Non-nociceptive pain in rheumatoid arthritis is frequent and affects disease activity estimation: cross-sectional data from the FRAME study

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Background: The painDETECT questionnaire (PDQ) is a mechanism-based pain classification tool assigning patients to one of three categories depending on the quality of the experienced pain. Patients with non-nociceptive pain score high on the PDQ. The objective was to assess the proportions of the three PDQ classification groups in patients with rheumatoid arthritis (RA) and to explore differences in clinical characteristics.

Method: RA patients initiating or escalating their RA therapy were included prospectively and underwent a thorough examination programme. Low (PDQ score < 13), medium (PDQ score 13–18), and high (PDQ score > 18) scores indicate nociceptive, unclear/possible neuropathic, or neuropathic pain mechanisms, respectively.

Results: The 102 included patients were classified into the following PDQ classification groups: low = 65%, medium = 23%, and high = 12%. Patients in the medium and high PDQ groups scored worse on indicators of anxiety, depression, disability, mental health-related quality of life, pain, and fatigue. They also had more tender points and an RA disease activity score based on 28 joints (DAS28) where a higher fraction of the composite score pertained to non-inflammatory factors compared to patients in the low PDQ classification group. There were no differences in objective inflammatory indices across groups. Multiple regression analysis demonstrated that the tender joint count (TJC) and the 36-item Short Form Health Survey (SF36) mental component summary (MCS) score were independently associated with the PDQ score.

Conclusions: In patients initiating or intensifying medical treatment for their RA, non-nociceptive pain (PDQ score ≥ 13) is common. In these patients, the pain mechanisms result in increased disease activity scores on a non-inflammatory basis.

Despite better inflammatory disease control, patients with rheumatoid arthritis (RA) still rate pain as a significant priority and the majority of European and US patients report dissatisfaction with their arthritis pain (1, 2). Even among patients who have been in sustained disease remission for more than 1 year, 12.5% continue to report clinically significant pain (3). This indicates that factors other than peripheral inflammation may contribute to the maintenance of pain in subgroups of RA patients. Assessment of pain quality rather than pain intensity in RA patients has revealed that the described experiences are multidimensional (4). Although most patients describe their pain using descriptors characteristic of nociceptive pain, some report hypersensitivity to mechanical and thermal stimuli, burning or prickling sensations as well as shooting pain, pain qualities assumed to reflect neuropathic pain (NP) (4). This further supports the notion that RA pain involves several mechanisms and not only peripheral inflammation. Several studies conducted in RA populations with low disease activity have found NP features in a significant proportion of patients (5–7).

Disease activity in RA is often assessed by composite indices, such as the disease activity score based on the 28 joint assessment (DAS28), which incorporates both objective markers of inflammation and subjective measures of pain and well-being. Although the DAS28 is associated with inflammatory activity, this relationship can be confounded by other factors resulting in a higher score, for example in the presence of chronic pain conditions (8, 9). The presence of a non-nociceptive pain component might also in part explain why treatments targeting anti-inflammatory pathways fail to bring some
RA patients into DAS28 remission (10). Assessment of underlying pain mechanisms in RA patients could therefore assist clinical decision making and help to balance the physician’s and patient’s expectations of the anti-inflammatory treatment. It might also prevent initiation or escalation of anti-inflammatory therapy on a non-inflammatory basis. To our knowledge, no such tool has yet gained ground in the clinical setting.

The painDETECT questionnaire (PDQ) is a mechanism-based pain classification tool that assigns patients to one of three categories depending on the predominant pain mechanism: nociceptive (PDQ score < 13), unclear/possible neuropathic (PDQ score 13–18), and neuropathic (PDQ score > 18). However, within RA, the PDQ has only been used in patients with low disease loads (5, 6) and knowledge about whether or not the presence of NP features might affect the overall disease activity estimation is most relevant at a time when initiation or escalation of anti-inflammatory medical treatment for RA is considered.

