

Is Swollen to Tender Joint Count Ratio a New and Useful Clinical Marker for Biologic Drug Response in Rheumatoid Arthritis? Results From a Swedish Cohort

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Objective. To study the impact of swollen to tender joint count ratio (STR) and other baseline characteristics on treatment response to a first course of anti-tumor necrosis factor (anti-TNF) therapy in rheumatoid arthritis (RA) patients.

Methods. Patients with RA initiating their first course of anti-TNF treatment were included in a structured clinical followup protocol. Based on pragmatic thresholds and plausibility, patients were categorized as having low (STR <0.5), moderate (0.5 ≤ STR ≤ 1.0), or high (STR >1.0) joint count ratios. The data were collected and followed during the period of March 1999 through December 2010.

Results. A total of 2,507 patients were included in the study (median age 56 years, 78% women). Of these patients, 344 (14%) had a low STR, 1,180 (47%) had a moderate STR, and 983 (39%) had a high STR. According to these STR thresholds, 23% of patients (95% confidence interval [95% CI] 18–29%) with low, 39% (95% CI 35–43%) with moderate, and 40% (95% CI 36–44%) with high STR achieved the American College of Rheumatology criteria for 50% improvement (ACR50) response at 6 months after initiation. Correlation tests showed that STR was associated with ACR50 response independent of both swollen and tender joint counts. Logistic regression analysis consistently showed that moderate STR, high STR, not using prednisolone, high baseline Disease Activity Score in 28 joints, and low baseline Health Assessment Questionnaire scores were significantly associated with favorable ACR50 response with odds ratios of 1.93 ($P < 0.01$), 2.82 ($P < 0.01$), 0.65 ($P < 0.01$), 1.49 ($P < 0.01$), and 0.47 ($P < 0.01$), respectively.

Conclusion. STR is a new and feasible predictor of treatment response in RA. RA patients with a moderate to high STR have a 2- to 3-fold increased likelihood of responding according to ACR50 criteria.

INTRODUCTION

Since tumor necrosis factor (TNF) blocking agents were introduced, their efficacy and tolerability have been studied in randomized controlled clinical trials (1–8), as well as in observational studies (9–14) of patients with rheumatoid arthritis (RA). Previous independent reports have shown that concomitant methotrexate (MTX) treatment, high functional level, younger age, male sex, and ultra-

sound Doppler activity are associated with good clinical response in RA patients (11–15). However, solid data regarding clinical predictors of treatment response to anti-TNF therapy suitable for decision making in the clinical setting are still limited (11–14). Identifying such predictors of response to biologic agents is important both for the individual patient and for reasons of health economics.

Chronic widespread pain in RA is a problem that has received increased interest in recent years (16), perhaps because the new and effective biologic treatments unmask this condition to a greater extent than what was seen

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Significance & Innovations

- Swollen to tender joint count ratio (STR) is a new and feasible predictor of treatment response in rheumatoid arthritis (RA).
- STR is a convenient and easily used clinical index without additional costs or hazards.
- The response rates and predictors of response reflect what has been found in other anti-tumor necrosis factor-treated RA cohorts.

previously. Thus, joint tenderness might indicate chronification of the pain reaction rather than ongoing inflammation having implications for the potential of response to antiinflammatory treatment (16). The mechanism behind this pain may be a central sensitization, which might be induced by inflammation especially driven by TNF cytokines (17). In this way, a disconnection between the number of swollen and tender joints may appear in RA patients who have developed widespread pain syndromes or other hyperalgesic conditions (18). Interestingly, absolute difference in tender minus swollen joint count has previously been used to classify fibromyalgia in a population of RA patients (19). Furthermore, joint pain due to sensitization may even confuse the clinician in some cases, leading to diagnostic troubles due to high numbers of tender joints (20). The notion of joint tenderness as a possible confounder led us to the idea that one should not solely look at either the number of swollen or tender joints but also study their relationship within the individual patient.

In this study, the aim was to investigate the impact of swollen to tender joint count ratio (STR) and other baseline characteristics on treatment response to the first course of anti-TNF therapy (biologics-naïve) in RA patients in an observational patient cohort.

