

## Original article

**Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis****Veena K. Ranganath<sup>1</sup>, Paul Maranian<sup>1</sup>, David A. Elashoff<sup>2</sup>, Thasia Woodworth<sup>1</sup>, Dinesh Khanna<sup>3</sup>, Theodore Hahn<sup>4</sup>, Catherine Sarkisian<sup>4</sup>, Joel M. Kremer<sup>5</sup>, Daniel E. Furst<sup>1,\*</sup> and Harold E. Paulus<sup>1,\*</sup>****Abstract**

**Objective.** To evaluate the impact of comorbidities on achieving remission by examining changes in the clinical disease activity index (CDAI) in RA patients in the community-based Consortium of Rheumatology Researchers of North America (CORRONA) registry.

**Methods.** A subcohort of 1548 RA subjects with varying disease duration met the following inclusion criteria: started a DMARD/biologic agent, continued therapy  $\geq 3$  months, CDAI  $\geq 2.8$  at study entry and followed longitudinally from baseline to follow-up (mean time 7.46 months). Patients reported comorbidities according to a standardized list of 33 conditions. Entry characteristics were compared across age categories using one-way analysis of variance. Linear and logistic regression models were constructed to assess characteristics [e.g. age, disease duration, number of previous DMARDs/biologics, baseline modified health assessment questionnaire (MHAQ), baseline CDAI and number of comorbidities] associated with primary outcomes: change in CDAI (baseline to follow-up) and CDAI remission (yes/no).

**Results.** Although disease activity measures at entry were similar across age categories, older patients had more comorbidities, less improvement in CDAI/MHAQ and were less likely to attain remission at follow-up. However, after adjusting covariates an increasing number of patient-reported comorbidities and higher baseline CDAI (but not age) were consistently and independently associated with a lower likelihood of clinical improvement or remission ( $P < 0.001$ ).

**Conclusion.** In this observational cohort of community RA patients an increasing number of patients reported comorbidities, independently correlated with less CDAI improvement over time. These results reaffirm that comorbidities may be an important factor in consideration of treat-to-target recommendations and aid in understanding achievable RA therapeutic goals.

**Key words:** comorbidities, rheumatoid arthritis, age, remission.

**Introduction**

The advent of biologic agents has increased expectations for therapeutic response in RA, and remission has been

proposed as a reasonable and highly desirable target for treatment results in all patients. Recently there has been international interest in the development of treat-to-target guidelines to facilitate tighter control of RA disease activity [1]. Studies demonstrate that achieving remission and low disease activity improves function, limits disability and perhaps limits comorbidities commonly associated with RA, thus these targets are reasonable to guide treatment decisions. However, the risk-benefit ratio of striving to achieve such goals requires consideration as well. Incorporation of comorbidities, long disease duration, drug-related risks, shared physician-patient decision making and chronological age are clearly important factors that require adjustments of treatment target goals [1].

Comorbid medical conditions commonly coexist with RA and frequently require management with additional

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medications and monitoring. Ageing may add another layer of complexity in the management of the RA patient, especially to mitigate adverse events and drug toxicities [2–5]. Approximately one-third of all RA patients in the United States are older than 65 [6, 7], and there is the expectation that these numbers will increase.

Several studies in RA have analysed age and comorbidities cross-sectionally [8–12], suggesting that functional status and disease activity measures are worse in older RA patients with a greater number of comorbidities. In contrast, older and younger RA patients respond comparably to therapeutic interventions depending on disease duration in controlled clinical trials, where all subjects must satisfy the same entry criteria [13–15]. Nevertheless, physicians in clinical practice tend to treat older RA patients less aggressively [16–19].

In contrast to patients participating in clinical trials, many patients seen in rheumatology practice have multiple comorbidities and would have been excluded from such trials. It is important to know how this group of patients responds to therapeutic interventions in RA. We hypothesized that older patients and/or patients with more comorbidities are less likely to achieve clinical remission, regardless of disease duration, possibly associated with less aggressive treatment. This hypothesis was tested in a large, prospective observational study of RA patients, the Consortium of Rheumatology Researchers of North America (CORRONA), who were started on a DMARD or biologic agent.