The primary objective of this cross-sectional study was to examine the proportions of the three PDQ classification groups in an RA sample about to initiate/escalate medical therapy. A secondary objective was to explore differences in the clinical, pain, and imaging characteristics of patients across the three PDQ classification groups. We hypothesized that a high PDQ score would be associated with a DAS28 in which a greater fraction of patients across the three PDQ classification or escalation of anti-inflammatory medical treatment for RA is considered.

Variables and outcome measures

Collection of data concerning patient demographics, medication, imaging, clinical examination, and biochemistry has been reported in detail elsewhere (12).

Clinical assessment. Standard 28 joint assessments according to European League Against Rheumatism (EULAR) guidelines and manual tender point (TP) examination according to 1990 ACR guidelines (15) were conducted by a trained health-care professional. The DAS28 is a commonly used disease activity score that combines an assessment of the number of tender joints out of a possible 28 (tender joint count, TJC), the number of swollen joints out of a possible 28 (swollen joint count, SJC), the C-reactive protein (CRP) level, and the patient’s global health assessment on a visual analogue scale (VAS-GH) into a single numerical value, where greater numbers indicate greater disease activity. For this study, the DAS28 was based on the CRP (DAS28-CRP) (4).

Imaging. Ultrasound (US) images were obtained from nine upper extremity projections and 15 lower extremity projections and graded (0–3) according to a semi-quantitative Doppler score (16, 17). The ultrasound Doppler (USD) score thus ranged from 0 to 72. Conventional magnetic resonance (MR) images of the wrist and four ulnar metacarpophalangeal joints (MCP2–5) were scored according to the RA magnetic resonance imaging (MRI) scoring system (RAMRIS), which was developed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (18, 19). Scores for synovitis in the wrist and MCP2–5 (0–3 per joint) were merged.

The PDQ. The PDQ is a mechanism-based questionnaire primarily assessing somatosensory signs and symptoms...
that are traditionally ascribed to NP. The PDQ comprises questions regarding pain intensity (not included in the total score), course of pain, subjective experience of a radiating quality of the pain (yes/no), and the presence and perceived severity of seven somatosensory symptoms of NP rated on a six-category Likert scale (never, hardly noticed, slightly, moderately, strongly, and very strongly). For diagnostic purposes, a validated algorithm (20) is used to calculate a total PDQ score ranging from −1 and 38 based on the patient’s answers in the questionnaire. The PDQ was developed as a screening tool to determine the likelihood of an NP component being present in patients with chronic low back pain (20). Since its development, the PDQ has been used in several musculoskeletal pain conditions and has identified a non-inflammatory pain component as being present in osteoarthritis, fibromyalgia, and RA patients (5, 6, 21–25). We interpreted a high score (PDQ score > 18) as an indicator of a non-inflammatory pain component, a medium score (PDQ score 13–18) as the possible presence of a non-inflammatory pain component, and a low score as (PDQ score < 13) as nociceptive pain. The PDQ is applicable to touch screens (26).

Depression and anxiety. The Major Depression Inventory (MDI) is a questionnaire that evaluates depression on the basis of the patients’ self-reported symptoms (27). It can be used as a diagnostic tool and to monitor the severity of depression based on a summed score (range 0–50). When using the summed score, cut points of 21–25, 26–30, and 31–50 are interpreted as mild, moderate, and severe depression, respectively. The Generalized Anxiety Disorder Assessment (GAD-10) is a questionnaire developed to assess generalized anxiety according to severity. The scores of each item are summed (range 0–50), with scores of 15–19, 20–29, and 30–50 indicating mild, moderate, and severe anxiety, respectively (28).

