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Association of Seropositivity and Mortality in Rheumatoid Arthritis and the Impact of Treatment With Disease-Modifying Antirheumatic Drugs: Results From a Real-World Study

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Objective. Seropositivity for anti–citrullinated protein antibody (ACPA)/rheumatoid factor (RF) in rheumatoid arthritis (RA) is associated with increased overall mortality; however, the association between antibody titers and mortality is not well established. Investigating relationships between antibody titers and mortality may clarify their role in RA pathogenesis. This study was undertaken to evaluate the association of antibody titers with mortality and its modification by disease-modifying antirheumatic drugs (DMARDs).

Methods. Eligible patients with established RA were identified through administrative claims data linked to laboratory results (2005–2016). Patients were categorized by positivity status for ACPA, RF, or both. Patients were further divided into groups by autoantibody titers. DMARD-exposed patients were categorized into biologic DMARD (bDMARD) and conventional DMARD (cDMARD) subcohorts. Crude mortality rates/1,000 patient-years and Kaplan-Meier curves were compared between antibody categories. Adjusted Cox proportional hazards regression and sensitivity (propensity-matched patients) analyses were conducted.

Results. Overall, 53,849 and 79,926 patients had evaluable ACPA and RF status, respectively. For both autoantibodies, mortality rates were significantly higher in seropositive versus seronegative patients (risk increase of 48.0% and 44.0% in ACPA- and RF-positive patients, respectively; $P < 0.001$ each). Mortality rates were greatest in patients with higher versus lower autoantibody titers (ACPA hazard ratio [HR] 1.60 [95% confidence interval (95% CI)] 1.45–1.76]; RF HR 1.78 [95% CI 1.66–1.91]). In cDMARD-exposed patients, HRs were higher in seropositive versus seronegative cohorts; in bDMARD-exposed patients, there was no difference in mortality by serostatus.

Conclusion. Elevated ACPA/RF titers were independently associated with increased mortality among patients with RA and persisted in patients treated with cDMARDs but not with bDMARDs.

INTRODUCTION

The production of autoantibodies, particularly anti–citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF), is characteristic of rheumatoid arthritis (RA) (1). ACPA antibody titers, directed against posttranslationally modified citrullinated proteins and primarily of the immunoglobulin G isotype, are estimated to be present in 50–70% of patients with RA (1).

Similarly, over 60% of patients with RA have detectable RF titers, primarily of the IgM isotype, which targets the Fc portion of IgG (1). Both autoantibodies can be present in the patient's serum in the absence of symptoms for up to 10 years before disease onset (2–6).

The presence of ACPA and/or RF is indicative of poor prognosis in RA (7), with ACPA being a stronger prognostic indicator for rapid disease progression (1,8). In patients with early RA

with disease duration of <2 years, ACPA positivity is associated with a higher joint destruction rate (9). Moreover, double ACPA and RF seropositivity in RA is associated with a higher disease activity and, consequently, greater disability (10).

Both ACPA and RF are included in the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) diagnostic criteria (11). Furthermore, EULAR treatment guidelines include ACPA and RF seropositivity as poor prognostic factors, indicating early, erosive RA that requires aggressive treatment (7,11,12). Nonetheless, the role of ACPA and RF in combination and at different concentrations in RA pathogenesis is not fully understood and thus the potential impact of these autoantibodies on prognosis remains unclear. Therefore, investigating the correlation between the presence and titer of these autoantibodies and disease outcomes, such as mortality, may help to elucidate the role of autoantibodies as diagnostic and prognostic markers for disease progression in RA.

RA is associated with reduced survival compared with the age- and/or sex-matched general population (13–15). Although the association between seropositivity and mortality in RA has been studied previously, findings have been inconsistent. The presence of autoantibodies has been shown to impact overall mortality (16,17), but the cause-specific mortality differs. Although some studies have found that autoantibody titers did not affect mortality (16), there is emerging evidence that titers could impact disease progression and joint destruction (18,19). Thus, the association between ACPA and RF status and their titers with mortality warrants further investigation. Moreover, while the impact of disease-modifying antirheumatic drugs (DMARDs) on ACPA (20) and RF in patients with RA has been studied (16,17,20–22), any subsequent effect on mortality is not known.

