Reevaluation of the Role of Duration of Morning Stiffness in the Assessment of Rheumatoid Arthritis Activity

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ABSTRACT. ***Objective.*** To evaluate the utility of the duration of morning stiffness (MS), as a patient-reported outcome (PRO), in assessing rheumatoid arthritis (RA) disease activity.

Methods. We acquired information on 5439 patients in QUEST-RA, an international database of patients with RA evaluated by a standard protocol. MS duration was assessed from time of waking to time of maximal improvement. Ability of MS duration to differentiate RA activity states, based on Disease Activity Score (DAS)28, was assessed by analysis of variance; and a receiver-operating characteristic (ROC) curve was plotted for discriminating clinically active (DAS28 > 3.2) from less active (DAS28 ≤ 3.2) RA. Mixed-effect analysis of covariance (ANCOVA) models were used to assess the utility of adding MS duration to Routine Assessment of Patient Index Data (RAPID)3, a PRO index based on physical function, pain, and general health (GH), in predicting the 3-variable DAS28 (DAS28v3).

Results. MS duration had moderate correlation (r = 0.41–0.48) with pain, Health Assessment Questionnaire, and GH; and weak correlation (r = 0.23–0.39) with joint counts and erythrocyte sedimentation rate. MS duration differed significantly among patients with different RA activity ($p < 0.001$). The area under the ROC curve of 0.74 (95% CI 0.72–0.75) showed moderate ability of MS duration to differentiate clinically active from less active RA. ANCOVA showed significant interactive effects between RAPID3 and the MS duration categories ($p = 0.0005$) in predicting DAS28v3. The effect of MS was found to be clinically important in patients with the low RAPID3 scores (< 6) in whom the presence of MS may indicate clinically active disease (DAS28v3 > 3.2).

Conclusion. MS duration has a moderate correlation with RA disease activity. Assessment of MS duration may be clinically helpful in patients with low RAPID3 scores. (J Rheumatol First Release Oct 15 2009; doi:10.3899/jrheum.081175)

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Stiffness in the joints after periods of rest is commonly experienced by patients with rheumatoid arthritis (RA) and is assessed clinically by morning stiffness (MS). Morning stiffness is listed in classification criteria[1] and is a component of American College of Rheumatology (ACR) remission criteria for RA[2]. Recognition of MS as a common symptom of RA led to the suggestion that MS might be useful for differentiating RA from noninflammatory joint diseases[3]. However, MS was found to have poor discriminative ability in differentiating such conditions from RA[1,4,5].

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Further, more than one-third of individuals older than 50 years without RA report MS of > 15 min[6]. Morning stiffness used to be included as a common outcome measure in RA clinical trials[7]. Although recent clinical trials of RA do not include MS as an outcome measure, it is still commonly used as an eligibility criterion for participation[8].

In clinical practice, MS assessment is used as one of the indicators of RA disease activity. The 2002 ACR guidelines for the management of RA recommend assessment of MS duration as one of the variables for evaluation of the disease activity[9]. The Rheumatoid Arthritis Disease Activity Index (RADAI)[10], one of the 6 composite indices recommended for RA activity assessment in the updated 2008 ACR treatment guidelines for RA[11], has MS duration as one of its components. MS duration was found to be the second strongest predictive factor for change of disease-modifying antirheumatic drug therapy in routine clinical care of patients with RA in a tertiary care center[12]. However, the utility of MS duration as an indicator of inflammatory activity of RA has been questioned. In a study with 93 RA patients, there was no significant difference in MS duration between active and inactive disease as assessed by their treating physician[4]. In a cohort of 337 patients with early RA, MS duration was associated at higher level with patient-reported measures such as functional status, pain, and patient's assessment of general health (GH) than joint counts and erythrocyte sedimentation rate (ESR), suggesting that MS may be an inadequate marker of inflammatory activity[13]. Removal of MS as a selection criterion for "active RA" in clinical trials has been advocated since it had little effect on classification of patients as having active or inactive disease[14].