PATIENTS AND METHODS

Patients. Data were collected using the South Swedish Arthritis Group (SSATG) register (10,11), a structured clinical protocol designed for drug monitoring. Because the protocol was designed to meet the legal documentation required in Sweden, no formal approval from the ethical committee was necessary. The patients were treated with anti-TNF therapy at centers in southern Sweden and data were reported to the register during the period of March 1999 through December 2010.

Patients eligible for the study had a diagnosis of RA according to the treating physician's clinical judgment. Subjects were selected for anti-TNF treatment based on disease activity and/or unacceptable oral glucocorticoid use. Although no formal level of disease activity was required, patients had to have received at least 2 disease-modifying antirheumatic drugs (DMARDs), including previous MTX, without acceptable response. However, in the past 4 years, patients with poor prognostic factors could proceed to anti-TNF treatment after failure to MTX only.

Patients with less than 3 months of followup or who had received previous courses of biologic therapy were excluded from this study. Evaluation at 3 and 6 months of followup was chosen as the outcome cut points in this open-label study.

Doses followed manufacturers' recommendations. Etanercept was administered as a 25-mg subcutaneous dosage twice weekly or as 50 mg once weekly. Infliximab was infused at 3 mg/kg at 0, 2, 6, and then every 8 weeks. Depending on primary or secondary failure, the dosage of infliximab could be increased in increments of 100 mg to a maximum of 500 mg administered at 4- to 8-week intervals. Certolizumab was administered subcutaneously at 400 mg initially at weeks 2 and 4, followed by 200 mg every 2 weeks. Adalimumab was administered as a 40-mg subcutaneous dosage every other week. Golimumab was administered by subcutaneous injection 50 mg once every fourth week.

Methods. Clinical data were collected prospectively at 0, 3, and 6 months. At inclusion, the following data were recorded: year of disease onset, previous and concomitant DMARD treatment, and current systemic prednisolone dose. At inclusion and at each followup visit, the following clinical data were registered: Health Assessment Questionnaire (HAQ) score, patient-scored visual analog scale for pain (VAS pain) and VAS for general health (VAS global), physician's global assessment of disease activity on a 5-point Likert scale (EVAL global), 28-joint tender and swollen joint count, erythrocyte sedimentation rate, and C-reactive protein (CRP) level (21). The joint counts were performed by experienced rheumatologists who have been rigorously schooled in how to perform joint counts for evaluation of arthritis patients.

The STR was defined as the ratio of the number of swollen joints in the numerator and number of tender joints in the denominator based on 28-joint counts at baseline. The level of STR was grouped into low, moderate, and high. The thresholds had to be discriminative, identifying patients with excess pain and little inflammation (tender joint count) in the lowest group, balanced pain and inflammation (swollen joint count) in the moderate group, and having excess of inflammation in relation to pain in the highest group. Furthermore, the thresholds were based on distribution plots of STR. There was a clustering of patients having an exact STR of 0.5 or 1.0. Otherwise, the patients were evenly distributed with few outlying patients having an STR <0.2 and >3.0. Thus, patients were categorized as having low (<0.5 STR), moderate (0.5 ≤ STR ≤ 1.0), or high (STR >1.0) joint count ratios.

Also, these cutoffs are easy to calculate in the clinical setting and readily available after a joint examination. Receiver operating curve (ROC) plots using different thresholds and continuous STR revealed no defined "shoulders," and thus no obvious cut points.

Treatment response was assessed according to the American College of Rheumatology 20% and 50% improvement criteria (ACR20/50). Clinical assessments were performed immediately prior to each infliximab administration, whereas patients receiving adalimumab, certoli-

zumab, etanercept, and golimumab were scored independently of drug administrations. Thus, patients receiving infliximab always had the lowest possible level of anti-TNF blocking capacity when evaluated for efficacy, biasing this group of patients. Therefore, no comparisons between individual anti-TNF preparations were made.

Statistical analysis. Baseline clinical characteristics were analyzed by the Mann-Whitney U test for between-group comparisons regarding continuous variables, and the chi-square test was used for categorical variables. For the treatment outcome, both per protocol and intent-to-treat (ITT)-corrected, using the Lundex principle, ACR20 and ACR50 responses are given. The Lundex adjustment is an ITT method developed for the observational setting to account both for withdrawals from therapy and for missing response recordings at certain points of followup (22).

