

Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis?

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Abstract

Objectives: To study which cutoff point of DAS28 corresponds to fulfillment of the ACR remission criteria, and clinical remission criteria in patients with rheumatoid arthritis (RA).

Methods: All adult patients diagnosed with RA at Jyväskylä Central Hospital 1997-1998 were assessed for remission at five years. Remission was defined as 1) the American Collage of Rheumatology (ACR) remission, 2) clinical remission (defined as no tender and no swollen joints and normal ESR). DAS28 was used to measure disease activity. A receiver operating characteristics curve (ROC) analysis was performed to calculate a cutoff point of DAS28 that corresponds best to the ACR remission criteria and the clinical remission criteria.

Results: The study included 161 patients (mean age 57 years, 67% female, 61% with positive rheumatoid factor, and 32% with erosions). At 5 years, 12% of them met the ACR remission criteria, and 34% met the clinical remission criteria. The cutoff value of DAS28 was 2.32 for the ACR remission criteria, and 2.68 for the clinical remission criteria. In patients with $DAS28 < 2.32$, 11 (19%) had tender joints, 6 (11%) had swollen joints, and 4 (7%) had both tender and swollen joints.

Conclusion: In our study the DAS28 cutoff point for the ACR remission was lower than in previous studies. The cutoff point of DAS28 remission remains controversial. A substantial proportion of patients under the DAS28 cutoff point for remission have tender and/or swollen joints. DAS28 may not be an appropriate tool for assessment of remission in RA.

The goal of treatment of RA is remission. Definition of remission, however, remains controversial. The preliminary remission criteria for RA proposed by Pinals et al. in 1981 (1), were adopted by the American College of Rheumatology (ACR). Other definitions such as “being symptom free” or “no arthritis on examination” have also been used (2-8).

Disease activity score (DAS) (9-11) and its modified version including 28 joint count (DAS28) (12) were developed to measure disease activity in RA patients. In patients with early RA, Prevoo et al. found that $DAS < 1.6$ best correlates with the ACR remission criteria (13). Later the corresponding cutoff point of < 2.6 for DAS28 was derived from a formula developed to convert DAS to DAS28 (14). Recently even higher DAS28 cutoff points of 2.81 and 2.66 have been reported to correspond to the ACR remission criteria in two separate patient populations (15, 16). Both $DAS < 1.6$ and $DAS28 < 2.6$ have been used in studies to define remission in RA (17-19).

Critique has been raised concerning the validity of DAS28 to assess remission (20, 21). Therefore, we aimed to study which cutoff point of DAS28 corresponds to fulfillment of the ACR defined remission criteria, and a simple set of clinical remission criteria (defined as no tender and no swollen joints and normal ESR). The positive predictive value of each individual ACR remission criterion was examined. Furthermore, we calculated the percentage of patients with the DAS28 remission who had swollen and/or tender joints.

Patients and Methods

Study population. Jyväskylä Central Hospital is the only rheumatology center in the Central Finland District and serves a population of 265 000. All new RA patients are referred to the hospital for diagnosis and initiation of therapy. All 237 patients with recent onset inflammatory arthritis, older than 16 years who did not meet criteria or show clinical signs of other specific arthritides (crystal deposit disease, reactive arthritis, ankylosing spondylitis, psoriatic arthritis etc.) were included in the RA 1997-1998 inception cohort. These patients received rheumatology care at Jyväskylä Central Hospital at least for two years after the diagnosis by a multidisciplinary team and subsequently were invited to participate in a 5-year study visit. A total of 161 patients who cumulatively fulfilled the ACR criteria for RA were included in this study.

Treatment strategies. Disease-modifying anti rheumatic drugs (DMARDs) were started at the time of diagnosis. Target of therapy was clinical remission.

Clinical and laboratory assessments. Measures at baseline and at 5 years included 68 tender and 66 swollen joint counts (22); laboratory tests including ESR, C-reactive protein (CRP), and rheumatoid factor (RF); self-report pain and global health on 100mm visual analog scales (VAS), functional capacity according to the Health Assessment Questionnaire (HAQ), morning stiffness in minutes on self-report; and radiographs of the hands and feet. The date of initiation and discontinuation of each DMARD was recorded.