No single variable is considered sufficient to assess RA disease activity. Composite indices [Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI)] derived from tender joint count, swollen joint count, an acute-phase reactant (except CDAI), patient assessment of GH (in DAS) or patient global assessment of disease activity (PGA; in SDAI and CDAI), and evaluator's global assessment of disease activity (EGA; in SDAI and CDAI), have been extensively validated for assessment of RA disease activity[15-17]. However, formal quantitative joint counts, an integral part of these indices, are frequently not performed in routine clinical practice[18]. Composite indices based solely on 3 patient-reported outcomes (PRO) in the ACR core data set (physical function, pain, and PGA or GH) have been validated and shown to effectively differentiate treatment response and be less susceptible to placebo response in randomized controlled trials of RA[19,20]. They have also been shown to predict institution of tumor necrosis factor inhibitor therapy and mortality in patients with RA[21]. There are no data about correlation of MS duration with a composite RA disease activity index based on quantitative joint counts and how well it differentiates disease activity states using such an index. MS duration is easily amenable to assessment as a PRO. However, there are no data whether addition of MS duration to a composite PRO index based on ACR core data set will improve RA disease activity assessment.

The purpose of our study was to clarify the utility of assessing MS in routine clinical practice. Our primary aim was to correlate the severity of MS (as assessed by duration) with activity of RA as assessed by a DAS28, and whether MS duration differentiates the disease activity categories (remission, low, moderate, and high) as classified by DAS28. The secondary aim was to assess utility of addition of MS duration to Routine Assessment of Patient Index Data 3 (RAPID3), a composite index based on PRO in the ACR core data set, in assessment of RA disease activity[22].

MATERIALS AND METHODS

Patients. QUEST-RA is an international database of 100 non-selected consecutive RA outpatients in ≥ 3 rheumatology clinics in several countries[23]. The database was started in 2005 and by January 2008 had information on > 5800 patients from 24 countries[24]. The patients were assessed by a standard protocol to evaluate RA[25].

Clinical information. Demographic information and clinical characteristics of RA were obtained from the database. Duration of RA was categorized as early (≤ 2 yrs) or late (> 2 yrs). MS duration (in min) was queried in the patient self-report questionnaire from the time of waking up to the time to maximal improvement in the stiffness that was experienced over the last week. For statistical analyses, MS duration was categorized as none, mild (1–30 min), moderate (31–60 min), and severe (> 60 min). Functional status was assessed by Health Assessment Questionnaire (HAQ; minimum–maximum: 0–3). The psychological HAQ (PSHAQ; minimum–maximum: 0–3) was used to evaluate psychological distress[26]. Pain, fatigue, GH, and evaluator global assessment were assessed on 0–10 cm visual analog scale (VAS). RAPID3 was calculated by adding HAQ score (after multiplying by 3.33 to convert scores to a 0–10 scale), pain and GH VAS scores. The scores of < 3, 3–6, 6.1–12, and > 12 have been proposed to represent "near remission" and low, moderate, and high RA activity, respectively[22]. Tender and swollen joint counts (28 joints) were assessed by the treating physician. ESR was obtained and DAS28 scores were calculated by the formula $0.56 \times \text{sqrt}(\text{tender28}) + 0.28 \times \text{sqrt}(\text{swollen28}) + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}$[15]. Since DAS28 and RAPID3 have GH as a common variable, we used DAS28 scores based on 3 variables (DAS28v3), as calculated by the formula $[0.56 \times \text{sqrt}(\text{tjc28}) + 0.28 \times \text{sqrt}(\text{sjc28}) + 0.70 \times \ln(\text{ESR})] \times 1.08 + 0.16$, when assessing the utility of adding MS duration to RAPID3[15].

RA disease activity was classified according to DAS28 score as remission (< 2.6), low (2.6 to ≤ 3.2), moderate (3.2 < to ≤ 5.1), and high (> 5.1). The current paradigm of RA management advocates aggressive treatment to achieve low disease activity state[27]. We also classified RA as clinically active (DAS28 score > 3.2), indicating moderate or high disease activity, and clinically less active (DAS28 score ≤ 3.2), indicating low disease activity or remission, to assess the diagnostic accuracy of MS.