In this real-world study, the role of ACPA and RF seropositivity in predicting the risk of mortality, either independently or combined, was investigated. In addition, we studied the association between ACPA and RF titers and all-cause mortality and whether DMARDs impacted these associations.

PATIENTS AND METHODS

Study design, data sources, and patients. This was a retrospective study of patients with RA using data obtained from 2 US administrative claims databases linked to laboratory data. Patients were followed from the day after the analysis-specific index date until the occurrence of death, end of health plan enrollment, or end of the study period (June 30, 2016), whichever came first. The index date was defined as the first date of ACPA or RF test (or a DMARD prescription date for analysis evaluating DMARD exposures). Baseline was specified as a timeframe between 180 days before and 30 days after the index date.

Data were extracted from Optum Clinformatics Data Mart (OptumInsight, Inc.) and Humana (Humana, Inc.) administrative claims databases. Optum Clinformatics Data Mart contains health claims data from approximately 17 million patients. The Humana research database includes anonymized patient-level data from approximately 20 million demographically diverse current and former Humana members.

Patients were enrolled if they had a diagnosis code of RA (714.xx, International Classification of Diseases, Ninth Revision, Clinical Modification) (23) and at least 1 year of enrollment. The eligibility criteria included age ≥18 years, ≥3 months of enrollment before and after the index date (index date during January 1, 2005 to December 31, 2014 for Optum Clinformatics Data Mart and January 1, 2007 to December 31, 2014 for the Humana database). Patients were excluded from the analysis if they had diagnosis codes for autoimmune comorbidities of ankylosing spondylitis, Crohn's disease, systemic lupus erythematosus, psoriatic arthritis, or ulcerative colitis at or before the index date.

Data from Optum Clinformatics Data Mart and Humana databases were pooled in this study and several patient categories were evaluated based on test result availability (Figure 1). Patients who had the ACPA test first were grouped into ACPA seropositive (ACPA+)
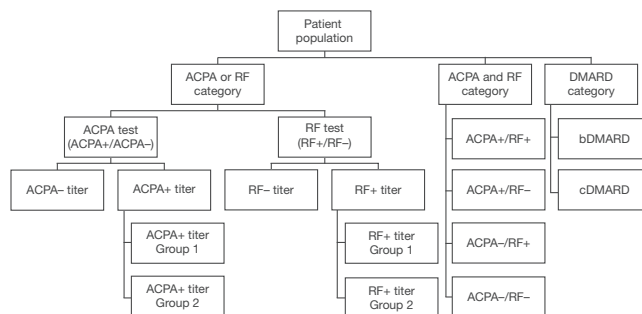

Figure 1. Analyzed patient population. ACPA = anti–citrullinated protein antibody; RF = rheumatoid factor; bDMARD = biologic disease-modifying antirheumatic drug; cDMARD = conventional disease-modifying antirheumatic drug.

and seronegative (ACPA–) groups, and those who had the RF test first were divided into RF seropositive (RF+) and seronegative (RF–) groups. ACPA and RF seropositive patients were further categorized into 2 subgroups, each based on median ACPA or RF titer. Another categorization was based on the availability of both ACPA and RF tests, with patients forming 4 groups: ACPA and RF double-positive, ACPA positive/RF negative, ACPA negative/RF positive, or ACPA and RF double-negative. Finally, patients were categorized based on DMARD exposure: the biologic DMARD (bDMARD) group comprised patients ever treated with abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab, and the conventional DMARD (cDMARD) group included patients who were exposed to ≥1 dose of a cDMARD (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, minocycline, cyclosporine, or azathioprine) but were bDMARD-naive.

Outcomes and independent variables of interest. The main outcome of the study was all-cause mortality. The Optum Clinformatics Data Mart database was linked to the Social Security Administration Death Master File (24). Available mortality data were recorded by year and month, but for simplicity of calculation, the last day of the month was used to record the date of death in this analysis. Mortality data in the Humana database were available for Medicare (Medicare Advantage Prescription Drug Plan) patients only, from the Centers for Medicare and Medicaid Services, by month. The date of disenrollment was used as a proxy for date of death, with sensitivity analysis using the date of the last claim in the database.