Definition of remission. We used two separate sets of criteria to define remission at 5 years. The ACR remission criteria require: 1) no joint or tendon sheath swelling 2) no joint tenderness, 3) normal ESR of <20 in men and <30 in women, 4) morning stiffness \leq 15 minutes, and 5) no joint pain by history (VAS \leq 10 mm on a scale of 1-100 mm) (23). The requirement of fatigue was excluded, but all the other five criteria had to be fulfilled. Since in previous studies only four of the five ACR remission criteria have been required for remission (fatigue excluded), we tested that set of the ACR criteria too. We did not require two months period of follow-up. Clinical remission was defined as 1) no tender and 2) no swollen joints and 3) normal ESR of <20 in men and <30 in women.

Disease activity score (DAS28). DAS28 is a validated index of RA disease activity. It consists of four parameters: 28 tender (TJC28) and swollen joint (SJC28) counts, ESR and patients general health (GH) measured on a 100mm VAS (12). It was calculated using the formula (12):

$$0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.014 \times (\text{GH})$$

Statistical methods. The receiver operating characteristic (ROC) curves were constructed to determine the cutoff point of DAS28 that corresponds to the ACR remission criteria and to the clinical remission criteria with bias corrected accelerated bootstrap confidence intervals (CI).

Sensitivity, specificity, positive predictive value, likelihood ratio, and their 95% CI values were calculated for each remission criteria.

Results

A total of 196 patients from 237 RA patients diagnosed in 1997-1998 at Jyväskylä Central Hospital participated in the 5-year study visit (twenty patients had died, seven patients refused, four patients were too sick to participate, five patients had moved, and the diagnosis of 5 patients had changed). A total of 161 of these patients cumulatively fulfilled the ACR criteria for RA and were included in the analysis. The patient characteristics of the 161 RA patients at baseline are shown in Table 1.

At 5 years, 19 (12% [95% CI: 7% to 18%]) of the 161 examined RA patients met the ACR remission criteria including 106 (66%) with no swollen joints, 69 (43%) with no tender joints, 119 (74%) with normal ESR, 65 (40%) with morning stiffness \leq 15 minutes, and 32 (20%) patients with no pain (Table 2).

The positive predictive value for the ACR remission criteria was lowest for normal ESR (16%), and highest for no history of joint pain (56%). Similarly, the likelihood ratio was lowest for normal ESR (1.40) and highest for no joint pain (10.00) (Table 2.). According to the less rigorous ACR remission criteria (four of the five ACR remission criteria had to be fulfilled and fatigue was excluded) 40 (25% [19% to 33%]) of the patients were in remission. A total of 55 patients [34% CI: 27% to 42%] met the simple set of clinical remission criteria at five years.

The ROC curves of DAS28 when used to define the presence or absence of remission using the ACR criteria (fatigue was excluded and all the other 5 criteria had to be fulfilled), and the clinical remission criteria are shown in Figure 1. The area under ROC was 0.87 (95% CI: 0.82 to 0.93) for the ACR remission criteria, and 0.90 (95% CI: 0.84 to 0.94) for the clinical remission criteria and 0.89 (95% CI: 0.83 to 0.94) for the less rigorous ACR remission criteria (Table 3.).

The cutoff value for DAS28 was 2.32 (sensitivity 100%, specificity 73%) for the ACR remission criteria (fatigue excluded), 2.6 (sensitivity 93%, specificity 76%) for less rigorous set of the ACR remission criteria, and 2.68 (sensitivity 91%, specificity 79%) for the clinical remission criteria (Table 3.).

