EXTENDED REPORT

Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan

Toshihiro Matsui, Yoshiaki Kuga*, Atsushi Kaneko, Jinju Nishino, Yoshito Eto, Noriyuki Chiba, Masayuki Yasuda, Koichiro Saisho, Kota Shimada, Shigeto Tohma

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See end of article for authors' affiliations
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Correspondence to:
Dr Toshihiro Matsui, Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization 18-1, Sakuradai Sagamihara-city, Kanagawa, 228-8522, Japan; t-matsui@ sagamihara-hosp.gr.jp

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Objectives: To compare disease activity and the improvement of disease activity evaluated between by Disease Activity Score 28 using erythrocyte sedimentation rate (DAS28-ESR) and by DAS28 using C-reactive protein (DAS28-CRP) in Japanese patients with rheumatoid arthritis (RA).

Methods: Data from 3073 RA patients registered in the large cohort database (*NinJa*: National Database of Rheumatic Diseases by iR-net in Japan) of 2003 was used to calculate DAS28-ESR and DAS28-CRP and disease activities were evaluated. Improvements in disease activities were also evaluated according to the European League Against Rheumatism (EULAR) response criteria in 1482 RA patients whose DAS28-ESR and DAS28-CRP could be calculated from data for both 2002 and 2003.

Results: The mean value of DAS28-CRP (3.59, SD 1.25) was significantly smaller than that of mean DAS28-ESR (4.31, SD 1.32) ($p < 0.0001$). The number of patients who satisfied the criteria of remission was 297 (9.7%) in DAS28-ESR versus 705 (22.9%) in DAS28-CRP and the number of patients with high disease activity was 842 (27.4%) versus 357 (11.6%) for DAS28-ESR and DAS28-CRP, respectively; there was a significant difference between the two ($p < 0.0001$). Change of respective DAS28 was significantly correlated (ΔDAS28-ESR −0.05, SD 1.14 versus ΔDAS28-CRP −0.10, SD 1.10) ($p < 0.0001$); however, the number of "good response" patients was significantly different ($p < 0.03$) between DAS28-ESR (97 patients, 6.5%) and DAS28-CRP (136 patients, 9.2%).

Conclusions: DAS28-CRP significantly underestimated disease activity and overestimated the improvement in disease activity compared with DAS28-ESR. DAS28-CRP should be evaluated using different criteria from that for DAS28-ESR.

At present, the Disease Activity Score (DAS) is a major scoring system for evaluating disease activity of rheumatoid arthritis (RA). The initial development of DAS was reported by van der Heijde *et al* in 1990[1] and 1992,[2] and then DAS was modified by a group of investigators from the Netherlands.[3–5] The use of DAS is officially recommended by the European League Against Rheumatism (EULAR) for evaluating disease activity and the improvement in disease activity in clinical trials and also in daily clinical practice.

For reasons of convenience, the modified DAS including 28-joint count (DAS28),[3] instead of the original DAS based on the Ritchie articular index and 44-swollen joint count,[1 2] was proposed and the response criteria and the remission criteria for DAS28 were also reported.[6] DAS28 is calculated according to the formula that is composed of the number of tender joints and swollen joints, patient's global assessment of disease activity on a visual analogue scale (VAS), and erythrocyte sedimentation rate (ESR), not C-reactive protein (CRP). ESR tends to reflect disease activity of the past few weeks, whereas CRP reflects more short-term changes in disease activity.[7] Therefore, the advantage of CRP is that it is more sensitive to short-term changes in disease activity. Furthermore, ESR can be influenced by confounding factors such as age, sex, fibrinogen levels, hypergammaglobulinemia, rheumatoid factor, and anemia.[8 9] For these reasons, DAS28 using CRP instead of ESR was recently proposed by Fransen *et al.*[10] and presented

on the DAS website[11] (To avoid confusion, we describe "DAS28-ESR" for DAS28 using ESR and "DAS28-CRP" for DAS28 using CRP in this paper.)

It was stated on the DAS website that the formula to calculate DAS28-CRP gives a good estimation of DAS28-ESR values on a group level,[11] whereas it was noted in the EULAR handbook of clinical assessments in RA that "as the agreement between ESR and CRP is imperfect, disease activity scores calculated with ESR and CRP will deviate to some extent in most individuals".[12] At present, the criteria of disease activity and the response criteria for DAS28-ESR are applied to DAS28-CRP; however, no reports have so far validated them.

