ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 4, April 2017, pp 720–727
DOI 10.1002/art.39988

Different Rating of Global Rheumatoid Arthritis Disease Activity in Rheumatoid Arthritis Patients With Multiple Morbidities

Helga Radner,[1] Kazuki Yoshida,[2] Sara Tedeschi,[3] Paul Studenic,[4] Michelle Frits,[3] Christine Iannaccone,[3] Nancy A. Shadick,[3] Michael Weinblatt,[3] Daniel Aletaha,[4] Josef S. Smolen,[4] and Daniel H. Solomon[3]

Objective. **To quantify differences and determine the factors contributing to the difference in patient global assessment of rheumatoid arthritis (RA) disease activity (PtGA) between RA patients with multiple morbidities (RA-MM) and those with RA only.**

Methods. **We compared the PtGA between RA-MM patients and those with RA only, followed up in a longitudinal cohort (n = 1,040). In analyses performed on RA-MM patients (n = 575) and those with RA only (matched for swollen joint count, tender joint count, evaluator global assessment, and disease duration), the mean difference in PtGA (ΔPtGA) between the 2 groups was assessed. The contribution of patient characteristics to the explained variation of ΔPtGA in the matched cohort was calculated as semipartial R^2 and summarized as the percentage of the total R^2 in linear regression models.**

Results. **RA-MM patients reported higher (or worse) PtGA, with an increased PtGA associated with more morbidities (*P* for linear trend < 0.01); this relationship remained significant after adjustment for disease activity, age, and disease duration. After matching 294 RA-MM patients to those with RA only, the pairwise comparison of mean PtGA (on a scale of 0–100 mm) was significantly higher (worse) for RA-MM patients (mean ± SD 30.5 ± 24.3) versus those with RA only (25.6 ± 22.9) (mean ΔPtGA 4.9 ± 26.7; *P* < 0.01 by paired *t*-test). Variables uniquely contributing to ΔPtGA were fatigue (18%), pain (17%), and modified Health Assessment Questionnaire scores (9%).**

Conclusion. **In RA patients with multiple morbidities, the perception of RA disease activity as measured by the PtGA might be impacted by the burden of multiple diseases in one individual. RA-MM patients have higher (worse) levels of PtGA scores compared to patients with RA only. The difference in PtGA is mainly explained by differences in fatigue and pain.**

The patient global assessment of disease activity (PtGA) is a key variable in management of rheumatoid arthritis (RA), as it is part of various composite measures of disease activity. Treatment strategies such as the one proposed by the Treat-to-Target (T2T) Expert Committee demand regular assessment of disease activity using standardized measures, many of them including PtGA (and modification of therapy if the target is not reached) (1). The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) provisional definition of remission in RA includes PtGA in both the Boolean-based as well as the index-based definition (2).

Previous studies have shown that in 30–60% of individuals, there is a discrepancy between disease activity estimations by physicians and those by patients (3,4); moreover, PtGA is often the reason that patients are not classified as having reached remission according to

The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study was supported with grants from Bristol-Myers Squibb, Crescendo Bioscience, and UCB. Dr. Radner's work was supported by the Austrian Science Fund (project J3476-B23).

[1]Helga Radner, MD: Brigham and Women's Hospital, Boston, Massachusetts, and Medical University of Vienna, Vienna, Austria; [2]Kazuki Yoshida, MD, MPH, MS: Brigham and Women's Hospital and Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [3]Sara Tedeschi, MD, MPH, Michelle Frits, Christine Iannaccone, MPH, Nancy A. Shadick, MD, MPH, Michael Weinblatt, MD, Daniel H. Solomon, MD, MPH: Brigham and Women's Hospital, Boston, Massachusetts; [4]Paul Studenic, MD, Daniel Aletaha, MD, Josef S. Smolen, MD: Medical University of Vienna, Vienna, Austria.

Address correspondence to Helga Radner, MD, Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria. E-mail: helga.radner@meduniwien.ac.at.

Submitted for publication August 13, 2015; accepted in revised form November 3, 2016.

ACR/EULAR standards (5). Various symptoms might influence patients' assessment of RA disease activity (6), especially in patients with longstanding disease who have accumulated structural joint damage or in patients with other chronic conditions in addition to RA. In an earlier study, we demonstrated that multiple morbidities negatively affect the therapeutic goal of remission, or even that of low disease activity, in patients in whom any disease-modifying antirheumatic drug (DMARD) therapy is initiated (7). This effect was also mentioned in one of the items among the original T2T recommendations (1) and reinforced in the updated T2T recommendations (8). The perception of RA disease activity as measured by the PtGA might be impacted by the burden of several additional diseases in a given person, leading to higher levels of PtGA. Furthermore, a given patient factor (i.e., pain, fatigue, or disability) might contribute differently to PtGA in RA patients with multiple morbidities (RA-MM) versus patients with RA only. We aimed to quantify differences in PtGA between RA-MM patients and those with RA only, and to determine the factors contributing to the differences in the perception of RA disease activity as measured by PtGA between the 2 groups.

