Lower ratings of pain intensity in older adults lead to underestimation of disease activity in patients with rheumatoid arthritis

Background: To investigate the influence of age on the components of the 28-joint Disease Activity Score (DAS28)-C-Reactive Protein (CRP) in patients with Rheumatoid Arthritis (RA) and whether DAS28-CRP can be equally interpreted in all age groups. Methods: The proportion of CRP and patient reported components of the DAS28 (DAS-P) were analyzed and compared between 2 age groups (younger RA <60, older RA ≥ 60) using Mann-Whitney U test. Inflammatory disease burden in the joint was calculated by modified DAS28 (MDAS28=0.49 x ln(C-Reactive Protein (CRP))+0.15 x swollen joint count 28+0.22 x physician global assessment (PhGA)+1). Multivariate analyses were used to design models best predicting the effect of age on CRP, the proportion of CRP, inflammation level calculated by MDAS28, DAS-P, and pain levels. Results: CRP and the proportion of CRP in DAS28-CRP were not influenced by age. MDAS28 did not increase with age but was associated with disease duration and anti-tumor necrosis factor (TNF) therapy. DAS-P and pain level had significant negative association with age. In subjects with moderate inflammation (defined by MDAS28 score above 50 percentile, N=370), older RA subjects (N=189) had lower pain level, tender joint count, patient and physician global assessment, DAS28-CRP than younger subjects (n=157). Conclusions: CRP, proportion of CRP in DAS28-CRP, and MDAS28 were not influenced by age but the proportion of subjective components of DAS28-CRP and pain level decreased with age. Therefore, disease activity could be underestimated by DAS28-CRP in older RA patients.

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Introduction

Rheumatoid Arthritis (RA) is the most common chronic immune-mediated disease causing joint destruction and functional disability [1-3]. The incidence of RA increases with age and the prevalence of RA in persons 60 years of age and older is about 2% [4]. RA among elderly people is increasingly an important health issue but little is known about their clinical characteristics and disease outcomes. Patients with elderly-onset RA have an increasingly steep trajectory of disability progression [5]. In addition, higher levels of ultrasound-detected inflammation despite comparable clinical disease activity score were found in patients with late onset rheumatoid arthritis [6]. Therefore, accurate disease activity assessment has utmost importance to optimize therapeutic outcomes by using a Treat-to-Target (T2T) approach to achieve low levels of disease activity or remission [7,8].

One of the most widely used disease activity measure is the Disease Activity Score (DAS) 28, which includes a count of 28 swollen and tender joints, a patient-rating of global disease, and an inflammatory marker [9-11]. The DAS28 based on erythrocyte sedimentation rate (DAS28-ESR) has been extensively validated for its use in clinical trials in combination with the European League against Rheumatism (EULAR) response criteria. C-Reactive Protein (CRP) has many advantages over ESR, which is influenced by age and sex and has a slow response to change [12-14]. Therefore, an alternative formulation of the DAS28 based on CRP (DAS28–CRP) has been increasingly used. However, DAS28 and the European League Against Rheumatism (EULAR) response criteria were both developed in a population with a mean age below 55 years [15,16]. Therefore, we hypothesized that current composite disease activity indices may not measure the severity of disease accurately in

older patients with RA and may not be adequate to guide treatment in this population. With this hypothesis, we evaluated the performance and validity of DAS28-CRP in older patients with RA. First, we investigated whether CRP and the proportion of CRP in DAS28-CRP are influenced by age. We used Modified Disease Activity Score (MDAS) to examine whether levels of inflammatory disease burden in the joint increase with age. Next, we examined whether subjective patient reported components of DAS are influenced by age. Finally, since patient's pain perception has the greatest influence on the subjective components of DAS, we investigated whether there is any difference in pain level to similar degree of inflammation with aging using MDAS.