NinJa (National Database of Rheumatic Diseases by iR-net in Japan; www.ninja-ra.jp)[13] is a nationwide cohort database of rheumatic diseases in Japan, and has collected data since 2002. For the database of RA, core information about disease activity (the number of tender and swollen joints, patient's and doctor's VAS, ESR, CRP, and modified health assessment questionnaire; mHAQ), treatment, complications, operation, and the incidence of malignancy and tuberculosis have been collected once a year. As of March 2006, 33 hospitals around Japan were participating

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in data collection and approximately 4000 RA patients had been registered.

In this study, we compared disease activity and the improvement in disease activity evaluated by DAS28-ESR and by DAS28-CRP, and examined whether DAS28-CRP can be evaluated by the same criteria as DAS28-ESR in Japanese patients with RA using data from *NinJa*.

METHODS
Data source
The data source employed was a nationwide observation cohort database of rheumatic diseases in Japan named *NinJa*.[13][14] *NinJa* started data collection in 2002, which has been performed annually. At the end of March in 2006, 33 institutions that are located throughout Japan and almost all of which are members of iR-net (Division of Rheumatology, Immunologic Disorder Network, National Hospital Organization in Japan), were participating in *NinJa*. The annual data for each patient with RA consist of two components; one component is about information during the year (outcome, death, hospitalization, operation, malignancy, and tuberculosis), and the other component is about information collected on an arbitrary day in daily clinical practice (the number of tender and swollen joints, mHAQ, patient's global and pain VAS, doctor's VAS, ESR, CRP, DA28-ESR, DAS28-CRP, use of corticosteroids, disease-modifying antirheumatic drugs, and non-steroidal anti-inflammatory drugs). All the hospitals participating in *NinJa* used a CRP test with a lower detection level of 1.0 mg/l. The CRP test was calibrated using a standardized method (CRM 470 of the International Federation of Clinical Chemistry). ESR was measured by the Westergren method.

So far, data of 1928 patients in *NinJa* 2002 (data for the period April 2002 to March 2003) and of 4026 patients in *NinJa* 2003 (data for the period April 2003 to March 2004) have been collected and analysed. The *NinJa* project was reviewed and approved by the National Hospital Organization research ethics committees, and all patients participating in the study provided informed consent.

Patients
For the cross-sectional study (evaluation of disease activity), data of 3073 patients in *NinJa* 2003, which had both DAS28-ESR and DAS28-CRP, were utilized. Of the 3073 patients included in the study, 2583 (84.1%) were women, with a mean age (SD) of 61.1 (11.4) years (range 18–89), and mean disease duration (SD) of 13.5 (10.6) years (range 0–56). Most of the patients (n = 2638, 86.9%) were taking disease-modifying antirheumatic drugs, 2046 patients (66.6%) were taking corticosteroids, and 2315 patients (75.3%) were using non-steroidal anti-inflammatory drugs.

For the longitudinal study (evaluation of the improvement in disease activity), 1482 patients whose DAS28-ESR and DAS28-CRP could be evaluated in both *NinJa* 2002 and 2003 were selected. Of the 1482 patients, 1270 (85.7%) were women, with a mean age (SD) of 61.7 (10.6) years (range 19–89), and mean disease duration (SD) of 15.7 (10.7) years (range 0–56) for the database of 2003.

Calculation and evaluation of disease activity and improvement in disease activity
According to the formula on the DAS website,[11] DAS28-ESR and DAS28-CRP were calculated and both DAS28 values were categorized as follows: > 5.1, high disease activity; ⩽ 3.2, low disease activity; and < 2.6, remission. Improvement in disease activity was evaluated according to EULAR response criteria.[6]

Statistics
DAS28-ESR and DAS28-CRP values were compared by calculating correlation coefficients and by linear regression analysis. Bland–Altman plots were generated for assessment of the variation between DAS28-ESR and DAS28-CRP.[15] Comparisons of the number of patients with each disease activity or with improvement in disease activity evaluated by DAS28-ESR and by DAS28-CRP were performed using Student's t-test and the χ^2 test. Data processing and analyses were conducted using SPSS software (Windows release 11.0; SPSS Inc., Chicago, Illinois, USA).