PATIENTS AND METHODS

Study cohort. The study was performed in patients enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS), an RA cohort in which information about demographics, multiple morbidity status, RA-specific treatment, and RA disease activity and functional status is collected (9). Patients were allowed to enter the analyses only once, using data from their first BRASS visit in which complete information on PtGA and multiple morbidity status was gathered. All patients enrolled in BRASS provided written informed consent, and the study was approved by the Partners HealthCare Institutional Review Board.

Assessement of multiple morbidity status. We identified chronic morbid conditions of BRASS patients using the International Classification of Diseases, Ninth Revision (ICD-9); these data were extracted using an automated search tool for the electronic medical record (10). To quantify multiple morbidities, we used our recently described counted multimorbidity index (cMMI), an index that is based on the impact of multimorbidity on health-related quality of life and includes 40 different morbid conditions (11) (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract). We calculated the cMMI by counting the number of morbidities for each patient. For the main analyses, RA patients were divided into those with multiple morbidities (patients with 1 or more morbid conditions in addition to RA [cMMI $\geq$2]) and those with RA only (cMMI 1). For additional analyses, patients were also classified into the following 4 groups, according to cMMI: RA only cMMI 1 (n = 465), cMMI 2–3 (n = 384), cMMI 4–5 (n = 112), and cMMI $\geq$6 (n = 79).

Study variables. The outcome of interest was the PtGA, collected on a 100-mm Likert scale with 5-mm increments, where 0 was considered "very well" and 100 was considered "very poor." The question was worded as: "Considering all the ways that your illness affects you, rate how you are doing on the following scale. Mark the response that best describes how you are doing on a scale of 0–100" (12,13). Demographic and disease-specific characteristics included age, sex, race (white or other), disease duration, highest level of education (7 categories ranging from 0 ["not graduated high school"] to 6 ["completed graduate education"]), 28-joint tender joint count (TJC28) and 28-joint swollen joint count (SJC28), pain and fatigue (both measured on a 100-mm visual analog scale), modified Health Assessment Questionnaire (M-HAQ) scores (14), and the evaluator global assessment (EGA) of disease activity measured on a 100-mm Likert scale with 5-mm increments.

Statistical analysis. In order to quantify the differences in PtGA between RA-MM patients and those with RA only, unadjusted analysis of variance (ANOVA) was used, and mean PtGA was compared across groups of patients with different morbidity burden and was tested for linear trend. As RA-MM patients had higher disease activity, we calculated a modified version of the Clinical Disease Activity Index (M-CDAI), without PtGA (15), and re-ran ANOVA in patients stratified into tertiles of M-CDAI. In a generalized linear model (GLM) with adjustment for age, disease duration, C-reactive protein (CRP) level, EGA, TJC28, and SJC28, estimated marginal means were calculated and then compared across groups of patients with different cMMIs. For our primary analyses we matched RA-MM patients with patients with RA only on SJC28, TJC28, tertiles of EGA ($\leq$20 mm, 20–40 mm, $>$40 mm), and category of disease duration ($\leq$2 years, 2–5 years, 5–10 years, 10–25 years, $>$25 years). Pairwise *t*-test of mean PtGA was performed and the difference in PtGA (ΔPtGA) (PtGA of RA-MM patients minus PtGA of patients with RA only) within the matched pairs was calculated.

We also performed several sensitivity analyses. First, to account for disease duration and potential joint damage, we tested our hypothesis in a subgroup of patients with disease duration of $\leq$1 year (inception cohort). Second, to test whether the association is specific to PtGA, we performed sensitivity analyses using EGA, a physician-derived instrument, and TJC28 as another patient-derived instrument, instead of PtGA.