Statistical methods. Data were analyzed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). The variables with skewed distribution (MS duration, tender joint count, swollen joint count, and ESR) were square-root transformed. Relationships between MS duration and demographic and disease activity variables were analyzed by calculating Pearson's correlation coefficient. Values of Pearson's correlation coefficient values were interpreted as representing slight (< 0.2), low (0.2–0.4), moderate (0.4–0.7), high (0.7–0.9),

and very high (> 0.9) correlation between variables[28]. Distribution of frequency of MS duration according to RA disease activity by DAS28 score was assessed. Differences in MS duration were compared with Student's t-test when there were 2 groups. Analysis of variance (ANOVA) was used to study whether MS duration differed among RA disease activity states. Pairwise comparisons, among different RA activity states, were made using Tamhane's T2 post-hoc test since there was unequal variance between different activity state groups. A receiver-operating characteristic (ROC) curve to assess diagnostic utility of MS duration to differentiate clinically active from less active RA was plotted. The area under the ROC curve indicates overall accuracy in discriminating 2 categorical states and varies from 0.5 to 1.0, where an area of 0.5–0.7 indicates low accuracy, 0.7–0.9 moderate accuracy, and > 0.9 high accuracy[29]. To further clarify clinical utility of MS duration assessment, positive likelihood ratios for assessing presence of active RA for each of its 4 categories were calculated.

Mixed-effect analysis of covariance (ANCOVA) models were used to assess the utility of adding MS duration to RAPID3 with DAS28v3 as dependent variable. To adjust for potential cultural effects, country of origin was included in these models as a random effect. MS duration was included as a categorical variable with the following groupings: 0 min, 1–30 min, 31–60 min, and > 60 min. The RAPID3 variable was included in the model as a continuous variable. The interaction between MS duration and RAPID3 was also evaluated. To further understand the role of individual PRO, a mixed-effect ANCOVA model was used to assess the strength of association of MS duration and PRO in the RAPID3 (GH, HAQ, and pain) with DAS28v3. All 2-way interactions involving MS duration were examined. Interactions not significant at the 0.10 level were removed, one at a time, in a backward elimination fashion. Finally, Pearson's and Spearman's partial correlation coefficients were used to describe the association between DAS28v3 and MS duration (continuous), GH, HAQ, and pain. The correlation between DAS28v3 and a predictor variable was adjusted for the remaining predictors.

RESULTS

The QUEST-RA database had 5848 patients from 24 countries at the time of analysis. This report includes 5439 (93%) patients on whom the information on MS duration was available. Patients whose MS information was available did not differ in DAS28 scores (4.24 vs 4.13; p = 0.2) and EGA rating (2.9 vs 2.8; p = 0.62) compared to those with missing MS information. However, patients with MS missing information had higher age (mean age 60 vs 56 yrs; p < 0.001), HAQ score (1.11 vs 1.01; p = 0.02), pain level (4.5 vs 4.1; p = 0.003), and GH score (4.3 vs 4.1; p = 0.03). Although statistically significant, we considered these differences to be small and not clinically relevant. Patient characteristics are shown in Table 1. The patients were mostly women and in the age group that is typical for RA. Eight hundred thirty patients (14.2%) had early RA. Table 2 shows the correlation of MS duration with different RA variables. There was moderate correlation of MS duration with pain, HAQ score, GH, RAPID3, and DAS28. The correlation with fatigue, PSHAQ, EGA, joint counts, and ESR was weak. There was no significant difference in MS duration between sexes (p = 0.47) and those with early or late RA (p = 0.25).

The distribution of MS duration among different RA activity states assessed by DAS28 scores is shown in Table 3, indicating that as RA activity increases, the percentage of patients with longer MS duration increases. MS duration differed significantly among patients with different RA disease activity states by ANOVA test [F(3,5226) = 273.8, p < 0.001]. As shown in Table 4, all the disease activity groups had significantly different MS duration by Tamhane's T2 test. The difference was smallest between the remission and low disease activity states. The difference in median MS duration between clinically active and less active RA was 40 min. Figure 1 shows the ROC curve to assess accuracy of MS duration to differentiate active from inactive disease. The area under the curve (AUC) is 0.74 (95% confidence

Table 1. Demographic characteristics and rheumatoid arthritis (RA) related disease variables.

