

## Letter

## Should Quantitative Measures and Management of Rheumatoid Arthritis Include More Than Control of Inflammatory Activity?

To the Editor:

We agree strongly with Kremer et al that "metrics are essential for evaluating disease activity in patients with rheumatoid arthritis (RA)." Nonetheless, data reported from the Corrona and the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS) registries for Clinical Disease Activity Index (CDAI) and Routine Assessment of Patient Index Data 3 (RAPID3) are quite similar to those reported in the initial 2008 RAPID3 report. In the Corrona, BRASS, and 2008 RAPID3 databases, mean scores, respectively, for CDAI were 11.2, 19.5, and 12.3; RAPID3 8.2, 7.6, and 8.7; correlations of CDAI and RAPID3 0.72, 0.58, and 0.74;  $\kappa$  0.24, 0.24, and 0.32; and weighted  $\kappa$  0.49, 0.39, and 0.51 (Table 1). The proportion of patients in remission (REM) or low disease activity (LDA) in the 3 databases, respec-

tively, were 60%, 39%, and 51% for CDAI, and 46%, 48%, and 51% for RAPID3 (Table 1).

Similar results may certainly be interpreted differently by different observers, and we respect that others may find "significant disparities" between indices that we suggested give similar results. At the same time, it appears disappointing that little change is seen in the Disease Activity Score in 28 joints, CDAI, and RAPID3 data after a decade of "treat to target" with a target of remission, recognizing that some patients were treated years before the reports and that the target may be modified to LDA or even to higher disease activity levels based on shared decisions.

The Kremer et al study notes that "both registries show close to one-third (34% Corrona and 28% BRASS) Corrona RAPID3 indicating potential acceleration [moderate/high disease activity (MDA/HDA)], whereas CDAI indicates REM/LDA." However, close to one-quarter (17% Corrona and 32% BRASS) have MDA/HDA by RAPID3, but LDA/REM by CDAI (Table 3 in Kremer et al¹). The CDAI appears regarded as a superior gold standard vs RAPID3 for management decisions; perhaps that is the case, but no supporting data concerning subsequent patient status are presented.

Table 1. Measures and indices to assess patients and RA in 3 databases (2 reported in 2021 and 1 in 2008).

	Corrona, 2021 <sup>1</sup>	BRASS, 2021 <sup>1</sup>	RAPID3, 2008 <sup>2</sup>
N	48,255	1343	285
Age, yrs	61.73 (13.91)	55.90 (14.16)	57.4 (14.6)
Female sex, %	76.36	82.20	73.0
Disease duration, yrs, median (IQR)	9 (4–17)	8 (3-19)	Mean 9.7 (SD 9.8)
Swollen joint count	2.71 (4.42)	6.20 (7.05)	3.7 (4.1)
Tender joint count	3.35 (5.46)	7.04 (7.71)	3.5 (5.2)
Physician global assessment	19.26 (20.40)	30.58 (21.79)	2.0 (1.4)
MDHAQ function			2.1 (1.9) <sup>a</sup>
Patient pain	35.11 (28.84)	34.56 (27.32)	3.5 (2.7) <sup>a</sup>
Patient global assessment	32.58 (27.41)	31.67 (25.18)	3.1 (2.5) <sup>a</sup>
Disease activity/severity			
CDAI	11.24 (11.50)	19.47 (16.45)	12.3 (10.6)
Remission (CDAI ≤ 2.8), %	25.34	12.51	18.0
Low $(2.8 < CDAI \le 10.0)$ , %	34.74	26.81	33.0
Moderate (10.0 < CDAI ≤ 22.0), %	24.75	24.65	32.0
Severe (CDAI > 22), %	15.17	36.04	17.0
RAPID3	8.15 (6.25) <sup>b</sup>	7.62 (5.45)	8.7 (6.6)
Remission (RAPID3 ≤ 3.0), %	31.22 <sup>b</sup>	28.74	37.0
Low $(3.0 < RAPID3 \le 6.0)$ , %	14.82 <sup>b</sup>	19.14	14.0
Moderate (6.0 < RAPID3 ≤ 12.0), %	25.09 <sup>b</sup>	31.57	32.0
Severe (RAPID3 > 12.0), %	28.87 <sup>b</sup>	20.55	17.0
Correlation (CDAI vs RAPID3)	$0.72^{b}$	0.58	0.74
κ (CDAI vs RAPID3)	0.24	0.24	0.32
Weighted κ (CDAI vs RAPID3)	0.49	0.39	0.51

Values are expressed as mean (SD) unless otherwise indicated. <sup>a</sup> Values multiplied by 10 to be comparable to Kremer et al<sup>1</sup> report. <sup>b</sup> cRAPID3 is a modified version of the RAPID3 that does not include 2 complex activities and scores are lower than RAPID3. <sup>1</sup> CDAI: Clinical Disease Activity Index; cRAPID3: Corrona RAPID3; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MDHAQ: Multidimensional Health Assessment Questionnaire; RA: rheumatoid arthritis; RAPID3: Routine Assessment of Patient Index Data 3.

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Perhaps the most informative comparison of the 2 measures may be the levels of agreement of 73% between CDAI and RAPID3 for MDA/HDA vs LDA/REM in Corrona and 70% in BRASS,¹ again similar to 77% in the 2008 RAPID3 report² (Table 2). In our view, these levels do not reflect "significant disparities" for clinical measures. For example, agreement between normal and abnormal erythrocyte sedimentation rate vs C-reactive protein were 77% and 70% in Finland and USA⁴ (Table 2). Even agreement between 2 major reference depression screening questionnaires, the Patient Health Questionnaire-9 (PHQ-9) and Hospital Anxiety and Depression Scale

Depression subscale (HADS-D), was 82%.<sup>5</sup> Many "disparities" result from conversion of continuous to categorical variables; if disparities were large, correlations between CDAI vs RAPID3 could not be > 0.72 in 2 databases and 0.58 in the third (Table 1).