Data on ACPA were collected using 2 commercially available tests. Both databases used Logical Observation Identifiers Names and Codes and had an internal laboratory test name specific to

each laboratory vendor. ACPA and RF were defined according to titers measured by the diagnostic tests. ACPA positivity was defined as a level of >5 U/ml or ≥20 U/ml (depending on the testing kit) and RF positivity was defined as a level of ≥14 IU/ml. The ACPA mean ± SD titers (U/ml) by group and test kit were ACPA–, kit 1: 1.45 ± 1.13, kit 2: 7.72 ± 5.77; ACPA+ group 1, kit 1: 34.57 ± 26.44, kit 2: 84.96 ± 65.97; ACPA+ group 2, kit 1: 120.80 ± 101.20, kit 2: 253.20 ± 33.90. The RF mean ± SD levels (IU/ml) by group were RF–: 8.32 ± 2.37; RF+ group 1: 24.83 ± 9.44; RF+ group 2: 281.90 ± 387.00.

Statistical analysis. Data from the 2 databases were pooled for this analysis. The cumulative overall mortality rates were assessed per 1,000 patient-years. Adjusted analysis was conducted using a full Cox proportional hazards regression model, with all-cause mortality as the dependent variable and 23 covariates incorporated. Covariates included age, sex, region, number of physician office visits during the last 3 months, an indicator variable for 714.0x diagnosis, an indicator variable for RA diagnosis before ACPA or RF testing, past hospitalization, use of medications (steroids, nonsteroidal antiinflammatory drugs, salicylates), use of DMARDs (if applicable), and comorbidity conditions. A fully specified Cox proportional hazards regression model was used to evaluate the association between ACPA positivity and mortality, and RF positivity and mortality, independently. The model was redeployed using data from the combined ACPA and RF category to evaluate the association between mortality and a status of either ACPA or RF.

To further explore the association between mortality risk and ACPA and RF titer, the Cox regression model was used for all

Table 1. Baseline characteristics of eligible patients from 2 administrative claims databases*

	ACPA subcohort			RF subcohort		
	ACPA+ (n = 17,182)	ACPA– (n = 36,667)	Total (n = 53,849)	RF+ (n = 33,550)	RF– (n = 46,376)	Total (n = 79,926)
Age, mean ± SD years	62.8 ± 14.1	60.8 ± 15.6	61.4 ± 15.2	63.2 ± 14.7	60.8 ± 16.1	61.8 ± 15.6
Female	74.3	75.0	74.8	74.5	74.0	74.2
Previous DMARDs	86.8	58.0	67.2	71.4	47.2	57.4
Corticosteroid use	61.0	58.2	59.1	52.1	49.6	50.6
Two diagnoses	96.7	72.7	80.3	93.1	69.7	79.5
Previous hospitalization	26.0	28.5	27.7	26.7	27.3	27.1
Office visits, mean ± SD	4.6 ± 3.9	5.2 ± 4.3	5.0 ± 4.2	4.7 ± 4.0	5.1 ± 4.4	4.9 ± 4.3
Coronary artery disease	17.9	19.3	18.8	18.8	19.5	19.2
Heart failure	7.1	7.0	7.0	8.0	6.9	7.3
Hypertension	61.3	62.2	61.9	63.2	61.8	62.4
Diabetes mellitus	23.7	25.7	25.1	25.0	26.3	25.8
Asthma	11.3	13.6	12.9	11.9	13.2	12.7
Chronic kidney disease	9.9	12.2	11.5	10.9	11.4	11.2
Smoker (former or current)	15.7	12.5	13.5	14.9	11.7	13.0
NSAIDs	62.9	66.7	65.5	59.0	62.4	61.0
COPD	17.6	14.2	15.3	17.6	13.7	15.3

* Values are the percentage unless indicated otherwise. The anti–citrullinated protein antibody (ACPA) subcohort comprised patients with rheumatoid arthritis (RA) and an ACPA test result in the baseline period. The rheumatoid factor (RF) subcohort comprised patients with RA and an RF test result in the baseline period. DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs; COPD = chronic obstructive pulmonary disease.