Characteristic	n	%	Mean (SD)	Median (Q1-Q3)
Age, yrs	5432		56.1 (13.8)	57.0 (47.2–66.2)
Sex, female	5400	79		
Disease duration, yrs	5439		11.2 (9.7)	8.6 (3.7–16)
RF-positive	5338	73		
Morning stiffness duration, min	5439		54.6 (73.8)	30 (0–60)
HAQ score, 0–3	5426		1.0 (0.77)	1.0 (0.37–1.5)
Pain score, 0–10 cm VAS	5387		4.1 (2.7)	4.1 (1.8–6.2)
GH, 0–10 cm VAS	5486		4.1 (2.6)	4.2 (1.9–5.9)
EGA, 0–10 cm VAS	5346		2.9 (2.4)	2.4 (0.8–4.7)
Fatigue, 0–10 cm VAS	5362		4.4 (2.9)	4.5 (1.9–6.8)
TJC, 0–28	5393		6.6 (7.5)	4 (1–10)
SJC, 0–28	5389		4.3 (5.4)	2 (0–7)
ESR, mm/h	5127		29 (25.5)	22 (12–40)
PSHAQ score, 0–3	5409		0.8 (0.7)	1 (0–1)
DAS28v3	5230		4.2 (1.7)	4.2 (2.9–5.5)
RAPID3, 0–30	5349		11.6 (6.9)	11.4 (6.2–16.7)

Q1-Q3: first to third quartile; RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; GH: patient's assessment of general health; EGA: evaluator's assessment of global disease activity; TJC: tender joint count, SJC: swollen joint count, ESR: erythrocyte sedimentation rate; PSHAQ: Psychological HAQ; DAS28: Disease Activity Score 28-joint count; RAPID3: Routine Assessment of Patient Index Data 3.

Table 2. Correlations between duration of morning stiffness† and other RA variables.

Feature	Correlation Coefficient
Age	–0.03*
Duration of disease†	0.01
HAQ	0.43**
Pain	0.48**
GH	0.41**
Fatigue	0.39**
EGA	0.39**
TJC28†	0.39**
SJC28†	0.33**
ESR†	0.23**
PSHAQ	0.28**
DAS28	0.46**
RAPID3	0.51**

† Variables tested after square-root transformation. * $p < 0.05$; ** $p < 0.001$. RA: rheumatoid arthritis; HAQ: Health Assessment Questionnaire; GH: patient's assessment of general health; EGA: evaluator's assessment of global disease activity; TJC28: tender joint count 28; SJC28: swollen joint count 28; ESR: erythrocyte sedimentation rate; PSHAQ: psychological HAQ; DAS28: Disease Activity Score 28-joint count; RAPID3: Routine Assessment of Patient Index Data 3.

interval 0.72–0.75). There was no significant difference among patients with early and late RA (data not shown). Table 5 shows likelihood ratios of having active disease for different MS duration categories.

The results of a test for fixed effects in an ANCOVA to understand the role of addition of MS duration to RAPID3 in predicting DAS28v3 are shown in Table 6. MS duration was significantly associated with DAS28v3. A highly significant interactive effect between RAPID3 and MS duration categories was revealed. This implies that for each MS category there is a separate line that describes the relationship between RAPID3 and DAS28v3 as shown in Table 7. The significant interaction also implies that differences between MS duration categories with respect to mean DAS28v3 values depend on RAPID3 values. Estimates of DAS28v3 means for the MS duration categories are presented for several RAPID3 values in Table 8. These results are clinically important at the RAPID3 scores (< 6) that are considered to represent low disease activity. In patients with the low RAPID3 scores, presence of MS may indicate presence of clinically active disease (DAS28v3 > 3.2). At higher RAPID3 scores, patients are likely to have clinically active disease irrespective of the MS duration.

The results of test for fixed effects in an ANCOVA to better understand the contribution of MS duration and individual PRO in RAPID3 are shown in Table 9. HAQ was the strongest variable, followed by pain, MS duration, and GH for association with DAS28v3 scores. The pain-by-MS-duration interaction contributed significantly to the model ($p = 0.01$), while the HAQ-by-MS interaction was not quite significant ($p = 0.052$). The effect of MS duration is complex and difficult to quantify, as it depends on both pain and HAQ values. What is clear is that MS duration contributes significantly to the model. Table 10 shows results of partial correlation between DAS28v3 with MS duration and RAPID 3 variables. HAQ has the strongest association with DAS28v3 after adjustment for GH, pain, and MS duration. The partial correlations for MS duration and pain are essentially the same, while GH appears to contribute the least.

