A Proposal to Standardize Low Disease Activity Criteria in Rheumatoid Arthritis Based on the Outcome Measures in Rheumatology Minimal Disease Activity Definition

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Objective. We aimed to standardize the definition of low disease activity in rheumatoid arthritis (RA) using the Outcome Measures in Rheumatology (OMERACT) group's proposed definition of minimal disease activity.

Method. Based on a nationwide RA database, we proposed new Boolean low disease activity criteria using OMERACT’s core set definition of minimal disease activity that requires the fulfillment of at least five of the following seven core set measures: a pain score of 2 or less, a swollen joint count (SJC28) of 1 or fewer, a tender joint count of 1 or fewer, a Health Assessment Questionnaire score of 0.5 or less, a Physician’s Global Assessment score of 1.5 or less, a Patient’s Global Assessment score of 2 or less, and an erythrocyte sedimentation rate (ESR) of 20 mm/h or less. Using receiver operating characteristic analysis, we determined the cutoffs for the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Routine Assessment of Patient Index Data 3 (RAPID3), and the Disease Activity Score in 28 joints (DAS28)–ESR.

Results. Of 8298 patients, 56.2% met the proposed Boolean low disease activity criteria. We determined an SDAI score of 5.5 or less and a CDAI score of 5 or less to be the new cutoffs, and we chose a DAS28 of 2.85 or less (the original cutoff for DAS-based minimal disease activity) and a RAPID3 score of 6 or less (with SJC of 2 or fewer) as the cutoffs for DAS28 and RAPID3. The agreement between the new cutoffs for DAS28 of 2.85 or less vs. CDAI score of 5 or less, CDAI score of 5 or less vs. RAPID3 score of 6 or less (with SJC of 2 or fewer), and DAS28 of 2.85 or less vs. RAPID3 score of 6 or less (with SJC of 2 or fewer), was 0.619, 0.612 (0.702), and 0.474 (0.531), respectively.

Conclusion. OMERACT’s minimal disease activity definition may be used to standardize the criteria for low disease activity.

INTRODUCTION

The ability to achieve remission has significantly improved outcomes in patients with rheumatoid arthritis (RA). With the endorsement of treat-to-target as a standard therapeutic strategy for RA by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), the Disease Activity Score in 28 joints (DAS28) (1), Clinical Disease Activity Index (CDAI) (2), Simplified Disease Activity Index (SDAI) (3), and Routine Assessment of Patient Index Data 3 (RAPID3) (4) are now frequently used to assess disease activity in RA (5,6). The treat-to-target strategy aims at remission as the treatment target (7,8). Both the ACR and EULAR proposed the following two sets of remission criteria: the Boolean criteria (the fulfillment of the four core set measures of tender joint count [TJC] of 1 or fewer, swollen joint count [SJC] of 1 or fewer, C-reactive protein [CRP] of 1 mg/dl or less, and patient global assessment [PtGA] score of 1 or less) and the SDAI-based criteria (an SDAI score of 3.3 or less), to which the CDAI-based criteria (a CDAI score of 2.8 or less) and the SDAI-based criteria (an SDAI score of 3.3 or less), to which the CDAI-based criteria (a CDAI score of 2.8 or less) and the SDAI-based criteria (an SDAI score of 3.3 or less), to which the CDAI-based criteria (a CDAI score of 2.8 or less) were considered equivalent in clinical practice (9). As for RAPID3, a RAPID3 score of 3 or less with an SJC of 1 or fewer is also similar to the ACR/EULAR remission criteria (10).
Low disease activity is considered an acceptable treatment goal in patients with difficulty achieving remission (7,8). However, unlike the ACR / EULAR remission criteria, the low disease activity state is not well defined. We separately determined the cutoffs for the DAS28-erythrocyte sedimentation rate (ESR), SDAI, CDAI, and RAPID3 for categorizing remission and low, moderate, and high disease activity but did not assess the interclass correlation in their validation. Although these measures strongly correlate with each other, categorization of the different disease activity states in terms of the cutoff values revealed significant disagreement (11).