To determine different characteristics contributing to PtGA, patient characteristics found to be significantly associated with PtGA in correlations were entered as independent variables in multivariable linear regression models. We used separate models for RA-MM patients and for those with RA only, to determine the independent contribution to the explained variation of PtGA for each of the characteristics entered into the models. In each model, the same characteristics were entered to allow comparison of the models. The proportion of independent contribution of each characteristic was calculated using semi-partial R-square (sR^2), which reflects the variation uniquely explained by the characteristic after removing the variation shared with other variables (overlap). Allowing comparison across different variables, sR^2 is a standardized parameter and is displayed as percentage of the total R^2. In bootstrapping analyses using the percentile method, we

Table 1. Characteristics of patients with RA only and those with multiple morbidities*

	Total cohort			Cohort matched for SJC28, TJC28, EGA, and disease duration		
	RA only (n = 465)	RA with multiple morbidities (n = 575)	*P*	RA only (n = 294)	RA with multiple morbidities (n = 294)	*P*
Age, years	53 ± 14	60 ± 13	<0.01	55 ± 14	60 ± 12	<0.01
Disease duration, years	12 ± 11	15 ± 12	<0.01	14 ± 12	15 ± 12	0.17
Female, %	86	80	0.01	86	81	0.43
White, %	98	95	0.01	99	99	0.32
Seropositive, %	72	72	0.97	65	69	0.24
Treatment, %						
Synthetic DMARD	71	70	0.78	70	68	0.06
Biologic DMARD	39	39	0.91	46	49	0.73
Steroids	24	33	<0.01	19	25	0.17
Education level, median (IQR)	4 (2–6)	3 (2–5)	<0.01	4 (2–6)	4 (2–6)	1
SJC28	6 ± 7	7 ± 8	<0.01	4 ± 6	4 ± 6	1
TJC28	7 ± 7	9 ± 8.1	<0.01	5 ± 7	5 ± 7	1
PtGA	28 ± 25	35 ± 24	<0.01	26 ± 23	31± 24	<0.01
EGA	29 ± 20	35 ± 22	<0.01	22 ± 17	21 ± 17	0.34
CDAI	18.3 ± 15.5	24.0 ± 17.4	<0.01	14.0 ± 14.1	14.4 ± 14.3	0.04
M-CDAI	15.5 ± 14.6	20.5 ± 16.4	<0.01	11.4 ± 13.2	11.4 ± 13.1	0.34
M-HAQ score	0.51 ± 0.48	0.70 ± 0.52	<0.01	0.28 ± 0.37	0.36 ± 0.43	<0.01
Pain, 0–100 mm	32 ± 26	38 ± 27	<0.01	29 ± 25	31 ± 25	0.57
Fatigue, 0–100 mm	38 ± 28	46 ± 29	<0.01	37 ± 29	42 ± 28	0.03
CRP, mg/liter	7.1 ± 12.3	11.0 ± 25.3	<0.01	5.6 ± 10.7	6.9 ± 24.6	0.35
cMMI	1 ± 0	3.4±1.9	<0.01	1 ± 0	2.6 ± 2.1	<0.01

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; SJC28 = swollen joint count (of 28); TJC28 = tender joint count (of 28); EGA = evaluator global assessment; DMARD = disease-modifying antirheumatic drug; IQR = interquartile range; PtGA = patient global assessment of disease activity; CDAI = Clinical Disease Activity Index; M-CDAI = modified CDAI; M-HAQ = modified Health Assessment Questionnaire; CRP = C-reactive protein; cMMI = counted multimorbidity index.

generated 1,000 samples and calculated the 95% confidence interval (95% CI) of sR^2 for each patient characteristic and compared it between models with RA-MM patients and those with RA only. In supplemental analyses stratifying patients into tertiles of M-CDAI, we re-ran regression models to calculate sR^2 for different components within different levels of disease activity.

In our main analyses, we were interested in the components contributing to the difference in PtGA between RA-MM patients and those with RA only, matched for SJC28, TJC28, EGA, and disease duration. Differences in characteristics associated with PtGA between matched RA-MM patients and those with RA only were calculated and entered into a multivariable regression model to determine their independent contribution to the explained variation of PtGA. Again, the proportion of independent contribution of each component was calculated using sR^2 and displayed as a percentage of the total R^2.

RESULTS

Of 1,040 RA patients in the BRASS cohort, 575 (55%) had multiple morbidities, with a mean cMMI of 2.4 (range 1–11). The prevalence of single morbidities is displayed in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract). RA-MM patients were older than patients with RA only (mean 60 years versus 53 years; $P < 0.01$) and had longer disease duration (mean 15 years versus 12 years; $P < 0.01$) and higher disease activity (mean CDAI 24.0 versus 18.3; $P < 0.01$) (Table 1).