DISCUSSION

In this study, we showed that MS duration correlates better with physical function, pain, and GH than with quantitative joint counts and ESR. This is consistent with the findings of a previous report[13]. MS duration correlates with the degree of inflammatory activity in patients with RA and has moderate accuracy in distinguishing clinically active from inac-

Table 3. Distribution of morning stiffness duration according to the RA severity as assessed by Disease Activity Score 28-joint count (DAS28).

RA Activity	n	0 min	1–30 min	31–60 min	> 60 min
Remission, n (%)	1016	630 (62.0)	249 (24.5)	73 (7.2)	64 (6.3)
Low, n (%)	578	264 (45.7)	189 (32.7)	68 (11.8)	57 (9.9)
Moderate, n (%)	1959	554 (28.3)	637 (32.5)	340 (17.4)	428 (21.8)
High, n (%)	1677	198 (11.8)	421 (25.1)	372 (22.2)	686 (40.9)
Total, n (%)	5230	1646 (31.5)	1496 (28.6)	853 (16.3)	1235 (23.6)

Table 4. Pairwise comparison of morning stiffness duration in patients with different rheumatoid arthritis activity. Values represent mean difference in morning stiffness duration (95% confidence interval for mean difference, p).

RA Activity	High	Moderate	Low
Remission	71.4 (64.8–78.0, < 0.001)	33.2 (27.8–38.6, < 0.001)	8.9 (2.5–15.2, 0.001)
Low	62.6 (54.9–70.2, < 0.001)	24.3 (17.7–30.9), < 0.001)	
Moderate	38.2 (31.4–45.0, < 0.001)		

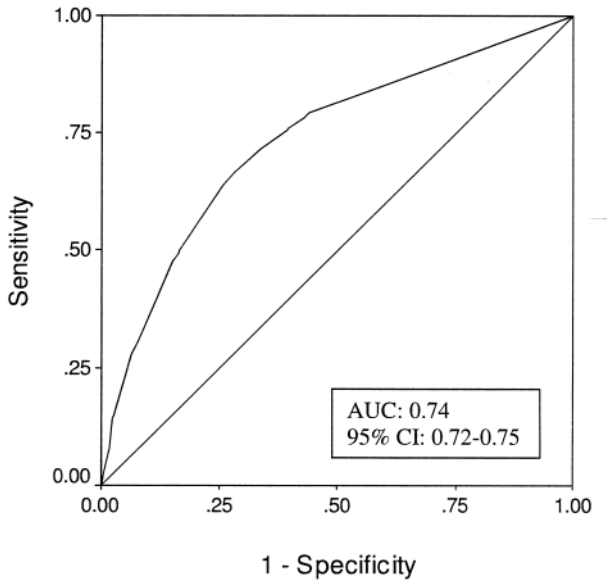

Figure 1. Receiver-operating characteristic (ROC) curve for morning stiffness duration to distinguish active from inactive disease. AUC: area under the curve.

tive RA. MS duration made a significant independent contribution and showed an interactive effect with RAPID3 in predicting DAS28v3. As an individual PRO, MS duration contributed more than GH in predicting DAS28v3. Partial correlation statistics also showed MS duration to have stronger correlation with DAS28v3 than GH.

Morning stiffness is a complex symptom. Most patients describe MS either alone or as a combination of difficulty moving, pain, or abnormal sensation of tightness[4,30]. All our patients were assessed by a standard self-report questionnaire, ensuring consistency in information collected. The questionnaire assessed the MS duration from time of waking up to its maximal improvement. This manner of assessing MS duration has been shown to have the least daily intra-individual variability and to be the best indicator of average MS duration experienced by the patient[31].

The pathophysiology of MS in RA has been linked to abnormalities in circadian rhythm of the hypothalamic-pituitary-adrenal (HPA) axis. Abnormally high levels of cytokines like interleukin 6 and tumor necrosis factor-α have been implicated in derangement of the HPA axis, resulting in earlier than normal peak in serum cortisol and inappropriately low or normal cortisol levels in relation to the degree of inflammation due to RA activity[32]. A modified-release form of prednisone that seeks to restore the normal circadian rhythm of endogenous cortisol has been shown to significantly improve MS duration without affecting other RA variables and disease activity[33]. This is in concordance with our finding that MS duration has a moderate correlation with RA disease activity.