Other patient-reported outcomes. The Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) is a generic, health-related quality of life instrument developed to compare various aspects of health status across a general and broad patient population (29–31). The SF-36 examines eight general health domains from which a physical (PCS) and a mental (MCS) component summary score can be derived. Each score ranges from 0 to 100, with higher values indicating better health status. The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a measure of limitation in activities of daily living used for patients with RA (32); the HAQ-DI assesses the responder’s ability to complete everyday tasks. Final scores range from 0 to 3, with 3 indicating the highest level of disability. The DAS28-P is a DAS28-derived index representing the contribution from the patient-reported components TJC and VAS-GH to the DAS28 (33). The formula used for calculating DAS28-P is as follows (with the denominator being the formula for calculating DAS28):

\[
\text{DAS}28 - P = \frac{(0.56 \times \sqrt{\text{TJC}}) + (0.28 \times \sqrt{\text{SJC}}) + 0.36 \times \ln(\text{CRP} + 1) + (0.014 \times \text{VAS} - \text{GH}) + 0.96}{(0.56 \times \sqrt{\text{TJC}}) + (0.28 \times \sqrt{\text{SJC}}) + 0.36 \times \ln(\text{CRP} + 1) + (0.014 \times \text{VAS} - \text{GH}) + 0.96}
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Statistical analysis

All analyses were conducted using SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA). The PROC UNIVARIATE and PROC FREQ statements were used to summarize the data. All descriptive statistics and tests are reported in accordance with the recommendations of the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network (34), using the STROBE (STrengthening the Reporting of OBServational studies in Epidemiology) statement for cross-sectional studies (35). Differences across groups were tested using the t-test and analysis of variance (ANOVA) for parametric data and the Mann–Whitney U test or the Kruskal–Wallis test for non-parametric data. The \( \chi^2 \) test was used for categorical data. To explore which variables best explained the variation in the PDQ score (ranging from −1 to 38), we used univariate linear regression and multiple regression with the PDQ score as the dependent variable. A priori selected confounders (age, sex, disease duration, and whether patients were planned to initiate a csDMARD or a bDMARD) were selected to be included in the adjusted model based on their assumed clinical importance. Other variables were only included in the adjusted model if they had a \( p \) value < 0.1 in a univariate regression with PDQ as the dependent variable. Of the variables fulfilling this criterion, several were removed due to high correlations (Spearman’s rho ≥ 0.4) with other variables addressing the same construct (multicollinearity). VAS-GH, VAS-pain, and VAS-fatigue were removed because of high correlations to multiple variables in several constructs. The MDI and GAD-10 had high correlations with SF-36 MCS, which was prioritized because it was thought to offer the broadest view into mental health. Likewise, SF-36 PCS correlated too much with HAQ-DI, which was prioritized for inclusion because it was thought to have the greatest clinical importance (being the most used self-reported measure of physical function in RA). The TP count had a high correlation to TJC, which was prioritized because it had the greatest clinical importance (being a subcomponent for calculating the DAS28). The assumptions of linearity, homogeneity of variance, and residuals being normally distributed were assessed based on the studentized residuals scattered against the value predicted by the model.
Results

Figure 1 shows the flow of patients assessed for the FRAME cohort. Of the 151 patients fulfilling the inclusion criteria, 48 (32%) patients were excluded for the following reasons: did not give informed consent (n = 18), diagnosed with a comorbid condition with increased risk of NP (n = 10), could not pause usage of antidepressants, anticonvulsants, or other centrally acting analgesics for 1 week (n = 7), initiated DMARD treatment more than 3 weeks ago (n = 5), received more than 10 mg prednisolone in < 3 weeks (n = 4), other reasons (n = 4). In total, 103 patients received a baseline assessment. It was later revealed that one patient had received an intramuscular steroid injection 5 days prior to inclusion; this constituted a protocol violation and the patient was excluded post-hoc. Thus, 102 patients were included in the analyses. One patient did not fill in any questionnaires and was not included in the analyses based on PDQ stratification.

Patient characteristics

Characteristics for the included participants are shown in Table 1. Of the 55 patients initiating a bDMARD, 42 were treated with methotrexate (MTX) and/or another csDMARD; 27 of the 55 bDMARD initiators had not previously received any biological therapy. The patients who initiated a bDMARD in the study period had significantly longer disease duration, more tender joints, and higher scores on the HAQ-DI, the VAS-pain, and the PDQ. Overall disease activity as measured by the DAS28 was higher among patients initiating a bDMARD, but a greater proportion of the DAS28 pertained to the patient-reported subcomponents as shown by the greater DAS28-P.

