitrullinated protein antibody; DMARD = disease-modifying antirheumatic drug; ED = emergency department; RA = rheumatoid arthritis; SD = standard deviation.

covariates. This approach was used both for the cost and utilization numbers; since the utilization numbers are annualized, they may not be integer values and thus the same GLM was used.

Sensitivity Analyses

We conducted 2 sensitivity analyses. First, rather than measure patients who are likely rapidly progressing or have a poor prognosis using a single ACPA-positive indicator, we used the ACR definition of rapidly progressing or poor prognosis patients, which requires the presence of at least 1 of the following clinical dimensions: anti-CCP test ≥ 60 AU/mL or RF test ≥ 15 IU/mL or the presence of RA vasculitis (ICD-9-CM diagnosis code 714.2) or Felty's syndrome (ICD-9-CM diagnosis code 714.1).¹⁹ We also compared differences in cost between patients who had no serological biomarkers against those with a single biomarker (ACPA-positive or RF-positive) compared against those who were both ACPA-positive and RF-positive. In our second sensitivity analysis, we no longer limited the analysis to patients with incident RA but also included patients with prevalent forms of RA. For the prevalent RA patient analysis, we no longer required a 6-month clean period prior to first diagnosis.

Results

Study Population

Of 647,171 patients diagnosed with RA, 89,296 were incident cases meeting inclusion criteria and 47% (n = 42,285) had an anti-CCP test. After restricting the sample to 9,747 patients with a linked EMR, 859 reported an ACPA test result (Figure 1). Of these 859 patients with newly diagnosed RA, 24.7% were ACPA-positive.

The ages of individuals in the study ranged from 18-84 years at index RA diagnosis. About 3 out of every 5 patients with RA were aged between 45 and 64 years, and 12% were 65 years or older. Three quarters of RA patients were female, similar to the gender composition nationally of patients with RA.³² Age and gender distributions were similar comparing ACPA-positive and ACPA-negative patients (Table 1).

Health Care Costs

Health care costs directly associated with the treatment of patients with RA were higher among ACPA patients, and all-cause costs were similar across ACPA status. Descriptive analysis showed no statistically significant difference in all-cause health care cost by ACPA status (Table 2). Results showed that overall expenditures for ACPA-positive patients were higher compared to ACPA-negative patients. On the other hand, ACPA-positive patients had significantly higher RA-associated prescription costs ($P < 0.01$), outpatient service costs ($P < 0.05$), and total costs ($P < 0.05$) compared with ACPA-negative patients. However, the differences were less significant and even reversed for all-cause costs. ACPA-positive patients had significantly lower all-cause expenditures for doctor visits and other outpatient services (i.e., all outpatient costs excluding costs associated with physician visits, ED visits, and outpatient hospital claims; $P < 0.01$).

Similar differences were observed in multivariable analyses controlling for differences in patient characteristics. After controlling for age, gender, and CCI score in the multivariate regression analysis (Table 3), all-cause cost was \$2,430 ($P = 0.236$) lower among ACPA-positive individuals, with higher prescription drug cost ($\Delta = +\$294$, $P = 0.707$) and lower medical cost ($\Delta = -\$2,725$, $P = 0.107$) among ACPA-positive compared

TABLE 3 Multivariable Analysis of Health Care Costs by ACPA Status, Baseline Analysis Using Incident Cohort (N=859)^a

	ACPA-Positive vs. ACPA-Negative			Adjusted Mean (SE)	
	Difference	95% CI	P Value	ACPA-Positive	ACPA-Negative
RA-associated costs					
Total	2,698	1,025 to 4,370	0.002	7,941 (740)	5,243 (423)
Prescription drug	1,743	753 to 2,734	0.001	3,560 (438)	1,817 (251)
Medical costs	953	-402 to 2,309	0.168	4,380 (600)	3,427 (343)
Inpatient	-388	-1,471 to 694	0.482	1,292 (479)	1,680 (274)
Outpatient	1,343	596 to 2,089	<0.001	3,089 (330)	1,746 (189)
Doctor visit	215	110 to 319	<0.001	758 (46)	543 (26)
ED visit	-28	-159 to 103	0.675	71 (58)	99 (33)
Outpatient hospital	1,175	449 to 1,901	0.002	2,170 (321)	995 (184)
Other outpatient	-19	-85 to 47	0.565	89 (29)	108 (17)
All-cause costs					
Grand total	-2,430	-6,453 to 1,592	0.236	15,981 (1,780)	18,411 (1,017)
Prescription drug	294	-1,240 to 1,828	0.707	5,079 (679)	4,785 (388)
Medical costs	-2,725	-6,033 to 585	0.107	10,901 (1,464)	13,626 (837)
Inpatient	-1,467	-3,520 to 586	0.161	2,619 (908)	4,086 (519)
Outpatient	-1,257	-3,422 to 909	0.255	8,283 (958)	9,540 (548)
Doctor visit	-448	-803 to -94	0.013	2,072 (157)	2,520 (90)
ED visit	-134	-322 to 55	0.164	169 (83)	303 (48)
Outpatient hospital	-39	-2,001 to 1,923	0.969	5,226 (868)	5,265 (496)
Other outpatient	-635	-1,014 to -257	0.001	816 (168)	1,451 (96)

^aCosts are given in 2015 U.S. dollars.