## Patients and methods

The CORRONA database is a prospective observational cohort and was assembled with the intention of facilitating cohort studies in rheumatological diseases (RA, PsA, undifferentiated arthritis) by accumulating longitudinal data representing community patients with rheumatic disease. This registry began in October 2001 and continues to recruit and follow patients from both academic and private practice sites. Details of this registry have been published previously [20–24]. All patients provided written informed consent prior to being enrolled in the cohort. In addition, the UCLA Institutional Review Board granted approval for performing this study.

### Patient population

Data from the CORRONA registry from October 2001 to August 2007 was included in the database for these analyses. RA patients were from 76 different sites and >200 rheumatologists in the USA. At entry, patients completed a patient enrolment form, which includes information regarding medical and surgical history, family history, review of systems, medication use, assessment of pain and global arthritis activity on a visual analogue scale (VAS) and a modified health assessment questionnaire (MHAQ) [25]. Patients reported comorbidities according a standardized list of 33 comorbid conditions on the enrolment form. The treating rheumatologist also recorded detailed information on drug utilization, with any new starts or changes in dose at the time of registration and at each

clinical encounter. Standard physician-derived measures include the 28 tender joint count (TJC), 28 swollen joint count (SJC) and physician global assessment (0–100 VAS). At follow-up visits, patients and physicians completed follow-up questionnaires of joint counts, VAS assessments, MHAQ and details reported elsewhere [20–24]. The gross number of patient-reported comorbidities was used in this cohort, as seen in other clinical studies [10, 11]. Published studies have shown high agreement between patient-reported and physician-reported comorbidities [26–29].

### Prespecified cohort

For our analysis, a subset of patients was selected from the CORRONA RA cohort in order to test the hypotheses, and prior to the performance of any analyses. Within the CORRONA database there were a total 14 811 RA patients; however, a majority of patients did not meet the pre-specified cohort criteria. Among the 4937 patients who started a DMARD/biologic agent, there were a total of 1658 patients who did not modify their RA medication regimen during the baseline to follow-up period of at least 3 months. A total of 1548 RA patients met the criteria of  $\geq 3$  months of treatment with the new DMARD/biologic, without changing background RA treatment, and were not in remission at baseline (CDAI  $\geq 2.8$ ). These criteria were used to develop a stringent homogeneous subcohort.

### Predictors of response

Change in CDAI (baseline to follow-up), change in CDAI disease activity category (baseline to follow-up) and CDAI remission at follow-up were the primary outcome measures used to evaluate disease activity. The baseline visit is defined as the visit when a change in therapy was instituted. CDAI is calculated by adding the sum of TJC and SJC as well as patient global and physician global assessment using a 10-cm VAS [CDAI = SJC28 + TJC28 + patient global (in cm) + physician global (in cm)]. Unlike the DAS28, it does not require an acute-phase reactant test result. Remission is defined as a score  $< 2.8$ , mild disease activity between 2.8 and 10, moderate disease activity between 11 and 22 and severe disease activity  $> 22$  [30].

The following clinical and laboratory factors were considered as potential baseline predictors of treatment response: disease duration, age, number of patient-reported comorbidities, time from baseline to follow-up, gender, prednisone use, number of prior DMARDs, physician global assessment, SJC, TJC, ESR, baseline CDAI, baseline MHAQ, RF positivity, ethnicity and education. Patients were subdivided based on age categories as follows:  $< 45$ , 45–65 and  $> 65$  years. DMARD/biologic agents were categorized into three groups: (i) HCQ, minocycline, AZA, cyclosporine (CYC), D-Pen or sulphasalazine (SSZ); (ii) MTX or LEF and (iii) TNF inhibitor or other biologic agent. HCQ and minocycline were combined with other DMARDs in group (i) due to the small numbers of patients who were started on these agents.

## Statistics

Patients were categorized based on age as follows: <45, 45–65 and >65 years. Demographic and clinical characteristics at entry were compared across age categories using one-way analysis of variance (ANOVA) or  $\chi^2$  tests as appropriate. Change scores of disease activity measures from baseline to follow-up were also compared across age groups using one-way ANOVA. The individual comorbidities (each with a weight of 1) were summed to calculate the total number of patient-reported comorbidities (range 0–33). For purposes of modeling, quintiles were reported to better describe the impact of increasing comorbid conditions on the outcome measures.