Spearman's correlation was used to check for correlations between STR and swollen and tender joint counts, respectively. Correlation tests between the Disease Activity Score in 28 joints (DAS28), STR, and swollen joint count, as well as STR and CRP levels, were performed to investigate potential collinearity and possible confounding. Independent predictors of ACR response at 6 months were identified using a multivariate, binary logistic regression model based on a priori assumptions of significant predictors. The following variables were included in the analysis: STR level, sex, disease duration at inclusion, baseline DAS28 and HAQ scores, and concomitant prednisolone and MTX treatment at the start of anti-TNF therapy. Secondary regression analyses substituting STR with swollen or tender joint counts and baseline CRP level were performed to further investigate the predictive ability of STR. Also, multivariate analyses omitting the DAS28 were performed. Finally, multivariate regression analyses divided according to adalimumab, etanercept, or infliximab treatment were performed. The influence of STR on anti-TNF drug survival was also investigated using log rank statistics and univariate Cox proportional hazards modeling. ROC plots were used to check for sensitivity and specificity of STR at the individual level. The level of significance was chosen at P less than 0.05.

RESULTS

Baseline data. Figure 1 shows the selection and dropout of patients during the study period. After initial selection, a total of 2,507 patients were enrolled in the study. A total of 285 patients (10.2%) were excluded prior to study inclusion due to lack of swollen and/or tender joint counts at baseline. There were no statistical differences in age, sex, disease duration, and concomitant DMARD usage between the dropouts and the patients included in the study (data not shown).

Demographic data and clinical characteristics of the patients studied are summarized in Table 1. Clear differences were seen between patients with low, moderate, and high STR at baseline. In general, patients with moderate or high STR were older, had longer disease duration as well as more previous DMARDs, and had higher swollen joint

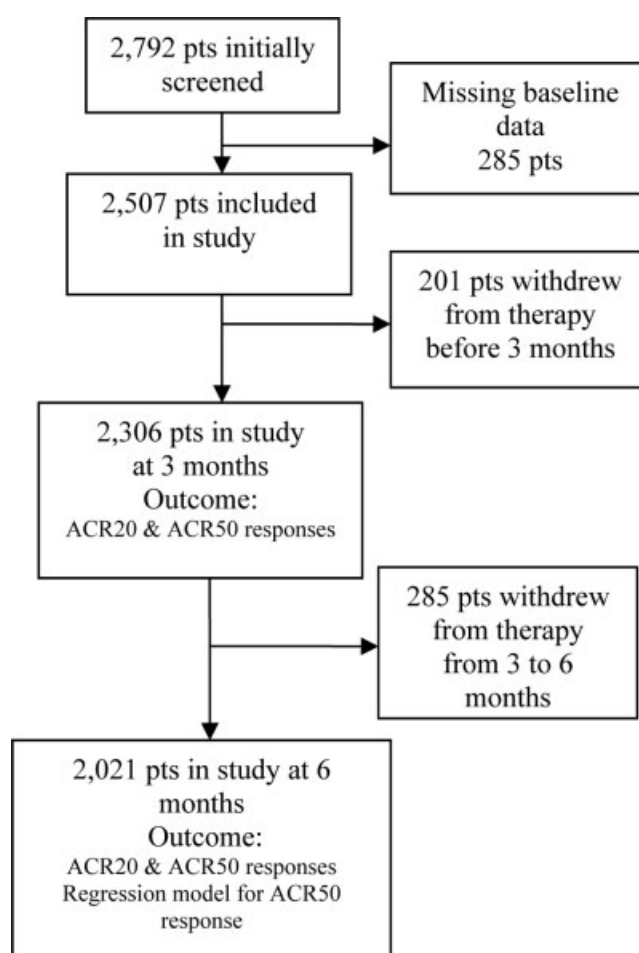


Figure 1. Number of patients included in the study and patients excluded due to missing data or premature treatment terminations. pts = patients; ACR 20/50 = American College of Rheumatology criteria for 20%/50% improvement.

counts, HAQ scores, EVAL global scores, and CRP levels than the group with low STR ($P < 0.001$). Conversely, patients with low and moderate STR had higher VAS pain, VAS global, and tender joint counts at baseline ($P < 0.001$). However, there was no difference in concomitant MTX usage, and the observed differences in type of anti-TNF treatment were small and mainly reflected availability and chronological sequence of drug introduction to the Swedish market.