Of the 57 patients who had $DAS28 < 2.32$, five (9%) patients had tender joints, four (7%) had swollen joints, and two (4%) had both tender and swollen joints on the 28 joint count. On the 66 joint count the corresponding figures were eleven (19%), six (11%) and four (7%) (Table 4.). If we had used the previously proposed cutoff point of 2.6 as the limit of DAS28 remission in our cohort, a higher proportion of our patients [66 (41%) patients] would have been included in the remission group. Of these 66 patients, 15 (23%) patients had tender and 6 (9%) swollen joints, and 4 (6%) had both tender and swollen joints (66 joint count) (Table 4.).

Discussion

In the present study, $DAS28 < 2.32$ corresponded to the fulfillment of the ACR remission criteria (five of the ACR remission criteria had to be fulfilled, fatigue was excluded) and $DAS28 < 2.68$ corresponded to the clinical remission criteria defined as no tender and no swollen joints and normal ESR. We also calculated the cutoff point of DAS28 using less rigorous set of ACR remission criteria like Balsa et al. (15) and Fransen et al. (16) did in their studies and the cutoff point was 2.6 in agreement to the study of Fransen et al. Even a higher cutoff point of DAS28 2.81 for this set of ACR remission criteria was reported by Balsa et al.(15).

The preliminary RA remission criteria by Pinals et al.(1) require that five of the six criteria have to be fulfilled. The criteria explicitly accept that patients with either tender or swollen joints can be considered to be in remission, although patients are not allowed to have both tender and swollen joints. In our study 7% of the patients who were in DAS28 remission ($DAS28 < 2.32$) had both tender and swollen joints. Furthermore, as many as 19% of patients had tender joints and 11% had swollen joints. The majority of rheumatologists, however, may agree that patients with swollen and/or tender joints are not in true clinical remission.

Landewe et al. (20) have presented a comparison of DAS28 remission to DAS remission and conclude that DAS ($DAS < 1.6$) remission is far more conservative than DAS28 ($DAS28 < 2.6$) remission. On the other hand, Fransen et al. (16) showed that $DAS < 1.6$ and $DAS28 < 2.6$ were equal when compared to ACR remission criteria. Landewe et al. suggested that discrepancy between DAS and DAS28 remission is explained by activity in joints which are not included in DAS28 (feet and ankles). We agree that DAS28 at a cut off level of 2.6 should not be used to define remission in clinical practice or clinical trials(20).

The criterion of no joint pain had the highest positive predictive value of the five ACR remission criteria in our study. A total of 56% of our patients with no joint pain fulfilled the ACR defined remission. On the other hand, ESR had the lowest positive predictive value; only 16% of the patients with normal ESR were in the ACR defined remission (Table 2.). Our results are in line with those obtained by Balsa et al. that pain has the highest positive predictive value and ESR the lowest (15). Therefore, normal ESR in a patient with RA does not tell much about whether he or she is in remission or not. On the contrary, when RA patient has no pain the chances to fulfill the ACR defined remission are considerable.

The likelihood ratio of ESR was low, 1.40. Accordingly, the criterion of normal ESR does not improve the accuracy of the ACR remission criteria. Further, minor changes in ESR may change the DAS28 value strikingly. For example, if a patient has 2 tender and no swollen joints with GH 10 and her/his ESR rises from 2 to 20 (ESR is normal in both cases) DAS28 rises from 1.41 to 3.02.

In the present study DAS28 remission cutoff point for the ACR remission was lower than in previous studies due to more strict way we used ACR remission criteria, and remains controversial. The small sample size is a limitation in our study and results needs to be confirmed in other studies. The DAS28 reflects disease activity, but it may not be an optimal tool for assessment of remission in RA. In fact, all remission criteria so far have included the domain of signs and symptoms of inflammation, while the two other major domains of RA, physical function and structural joint damage have gained less attention (24-26). We still lack a good definition of remission for daily clinical needs as well as for investigational purposes.

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Table 1.Characteristics of 161 patients with rheumatoid arthritis at baseline.