Materials and methods

Materials

The subjects studied were from the University of Pittsburgh's Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry. Since its inception in February 2010, RACER has enrolled patients older than 18 years who have been diagnosed with RA by a rheumatologist at the University of Pittsburgh Medical Center (UPMC) [17,18]. Subjects were followed longitudinally, and at each follow-up visit with their physician, self-administered questionnaire data including a Routine Assessment of Patient Index 3 (RAPID3), 12-Item Short Form Health Survey (SF12), and patient Visual Analog Scale (VAS) for global health were collected. Physicians also provided the results of a 28 joint tender and swollen joint count and a visual analog scale (VAS) for global health. A blood sample for determination of a CRP level was also collected at each study visit. Data related to medication use and RA classification criteria were extracted from the Medical Archival Retrieval System (MARS) electronic health record (EHR) system at UPMC. This study's subjects were enrolled in RACER between 2/15/10 and 5/9/11. If a subject had more than one visit with a DAS28-CRP, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Routine Assessment of Patient Index Data 3 (RAPID3) recorded, the earliest visit was used. 740 RACER subjects were eligible for this study. The RACER registry protocol was approved by the University of Pittsburgh Institutional Review Board and all RACER subjects gave informed consent prior to enrollment.

Composite measures and levels of inflammation

DAS28-CRP, CDAI, SDAI, and RAPID3 were measured according to established methods [19,20]. In order to translate the effect of the CRP and subjective components on the DAS28, we calculated the proportions of CRP and subjective patient reported components in the DAS28-CRP (DAS-P). The share is expressed as a proportion and calculated by dividing the formula the DAS28 by the entire DAS28 (for example: CRP share=[0.36 × ln (CRP+1)/ DAS28, Relative of the contribution of the patient reported measures (tender joint count [TJC] and patient global assessment [PtGA] in DAS28-CRP [DAS-P]=[0.56 × √(TJC)+0.014 × PtGA]/DAS28-CRP). Levels of inflammatory disease burden in the joint were calculated by MDAS28 score (0.49 × ln (CRP)+0.15 × swollen joint count 28 (SJC)+0.22 × physician global assessment (PhGA)+1) [21]. The single measures of disease activity and the share of the CRP and subjective components of the DAS28 were analyzed and compared between the two age groups (younger RA <60, older RA ≥60). Analyses were carried out in subgroups of moderate to high inflammation (MDAS>50 percentile) and low inflammation (MDAS less than or equal to 50 percentile) as well.

Health related quality of life and comorbidity

Health-related quality of life was measured by SF12, which measures 8 domains (physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional and mental health) [22,23]. These domains result in 2 scores, a Physical Component Summary (PCS) and Mental Component Summary (MCS). We used the SF12v2, which differs from the original SF12 in that norms (1998 U.S. population) are available for comparisons. We used the Deyo-Charlson Comorbidity Index which was developed and validated as a method to use ICD-9 codes to calculate the Charlson Comorbidity Index [24].

Statistical analysis

Summary statistics were presented as means and standard deviations for continuous variables, and percentages for discrete variables. To compare demographic, clinical and disease activity variables between the different age and gender groups, age was categorized into 2 groups (younger RA <60, older RA ≥ 60). Mann-Whitney U test was used to detect differences between two age groups. Spearman's correlations

among pain (visual analog scale, VAS), disease characteristics, comorbidities and American College of Rheumatology (ACR) Core Data Set measures were calculated.

First, we investigated the effect of age on CRP, and the proportion of CRP in DAS28-CRP. Log-transformation of variables was performed when indicated to achieve Gaussian distribution. In primary multivariate analysis, we adjusted for demographic variables (gender, race, comorbidities). We also further adjusted for disease characteristics (disease duration and disease activity measured by CDAI) and treatment (use of Anti-tumor Necrosis Factor (TNF) therapy, use of non-anti-TNF biologic therapy). CDAI was used to adjust for disease activity since it does not include laboratory measures such as CRP or ESR. Interaction between age and gender was also assessed. Next, we explored the influence of age on inflammation level calculated by MDAS28, the proportion of subjective components of DAS28-CRP (DAS-P), adjusting for all covariates as described above. Finally, we studied whether pain level is influenced by age. In this analysis, we adjusted for demographic factors, disease duration, and treatment as described above. To adjust for level of inflammatory disease burden in the joint, we used MDAS28 instead of composite disease activity measures such as DAS28-CRP or CDAI since they are influenced by level of pain and pain perception. Analysis was performed using the R software package for statistical programming, version 3.2.4.

Results

Comparison of the two age groups

For the 740 subjects analyzed, subject age was 61.2 ±13.7 (median ±SD) years with disease duration of 14.4 ±12.4 (median ±SD) years. Demographic characteristics and variables of disease activity in the two age groups were shown **(TABLE 1)**. Mean value of rheumatoid factor (RF) and anti-cyclic Citrullinated Peptide (CCP) antibody were higher in the older group but they were not statistically significant difference among them. There was no significant difference in CRP, SJC, and PhGA. Significant difference was present in TJC, TJC/SJC ratio, PtGA, pain (VAS), RAPID3, Mental Health (SF12-MCS), Charlson score, and TNF inhibitor use. There was no significant difference on CRP level between genders but SJC/TJC ratio was higher in female.