Before the development of the ACR/EULAR remission criteria, Outcome Measures in Rheumatology (OMERACT), an international initiative aimed at harmonizing outcome metrics in RA, defined minimal RA disease activity as a state considered acceptable by both the patient and physician (12). OMERACT asked rheumatologists to assess 60 patient profiles describing real patients with RA seen in routine clinical practice. Based on their responses, OMERACT designed and discussed several candidate definitions for minimal disease activity. Feedback from participants and additional on-site analyses using a cross-sectional database allowed the formulation of two preliminary equivalent definitions of minimal disease activity: one based on the DAS28-ESR and one based on the seven core set measures. OMERACT then defined minimal disease activity, stating that any patient in remission should be considered to have minimal disease activity. Thus, zero tender and swollen joints and an ESR of less than 10 mm/h are considered to be indicative of minimal disease activity. In the DAS28-based definition, a DAS28-ESR of 2.85 or less was the best combination of sensitivity (94%) and specificity (86%), and for the core set definition of minimal disease activity, the seven core set measures of a pain score of 2 or less, an SJC of 1 or fewer, a TJC of 1 or fewer, a Health Assessment Questionnaire (HAQ) score of 0.5 or less, a physician global assessment (PhGA) score of 1.5 or less, a PtGA score of 2 or less, and an ESR of 20 mm/h or less were selected based on an 80% consensus among the stakeholders. Fulfillment of five of the seven core set measures had the best combination of sensitivity (88%) and specificity (82%).

If low disease activity is used as an alternative treatment target in the treat-to-target strategy, low disease activity should be redefined. OMERACT’s proposed definition of minimal disease activity may serve to define low disease activity. Patients with minimal disease activity showed substantially better outcomes, including a tenfold reduction in work disability and an approximately twofold reduction in total joint replacement and mortality (13). Herein, we propose Boolean low disease activity criteria for clinical research and new cutoffs for the DAS28-ESR, SDAI, CDAI, and RAPID3 for use in routine clinical practice.

**PATIENTS AND METHODS**

**Patients.** We analyzed data from patients registered with the NinJa database in 2015 for this cross-sectional study. The NinJa database is a nationwide, multicenter observational database that was established in 2002 and contains data on patients with RA treated in Japan. Patients with RA at each participating medical institution were enrolled in NinJa. The clinical data on patients with RA registered in NinJa are collected once a year from each patient at any time point. This study was reviewed and approved by the research ethics committees of the participating institutions.

**Methods.** We defined the Boolean low disease activity criteria as the fulfillment of at least five of seven core set measures, namely, a pain score of 2 or less, an SJC of 1 or fewer, a TJC of 1 or fewer, an HAQ score of 0.5 or less, a PhGA score of 1.5 or less, a PtGA score of 2 or less, and an ESR of 20 mm/h or less. First, we evaluated the current cutoff for DAS28-based minimal disease activity and the current cutoffs for low disease activity for the DAS28, SDAI, CDAI, and RAPID3. If we considered these cutoffs to be inappropriate, we used receiver operating characteristic (ROC) curve analysis to determine the cutoffs for the proposed Boolean low disease activity criteria. We then compared the degree of agreement between the new and current cutoffs.

**Statistics.** We measured the correlation among the disease activity indices using Spearman’s rank correlation coefficient and measured the agreement among the various categories of the disease indices using κ statistics. We used ROC curve analysis to calculate the best trade-off between sensitivity and specificity. We considered a two-sided P of less than 0.05 to be statistically significant and performed all the analyses using JMP version 11.2.0 (SAS Institute, Inc).
RESULTS

We used data from NinJa 2015, which contains data on 15,100 patients with RA collected between April 1, 2015, and March 31, 2016. We excluded patients missing any of the following values needed to assess the DAS28-ESR and the SDAI, CDAI, and RAPID3 scores: SJC, TJC, PhGA score, PtGA score, pain score, CRP, ESR, HAQ score, or multi-dimensional health assessment questionnaire (MDHAQ). Table 1 shows a summary of the patient characteristics.

