



Remission or Not Remission, That's the Question: Shedding Light on Remission and the Impact of Objective and Subjective Measures Reflecting Disease Activity in Rheumatoid Arthritis

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Received: July 24, 2022 / Accepted: August 26, 2022 / Published online: September 21, 2022
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ABSTRACT

Introduction: The inclusion of certain variables in remission formulas for rheumatoid arthritis (RA) may give rise to discrepancies. An increase in patient global assessment (PGA), a variable showing the patient's self-evaluation of their disease activity, may alone tilt a patient out of remission when using certain remission-assessing methods. This study aimed to explore differences in remission rates among various formulas and the impact of PGA and other clinical variables on the calculation of remission.

Methods: Data were collected from RA patients monitored during the years 2015–2019 at an

outpatient clinic in southern Norway. Linear and logistic regression assessed associations between PGA, other RA-related variables, and remission-assessing methods.

Results: Remission rates were 23%, 65%, and 73% in 2019 when assessing the same 502 RA patients using Boolean remission, Boolean remission without PGA, and the disease activity score (DAS) with C-reactive peptide [DAS28(3)-CRP] method, respectively. Among the same population that year, 27% reported $PGA \leq 10$, 74% had a tender joint count of ≤ 1 , 85% had a swollen joint count of ≤ 1 , and 86% had $CRP \leq 10$. Pain (standardized coefficient $\beta = 0.7$, $p < 0.001$) was most strongly associated with PGA. Pain, fatigue, and morning stiffness were substantially associated with the remission-assessing methods that incorporated PGA.

Conclusions: Since PGA is strongly associated with the patient's perception of pain and may not reflect the inflammatory process, our study

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40744-022-00490-5>.

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challenges the application of remission-assessing methods containing PGA when monitoring RA patients in the outpatient clinic. We recommend using measures that are less likely to be associated with noninflammatory pain and psychosocial factors.

Keywords: Rheumatoid arthritis; Disease activity; Remission; Patient global assessment; Real-life data

Key Summary Points

Why carry out this study

Several composite measures are recognized to define remission status in rheumatoid arthritis, but they do not provide comparable scores

Most measures incorporate patient self-evaluation, which, while elevated, can be solely responsible for not reaching remission even though the remaining variables reflect an absence of inflammation

This study seeks to assess the comparability of remission rates calculated using different remission-assessing methods in a rheumatoid arthritis outpatient clinic cohort

What was learned from the study

Remission rates calculated for the same group of rheumatoid arthritis patients differ when using various remission-assessing measures, particularly as patient self-evaluation is integrated into their calculation

Patient self-evaluation is important when assessing disease burden; however, this study challenges the applicability of the patient self-evaluation variable when utilizing potent and costly anti-inflammatory drugs for a noninflammatory status

INTRODUCTION

In 1981, the American College of Rheumatology (ACR) defined rheumatoid arthritis (RA) remission as the absence of any inflammatory RA disease activity [1]. According to the European League Against Rheumatism (EULAR) recommendations for managing RA, treatment should aim for remission or low disease activity [2]. An analysis by Mian et al. of 22 RA treatment guidelines (2000–2017) found the disease activity score-28 (DAS28) to be the most frequently recommended parameter to guide RA treatment and assess remission [3], despite the possibility of having multiple swollen joints while in DAS28 remission [4].

A less frequently recommended [3] and more stringent alternative for assessing remission (defined by the ACR/EULAR committee) is Boolean remission, which has the criteria of a score of ≤ 1 for the tender 28-joint count (TJC28), the swollen 28-joint count (SJC28), C-reactive peptide (CRP) (mg/dl), and the patient global assessment (PGA) [visual analog scale (VAS) 0–10] [4]. However, a recent meta-analysis of randomized clinical trials by Ferreira et al. has questioned the importance of using PGA in Boolean remission, as it places greater emphasis on the patient's perception of disease burden, which may be influenced by noninflammatory mechanisms [5]. The incorporation of PGA scoring into other remission-assessing methods should also be questioned, as it may potentially lead to misestimation of inflammatory remission rates and consequently to overtreatment.

The primary aim of this study was to compare remission rates using different remission-assessing methods in a RA outpatient clinic cohort, in particular, to reveal the impact of PGA. The second aim was to examine associations of RA-related variables with PGA, and the third was to explore associations of different RA-related variables with remission status in various measures.

METHODS

Patient Inclusion and Data Collection

Data for this cross-sectional study were obtained (2015–2019) from a rheumatological outpatient clinic in southern Norway. Patient monitoring at the outpatient clinic was standardized using the computer tool GoTreatIT® Rheuma (www.diagraphit.com). Data were extracted from the clinic database using predefined queries. One query extracted RA patients data who had at least one registered visit in the analysed year. The most recent visit was extracted if there were multiple visits during the same year. The anonymized data files were analysed using EXCEL and the Statistical Package for the Social Sciences (SPSS).

Descriptive variables included age, sex, body mass index (kg/m^2), current smoking status, years of education, disease duration, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (aCCP). Variables reflecting disease activity encompassed erythrocyte sedimentation rate (ESR) (mm/h), CRP (mg/L), SJC28 (0–28 joints), TJC28 (0–28 joints), and investigator global assessment (IGA) (VAS 0–100 mm). The patient-reported outcome measures (PROMs) included PGA, pain (VAS 0–100 mm), fatigue (VAS 0–100 mm), morning stiffness (reported in 15-min units), and the modified health assessment questionnaire (MHAQ) [6].

