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Title: Understanding Differences in Patient Descriptions of RA Flares Using OMERACT Core Domains

Running Title: Patient Descriptions of RA Flares Using OMERACT Domains

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Abstract

Objective: Recently, there has been consensus on domains that constitute flares in Rheumatoid Arthritis (RA); however, variations in patients' flare descriptions continue to be observed. This study evaluates how demographic and clinical characteristics influence these differences.

Methods: Participants enrolled in a prospective RA registry completed a qualitative survey which included the open-ended question "What does a flare mean to you?". Responses were categorized into OMERACT core and research domains. Univariate analyses evaluated demographic and clinical characteristics. Regression analyses determined independent variables associated with flare description variations.

Results: Among 645 participants, median (IQR) DAS28-CRP3 was 2.1 (1.6, 2.9); 58% reported at least 1 flare in the past 6 months. Participants reported a median (IQR) of 3 (2, 5) OMERACT domains when describing flares. Fatigue was more commonly noted among females (OR=6.12, p=0.0006) while older participants were less likely to report emotional distress (OR=0.97, p=0.0275), swollen joints (OR=0.99, p=0.0430), physical function decrease (OR=0.98, p=0.0186), and a general increase in RA symptoms (OR=0.98, p=0.0053). Participants with a higher DAS28 score less likely reported symptoms of stiffness (OR=0.70, p=0.0092) and those who experienced a flare within the last 6 months more likely described flares as pain (OR=2.53, p=0.0001) and fatigue (OR=2.0, p=0.0066).

Conclusion: Variations in patients' flare descriptions can be driven by a patient's disease activity the experience of a recent flare as well as different demographic characteristics such as age and gender. Understanding the interplay of these characteristics can guide a physicians' approach to the management of patients' RA flares.

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Keywords: patient perspective, rheumatoid arthritis, flare, qualitative, OMERACT

Significance and Innovations

-This prospective analysis demonstrates that patient flare definitions vary according to clinical and demographic characteristics.

-The majority of patients describe their flares as multidimensional corresponding to several different OMERACT domains.

-Patients describe the impact of their flares differently and understanding how these differences arise may help physicians better manage patients' disease.

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1. Introduction:

Flare is an important, distinct feature of RA, often rendering patients immobile and contributing to a poor quality of life [1]. Despite its significant presence in disease activity, a standardized definition for RA flare has yet to be determined. As various studies have previously stated, variability in flare definitions can impact communication between a clinician and patient, as a patient's perspective on a flare can differ from a physician's [1-4].

Although several studies in recent years have begun to evaluate the possible measures in which to standardize criteria for a flare, one group in particular, the Outcome Measures in Rheumatology (OMERACT) RA Flare group, has come to a consensus on outcome measures to determine a flare. OMERACT, an international group composed of RA patients and healthcare professionals, was able to develop 8 core domains that constitute a flare via combined rounds of Delphi exercises. These core domains represent the domains agreed upon by both healthcare professionals and patients in focus groups, with additional domains still being explored [3,5-8].

In originally identifying the core domains, several patient and physician characteristics were observed throughout the Delphi process as part of an exploratory analyses, however, it is unclear how these specific factors affect patients' flare descriptions [7]. The importance of understanding which characteristics drive differences in flare description may assist physicians in clearly communicating treatment of flares specifically for each patient. In order to analyze the interplay between different clinical characteristics, specifically, disease activity and patients' experience of a recent flare, we evaluated how these variables affect variations in patient's perspectives.

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2. Methods:

2.1 Patient Population. Data were collected from patients enrolled in the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS) located in Boston, MA. BRASS, which began enrollment in March 2003, is a prospective, observational cohort of more than 1,500 patients. Patients (ages ≥ 18) with a clinical diagnosis of RA were recruited from practices of attending rheumatologists and fellows. All diagnoses of RA were either verified according to the 1987 American College of Rheumatology (ACR) criteria or met the rheumatologists' clinical opinion.