Multiple linear regression analyses were performed to assess the simultaneous effect of combinations of predictors on the change in CDAI. Multiple logistic regression models were created to evaluate predictors of CDAI remission and change in CDAI category. The components of CDAI (i.e. SJC, physician global, etc.) were not used in the models due to collinearity. Age, race, treatment variables, gender, disease duration, baseline MHAQ and baseline CDAI were included as covariates in each of the models. Interaction effects between patient-reported comorbidities with age categories, baseline CDAI categories and disease duration were also evaluated in the linear and logistic models.

## Results

### Baseline demographics and clinical measures

In the cohort the mean age was 58.1 (s.d. 13, range 19–91) years and the mean number of patient-reported comorbidities was 5.6 in the entire cohort (s.d. 3.3, range 0–22). Several demographic factors captured at registry entry were statistically different across the age groups (Table 1).

Increased age (across the age groups) was significantly associated with an increased percentage of male gender patients, longer disease duration and greater number of comorbidities ( $P \leq 0.001$ ). The mean number of comorbidities in the oldest group was almost double that in the youngest group (mean 6.7 vs 3.7,  $P < 0.001$ ). Disease duration was greater in the >65 age group compared with the <45 age group (mean 14.1 vs 5.6 years,  $P < 0.001$ ).

Older RA patients were less likely to start a biologic agent than younger patients (44% vs 60%,  $P = 0.003$ ; Table 1). However, the distribution of the types of DMARD/biologic agents started did not significantly differ across three categories of the number of patient-reported comorbidities (0–2, 3–5 and >5 comorbidities;  $P = 0.78$ ). In addition, older RA patients were more likely to be taking prednisone; approximately 45% in patients >65 years vs 36% in patients <45 years ( $P = 0.03$ ).

Overall, in these patients who were starting a new DMARD/biologic agent, most disease activity measures were clinically similar across the age categories at baseline (Table 1). Although the swollen joint count was statistically significantly different across age categories, the difference across groups was minimal (mean 7.0 in the

<45 years age group vs 7.6 in the  $\geq 65$  years age group,  $P = 0.01$ ). ESR increased with age in this cohort as well. At baseline, CDAI, physician global VAS, patient global VAS, pain VAS, number of minutes of morning stiffness, fatigue and TJC28 were similar in the three age groups. The mean MHAQ was statistically significantly higher in the 45–64 years age category (mean 0.52), and age categories <45 and  $\geq 65$  years both had the same mean MHAQ of 0.44 ( $P < 0.001$ ).

### Patient-reported comorbidities

Supplementary data (available at *Rheumatology* Online) describes the frequency of each of the 33 patient-reported comorbid conditions in the RA cohort. Of the 33 reported conditions, hypertension (HTN), back problems, dry mouth/eyes, gastroesophageal reflux disease (GERD), OA, anaemia, chronic obstructive pulmonary disease (COPD) and depression made up the highest frequencies, ranging from 26% to 38% for each. The conditions with a frequency <5% included myocardial infarction, gastrointestinal bleed, stroke, skin cancers, SLE, alcoholism, other mental disease and Parkinson's disease.

### Changes in disease activity measures over time

The duration of follow-up for this cohort ranged from 3.01 to 43.80 months, with the mean duration of follow-up being 7.46 months overall. These patients had been followed in CORRONA for varying periods of time prior to qualifying for the cohort analyses. CDAI remission at follow-up was significantly less likely in the older age group in comparison with the younger RA group (11% vs 20%,  $P = 0.01$ ) (Table 2). The patients in the older age category also improved less overall than the patients in the younger group (–5.9 vs –8.6,  $P < 0.01$ ). Patients were categorized into low, moderate and severe disease activity states based on their CDAI disease status at baseline and at follow-up. Patients improved if they moved to a lower disease activity category, worsened if they moved to a higher disease activity category and were unchanged if the disease activity category remained unchanged. Older patients were less likely to improve a CDAI category; 57% of patients in the <45 years age group improved a disease activity category compared with 44% in the  $\geq 65$  years age group ( $P = 0.045$ ). MHAQ improvement was shown to have less improvement in the older age category than the other two (–0.09 vs –0.05,  $P = 0.02$ ). Other disease activity measure changes were similar across the age categories. The time between baseline and follow-up assessments was similar across the age groups (Table 2).