We also agree strongly that RAPID3 "scores should not be used in isolation to either evaluate ongoing RA inflammation or to adjust treatment," but suggest that this principle applies to the CDAI and every RA measure or index. Measures of inflammatory activity only are adequate for selected patients in clinical trials<sup>6</sup>; in routine care, joint and other organ damage, distress seen in fibromyalgia (FM) and depression, and comorbidities

Table 2. Agreement for CDAI with RAPID3 in 3 databases<sup>1,2</sup> as well as ESR vs CRP.<sup>4</sup>

				Overall Agreement
Corrona <sup>1</sup>		cRAPID3 <sup>a</sup>		
CDAI REM/LDA MDA/HDA Agree Disagree	REM/LDA 19,014 (65.6) 3201 (16.6)		MDA/HDA 9977 (34.4) 16,063 (83.4)	35,077 (72.7) 13,178 (27.3)
Total				48,255
BRASS <sup>1</sup>		cRAPID3 <sup>a</sup>		
CDAI REM/LDA MDA/HDA Agree Disagree Total	REM/LDA 382 (72.4) 261 (32.0)		MDA/HDA 146 (27.7) 554 (68.0)	936 (69.7) 407 (30.3) 1343
2008 report <sup>2</sup>		RAPID3		
CDAI REM/LDA MDA/HDA Agree Disagree	REM/LDA 101 (81.4) 44 (27.3)		MDA/HDA 23 (18.6) 117 (72.7)	218 (76.5) 67 (23.5)
Total				285
2009 report <sup>4</sup>		ESR		
Jyväskylä cohort, 2009 <sup>4</sup>	≥ 28 mm/h		< 28 mm/h	
CRP ≥ 10 mg/L CRP < 10 mg/L Agree	775 (44.0) 199 (11.0)		202 (12.0) 568 (33.0)	1343 (77.0)
Disagree Total				401 (23.0) 1744
Nashville cohort, 2009 <sup>4</sup>				
CRP ≥ 10 mg/L	48 (28.0)		22 (13.0)	
CRP < 10 mg/L Agree Disagree Total	29 (17.0)		71 (42.0)	119 (70.0) 51 (30.0) 170

Values are n (%) unless otherwise indicated. <sup>a</sup> cRAPID3<sup>1</sup> is a modified version of the RAPID3 that does not include 2 complex activities and scores are lower than RAPID3. <sup>2</sup> CDAI: Clinical Disease Activity Index; cRAPID3: Corrona RAPID3; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MDA/HDA: moderate/high disease activity; RAPID3: Routine Assessment of Patient Index Data 3; REM/LDA: remission/low disease activity.

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are common in many patients, and might be quantitated. It is possible—perhaps likely—that similar scores for CDAI and RAPID3 in the 2008 and 2021 reports may result more from inflammation in 2008 and from damage in 2021<sup>1,2</sup>; this hypothesis cannot be studied without data concerning damage.

Joint damage may be assessed quantitatively by including limited motion/deformity, in addition to swelling and tenderness/pain on motion, as described in the initial 28-joint count report.<sup>7</sup> Limited motion/deformity has been omitted in clinical trials (appropriately), as noted above, but that omission has been adopted in routine care (perhaps inappropriately), losing a possible measure of damage over long periods. Joint damage also may be quantitated on a physician RheuMetric checklist, with 0–10 visual numeric scales for inflammation, damage, and patient distress.<sup>8</sup> In a previous study, higher scores for damage than for inflammation were seen in patients with RA,<sup>8</sup> suggesting that most patients may have joint damage, which may progress on a biomechanical basis regardless of optimal control of inflammation.

Patient distress also may be screened for quantitatively, using 2 indices within the Multidimensional Health Assessment Questionnaire (MDHAQ) beyond RAPID3: the FAST4 (Fibromyalgia Assessment Screening Tool 4)9 and DEP2 (depression).5 These indices agree > 80% with formal 2011 FM criteria9 and reference PHQ-9 and HADS-D questionnaires (similar to the level of agreement of PHQ-9 with HADS-D),5 without an additional questionnaire such as the 2011 FM criteria, PHQ-9, HADS, or other 1-page questionnaire, and can be helpful to clarify patient global assessment.

Rheumatologists care for patients, not inflammation, although control of inflammation remains a primary (and most satisfying) goal. The full MDHAQ beyond RAPID3, which we have always used in clinical care and published reports, and a physician RheuMetric checklist may recognize that many (perhaps most) patients have some joint damage as well as distress and/or comorbidities. These problems might be assessed quantitatively by rheumatologists beyond inflammatory activity, since "metrics are essential" to advance care and outcomes for our patients.

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TP is president of Medical History Services LLC, which receives royalties and license fees from for-profit pharmaceutical companies and electronic medical record companies for use of MDHAQ and RAPID3. All license fees are used to support further development of quantitative measurement in clinical rheumatology care using patient and physician questionnaires. MJB receives speaking/consulting fees from AbbVie, Amgen, BMS, GSK, Janssen, Merck, Novartis, Pfizer, Sandoz, Sanofi, and Scifer; and is a shareholder of Merck and Johnson & Johnson. YY receives research support from Amgen and BMS, and is a consultant for Amgen, BMS, and Sanofi. Address correspondence to Dr. T. Pincus, Rush University, 1611 West Harrison Street, Suite 510, Chicago, IL 60612, USA. Email: tedpincus@gmail.com.

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