Among the 8298 patients analyzed, the mean (SD) of the DAS28 and the SDAI, CDAI, and RAPID3 scores was 2.94 (1.21), 6.9 (7.2), 6.4 (6.8), and 6.4 (5.9), respectively. Spearman’s rank correlation coefficient of the DAS28 vs. the SDAI (CDAI), the SDAI (CDAI) vs. the RAPID3, and the DAS28 vs. the RAPID3 was 0.891, 0.953, 0.952, and 0.941, respectively (Supplementary Material).

We used a DAS28 of 2.85 or less, the DAS28 definition of minimal disease activity, as the DAS28-based definition because the sensitivity and specificity of the DAS28 of 2.85 or less for detecting the proposed Boolean criteria was 79% and 82%, respectively.

Using the Youden index, we determined the SDAI score of 5.5 or less, the CDAI score of 5 or less, the RAPID3 score of 6 or less, and the DAS28 of 3.2 or less vs. the CDAI score of 10 or less, and a RAPID3 score of 6 or less, and a CDAI score of 10 or less as the RAPID3-based definition. The agreements between the current cutoffs of the DAS28 of 2.85 or less, an SDAI score of 5.5 or less, and a RAPID3 score of 6 or less, and a CDAI score of 10 or less with an SJC of 2 or fewer, respectively (Table 2).

The agreements between the current cutoffs of the DAS28 of 3.2 or less vs. the CDAI score of 10 or less, the CDAI score of 10 or less vs. the RAPID3 score of 6 or less, and the DAS28 of 3.2...

Table 1. Patient characteristics (N = 8298)

| Characteristics          | Results          |
|--------------------------|------------------|
| Age, y                   | 64.4 (13.0)      |
| Disease duration, mean (SD), y | 13.1 (11.0)      |
| Female, n (%)            | 6680 (80.5)      |
| Steinbrocker classification of radiographic stages, %a |                      |
| Stage I                  | 26               |
| Stage II                 | 27               |
| Stage III                | 20               |
| Stage IV                 | 28               |
| Steinbrocker classification of functional classes, %a |                      |
| Class 1                  | 40               |
| Class 2                  | 40               |
| Class 3                  | 17               |
| Class 4                  | 3                |
| Prosthetic joint replacement, n (%) | 1224 (14.8)      |
| Glucocorticoid use, n (%) | 2814 (33.9)      |
| Equivalent dose of prednisolone, mean (SD), mg/d | 4.0 (2.7)        |
| csDMARD use, n (%)       | 7120 (85.8)      |
| Methotrexate use, n (%)  | 5404 (65.1)      |
| bDMARD use, n (%)        | 2464 (29.7)      |
| tsDMARD use, n (%)       | 106 (1.3)        |
| Pain score (0-10), mean (SD) | 2.3 (2.3)       |
| PhGA score (0-10), mean (SD) | 2.4 (2.2)       |
| HAQ score (0-3), mean (SD) | 0.6 (0.8)       |
| CRP, mean (SD), mg/dl    | 0.5 (1.2)        |
| ESR, mean (SD), mm/h     | 26.2 (22.3)      |
| SJC28, mean (SD)         | 1.1 (2.3)        |
| TJC28, mean (SD)         | 1.5 (3.0)        |
| SJC66, mean (SD)         | 1.3 (2.7)        |
| TJC68, mean (SD)         | 1.5 (3.0)        |
| DAS28, mean (SD)         | 2.94 (1.21)      |
| SDAI score, mean (SD)    | 6.9 (7.2)        |
| CDAI score, mean (SD)    | 6.4 (6.8)        |
| RAPID3 score, mean (SD)  | 6.4 (5.9)        |
| Boolean remission criteria, n (%) | 2500 (30.1) |
| Boolean LDA, n (%)       | 4660 (56.2)      |