Fig. 1A describes the unadjusted relationship among the number of patient-reported comorbid conditions (range 0–33) and the percentage of patients achieving CDAI remission (not adjusted for baseline factors). As the number of comorbidities decreases, the chance that an RA patient will achieve remission increases, as seen for increasing disease duration. Patients with more than eight comorbid conditions had <10% chance of attaining remission, compared with patients with zero to two comorbidities, who had a 22.5–26% chance. Fig. 1B depicts the

**TABLE 1** Baseline characteristics and details of DMARD/biologic started by age and comorbidities (*n* = 1548)

Baseline characteristics	Age <45 years ( <i>n</i> = 217), mean/% (s.d.)	Age 45–64 years ( <i>n</i> = 823), mean/% (s.d.)	Age ≥ 65 years ( <i>n</i> = 488), mean/% (s.d.)	<i>P</i> -value
Age, years	36.9 (6.2)	55.1 (5.6)	72.6 (6)	
Disease duration, years	5.6 (4.7)	11.0 (9.4)	14.1 (12.2)	<0.001
RF/CCP ab, %	74	74	77	0.60
Gender, % female	88.48	75.82	71.31	<0.001
Current smoker, %	21.6	19.08	7.76	<0.001
BMI	29.1 (7.7)	30.3 (7.5)	28.3 (6.4)	<0.001
Race, %				0.09
White	81.52	84.4	86.83	
Other	18.48	15.60	13.17	
No. comorbidities (0–33)	3.7 (2.6)	5.5 (3.2)	6.7 (3.4)	<0.001
No. prior DMARDs	2.1 (1.5)	2.3 (1.7)	1.83 (1.7)	<0.001
Prednisone dose, %				<0.001
No prednisone use	64	62	55	
1–5 mg	6	10	17	
5–10 mg	15	18	20	
≥10 mg	13	9	9	
ESR	23.9 (18)	26.6 (22)	34.4 (26.8)	<0.001
Stiffness, min	80 (124)	100 (180)	85.0 (174.8)	0.13
TJC 28	7.3 (7.2)	6.4 (6.7)	6.0 (6.4)	0.16
SJC 28	7.0 (6.8)	7.2 (6.3)	7.6 (6.3)	0.01
MD global VAS	34.4(22.3)	34.8 (21)	35.6 (21.3)	0.12
Patient global VAS	38.3 (23.1)	42.1 (26)	40.0 (26.7)	0.25
Pain VAS	41.4 (24.6)	43.1 (26)	42.1 (26.5)	0.051
MHAQ	0.44 (0.5)	0.52 (0.5)	0.44 (0.5)	<0.001
CDAI	21.5 (14)	21.3 (13)	21.1 (13)	0.52
CDAI mild, %	23.0	21.5	24.4	0.80
CDAI moderate, %	36.9	37.4	35.0	
CDAI severe, %	40.1	41.1	40.6	

Details of DMARD/biologic started by age and comorbidities				
	Age <45 years ( <i>n</i> = 217), %	Age 45–64 years ( <i>n</i> = 823), %	Age ≥65 years ( <i>n</i> = 488), %	<i>P</i> -value
DMARD started, %				0.003
HCQ, minocycline, AZA, CYCL, c-PEN, SSZ	12.44	15.92	17.21	
MTX, LEF	28.11	32.93	38.93	
Biologic agent	59.45	51.15	43.85	

	Comorbidity 0–2 ( <i>n</i> = 550), %	Comorbidity 3–5 ( <i>n</i> = 612), %	Comorbidity >5 ( <i>n</i> = 386), %	<i>P</i> -value
DMARD started, %				0.78
HCQ, minocycline, AZA, CYCL, c-PEN, SSZ	14.4	16.3	17.4	
MTX, LEF	34	34	33.4	
Biologic agent	51.6	49.7	49.2	

unadjusted relationship between the patient’s age and the percentage of patients achieving CDAI remission as already described in Table 1. The figures demonstrate an inverse linear relationship between the number of comorbid conditions and the probability of attaining CDAI remission.

