Musculoskeletal ultrasound may narrow the gap between patients and physicians in the assessment of rheumatoid arthritis disease activity.

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ABSTRACT

OBJECTIVES

To investigate the association between patient-physician discordance in the assessment of disease activity and residual ultrasound (US) synovitis/tenosynovitis in a cohort of patients with rheumatoid arthritis (RA) in clinical remission.

METHODS

A post-hoc analysis of the STARTER study, promoted by the Musculoskeletal-US (MSUS) Study Group of the Italian Society for Rheumatology, was performed using data from 361 consecutive patients with RA in clinical remission. The global assessment of disease activity by each patient (PGA) and evaluator/physician (EGA) was recorded on a 100-mm visual analogue scale. The PGA-EGA discordance was classified as positive (PGA>EGA) or negative (PGA<EGA) using a cut-off of ±10 mm. The association of discordance with grey-scale (GS) and power Doppler (PD) synovitis (S) and tenosynovitis (T) scores was evaluated through logistic regression analysis. The odds ratio for each point of the scores, adjusted for prespecified confounders (adjOR), was calculated.

RESULTS

The mean (SD) PGA and EGA scores were 6.1 (±7.1) and 8.8 (±12) mm, respectively, with a median (IQR) absolute difference of 4 (0-10) mm. Positive and negative discordances were recorded in 39 (10.8%) and 65(18.0%) patients, respectively. The GS-S (adjOR 1.099) and PD-S (adjOR 1.167) scores were associated with positive discordance ($p<0.01$), while the GS-T (adjOR 1.083), GS-S (adjOR 1.063) and PD-S (adjOR 1.089) scores were associated with negative discordance ($p<0.05$). The PGA-EGA discordance did not predict flares at 6 and 12 months.

CONCLUSIONS

Patient-physician discordance is associated with the lack of US remission in patients with RA and may represent a further indication for MSUS.

KEY MESSAGES

- Despite clinical remission, patient-physician discordance in disease activity assessment occurs in 28.8% of cases.
- Patient-physician discordance is significantly associated with ultrasonographic grey-scale and power-Doppler synovitis and tenosynovitis.
- Patient-physician discordance may represent a further indication for musculoskeletal ultrasonography in patients in clinical remission.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the primary involvement of synovial joints and tendon sheaths with a high prevalence of extra-articular manifestations, potentially resulting in accrual of irreversible damage and disability, impaired quality of life, and increased morbidity. [1,2]

According to the European Alliance of Associations for Rheumatology (EULAR) recommendations, treatment of RA should aim at reaching a target of sustained remission, and it must be based on a shared decision between the patient and his or her rheumatologist. [3] However, there are still significant issues with the application of such recommendations in clinical practice, particularly because of the difficulty in defining remission and the management of possible disagreement between patients and physicians in assessing disease activity. [4,5]

Ideally, remission is defined as a state characterized by the absence of clinically detectable disease activity that is associated with normalization (or optimization) of physical function, halt of damage progression, and prevention of inflammation-related comorbidities. [4] Several operative definitions of remission have been developed by using different composite indices based on objective and patient-reported variables. However, subclinical disease activity, detected by different imaging modalities, including ultrasonography, has been identified in a remarkable proportion of patients in clinical remission and has been reported to be associated with an increased risk of flares. [6,7]

In RA, as in other rheumatic diseases, shared decision-making is recommended, since a collaborative approach between the patient and physician can increase treatment adherence and may improve the final outcomes. [5] However, it has been widely reported that patients' opinions do not always match those of their physicians. [8–11] In particular, a high prevalence of discordance between patients and their rheumatologists in the assessment of disease activity has been reported in several RA cohorts. [8,12,13]

To date, no studies have specifically investigated the phenomenon of patient-physician discordance in a cohort of subjects with RA in clinical remission, and no studies have investigated subclinical ultrasonographic (US) findings as a potential determinant of this discordance.