Composite Disease Activity Score and Remission Definitions

The composite disease activity scores (CDAs) included in this study cover the addition-based methods, the simple disease activity index (SDAI) (TJC28, SJC28, CRP, PGA, IGA) [7] and the clinical disease activity index (CDAI) (TJC28, SJC28, PGA, IGA) [8], and the algorithm-based DAS28(3) (TJC28, SJC28, CRP) [9] and DAS28(4) (TJC28, SJC28, CRP, PGA) [9]. Among the assessed CDAs, remission cutoff values were ≤ 2.6 for both DAS28(3) and DAS28(4) [9], ≤ 2.8 for CDAI [8], and ≤ 3.2 for SDAI [7]. Patients were stratified for analysis as having either remission or non-remission.

ACR/EULAR Boolean remission (4-variable remission) is defined as scores of ≤ 1 for TJC28, SJC28, CRP, and PGA [4]. However, since the extracted CRP is measured in mg/L and the PGA by a VAS of 0–100 mm, the Boolean remission CRP and PGA were redefined as ≤ 10 . Modified 4-variable remission rates were examined using different PGA cutoffs of ≤ 20 , ≤ 30 , ≤ 40 , ≤ 50 , ≤ 60 , ≤ 70 , ≤ 80 , and ≤ 90 (Fig. 1). PGA ≤ 100 was not included, as only 11 patients (2%) scored a PGA of 91–100. A 3-variable remission was defined as Boolean remission without PGA (i.e. TJC28 ≤ 1 , SJC28 ≤ 1 , and CRP ≤ 10). Subjective 2-variable remission (TJC28 ≤ 1 and PGA ≤ 10) and objective 2-variable remission (SJC28 ≤ 1 and CRP ≤ 10) were also reported (Table 2). RA patients in the study were also assessed with single-component cutoffs: TJC28 ≤ 1 , SJC28 ≤ 1 , CRP ≤ 10 , PGA ≤ 10 , PGA ≤ 20 , and IGA ≤ 10 . Since the difference in the remission rates between the assessed years was only minimally statistically significant, the comparison in Fig. 1 is for 2019 only.

Treatment

The annual data collection (2015–2019) from the RA patients included information on biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), which comprised tumour necrosis factor inhibitors (TNFi) (etanercept reference, etanercept SB4, infliximab reference, infliximab CT-P13, adalimumab, golimumab, certolizumab pegol), non-TNFi (rituximab reference, rituximab GP2013, abatacept, and tocilizumab), and tsDMARDs (baricitinib and tofacitinib). The collected data also contained information on prednisolone and conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX). Monotherapy for b/tsDMARDs and TNFi, as well as no treatment, i.e. neither b/tsDMARD, csDMARDs, nor prednisolone, was also reported.

Statistical Analysis

Categorical variables are reported as numbers and percentages, and continuous variables as

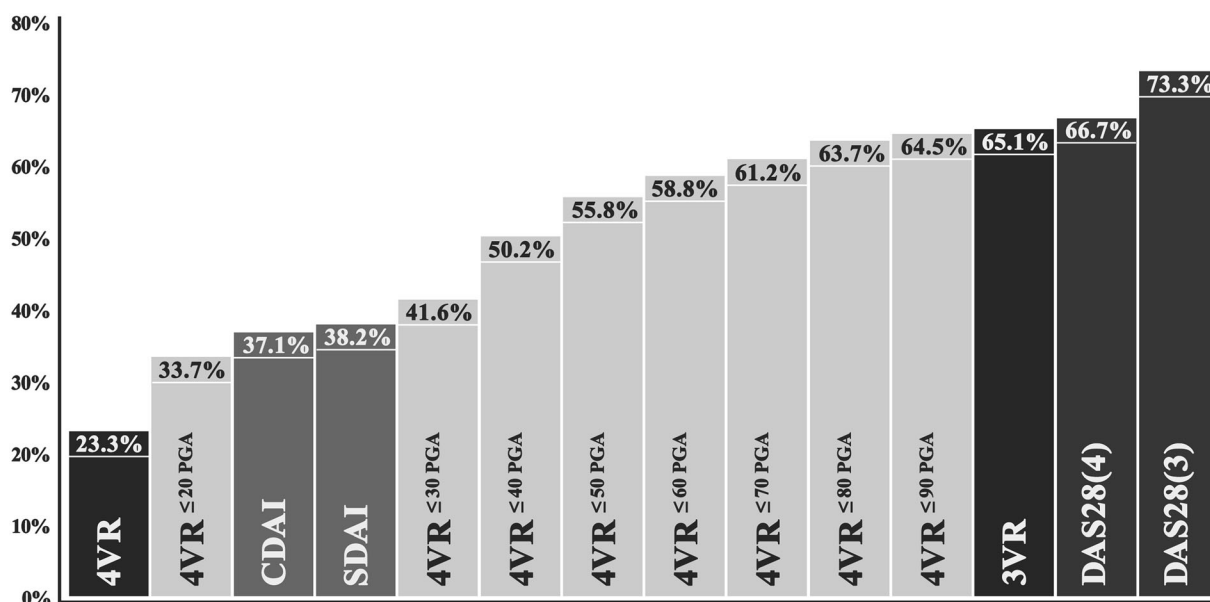


Fig. 1 Comparing composite measures of disease activity and variants of Boolean remission in 2019. *Note:* data are presented as percentages of $n = 502$ in 2019. The figure compares various cutoffs of the patient global assessment in Boolean remission with the remission of composite measures of disease activity and 3-variable remission in rheumatoid arthritis patients in an ordinary outpatient clinic in southern Norway. 4-variable remission

is achieved when C-reactive peptide (CRP) ≤ 10 , tender 28-joint count (TJC28) ≤ 1 , swollen 28-joint count (SJC28) ≤ 1 , and PGA ≤ 10 . 3-variable remission is achieved when CRP ≤ 10 , TJC28 ≤ 1 , and SJC28 ≤ 1 . 4VR 4-variable remission, PGA patient global assessment, CDAI clinical disease activity index, SDAI simple disease activity Index, 3VR 3-variable remission, DAS28 disease activity score with CRP

means with standard deviations (SDs) or means with ranges. Changes in and associations between variables over 5 years were analysed with SPSS using a one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Only patients with a complete dataset for TJC28, SJC28, CRP, PGA, and IGA were analysed. To examine bias due to missing data, the included patients were compared with those without a complete dataset. A p -value of < 0.05 was considered statistically significant.