Influence of age on the CRP and proportion of CRP in DAS28-CRP

Age or gender was not significantly correlated with CRP and there was no significant difference in CRP between 2 age groups. We investigated the effect of age on the CRP, corrected for gender, and other measures that can affect the CRP level or disease activity (race, disease duration, disease activity measured CDAI, use of anti-TNF therapy or other biologic therapy, glucocorticoid therapy, or comorbidities). For this purpose, we used multiple regression analyses, which confirmed no significant effect of age on CRP levels. Next we calculated the proportion of the CRP in DAS28-CRP as explained above. CRP share (%) was not influenced by age, even after adjustments for gender, race, comorbidities, anti-TNF therapy, other non-anti-TNF biologic therapy, glucocorticoid use, and disease activity by CDAI.

Influence of age on the inflammatory burden using MDAS

There is no significant the effect of age on the CRP and CRP share in DAS28 CRP **(TABLE 2; FIGURE 1A and 1B)**. We next explored if the level of inflammatory disease burden in the joint is influenced by age. We used MDAS28 to calculate the degree of inflammatory burden. Modified Disease Activity Score (MDAS) was shown to have superior correlation with Magnetic Resonance Image (MRI) detected synovitis and radiographic progression, in comparison with conventional measures [21]. Our multiple regression models demonstrated that inflammatory burden calculated by the MDAS28 does not increase significantly with aging. In this model, MDAS28 was significantly associated with disease duration, disease activity measured by CDAI, and TNF inhibitor use.

Influence of age on the proportion of subjective components of DAS28-CRP

There were significant differences in TJC, and patient global assessment, pain, RAPID3, and SF12-MCS between 2 age groups. They are known to be influenced by pain perception, comorbid conditions, and psychosocial factors [25]. We calculated share of patient reported subjective component using DAS-P as described above. Relative contribution of patient reported components to DAS28-CRP was increased with higher disease activity measured by DAS28-CRP **(FIGURE 2A)**. In contrast, relative of the contribution of the patient reported measures in

Table 1. Demographic and disease characteristics of subjects (N=740) and comparison between 2 age groups (younger <60, older ≥60).

	Total	Age<60	Age ≥ 60	P value
N	740	343	397	-
Age (years)*	61.2 ± 13.7	51.1 ± 9.1	68.8 ± 7.5	-
Disease duration *	10.9 ± 12.6	8.7 ± 9.7	15.3 ± 14.0	<0.001
Female (%) Race	577 (78%)	277 (80.8)	300 (75.6)	0.089
White	660 (89.2)	301	359	0.367
African American	73 (9.9)	38	35	-
Others	7	4	3	-
RF/CCP positive (%)‡	514 (69.5%)	235 (68.5)	279 (70.3)	0.603
CRP (mean ± /- SD)	-	1.0 ± 2.0	0.9 ± 1.4	0.894
SJC	-	3.7 ± 5.2	4.1 ± 5.3	0.449
TJC	-	3.9 ± 5.6	2.6 ± 4.4	0.002
TJC/SJC †	-	1.3 ± 1.9	0.8 ± 1.2	0.001
Patient global	-	4.4 ± 2.7	3.9 ± 2.5	0.006
Physician global	-	3.0 ± 2.6	2.7 ± 2.2	0.445
Pain (VAS)	-	5.1 ± 3.0	4.3 ± 2.7	<0.001
DAS28-CRP	-	3.4 ± 1.5	3.2 ± 1.2	0.079
CDAI	-	15.2 ± 13.4	13.2 ± 11.3	0.164
SDAI	-	16.2 ± 14.1	14.2 ± 11.7	0.211
RAPID3 (0-10)	-	3.9 ± 2.3	3.4 ± 2.0	0.005
M-DAS	-	1.8 ± 1.6	1.8 ± 1.5	0.670
DAS-P (%)	-	20.1 ± 15.6	16.9 ± 14.3	0.001
SF12-PCS (t score)	-	38.6 ± 11.2	37.7 ± 10.0	0.280
SF12-MCS (t score)	-	46.5 ± 11.0	50.2 ± 10.7	<0.001
M-HAQ	-	0.5 ± 0.5	0.4 ± 0.4	0.067
Synthetic DMARD use (%)	674 (91.1)	315 (91.8)	359 (90.4)	0.503
Anti-TNF use (%)	290 (39.2)	179 (52.2)	111 (28.0)	<0.001
Non-anti-TNF biologic therapy (%)	64 (8.6)	37 (10.8)	27 (6.8)	0.054
Opiate use (%)	244 (33)	122 (35.6)	122 (30.7)	0.163
Glucocorticoid use (%)	348 (47)	163 (47.5)	185 (46.6)	0.802
Comorbidities	-	1.6 ± 1.1	2.0 ± 1.5	<0.001