Furthermore, no studies have assessed the potential role of patient-physician discordance in predicting the occurrence of flares.

The primary objective of this study was to investigate the association between patient-physician discordance in the assessment of disease activity and US synovitis/tenosynovitis in a cohort of RA patients in clinical remission. The secondary objective was to prospectively evaluate the independent role of patient-physician discordance in predicting the occurrence of disease flares over 6 months of follow-up.

METHODS

Patients and study design

A post hoc analysis of the Sonographic Tenosynovitis/Arthritis Assessment in Rheumatoid Arthritis Patients in Remission (STARTER) study was performed. [6,7] The STARTER multicentre study was promoted by the Musculoskeletal US (MSUS) Study Group of the Italian Society of Rheumatology [6] to determine the prevalence and outcomes of US tenosynovitis and synovitis in patients with RA in clinical remission. The STARTER study cohort consisted of consecutive patients affected by RA according to the 1987 American College of Rheumatology (ACR) or 2010 ACR/EULAR criteria and classified as being in clinical remission according to at least one of the following definitions: a 28-joint Disease Activity Score (DAS28) <2.6, [14] a Simplified Disease Activity Index (SDAI) ≤ 3.3, [15] a Clinical Disease Activity Index (CDAI) of ≤2.8, [16] ACR/EULAR Boolean definition, [15] or the absence of swollen/tender joints on 28 joints [17] or remission based on clinical evaluation of an expert rheumatologist. Since there is currently no unique and universally accepted definition of remission, different definitions were applied to ensure a more comprehensive approach and mitigate the risk of selection bias.

The STARTER study was approved by the local ethics committee for each of the participating sites. Written informed consent was obtained from all participants.

Clinical assessment

Demographic (i.e., age, sex, and education level), anamnestic (i.e., date of disease onset and diagnosis), laboratory (C-reactive protein level, erythrocyte sedimentation rate (ESR), rheumatoid factor, and anti-cyclic citrullinated peptide antibody level) and clinimetric (i.e., health assessment questionnaire (HAQ) and DAS28) variables were recorded at baseline. Furthermore, the global assessment of disease activity by the patient (PGA) and the evaluator/physician (EGA) were

recorded at baseline through a 100-mm visual analogue scale, where 0 corresponded to “no disease activity” and 100 to “the highest disease activity”. The occurrence of flares was assessed at 6 and 12 months from the baseline visit and was defined as a change in the DAS28 ≥1.2. [17] A full description of the clinical assessment was previously reported. [6,7]

US assessment

The ultrasonographers were rheumatologists with expertise in MSUS who were selected by an inter-observer and intra-observer reliability exercise against a reference standard on static images using an e-learning platform. A good to excellent reliability (weighted kappa ≥0.7) was required. At each site, MSUS was performed according to the EULAR guidelines [18,19] by a single ultrasonographer who was blinded to the clinical data, using high-end equipment and an optimised setting that was standardised among sites. The flexors of the fingers, the flexor carpi radialis and the extensor tendons of the wrist were scanned bilaterally. The dorsal aspects of the wrists (radiocarpal and midcarpal joints), metacarpophalangeal joints and the palmar aspects of proximal interphalangeal joints were scanned bilaterally. Tenosynovitis, joint effusion, and synovial hypertrophy were defined according to the Outcome Measures in Rheumatology Clinical Trials [20,21]. Representative images were recorded. Grey-scale (GS) and PD synovitis (S) and tenosynovitis (T) were semiquantitatively scored from 0 to 3. Total scores for GS and PD S and T were obtained as the sum of single sites. Thus, S and T were treated as total scores ranging from 0 to 66 for GS-S and PD-S and from 0 to 78 for GS-T and PD-T. A detailed description of the scanning protocol was published previously. [6]

Definition of discordance

A discrepancy score was calculated by subtracting the EGA from the PGA (PGA − EGA). As a validated definition of a clinically relevant difference between such measures does not exist, a cut-off of ± 10 mm was chosen by rounding to the standard deviation of the mean absolute discrepancy score. Thus, the relationship between PGA and EGA was classified into three categories: (a) positive discordance, when the patient rated higher than her or his physician (PGA − EGA ≥ +10 mm); (b) negative discordance, when the patient rated lower than her or his physician (PGA − EGA ≤ − 10

mm); and (c) concordance, when the discrepancy score was > −10 and < +10 mm (Figure 1). A sensitivity analysis was also performed by using ± 5 mm as the discrepancy score threshold.