RESULTS
Comparison of disease activity between DAS28-ESR and DAS28-CRP
DAS28-ESR and DAS28-CRP values of 3073 patients in *NinJa* 2003 were normally distributed (fig 1A and B), although the peak of DAS28-CRP was shifted to the left compared with that of DAS28-ESR. The means (SD) of DAS28-ESR and DAS28-CRP were 4.31 (1.32) and 3.59 (1.25), respectively (table 1), and these differences were statistically significant (p < 0.0001). Linear regression analysis showed a significant correlation between DAS28-ESR and DAS28-CRP (DAS28-CRP = $0.893 \times$ DAS28-ESR $- 0.253$, $R^2 = 0.893$; p < 0.0001) (fig 1C). The Bland–Altman analysis showed that as the average value of DAS28 increases, the difference between DAS28-CRP and DAS28-ESR (DAS28-CRP minus DAS28-ESR) becomes larger (r = -0.059, 95% CI -0.070 to -0.047, p < 0.0001) (fig 1E).

The difference in the mean values between DAS28-ESR (4.36 [SD 1.31]) and DAS28-CRP (3.61 [SD 1.26]) in women was statistically larger than that in men (4.02 [SD 1.41] versus 3.50 [SD 1.25], p < 0.0001; table 2). Furthermore, differences in the mean values between DAS28-ESR and DAS28-CRP tended to be larger as disease duration and age increased (table 2).

The number of patients categorized by each criteria of disease activity, i.e. remission (DAS28 < 2.6) and low disease activity criteria (DAS28 ⩽ 3.2) included 297 (9.7%) and 653 (21.2%) patients, respectively, evaluated by DAS28-ESR, whereas there were 705 (22.9%) and 1218 (39.6%) patients, respectively, by DAS28-CRP. On the other hand, patients categorized by high disease activity criteria (DAS28 > 5.1) included 842 (27.4%) patients by DAS28-ESR criteria, and 357 (11.6%) patients by DAS28-CRP criteria (table 3). These differences were statistically significant (p < 0.0001).

Comparison of the improvement in disease activity between DAS28-ESR and DAS28-CRP
The improvement in disease activity was examined using data from 1482 patients whose DAS28-ESR and DAS28-CRP could be evaluated in both *NinJa* 2002 and 2003. Linear regression analysis showed a significant correlation between the differences in DAS28 values in each DAS28 between *NinJa* 2002 and 2003 (p < 0.0001), which could be fitted to the equation: ΔDAS28-CRP = $0.902 \times \Delta$DAS28-ESR $- 0.053$, $R^2 = 0.879$ (fig 1D). The means (SD) of ΔDAS28-ESR and ΔDAS28-CRP were -0.05 (1.14) and -0.10 (1.10), respectively, and the difference was statistically significant (p < 0.0001). The Bland–Altman analysis showed that as an absolute value of the average of ΔDAS28 increases, that of the difference between ΔDAS28-CRP and ΔDAS28-ESR (ΔDAS28-CRP minus ΔDAS28-ESR) becomes larger (r = -0.039, 95% CI -0.057 to -0.020, p < 0.0001) (fig 1F).