Responders. Figure 2 shows the per-protocol proportions of patients fulfilling the ACR20 and ACR50 response criteria at 3 months ($n = 1,808$) and 6 months ($n = 1,329$) of followup, divided according to low, moderate, or high STR at baseline. According to these STR thresholds, 40% and 23% of patients with low, 65% and 39% with moderate, and 63% and 41% with high STR acquired ACR20 and ACR50 response, respectively, at 3 months ($P < 0.001$ for both ACR20 and ACR50 when comparing low STR to moderate and high STR, respectively). Corresponding values at 6 months of followup were 51% and 23% of patients with low, 68% and 39% with moderate, and 63% and 43% with high STR for ACR20 and ACR50 response, respec-

Table 1. Demographic and clinical characteristics at baseline, divided according to swollen to tender joint count ratio (STR)*

	STR <0.5	STR 0.5–1.0	STR >1.0	P
Patients, no.	344	1,180	983	
Age, years	55.6 (45.3–64.0)	57.0 (47.2–65.0)	59.3 (50.0–66.5)	< 0.001
Women, %	77	80	73	< 0.001
Swollen 28-joint count	2 (1–5)	8 (5–12)	10 (7–15)	< 0.001
Tender 28-joint count	10 (6–17)	10 (6–15)	4 (2–8)	< 0.001
Disease duration, months	64.8 (25.3–176.5)	92.1 (36.5–195.2)	115.3 (50.5–210.2)	< 0.001
HAQ score	1.25 (0.88–1.63)	1.25 (0.88–1.75)	1.13 (0.75–1.63)	< 0.001
DAS28 score	5.2 (4.2–6.1)	5.8 (4.9–6.6)	5.3 (4.5–6.0)	< 0.001
Previous DMARDs	2 (1–3)	3 (2–4)	3 (2–4)	< 0.001
VAS global, mm	69 (52–80)	68 (50–80)	61 (44–75)	< 0.001
VAS pain, mm	70 (50–80)	68 (50–80)	60 (43–76)	< 0.001
EVAL global (Likert scale 0–4)	2 (2–2)	2 (2–3)	2 (2–3)	< 0.001
Concomitant MTX, no. (%)	231 (67)	759 (64)	651 (66)	0.505
CRP, mg/dl	7.8 (1.7–22.2)	16.0 (6.0–36.0)	20.0 (9.0–43.0)	< 0.001
Medications, no. (%)				
Adalimumab	72 (14)	262 (53)	163 (33)	0.001
Certolizumab	2 (18)	5 (46)	4 (36)	
Etanercept	150 (14)	508 (48)	403 (38)	
Golimumab	2 (8)	18 (72)	5 (20)	
Infliximab	118 (13)	387 (42)	408 (45)	

* Values are the median (interquartile range) unless indicated otherwise. HAQ = Health Assessment Questionnaire; DAS28 = Disease Activity Score in 28 joints; DMARDs = disease-modifying antirheumatic drugs; VAS = visual analog scale; EVAL = physician's global assessment; MTX = methotrexate; CRP = C-reactive protein.

tively ($P < 0.001$ for both ACR20 and ACR50 when comparing low STR to moderate and high STR, respectively).

When using the Lundex correction, the differences in response rates and significance remained the same. Thus, 39% and 23% of patients with low, 65% and 39% with moderate, and 62% and 40% with high STR acquired ACR20 and ACR50 response, respectively, at 3 months ($P < 0.001$). The corresponding Lundex-corrected values at 6 months of followup were 46% and 21% of patients with low, 64% and 37% with moderate, and 59% and 40% with high STR acquiring ACR20 and ACR50 response, respectively ($P < 0.001$).