Table 2. Mortality rates according to autoantibody status*

	Patients, no.	Deaths, no.	Patient-years	Mortality†	Adjusted HR‡
ACPA status					
ACPA−	36,667	1,798	126,451	14.2 (13.6–14.9)	1.00
ACPA+	17,182	1,276	57,719	22.1 (20.9–23.4)	1.48 (1.37–1.60)
ACPA+ group 1	8,321	606	29,518	20.5 (18.9–22.1)	1.38 (1.25–1.52)
ACPA+ group 2	8,861	670	28,201	23.8 (22.0–25.6)	1.60 (1.45–1.76)
Total	53,849	3,074	184,170	16.7 (16.1–17.3)	–
RF status					
RF−	46,376	2,522	179,247	14.1 (13.5–14.6)	1.00
RF+	33,550	2,688	118,583	22.7 (21.8–23.5)	1.44 (1.36–1.53)
RF+ group 1	16,758	1,098	60,393	18.2 (17.1–19.3)	1.18 (1.09–1.27)
RF+ group 2	16,792	1,590	58,190	27.3 (26.0–28.7)	1.78 (1.66–1.91)
Total	79,926	5,210	297,830	17.5 (17.0–18.0)	–

* The anti–citrullinated protein antibody (ACPA) subcohort comprised patients with rheumatoid arthritis (RA) and an ACPA test result in the baseline period. The rheumatoid factor (RF) subcohort comprised patients with RA and an RF test result in the baseline period. HR = hazard ratio.
† Incidence rate per 1,000 patient-years (95% confidence interval).
‡ HR per 1 unit increase in Z score or per 1 increase in SD (95% confidence interval).

prior applications using data from patients separated into 2 subgroups, each based on median ACPA or RF titer in the entire sample, and 2 groups in patients who were ACPA positive and RF positive, and Z scores were calculated. The grouping and calculation of Z scores were conducted separately for the 2 ACPA testing kits.

To assess the stability of the main findings and to balance the ACPA/RF positive and negative patient groups, 1:1 propensity-score matching within each separate database was used to construct Kaplan-Meier curves to investigate the difference in mortality over time between ACPA positivity/negativity and RF positivity/negativity scores. Propensity scores were calculated for ACPA positivity versus ACPA negativity and RF positivity versus RF negativity based on all covariates. In the analysis of patients exposed to DMARDs, a fully specified Cox proportional hazards regression model was used to investigate the effect of DMARD treatment on the association between mortality and ACPA or RF serostatus.

All analyses were performed using SAS software, version 9.4. All statistical tests were 2-tailed with P values less than or equal to 0.05 considered statistically significant. Results were expressed as the percentage of patients for categorical data and mean ± SD or median (interquartile range) for continuous data, unless specified otherwise.

RESULTS

A total of 133,775 patients with RA from both databases were included: 53,849 in the ACPA group and 79,926 patients in the RF group. Baseline characteristics were mostly balanced between the ACPA and the RF groups, with previous use of DMARDs, presence of 2 RA diagnoses, previous/current
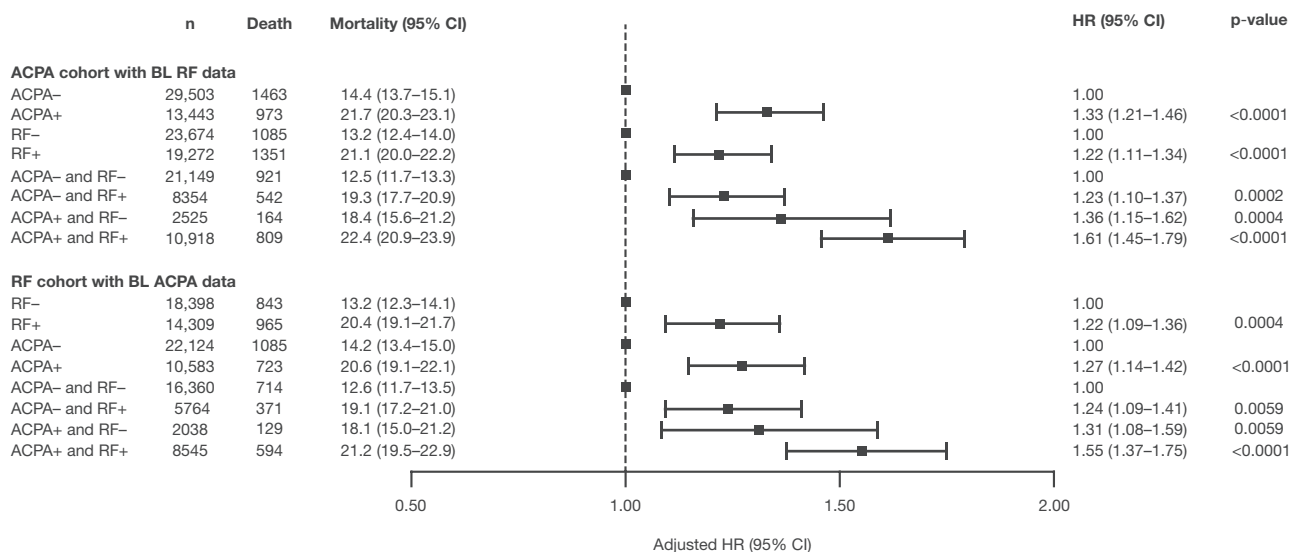