The improvements in disease activity evaluated by DAS28-ESR and DAS28-CRP were compared using the EULAR response criteria (table 4). The numbers of ''moderate'' and ''no'' response patients were comparable between DAS28-ESR
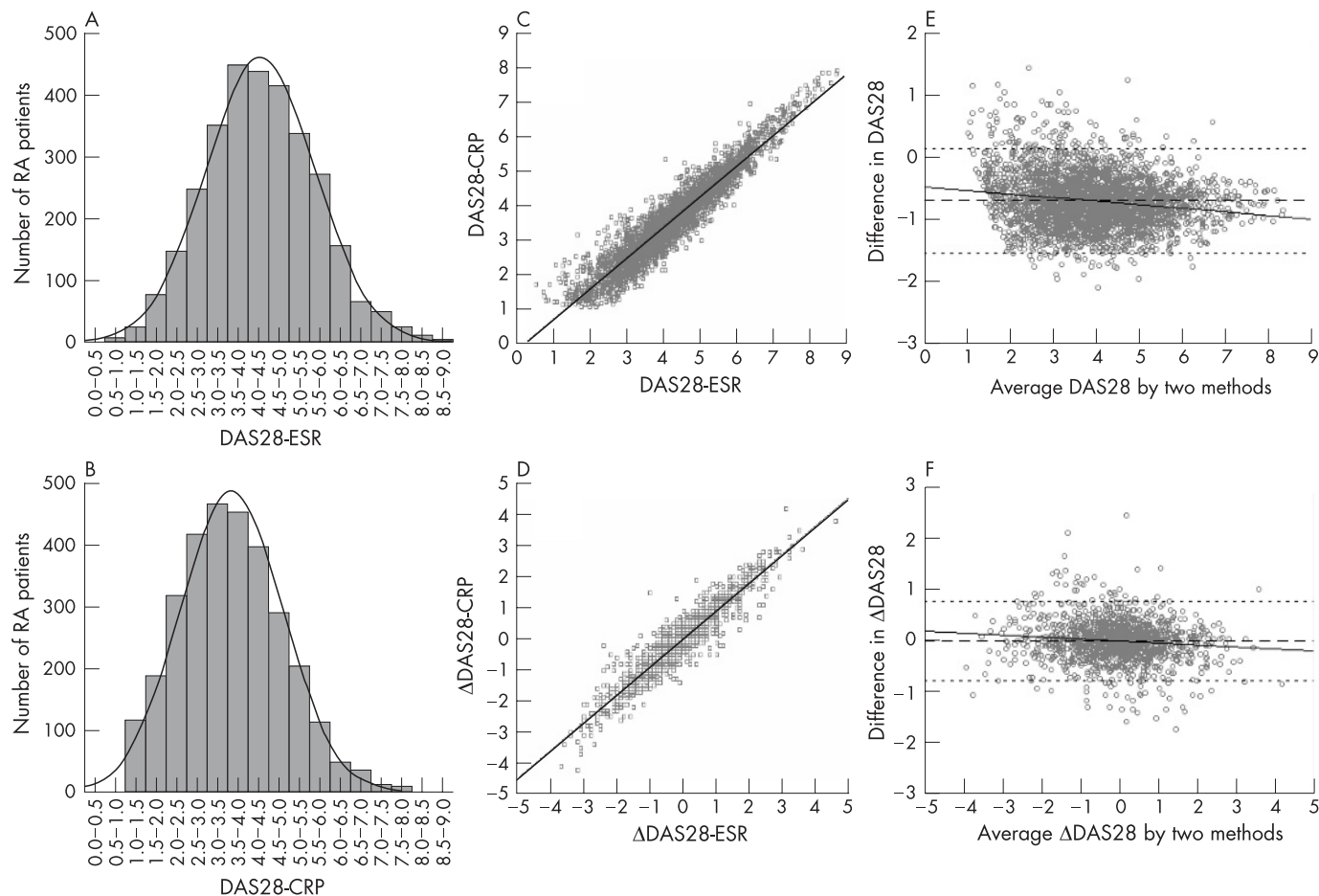
Figure 1 Distribution, correlation and difference of DAS28-ESR and DAS28-CRP. Distribution of DAS28-ESR (A) and DAS28-CRP (B) scores from 3073 patients with rheumatoid arthritis in *NinJa* 2003. Correlation of the values of DAS28-ESR and DAS28-CRP from 3073 patients in *NinJa* 2003 (C), and correlation of the changes of DAS28-ESR and DAS28-CRP scores (Δ: score of 2003 minus that of 2002) from 1482 patients whose DAS28-ESR and DAS28-CRP could be evaluated in both *NinJa* 2002 and 2003 (D). Solid line indicates the regression line of DAS28-CRP on DAS28-ESR (C, D). Bland–Altman plot analysis of the absolute values of DAS28 (E) and the changes of DAS28 scores (F). The ordinate scale represents the difference between DAS28-CRP and DAS28-ESR (i.e. DAS28-CRP minus DAS28-ESR). The abscissa scale represents the average of DAS28-ESR and DAS28-CRP (i.e. DAS28-ESR plus DAS28-CRP divided by 2). The middle dashed line indicates the bias (mean difference), and the upper and lower dotted lines represent the limits of agreement (mean ± 2 SD). The solid line indicates the regression line of difference on average.