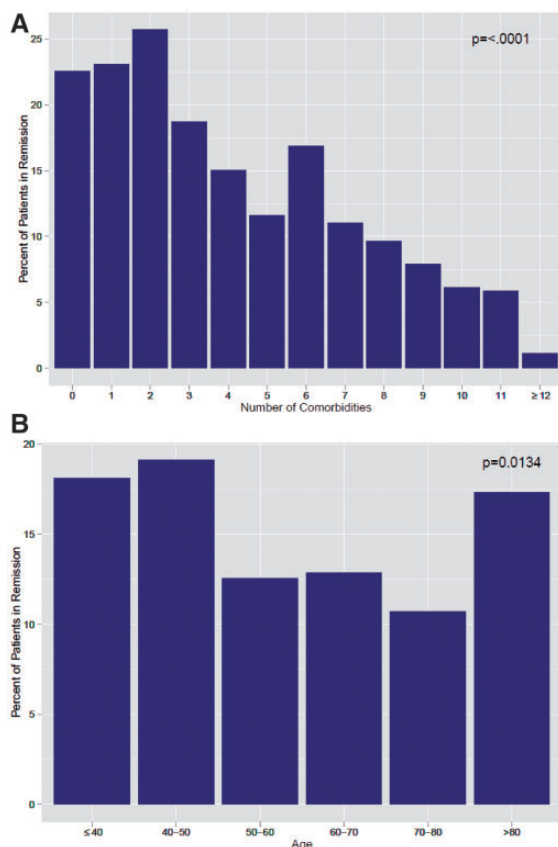
In addition, we evaluated the unadjusted probability of attaining CDAI remission as modified by interactions between the comorbidity measure and age. This was done to assess whether the effect of comorbidity is consistent across age and baseline CDAI disease activity categories. Fig. 2 illustrates the unadjusted relationship between CDAI remission and the number of comorbid conditions

across the three different age categories. There was a statistically significant relationship between remission achievement and number of comorbidities for the age groups 45–65 and >65 years. When adjusted for other covariates, the significance seen in the figure disappeared [*P* = 0.93 for comorbidity × age (45–64 years) and *P* = 0.85 for comorbidity × age (≥ 65 years)]. For completeness, we evaluated the interaction effect of the number of patient-reported comorbidities with other variables known to influence remission rates, baseline CDAI and disease duration. Similarly we did not see statistically significant interaction effects (all *P* > 0.09).

TABLE 2 Change scores from baseline to follow-up

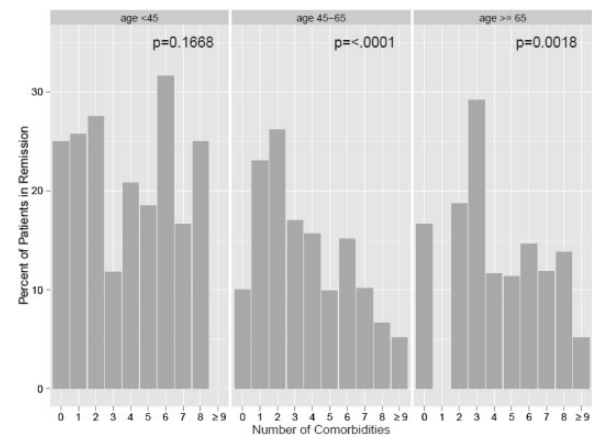
	Age <45 years (n = 217), mean (s.d.)	Age 45–64 years (n = 823), mean (s.d.)	Age ≥65 years (n = 488), mean (s.d.)	P-value
ESR	−7.2 (15.7)	−4.07 (16)	−6.82 (20.1)	0.08
TJC28	−3.81 (6.9)	−2.64 (6.9)	−2.41 (7.0)	0.001
SJC28	−2.61 (6.2)	−2.32 (5.5)	−2.01 (5.9)	0.16
Physician global VAS	−13.4 (22.4)	−12.9 (20.8)	−11.4 (21.2)	0.15
Patient global VAS	−8.34 (26.7)	−9.83 (27.8)	−7.39 (27.2)	0.10
MHAQ	−0.09 (0.33)	−0.09 (0.38)	−0.05 (0.38)	0.02
CDAI	−8.57 (14.2)	−7.22 (13.1)	−5.93 (13.5)	0.003
CDAI remission, %	19.82	13	11.27	0.01
CDAI category				0.045
Improve, %	57	50.7	44.42	
No change, %	33.33	38.75	43.05	
Worsen, %	9.66	10.55	12.53	
Time baseline to follow-up, months	7.32 (3.6)	7.35 (3.5)	7.66 (3.9)	0.08

FIG. 1 Unadjusted relationship percentage of patients achieving CDAI remission for the number of (A) patient-reported comorbidities and (B) patient age.