2.2 Study Design. Participants completed annual study visits which collected patient-reported and clinical data via an interview, physician assessment (including a 28-joint count), a self-administered questionnaire, and a blood draw. Additionally, disease activity was ascertained annually via the DAS28-CRP3 score [9]. Further details regarding the study protocol in the BRASS registry are reported elsewhere [10,11]. The flare questionnaire was added to the annual study visits in 2015 and flare data were analyzed from 2015-2019.

2.3 Ethics & Consent. All the study procedures, informed consent and materials used under BRASS registry are approved by Institutional Review Board of Brigham and Women's Hospital, Partners Health Care, Boston, MA. The registry is approved under IRB protocol number 2002P001762 and written informed consent to publish the material were obtained from all participants. The BRASS clinical registration number is NCT01793103.

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2.4 Measures. As part of their study visit, patients were asked to answer several questions pertaining to RA flares. Participants were asked to report whether they have experienced a flare in the past 6 months and answer the open-ended question "What does a flare mean to you?". Flare descriptions were then recorded and independently categorized by two reviewers. Patient responses were sorted into OMERACT core domain(s) or research domain(s). Research domains were defined as domains that were still being analyzed as potential flare domains per OMERACT [5]. The following flare domains: pain, tender joints, swollen joints, physical function decrease, fatigue, stiffness, patient global, and participation were classified as OMERACT core domains [5,7]. Pain included painful/tender joints as a subcategory. Participation was defined as a decrease in activities (work, family, social). In addition, the physical function decrease domain encompassed five subgroups: immobility, hard to do normal tasks, ask for help, cut back on physical activity, and need for medical equipment (such as cane, walker, arthritis gloves). Emotional distress and sleep disturbance were characterized as research domains. Depressive symptoms, irritability were groups categorized under emotional distress. For example, in the following patient flare description,

> "A flare means pain or discomfort (swelling) in the joints. Would do everything but would be in pain while completing errands."

one can see that after the two reviewers independently categorized this recorded response, the final classification would have been the painful and swollen joint domains. In the event of discordance, a 3rd reviewer was selected as an arbitrator.

2.4 Statistical Analyses. Univariate analyses evaluated demographics such as: age, gender, race and clinical characteristics. Descriptive statistics used non-parametric measures for non-

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normally distributed variables. Multivariable logistical regression analyses were then used to determine the primary predictors of variations found in patients' descriptions of RA flares. The primary predictors were age, gender, race, education, experiencing flare or not in the past 6 months, disease duration, DAS28-CRP3, and obesity. The primary outcomes were the OMERACT core and research domains. Sleep and participation decrease were not outcomes in the model since they had too few responses (15 and 6 respectively).

3. Results:

Out of the >1500 patients enrolled in our BRASS study, 696 patients completed the flare baseline questionnaire. Out of the 696 individuals, 645 participants completed all the necessary components needed for analysis including the question “What does a flare mean to you?” and had a disease activity score. Table 1 describes the baseline clinical and demographic characteristics of these 645 patients. The study cohort had a mean (SD) age of 60 (13) years and long-standing disease with a median (IQR) disease duration of 14 (6, 23) years. Approximately 82% of the participants were female, 92% were white, 26% were obese with BMI >=30, and 76% had a college education or greater. Participants who were on corticosteroids comprised 24% of the cohort, while 56% of patients were on a biologic DMARD. At least half of the participants were on methotrexate and 38% of participants were on TNF inhibitors. 38% of the patients at the time of the analysis were on NSAIDS. This cohort had a median (IQR) DAS28-CRP3 score of 2.1 (1.6, 2.9) indicating low disease activity, with 58% of the participants reporting at least one flare in the past 6 months. Shown in the supplementary table 1 is a comparison of the demographic characteristics between participants who completed the flare questionnaire and those who didn’t using data from their BRASS baseline study visit. The

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statistically significant differences between these two groups were that those who didn't complete the flare questionnaire were older when enrolled at a mean (SD) age of 58 (15). There was also a higher percentage of individuals who did not graduate college among the non-participants group (41% versus 24% who did not graduate college in the participant cohort).