Table 1 Characteristics of patients in the cross-sectional and longitudinal studies

		Longitudinal *NinJa* 2002–2003	
	Cross-sectional *NinJa* 2003	2002	2003
Patients (n)	3073	1482	
Age (years; mean [SD])	61.1 [11.4]	61.7* [10.6]	
Women (%)	2583 (84.1%)	1270 (85.7%)	
Disease duration (years; mean [SD])	13.5 [10.6]	15.7* [10.7]	
Disease activity score (mean [SD])			
DAS28-ESR	4.31[†] [1.32]	4.29[†] [1.22]	4.24[†] [1.30]
DAS28-CRP	3.59 [1.25]	3.61[1.20]	3.51 [1.23]
Disease activity characteristics (median [first; third quartile])			
Tender joint count (0–28)	2 [0; 4]	2 [1; 5]	2 [1; 5]
Swollen joint count (0–28)	1 [0; 4]	2 [0; 5]	1 [0; 4]
ESR (mm/h; normal <20)	39 [21; 60]	38 [20; 58]	40 [22; 60]
CRP (mg/dl; normal <0.4)	0.78 [0.23;2.09]	0.82 [0.27; 2.30]	0.72 [0.22; 1.98]
mHAQ score (range 0–3)	0.50 [0.10; 1.10]	0.50 [0.12; 1.00]	0.60 [0.12; 1.25]
Patient's pain VAS (10 cm)	3.7 [1.9; 5.5]	3.4 [3.4; 5.4]	3.8 [2.0; 5.8]
Patient's global VAS (10 cm)	4.0 [2.0; 5.6]	3.8 [2.0; 5.8]	4.1 [2.1; 5.7]
Doctor's global VAS (10 cm)	2.9 [1.6; 4.7]	3.1 [2.0; 4.9]	3.1 [1.9; 4.9]

CRP, C-reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale.
*Age and disease duration at the time of data collection in 2003.
[†]The mean value of DAS28-ESR was significantly larger than that of DAS28-CRP (p < 0.0001).

Table 2 Effects of sex, disease duration, and age on the differences between DAS28-ESR and DAS28-CRP

	n (%)	DAS28-ESR	DAS28-CRP	Difference (z)
Sex				
Women	2583 (84.1)	4.36 [1.31]*	3.61 [1.26]	0.75**
Men	490 (15.9)	4.02 [1.41]	3.50 [1.25]	0.52
Disease duration (x) (years, women)				
0~2	306 (11.8)	4.22 [1.42]	3.50 [1.37]	0.72
3~5	385 (14.9)	4.14 [1.31]	3.41 [1.26]	0.73
6~10	469 (18.2)	4.29 [1.26]	3.57 [1.20]	0.72
11~15	441 (17.1)	4.54 [1.34]	3.79 [1.26]	0.75
16~20	336 (13.0)	4.42 [1.24]	3.64 [1.20]	0.78
21~25	246 (9.5)	4.43 [1.24]	3.63 [1.24]	0.80
26~?	400 (15.5)	4.49 [1.27]	3.69 [1.24]	0.80
Disease duration (x) (years, men)				
0~2	104 (21.2)	4.09 [1.42]	3.59 [1.28]	0.50
3~5	79 (16.1)	3.70 [1.57]	3.34 [1.30]	0.36
6~10	118 (24.1)	3.94 [1.32]	3.42 [1.13]	0.52
11~15	66 (13.4)	4.22 [1.49]	3.67 [1.43]	0.55
16~20	40 (8.2)	4.39 [1.35]	3.74 [1.24]	0.65
21~25	40 (8.2)	3.84 [1.27]	3.23 [1.15]	0.61
26~?	43 (8.8)	4.20 [1.31]	3.59 [1.18]	0.61
Age (y) (years, women)				
~40	159 (6.2)	4.16 [1.41]	3.56 [1.31]	0.60
41~50	228 (8.8)	4.26 [1.37]	3.55 [1.28]	0.71
51~60	780 (30.2)	4.32 [1.29]	3.56 [1.25]	0.76
61~70	911 (35.3)	4.41 [1.30]	3.64 [1.25]	0.77
71~80	443 (17.2)	4.47 [1.26]	3.68 [1.23]	0.79
81~?	62 (2.4)	4.39 [1.23]	3.57 [1.17]	0.82
Age (y) (years, men)				
~40	23 (4.7)	3.39 [1.63]	3.38 [1.24]	0.01
41~50	38 (7.8)	3.79 [1.43]	3.41 [1.21]	0.38
51~60	118 (24.1)	4.05 [1.33]	3.63 [1.13]	0.42
61~70	171 (34.9)	4.01 [1.46]	3.44 [1.32]	0.57
71~80	127 (25.9)	4.26 [1.34]	3.60 [1.25]	0.66
81~	13 (2.7)	3.38 [1.25]	2.71 [1.30]	0.67