Patients were classified according to the PDQ score in the following three groups: low (PDQ score < 13) = 65%, medium (PDQ score 13–18) = 23%, and high (PDQ score > 18) = 12%. The differences in characteristics among the three PDQ classification groups are shown in Table 2. Statistically significant differences across the three PDQ groups were seen for TJC, TP count, DAS28, DAS28-P, and the following patient-reported outcomes: physical function (HAQ-DI), VAS-fatigue, VAS-pain, VAS-GH, anxiety (GAD-10), depression (MDI), SF-36 PCS, and SF-36 MCS. We observed a greater percentage of patients having a TP count ≥ 11 with higher PDQ classification groups but this was not statistically significant. However, when merging the medium and high PDQ classification categories, the proportion of patients with a TP count ≥ 11 among those with high vs. low PDQ scores was statistically significant (Supplementary Table A). There were no differences in inflammatory indices: USD score, RAMRIS synovitis score, or CRP among the groups.

Post-hoc analyses of subgroup differences showed that there were no significant differences between patients in the medium vs. high PDQ classification groups except for the SJC. All significant differences were between patients in the low PDQ classification group vs. the medium PDQ classification group (TJC, HAQ-DI, VAS-fatigue, VAS-pain, VAS-GH, SF-36 PCS, SF-36 MCS, MDI, GAD-10) and patients in the low vs. the high PDQ classification group (TJC, HAQ-DI, VAS-fatigue, VAS-pain, VAS-GH, SF-36 PCS, SF-36 MCS, MDI). Data obtained by merging the medium and high PDQ classification groups are presented in Supplementary Table A.

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**Figure 1. Flow diagram of included patients.**

* See text for details. # Excluded due to receiving an intramuscular steroid injection 5 days prior to assessment.
Table 1. Participant characteristics by group.

|                          | Initiated csDMARDs (n = 47) | Initiated bDMARDs (n = 55) | p value |
|--------------------------|------------------------------|-----------------------------|---------|
| Female, n (%)            | 34 (72.3)                    | 42 (76.4)                   | 0.64    |
| Age (years), mean (sd)   | 55.8 (16.2)                  | 54.0 (15.7)                 | 0.56    |
| BMI (kg/m²), mean (sd)   | 26.5 (4.5)**                 | 26.0 (5.6)*                 | 0.65    |
| Disease duration (months)| 2.0 (1–11)                   | 83.0 (37–190)               | < 0.0001|
| Current smoker, n (%)    | 8 (17.4)*                    | 12 (22.2)*                  | 0.55    |
| Corticosteroid usage, n (%) | 4 (8.5)          | 12 (21.8)                   | 0.07    |
| 28 Swollen joint count   | 2 (1–6)                      | 2 (1–7)                     | 0.72    |
| 28 Tender joint count    | 5 (2–10)                     | 9 (5–13)                    | 0.001   |
| DAS28, mean (sd)         | 4.3 (1.2)                    | 4.7 (1.0)                   | 0.050   |
| DAS28-P, 0–1, mean (sd)  | 0.41 (0.13)                  | 0.55 (0.10)                 | < 0.0001|
| Tender point count, 0–18 | 6 (4–12)                     | 10 (4–15)                   | 0.07    |
| HAQ-DI, 0–3              | 0.63 (0.25–1.5)              | 1.0 (0.76–1.63)             | 0.003   |
| VAS-fatigue (mm)         | 56 (25–77)                   | 63 (43–76)                  | 0.24    |
| VAS-pain (mm)            | 48 (22–68)                   | 54 (38–71)                  | 0.048   |
| VAS-global health (mm)   | 57 (28–81)                   | 68 (48–81)                  | 0.15    |
| PDQ score < 13, n (%)    |                            |                             |         |
| PDQ score 13–18, n (%)   |                            |                             |         |
| PDQ score > 18, n (%)    |                            |                             |         |
| CRP (mg/mL)              | 10 (4–16)                    | 4 (2–13)                    | 0.055   |
| IgM-RF positive, n (%)   | 29 (61.7)                    | 36 (65.5)                   | 0.69    |