Abbreviation: bDMARD, biologic disease-modifying antirheumatic drug; Boolean LDA, proposed Boolean low disease activity criteria; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional disease-modifying antirheumatic drug; DAS28, Disease Activity Score 28 (ESR); ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PhGA, physician global assessment; PtGA, patient global assessment; RAPID3, Routine Assessment of Patient Index Data 3; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

aRequires the fulfillment of at least five of the seven core set measures (a pain score of 2 or less, an SJC of 1 or fewer, a TJC of 1 or fewer, an HAQ score of 0.5 or less, a PtGA score of 1.5 or less, a PhGA score of 2 or less, and an ESR of 20 mm/h or less).

bRequires the fulfillment of at least five of the seven core set measures (a pain score of 2 or less, an SJC of 1 or fewer, a TJC of 1 or fewer, an HAQ score of 0.5 or less, a PtGA score of 1.5 or less, a PhGA score of 2 or less, and an ESR of 20 mm/h or less).

patients met the new cutoffs of a DAS28 of 2.85 or less, an SDAI score of 5.5 or less, a CDAI score of 5 or less, and a RAPID3 score of 6 or less, and a RAPID3 score of 6 or less with an SJC of 2 or fewer, respectively (Table 2).

Table 2. Agreement between current and new cutoffs

| Current Cutoff | New Cutoff | Agreement |
|---------------|------------|-----------|
| DAS28 of 2.85 | DAS28 of 3.2 | 79%       |
| SDAI of 5.5   | SDAI of 5.2 | 82%       |
| CDAI of 5     | CDAI of 5.5 | 80%       |
| RAPID3 of 6   | RAPID3 of 6.5 | 93%       |
Table 2. Comparison of current and new cutoffs for low disease activity

| Boolean LDA* | DAS28 ≤3.2 | DAS28 ≤2.85 | CDAI ≤10 | CDAI ≤5 | SDAI ≤11 | SDAI ≤5.5 | RAPID3 ≤5 | RAPID3 ≤6 Without SJC | RAPID3 ≤6 With SJC28 ≤1 | RAPID3 ≤6 With SJC28 ≤2 |
|--------------|------------|-------------|---------|--------|---------|---------|----------|------------------------|--------------------------|--------------------------|
| n (%)        | 4660 (56)  | 5248 (63)   | 3712 (52)| 6597 (80)| 4517 (54)| 6656 (80)| 4523 (55) | 4855 (59)             | 4069 (49)                | 4436 (53)                |
| Pain score (0-10), mean (SD) | 1.0 (1.1)   | 1.5 (1.6)   | 1.0 (1.1) | 1.7 (1.7) | 1.7 (1.7) | 1.7 (1.7) | 1.7 (1.1) | 0.9 (0.8)             | 0.9 (0.8)                | 0.9 (0.8)                |
| PtGA score (0-10), mean (SD) | 1.0 (1.2)   | 1.5 (1.6)   | 1.0 (1.2) | 1.7 (1.7) | 1.7 (1.7) | 1.7 (1.7) | 1.7 (1.0) | 0.9 (0.8)             | 0.9 (0.8)                | 0.9 (0.8)                |
| PhGA score (0-10), mean (SD) | 0.7 (0.7)   | 0.9 (1.0)   | 0.6 (0.7) | 0.9 (0.9) | 0.9 (0.9) | 0.9 (0.9) | 0.9 (0.6) | 0.8 (0.8)             | 0.6 (0.7)                | 0.7 (0.8)                |
| HAQ score (0-3), mean (SD) | 0.3 (0.5)   | 0.4 (0.6)   | 0.2 (0.5) | 0.5 (0.7) | 0.5 (0.7) | 0.5 (0.7) | 0.5 (0.3) | 0.2 (0.3)             | 0.2 (0.3)                | 0.2 (0.3)                |
| CRP, mean (SD), mg/dl | 0.3 (0.6)   | 0.2 (0.6)   | 0.2 (0.5) | 0.4 (0.9) | 0.3 (0.7) | 0.3 (0.5) | 0.2 (0.4) | 0.3 (0.7)             | 0.3 (0.6)                | 0.3 (0.6)                |
| ESR, mean (SD), mm/h | 20 (17)     | 17 (13)     | 15 (11)  | 24 (20)  | 22 (18)  | 23 (19)  | 21 (17)   | 22 (18)               | 20 (17)                  | 21 (18)                  |
| SJC28, mean (SD) | 0.4 (1.0)   | 0.4 (1.0)   | 0.3 (0.7) | 0.5 (1.0) | 0.2 (0.6) | 0.5 (1.0) | 0.2 (0.6) | 0.7 (1.6)             | 0.2 (0.4)                | 0.3 (0.6)                |
| SJC66, mean (SD) | 0.5 (1.2)   | 0.5 (1.2)   | 0.3 (0.9) | 0.6 (1.2) | 0.3 (0.7) | 0.6 (1.3) | 0.3 (0.7) | 0.8 (1.8)             | 0.2 (0.6)                | 0.4 (0.8)                |
| TJC28, mean (SD) | 0.4 (1.1)   | 0.4 (0.9)   | 0.2 (0.6) | 0.6 (1.0) | 0.2 (0.5) | 0.6 (1.1) | 0.3 (0.6) | 0.6 (1.5)             | 0.5 (1.3)                | 0.5 (1.3)                |
| TJC68, mean (SD) | 0.6 (1.4)   | 0.6 (1.4)   | 0.3 (0.9) | 0.8 (1.4) | 0.4 (0.8) | 0.8 (1.5) | 0.4 (0.8) | 0.8 (1.9)             | 0.6 (1.6)                | 0.7 (1.7)                |