Higher PtGA scores in RA patients with multiple morbidities. In unadjusted analyses, the mean PtGA score was significantly higher in RA patients with multiple morbidities compared to patients with RA only, increasing with the number of morbidities per patient (*P* for linear trend < 0.001, by ANOVA) (Figure 1A). To account for disease activity, we stratified patients into levels of disease activity determined by 3 tertiles of M-CDAI (≤7 [n=354], 7.1–23 [n = 334], and ≥23.1 [n = 352]). Using ANOVA testing for linear trend within each stratum, we again found a significant increase of PtGA with increasing number of morbidities per patient ($P \leq 0.01$) (Figure 1C). In the GLM adjusted for disease activity (SJC28, TJC28, EGA, CRP), age, and disease duration, we calculated estimated marginal means, which demonstrated a significant increase in PtGA from 29.4 mm in patients with RA only to 42.4 mm in RA patients with 5 or more additional morbid conditions ($P < 0.01$) (Figure 1B).

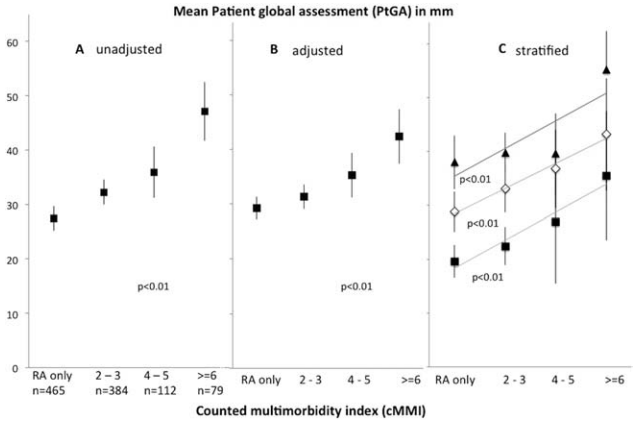

Figure 1. Higher mean values of patient global assessment of disease activity (PtGA) in rheumatoid arthritis (RA) patients with higher numbers of morbidities according to the counted multimorbidity index (cMMI) separated into 3 strata, compared to patients with RA only. **A,** Unadjusted analysis of variance (ANOVA) (*P* for linear trend < 0.001). **B,** Adjusted ANOVA. Estimated marginal means were generated by general linear model considering all covariates set to the cohort mean (tender joint count 7.9, swollen joint count 7.1, evaluator global assessment 32.2, C-reactive protein 9.3 mg/liter, age 56.8 years, disease duration 13.7 years). **C,** Analyses stratified by tertile of the modified Clinical Disease Activity Index (M-CDAI) (tertile 1 M-CDAI ≤7 [n = 354] [square], tertile 2 M-CDAI 7.1 to ≤23 [n = 334] [diamond], tertile 3 M-CDAI ≥23.1 [n = 352] [triangle]). ANOVA showed a significant linear trend of increase in PtGA with increasing number of morbidities within each cMMI stratum, with an almost parallel increase across different strata (trendline). Bars show the mean and 95% confidence interval. cMMI = counted multimorbidity index.

In sensitivity analyses using an inception cohort (n = 141), we found similar results, showing a linear increase in PtGA with an increasing number of morbidities per patient (*P* for linear trend = 0.01, by ANOVA; *P* = 0.04 in the GLM) (see Supplementary Figure 1 available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract). We also examined whether these findings were specific for the PtGA. After adjustment for disease activity, we found no significant association of EGA or TJC28 with the number of morbid conditions (see Supplementary Figure S, http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract).

Characteristics contributing to PtGA differ between matched RA patients with multiple morbidities and patients with RA only. There were no differences between the RA-MM patients and those with RA only in regard to variables associated with the PtGA from univariate correlation analyses (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract). Variables significantly correlating with PtGA (pain, fatigue, M-HAQ, TJC28, SJC28, EGA, education, and cMMI) were entered into multivariable regression analyses to calculate sR^2. In RA-MM patients, fatigue independently contributed the highest proportion to the total variation of PtGA, followed by pain and M-HAQ scores (total R^2 0.60, fatigue sR^2 0.08 [13%], pain sR^2 0.05 [8%], M-HAQ sR^2 0.02 [3%]). However, in patients with RA only, pain showed the highest proportion of unique variation explained (total R^2 0.57, pain sR^2 0.08 [14%], fatigue sR^2 0.03 [5%], M-HAQ sR^2 0.02 [4%]) (Figure 2A). The 95% CI of the sR^2 for each component entered into the model was obtained by the bootstrap method and is displayed in Supplementary Table 3 (http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract).