Crude response rates revealed the relative risk (RR) for response to therapy having medium to high STR compared to low were 1.6 (95% confidence interval [95% CI] 1.4–1.9) and 1.7 (95% CI 1.4–2.2) for ACR20 and ACR50 response, respectively, at 3 months. The corresponding RRs at 6 months of followup were 1.4 (95% CI 1.2–1.7) and 1.7 (95% CI 1.3–2.2) for ACR20 and ACR50, respectively. Spearman's correlation was used to check for covariance between swollen or tender joint count scores and STR values. At baseline, the correlation coefficients between STR and swollen and tender joint counts were 0.44 ($P < 0.001$) and -0.51 ($P < 0.001$), respectively. STR was weakly correlated to baseline DAS28 and CRP level with a correlation coefficient of -0.14 ($P < 0.001$) and 0.13 ($P < 0.001$), respectively. Swollen joint count was correlated to DAS28 with a coefficient of 0.59 ($P < 0.001$).

Regression analyses. In order to search for predictors of treatment response, a multivariate, binary logistic regression model was created. Figure 3 shows odds ratios (ORs) and 95% CIs for the predictors studied. Patients with

moderate baseline STR had almost twice the chance (OR 1.93, $P = 0.004$) of achieving an ACR50 response at 6 months of followup than did those with low STR. Likewise, patients with high STR showed a nearly 3-fold increased chance of achieving an ACR50 response when compared to the group with low STR (OR 2.82, $P < 0.001$). In addition, high baseline DAS28 (OR 1.49, $P < 0.001$) and HAQ scores (inverse association; OR 0.47, $P < 0.001$), and initial prednisolone usage (inverse association; OR 0.65, $P = 0.002$) were found to be significantly associated with ACR50 response at 6 months, whereas concomitant MTX use showed a nonsignificant trend for favorable treatment response (OR 1.02, $P = 0.077$).

Secondary regression analyses. Due to collinearity between STR and swollen and tender joint counts, a secondary analysis was performed substituting STR with either swollen or tender joint counts as covariates in the multivariate regression model. In these analyses, tender joint count was a nonsignificant predictor of ACR50 response (OR 0.99, 95% CI 0.95–1.03; $P = 0.510$), whereas swollen joint count was identified as a significant but weak predictor of ACR50 response at 6 months (OR 1.06, 95% CI 1.03–1.09; $P < 0.001$). When omitting DAS28 from the multivariate regression model, ORs for ACR50 response at 6 months for STR and swollen joint count only changed slightly: swollen joint count (OR 1.08, 95% CI 1.05–1.11; $P < 0.001$), moderate STR versus low STR (OR 2.34, 95% CI 1.44–3.81; $P = 0.001$), and high STR versus low STR (OR 2.50, 95% CI 1.54–4.07; $P < 0.001$).

Stratified multivariate regression tests were performed for patients receiving adalimumab, etanercept, or infliximab. These tests consistently showed a 2- to 3-fold in-