Age, mean (range)	57 (22, 85)
Female, n (%)	107 (67%)
Duration of symptoms before diagnosis, months, median (IQR)	5 (3, 11)
RF positive ever, n (%)	98 (61%)
Met ACR 1987 criteria for RA, n (%)	152 (94%)
Patients with erosions, n (%)	51 (32%)

Table 2. Patients fulfilling each ACR remission criterion and the positive predictive value and likelihood ratio of each criterion

Criteria	Criteria present	ACR remission				Clinical remission			
		Sensitivity	Specificity (95% CI)	LR+ ¹ (95% CI)	PPV ² % (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	PPV% (95% CI)
No swollen joints	106 (66)	100	39 (31 to 47)	1.63 (1.27 to 1.85)	18 (11 to 27)	100	52 (42 to 62)	2.08 (1.72 to 2.55)	52 (42 to 62)
No tender joints	69 (43)	100	65 (56 to 73)	2.84 (2.13 to 3.52)	28 (17 to 40)	100	87 (79 to 93)	7.57 (4.72 to 12.34)	80 (68 to 88)
No pain ³	32 (20)	100	90 (84 to 94)	10.00 (5.97 to 16.15)	56 (38 to 74)	41 (28 to 55)	90 (83 to 95)	4.24 (2.20 to 8.24)	69 (50 to 84)
Normal ESR	119 (74)	100	29 (21 to 37)	1.40 (1.10 to 1.55)	16 (10 to 24)	100	37 (28 to 47)	1.56 (1.36 to 1.85)	45 (35 to 54)
Morning stiffness ⁴	65 (40)	100	65 (57 to 73)	2.87 (2.13 to 3.59)	28 (17 to 40)	62 (47 to 74)	67 (57 to 76)	1.88 (1.32 to 2.68)	49 (37 to 62)

¹ Likelihood Ratio Positive (ratio of the sensitivity of a test to the false-positive error rate of the test).

² Positive predictive value (proportion of the subjects who had positive test results who were in remission).

³ Pain VAS ≤10 mm.

⁴ Duration of morning stiffness ≤15 min.

Table 3. The estimated cut off points of DAS28 corresponding to the ACR and the clinical remission criteria

Characteristics	Remission criteria		
	ACR [•] (95% CI)	ACR [‡] (95% CI)	Clinical (95% CI)
Cut-off point	2.32	2.60	2.68
Area under ROC [†]	0.87 (0.82 to 0.93)	0.89 (0.83 to 0.94)	0.90 (0.84 to 0.94)
Sensitivity, %	100 (82 to 100)	93 (80 to 98)	91 (80 to 97)
Specificity, %	73 (64 to 80)	76 (67 to 83)	79 (70 to 87)
PPV [‡] , %	33 (21 to 46)	56 (43 to 68)	69 (57 to 80)
LR+ [*]	3.64 (2.66 to 4.71)	3.80 (2.76 to 5.32)	4.38 (3.05 to 6.48)

•ACR remission criteria, all the five criteria must be fulfilled (fatigue excluded)

‡ACR remission criteria, four of the five criteria must be fulfilled (fatigue excluded)

† Area under the Receiver operation characteristic curves. 95% confidence interval obtained by bias corrected and accelerated bootstrapping (5000 replications).

‡ Positive predictive value (proportion of the subjects who had positive test results who were in remission).

* Likelihood Ratio Positive (ratio of the sensitivity of a test to the false-positive error rate of the test).

Table 4. Cutoff values of DAS28 and number of patients not fulfilling each individual ACR remission criterion

	¹⁾ DAS28<2.32	²⁾ DAS28<2.6	³⁾ DAS28<2.68
Patients n	57	66	72
Patients with tender joints n (%)			
28 joint count	5 (9%)	6 (9%)	7 (8%)
66 joint count	11 (19%)	15 (23%)	17 (24%)
Patients with swollen joints n (%)			
28 joint count	4 (7%)	5 (8%)	5 (7%)
66 joint count	6 (11%)	6 (9%)	6 (8%)
Patients with tender and swollen joints n (%)			
28 joint count	2 (4%)	2 (4%)	2 (3%)
66 joint count	4 (7%)	4 (6%)	4 (6%)
Patients with elevated ESR n (%)	2 (4%)	3 (5%)	4 (6%)
Patients with morning stiffness n (%)	23 (40%)	25 (38%)	27 (38%)
Patients with joint pain n (%)	33 (58%)	38 (58%)	44 (61%)