Univariable and multivariable linear regression with stepwise variable selection was used to assess the association between demographic and disease characteristic variables and PGA. Logistic regression was used to assess the association between demographic and disease characteristic variables and various remission-assessing methods. The variables responsible for the different calculations or assessments of the various remissions were omitted in the logistic

regression analysis. For linear regression, the standardized coefficient β and unstandardized coefficient B were reported along with the 95% confidence intervals. For logistic regression, the odds ratios (OR) were reported along with the 95% confidence intervals. Due to the minimal differences in the assessed demographics, disease activity measures, and patient-reported outcomes among the 5 years of the study period, we decided to report only the 2019 regression analysis for clarity purposes. Supplementary Table 2 shows a variant of the multivariate regression analysis, albeit subgrouped based on the 3-variable remission and moderate–high disease activity in RA patients with DAS28(4), CDAI, and SDAI.

Ethics

The study was approved by the Regional Ethics Committee (REC) of Middle Norway (2010/

3078) and followed the ethical principles of medical research involving human subjects of the 1964 Declaration of Helsinki (and its later amendments). No consent from the patients was required by the REC of Middle Norway, as all data were anonymized and collected as part of routine clinical care.

RESULTS

Demographics, Disease Activity, and Patient-Reported Outcomes

Table 1 presents the demographic variables, RF, aCCP, disease activity variables, PROMs, and treatment for the years 2015–2019. The number of RA patients in the included dataset ranged from 613 to 502 (2015–2019). Over the 5 years, no significant change in the mean values of the demographic variables, PROMs, aCCP positive rate (73.8%), RF positive rate (68.8%), TJC28 (1.3), SJC28 (0.9), and CRP (6.1 mg/L) was observed. The mean changes in ESR (14.6, range 12.6–18.0 mm/h) and IGA (9.6, 7.8–10.6) across the 5 years were significant; however, no significant change was noted for DAS28(3) (2.3), DAS28(4) (2.4), CDAI (6.4), or SDAI (7.0).

Approximately 40% of the patients did not have a complete dataset and were excluded from the analysis. As shown in Supplementary Table 3, there were only minor differences between the excluded and included patients.

Comparison of Remission Rates and the Impact of PGA

Table 2 presents the remission rates based on DAS28(3), DAS28(4), CDAI, SDAI, ACR/EULAR Boolean remission, various subgroups of Boolean remission, and individual measures. Over the 5 years, none of the mean remission rates were significantly different except for $IGA \leq 10$. The average remission rates ordered from lowest to highest are shown in Fig. 1. A gradual increase in the PGA cutoff in Boolean 4-variable remission was linked to an observable increase in the remission rate. When comparing these different remission rates using an increasing

PGA cutoff in 4-variable remission (Fig. 1), the remission rates based on SDAI and CDAI were similar to Boolean 4-variable remission with PGA cutoffs of ≤ 20 and ≤ 30 . In comparison, the 3-variable, DAS28(3), and DAS28(4) remission rates were located beyond a cutoff of ≤ 90 PGA.

Treatment

The mean 5-year percentage of RA patients who received any type of b/tsDMARD was 41.3%, and it was 10.1% for those who received b/tsDMARDs as monotherapy. Among the same analysed study population, the 5-year average percentage of patients who received TNFi (no csDMARDs or prednisolone) was 21.5%, and it was 5.0% for those who only received TNFi. Also, an average of 65.7% of the patients were registered as receiving csDMARDs, 56.2% were registered as receiving MTX, and 47.5% were registered as receiving prednisolone. An average of 7.3% did not receive either b/tsDMARDs, csDMARDs, or prednisolone. Both TNFi and b/tsDMARD monotherapy showed statistically significant changes over the 5 years. Supplementary Table 3 includes a treatment comparison between the examined and excluded patients.

Associations of Relevant Variables with Patient Global Assessment

Table 3 shows the associations of different variables (univariate and multivariate models) with PGA in 2019 according to a linear regression. For a univariable linear regression, only PROM variables achieved $\beta \geq 0.5$ with a p -value < 0.001 ; these variables included pain ($\beta = 0.9$), MHAQ ($\beta = 0.7$), fatigue ($\beta = 0.7$), and morning stiffness ($\beta = 0.5$). In a multivariable regression model with all covariates included, only pain ($\beta = 0.7$), fatigue ($\beta = 0.2$), and MHAQ ($\beta = 0.1$) were significantly associated with PGA, with pain having the strongest association. Similar outcomes were observed for the multivariable regression model after stepwise variable selection. Interestingly, similar findings were observed for the association between pain

Table 1 Demographics, disease characteristics, and treatment of rheumatoid arthritis patients during 2015–2019