Abbreviation: Boolean LDA, proposed Boolean low disease activity criteria; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score 28 (ESR); ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PhGA, physician global assessment; PtGA, patient global assessment; RAPID3, Routine Assessment of Patient Index Data 3; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.

*The Boolean LDA is the fulfillment of at least five of the seven core set measures, namely, a pain score ≤2, an SJC ≤1, a TJC ≤1, an HAQ score ≤0.5, a PhGA score ≤1.5, a PtGA score ≤2, and an ESR ≤20 mm/h.
or less vs. the RAPID3 score of 6 or less were 0.525, 0.427, and 0.481, respectively.

The agreements between the new cutoffs of the DAS28 of 2.85 or less vs. the CDAI score of 5 or less, the CDAI score of 5 or less vs. the RAPID3 score of 6 or less, and the DAS28 of 2.85 or less vs. the RAPID3 score of 6 or less were 0.619, 0.616, and 0.474, respectively. By adding an SJC to the RAPID3, the agreements between the new cutoffs improved to 0.702 for CDAI score of 5 or less vs. the RAPID3 score of 6 or less with an SJC of 2 or fewer and 0.531 for DAS28 of 2.85 or less vs. the RAPID3 score of 6 or less with an SJC of 2 or fewer (Table 3).

**DISCUSSION**

Like the ACR/EULAR remission criteria, the Boolean low disease activity criteria may be helpful for standardizing the cutoffs of composite disease activity scores. Based on the core set criteria of minimal disease activity, the fulfillment of five of the seven core set measures (a pain score of 2 or less, an SJC of 1 or fewer, a TJC of 1 or fewer, an HAQ score of 0.5 or less, a PhGA score of 1.5 or less, a PtGA score of 2 or less, and an ESR of 20 mm/h or less) may serve as the Boolean low disease activity criteria.

The new cutoffs based on the Boolean low disease activity criteria showed better agreement among themselves than the current cutoffs. The RAPID3 requires a complementary careful joint examination for clinical decision-making. Just as a RAPID3 score of 3 or less with an SJC of 1 or fewer is similar to the Boolean remission criteria (10), a RAPID3 score of 6 or less with an SJC of 2 or fewer is similar to the Boolean low disease activity criteria.