csDMARD, Conventional synthetic disease-modifying anti-rheumatic drug; bDMARD, biological DMARD; BMI, body mass index; DAS28, Disease Activity Score based on 28 joint counts; DAS28-P, the subjective components of the DAS28 relative to the total DAS28 (see text for calculation); HAQ-DI, Health Assessment Questionnaire Disability Index; VAS, visual analogue scale; PDQ, painDETECT questionnaire; CRP, C-reactive protein; IgM-RF, immunoglobulin M rheumatoid factor; sd, standard deviation. Values are median (25th, 75th percentiles) unless specified otherwise.

Differences between groups were tested using the t-test or the Mann–Whitney U test for continuous data and the χ² test for categorical data.

* One missing observation. ** Two missing observations.

Regression analyses

As shown in Table 3, the 28 TJC, SF-36 MCS, and HAQ-DI were statistically significant predictors of the PDQ score in the univariate regression analyses. After adjusting for age, sex, disease duration, and whether patients initiated a bDMARD or csDMARD treatment, only TJC and SF-36 MCS remained as significant independent predictors of the PDQ score: β = 0.22 [95% confidence interval (CI) 0.04–0.40] and β = −0.16 (95% CI −0.25 to −0.06), respectively. As there were no significant differences between patients in the medium and high PDQ classification groups, a post-hoc logistic regression model was also conducted to determine whether the above selected predictors were independently associated with having a PDQ score ≥ 13 (Supplementary Table B). When using this approach, TJC and SF-36 MCS remained the only two independent predictors.

Discussion

There has been much research into the pain mechanisms involved in musculoskeletal diseases traditionally considered to be non-inflammatory (e.g. osteoarthritis and fibromyalgia). However, application of similar methods has only recently been used in inflammatory diseases because of increased awareness of pain as a multidimensional experience caused by several factors. Our findings showed that 12% of the patients initiating or escalating their RA medication, based on expert opinion, rated themselves to be in the high PDQ classification group (likely NP component). Furthermore, 23% of the patients rated themselves to be in the medium PDQ classification group (possible NP component). These proportions are similar to those found by Koop et al (17% in the high PDQ classification group and 21% in the medium PDQ classification group) and Ahmed et al (5% in the high PDQ classification group and 28% in the medium PDQ classification group), who both assessed RA patients with low disease activity (5, 6). Our results therefore suggest that the proportion of RA patients with PDQ scores ≥ 13 remains the same irrespective of the disease activity.

Furthermore, our post-hoc analyses demonstrated no statistically significant differences in the variables between the medium and high PDQ classification groups except for the SJC. That is, patients in the medium and high PDQ classification groups presented with very similar clinical features. It could therefore be speculated that a PDQ score ≥ 13 indicated the presence of a non-nociceptive pain mechanism in our study sample, corresponding to 35% of the patients. This approach would also increase the consistency when comparing our results with those of Koop et al (38% with a PDQ score ≥ 13) and Ahmed et al (33% with a PDQ score ≥ 13).
Table 2. Differences between participants stratified by the PDQ group.