	2015	2016	2017	2018	2019	Mean (SD/%) [range]	Missing data Median, mean, range	P-value
Original dataset, N	1067	908	953	825	871			0.502
Included dataset, N	613 (57.5%)	554 (61.0%)	555 (58.2%)	490 (59.4%)	502 (57.6%)	543 (58.7%) [57.5–61.0%]	0%, 0%, 0–0%	
Demographics								
Age (years)	62.8 (12.6)	61.2 (13.5)*	62.0 (13.1)*	60.8 (13.8)*	61.8 (14.0)*	61.7 (13.4) [60.8–62.8]	0%, 0%, 0–0%	0.102
Female	410 (66.9%)*	377 (68.1%)	362 (65.2%)*	334 (68.2%)	335 (66.7%)	364 (67.0%) [65.2–68.2%]	0%, 0%, 0–0%	0.847
BMI (kg/m ²)	26.5 (4.7)*	26.2 (4.4)	26.2 (4.4)	26.3 (4.4)	26.4 (4.5)	26.3 (4.5) [26.2–26.5]	1.8%, 1.7%, 1–2%	0.780
Education (years)	11.6 (3.4)	12.0 (3.6)*	12.0 (3.6)	12.1 (3.5)	12.2 (3.5)	12.0 (3.5) [11.6–12.2]	1.4%, 1.1%, 0–2%	0.090
Current smokers	118 (19.3%)	101 (18.3%)	90 (16.4%)	82 (16.9%)	78 (15.7%)	94 (17.3%) [15.7–19.3%]	1.0%, 0.8%, 0–1%	0.503
Disease duration (years)	11.7 (10.0)*	11.6 (9.9)	12.1 (10.4)	11.3 (11.1)	10.8 (10.9)*	11.5 (10.5) [10.8–12.1]	0%, 0%, 0–0%	0.376
Biomarkers								
aCCP positive	421 (72.2%)	393 (74.6%)	380 (72.1%)	356 (76.4%)*	357 (73.6%)	381 (73.8%) [72.1–76.4%]	4.9%, 4.6%, 3–5%	0.507
RF positive	409 (69.1%)	374 (70.3%)	370 (69.5%)	311 (68.1%)	318 (67.1%)	356 (68.8%) [67.1–70.3%]	4.1%, 4.8%, 3–7%	0.803
Disease activity variables								
ESR (mm/h)	18.0 (15.1)*	14.8 (14.0)*	13.5 (13.4)	14.2 (14.6)*	12.6 (12.2)*	14.6 (13.9) [12.6–18.0]	14.8%, 14.4%, 9–21%	< 0.001
CRP (mg/L)	6.5 (10.5)	5.9 (11.4)*	6.2 (14.4)	6.0 (10.4)*	5.8 (10.2)*	6.1 (11.4) [5.8–6.5]	0%, 0%, 0–0%	0.860
TJC28 (0–28)	1.4 (2.9)	1.4 (2.9)	1.2 (2.6)*	1.3 (2.9)	1.4 (2.8)*	1.3 (2.8) [1.2–1.4]	0%, 0%, 0–0%	0.837
SJC28 (0–28)	0.9 (1.8)	1.0 (2.3)	0.9 (2.3)*	0.9 (2.1)	0.7 (1.9)	0.9 (2.1) [0.7–1]	0%, 0%, 0–0%	0.320
IGA (VAS, 0–100 mm)	10.1 (11.9)	10.1 (12.6)	9.2 (13.1)*	10.6 (13.7)	7.8 (12.2)	9.6 (12.7) [7.8–10.6]	0%, 0%, 0–0%	0.004

Table 1 continued

	2015	2016	2017	2018	2019	Mean (SD/%) [range]	Missing data, median, mean, range	P-value
Clinical-reported outcome measures								
DAS28(3) score	2.3 (0.9)	2.3 (0.9)*	2.2 (0.9)*	2.3 (0.9)*	2.2 (0.9)*	2.3 (0.9) [2.2–2.3]	0%, 0%, 0–0%	0.294
DAS28(4) score	2.5 (1.0)	2.4 (1.0)	2.4 (1.0)	2.4 (1.1)	2.4 (1.1)	2.4 (1.0) [2.4–2.5]	0%, 0%, 0–0%	0.255
CDAI value	6.6 (6.5)	6.5 (6.9)	6.1 (6.9)	6.5 (6.7)	6.1 (6.6)	6.4 (6.7) [6.1–6.6]	0%, 0%, 0–0%	0.555
SDAI value	7.2 (6.8)	7.1 (7.3)	6.7 (7.5)	7.2 (7.0)	6.7 (7.0)	7.0 (7.1) [6.7–7.2]	0%, 0%, 0–0%	0.571
Patient-reported outcome measures								
PGA (VAS, 0–100 mm)	33.4 (26.4)	31.9 (25.0)	30.2 (24.4)	32.5 (25.5)	32.7 (25.7)	32.2 (25.4) [30.2–33.4]	0%, 0%, 0–0%	0.284
Pain (VAS, 0–100 mm)	32.5 (25.5)	31.6 (24.7)*	32.1 (25.1)	33.1 (25.6)*	32.6 (26.0)	32.4 (25.4) [31.6–33.1]	7.4%, 7.9%, 7–9%	0.917
MHAQ (0–3)	0.5 (0.5)	0.4 (0.5)*	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)*	0.4 (0.5) [0.4–0.5]	6.5%, 5.9%, 3–8%	0.263
Fatigue (VAS, 0–100 mm)	36.7 (30.3)	36.4 (29.9)	37.8 (29.4)	38.1 (30.8)	37.6 (29.6)	37.3 (30.0) [36.4–38.1]	6.7%, 6.6%, 4–9%	0.872
Morning stiffness (h)	1.0 (1.3)	0.9 (1.3)	0.8 (1.1)	0.9 (1.2)	0.9 (1.3)	0.9 (1.3) [0.8–1.0]	9%, 8.3%, 7–9%	0.390
Treatment								
b/tsDMARDs	255 (41.6%)*	247 (44.6%)*	216 (38.9%)*	199 (40.6%)*	206 (41.0%)*	225 (41.3%) [38.9–44.6%]	0%, 0%, 0–0%	0.421
TNFi	155 (25.3%)	153 (27.6%)*	129 (23.2%)	102 (20.8%)	102 (20.3%)	128 (23.5%) [20.3–27.6%]	0%, 0%, 0–0%	0.026
Monotherapy b/tsDMARDs	40 (6.5%)*	51 (9.2%)*	52 (9.4%)*	61 (12.4%)*	65 (12.9%)*	54 (10.1%) [6.5–12.9%]	0%, 0%, 0–0%	0.002
Monotherapy TNFi	19 (3.1%)*	30 (5.4%)*	26 (4.7%)*	31 (6.3%)*	28 (5.6%)*	27 (5.0%) [3.1–6.3%]	0%, 0%, 0–0%	0.125
csDMARDs	405 (66.1%)*	362 (65.3%)*	366 (65.9%)*	325 (66.3%)*	325 (64.7%)*	357 (65.7%) [64.7–66.3%]	0%, 0%, 0–0%	0.985