P-value represents unadjusted association (logistic regression) between remission and either (A) comorbidities or (B) age.

FIG. 2 Equal rates of remission based on the number of comorbidities and three age categories.



P-value represents the unadjusted association (logistic regression) between remission and comorbidities within each age strata.

### Multivariate analyses

Patient-reported comorbidities and age were evaluated in the multivariate models as continuous and as categorical variables, yielding very similar results. Comorbidities were categorized as the closest approximation to quintiles across the cohort (see the Statistics section). These categories were incorporated in the models.

The results of the multivariate linear regression analysis for change in CDAI demonstrated that fewer comorbidities, white race and higher baseline CDAI were associated with a greater improvement in CDAI (Table 3). For example, when evaluating the change in CDAI from baseline to follow-up in the model, the improvement in CDAI was 3.89 units greater in patients with three or fewer

**TABLE 3** Multivariate linear model for change in CDAI (baseline to follow-up) and logistic model for CDAI remission

Linear model for change in CDAI		
	$\beta$ -coefficient (s.e.)	P-value
Age, years	0.02 (0.02)	0.48
4 comorbidities <sup>a</sup>	0.88 (0.98)	0.37
5–6 comorbidities <sup>a</sup>	0.74 (0.83)	0.37
7–8 comorbidities <sup>a</sup>	2.79 (0.95)	0.003
≥9 comorbidities <sup>a</sup>	3.89 (0.98)	<0.001
Baseline CDAI	−0.68 (0.02)	<0.001
Baseline MHAQ	0.93 (0.67)	0.17
Female	0.99 (0.71)	0.16
White	−2.27 (0.81)	0.005
RA duration, years	0.02 (0.03)	0.60
MTX, LEF <sup>b</sup>	1.23 (0.87)	0.16
Biologics <sup>b</sup>	−0.32 (0.84)	0.70
Prednisone	−0.56 (0.6)	0.35

Logistic model for CDAI remission (≤2.8)		
	OR (95% CI)	P-value
Age, years	1 (0.99, 1.01)	0.10
4 comorbidities <sup>a</sup>	0.82 (0.49, 1.37)	0.45
5–6 comorbidities <sup>a</sup>	0.73 (0.47, 1.15)	0.17
7–8 comorbidities <sup>a</sup>	0.63 (0.36, 1.11)	0.11
≥9 comorbidities <sup>a</sup>	0.29 (0.13, 0.62)	0.001
Baseline CDAI	0.97 (0.95, 0.98)	<0.001
Baseline MHAQ	0.76 (0.48, 1.19)	0.23
Female	0.7 (0.48, 1.03)	0.07
White	1.31 (0.8, 2.16)	0.29
RA duration, years	0.94 (0.92, 0.97)	<0.001
MTX, LEF <sup>b</sup>	1.03 (0.62, 1.71)	0.90
Biologics <sup>b</sup>	1.4 (0.87, 2.27)	0.17
Prednisone	0.79 (0.55, 1.13)	0.19

Logistic model for improvement of CDAI category		
	OR (95% CI)	P-value
Age, years	0.99 (0.98, 1)	0.25
4 comorbidities <sup>a</sup>	0.8 (0.55, 1.19)	0.27
5–6 comorbidities <sup>a</sup>	0.85 (0.62, 1.19)	0.35
7–8 comorbidities <sup>a</sup>	0.64 (0.44, 0.94)	0.02
≥9 comorbidities <sup>a</sup>	0.62 (0.42, 0.92)	0.02
Baseline CDAI	1.03 (1.02, 1.04)	<0.001
Baseline MHAQ	0.85 (0.65, 1.12)	0.25
Female	0.71 (0.54, 0.95)	0.02
White	1.21 (0.88, 1.67)	0.24
RA duration, years	1 (0.98, 1.01)	0.54
MTX, LEF <sup>b</sup>	0.94 (0.67, 1.32)	0.72
Biologics <sup>b</sup>	1.3 (0.93, 1.81)	0.12
Prednisone	1.25 (0.99, 1.59)	0.07

<sup>a</sup>In reference to ≤3 comorbidities. <sup>b</sup>In reference to other DMARDs (i.e. plaquinel, SSZ, etc.).

comorbidities as compared with patients with nine or more comorbidities. Age, category of DMARD/biologic agent and prednisone use were not independently associated with the change in CDAI.