ACPA=anticitrullinated protein antibody; CI=confidence interval; ED=emergency department; RA=rheumatoid arthritis; SE=standard error.

with ACPA-negative individuals. None of these results, however, were statistically different from zero.

On the other hand, annual RA-associated total expenditures were \$7,941 for ACPA-positive and \$5,243 for ACPA-negative patients ($\Delta = \$2,698$, $P = 0.002$; Figure 2). This difference represents a 51% increase in overall RA-associated costs. RA-associated medical expenditures (excluding prescription drug costs) were \$4,380 for ACPA-positive and \$3,427 for ACPA-negative patients ($\Delta = \$953$; $P = 0.168$).

Health Care Resource Utilization

Descriptive analysis of health care resource utilization also showed higher RA-associated health care utilization among ACPA-positive patients compared with ACPA-negative patients (Appendix A, available in online article). Specifically, ACPA-positive patients were more likely to use either conventional (71.2% vs. 49.6%; $P < 0.001$) or biologic (20.3% vs. 11.8%; $P < 0.001$) DMARDs during the first year after diagnosis and had more physician visits (5.58 vs. 3.91 times per year; $P < 0.001$).

Sensitivity Analyses

The results were similar among the rapidly progressing subgroup; ACPA-positive patients had higher costs than ACPA-negative patients (Appendix B, available in online article). Compared with patients without serological biomarkers

(i.e., neither ACPA-positive nor RF-positive), patients with 1 (but not both) biomarkers had similar RA-related total cost ($\Delta = \$701$; $P = 0.477$), but patients who were ACPA-positive and RF-positive had significantly higher RA-related total cost ($\Delta = \$2,748$; $P = 0.021$). In addition, the overall pattern of disease burden by ACPA status in the prevalent cohort (N=2,524) was similar to the findings from the primary analysis in the incident cohort. However, differences in cost by ACPA status are less apparent, potentially due to the more heterogeneous nature of the prevalent cohort, which contains a mix of patients who have varying disease prognosis and severity or unobserved differences in disease severity across ACPA-positive and ACPA-negative patients.

Discussion

ACPA-positive patients generally had higher RA-related costs. Annual RA-associated expenditures were \$2,698 higher for ACPA-positive compared with ACPA-negative patients ($P = 0.002$). Setting aside the cost for DMARDs, annual medical cost was \$954 higher for ACPA-positive compared with ACPA-negative patients ($P = 0.168$). The difference in medical cost by ACPA status was mainly driven by outpatient hospital costs (\$1,175 higher; $P = 0.002$) and doctor visit costs (\$214 higher; $P < 0.001$). Similar patterns were observed in sensitivity analyses conducted using rapidly progressing status and a prevalent

FIGURE 2 Baseline Results: Annual RA-Associated Health Care Costs by ACPA Status in Incident Cohort (N=859)

^aP < 0.05.

ACPA = anticitrullinated protein antibody; RA = rheumatoid arthritis.

cohort. On the other hand, we found no statistically significant difference in overall cost between patients with RA who were ACPA-positive compared with ACPA-negative.

Overall, the results suggest that ACPA-positive patients may have more aggressive treatment of RA and higher RA-related disease burden but also may be in better overall health due to a decreased prevalence of comorbid conditions. Although speculative, the observed difference in RA-related cost aligns with results from the literature that ACPA positivity is associated with more severe disease progression and joint damage.^{6,16} At the same time, the failure to find any difference in overall cost between ACPA-positive and ACPA-negative patients could be interpreted to mean that there is truly no difference in spending across these groups or that overall disease burden outside of RA or RA disease progression itself may vary across patients by ACPA status. For instance, whereas 74.1% of ACPA-positive patients had a CCI score of 0, for ACPA-negative patients, this figure was 68.3%. More broadly, this study's

estimates of the economic burden of being ACPA-positive align with the findings from a study of the economic burden of patients with RA in Italy.³³

Research from other studies has provided some suggestions of clinical approaches to improve patient health outcomes among ACPA-positive patients, although the effect of these treatments on economic burden is uncertain. The ACR suggests the use of DMARDs and biologic agents or biologics based on indications of early RA followed by established RA.¹⁹ Although many of the biologic agents are expensive relative to conventional DMARDs, recent research suggests, however, that certain bDMARDs may be more efficacious among ACPA-positive patients compared with ACPA-negative patients compared with the more widely used tumor necrosis factor inhibitor class.²³ Given the various options for treatment, the results for this study imply that evidence on ACPA status can be important in the choice of treatment.

Limitations

This study has a number of limitations. First, not all patients or even all patients with RA receive regular anti-CCP or RF tests, and it is likely that these lab tests were not applied randomly. Although our baseline approach is limited to patients receiving an anti-CCP test, our sensitivity analysis also examines the economic burden among RA patients based on whether they are ACPA-positive or RF-positive.