There is dearth of data on the actual effect of MS on patients with RA, although a recent study showed that severe baseline MS (by VAS) in patients with early RA was predictive of premature retirement. However, when DAS28 and HAQ scores were entered into the analysis, MS lost its predictive power[34]. Our data do not address this aspect of MS. There is a need to identify which groups of patients are significantly affected and in what manner by MS before using it as a therapeutic target.

Quantitative joint counts are commonly not performed, and frequently the acute-phase reactants are unavailable during the patient's assessment in routine clinical practice. This has driven the interest in development of composite indices based solely on PRO variables to improve the feasibility and efficiency of quantitative RA activity assessment in a standardized manner. Resources (time and personnel) are limited in clinical practice. Assessment of RA variables that provide maximum information about disease activity in a non-overlapping manner would facilitate most efficient use of clinical resources. As MS duration can easily be inquired in a standardized manner by a patient questionnaire, we were particularly interested in assessing its possible value as part of a composite PRO index. We did this indirectly by assessing whether addition of MS duration to RAPID3 improved its correlation with and prediction of DAS28v3 scores. We used DAS28v3 instead of DAS28 based on 4 variables to avoid confounding by GH as a common shared variable. The results showed that MS duration made significant important contribution in addition to RAPID3 in explaining DAS28v3 variance. However, a highly significant interaction between MS duration and RAPID3 implies that the effect of MS duration on DAS28v3

Table 5. Positive likelihood ratios for having active rheumatoid arthritis with different durations of morning stiffness.

Morning Stiffness Duration, min	Active Disease† n (%)	Less Active Disease† n (%)	Positive Likelihood Ratio (95% CI)
0	752 (21)	894 (59)	0.35 (0.32–0.38)
1–30	1058 (29)	352 (24)	1.06 (0.96–1.16)
31–60	712 (19)	141 (9)	2.21 (1.87–2.63)
> 60	1114 (31)	121 (8)	4.04 (3.38–4.82)
Total, n	3636	1508	

† Active disease (DAS 28 > 3.2) and less active disease (DAS28 ≤ 3.2). DAS: Disease Activity Score.

Table 6. Type 3 tests of fixed effects in analysis of covariance to assess the utility of adding morning stiffness (MS) duration to RAPID3 in predicting the DAS28v3.

Effect†	NDF	DDF	F value	p
MS duration	3	5120	35.6	< 0.0001
RAPID3	1	5133	742.8	< 0.0001
RAPID3*MS	3	5119	5.92	0.0005

† Country of origin was included as a random effect to adjust for cultural effects. MS duration is included as a categorical variable with the following groupings: 0 min, 1–30 min, 31–60 min, and > 60 min. The RAPID3 variable was included in the model as a continuous variable. NDF: numerator degree of freedom; DDF: denominator degree of freedom; DAS28v3: Disease Activity Score 28 based on 3 variables; RAPID3: Routine Assessment of Patient Index Data 3.

Table 7. Linear regression equations for each category of morning stiffness (MS) duration describing relationship between DAS28v3 and RAPID3.

MS Duration, min	Equation	p
0	DASv3 = 2.759 + 0.1293*RAPID3	< 0.001
1–30	DASv3 = 3.189 + 0.1077*RAPID3	< 0.001
31–60	DASv3 = 3.692 + 0.0833*RAPID3	< 0.001
> 60	DASv3 = 3.637 + 0.1063*RAPID3	< 0.001

DAS28v3: Disease Activity Score 28 based on 3 variables; RAPID3: Routine Assessment of Patient Index Data 3.

depends upon level of RAPID3. We estimated DAS28v3 at several RAPID3 levels to understand the clinical implications of these results. Our findings are clinically relevant for patients with low RAPID3 scores (< 6). In these patients, assessment of MS duration would be valuable and may lead to change in assessment of level of RA activity. For patients with higher RAPID3 scores, RA activity remains clinically unchanged irrespective of MS duration.