After patients were stratified into levels of disease activity based on tertiles of the M-CDAI, most of the independent variation of PtGA in RA-MM patients in lower tertiles was explained by fatigue (sR^2 0.10 [18%] and sR^2 0.12 [22%] in the lowest and middle tertiles, respectively; both $P < 0.01$); in patients with RA only (of the same M-CDAI disease activity level), the sR^2 of fatigue was lower (0.05 [8%] in the lowest tertile and 0.01 [2%] in the middle tertile; $P < 0.01$ and $P = 0.16$, respectively). Values of sR^2 for each component and 95% CIs obtained with the bootstrap method are summarized in Table 2.

After matching RA-MM patients with those with RA only for equal measures of SJC28, TJC28, EGA,

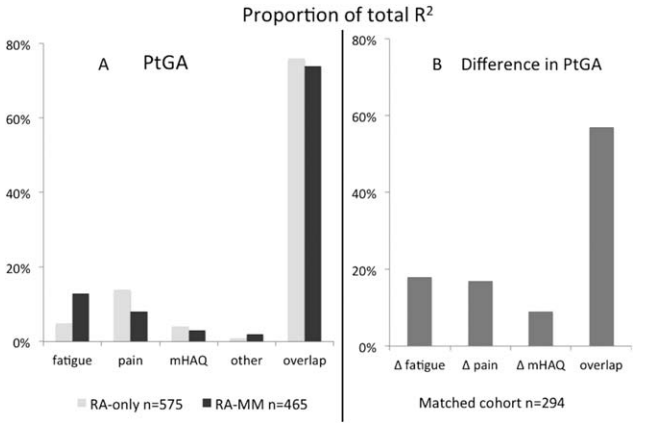

Figure 2. Contribution of different characteristics to the explained variation of the patient global assessment of disease activity (PtGA) **(A)**, and difference in PtGA (ΔPtGA) between rheumatoid arthritis patients with multiple morbidities (RA-MM) and patients with RA only, matched for swollen joint count, tender joint count, evaluator global assessment of disease activity, and disease duration **(B)**. The proportion of variation obtained by multivariable regression analyses is calculated as semi-partial R^2 and displayed as percentage of the total R^2 (only significant characteristics with a proportion of >1% are displayed). Overlap proportion of R^2 is explained by the different components. M-HAQ = modified Health Assessment Questionnaire.

Table 2. Characteristics contributing to the explained variation of patient global assessment of disease activity in patients with different levels of RA disease activity (expressed as tertiles of the M-CDAI)*

	Patients with RA only		RA patients with multiple morbidities‡	
	Semi-partial R^2 (95% CI)	% of R^2	Semi-partial R^2 (95% CI)	% of R^2
First tertile (M-CDAI ≤7)†				
Pain	0.04 (0.00–0.12)	7.4	0.03 (0.00–0.08)	5.4
Fatigue	0.05 (0.01–0.10)	8.1	0.10 (0.04–0.18)	18.4
M-HAQ score	0.03 (0.00–0.09)	5.2	0.01 (0.00–0.03)	0.9
SJC2	0.00 (0.00–0.02)	0	0.00 (0.00–0.02)	0
TJC	0.00 (0.00–0.02)	0.4	0.00 (0.00–0.02)	0
EGA	0.01 (0.00–0.06)	2.7	0.03 (0.00–0.08)	5.1
Education level	0.01 (0.00–0.03)	0.9	0.01 (0.00–0.04)	1.6
cMMI	NA	NA	0.01 (0.00-0.03)	0.9
Second tertile (M-CDAI 7 to ≤23)‡				
Pain	0.12 (0.04–0.23)	25.7	0.04 (0.07–0.11)	7.7
Fatigue	0.01 (0.00–0.04)	1.5	0.12 (0.06–0.19)	21.8
M-HAQ score	0.02 (0.00–0.06)	5.1	0.00 (0.00–0.03)	0.7
SJC28	0.01 (0.00–0.04)	2.6	0.01 (0.00–0.05)	2.5
TJC28	0.00 (0.00–0.02)	0.2	0 (0.00–0.01)	0
EGA	0.00 (0.00–0.02)	0.4	0.01 (0.00–0.03)	1.1
Education level	0.01 (0.00–0.04)	1.7	0.00 (0.00–0.02)	0.7
cMMI	NA	NA	0.01 (0.00–0.03)	1.1
Third tertile (M-CDAI >23)§				
Pain	0.07 (0.01–0.17)	11.7	0.08 (0.03–0.14)	14.3
Fatigue	0.08 (0.02–0.16)	13.2	0.04 (0.01–0.08)	6.7
M-HAQ score	0.02 (0.00–0.06)	3.1	0.03 (0.01–0.07)	5.8
SJC28	0.00 (0.00–0.02)	0.2	0.00 (0.00–0.01)	0.2
TJC28	0.00 (0.00–0.04)	0.7	0.01 (0.00–0.03)	0.9
EGA	0.00 (0.00–0.02)	0.2	0.00 (0.00–0.01)	0.2
Education level	0.00 (0.00–0.02)	0.2	0.00 (0.00–0.02)	0.3
cMMI	NA	NA	0.00 (0.00–0.01)	0.3