Patients' flare descriptions were recorded and categorized according to flare domains shown in Table 2. Participants reported a median (IQR) of 3 (2, 5) OMERACT domains when describing flares. Of the OMERACT Core domains mentioned, pain and its subcategory painful joints, along with a decrease in physical function were the most commonly reported (79.2%, 35.5% and 41.2% respectively). Among the participants who voiced a decrease in physical function as part of their flare description, hard to do normal tasks (20.8%) was frequently noted in their descriptions followed by immobility (18.6%). With regards to the OMERACT research domains, emotional distress was reported more often (9.3%) than sleep disturbance (2.3%). Patients mentioned irritability the most (3.6%) out of the categories that comprise emotional distress when prompted to describe a flare.

Selected examples of flare descriptions given by RA patients in our analysis are depicted in Figure 1. As one can see in panel A of Figure 1, flare descriptions from patients in low DAS28-CRP3 score (DAS28-CRP3 < 3.2) versus moderate or high DAS28-CRP3 score (DAS28-CRP3 ≥ 3.2) expressed several of the same domains from both OMERACT core and research domains. However, patients with a low DAS are more likely to describe a flare as increased stiffness (see Table 3). Figure 1 also highlights differences in flare definitions when looking at selected quotes from female versus male patients (panel B). Female patients were more likely to include fatigue as part of their flare definition (see Table 3).

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Table 3 demonstrates the primary covariates associated with variations in patients' flare descriptions via logistical regression analyses. 7 flare domains modeled had statistically significant differences between patient characteristics and the descriptions they used for flares. Age becomes a significant factor in variations to flare definitions when the following flare domains are analyzed as outcomes: swollen joints, physical function decrease, emotional distress, and patient global (Model 2, 4, 5, and 6 respectively). Patients who are older are less likely to include swollen joints (OR=0.99, p=0.0430), physical function decrease (OR=0.98, p=0.0186), emotional distress (irritable) (OR=0.97, p=0.0275) and a general increase in RA symptoms (OR=0.98, p=0.0053) as part of their flare description. Females are more likely (OR=6.12, p=0.0006) to describe a flare as fatigue (Model 3). Patients with a lower DAS28-CRP3 score tend to describe a flare as stiffness (OR=0.70, p=0.0112) (Model 7). According to Model 1 and 3, patients who experienced a flare in the past 6 months are more likely to describe a flare as pain (OR=2.53, p=0.0001) and fatigue (OR=2.0, p=0.0066). Disease duration is another significant factor, as patients with longer disease duration tend to mention pain (OR=1.02, p=0.0296) and fatigue (OR=1.03, p=0.0153) more often in their flare descriptions. Race, obesity, and education are patient characteristics that had no impact on driving differences in flare descriptions across all 7 flare domains modeled.

4. Discussion:

Our analysis demonstrated that there were variations in how patients defined their flares and that these differences varied by patient clinical and demographic characteristics. The majority of patients described their flares as multidimensional, corresponding to more than 1 OMERACT core domain. We were interested in investigating how the interplay of clinical factors

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such as one between a patient's disease activity and occurrence of a recent flare would affect patients' flare descriptions. In doing so, we observed that a patient's disease activity or recent flare status individually can have a significant influence on the variations in patient reported domains.