We recognize several limitations of our findings. First, we have used DAS28 as a surrogate for RA disease activity. Although widely used, DAS28 may not be a completely accurate measure of inflammatory activity of RA. A patient may have tenderness or swelling in several joints while having a DAS28 in the "remission" state[35]. DAS28 is also more sensitive to ESR, and clinically small changes in ESR may cause changes in DAS28[36]. Nevertheless, DAS28 has been extensively validated in both clinical trials and clinical practice, and is significantly correlated with disability and radiographic progression[37].

Table 9. Type 3 test of fixed effects for an analysis of covariance model with DAS28v3 as dependent variable that includes morning stiffness (MS) duration and individual RAPID3 variables.

Effect	NDF	DDF	F value	p
MS duration	3	5112	36.9	< 0.0001
HAQ	1	5112	249.4	< 0.0001
Pain	1	5112	93.9	< 0.0001
GH	1	5112	13.3	0.0003
HAQ*MS	3	5112	2.02	0.0519
Pain*MS	3	5112	2.37	0.0104

NDF: numerator degree of freedom; DDF: denominator degree of freedom; DAS28v3: Disease Activity Score 28 based on 3 variables; RAPID3: Routine Assessment of Patient Index Data 3; HAQ: Health Assessment Questionnaire; GH: general health.

Table 10. Partial correlation coefficients between DAS28v3 and general health (GH), HAQ, pain, and morning stiffness (MS) duration.

	Partial Correlation Coefficients		
Predictor	Pearson's	Spearman's	p
GH	0.0836	0.0732	< 0.001
HAQ	0.2621	0.2589	< 0.001
Pain	0.1696	0.1543	< 0.001
MS duration	0.1348	0.1678	< 0.001

DAS28v3: Disease Activity Score 28 based on 3 variables; HAQ: Health Assessment Questionnaire; GH: general health.

Second, our data were collected from a very diverse range of patients in many countries. Although collected in a standardized manner, it is possible that socioeconomic and cultural factors may have affected the assessment, particularly of the PRO. On the other hand, our results derived from a diverse group of patients with RA are more generalizable. While not a perfect solution, we did use mixed-effect ANCOVA models with country of origin as a random effect to adjust for potential cultural effects.

Third, we assessed MS in the form of a time interval. The

Table 8. Estimates of mean DAS28v3 of categories of morning stiffness duration at several levels of RAPID3. Values are estimated mean (95% confidence interval).

RAPID3	Morning Stiffness duration, min			
	0	1–30	31–60	> 60
1	2.89 (2.62–3.16)	3.30 (3.02–3.57)	3.77 (3.46–4.09)	3.74 (3.43–4.05)
3	3.15 (2.89–3.41)	3.51 (3.24–3.78)	3.94 (3.64–4.24)	3.96 (3.66–4.25)
6	3.54 (3.28–3.79)	3.83 (3.57–4.10)	4.19 (3.91–4.47)	4.27 (4.00–4.55)
12	4.31 (4.04–4.58)	4.48 (4.22–4.74)	4.69 (4.43–4.96)	4.91 (4.65–5.17)
20	5.34 (5.03–5.66)	5.34 (5.05–5.64)	5.36 (5.05–5.66)	5.76 (5.48–6.04)

DAS28v3: Disease Activity Score 28 based on 3 variables; RAPID3: Routine Assessment of Patient Index Data 3.

2002 ACR guidelines for management of RA do recommend collecting MS information in the form of duration[9]. However, MS has also been evaluated by other means, such as assessing severity by VAS and a numerical rating scale[30,38]. Compared with MS duration, MS by VAS has been reported to have a normal distribution, better correlation with RA disease activity, and more responsiveness to treatment effect[38]. MS assessment by severity scale may need to be studied for its possible utility as a component of a PRO index.

Fourth, our data are based on cross-sectional assessment of patients with RA. We cannot comment upon the responsiveness of MS duration to effective treatment.

Finally, it is important to stress that we assessed the role of MS duration in patients with an established RA diagnosis. MS duration has been shown to be predictive of development of persistent arthritis, and erosive arthritis in patients presenting with early undifferentiated arthritis[39]. Our results do not preclude other possible applications of MS duration in inflammatory arthritis.

In conclusion, we found that duration of MS correlates better with other PRO than joint counts and ESR. As an individual variable, the duration of MS had a moderate ability to differentiate active from inactive RA. Assessment of duration of MS in patients with low RAPID3 scores may be clinically relevant.

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