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
*Mean [SD].
†Differences in the mean values between DAS28-ESR and DAS28-CRP in women were statistically larger than those in men (p < 0.0001)
x, Disease duration; y, age; z, difference between DAS28-ESR and DAS28-CRP.
Women: z = 0.0024x + 0.718 (R2 = 0.004, p = 0.002), z = 0.0041y + 0.502 (R2 = 0.013, p < 0.001).
Men: z = 0.0059x + 0.456 (R2 = 0.013, p = 0.01), z = 0.0141y − 0.369 (R2 = 0.100, p < 0.001).

and DAS28-CRP; however, the number of "good response" patients was significantly different (p < 0.03) between DAS28-ESR (97 patients, 6.5%) and DAS28-CRP (136 patients, 9.2%).

Relationship between ESR and CRP

To address the differences between DAS28-ESR and DAS28-CRP noted above, the formula of DAS28-ESR was compared with that of DAS28-CRP. If DAS28-ESR and DAS28-CRP were equivalent, that is, the relationship of 0.70 × ln (ESR) = 0.36 × ln (CRP + 1) + 0.96 (CRP: mg/l) held true, the relationship between ESR and CRP would be as shown in Figure 2A. The curve on Figure 2A indicated that an ESR of 50 mm/h is approximately equivalent to a CRP of 14 mg/dl. Next, we plotted the raw values of ESR and CRP of patients tested above (fig 2B). A best-fit procedure suggested a curvilinear relationship

(CRP = 0.0002 × ESR^2 + 0.0214 × ESR + 0.1014, R^2 = 0.372, p < 0.0001), and an ESR of 50 mm/h was approximately equivalent to a CRP of 1.7 mg/dl. However, the actual relationship between ESR and CRP varies. For example, an ESR of 50 mm/h can be equivalent to 0 or 9 mg/dl CRP, which according to the DAS28-CRP formula indicates an absolute difference in DAS28-CRP of 0.83 (fig 2C).

DISCUSSION

In this study, using *NinJa*, a large observational cohort of RA patients in Japan, we showed that values of DAS28-CRP are significantly lower than those of DAS28-ESR, and that it is inappropriate to evaluate DAS28-CRP using the criteria of evaluation for DAS28-ESR. In several previous studies, although the backgrounds of patients were diverse, both

Table 3 Comparison of disease activity between DAS28-ESR and DAS28-CRP

		DAS28-CRP (y)				
		y<2.6	2.6≤y≤3.2	3.2<y≤5.1	5.1<y	Total (%)
DAS28-ESR (x)	x<2.6	282 (9.2)	13 (0.4)	2 (0.07)	0	297 (9.7)*
	2.6≤x≤3.2	251 (8.2)	83 (2.7)	22 (0.72)	0	356 (11.6%)
	3.2<x≤5.1	172 (5.6)	417 (13.6)	986 (32.1)	3 (0.98)	1578 (51.4)
	5.1<x	0	0	488 (15.9)	354 (11.5)	842 (27.4)*
	Total (%)	705 (22.9)	513 (16.7)	1498 (48.7)	357 (11.6)	3073

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
*The number of patients with remission and high disease activity evaluated by DAS28-ESR was significantly different from that by DAS28-CRP (p < 0.0001).

