Correlates of Successful Rheumatoid Arthritis Flare Management: Clinician-driven Treatment, Home-based Strategies, & Medication Change

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Abstract

Objective: Describe strategies used to manage rheumatoid arthritis (RA) flares that contribute to a successful post flare outcome.

Methods: Data were collected from the BRASS registry, including clinical and patient reported outcomes, and a survey with a Likert scale assessing post flare symptoms (better, unchanged, or worse). A logistic regression analysis adjusting for age, sex, flare number in the past 6 months, flare pain severity, home management, clinical consultation, and medication change was performed to evaluate factors influencing flare outcome. Clinical trial registration: NCT01793103.

Results: Of 503 participants, 185 reported at least one flare that had resolved in the past 6 months, median (IQR) DAS28-CRP3 score 2.1 (1.7, 2.8). Compared with RA symptoms before the flare, 22 (12%) patients felt worse, 125 (68%) were unchanged, and 38 (20%) felt better. To manage flares, 72% of patients used home-based remedies, 23% sought clinical consultation, and 56% made medication change. Of 103 patients who changed medication, 70% did so without seeking clinical advice. Making a medication change [OR 3.48 (1.68, 7.21)] and having lower flare pain [OR 0.83 (0.71, 0.97)] were associated with better flare outcome.

Conclusion: Flares occur frequently even in patients with low disease activity. Independent of home-based or clinically guided care, making a medication change and having less severe pain during a flare were associated with better flare outcomes. Of interest, the decision to change medications was frequently made without clinical advice. Future directions might address how

best to intervene when patients experience flares and whether patient initiated medication changes have adverse outcomes.

Key Messages:

- Rheumatoid arthritis patients, even those in low disease activity, frequently experience flares.
- Medication modification and having less severe pain during flare were associated with better flare outcomes.
- Patients' decision to manage a flare by changing medication was frequently made without clinical advice.

Key words:

- Rheumatoid arthritis
- Disease modifying antirheumatic drugs
- Pain

Introduction:

Rheumatoid arthritis (RA) is a chronic, multisystem autoimmune disease primarily affecting the joints. Uncontrolled RA disease activity can lead to joint deterioration and disability (1). While therapeutic advancements have been made in treating RA, patients still experience episodes of worsening disease activity, called flares, which can have a detrimental impact on long term functional outcomes (2-5).

RA patients, even those in remission, can experience frequent flares (6). Recurring flares can increase the risk for cardiovascular disease, radiographic progression, and disability (2-4, 7). Several qualitative studies have been published that report on the range of strategies patients use to manage RA flares (8-10). These included self-management with rest, heat/cold, or exercise. Additionally, patients sometimes sought assistance from family and friends to help with daily activities. Patients frequently reported adding or changing medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Seeking clinical consultation from a rheumatologist or a primary care physician was often described as a last resort after other remedies have failed (9, 10).

Little is known about the effectiveness of these types of flare management strategies. A better understanding of these strategies and their efficacy is needed to improve home and clinical care and improve long term outcomes. This study intends to examine in depth how patients manage their flares and expand on previous work (11) with this cohort. The aim is to learn about the types of strategies patients use and how they affect post flare outcomes with the goal of improving long term clinical and functional outcomes.

Materials and Methods:

Study Population:

Data were collected from participants in the Brigham Rheumatoid Arthritis Sequential Study (BRASS) which was initiated in 2003. BRASS is a single centered prospective RA registry of patients with a clinical diagnosis of rheumatoid arthritis followed by a hospital-based practice of rheumatologists in Boston. Participants completed yearly study visits that included an interview, a physician assessment (including a joint count), and a self-administered questionnaire (SAQ) collecting patient reported outcomes (PROs). Participants were also mailed a SAQ to collect data at the midpoint between annual visits. The registry collects a wide range of clinical and PROs including, but not limited to, medications, comorbidities, disability, healthcare utilization, functional status, and DAS28-CRP3. Additional details related to the BRASS registry are described elsewhere (12). All patients enrolled in the BRASS study provided informed written consent before starting study procedures. All questionnaires and methods for this study were done in compliance with the Partners Healthcare Institutional Review Board (approval number: 2002P001762, clinical trial registration number: NCT01793103).