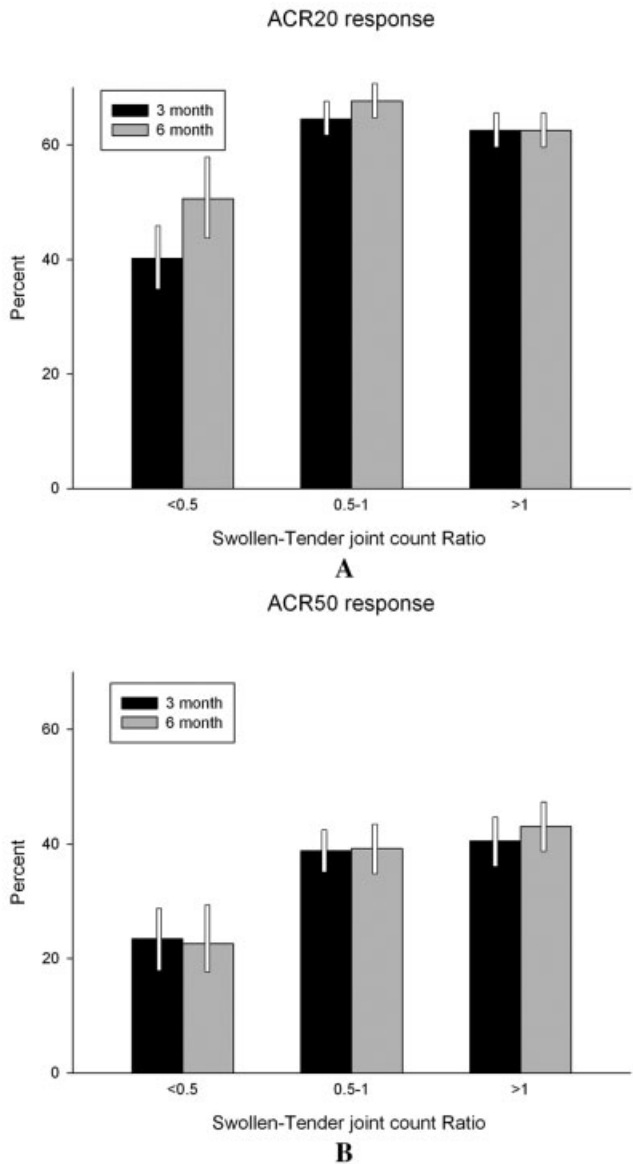


Figure 2. A, American College of Rheumatology criteria for 20% improvement (ACR20) and B, ACR50 treatment response rates with 95% confidence interval error bars at 3 and 6 months of anti-tumor necrosis factor therapy in biologically naive rheumatology patients, divided according to the swollen to tender joint count ratios at treatment initiation.

creased chance of achieving ACR50 response at 6 months of followup for patients with moderate to high STR compared to those with low STR at baseline (adalimumab [OR 3.26, 95% CI 1.10–9.70; $P = 0.034$], etanercept [OR 3.00, 95% CI 1.33–6.76; $P = 0.008$], and infliximab [OR 2.26, 95% CI 1.11–4.62; $P = 0.025$]). Baseline CRP level had no significant association with treatment response when substituting STR with CRP level in the multivariate regression model (OR 0.99, 95% CI 0.99–1.01; $P = 0.834$).

Drug survival. Patients with moderate to high STR were associated with better drug survival compared to patients having low STR at baseline ($P = 0.041$). Univariate Cox proportional hazards modeling revealed a significant haz-

ards ratio of 0.86 (95% CI 0.74–0.99, $P = 0.042$) in favor of moderate to high STR.

ROC. An ROC plot was created to test the performance of STR as a predictor on the individual patient level. The area covered by the curve was 0.55 (SE 0.015). No significant improvement in the area covered was seen when changing thresholds for STR or when plotting STR as a continuous variable (data not shown).

DISCUSSION

The current study found that RA patients with moderate to high STR were 2 to 3 times more likely to achieve an ACR50 response during 6 months of anti-TNF therapy than were patients with low baseline STR. Moreover, high disease activity was also identified as a predictor of good treatment response, whereas higher HAQ scores and prednisolone usage at treatment initiation predicted a reduced chance of responding to therapy. These latter findings are consistent with previous study reports (12–14).

The observation that STR is closely associated with treatment response is an important and novel finding. STR is a convenient and easily used index, based on the routine joint examination of an arthritis patient visiting a rheumatologist. In this way, valuable additional information about the likelihood of treatment response is obtained without requiring any extra resources or potential hazards for the patients. STR has previously been used as a patient characteristic, but it has not been related to treatment response or prediction thereof (23).

Data in this study support the finding that STR offers additional information to the standard swollen and tender joint examination. Although the correlation tests between STR and swollen and tender joint counts were both signif-

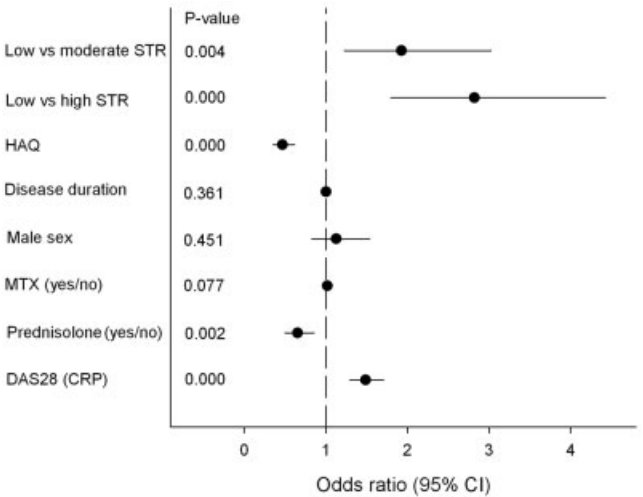


Figure 3. Odds ratios, 95% confidence intervals (95% CIs), and levels of significance for predictors of American College of Rheumatology criteria for 50% improvement response at 6 months of anti-tumor necrosis factor therapy in biologically naive patients with rheumatoid arthritis. STR = swollen to tender joint count ratio; HAQ = Health Assessment Questionnaire; MTX = methotrexate; DAS28 = Disease Activity Score in 28 joints; CRP = C-reactive protein. For more details, see Results.