Table 4 Comparison of the improvement of disease activity between DAS28-ESR and DAS28-CRP

		DAS28-CRP			
		Good	Moderate	No response	Total (%)
DAS28-ESR	Good	71 (4.8)	20 (1.4)	6 (0.4)	97 (6.5)*
	Moderate	64 (4.3)	178 (12.0)	40 (2.7)	282 (19.0%)
	No response	1 (0.07)	85 (5.7)	1017 (68.6)	1103 (74.4)
	Total (%)	136 (9.2)	283 (19.1)	1063 (71.7)	1482

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
*The number of patients with "good" response evaluated by DAS28-ESR was significantly smaller than that by DAS28-CRP (p < 0.03).

DAS28-ESR and DAS28-CRP were calculated and the mean values were presented as follows: DAS28-ESR versus DAS28-CRP: 6.29 (SD 1.16) versus 5.97 (SD 1.05) in early RA,[16] 2.89 (SD 1.00) versus 2.67 (SD 0.84) in stable RA, and 4.73 (SD 1.18) versus 4.44 (SD 1.08) in active RA;[17] the medians (first and third quartile) were 4.09 (2.99; 5.17) versus 3.78 (2.71; 4.82) in a routine cohort study and 5.62 (4.81; 6.44) versus 4.67 (4.04; 5.50) in an inception cohort study.[18] Although DAS28-CRP tends to be lower than DAS28-ESR, except in the original paper that reported the development of DAS28-CRP (DAS28-ESR versus DAS28-CRP: 4.38 [SD 1.47] versus 4.41 [SD 1.27]),[10] surprisingly, whether the criteria of disease activity and the response criteria for DAS28-ESR could be applied to DAS28-CRP has never been questioned.

As stated above, the values of DAS28-ESR and those of DAS28-CRP were comparable in the original report; however, it is not clear why other studies including ours did not show similar results. It may be that the relationship between ESR and CRP is different among patients examined in different studies. ESR is well known to be affected by sex, age, immunoglobulin levels, and abnormal size or shape of red blood cells,[8][9] whereas CRP is less affected by these factors. Therefore, the relationship between ESR and CRP might differ with various factors, such as the ratio of women to men, age, disease activity (which has an influence on anemia), and the ratio of patients with Sjögren's syndrome that often accompanies hypergammaglobulinemia in RA patients in such studies. Our results support the findings that sex, disease duration, and age could affect the relationship between DAS28-ESR and DAS28-CRP (table 2). It is interesting, but not clear, whether the race of patients also has an influence on this relationship. Further investigations will be needed.

In the two previous reports about the relationship between ESR and CRP in RA, similar results were obtained; an ESR of 48 mm/h approximated to a CRP of 2.45 mg/dl[19] and to 2.7 mg/dl.[20] On the basis of these results, it is not acceptable to propose a relationship between ESR and CRP when an ESR of 50 mm/h is almost equivalent to a CRP of 14 mg/dl, if the formula of DAS28-ESR and that of DAS28-CRP are equivalent (fig 2A). As noted, it may be inappropriate to compare DAS28-CRP with DAS28-ESR directly. However, our results show that there is a significant correlation between DAS28-ESR and DAS28-CRP (fig 1C) and that DAS28-CRP values are systematically shifted to the left compared with DAS28-ESR (fig 1A and B). Therefore, DAS28-CRP can be a more useful and reliable score if the appropriate cut-off points of disease activity and those of response criteria for DAS28-CRP are set. As noted above, DAS28-CRP was developed by the modification of DAS28-ESR, which had also previously been developed by modification of the original DAS. Similarly, the criteria of disease activity and the response criteria for DAS28-ESR had been proposed by modification of those of the original DAS, which was developed in a cohort of patients in the early stages of RA. Our study also has a tendency to validate DAS28-CRP because there is no external standard, such as treatment changes or the patient's or the doctor's perspective. Therefore, the original criteria of disease activity and the original response criteria for DAS28-CRP should be studied and validated among various kinds of RA patient groups.