*Median ± SD † TJC/SJC ratio was calculated for subjects who have at least SJC ≥ 1. ‡ RF>=40, CCP ≥ 20. RF: Rheumatoid factor, CCP: Citrullinated Cyclic Peptide, CRP: C- Reactive Protein, SJC: Swollen Joint Count, TJC: Tender Joint Count, VAS: Visual Analog Scale, DAS: Disease Activity Score, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, RAPID3: Routine Assessment of Patient Index Data 3, DAS-P: Patient Reported Components in the DAS28-CRP, SF12: 12-Item Short form Health Survey, PCS: Physical Component Summary, MCS: Mental Component Summary, M-HAQ: Modified Health Assessment Questionnaire, DMARD: Disease Modifying Anti-Rheumatic Drug, TNF: Tumor Necrosis Factor.

CDAI (CDAI-P=[TJC+PtGA]/CDAI) remains similar regardless of disease activity categories with wider variation in remission or low disease activity (CDAI ≤ 10) **(FIGURE 2B)**. We investigated whether DAS-P is influenced by age. DAS- P was associated with both age and gender. There was no significant interaction between age and gender. Female gender had significantly higher DAS-P, while age was associated with lower DAS-P **(TABLE 3)**.

Influence of age on the pain level

Patient reported subjective components (DAS-P) differed considerably depending on patient's pain level and gender [25]. Since pain level was associated with patient reported subjective components such as TJC (r=0.73,

p<0.001) and PtGA (r=0.45, p <0.001), we investigated whether age contributes to difference in pain level. In regression analyses, pain level had significant negative association with age even after adjustment for race, gender, disease duration, comorbidities, use of biologic therapy, and level of inflammatory burden **(TABLE 3)**.

Comparison between younger and older RA patient according to the level of inflammatory disease burden in the joint

Relative contribution of subjective components to DAS28-CRP was more prominent in higher disease activity categories by DAS28-CRP **(FIGURE 2A and 2B)**. Therefore, we compared ACR core date set measures, SF12-Physical Health(PCS), Mental Health (MCS),

Table 2. Multiple regression analysis of influence of age on C reactive protein (CRP) level and CRP share (β denotes the standardized regression coefficient, SE denotes the standard error).

Model	Variables	β	SE	P value
Log CRP	Age	-0.003	0.004	0.467
	Gender	-0.074	0.119	0.534
	Race	0.188	0.161	0.242
	Charlson Score	0.024	0.038	0.530
	Disease duration	0.008	0.004	0.043
	Anti-TNF therapy	-0.301	0.106	0.005
	Other biologic therapy*	-0.104	0.175	0.553
	Glucocorticoid therapy	0.202	0.102	0.049
	CDAI	0.029	0.004	0.000
CRP share	Age	-0.004	0.013	0.723
	Gender	-0.525	0.383	0.171
	Race	0.714	0.517	0.168
	Charlson Score	0.077	0.122	0.526
	Disease duration	0.024	0.013	0.069
	Anti-TNF therapy	-10.013	0.343	0.003
	Other biologic therapy	-0.530	0.565	0.349
	Glucocorticoid therapy	0.576	0.329	0.081
	CDAI	-0.029	0.013	0.033
MDAS28	Age	0.002	0.002	0.316
	Gender	-0.076	0.070	0.276
	Race	0.112	0.094	0.232
	Charlson Score	-0.014	0.022	0.538
	Disease duration	0.006	0.002	0.012
	Anti-TNF therapy	-0.182	0.062	0.004
	Other biologic therapy	-0.099	0.103	0.336
	Glucocorticoid therapy	0.157	0.060	0.009
	CDAI	0.104	0.002	0.000