Statistical analysis

Descriptive statistics were performed for demographic, clinical and US variables, reporting results as percentages, the mean with standard deviation (SD) or the median and interquartile range (IQR).

The association between total US scores and both positive and negative discordance was evaluated through logistic regression, and the results are presented as odds ratios (ORs) and 95% confidence intervals (CIs), both crude and adjusted for prespecified confounders: age, sex, disease duration, DAS28, HAQ, glucocorticoids, and number of previous treatments. Similarly, the association between positive or negative discordance (assessed as an ordinal variable) and the occurrence of flares at 6 and 12 months was evaluated through crude and adjusted logistic regression analyses, including US variables as confounders. The statistical significance was set for $p < 0.05$. Analyses were performed using the STATA software package (2009, release 11; StataCorp, Texas, USA) and R statistical software (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

In total, 361 patients from the STARTER study cohort were eligible for this post hoc analysis (both the cross-sectional and longitudinal phases). The mean (SD) age at enrolment was 56.2 (13.3) years, and 261/361 patients (72.3%) were women. The mean (SD) disease duration was 9.8 (8.1) years. Details of the baseline demographic and clinical characteristics of the analysed cohort have been previously reported [6] and are summarized in Table 1.

The median (IQR) GS-S score was 2 (0-5) in the whole cohort and 3 (2-6) in 260/361 (72.0%) GS-S-positive patients. The median (IQR) PD-S score was 0 (0-2) in the whole cohort and 3 (2-5) in 161/361 (44.6%) GS-S-positive patients. The median (IQR) GS-T score was 1 (0-3) in the whole cohort and 2 (1-4) when calculated only in 189/361 (52.3%) GS-T-positive patients. The median (IQR) PD-T score was 0 (0-0) in the whole cohort and 2 (1-4) in 85/361 (23.6%) GS-T-positive patients.

Prevalence and magnitude of PGA-EGA discordance

In the whole cohort, the mean (SD) PGA and EGA scores were 6.1 (±7.1) and 8.8 (±12) mm, respectively, with a median (IQR) absolute difference of 4 (0-10).

Using ± 10 mm as a threshold for a significant discrepancy score, positive (PGA > EGA) and negative (PGA < EGA) discordance were recorded in 39 (10.8%) and 65 (18.0%) patients, respectively. Concordance was observed in the remaining 257 (71.2%) subjects. In the patients with positive and negative PGA-EGA discordance, the mean (SD) absolute differences were 13.5 (4.5) and 21.0 (12.9), respectively.

When the prevalence of the discordance was assessed in different definitions of remission, similar results were obtained, with a slightly tendency towards a lower concordance in patients with DAS28 ≤2.6 (71.6%), than those with SDAI ≤3.3, CDAI ≤2.8 or ACR/EULAR Boolean remission (82.0%, 82.6% and 75.9%, respectively) (Supplementary Table S1, available at *Rheumatology* online).

In the sensitivity analysis (discrepancy score threshold ± 5 mm), positive (PGA > EGA) and negative (PGA < EGA) discordance were recorded in 66 (18.3%) and 105 (29.1%) patients, respectively; concordance was observed in the remaining 190 (52.6%) patients. The mean (SD) absolute differences in the group of patients with positive and negative PGA-EGA discordance were 10.6 (4.9) and 15.4 (12.5), respectively.