Figure 2. Association between anti–citrullinated protein antibody (ACPA) and rheumatoid factor (RF) and mortality in an analysis of data from patients with ACPA and/or RF seropositivity. 95% CI = 95% confidence interval; HR = hazard ratio; BL = baseline (the time period of within 180 days before and 30 days after the index date).

positive smoking status, and presence of chronic obstructive pulmonary disease significantly elevated in the seropositive versus seronegative patients (*P* < 0.001) (Table 1).

The ACPA patient category had 184,170 patient-years of follow-up; 5.7% of patients (3,074 of 53,849) died and the incidence rate for mortality was 16.7 per 1,000 patient-years (95% confidence interval [95% CI] 16.1–17.3). The RF patient category had 297,830 patient-years of follow-up; 6.5% of patients (5,210 of 79,926) died and the incidence rate for mortality was 17.5 per 1,000 patient-years (95% CI 17.0–18.0). ACPA and RF positivity were both associated with a significant increase in mortality risk (*P* < 0.0001 for both) (Table 2).

In the ACPA group with baseline RF data, ACPA positivity was associated with increased mortality compared with RF positivity (Figure 2). Mortality risk was the highest with double ACPA and RF positivity (ACPA and RF double-positive versus ACPA and RF double-negative group hazard ratio [HR] 1.61 [95% CI 1.45–1.79]). Single ACPA positivity was generally associated with a higher risk than single RF positivity (Figure 2). In the RF group with baseline ACPA data, the highest mortality risk was also observed in the ACPA and RF double-positive group (HR versus ACPA and RF double-negative group 1.55 [95% CI 1.37–1.75]), and a higher risk in RF-positive patients compared with RF-negative patients (HR versus RF-negative group 1.22 [95% CI 1.09–1.36]). All other combinations of the presence of ACPA and RF were associated with a significantly increased mortality risk compared with ACPA and/or RF seronegativity (Figure 2).

Mortality risk positively correlated with titers of ACPA and RF and was the highest in groups comprising patients with the highest titers for both ACPA (HR versus ACPA-negative group 1.60 [95% CI 1.45–1.76]) and RF (HR versus RF-negative group 1.78 [95% CI 1.66–1.91]). Findings were consistent when combining all groups, with adjusted HRs of 1.48 (95% CI 1.37–1.60) in ACPA-positive patients versus ACPA-negative patients and 1.44 (95% CI 1.36–1.53) in RF-positive patients versus RF-negative patients.