Other investigators have explored how patients define their flares and this has contributed to the work developing the OMERACT core domains for a Rheumatoid Arthritis flare [2-5,7]. Previous work from Bartlett et. al [7] demonstrated that age, education, disease duration and a patient's primary language influenced their descriptions of flares. Bartlett's analysis sought to develop domains that would represent flares as a worsening of signs and symptoms with an intensity and duration that would prompt a change in treatment [7]. From her patient Delphi panel, older patients were more likely to identify physician global assessment and labs as important when describing a flare. However, in our present analysis, older patients were less likely to include swollen joints, physical function decrease, emotional distress, and a general increase in RA symptoms when describing a flare. Disease duration demonstrated effects on variations seen in patient flare descriptions in our study, with patients in this BRASS cohort reporting a median (IQR) disease duration of 14 years (6, 23) which is similar to the average disease duration of 18 years in Bartlett's analysis. We were unable to look at language as a covariate since all participants in our study were English-speaking. Unlike in Bartlett's study, gender was a patient characteristic that was significant in driving differences in flare descriptions in our analysis while education had no statistical influence on flare descriptions in our study. The differences between Bartlett's analysis and our study may be partially due to our inclusion of each patients' current DAS-CRP3 score. Although our analysis demonstrated that

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patients with a higher DAS28-CRP3 score are less likely to describe a flare as increased stiffness, this observation is important in understanding that despite a higher DAS28-CRP3 score, patients may become used to certain symptoms in their disease course (such as stiffness), and therefore they would be more attuned to other symptoms that become more prominent during a flare.

Our study also considered how the presence or absence of a recent flare influenced which domains were reported more often by patients. Among the domains used in our analysis, certain domains describe mostly symptoms of a flare versus others that focus on the effect of these symptoms. For example, we found that it was the experience of having a recent flare in the past 6 months that drove patients to describe their flares more often with domains that depicted symptoms: pain and fatigue. This seems to parallel work done by van Tuyl LHD et. al on the patient perspective on remission in RA and how patients describe remission [12]. In van Tuyl's study, patients characterize remission not only by mentioning the absence or decrease of specific symptoms, but also by drawing upon their experiences of the impact of these symptoms. Our analysis demonstrates there is a complex interplay between a patient's flare experience, their disease activity, and whether they describe flares with specific symptoms or depiction of the impact of these symptoms.

Our study had several limitations. Most participants had longstanding disease and had lower disease activity which may limit how representative the participants are of all RA patients. Although we attempt to gather information on the smoking status of our study participants, we were unable to analyze smoking status as a potential covariate in the association of reported flare domains due to missing data. Differences in flare descriptions can

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also be due to the length of our recall period [13]. Therefore, it is possible that certain core domains are influenced by how recent the flare was for those domains reported more often by a positive flare status. Future studies that collect information about the flare experience in real time can address this concern. On the other hand, our study has several strengths which are: the large number of patients included in the cohort, our ability to include patients' disease activity score, and the design of our flare questionnaire where participants were asked to define a flare in an open-ended question. This follows the bottom-up approach in Hewlett et. al's study on patient perspective on RA flares [1,14].

Similar to other studies analyzing patient perspectives on RA flares, we found that there are clinical and demographic characteristics which differentially impact how a patient describes their flares and that disease activity also affects the way patients may depict their flares to physicians. This analysis sheds light on how important it is for a clinician to consider that in general, patients describe the impact of their flares differently and understanding how these differences arise may help physicians better manage patients' disease. This may be an important component moving forward in operationalizing the standard definition of RA flare using OMERACT core domains, to ensure that these domains can serve as an effective communication tool for RA patients and their physicians.

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Figure 1. Selected examples of flare descriptions given by RA patients. Panel A demonstrates flare descriptions from patients with a low disease activity score (DAS) and a moderate-high disease activity score. Panel A depicts how patients from both DAS groups express similar OMERACT domains when describing a flare. However, patients with a low DAS are more likely to describe a flare as stiffness (not seen in this figure, see Table 3). Panel B demonstrates flare definitions from both female and male patients, highlighting differences in how female patients will describe a flare as increased fatigue more than male patients.

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"What does a flare mean to you?"