Association of US synovitis and tenosynovitis with PGA-EGA discordance

The GS-S and PD-S scores were significantly associated with positive discordance (PGA>EGA), with ORs (95% CIs) of 1.080 (1.024, 1.140) and 1.147 (1.054, 1.248), respectively, in crude analyses and adjORs (95% CIs) of 1.099 (1.029, 1.173) and 1.167 (1.061, 1.284), respectively, in the adjusted analysis for each point of the score (**Figure 2**). Such results were confirmed in the sensitivity analysis (Supplementary Table S2, available at *Rheumatology* online).

Furthermore, the GS-S, PD-S, and GS-T scores were associated with negative discordance (PGA<EGA), with ORs (95% CIs) of 1.045 (0.995-1.097), 1.053 (0.974, 1.138), and 1.089 (1.010, 1.174), respectively, in the crude analysis and adjORs (95% CIs) of 1.063 (1.001, 1.129), 1.089 (0.991, 1.197) and 1.083 (0.995-1.178), respectively, in the adjusted analysis for each point of the score (**Figure 3**). In the sensitivity analysis, significant associations were recorded between GS-S, PD-T, and GS-S and negative discordance, whereas a tendency towards a significant association was

recorded between negative discordance and PD-S (Supplementary Table S2, available at *Rheumatology* online).

When the patients were stratified according to the different definitions of remission, the association between US findings and both positive and discordance was particularly meaningful in those with DAS28 ≤2.6 (Supplementary Table S3, available at *Rheumatology* online).

PGA-EGA discordance in predicting disease flares

At the 6- and 12-month follow-up visits, 39 (10.8%) and 53 (14.7%) patients, respectively, presented at least a flare, as defined by an increase in DAS28 to ≥1.2. Neither positive (PGA>EGA) nor negative (PGA<EGA) discordance in the assessment of disease activity significantly predicted the occurrence of flares at 6 or 12 months.

DISCUSSION

This is the first study that specifically evaluated patient-physician discordance in the assessment of disease activity in a cohort of patients with RA in clinical remission and investigated US findings of synovitis and tenosynovitis as potentially associated factors. Furthermore, this is the first study that assessed PGA-EGA discordance as a predictor of disease flares.

Previous studies have investigated PGA-EGA discordance in heterogeneous cohorts of patients affected by RA with variable disease activity states ranging from remission to highly active disease. [4, 7, 11, 12, 17] In such cohorts, even when using a more stringent definition of discordance (20-30 mm as the most widely used discrepancy threshold), up to half of the patients were found to be discordant, and in most cases of discordance (up to 80%), the PGA score was higher than the EGA score. The same studies attempted to identify the determinants of discordance, being substantially consistent in concluding that the PGA score seems to be more heavily affected by the patients' perception of pain, disability, fatigue and comorbidities, such as fibromyalgia and depression, whereas the EGA score is driven more by objective signs of inflammation, including swollen and tender joint counts and acute phase reactants. [4, 7, 11, 12, 17] Several studies have demonstrated a relatively frequent occurrence of discordances between clinical and ultrasound measurements of disease activity in patients with RA [22–24]; however few authors have investigated MSUS findings as determinants of discordant ratings of disease activity between patients and their physicians [25].

Challa DN et al, in a sub-analysis of a cross-sectional study in patients with RA with different levels of disease activity, found that positive discordance between patients and rheumatology providers (nurse practitioner or physician assistant, attending physician, or fellow) was not associated with unrecognized joint inflammation by ultrasonography. [25] Similar results were reported by Lackner A et al. in patients with psoriatic arthritis. [26]
The consequences in terms of clinical outcomes of patient-physician discordance have not been investigated.