Figure 3. Kaplan-Meier curve for differences in mortality over time between anti–citrullinated protein antibody (ACPA) positivity/negativity (**A** and **C**) and rheumatoid factor (RF) positivity/negativity (**B** and **D**) scores (both databases) after 1:1 propensity-score matching. n = total numbers of patients for the 2 groups. The hazard ratio (HR) is from a Cox model with the ACPA or RF variable only. Propensity scores were calculated for ACPA positivity versus ACPA negativity and RF positivity versus RF negativity based on all covariates. Covariates included age, sex, region, number of physician office visits during the past 3 months, an indicator variable for 714.0x diagnosis, an indicator variable for RA diagnosis before ACPA or RF testing, past hospitalization, use of medications (steroids, nonsteroidal antiinflammatory drugs, salicylates), use of disease-modifying antirheumatic drugs (if applicable), and comorbidity conditions. 95% CI = 95% confidence interval.
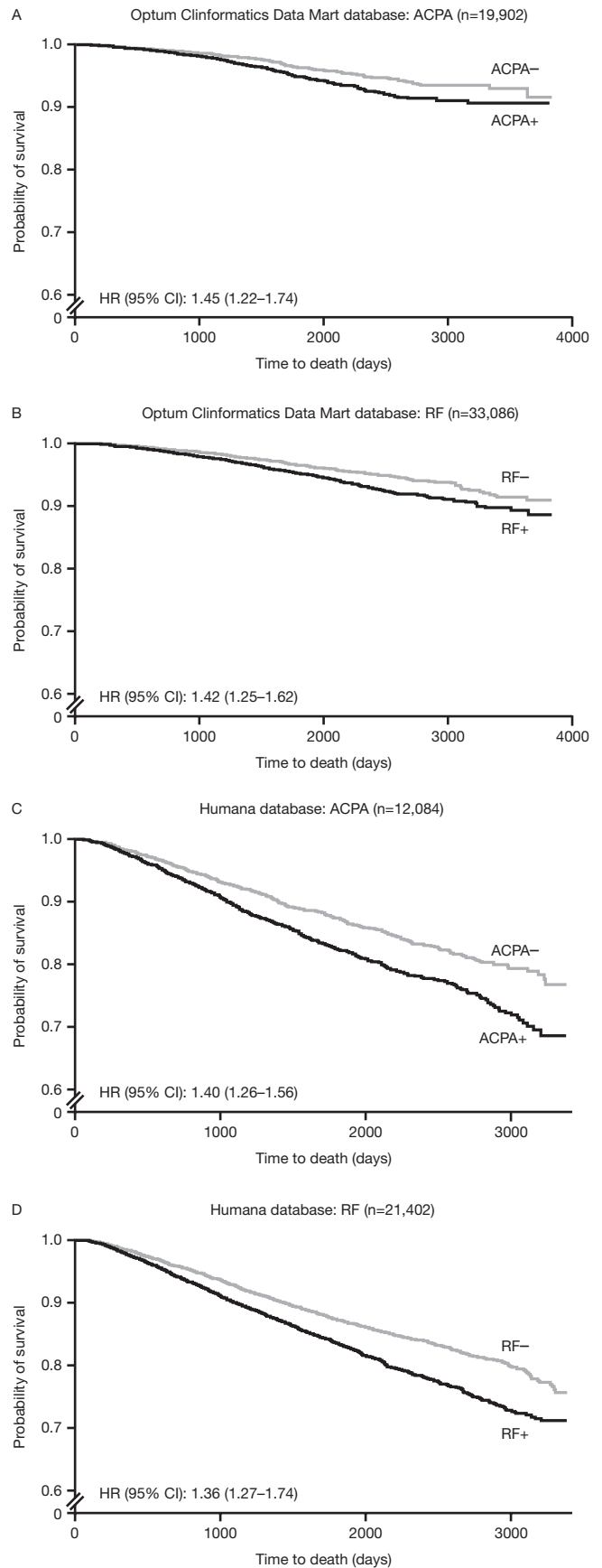
Following propensity-score matching, survival curves comparing patients with available ACPA and RF serostatus from each database showed similar patterns of divergence (Figure 3). Single ACPA and RF negativity were associated with a higher survival rate in patients than ACPA and RF positivity. For ACPA-positive versus -negative patients, the HR was 1.45 (95% CI 1.22–1.74) for the Optum Clinformatics Data Mart database and 1.40 (95% CI 1.26–1.56) for the Humana database. For RF-positive versus -negative patients, the HR was 1.42 (95% CI 1.25–1.62) in the Optum Clinformatics Data Mart database and 1.36 (95% CI 1.27–1.47) in the Humana database.

ACPA and RF single-positive patients receiving cDMARDs had a statistically significant increase in mortality risk (ACPA HR 1.52 [95% CI 1.32–1.74]; RF HR 1.47 [95% CI 1.30–1.67]; both versus seronegative subcohorts). Patients with single ACPA or RF positivity receiving cDMARDs had, respectively, a 46% and 62% increased mortality risk versus patients with double ACPA and RF negativity (Figure 4). ACPA and RF single-positive patients receiving bDMARDs had no increase in mortality risk compared with ACPA- and RF-negative patients (ACPA HR 1.03 [95% CI 0.67–1.59]; RF HR 1.22 [95% CI 0.80–1.85]) (Figure 4). Further results from a sensitivity analysis performed to explore the potential for selection bias are available in Section 1 of Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24071/abstract.