The multivariate logistic analysis for likelihood of attaining CDAI remission demonstrated that patients with fewer comorbidities, shorter disease duration and higher CDAI baseline scores were more likely to achieve remission (Table 3). For patients with nine or more comorbidities, the odds of achieving remission decreased by 71% when compared with patients with three or fewer comorbidities ( $P=0.001$ ).

Another logistic multivariate analysis was performed for improvement in CDAI category (i.e. improving from severe to moderate disease activity, moderate to low, etc., Table 3). Fewer comorbidities and baseline CDAI were significantly associated with improvement in CDAI category. Interestingly, the number of comorbidities did not appear to influence whether a biologic was started. Nevertheless, patients who had seven to eight comorbidities and nine or more comorbidities had a respective 36% ( $P=0.02$ ) and 38% ( $P=0.02$ ) decreased odds of improving a disease activity category.

MHAQ was not significantly associated with any of the three outcomes of interest after adjusting for other covariates (Table 3), despite evidence that baseline and change in MHAQ was different across the age groups (Tables 1 and 2). Overall, baseline CDAI and the number of patient-reported comorbidities (not age) were consistently significantly related to all three outcomes of interest: change in CDAI, CDAI remission and improvement of CDAI category.

## Discussion

This prospective analysis of data for a large cohort of patients initiating a new treatment in the CORRONA registry provides a detailed evaluation of the relationship between age and comorbidities on response to therapy after the start of a new DMARD/biologic agent. Overall, older RA patients who tended to have longer disease duration had less improvement in CDAI and were less likely to attain CDAI remission, but age was not a significant independent predictor of response in the multiple regression models. In contrast, the number of patient-reported comorbidities and baseline CDAI were a consistent, statistically significant predictor of response (CDAI remission, change in CDAI and improvement in CDAI category). Regression models demonstrated a dose effect for the comorbidity categories association to the response outcome measures. As an aside, the number of comorbidities did not appear to influence treatment decision making, and our results confirm other reports that rheumatologists may be age-biased in their decision to initiate a biologic (Table 1) [16–19].

The exact pathophysiology by which comorbidities associate with response to treatment is unclear. Perhaps comorbid conditions directly alter the measures we use to assess RA outcomes. For example, concomitant fibromyalgia has been shown to potentially confound RA response measures [31, 32]. Other commonly patient-reported comorbidities that could conceivably influence response measures include OA, back problems and depression.

Our observations in these analyses suggest that in treatment-targeted guidelines aimed at tighter control of RA disease activity, rheumatologists should also consider comorbidities as an important aspect of therapeutic management, as patients with more comorbidities appear less likely to achieve remission. However, specific methods for doing so have yet to be characterized. The results of this study provide evidence that research in this area is needed.

Several published studies have described a cross-sectional relationship between the comorbidities and a reduced probability of remission [8–10]. A large multinational cross-sectional study of 5848 RA patients demonstrated that the number of comorbidities is independently associated with CDAI [odds ratio (OR) 0.75, CI 0.68, 0.83] [10]. Burmester *et al.* [8] evaluated 6610 active RA patients who were treated with adalimumab for 3 months for predictors of achieving remission. Patients with one or no comorbidity had an OR of 0.86 of attaining DAS28 remission compared with those with more than one. Krishnan *et al.* [33] studied a random sample of 1530 Finnish patients in the general population and demonstrated that age and comorbidities correlated with pain and patient global VAS. In a later article, Sokka *et al.* [9] suggested that only 15% of non-RA patients >50 years of age met ACR remission criteria. This suggests that even in a non-RA population, a population where remission should be easier to attain, comorbidities may play a substantial role in negatively impacting the ability to achieve remission.