In the STARTER study cohort, PGA-EGA discordance, as defined by a discrepancy score of ≥ ± 10 mm, occurred in approximately one-third of the patients, of which 35% had positive discordance (PGA>EGA) and 65% had negative discordance (PGA<EGA). [4, 7, 11, 12, 17] Despite using a lower threshold than that in previous studies to describe a discordance between EGA and PGA, we found a lower prevalence of discordance in our cohort. This can be due to the exclusive recruitment of patients in clinical remission. Indeed, the observation that the rate of PGA-EGA discordance proportionally varies according to the overall disease activity state, resulting in a higher prevalence of disagreement in patients with highly active disease and a lower prevalence in patients with low disease activity has already been described. [10,12] This explanation is further supported by the finding of a higher level of PGA-EGA concordance in patients fulfilling more stringent definitions of remission. Thus, since this is the first study based on an RA cohort solely consisting of patients in clinical remission, a 30% prevalence of PGA-EGA discrepancy ≥10 mm may be deemed clinically remarkable. Furthermore, the inclusion of PGA and EGA in some definitions of remission applied as recruitment criteria may have contributed to selecting patients with a low and overall concordant value of the two scores.

Regarding the relationship between PGA-EGA discrepancy and US findings, the analysis of the STARTER cohort showed that both positive and negative discordance were independently associated with a higher grade of US synovitis and, to a lesser extent, tenosynovitis. This suggests that the presence of a residual degree of disease activity, differently and alternatively recognized by patients and their physicians, could be at the basis of the PGA-EGA discrepancy, especially in patents classified as in remission according with less stringent definitions. In addition, the recruitment of a homogeneous cohort of patients in clinical remission may have been one of the main reasons for recording this association in our analysis but not in previous studies recruiting patients with variable clinical disease activity. In the longitudinal phase of the present study, no

association was demonstrated between PGA-EGA discordance and the occurrence of disease flares over the following 6 and 12 months.

Overall, these findings suggest that although the PGA-EGA discordance was not an independent predictor of flares, it is clinically relevant since it was significantly associated with the presence of US synovitis and tenosynovitis, which, in turn, have been demonstrated to be associated with the occurrence of relapses in the original STARTER study. Indeed, in the previously published data from the STARTER cohort, the concurrent presence of PD-positive tenosynovitis and synovitis predicted disease flares at 12 months, with an adjusted OR of 2.09 (95% CI 1.06 to 4.13). [7] Similar results were recorded in a metanalysis, wherein a significant association was reported between PD positivity and the risk of flares (OR 4.52, 95% CI 2.61-7.84), as well as the risk of progressive bone erosion (OR 11.85, 95% CI 5.01-28.03).[27] Thus, from a clinical point of view, the demonstration of PGA-EGA discordance in patients in clinical remission may represent an appropriate indication to perform MSUS, aiming at identifying subjects with persistent US synovitis and tenosynovitis who have a higher risk of flares and who need tighter control and more caution regarding the potential reduction or withdrawal of the ongoing treatment. Furthermore, performing MSUS in these patients may help further reduce the gap between patient's and physician's points of view in the assessment of disease activity, further supporting compliance and partnership in the management of RA. [18] However, more research and specific prospective data are needed to determine how US findings may drive subsequent therapeutic choices.

Some limitations should be considered in interpreting the results of our study. PGA and EGA refer to a global assessment of disease activity, whereas the US assessment in our analysis was limited to the hands, excluding some potentially relevant structures in RA. Furthermore, although of interest, the effect of depression or impairment in the mental domains of quality of life on the PGA-EGA discordance was not evaluated as cofounders because no validated measures were available in the STARTER study.

In conclusion, in patients with RA in clinical remission, both positive and negative patient-physician discrepancies in the assessment of disease activity may be associated with the incomplete achievement of US remission due to the persistence of signs of synovitis and, to a lesser extent, tenosynovitis. Pending further research to validate our results, the occurrence of patient-physician discordance in the assessment of the disease activity state may represent an appropriate indication for performing MSUS in the follow-up of RA patients in clinical remission.