DISCUSSION

This study investigated the association between ACPA and RF autoantibody titers and mortality in patients with RA, and the impact of treatment with DMARDs on this association. Both ACPA and RF single seropositivity and double seropositivity

were associated with a decreased survival rate, which positively correlated with the ACPA and RF autoantibody titer. In DMARD-exposed patients, those with single ACPA or RF positivity receiving cDMARDs had a statistically significant increase in mortality risk versus double-negative ACPA and RF patients exposed to cDMARDs, whereas no increased mortality risk was observed in the bDMARD-exposed patients with single ACPA or RF positivity versus those with double ACPA and RF negativity.

In this study, ACPA and RF positivity were independently associated with a greater mortality risk than ACPA and RF negativity; this finding was seen consistently across 2 databases (data not shown). Despite ACPA being found to predict mortality independently of RF, when combined with RF the impact on mortality was greater, a finding consistent with a preceding report (25). Both ACPA and RF positivity were associated with increased all-cause mortality risk in patients with RA, while previously only RF positivity has been linked to increased overall mortality risk (26,27). However, these previous reports analyzed a markedly lower number of patients compared with the current study, and the patient population employed was exclusively from Europe (UK, The Netherlands, and Sweden).

Contrary to findings previously reported (25), higher titers of both autoantibodies were found to be associated with increased risk of mortality in our analysis. One possible explanation for this difference was that the study by Humphreys et al (25) limited their analysis to only patients with early inflammatory arthritis, whereas in our study, patients with established RA were included. Additionally, as outlined above, the sample size and geographical region differed from those of the present analysis.

We found that the associations between ACPA and RF with mortality seen in the overall patient population were also evident in patients treated with cDMARDs but not in those receiving bDMARDs. This is an interesting finding, particularly
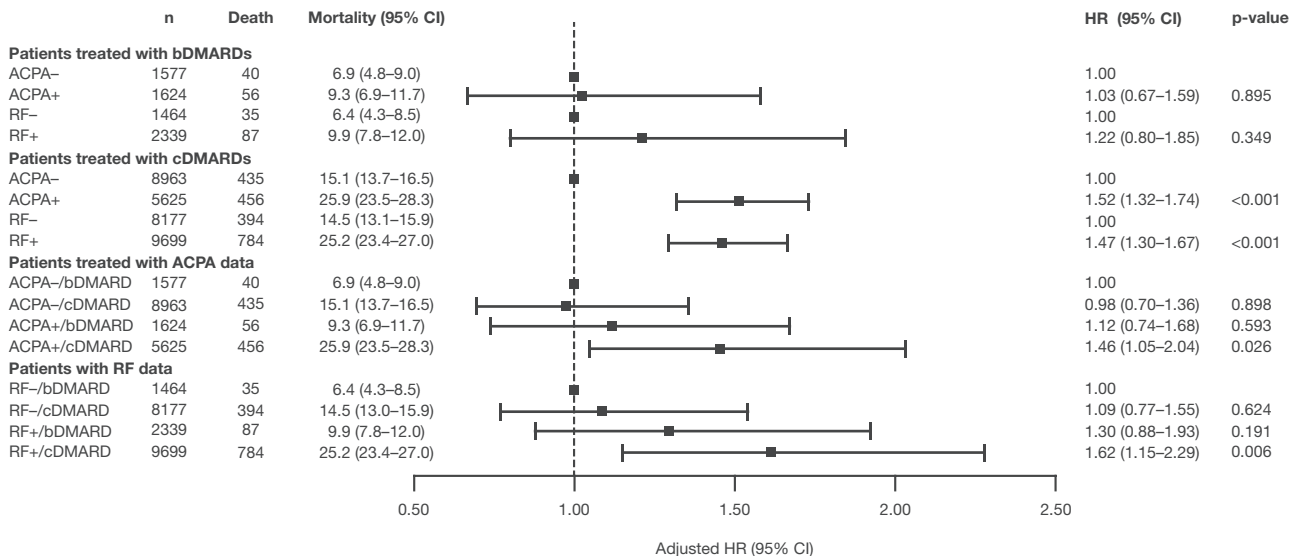
	n	Death	Mortality (95% CI)		HR (95% CI)	p-value
Patients treated with bDMARDs						
ACPA–	1577	40	6.9 (4.8–9.0)		1.00	
ACPA+	1624	56	9.3 (6.9–11.7)		1.03 (0.67–1.59)	0.895
RF–	1464	35	6.4 (4.3–8.5)		1.00	
RF+	2339	87	9.9 (7.8–12.0)		1.22 (0.80–1.85)	0.349
Patients treated with cDMARDs						
ACPA–	8963	435	15.1 (13.7–16.5)		1.00	
ACPA+	5625	456	25.9 (23.5–28.3)		1.52 (1.32–1.74)	<0.001
RF–	8177	394	14.5 (13.1–15.9)		1.00	
RF+	9699	784	25.2 (23.4–27.0)		1.47 (1.30–1.67)	<0.001
Patients treated with ACPA data						
ACPA–/bDMARD	1577	40	6.9 (4.8–9.0)		1.00	
ACPA–/cDMARD	8963	435	15.1 (13.7–16.5)		0.98 (0.70–1.36)	0.898
ACPA+/bDMARD	1624	56	9.3 (6.9–11.7)		1.12 (0.74–1.68)	0.593
ACPA+/cDMARD	5625	456	25.9 (23.5–28.3)		1.46 (1.05–2.04)	0.026
Patients with RF data						
RF–/bDMARD	1464	35	6.4 (4.3–8.5)		1.00	
RF–/cDMARD	8177	394	14.5 (13.0–15.9)		1.09 (0.77–1.55)	0.624
RF+/bDMARD	2339	87	9.9 (7.8–12.0)		1.30 (0.88–1.93)	0.191
RF+/cDMARD	9699	784	25.2 (23.4–27.0)		1.62 (1.15–2.29)	0.006