| Variable                        | PDQ score < 13 (n = 66) | PDQ score 13–18 (n = 23) | PDQ score ≥ 19 (n = 12) | p value |
|---------------------------------|-------------------------|---------------------------|--------------------------|---------|
| Female, n (%)                   | 45 (68.2)               | 20 (87.0)                 | 31 (91.7)                | 0.09    |
| Age (years), mean (sd)          | 56.1 (14.7)             | 54.6 (18.9)               | 47.4 (15.6)              | 0.22    |
| BMI (kg/m²), mean (sd)          | 25.8 (4.7) ***           | 27.0 (5.2)                | 26.7 (7.0)               | 0.60    |
| Disease duration (months)       | 15.5 (1–104)            | 53 (9–47)                 | 34.5 (24–149.5)          | 0.12    |
| Current smoker, n (%)           | 11 (16.9)*              | 7 (30.4)                  | 2 (16.7)                 | 0.39    |
| Corticosteroid usage, n (%)     | 11 (16.7)               | 2 (8.7)                   | 3 (25.0)                 | 0.42    |
| 28 Swollen joint count          | 2 (1–7)                 | 5 (2–8)                   | 2 (1–4)                  | 0.09    |
| Tender joint count              | 5 (3–10)                | 13 (8–16)                 | 9.5 (6.5–15)             | <0.0001 |
| Tender point count, 0–18        | 6 (4–14)                | 10 (7–16)                 | 12 (6–14)                | 0.02    |
| Tender point count ≥ 11, n (%)  | 20 (30.3)               | 11 (47.8)                 | 7 (58.3)                 | 0.09    |
| DAS28, mean (sd)                | 2.8 (1.1)               | 5.0 (1.2)                 | 4.8 (0.7)                | 0.007   |
| BMI (kg/m²), mean (sd)          | 27.0 (5.2) ***           | 26.7 (7.0)                | 25.8 (4.7) ***           | 0.60    |
| Disease duration (months)       | 15.5 (1–104)            | 53 (9–47)                 | 34.5 (24–149.5)          | 0.12    |
| Current smoker, n (%)           | 11 (16.9)*              | 7 (30.4)                  | 2 (16.7)                 | 0.39    |
| Corticosteroid usage, n (%)     | 11 (16.7)               | 2 (8.7)                   | 3 (25.0)                 | 0.42    |
| 28 Swollen joint count          | 2 (1–7)                 | 5 (2–8)                   | 2 (1–4)                  | 0.09    |
| Tender joint count              | 5 (3–10)                | 13 (8–16)                 | 9.5 (6.5–15)             | <0.0001 |
| Tender point count, 0–18        | 6 (4–14)                | 10 (7–16)                 | 12 (6–14)                | 0.02    |
| Tender point count ≥ 11, n (%)  | 20 (30.3)               | 11 (47.8)                 | 7 (58.3)                 | 0.09    |
| DAS28, mean (sd)                | 2.8 (1.1)               | 5.0 (1.2)                 | 4.8 (0.7)                | 0.007   |
| HAQ-DI, 0–3                     | 0.75 (0.28–1.25)        | 1.13 (0.88–1.75)          | 1.63 (1.19–1.88)         | 0.0004  |
| VAS-fatigue (mm)                | 53.5 (27–71)            | 75 (52–89)                | 72.5 (60.5–87)           | 0.002   |
| VAS-pain (mm)                   | 42 (24–60)              | 69 (50–82)                | 63 (45.5–80.5)           | 0.0003  |
| VAS-global health (mm)          | 56 (32–77)              | 73 (46–85)                | 78 (61.5–90)             | 0.03    |
| GAD-10 score, 0–50              | 6 (3–10)*               | 10 (6–17)                 | 9 (9–12)                 | 0.008   |
| MDTI score, 0–50                | 8 (4–12)*               | 11 (6–25)                 | 13.5 (9–19.5)            | 0.01    |
| SF-36 MCS, 0–100                | 35 (29–42)              | 33 (26–37)                | 28 (24–32)               | 0.02    |
| SF-36 MCS, 0–100                | 51 (40–57)              | 43 (31–51)                | 37 (31–49)               | 0.005   |
| CRP (mg/mL)                     | 8 (3–15)                | 4 (0.5–19)                | 3 (0.8–8.5)              | 0.13    |
| IgM-RF positive, n (%)          | 41 (62.1)               | 15 (65.2)                 | 8 (66.7)                 | 1.0     |
| USD score, 0–72                  | 9 (5–15)                | 10 (6–15)                 | 8.5 (3–14)               | 0.84    |
| RAMRIS synovitis (0–21)†        | 7.5 (5–10)              | 9.5 (7–11)                | 7 (6–9)                  | 0.18    |