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DECLARATION SECTION

Ethics approval: This study was approved by the Ethics Committee of each recruiting Centre (Azienda Ospedaliero Universitaria S. Anna, Cona-Ferrara; IRCCS Policlinico San Matteo Foundation, Pavia; Ospedale Mauriziano, Turin; Policlinico Le Scotte Torino; Luigi Sacco University Hospital, Milan; IRCCS Istituto Clinico Humanitas, Rozzano; Azienda Ospedaliera Sant'Andrea, Rome; A.O.U.P. Santa Chiara, Trento; ASST Centro traumatologico ortopedico G. pini-Cto, Milan; Università Policlinica delle Marche, Jesi; Ospedale Infermi, Rimini; Azienda Ospedaliero Universitaria di Cagliari; Ospedale Civile Maggiore, Verona; A.O.S. Maria della Misericordia, Perugia; Arcispedale Santa Maria nuova IRCCS, Reggio Emilia; Moriggia-Pelascini Hospital, Gravedona; A. Galateo Hospital, San Cesario di Lecce; Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Turin; Azienda Ospedaliera regionale San Carlo, Potenza; Azienda Ospedaliera di Padova, Padova; Bolzano Hospital, Bolzano; G. Bosco Hospital, Turin; Presidio Ospedaliero Destra Secchia, Pieve di Coriano; Policlinico Universitario di Bari; and Aziende Ospedaliera Rummo di Benevento, Benevento).

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Table 1. Demographic and clinical features at baseline

Demographics	
N	361
Male, n (%)	100 (27.7)
Age, mean (SD) years	56.2 (13.3)
Disease duration, mean (SD) years	9.8 (8.1)
Disease activity	
DAS28, mean (SD) score	2.0 (0.7)
CDAI, median (IQR)	1.5 (0.3-3.3)
SDAI, median (IQR)	1.7 (0.7-3.5)
TJC, mean (SD)	2.5±3.2
SJC, mean (SD)	0.4±0.9
ESR, mean (SD) mm/h	13.4 (10.6)
CRP, mean (SD) mg/dl	0.2 (0.4)
PGA, mean (SD), mm	6.1 (±7.1)
EGA, mean (SD), mm	8.8 (±12)
HAQ, median (IQR) score	0 (0-0.38)
Definition of remission	
DAS28 < 2.6, n (%)	283 (78.4%)
SDAI <= 3.3, n (%)	261 (72.3%)
CDAI <= 2.8, n (%)	253 (70.1%)
TJC and SJC =0, n (%)	235 (65.1%)
ACR/EULAR2010, n (%)	245 (67.9%)
Evaluation of expert rheumatologist, n (%)	361 (100%)
Treatment	
N previous treatments, median (IQR)	2 (1-2)
Glucocorticoid use, n (%)	163 (45.2)
cs-DMARDs	297 (82.3%)
b-DMARDS	128 (35.5%)
Ultrasonography findings	
GS-S, median (IQR) score*	3 (2-6)
PD-S, median (IQR) score*	2 (2-5)
GS-T, median (IQR) score*	2 (1-4)
PD-T, median (IQR) score*	2 (1-4)

DAS28: disease activity score on 28 joints. SDAI, Simplified Disease Activity Index. CDAI, Clinical Disease Activity Index. TJC, tender joints count. SJC , swollen joint count. Cs-DMARDs, conventional synthetic disease modifying anti-rheumatic drug. b-DMARD, biologic DMARD. IQR: interquartile range; HAQ: Health Assessment Questionnaire; GS: grey scale; PD: power Doppler; S: synovitis, T: tenosynovitis. *mean was calculated in patients with a score of ≥1 (GS-S, n = 260; PD-S, n = 161; GS-T, n = 189; PD-T, n = 85).

Figure legends

Figure 1. Definition and classification of the PGA-EGA discordance.

PGA, patient global assessment of disease activity; EGA, evaluator/physician global assessment of disease activity.

Figure 2. Association between ultrasonographic (US) variables and positive discordance (PGA > EGA).

