The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.210953
First Release October 15 2021

The Journal of Rheumatology

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)."[1] 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.[2] 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, respectively, 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"[1] between indices that we suggested give similar results.[2] 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,[3] 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.[3]

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."[1] 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 al[1]). 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[1] | BRASS, 2021[1] | RAPID3, 2008[2] |
|---|---|---|---|
| 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)[a] |
| Patient pain | 35.11 (28.84) | 34.56 (27.32) | 3.5 (2.7)[a] |
| Patient global assessment | 32.58 (27.41) | 31.67 (25.18) | 3.1 (2.5)[a] |
| 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 ≤ 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)[b] | 7.62 (5.45) | 8.7 (6.6) |
| Remission (RAPID3 ≤ 3.0), % | 31.22[b] | 28.74 | 37.0 |
| Low (3.0 < RAPID3 ≤ 6.0), % | 14.82[b] | 19.14 | 14.0 |
| Moderate (6.0 < RAPID3 ≤ 12.0), % | 25.09[b] | 31.57 | 32.0 |
| Severe (RAPID3 > 12.0), % | 28.87[b] | 20.55 | 17.0 |
| Correlation (CDAI vs RAPID3) | 0.72[b] | 0.58 | 0.74 |
| $\kappa$ (CDAI vs RAPID3) | 0.24 | 0.24 | 0.32 |
| Weighted $\kappa$ (CDAI vs RAPID3) | 0.49 | 0.39 | 0.51 |

Values are expressed as mean (SD) unless otherwise indicated. [a] Values multiplied by 10 to be comparable to Kremer et al[1] report. [b] cRAPID3 is a modified version of the RAPID3 that does not include 2 complex activities and scores are lower than RAPID3.[1] 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.

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 report[2] (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 USA[4] (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%.[5] 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,"[1] 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[6]; 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[1,2] as well as ESR vs CRP.[4]

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

Values are n (%) unless otherwise indicated. [a] cRAPID3[1] is a modified version of the RAPID3 that does not include 2 complex activities and scores are lower than RAPID3.[2] 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.

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[1,2]; 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.[7] 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.[8] In a previous study, higher scores for damage than for inflammation were seen in patients with RA,[8] 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 criteria[9] 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"[1] to advance care and outcomes for our patients.

Theodore Pincus[1], MD
Martin J. Bergman[2], MD
Yusuf Yazici[3], MD
[1]Rush University Medical Center, Chicago, Illinois;
[2]Drexel University, College of Medicine, Philadelphia, Pennsylvania;
[3]NYU School of Medicine, New York, New York, USA.

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.

## REFERENCES

1. Kremer JM, Pappas DA, Kane K, et al. The Clinical Disease Activity Index and the Routine Assessment of Patient Index Data 3 for achievement of treatment strategies. J Rheumatol xxxxxxxxxx.
2. Pincus T, Swearingen CJ, Bergman M, Yazici Y. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol 2008;35:2136-47.
3. Smolen JS, Aletaha D, Bijlsma JW, et al; T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
4. Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J Rheumatol 2009;36:1387-90.
5. Morla RM, Li T, Castrejon I, Luta G, Pincus T. Multidimensional Health Assessment Questionnaire as an effective tool to screen for depression in routine rheumatology care. Arthritis Care Res 2021;73:120-9.
6. Pincus T, Richardson B, Strand V, Bergman MJ. Relative efficiencies of the 7 rheumatoid arthritis Core Data Set measures to distinguish active from control treatments in 9 comparisons from clinical trials of 5 agents. Clin Exp Rheumatol 2014;5 Suppl 85:S47-54.
7. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32:531-7.
8. Castrejon I, Gibson KA, Block JA, Everakes SL, Jain R, Pincus T. RheuMetric A physician checklist to record patient levels of inflammation, damage and distress as quantitative data rather than as narrative impressions. Bull Hosp Jt Dis 2015;73:178-84.
9. Gibson KA, Castrejon I, Descallar J, Pincus T. Fibromyalgia Assessment Screening Tool: clues to fibromyalgia on a Multidimensional Health Assessment Questionnaire for Routine Care. J Rheumatol 2020;47:761-9.