PDQ, PainDETECT questionnaire; BMI, body mass index; DAS28, Disease Activity Score based on 28 joint counts; DAS28-P, the subjective components of the DAS28 relative to the total DAS28 (see text for calculation); HAQ-DI, Health Assessment Questionnaire Disability Index; VAS, visual analogue scale; GAD-10, Generalized Anxiety Disorder Assessment; MDTI, Major Depression Inventory; SF-36; 36-item Short Form Health Survey; CRP, C-reactive protein; IgM-RF, immunoglobulin M rheumatoid factor; USD, ultrasound Doppler; RAMRIS, rheumatoid arthritis magnetic resonance imaging scoring system; sd, standard deviation.

Values are median (25th, 75th percentiles) unless specified otherwise.

Differences between groups were tested using the analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous data and the χ² test for categorical data.

* One missing observation. ***Three missing observations.
† Wrist plus metacarpophalangeal joint (MCP) scores. Due to contraindications or participant refusal, 26 patients did not receive an MRI scan. Distributions were as follows: PDQ score < 13: n = 50; PDQ score 13–18: n = 18; PDQ score ≥ 19: n = 6.

Table 3. Regression using PDQ score as the dependent variable.

| Variable                        | Univariate regression analysis | Multiple regression analysis |
|---------------------------------|--------------------------------|------------------------------|
|                                | β  | 95% CI                  | β  | 95% CI                  |
| 28 Tender joint count          | 0.40† | 0.23 to 0.58            | 0.22† | 0.04 to 0.40            |
| SF-36 MCS                      | -0.19† | -0.29 to -0.09          | -0.16† | -0.25 to -0.06          |
| HAQ-DI                         | 3.55†  | 1.87 to 5.22            | 1.49  | -0.34 to 3.33           |
| CRP† mg/mL                     | -1.86* | -3.76 to 0.06           | -1.57* | -3.33 to 0.19           |
| Female sex §                   | 0.40†  | 0.40 to 5.72            | 0.81  | -1.75 to 3.36           |
| Age §                          | 0.06  | -0.13 to 0.02           | -0.02 | -0.09 to 0.04           |
| Disease duration §             | 0.01  | -0.01 to 0.02           | 0.001 | -0.01 to 0.01           |
| Initiated bDMARD §             | 3.51†  | 1.26 to 5.76            | 1.90  | -0.48 to 4.28           |

PDQ, PainDETECT questionnaire; HAQ-DI, SF-36; 36-item Short Form Health Survey; MCS, mental component summary score; HAQ-DI, Health Assessment Questionnaire Disability Index; CRP, C-reactive protein; bDMARD, biological disease-modifying anti-rheumatic drug; CI, confidence interval.

All variables were included as continuous scores except for ‘female sex’ and ‘initiated bDMARD’.

* p < 0.1. † p < 0.05.
‡ CRP was log transformed in the analyses.
§ Pre-specified confounder to be included in the adjusted model.

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Several important differences were seen across the three PDQ classification groups. As hypothesized, our study shows that, among patients in the high PDQ classification group, a greater proportion of the DAS28 was explained by contributions from the patient-reported DAS28 subcomponents (TJC and VAS-GH score), that is a higher DAS28-P. This supports our assumption that a high PDQ score influences the DAS28 through the patient-reported subcomponents, and this assumption was further supported by the finding of TJC as an independent predictor of PDQ in the multiple regression model. However, contrary to our hypothesis, we did not find lower degrees of inflammation in patients with high PDQ scores. Our study is the first to relate findings by USD and MRI to the PDQ score in RA patients. Even when using these imaging modalities, there were no statistically significant differences in the objectively inflammatory indices (USD score, RAMRIS synovitis score, or CRP) across the PDQ classification groups.