Table 1 continued

	2015	2016	2017	2018	2019	Mean (SD/%) [range]	Missing data Median, mean, range	P-value
Methotrexate	346 (56.4%)*	302 (54.5%)*	315 (56.8%)*	275 (56.1%)*	286 (57.0%)*	305 (56.2%) [54.5–57%]	0%, 0%, 0–0%	0.932
Prednisolone	311 (50.7%)	265 (47.8%)*	266 (47.9%)	226 (46.1%)	227 (45.2%)	259 (47.5%) [45.2–50.7%]	0%, 0%, 0–0%	0.405
No treatment	53 (8.6%)*	44 (7.9%)*	42 (7.6%)*	31 (6.3%)*	31 (6.2%)*	40 (7.3%) [6.2–8.6%]	0%, 0%, 0–0%	0.467

All data were collected from an ordinary outpatient clinic in southern Norway. Categorical variables are presented as percentages (%) and continuous variables as means with standard deviations (SDs). Missing data are presented as the median and the mean with the range. The χ^2 test was used for categorical variables and one-way ANOVA was used for continuous variables to test for differences during a follow-up of 5 years. The asterisk symbol (*) represents a significant *p*-value when compared with excluded data (see Supplementary Table 3). *BMI* body mass index, *aCCP* anti-cyclic citrullinated peptide, *RF* rheumatoid factor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC28* tender 28-joint count, *SJC28* swollen 28-joint count, *IGA* investigators global assessment, *VAS* visual analog scale (measured 0–100), *DAS28* disease activity score with CRP, *CDAI* clinical disease activity index, *SDAI* simple disease activity index, *PGA* patient global assessment, *MHAQ* modified health assessment questionnaire, *b/tsDMARDs* biological and target synthetic disease-modifying antirheumatic drugs, *TNF* tumour necrosis factor, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *No treatment* implies that the patient did not receive b/tsDMARDs, *csDMARDs*, nor prednisolone

Table 2 Remission rates in rheumatoid arthritis patients during 2015–2019

	2015 (<i>n</i> = 613)	2016 (<i>n</i> = 554)	2017 (<i>n</i> = 555)	2018 (<i>n</i> = 409)	2019 (<i>n</i> = 502)	Mean (%) [range]	<i>P</i> - value
Remission rates							
DAS28(4) remission	62.8%	64.4%	66.8%	65.1%	66.7%	353 (65.2%) [62.8–66.8%]	0.581
DAS28(3) remission	70.1%	72.0%	71.7%	70.4%	73.3%	388 (71.5%) [70.1–73.3%]	0.786
CDAI remission	34.4%	33.6%	39.8%	36.1%	37.1%	196 (36.2%) [33.6–39.8%]	0.214
SDAI remission	34.3%	33.9%	39.5%	34.5%	38.2%	196 (36.1%) [33.9–39.5%]	0.178
Boolean-remission-based remission rates (PGA ≤ 10, SJC28 ≤ 1, TJC28 ≤ 1, CRP ≤ 10)							
4vRemission (Normal)	22.2%	19.7%	23.4%	23.1%	23.3%	121 (22.3%) [19.7–23.4%]	0.546
4vRemission (PGA ≤ 20)	30.8%	31.4%	34.2%	33.3%	33.7%	177 (32.7%) [30.8–34.2%]	0.688
3vRemission (SJC28, TJC28, CRP)	61.3%	62.8%	64.0%	63.1%	65.1%	343 (63.3%) [61.3–65.1%]	0.753
Objective 2vRemission (SJC28, CRP)	72.4%	73.5%	73.2%	71.6%	75.7%	398 (73.3%) [71.6–75.7%]	0.660
Subjective 2vRemission (TJC28, PGA)	25.1%	23.3%	26.1%	25.5%	25.1%	136 (25.0%) [23.3–26.1%]	0.858
Proportion rates of 1-variable cutoffs							
SJC28 (0–28) ≤ 1	81.7%	82.1%	82.3%	81.0%	85.3%	448 (82.5%) [81.0–85.3%]	0.449
CRP (mg/L) ≤ 10	85.2%	87.0%	86.8%	84.7%	86.1%	467 (86.0%) [84.7–87.0%]	0.764
TJC28 (0–28) ≤ 1	75.0%	76.7%	77.5%	74.3%	74.1%	410 (75.5%) [74.1–77.5%]	0.626
PGA (0–100) ≤ 10	26.8%	25.3%	27.9%	26.7%	26.9%	145 (26.7%) [25.3–27.9%]	0.907
PGA (0–100) ≤ 20	39.6%	41.3%	42.9%	40.4%	40.2%	222 (40.9%) [39.6–42.9%]	0.829
IGA (0–100) ≤ 10	65.1%	66.6%	71.4%	65.1%	74.3%	371 (68.5%) [65.1–74.3%]	0.002