* The proportion of variation obtained by multivariable regression analysis was calculated as the semi-partial R^2 (sR^2) (which reflects the variation uniquely explained by the characteristic after removing the variation shared with other variables [overlap]), and is displayed as a percentage of the total R^2, separately for RA patients with multiple morbidities (RA-MM) and patients with RA only. NA = not applicable (see Table 1 for other definitions).
† Patients with RA only: total R^2 0.57 (95% confidence interval [95% CI] 0.47–0.72); RA-MM patients: total R^2 0.58 (95% CI 0.47–0.70).
‡ Patients with RA only: total R^2 0.50 (95% CI 0.35–0.64); RA-MM patients: total R^2 0.58 (95% CI 0.46–0.69).
§ Patients with RA only: total R^2 0.64 (95% CI 0.51–0.75); RA-MM patients: total R^2 0.59 (95% CI 0.51–0.67).

and disease duration (n = 294 for each group), we found significantly higher PtGA scores in RA-MM patients (mean ± SD 30.5 ± 24.3 mm) compared to those with RA only (25.6 ± 22.8 mm) (mean ± SD ΔPtGA 4.9 ± 26.7 mm; $P < 0.01$, by paired *t*-test). Despite matching of patients, ΔPtGA was significantly higher in patients with a higher number of morbidities (cMMI 2–3 ΔPtGA 3.3 ± 26.3 mm [n = 193], cMMI 4–5 ΔPtGA 1.8 ± 24.8 mm [n = 57], cMMI ≥6 ΔPtGA 15.6 ± 28.6 mm [n = 44]; *P* for linear trend = 0.02, by ANOVA). RA-MM patients showed significantly higher levels of fatigue compared to those with RA only (41.9 ± 28.4 mm versus 36.9 ± 28.6 mm, mean ± SD Δfatigue 5.1 ± 38.8 mm; $P < 0.025$), but similar levels of pain (RA-MM patients, 30.6 ± 24.9 mm versus patients with RA only, 29.2 ± 25.4 mm [$P = 0.57$]; mean ± SD Δpain 1.3 ± 32.7 mm) (Table 1).

Characteristics independently explaining the variation of ΔPtGA in the matched cohort were Δfatigue (sR^2 0.26 [18% of total R^2]), Δpain (sR^2 0.25 [16% of total R^2]), and ΔM-HAQ score (sR^2 0.18 [9% of total R^2]; total $R^2 = 0.60$) (Figure 2B). Differences in age, CRP level, and education level were not statistically significant, and were therefore dropped from the model.

DISCUSSION

In this study, we were interested in differences in patient perceptions of RA disease activity, as measured by the PtGA, comparing RA patients with multiple

morbidities to patients with RA only. We found that with an increasing number of morbid conditions per patient, the mean value of PtGA increased significantly, independent of RA disease activity. On average, the PtGA of RA-MM patients was ~5 mm higher than that of patients with RA only who had similar disease activity and disease duration. Variations in fatigue and pain were two of the main components explaining this difference. While a 5-mm difference may seem small on an absolute range, when aiming to fulfill Boolean remission criteria (16) in observational studies, this difference may have a large impact.

Regular measurement of disease activity using standardized tools is a key feature in the treatment of patients with RA. Common composite indices that rely on PtGA as an integral part of treatment strategies are used to support therapeutic decisions and define thresholds of disease activity. Remission, or at least low disease activity, is the ultimate goal when treating RA to target (1). Due to the nature of multiple morbidities, even under optimal therapy the target may never be reached because of elevated PtGA from factors not related to RA (7,17). In our study, we demonstrated that with an increasing number of morbidities, patients reported significantly higher PtGA (which could explain why certain patients never achieve target disease activity). We found an almost parallel increase in mean PtGA with an increasing number of morbidities in each level of disease activity, with a mean PtGA ~15 mm higher in patients with the highest burden of multiple morbidities (cMMI ≥6) compared to patients with RA only (Figure 1C). Moreover, a mean difference of 5 mm was found between RA-MM patients and those with RA only who had exactly the same number of swollen and tender joints. We also ran sensitivity analyses using different matching processes to ascertain that our findings were not driven by a specific instrument (data not shown).