In addition, several studies have examined the relationship between comorbidities and worsening functional disability [34–38]. Functional disability is an important outcome measure in RA. In 1991 Verbrugge *et al.* [38] evaluated chronic conditions in general in RA and showed a strong relationship between the number of comorbidities and functional disability in a cross-sectional and longitudinal cohort. In a more recent study, Radner *et al.* [36] evaluated the impact comorbidities have on the components of the HAQ in a cross section of 380 RA patients; they suggest that comorbidities may partly account for a portion of irreversible disability. Michaud *et al.* [39] recently reported that age and comorbidities were independently associated with the loss of functional status in RA in a cohort of 18 485 patients in the US National Data Bank for Rheumatic Diseases. Interestingly, our analyses demonstrated that after adjustment of factors known to impact treatment response in RA, MHAQ was not significantly associated with CDAI response, yet patient-reported comorbidities remained consistently associated with various formulations of CDAI response. Clinical trials often exclude older RA patients with multiple comorbid conditions. Our study is distinctive in its prospective quantitation of the influence of comorbidities on therapeutic response in a large community-based RA cohort of patients who started a new DMARD or biologic agent. Several comorbidity indices exist, including the Charlson Comorbidity Index (CCI), Index of Coexistent Disease (ICED), Chronic Disease Score (CDS), Composite Comorbidity Index (CompCI) and Gross Number of Comorbidities [40–43]. The CCI is used to estimate

survival and thus is not appropriate for this study, where response to treatment in terms of disease activity is of interest, not mortality. A recent article describes the CCI's association with RA mortality [44]. In addition, Wolfe *et al.* [45] assessed the prevalence of comorbidities in four rheumatic diseases and the impact of the CompCI. The ICED and CDS are most useful when prescriptions are obtained from electronic pharmacy databases; the information needed to calculate the CCI, ICED and CDS was not captured in the CORRONA database. The evaluation of the gross number of patient-reported comorbidities may be questioned due to possibilities of misclassification [46]. This is a limitation of the study; however, there are some data to support that patient-reported histories are often as accurate as histories recorded by physicians [26–29]. In addition, this specific list of the association of patient-reported comorbidities with response to RA treatment has yet to be validated in another cohort. Lastly, the specific patient-reported comorbidities do not include some comorbidities such as kidney disease and some extra-articular manifestations.

Additional limitations include the fact that the CORRONA database was not specifically designed for the purpose of this study and the results should be corroborated in additional cohorts. In order to overcome this, we identified a cohort of patients in the database to address our hypotheses. Notably, the results described from this cohort cannot be applied to an early RA cohort nor to RA patients with higher disease activity often seen in European registries. The reasons for these features have been reviewed, but they are representative of patients using biologic drugs in the USA, where approximately 45% of patients with RA are receiving biologic agents [47]. Nevertheless, the cohort that we studied had moderate to severe baseline disease activity (mean CDAI 21), probably because they were selected based on initiating a new treatment. In addition, this study evaluated RA patients who remained on the drug for at least 3 months and evaluated the patients after an average of 7 months, emphasizing early response. Despite these limitations, the data provide useful observations that have clinical relevance, especially as they represent results in a largely community-based cohort.

In conclusion, this large prospective cohort of RA patients demonstrates that increasing numbers of comorbidities decrease the likelihood of CDAI improvement and CDAI remission following the institution of a new DMARD/biologic agent. The patient's chronological age was not independently associated with the outcome measures examined in this study cohort. Nevertheless, the decision to start a biologic agent was based to a greater extent on the RA patient's age than on the number of patient-reported comorbidities. These results suggest that older patients with few comorbid conditions are likely to respond better to new treatments than younger patients with multiple comorbidities and should not be deprived of aggressive therapies only because of age. It is of course prudent to keep in mind the risks and benefits for an individual patient as well. Further studies

are needed to gain a better understanding of which specific comorbidities influence response to therapy and factors that influence physicians' treatment decisions in RA.

#### Rheumatology key messages

- RA patients with a greater number of comorbidities are less likely to achieve therapeutic response.
- Age is not independently associated with RA therapeutic response.
- RA treatment decisions may be age-biased rather than based on the number of comorbid conditions.

### Supplementary data

Supplementary data are available at *Rheumatology* Online.

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