DAS28 disease activity score with CRP, *CRP* C-reactive protein, *CDAI* clinical disease activity index, *SDAI* simple disease activity index, *PGA* patient global assessment, *SJC28* swollen 28-joint count, *TJC28* tender 28-joint count. All data were collected from an ordinary outpatient clinic in southern Norway. All remission percentages (compared to non-remission) were estimated from the total (*n*). There are no missing data. *4vRemission* is achieved when CRP ≤ 10, TJC28 ≤ 1, SJC28 ≤ 1, and PGA ≤ 10. *3vRemission* is achieved when CRP ≤ 10, TJC28 ≤ 1, and SJC28 ≤ 1. *Objective 2vRemission* is achieved when CRP ≤ 10 and SJC28 ≤ 1. *Subjective 2vRemission* is achieved when PGA ≤ 10 and TJC28 ≤ 1

and PGA in other disease activity subgroups, including moderate–high disease activity and 3-variable remission (Supplementary Table 2).

Association of Variables with Remission Status

Supplementary Table 1 reports the associations as ORs between different variables and remission assessed through logistic regression. TJC28 had a significant association with objective 2-variable remission, and IGA had significant associations with all except subjective 2-variable remission. Among the PROMs, pain had significant associations with DAS28(4), CDAI, SDAI, 4-variable remission, 4-variable-remission with a PGA cutoff of ≤ 20 (4-variable remission^{PGA20}), and subjective 2-variable remission. Fatigue had significant associations with CDAI remission, SDAI remission, 4-variable remission, 4-variable remission^{PGA20}, and subjective 2-variable remission. Morning stiffness had significant associations with CDAI remission, SDAI remission, and 4-variable remission^{PGA20}. PGA had no significant associations with scores that did not incorporate the variable [3-variable remission, DAS28(3) remission, objective 2-variable remission].

DISCUSSION

The main finding of our study is the large variation in RA remission rate between the remission-assessing methods: rates ranged from 23% for Boolean remission to 73% for DAS28(3) remission (in 2019). For Boolean remission in particular, we should highlight the impact of PGA, which is strongly associated with pain, on the remission rates.

In Fig. 1, among the remission-assessing methods incorporating PGA, 4-variable remission (23%), CDAI (37%), and SDAI (38%) had substantially lower remission rates than DAS28(4) (67%). A discrepancy in remission rate when using different remission-assessing methods has been reported previously across Europe [10]. The DAS28(4) calculation differs as it uses an algorithm that gives PGA much weaker power, giving it a reduced impact

compared to the other variables. In contrast, 4-variable (Boolean) remission, CDAI, and SDAI all give equal power to their variables. The remission-assessing methods without PGA produced remission rates of 65% and 73% for 3-variable remission and DAS28(3), respectively. Similar discrepancies between methods have been demonstrated elsewhere [11, 12]. We confirmed that attaining remission is dependent on the method of assessment [12–16].

While DAS28 deprioritizes PGA, the same algorithm allows remission to be attained with multiple swollen joints, which can consequently lead to radiographic joint damage despite the patient being “in remission” [17]. As a reciprocal, a patient must have TJC28, SJC28, CRP, and PGA ≤ 1.0 to attain a 4-variable remission [4]. However, this approach may overemphasize subjectivity, as patients without active joints and normal CRP levels can still report elevated PGA scores, which shift disease activity above the remission threshold due to noninflammatory causes, e.g. fibromyalgia, osteoarthritis, depression, psychological pain and distress, and other comorbidities [18–21]. A study by Inanc et al. observed an increase in anxiety, fatigue, and depression among RA patients who did not attain 4-variable remission but achieved a DAS28-ESR remission [22]. Among these measures, PGA and depression were the most important contributors to non-concordance between DAS28-ESR and Boolean remission rates. In order to avoid false nonremission and possibly improper targeted treatment, Inanc et al. proposed the implementation of separate supplementary assessments for anxiety, fatigue, fibromyalgia, and depression among RA patients who do not attain 4-variable remission [22].

Solutions to lessen the restrictiveness of 4-variable remission include threshold modification [23] and 3-component variant remission definition [24]. The latter is exemplified by excluding PGA from Boolean remission when assessing disease activity, albeit restricting it to disease impact [5]. We evaluated the threshold modifications, Boolean 3- and 2-variable remission and the individual Boolean components. Figure 1 shows that the remission rates for 3-variable remission, DAS28(4), and

Table 3 Associations between PGA and the patient variables in rheumatoid arthritis patients using linear regression