The impact of multiple morbidities seems specific for PtGA. Analyses using different outcome measures (EGA or TJC28) instead of PtGA showed no significant association of multiple morbidity status and the outcome of interest (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39988/abstract).

We found that fatigue was one of the most important independent characteristics explaining the variation of PtGA in RA-MM patients compared to those with RA only. Although only 13% of the variation was uniquely explained by fatigue, the proportion was 2–3-fold higher in RA-MM patients compared to patients with RA only. In RA-MM patients in the lowest 2 tertiles of M-CDAI, the proportion of variation explained by fatigue was approximately one-quarter of the total R^2, whereas in patients with RA only who had similar disease activity, pain was the main contributor to PtGA. Interestingly, in RA-MM patients with higher disease activity (the highest tertile), the proportion of sR^2 for fatigue decreased and pain contributed mainly to PtGA. This may be due to the fact that pain might be more influenced by symptoms related to RA (joint swelling and tenderness), which are more present in patients with higher levels of RA disease activity. Sex, CRP level, and disease duration were not significantly associated with PtGA, and therefore were not included in our models. Previous studies have already shown a strong association between pain, fatigue, and PtGA (3,4), but to our knowledge there is no published study specifically addressing the differences between RA-MM patients and those with RA only.

When we investigated the discrepancy in PtGA between RA-MM patients and those with RA only, with the same amount of joint swelling, tenderness, and disease duration, higher levels of fatigue were observed in the former group. This difference in fatigue mainly contributed to the explained variation of the difference in PtGA. Patients with a higher burden of multiple morbidities may experience more fatigue unrelated to RA, which could influence their rating of global disease activity.

Several limitations of this study need to be addressed. First, the phrasing of the PtGA may impact individual patient ratings. The exact wording used for this cohort, "Considering all the ways that your illness affects you, rate how you are doing on the following scale" differs from the widely employed phrase "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?" (2). The language used is in accordance with that used in the clinical HAQ and the patient activity scale, which have both been validated previously in patients with RA (12,13,18). The BRASS consent form specifically states that subjects will provide information on RA treatments, the extent to which they are able to function with RA, how active their RA is, and how RA affects their daily living; therefore we can assume that subjects in our cohort interpreted the word "illness" as "RA." Furthermore, all patients responded to the same question, making it unlikely that this wording influenced our results.

Second, our findings are based only on a single-center study. Patients included in the BRASS cohort are mostly white (98%) with a higher education level compared to typical RA populations, and therefore may not be representative. Nevertheless, we included a large sample of RA patients from clinical practice with a wide range of disease duration and activity and morbid conditions.

Third, we did not include any radiologic outcomes in our analyses. Joint damage may influence patients' perception of disease activity and therefore could lead to higher levels of PtGA. To account for joint damage, we included disease duration and HAQ scores in our models, which are both closely related to joint damage (19–21). We also performed subgroup analyses on patients with complete data on the modified total Sharp scores (n = 766) (22). When re-running regression models including modified total Sharp scores, we found no significant association between modified total Sharp scores and PtGA. Interestingly, disease duration and age were not significantly associated with PtGA and therefore were dropped from regression models. Fourth, we had no data on corticosteroid or DMARD dosages. However, we found no significant difference in the proportion of patients receiving corticosteroids or biologic DMARDs in the RA-MM and RA only groups.

Last, predictor variables entered into regression models were intercorrelated, leading to colinearity. This was reflected by the overlapping part of R^2, depicting the variation shared across different characteristics. Using sR^2 we were able to specifically investigate the unique contribution of each characteristic, taking colinearity into account.

To assess multiple morbidities, we decided to use the cMMI (instead of the commonly used Charlson Comorbidity Index) as the cMMI includes 40 different chronic conditions and is based on quality of life rather than mortality. In previous studies, we tested the validity of the cMMI using different cohorts (7,11,23). The assessment of morbid conditions was based on assigned ICD-9 codes reported in a centralized clinical data registry. Diagnoses assigned outside the Partners Healthcare system might be missing. When we further assessed the prevalence rates of morbidities, we did not observe a systematic error; for many morbidities, we observed prevalence rates similar to those reported in previous literature. The association of multiple morbidities and PtGA might be stronger in patients with certain morbid conditions, such as cancer or depression. Due to relatively small numbers of patients with any given morbidity, we did not perform analyses in these subgroups. Furthermore, the aim of this study was to assess the overall impact of multiple morbidities on PtGA, rather than evaluating the impact of specific diseases.