- 1) The cutoff point corresponding to the ACR remission criteria in this study (all the five ACR remission must be fulfilled and fatigue excluded)
- 2) The generally accepted cutoff point of DAS28 in remission and the cutoff point of ACR remission in this study when modified ACR criteria are used (four of the five ACR remission criteria must be fulfilled and fatigue excluded)
- 3) The cutoff point corresponding to the clinical remission criteria defined as no tender or swollen joints and normal ESR

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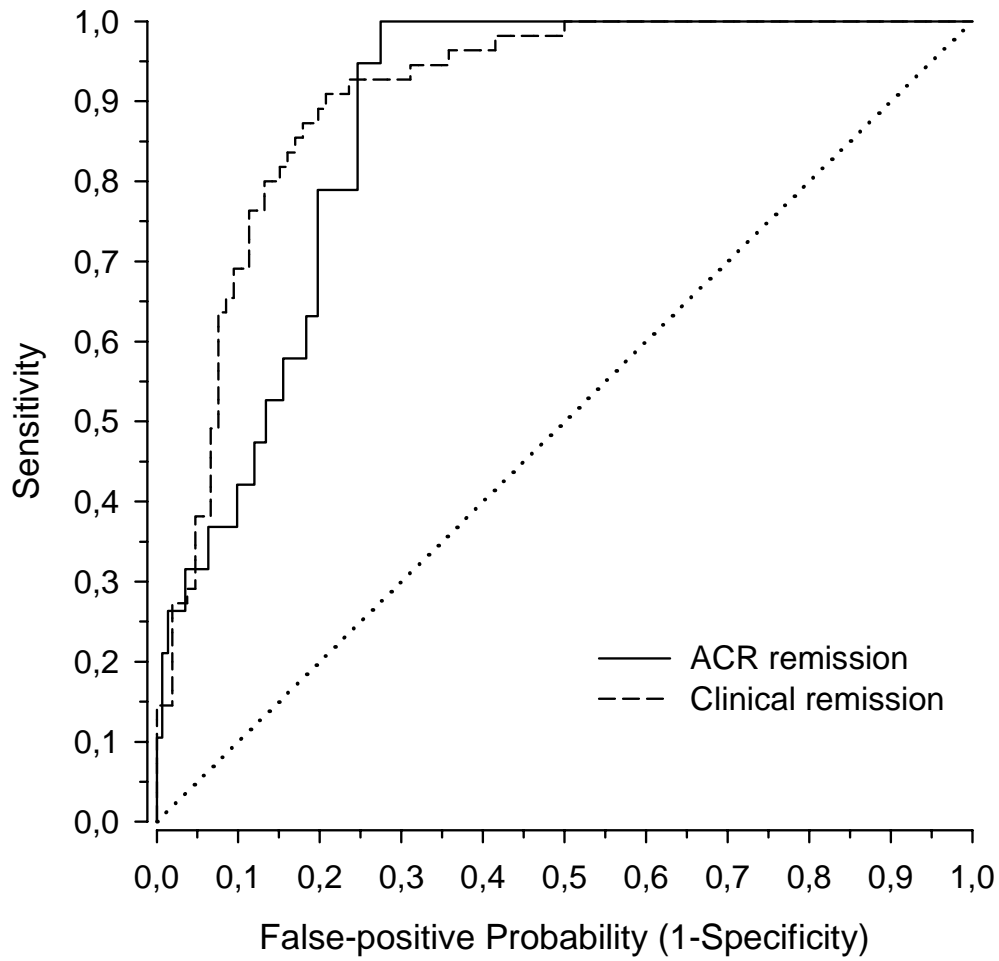


Figure 1. The ROC curves of DAS28 when used to define the presence or absence of the ACR remission criteria and the clinical remission criteria.