	Univariate			Multivariate								
	Enter			Enter			Forward			Backward		
	β	B (95% CI)	P	β	B (95% CI)	P	β	B (95% CI)	P	β	B (95% CI)	P
Demographics												
Age (years)	0.1	0.1 (0.1, 0.3)		0	0 (-0.1, 0.1)							
Female	0.1	5.9 (1.1, 10.7)	*	0	-1.4 (-4.2, 1.4)							
BMI (kg/m ²)	0.1	0.5 (0, 1.0)	*	0	0 (-0.3, 0.3)							
Education (years)	-0.2	-1.1 (-1.8, -0.5)	***	0	0.2 (-0.1, 0.6)							
Smoker	0.1	5.2 (-1.1, 11.4)		0	-0.9 (-4.5, 2.7)							
Disease duration (years)	0.1	0.3 (0.1, 0.5)	*	-0.1	-0.1 (-0.3, 0)							
Biomarkers												
aCCP positive	0	-1.1 (-6.3, 4.1)		0	-1.6 (-5.5, 2.3)							
RF positive	0.1	2.6 (-2.4, 7.5)		0	1.9 (-1.7, 5.6)							
Disease activity variables												
ESR (mm/h)	0.3	0.5 (0.3, 0.7)	***	0.1	0.2 (0, 0.3)	*	0.1	0.1 (0, 0.2)	*	0.1	0.1 (0, 0.2)	*
CRP (mg/L)	0.2	0.5 (0.3, 0.7)	***	0	-0.1 (-0.2, 0.1)							
TJC28 (0–28)	0.4	3.8 (3.0, 4.5)	***	0	0.1 (-0.5, 0.6)							
SJC28 (0–28)	0.3	3.5 (2.3, 4.6)	***	0	0.1 (-1.0, 1.1)							
IGA (VAS, 0–100 mm)	0.4	0.8 (0.7, 1.0)	***	0.1	0.2 (0, 0.3)		0.1	0.2 (0.1, 0.3)	**	0.1	0.2 (0.1, 0.3)	**
Patient-reported outcome measures												
Pain (VAS, 0–100 mm)	0.9	0.9 (0.8, 0.9)	***	0.7	0.7 (0.6, 0.7)	***	0.7	0.7 (0.6, 0.7)	***	0.7	0.7 (0.6, 0.7)	***
MHAQ (0–3)	0.7	40.7 (37.1, 44.2)	***	0.1	4.9 (0.5, 9.4)	*	0.1	4.1 (0.0, 8.1)	*	0.1	4.5 (0.5, 8.6)	*
Fatigue (VAS, 0–100 mm)	0.7	0.6 (0.6, 0.7)	***	0.2	0.2 (0.1, 0.2)	***	0.2	0.2 (0.1, 0.2)	***	0.2	0.2 (0.1, 0.2)	***

Table 3 continued

	Univariate			Multivariate								
	Enter			Enter			Forward			Backward		
	β	<i>B</i> (95% CI)	<i>P</i>	β	<i>B</i> (95% CI)	<i>P</i>	β	<i>B</i> (95% CI)	<i>P</i>	β	<i>B</i> (95% CI)	<i>P</i>
Morning stiffness (h)	0.5	10.6 (9.0, 12.2)	***	0	0.1 (-1.2, 1.3)							
Adjusted <i>R</i> square		0.8	0.8	0.8								

β standardized coefficient, *B* unstandardized coefficient, *BMI* body mass index, *aCCP* anti-cyclic citrullinated peptide, *RF* rheumatoid factor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC28* tender 28-joint count, *SJC28* swollen 28-joint count, *IGA* investigators global assessment, *VAS* visual analog scale (measured 0–100), *PGA* patient global assessment, *MHAQ* modified health assessment questionnaire. All data were collected from an ordinary outpatient clinic in southern Norway. All values marked in bold have significant *p*-values: *** < 0.001, ** < 0.01, * < 0.05

DAS28(3) remained highest regardless of the PGA threshold used in 4-variable remission.

In a meta-analysis by Ferreira et al. (2020) [25], which included 12 studies reporting indirect 3-variable remission rates, a paper by Furu et al. [26] reported the highest 3-variable remission prevalence of 51% in a Japanese cohort in 2014. The average 3-variable remission prevalence from the 12 studies in the meta-analysis was 31% [25]. In other non-single-timepoint studies, Studenic et al. reported a 3-variable remission rate of 30% after 12 months of treatment for early RA [23]. Interestingly, a study of DMARD-naïve patients with early RA showed a similar remission rate when they were only treated with csDMARDs and prednisolone [27]. Our high 3-variable remission rate may be explained by the lower disease activity in our outpatient RA cohort (mean DAS28 2.4 and CDAI 6.4), where a high proportion of the patients (~ 40%) were treated with b/tsDMARDs.

When the 4-variable remission was divided into subjective (PGA, TJC28) and objective (CRP, SJC28) categories, only 25% of patients achieved subjective remission, whereas 76% reached objective remission. During the same year, among the one-variable cutoffs, $PGA \leq 10$ had the lowest rate, 27%, the rate for $TJC28 \leq 1$ was 74%, that for $SJC28 \leq 1$ was 85%, and that for $CRP \leq 10$ was the highest: 86%. We believe that these numbers reflect two valuable issues: (1) despite considering tender joints to be subjective, similar rates are reported for the objective SJC28 and CRP, and (2) there are considerable differences in rate between patients expressing $PGA \leq 10$ and $TJC28 \leq 1$, $SJC28 \leq 1$, and $CRP \leq 10$ (27% vs 74–86%).

Based on these numbers, remission-assessing methods that use PGA, at least for Boolean criteria, CDAI, and SDAI, do not appear favourable. The argument for including PGA was its ability to help differentiate active treatment from control treatment, which in turn meant a significant contribution to defining remission. Together with CDAI and SDAI, 4-variable remission was also considered to predict good radiographic outcomes [4]. In addition, PGA and CRP were considered a safeguard when

using the standardized 28 joint count, which omits ankle and feet joints [4].

However, studies have shown that only swollen joints and acute phase reactants, not PGA, are robustly associated with radiographic progression [17, 23, 28]. This may further weaken the rationale for incorporating PGA into remission assessments, since stopping the progression of joint damage is one of the most important goals of RA treatment. With the introduction of modern imaging techniques, subclinical signs of inflammation have been demonstrated, highlighting the challenges of defining true remission in RA [29–32].