OR, odds ratio for one-unit increase in the US scores; 95% CI, 95% confidence interval; GS, grey scale; PD, power Doppler; S, synovitis; T, tenosynovitis.

Figure 3. Association between ultrasonographic (US) variables and negative discordance (PGA < EGA).

OR, odds ratio for one-unit increase in the US scores; 95% CI, 95% confidence interval; GS, grey scale; PD, power Doppler; S, synovitis; T, tenosynovitis.

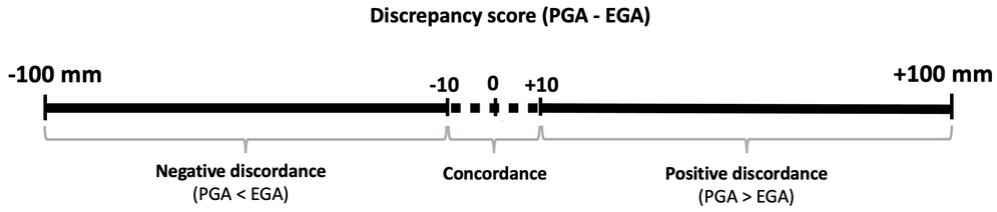

Figure 1

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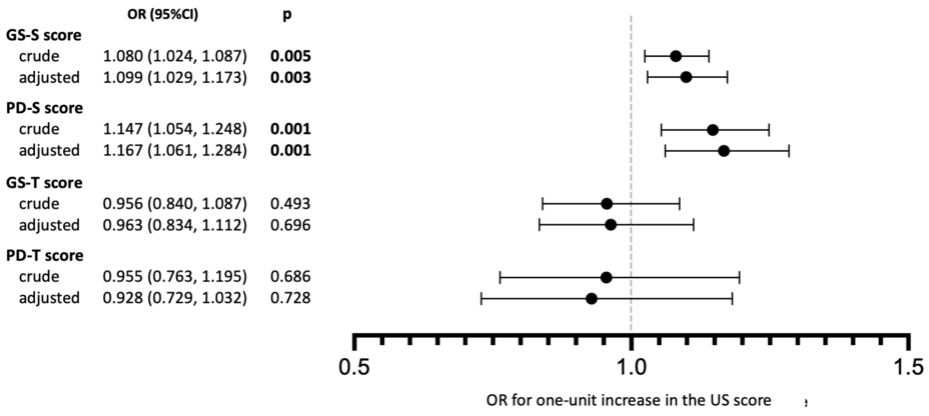

Figure 2

84x36mm (300 x 300 DPI)

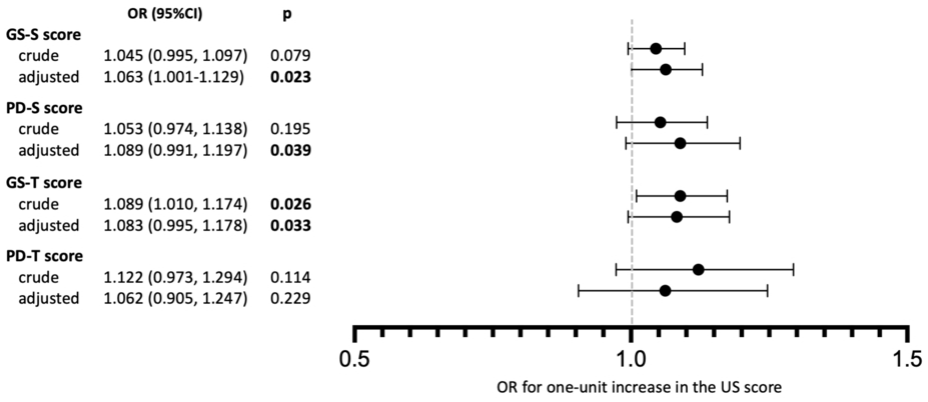

Figure 3

84x36mm (300 x 300 DPI)