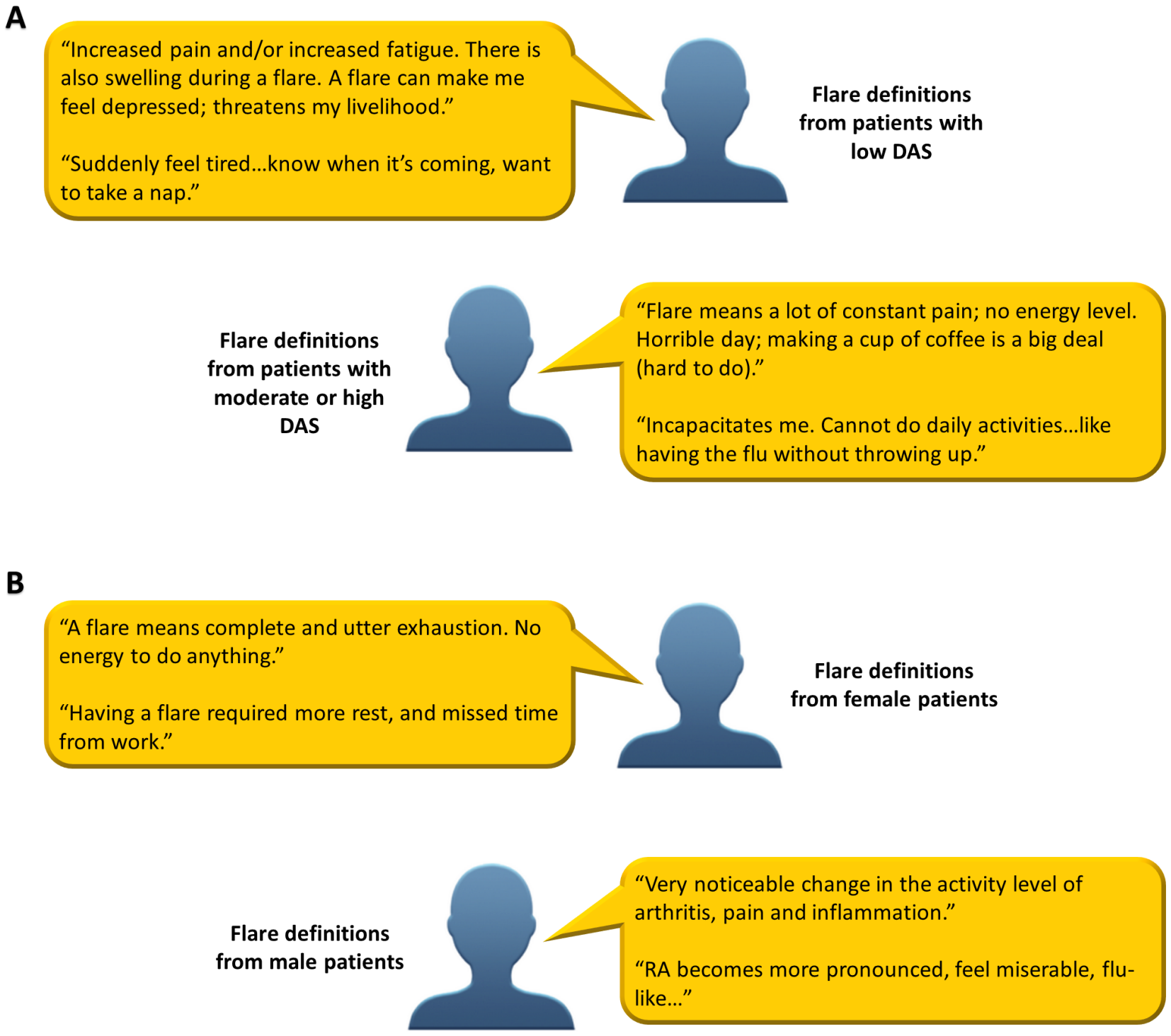

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Table 1. Clinical and Demographic Characteristics of Cohort (n=645)