Moreover, RA patients in remission by any established criteria can experience radiographic progression [33]. A recent study showed that the increase in tender joints correlated best with other subjective variables (i.e. pain) but not with ultrasonographic synovitis, whereas swollen joints correlated significantly with ultrasonographic synovitis [34]. Furthermore, Hensor et al. found that a score based on SJC28 and CRP alone had a stronger association with ultrasonography synovitis and radiographic progression than the original DAS28 in early RA [35]. A recently published paper by Sundlisæter et al. (2022) observed no increase in inflammation measured with ultrasound and MRI in patients who failed to attain 4-variable remission due to PGA and/or TJC compared to those who achieved 4-variable remission [36]. Brites et al. (2021) did not observe any significant changes in inflammation on ultrasound either when comparing 4-variable remission and 3-variable remission [37]. This again supports the view that objective measures reflect inflammatory disease status better than subjective measures, which may also be impacted by noninflammatory mechanisms.

To distinguish between patients with treatment failure with and without the presence of objective inflammation, Buch and colleagues recently introduced the terms “persistent inflammatory refractory RA” (PIRRA) and “noninflammatory refractory RA” (NIRRA) [38]. Distinguishing between PIRRA and NIRRA from a clinical perspective is important, as the two require different treatments and treatment strategies. It is particularly relevant in patients

who only fail to attain a 4-variable remission because $PGA > 10$ [38]. Real-life data, as collected in our study, are thus of great importance, as they reveal the strength and weaknesses of the present remission criteria when they are used to treat patients to remission in ordinary clinical practice.

In addition, the use of PGA in RA comes with numerous challenges due to its subjective and heterogeneous formulation. PGA is often a single unstandardized question with global-health-oriented or disease-activity-oriented wording. In our study, we used PGA with a more general description. Khan et al. showed that disease activity and general PGA could be used interchangeably for the calculation of RA activity when using CDAI, DAS28, and Routine Assessment of Patient Index Data 3 [39]. However, Gossec et al. reported discordance between the global-health-formulated and disease-activity-formulated PGA in Boolean remission for early arthritis patients [40]. PGA can also be expressed using various phrases or with an open question, where the answer is transformed to either a 0–10 or a 0–100 scale. Graphics can also be used, such as lines (horizontal or vertical) or tick marks with intervals [20]. In summary, numerous possible results increase the chance of generating various interpretations.

In the multivariable regression analyses, pain had the strongest and fatigue the second strongest association with PGA. When the analysis was based on disease activity, the strong association between pain and PGA was very similar for the subgroups. In the logistic regression assessment, these two variables were also only significant when compared with PGA-incorporated remission-assessing methods. Pain and fatigue are considered the leading sources of discomfort among RA patients and key contributing factors for reporting elevated PGA levels [20, 22, 41–44], especially in near-4-variable remission cases, i.e. in those who only failed to attain 4-variable remission because $PGA > 10$ [18, 24, 45]. The three most essential domains for achieving patient-perceived remission are pain, fatigue, and independence [46, 47]. From the patient’s perspective, being in remission means reducing the impact of RA on

their life, “eventually leading to a feeling of normality” [48].

Since PGA is strongly associated with the patient’s perception of pain, using remission methods impacted by PGA to guide medical treatment decisions when monitoring RA patients in an outpatient clinic may not reflect the inflammatory disease process. However, a less restrictive variant in which PGA has only a weak impact (DAS28 remission) can also cause the misestimation and omission of swollen joints.

This study should be seen in the context of its limitations. Like all observational studies, there are issues related to a certain level of missing data, confounding factors, and attrition bias. Only a selected group of patients without missing data were included. As shown in Supplementary Table 3, differences between the included and excluded patients were small and mostly nonsignificant, indicating a high grade of internal validity. Another limitation is the lack of radiographic data. The study’s strengths are its real-life setting, the application of a spectrum of RA remission measurements, and the evaluation of PGA associations for relevant RA-related variables and remission definitions.

CONCLUSION

In conclusion, our study challenges the value of the currently used remission-assessing methods. Based on our results and available data, we suggest using methods without measures impacted by noninflammatory pain and psychosocial factors such as PGA when treating patients to remission with DMARDs. Interestingly, among all the variables used to assess the remission rate, only the IGA (used in both CDAI and SDAI) improved significantly, while the rest of the variables remained stable over the 5-year period.

Based on growing evidence, as supported by our study, we suggest that it may be time for a paradigm shift to develop new remission criteria and a new definition for use in ordinary clinical practice, with objective variables and imaging favoured to avoid treating noninflammatory pain with DMARDs.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Editorial Assistance. We share our gratitude to the proof-reading company (<https://www.proof-reading-service.com>) for their evaluation.

Authorship. All authors fulfil the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All authors have given their consent to submit and publish the manuscript.

Author Contributions. Alen Brkic, Katarzyna Łosińska, Are Hugo Pripp, Mariusz Korkosz, and Glenn Haugeberg were involved in the conception, design, and interpretation of data. Alen Brkic was mainly responsible for drafting the manuscript and analysing the data, with contributions from Katarzyna Łosińska, Are Hugo Pripp, Mariusz Korkosz, and Glenn Haugeberg. All authors critically reviewed the results and contributed to the interpretation of the data. All authors read and approved the final manuscript.

Disclosures. Alen Brkic, Katarzyna Łosińska, Are Hugo Pripp, Mariusz Korkosz, and Glenn Haugeberg have nothing to disclose. They have no financial interests that could create a potential conflict of interest or the appearance of a conflict of interest concerning the submitted work.

Compliance with Ethics Guidelines. The study was approved by the Regional Ethics Committee (REC) of Middle Norway (2010/3078) and followed the ethical principles of medical research involving human subjects of the 1964 Declaration of Helsinki (and its later amendments). No consent from patients was required by the REC of Middle Norway, as all data were anonymized and collected as part of routine clinical care.

Data Availability. Data are available on reasonable request and must be approved by all participating centres.

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