Although the changes of DAS28 values in DAS28-ESR and DAS28-CRP were very similar and were significantly correlated
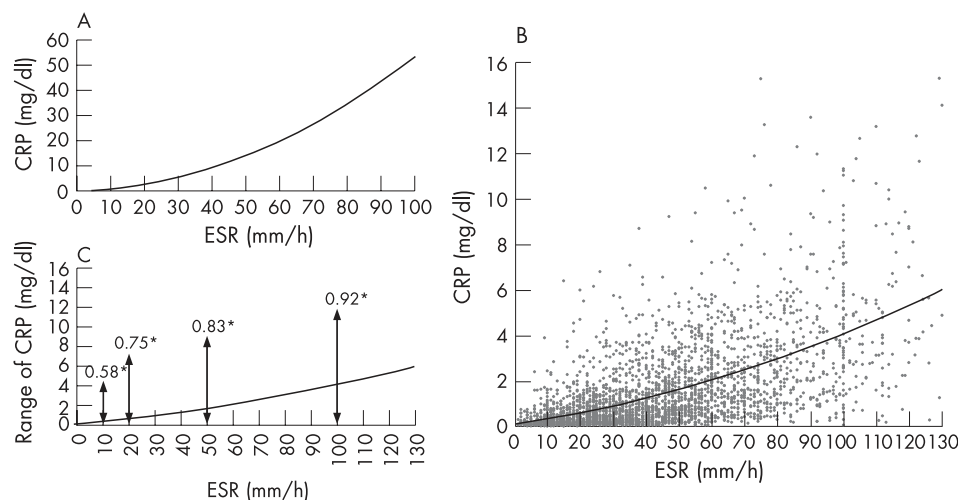

Figure 2 Relationship between erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Plot of the relationship between ESR and CRP in the condition that the correlation formula of DAS28-ESR and DAS28-CRP was correct, that is, the relationship of $0.70 \times \ln (ESR) = 0.36 \times \ln (CRP + 1) + 0.96$ (CRP: mg/l) held true (A). Plot of the distribution of ESR and CRP in rheumatoid arthritis patients tested in this study (B). The solid line indicates the curvilinear regression line of ESR and CRP (CRP $= 0.0002 \times ESR^2 + 0.0214 \times ESR + 0.1014$, $R^2 = 0.372$, p < 0.0001). Range of CRP for a representative value of ESR in patients (C). Solid line is the same as drawn in (B). *Absolute difference in DAS28-CRP while ESR is fixed at 10, 20, 50, and 100 mm/h.

(fig 1D), DAS28-CRP overestimated the EULAR response criteria compared with DAS28-ESR (table 3). This may be because of differences in the current values of DAS28. Unlike American College of Rheumatology improvement criteria,[21] the EULAR response criteria include changes in disease activity as well as current disease activity. Therefore, revising the threshold of disease activity may make it possible to evaluate the improvement in disease activity of DAS28-CRP.

In conclusion, both DAS28-ESR and DAS28-CRP are useful outcome measures in RA; however, DAS28-CRP significantly underestimated disease activity and overestimated the improvement in disease activity compared with DAS28-ESR. DAS28-CRP should be evaluated using different criteria from those for DAS28-ESR.

ACKNOWLEDGEMENTS

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Authors' affiliations

Toshihiro Matsui, Department of Rheumatology, Sagamihara National Hospital, National Hospital Organization (NHO), Kanagawa, Japan
Yoshiaki Kuga, Division of Rheumatic Diseases, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan
Atsushi Kaneko, Yoshito Eto, Department of Orthopedics, Nagoya Medical Center, NHO, Nagoya, Japan
Jinju Nishino, Nishino Orthopedics Clinic, Tokyo, Japan
Noriyuki Chiba, Department of Rheumatology, Morioka National Hospital, NHO, Iwate, Japan
Masayuki Yasuda, Department of Rheumatology, Beppu Medical Center, NHO, Oita, Japan
Koichiro Saisho, Department of Rheumatology, Miyakonojo Hospital, NHO, Miyazaki, Japan
Kota Shimada, Shigeto Tohma, Division of Rheumatology, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, NHO, Kanagawa, Japan

Toshihiro Matsui, Yoshiaki Kuga, Atsushi Kaneko, Jinju Nishino, Yoshito Eto, Noriyuki Chiba, Masayuki Yasuda, Koichiro Saisho, Kota Shimada, Shigeto Tohma, iR-net (Division of Rheumatology, Immunological Disorder Network, National Hospital Organization, Japan)

*Present address: Department of Orthopedic Surgery, Ogawa Red Cross Hospital, Saitama, Japan.

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