These findings indicate that, among RA patients with high PDQ scores, there is a non-inflammatory pain component that affects the DAS28 and patient-reported outcomes in general. It therefore seems that the validity of the DAS28 may be reduced when applied to assess disease activity and inform treatment decisions in RA patients with high PDQ scores. Consequently, initiation of anti-inflammatory treatments might not produce the expected DAS28 response or meet patients’ expectations of improvement. Other strategies, such as imaging-based strategies (36), where the anti-inflammatory therapy is only intensified based on objective findings (imaging), may produce better results in this subgroup and prevent unnecessary exposure to anti-inflammatory therapies (e.g. bDMARDs). Furthermore, pharmacological and non-pharmacological intervention strategies that focus on treating pain and pain-related disability should probably also be considered.

In our multiple regression model, the SF-36 MCS was found to independently predict the PDQ score, which is consistent with the findings of Koop et al. They also tested, but did not find, TJC to be an independent predictor. However, this is probably because of the very few tender joints in the population they examined (median = 0, interquartile range 0 to 1).

Some studies have indicated that the PDQ might assist in identifying patients with central sensitization (CS). CS is not a uniformly agreed upon concept but can be described as a functional shift in the somatosensory system, where the peripheral nociceptive input is amplified by spinal and supraspinal neurons (central nervous system) resulting in pain hypersensitivity and widespread pain. Although this condition is different from NP, which the PDQ was designed to detect, there seem to be similarities with regard to how patients with CS and patients with NP answer the PDQ. In support of this, CS assessed by quantitative sensory testing and functional MRI has been shown to be associated with higher PDQ scores (22, 23). In addition, patients with fibromyalgia score high on the PDQ (24) and the number of manually assessed tender points and the pressure pain threshold correlate with the PDQ score (21). The interpretation of a high PDQ score as a marker of CS was supported in our study by the finding of worse scores on several variables related to mental health and/or psychological distress (VAS-fatigue, GAD-10, MDI, SF-36-MCS) in the patients in the higher PDQ classification groups. These results are in line with previous studies linking fatigue and psychological distress with CS (37, 38).

It has been shown that RA leads to widespread pain and pain hypersensitivity in 10–20% of the patients (8, 39). Manual TP examination has traditionally been considered a primary clinical identifier of pain hypersensitivity and is included in the 1990 criteria for the classification of fibromyalgia (15). In our study, the TP count increased within each PDQ classification group and patients in the high PDQ classification group had a median TP count of 12 (the 1990 ACR classification criteria for fibromyalgia sets the cut-off at 11 or more tender points). The proportion of patients having a TP count ≥ 11 did not reach statistical significance across the three groups (p = 0.09). However, in the post-hoc analyses (Supplementary Table A), where the PDQ responses were dichotomized using the PDQ score ≥ 13 as a cut-off, there was significantly more patients with a TP count ≥ 11 in the high PDQ group (p = 0.04).

A significant difference in the extent of self-reported disability on the HAQ-DI was also observed across the three PDQ groups. Most of the patients in the low PDQ classification group reported a low level of disability, while patients in the medium and high PDQ classification groups reported increasing levels of disability. Patients in the high PDQ classification group had a median HAQ-DI of 1.63, comparable to levels reported in RA patients with comorbid fibromyalgia (39, 40). Although these findings are not conclusive, they do show that the PDQ is able to identify groups of RA patients who share clinical characteristics with fibromyalgia patients.

In conclusion, the results of our study support the notion that the PDQ may be an easily applied screening tool to assist identification of a non-inflammatory pain component in patients with RA. Among RA patients who, based on expert opinion, were about to initiate/escalate medical treatment, 23% and 12% were categorized in the medium and high PDQ classification groups, respectively. There were no differences in inflammatory indices across the three PDQ classification groups (USD, MRI, or CRP) but the proportion of the DAS28 that pertained to the subjective subcomponents increased across groups. Patients who rated themselves to be in the medium or high PDQ classification group shared common clinical features and were characterized by higher DAS28, more pain, disability, fatigue, psychological distress, and tender joints and poorer health-related quality of life when compared to patients in the low PDQ classification group.
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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table A. Differences between participants with high and low PDQ scores.
Supplementary Table B. Logistic regression.

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