Second, although our health insurance claims data captured any patient out-of-pocket payments from services covered in part by insurers, we could not observe any patient health care spending made without knowledge of the payer. Furthermore, we allowed for ICD-9-CM codes to count as valid diagnoses if they were listed in any diagnosis position on the claim, which may be a less specific indicator of RA status than would be the case of requiring a primary diagnosis code.³⁴

Third, the sample size of our analysis is fairly small, less than 1,000 people. To address this issue, we conducted a sensitivity analysis to expand our comparison to patients with prevalent RA and we found qualitatively similar results. Fourth, the sample comes from a largely commercially insured patient population, and individuals aged 65 years and above are underrepresented. This challenge has been faced by other studies using administrative datasets,^{35,36} and researchers should be cautious in extrapolating the results of this study beyond the commercially insured population. Fifth, the EMR data for this study only included the lab results; thus, we were unable to include disease severity measures to assess baseline disease states for the ACPA subpopulations. In other words, the demographics and comorbidities captured in this study do not fully capture disease severity. However, DMARD use is much higher among ACPA-positive patients in the study sample, suggesting higher disease severity.

Finally, the results of this study should be interpreted as demonstrating the correlation between ACPA status and economic burden as there exists significant uncertainty regarding the direction of causation of ACPA status on economic burden. On one hand, it could be the case that physicians believe that these patients who are ACPA-positive will have higher RA-related disease burden and thus they would be more likely to prescribe more aggressive medications and request more frequent follow-up visits. On the other hand, physicians may treat ACPA-positive patients similarly to ACPA-negative patients, but ACPA-positive patients may be more likely to have RA-related complications due to more rapidly progressing disease.

Conclusions

This study found that patients who were ACPA-positive had a similar overall cost burden but had higher RA-related costs compared with patients who were ACPA-negative. Future research should examine the relationship between ACPA status, disease severity, and economic outcomes and should also

examine whether targeting RA-related treatment based on clinical factors such as ACPA-positive status leads to differential clinical and economic outcomes.

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The following 2 appendices provide additional details on our baseline analysis and the results from 2 sensitivity analyses. The first analysis (Appendix A) contains results from the analysis of differences in health care utilization by ACPA status. Outcomes of interest include the number of prescriptions filled, inpatient admissions, ED visits, and physician visits. Next, the results of 2 sensitivity analyses are presented (Appendix B). Appendix A compares patients with the ACR's definition of patients with early and rapidly progressing RA and compares costs to patients without this designation. Note that being ACPA-positive would qualify a person as being with early and rapidly progressing RA under the ACR definition. Appendix B examines a cohort of patients with prevalent cases of RA; our baseline analysis, on the other hand, only examines cases with incident RA.

APPENDIX A Descriptive Analysis of Health Care Utilization by ACPA Status, Baseline Analysis Using Incident Cohort (N=859)^a

	RA-Associated Utilization			All-Cause Utilization		
	ACPA-Negative n = 647	ACPA-Positive n = 212	Difference	ACPA-Negative n = 647	ACPA-Positive n = 212	Difference
Prescriptions	4.50 (6.49)	7.70 (7.00)	3.20 ^b	38.30 (34.00)	36.50 (28.20)	-1.80
Hospital stays	0.12 (0.41)	0.11 (0.38)	-0.01	0.41 (1.17)	0.18 (0.57)	-0.23
ED visits	0.06 (0.37)	0.03 (0.19)	-0.03	16.90 (13.90)	14.30 (11.20)	-2.60 ^c
Doctor visits	3.90 (4.20)	5.60 (4.20)	1.70 ^b	38.30 (34.00)	36.50 (28.20)	-1.80 ^c

^aAll values are shown as mean (SD).

^bP < 0.01.

^cP < 0.05.

ACPA = anticitrullinated protein antibody; ED = emergency department; RA = rheumatoid arthritis; SD = standard deviation.

APPENDIX B Summary of Baseline and Sensitivity Analyses of RA-Associated Health Care Costs

Estimated Marginal Effect (SE)	Incident Cohort		Sensitivity I (n = 859)		Prevalent Cohort	
	Baseline (n = 859)				Sensitivity II (n = 2,524)	
	ACPA-Negative (n = 647)	ACPA-Positive (n = 212)	RP-Negative (n = 647)	RP-Positive (n = 212)	ACPA-Negative (n = 1,917)	ACPA-Positive (n = 607)
Total cost	5,222 (423)	8,007 (738)	5,367 (474)	6,737 (585)	9,259 (378)	10,299 (672)
Prescription drug cost	1,798 (250)	3,617 (437)	1,988 (280)	2,642 (347)	4,643 (226)	5,544 (402)
Total medical cost	3,423 (342)	4,390 (598)	3,378 (382)	4,095 (472)	4,615 (295)	4,755 (524)

ACPA = anticitrullinated protein antibody; RP = rapidly progressing; SE = standard error.