*Biologic therapy other than anti-tumor necrosis factor (TNF), CDAI: Clinical Disease Activity Index, MDAS28: Modified Disease Activity Score 28

DAS28-CRP, RAPID3, CDAI, SDAI in patients with RA according to the level of inflammatory burden in the joint using MDAS28 **(TABLE 4)**. In subjects with moderate inflammation (defined by MDAS28 score above 50 percentile, N=370), older RA subjects (age ≥ 60, N=189) had significantly lower pain level, TJC, PtGA, PhGA, RAPID3, DAS 28-CRP than younger subjects (age<60, n=157) but SJC, ESR/CRP, SF12-PCS were not different between them. Of note, T score of SF12-MCS was significantly better in older RA subjects. There were no significant differences between two age groups in subjects with lower levels of inflammation (MDAS ≤ 50 percentile, N=370) **(TABLE 4)**.

Discussion

We comprehensively evaluated impact of age on validity of DAS28-CRP. During active arthritis, synovial inflammation is mirrored by a systemic acute-phase response. Therefore, measurements of the levels of ESR or CRP have been an integral part of the disease activity assessment for many years as an indicator of severity of disease, progression and prognosis of patients with RA. CRP has recently become the more preferred serological marker for evaluating acute disease activity given its advantages over ESR [12-14]. However, the impact of age on CRP was not yet fully investigated in patients with RA. We demonstrated that CRP and share of CRP in DAS28-CRP are not influenced by age.

Most rheumatologists regard joint count as pivotal component of RA disease activity measurement. DAS28, CDAI, and SDAI all include swollen and tender joint counts as core components. For patients, pain is the main driver of their ratings of tender joint counts and global disease assessment, while for providers the number of swollen joints is most important [21,26]. Since composite indices integrate various aspects of the disease into a single numerical value, there can be a great discrepancy between patient and provider assessments of disease activity. Previous studies showed that there were no significant differences in each component of
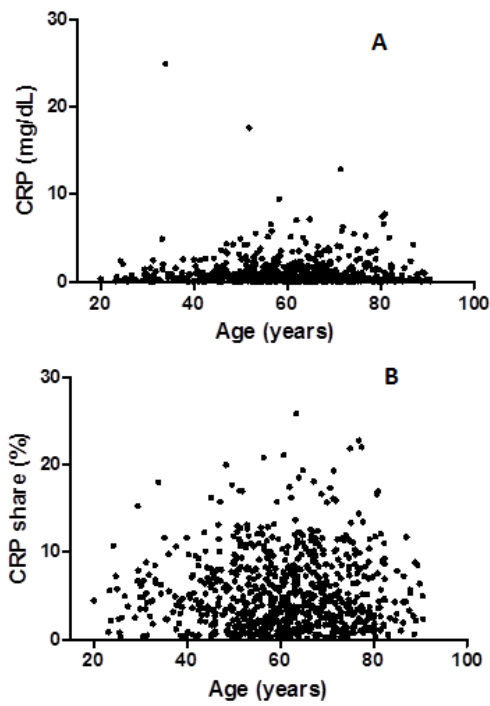
Figure 1. C reactive protein (CRP) level and CRP share (%) according to age. (A) CRP (mg/dL) vs. age, (B) CRP share (%) vs. age.
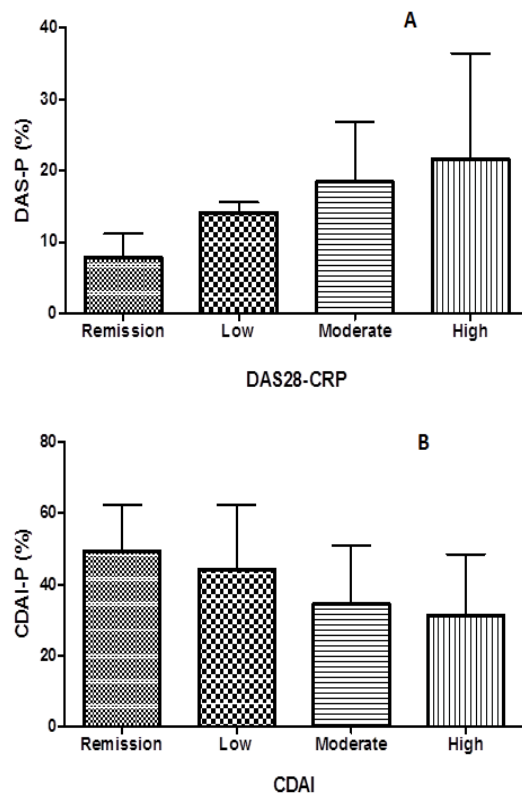
Figure 2. Contribution of subjective patient reported components by disease activity categories (remission, mild, moderate, severe). (A) DAS-P (%) vs. DAS28-CRP, (B) CDAI-P (%) vs. CDAI. (DAS-P: Subjective components of DAS28 relative to the total DAS28, CDAI-P: Subjective components of CDAI relative to the total CDAI). Error bars represent one standard deviation from the mean.