icant, the R squared values were only approximately ± 0.25 , showing that STR contains a high degree of variance of its own, explained by neither swollen nor tender joint counts, independently. Thus, STR remains an interesting predictor in its own right. Moreover, secondary regression analyses underscore that baseline STR levels yield additional value compared to either joint count score alone. Thus, swollen or tender joint counts did not reproduce the strong association with the ACR50 response at 6 months that was found when using STR. Although swollen joint count did indeed show a significant OR of 1.06, given the magnitude and the ready usability of STR we believe this to be a novel and superior predictor than either swollen or tender joint count alone.

In addition, the results of other sensitivity analyses investigating the potential of various confounders consistently showed STR to be a robust and important predictor of drug response in RA. Thus, controlling for CRP level, type of anti-TNF treatment, and collinearity with DAS28 did not change the predictive importance of STR. Also, patients with moderate to high STR showed a significant better drug survival than patients with low STR. This further indicates that STR is an important marker for drug efficacy and tolerability.

ACR criteria were chosen as the sole treatment response outcome measure in this study due to the inherent direct dependency between European League Against Rheumatism, Clinical Disease Activity Index, and Simplified Disease Activity Index response and joint counts, which introduces circularity and hampers subsequent regression testing due to collinearity.

Due to the clinically embedded nature of data collection in the SSATG registry, joint counts were performed by various physicians and at different time points, and no measures were taken to compare accuracy or reproducibility of the clinical examinations. As a consequence, no statistical methods were used to quantify uncertainty in the joint counts. Thus, it is plausible that significant inter-observer variations remain, possibly explaining why STR is a convincing predictor at the group level but performs rather poorly at the level of the individual RA patient, as seen in the ROC plots (see Results).

Standardizing the joint examinations for the clinical registries would possibly be advantageous and generate more robust data from joint examinations performed by trained and synchronized health care professionals. Such joint examinations might improve the sensitivity and specificity of STR, and would be an obvious subject for further investigations.

The other baseline predictors of ACR50 response found in our analysis have all been independently found in other studies (12–14). HAQ score, especially in established RA, is directly related to the patient's level of disability (24). The negative predictive impact found for higher HAQ scores thus seems reasonable, as patients already disabled by their RA are likely to have less potential for good clinical responses to TNF blocking therapy. Likewise, in established RA prednisolone usage may be a marker for patients with refractory disease with less potential for response to DMARDs, whether biologic or nonbiologic (14).

Patients with a high baseline DAS28 have more disease activity and thus a greater potential for treatment response according to ACR response criteria (13). Finally, the previously demonstrated ability of ultrasound Doppler activity to predict treatment response to biologic agents corroborates the present results (15), underlining the importance of treating ongoing inflammation in the joint, rather than chronification of pain.

The open, nonrandomized nature of observational studies generates some methodologic limitations (25–27). Confounding by indication and assessment and performance bias cannot be excluded from this study. However, all data entries were centralized to ensure uniform interpretation of registration forms. Moreover, at present no single perfect predictor for good treatment response is available in the observational setting, thus giving no obvious reason for biasing measurements of patients with certain characteristics. In addition, multivariate logistic regression, including various sensitivity analyses, was used to control for and study potential confounding variables. Nonetheless, it should be stressed that additional studies are warranted to further validate the predictive value of STR. Also, the exact thresholds for low, moderate, and high STR need further validation.

In conclusion, this study identifies STR as a new and feasible predictor of treatment response in RA, demonstrating a predictive ability not explained by and surpassing that of independent swollen or tender joint counts. The distinction between predominantly tender versus swollen joints indicates a bimodal distribution in the RA population with signs of interwoven inflammatory reactions and chronic widespread pain.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kristensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kristensen, Bliddal, Christensen, Gülfe, Saxne, Geborek.

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