In our study we found a mean ΔPtGA of 5 mm between RA-MM patients and those with RA only, which is below the minimal clinically important difference. It is likely that at these low levels of disease activity, the effect of morbidities is less than it might be at higher levels of disease activity. Furthermore, in the presence of a simple cutoff-based definition of disease activity, a 5-mm higher rating of PtGA might be enough to prevent a patient from achieving REM or even LDA, irrespective of clinically meaningful differences. This can impact treatment strategies, and might lead to overtreatment and higher costs. Therefore, differences in ratings of PtGA, even if small, must be taken into account when defining and assessing treatment targets in RA patients with multiple morbidities, to guarantee the best quality of care.

In summary, RA-MM patients have higher levels of PtGA compared to patients with RA only, even after adjustment for disease activity and disease duration. PtGA is ~5 mm higher in RA-MM patients compared to patients with RA only who have the same amount of joint swelling and tenderness. Different levels of fatigue and pain are the main contributors to the difference in PtGA between RA-MM patients and those with RA only. Definitions and ratings of PtGA might be different in RA patients with multiple morbidities, and this warrants further investigation

ACKNOWLEDGMENTS

The authors would like to thank all patients and investigators who participated in this study.

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. Radner 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. Radner, Yoshida, Tedeschi, Studenic, Frits, Iannaccone, Shadick, Weinblatt, Aletaha, Smolen, Solomon.

Acquisition of data. Radner, Yoshida, Tedeschi, Studenic, Frits, Iannaccone, Shadick, Weinblatt, Aletaha, Smolen, Solomon.

Analysis and interpretation of data. Radner, Yoshida, Tedeschi, Studenic, Frits, Iannaccone, Shadick, Weinblatt, Aletaha, Smolen, Solomon.

REFERENCES

1. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
2. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404–13.
3. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814–23.
4. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;64:206–14.

5. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.
6. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139–45.
7. Radner H, Yoshida K, Frits M, Iannaccone C, Shadick NA, Weinblatt M, et al. The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2015; 54:2076–84.
8. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.
9. Iannaccone CK, Lee YC, Cui J, Frits ML, Glass RJ, Plenge RM, et al. Using genetic and clinical data to understand response to disease-modifying anti-rheumatic drug therapy: data from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study. Rheumatology (Oxford) 2011;50:40–6.
10. Nalichowski R, Keogh D, Chueh HC, Murphy SN. Calculating the benefits of a research patient data repository. AMIA Annu Symp Proc 2006:1044.
11. Radner H, Yoshida K, Mjaavatten MD, Aletaha D, Frits M, Lu B, et al. Development of a multimorbidity index: impact on quality of life using a rheumatoid arthritis cohort. Semin Arthritis Rheum 2015;45:167–73.
12. Wolfe F. A brief clinical health assessment instrument: CLINHAQ [abstract]. Arthritis Rheum 1989;32 Suppl 4:99.
13. Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies, and clinical trials: the patient activity scale (PAS/PAS-II). J Rheumatol 2005;32:2410–5.
14. Pincus T, Sokka T, Kautiainen H. Further development of a physical function scale on a MDHAQ [corrected] for standard care of patients with rheumatic diseases. J Rheumatol 2005;32: 1432–9.
15. Baer PB, Bensen WG, Thorne C, Haraoui B, Choquette D, Arendse R, et al. Improvements in the proportion of patients achieving DAS, CDAI, and SDAI remission by omitting the Patient Global Assessment (PtGA): an analysis from a prospective, observational registry. Arthritis Rheumatol 2014;66 Suppl: S419.
16. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
17. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology (Oxford) 2013;52:1809–17.
18. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003;30:167–78.
19. Smolen JS, Aletaha D, Grisar JC, Stamm TA, Sharp JT. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. Ann Rheum Dis 2010;69:1058–64.
20. Clarke AE, St-Pierre Y, Joseph L, Penrod J, Sibley JT, Haga M, et al. Radiographic damage in rheumatoid arthritis correlates with functional disability but not direct medical costs. J Rheumatol 2001;28:2416–24.
21. Scott DL. Radiological progression in established rheumatoid arthritis. J Rheumatol Suppl 2004;69:55–65.
22. Van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method [corrected and republished in J Rheumatol 2000;27:261–3]. J Rheumatol 1999;26:743–5.
23. Radner H, Yoshida K, Hmamouchi I, Dougados M, Smolen JS, Solmon DH. Treatment patterns of multimorbid rheumatoid arthritis patients: results from an international cross-sectional study. J Rheumatol 2015;42:1099–104.