Table 3. Multiple regression analysis of influence of age on Subjective components of DAS28 relative to the total DAS28 (DAS-P), pain level (visual analog scale, VAS) (β denotes the standardized regression coefficient, SE denotes the standard error).

Model	Variables	β	SE	p value
DAS-P	Age	-0.088	0.040	0.030
	Gender	20.894	10.227	0.019
	Race	10.443	10.659	0.385
	Charlson Score	-0.294	0.389	0.451
	Disease duration	-0.036	0.042	0.397
	Anti-TNF therapy	10.841	10.101	0.095
	Other biologic therapy*	0.611	10.811	0.736
	Glucocorticoid therapy	20.279	10.058	0.032
	MDAS28	30.977	0.350	0.000
Pain (VAS)	Age	-0.024	0.008	0.002
	Gender	0.134	0.236	0.569
	Race	0.990	0.319	0.002
	Charlson Score	0.161	0.075	0.032
	Disease duration	0.005	0.008	0.527
	Anti-TNF therapy	0.241	0.212	0.256
	Other biologic therapy	0.395	0.348	0.256
	Glucocorticoid therapy	0.605	0.203	0.003
	MDAS28Tabl	0.680	0.067	0.000

*Biologic therapy other than anti-tumor necrosis factor (TNF), CDAI: Clinical Disease Activity Index, MDAS28: Modified Disease Activity Score 28

Table 4. Comparison between 2 age groups according to the level of inflammation in the joint calculated by modified disease activity score 28 (MDAS28).

	Low grade inflammation (n=370)		P value†	Moderate to high grade inflammation (n=370)		P value†
Age groups	Age<60	Age ≥ 60	-	Age<60	Age ≥ 60	-
Pain (VAS)	3.9 ± 2.9	3.4 ± 2.43	0.448	6.4 ± 2.7	5.1 ± 2.7	<0.001
SJC	0.9 ± 1.7	1.1 ± 1.8	0.884	6.8 ± 5.9	6.8 ± 6.0	0.963
TJC	1.3 ± 3.0	0.8 ± 1.6	0.884	6.7 ± 6.7	4.2 ± 5.5	<0.001
PhGA	1.3 ± 1.3	1.5 ± 1.2	0.175	4.9 ± 2.4	4.0 ± 2.3	<0.001
PtGA	3.3 ± 2.5	3.2 ± 2.4	0.884	5.6 ± 2.4	4.4 ± 2.5	<0.001
ESR*	11.8 ± 10.0	18.6 ± 16.1	0.175	26.8 ± 21.9	33.1 ± 26.9	0.255
CRP	0.3 ± 0.3	0.3 ± 0.3	0.884	1.7 ± 2.6	1.6 ± 1.8	0.723
DAS28-CRP	2.4 ± 0.8	2.3 ± 0.7	0.884	4.5 ± 1.2	4.0 ± 1.1	<0.001
CDAI	7.0 ± 5.7	6.6 ± 4.3	0.884	23.9 ± 13.8	19.5 ± 12.2	<0.001
SDAI	7.2 ± 5.6	6.9 ± 4.2	0.884	25.7 ± 14.3	21.1 ± 12.4	<0.001
RAPID3	8.7 ± 6.2	8.3 ± 5.2	0.884	14.8 ± 6.0	12.1 ± 6.1	<0.001
SF12-PCS	42.1 ± 11.2	40.3 ± 9.0	0.176	34.8 ± 9.9	35.3 ± 20.3	0.755
SF12-MCS	48.6 ± 10.1	51.3 ± 10.3	0.176	44.3 ± 11.6	49.3 ± 10.9	<0.001