Baseline Characteristics	Value
Age, years (M, SD)	60 (13)
Gender, female (n, %)	532 (82%)
Race, white (n, %)	596 (92%)
Education (n, %)	
Did not graduate college	153 (24%)
Graduated college	492 (76%)
Obesity, BMI >= 30 (n, %)	149 (26%)
Disease duration, years (Median, IQR)	14 (6, 23)
DAS28-CRP3 (Median, IQR)	2.1 (1.6, 2.9)
Reported flare in the past 6 months (n, %)	354 (58%)
Disease Activity (n, %)	
Remission-Low DAS28-CRP3	538 (83%)
Moderate-High DAS28-CRP3	107 (17%)
RA Medication (n, %)	
Corticosteroids	153 (24%)
Biologic DMARD	360 (56%)
TNF inhibitor	248 (38%)
Non-biologic DMARD	442 (69%)
Methotrexate	352 (55%)
NSAIDS	242 (38%)

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Table 2. Domain frequencies (n=645)

Variable	Values, N (%)
Pain	511 (79.2)
Painful joints	229 (35.5)
Swollen joints	225 (34.9)
Patient global	131 (20.3)
Stiffness	106 (16.4)
Physical function decrease	266 (41.2)
Immobility	120 (18.6)
Hard to do normal tasks	134 (20.8)
Ask for help	10 (1.6)
Cut back on physical activity	58 (9)
Need medical equipment	2 (0.3)
Fatigue	130 (20.2)
Emotional distress	60 (9.3)
Depressed	18 (2.8)
Irritable	23 (3.6)
Participation decrease	6 (0.9)
Sleep Disturbance	15 (2.3)

***Patient global defined as an increase in RA symptoms**

****Participation defined as a decrease in activities (work, family, social)**

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Table 3. Adjusted Odds Ratios (OR with 95% CI) of Clinical and Demographic Characteristics Associated with Flare Description by Flare Domains (N=645)

Patient Characteristics	Flare Description						
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**
	Pain	**Swollen Joints**	**Fatigue**	**Physical Function Decrease**	**Emotional Distress**	**Global Increase in RA**	**Stiffness**
Age	1.00 (0.98, 1.01)	**0.99 (0.97, 0.99)**	0.98 (0.96, 1.00)	**0.98 (0.97, 0.99)**	**0.97 (0.95, 0.99)**	**0.98 (0.96, 0.99)**	0.99 (0.97, 1.01)
Female	1.07 (0.61, 1.86)	0.92 (0.58, 1.47)	**6.12 (2.17, 17.20)**	1.35 (0.84, 2.17)	2.02 (0.76, 5.36)	1.02 (0.58, 1.80)	0.89 (0.49, 1.62)
White	1.86 (0.87, 3.98)	1.07 (0.53, 2.17)	1.88 (0.70, 5.10)	1.34 (0.67, 2.69)	1.43 (0.41, 4.97)	1.18 (0.50, 2.80)	0.57 (0.25, 1.29)
College Degree (or higher)	1.27 (0.75, 2.13)	0.90 (0.58, 1.40)	0.94 (0.54, 1.61)	0.75 (0.49, 1.15)	0.62 (0.31, 1.23)	0.63 (0.38, 1.04)	0.84 (0.48, 1.48)
DAS28-CRP3	0.81 (0.65, 1.02)	0.93 (0.76, 1.13)	1.10 (0.87, 1.37)	0.92 (0.76, 1.12)	0.97 (0.71, 1.32)	0.83 (0.65, 1.05)	**0.70 (0.52, 0.92)**
Had Flare in the past 6 months	**2.53 (1.58, 4.04)**	1.22 (0.83, 1.79)	**2.00 (1.21, 3.31)**	1.20 (0.82, 1.74)	1.23 (0.64, 2.36)	1.01 (0.64, 1.58)	1.41 (0.86, 2.30)
Disease Duration	**1.02 (1.00, 1.04)**	1.00 (0.98, 1.01)	**1.03 (1.01, 1.05)**	1.01 (1.00, 1.03)	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)	1.00 (0.98, 1.03)

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Obesity	0.95 (0.58, 1.57)	1.36 (0.91, 2.04)	0.84 (0.5, 1.43)	1.26 (0.85, 1.88)	1.55 (0.81, 2.97)	0.88 (0.53, 1.45)	0.67 (0.38, 1.19)

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