0.50   1.00   1.50   2.00   2.50

Adjusted HR (95% CI)

Figure 4. Association between anti–citrullinated protein antibody (ACPA) and rheumatoid factor (RF) and mortality among patients treated with biologic disease-modifying antirheumatic drugs (bDMARDs) and conventional DMARDs (cDMARDs) and with ACPA or RF seropositivity. 95% CI = 95% confidence interval; HR = hazard ratio.

for bDMARDs, because these are generally used later in the disease process when patients would be expected to have higher disease activity versus those treated with cDMARDs (7). Therefore, if mortality was driven by baseline disease, one would hypothesize that patients treated with bDMARDs would be at a higher risk of mortality versus those treated with cDMARDs. The effect-modifying role of bDMARDs observed in our analysis could possibly be due to the systemic antiinflammatory effects and disease-modifying aspect of these agents. There is some evidence to suggest that bDMARDs with different mechanisms of action may be effective in various populations based on patient serostatus (16,28,29); an effect of bDMARD therapy on seropositivity has also been shown (20,21). However, how these effects on ACPA and disease activity translate into differences in mortality risk is unknown. Overall, although an impact of treatment with bDMARDs on the association between ACPA and RF and mortality was suggested, additional direct studies are needed to explore this further.

The findings reported here may provide understanding of the impact of therapy on disease course and mortality in RA and may enable physicians to make informed treatment decisions. However, further investigations are warranted, particularly to fully confirm the notion that bDMARDs may have an impact on mortality in seropositive patients with RA.

This study has some important strengths. Retrospective data provide insights into the real-world management of patients with RA in the clinical setting, without the constraints and limitations of a randomized controlled trial. Furthermore, the large sample size from the 2 databases analyzed here has the potential to provide generalizable results. However, observational studies, by design, do have certain limitations: namely, the absence of randomization makes extrapolation of findings to a randomized controlled trial setting impossible. While the current study has the limitation of using administrative databases, it also has the advantage of controlling for measured confounding using a propensity score–based method. Additional analyses are warranted, including evaluation of the association of disease activity and mortality.

In conclusion, elevated ACPA and RF titers were independently associated with increased mortality among patients diagnosed with RA. The mortality risk was greater in patents with higher ACPA and RF titers. The association persisted in patients treated with cDMARDs but not in those treated with bDMARDs.

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 submitted for publication. Dr. Alemao 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. Alemao, Weinblatt, Shadick.
Acquisition of data. Alemao, Shadick.
Analysis and interpretation of data. Alemao, Weinblatt, Bao, Shadick.

ROLE OF THE STUDY SPONSOR

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