None of the current cutoffs of any of the DAS28s derived from a formal study, whereas those of the SDAI did. Using 32 patient profiles from an observational RA database, 35 rheumatologists classified these profiles into one of the following four categories: remission, low disease activity, moderate disease activity, or high disease activity. The categories were selected based on more than 50% agreement. Accordingly, they proposed an SDAI score of 11 or less as the cutoff between moderate disease activity and low disease activity (14). In the present study, an SDAI score of 11 or less corresponded with a DAS28 of 3.6 or less. For example, the profile of a patient with an SJC of 4, a TJC of 1, a PhGA score of 1.4, a PtGA score of 1.2, an ESR of 11 mm/h, a CRP of 0.76 mg/dl, and a pain score of 1.1 (an SDAI score of 10.4 or a DAS28 of 3.47) was categorized as low disease activity, with 85.3% agreement (14). Thus, under the current definition of the SDAI and DAS28, patients with low disease activity can have significant disease activity, and the goal is more stringent than that required by the current definition of low disease activity, even in patients who have difficulty achieving remission. The cutoff of a DAS28 of 2.85 or less, an SDAI score of 5.5 or less, a CDAI score of 5 or less, and a RAPID3 score of 6 or less with an SJC of 2 or fewer based on the proposed Boolean remission criteria may be a better alternative treatment target than the target set by the current definition of low disease activity.

This study has several limitations. First, the original concept of low disease activity and minimal disease activity differed but were used almost interchangeably. To avoid confusion and to promote the implementation of the treat-to-target strategy, we proposed revising the definition of low disease activity. Second, the validation of the minimal disease activity needs to be updated. The consensus analysis may differ in keeping with progress in RA management. Like the remission criteria, developing new Boolean criteria of low disease activity with the collaboration of the OMERACT is desirable. Third, the population in the present study was better controlled than the cohorts in previous studies. Some 56.2% of patients in our database, compared with only 20.2% of patients registered with the US National Data Bank, met these criteria (13). The greater number of patients meeting these criteria in the NinJa databank is likely due to the progress in RA treatment spanning more than a decade and better accessibility to rheumatologists in Japan. The proportion of patients meeting DAS28-CRP score of less than 2.6 was 55.9% in a large observational cohort study in Japan that included over 6000 patients (15). Future external validation using different patient cohorts and clinical trials should be performed.

In conclusion, OMERACT’s minimal disease activity criteria may help redefine low disease activity. The fulfillment of at least five of the seven core set measures, namely, a pain score of 2 or less, an SJC of 1 or fewer, a TJC of 1 or fewer, an HAQ score of 0.5 or less, a PhGA score of 1.5 or less, a PtGA score of 2 or less, and an ESR of 20 mm/h or less, may serve as Boolean low disease activity criteria, and the cutoffs of a DAS28 of 2.85 or less, an SDAI score of 5.5 or less, a CDAI score of 5 or less, and a RAPID3

**Table 3.** Agreement of proposed Boolean definition, new DAS28, CDAI, RAPID3-based definition of LDA*

|                | DAS28 ≤2.85 | SDAI Score ≤5.5 | CDAI Score ≤5 | RAPID3 Score ≤6 | RAPID3 Score ≤6 With an SJC ≤1 | RAPID3 ≤6 With an SJC ≤2 |
|----------------|-------------|-----------------|--------------|----------------|-------------------------------|---------------------------|
| Boolean LDA    | 0.607       | 0.754           | 0.756        | 0.738          | 0.754                         | 0.759                     |
| DAS28 ≤2.85    | ...         | 0.643           | 0.619        | 0.474          | 0.544                         | 0.531                     |
| SDAI score ≤5.5| ...         | ...             | 0.951        | 0.613          | 0.702                         | 0.698                     |
| CDAI score ≤5  | ...         | ...             | ...          | 0.616          | 0.704                         | 0.702                     |

Abbreviation: CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score 28 (ESR); LDA, low disease activity; RAPID3, Routine Assessment of Patient Index Data 3; SDAI, Simplified Disease Activity Index; SJC, swollen joint count.

*The numbers represent κ statistics; all P values were <0.0001.
score of 6 or less (with an SJC of 2 or fewer) may be used for the cutoffs of low disease activity in routine clinical practice.

**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. Yokogawa 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.** Yokogawa.

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**Analysis and interpretation of data.** Yokogawa.

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