*ESR total n for low grade inflammation group =90, high grade inflammation group n=150, † P-values were adjusted for multiple comparisons using the Benjamini-Hochberg procedure. VAS: Visual Analog Scale, SJC: Swollen Joint Count, TJC: Tender Joint Count, PhGA: Physician Global Assessment, PtGA: Patient Global Assessment, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, DAS: Disease Activity Score, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, RAPID3: Routine Assessment of Patient Index Data 3, DAS-P: Patient Reported Components in the DAS28-CRP, SF12: 12-Item Short form Health Survey, PCS: Physical Component Summary, MCS: Mental Component Summary

disease activity score between young and old RA patients [27-29].

Although aging is generally associated with greater expectations of pain and disability, prior studies suggested that the elderly complain pain less frequently, resulting in under-recognition and under-treatment of pain [30,31]. Subjective patient reported components of DAS are strongly influenced by pain perception, comorbid conditions, and psychosocial factors [25]. Among them, patient's pain perception has the greatest influence on the DAS [25,32]. Therefore, disease activity score values differ considerably depending on patient's pain

perception [25]. Since pain experiences in the elderly differ from the experiences in the young on multiple dimensions (sensory, affective, and cognitive), we performed further analysis of the impact of age on the share of patient-reported components and pain levels [33]. In this study, we demonstrated that the share of subjective components of DAS28-CRP and pain level decrease with age. Our results showed that clinicians may underestimate disease activity when they make their clinical decision solely based on DAS28-CRP in older patients with moderate to high grade inflammation from RA.

It has not been clearly established whether pain perception is different according to age in RA patients. Experimental evidences on age-related changes in pain perception have so far been unclear but seem that there are stimulus-specific changes in pain perception in the elderly [34]. Animal studies suggested that age-induced modifications are associated with decrease in pain perception. An age-related reduction in nociceptive behavior during inflammation as well as lesser behavioral sensitization to mechanical stimuli was observed in aged mice compared to young [35,36]. Gender differences concerning pain level in RA have been reported [37,38]. However, we were not able to see gender difference in pain levels in older patients with RA. Our result is consistent with the observation which showed no gender differences in pain threshold and pain self-report in the elderly [33].

Our study has some limitations. Subjects in our study were relatively old (60.3 ± 13.6 years) and had long disease duration (14.6 ± 12.6 years), which may limit generalization. Younger or early RA patients might be under-represented. There is difference in pain perception during acute inflammation and chronic inflammation/damage. Given long disease duration, we were not able to see whether there are significant difference in pain perception between early RA and chronic established RA. The mean DAS28-CRP in our study was fairly low in average (DAS28-CRP, 3.3 ± 1.3). Relatively low disease activity in average might under-estimated the impact of age on the validity of the DAS28. MDAS28 was used as a surrogate for inflammatory burden in the joint. Although MDAS showed superior correlation with MRI detection of synovitis and more accurately predicted radiographic progression in patients with RA, MDAS was developed and validated in a clinical trial setting [21]. The validity of MDAS in usual practice settings, especially elderly patients with lower

disease activity score remains unclear. Since pain level, patient reported outcomes, physical function, and biomarkers are likely to be influenced by disease duration and treatment, the relationships among disease activity measures that we observed in this cross-sectional study needs to be assessed longitudinally. In addition, comprehensive evaluation of patient reported outcomes and psychosocial factors was lacking, and other confounders for biomarker levels were not fully assessed. We did not collect information on chronic low back pain that can increase pain perception regardless RA disease status [39,40]. Lastly, it remains unclear whether lower pain levels in the elderly RA patients are associated with decreased pain perception or lower pain reporting.

Nonetheless, we comprehensively evaluated the performance and validity of DAS28-CRP in the old patients with RA and demonstrated that DAS28-CRP may not fully reflect the severity of disease in older RA patients, especially with moderate to high grade inflammation from RA.

Funding

Competing interests

The authors declare that they have no completing interests.

Authors' contributions

YH: study conception, study design, data analyses, and manuscript preparation and revision. JF: data acquisition, and manuscript revision. JL: data acquisition, and manuscript revision. HE: Data acquisition and manuscript revision. AF: study conception, data analyses, and manuscript revision. LM: study conception, data acquisition, and manuscript revision. All authors read and approved the final manuscript.

Acknowledgements

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