Questionnaire:

As part of the annual visit, participants were given a survey which collected information about flares. The survey asked participants “During the past 6 months, have you had a flare in your rheumatoid arthritis?”. The survey also asked about the number of flares, the severity of pain for the most recent flare, the duration of the flare, and management strategies for the most recent flare. Strategies included methods used by patients at home (home management)

and whether they consulted any physician or clinical service (clinical consultation). Participants were also asked if they increased the strength of a medication already being used or added a new medication to manage their flare, and if so, they were asked details about dosage and duration of use.

Participants included in this analysis were BRASS patients who reported a flare in the past 6 months that had ended by the time of the survey. The primary outcome was a Likert scale assessing post flare symptoms. Participants were asked to complete the following: "As compared to the symptoms just before my most recent flare, my overall RA symptoms after my flare were…" with 'much worse', 'worse', 'a little worse', 'unchanged', 'a little better', 'better', 'or much better'. This, combined with a visual representation, prompted participants to compare their post flare symptoms relative to their pre-flare symptoms. For the purposes of the analysis, the 7 categories were collapsed into 3; worse, unchanged, or better (Figure 1).

Statistical Analyses:

Descriptive statistics were used to generate summary tables of the cohort. Different statistical methods were utilized based on type of variable to test whether there were significant differences between the response groups (worse, unchanged, or better post flare symptoms). For the normally distributed variable (age), a one-way ANOVA test was performed. The non-normally distributed variables (number of flares and flare pain severity) were analyzed with a non-parametric Kruskal-Wallis test. The categorical variables (gender, any home management, any clinical management, flare duration, and any medication change) were examined with the exact Mantel-Haenszel Chi-square test. From the univariate analyses, age,

gender, and all variables with a p≤0.2 were included in the final model. In the next step, a proportional odds logistics regression analysis was performed using post flare symptoms (worse, unchanged, or better) as the dependent variable, and age, number of flares, flare pain severity, gender, any home management, any clinical management, and any medication change as the independent variables. A secondary analysis was performed with the individuals who had a previous DAS28-CRP3 measured and this covariate was included in the model. The results of the final model were presented as odds ratio estimates with their 95% Wald confidence intervals calculated. Model assumptions were also tested using a backward selection analysis.

In an additional analysis, proportional odds logistics regression was performed with all the same independent variables, but with the any medication variable separated by type; NSAIDS (yes/no), corticosteroid (yes/no), and DMARDS (yes/no). A p-value <0.05 was considered statistically significant. Data collected in the surveys were maintained using a Microsoft Access Database. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results:

Of the 503 participants who completed the survey, 185 reported at least one prior flare that had ended in the last 6 months and were included in these analyses. Most participants were female, white, and had a college or graduate school degree (86%, 93%, and 72% respectively). Their mean (SD) age was 59 (14) years, 76% had seropositive RA, and the median (IQR) disease duration was 15 (9, 24) years. Participants already on biologics made up 63% of the cohort and 23% used oral corticosteroids as part of their ongoing therapy. More than 85%

of this cohort had low disease activity at the time of the survey and the median DAS28-CRP3 was 2.1 (1.7, 2.8) (Table 1).

The median number of flares in the previous 6 months was 2 (1, 4), with a median flare pain severity of 7 (5, 8) for the most recent flare. The most common flare duration category for the most recent flare was 1-3 days (Table 2). While only 20% of participants reported that their RA symptoms were improved after their flare, 12% reported that their symptoms worsened, and 68% reported that their symptoms were unchanged.

Seventy-two percent of participants (n=133) who had a flare utilized home management strategies as part of their treatment for the most recent flare. The most commonly reported strategies were rest, application of heat/cold, and/or use of an assistive device (brace, splint, cane). Fifty-six percent (n=103) made a medication change (increasing dosage and/or adding new medication) to treat their flare symptoms, and 23% (n=43) sought clinical consultation. Of the 43 participants who sought clinical consultation, 36 (84%) sought the advice of their rheumatologist. Those 36 used multiple modes of contacting their rheumatologist; including 22 in person visits, 15 phone calls, and 7 emails. Only 3 (7%) participants consulted a primary care physician for help managing their flare (Table 2). Among those who consulted with their primary care physicians, there were 2 office visits, 2 phone calls, and 1 email.

Of the 103 participants who made a medication change to manage their flares, 50 modified their NSAID regimen, 28 modified their corticosteroid use, and 22 modified their DMARD regimen. Out of the 50 NSAID changes, 16 participants increased their current dose, 34 added a new NSAID. Seven of the 28 corticosteroid alterations were increases in dose (mean

increase in dosage was 6.4 mg (5.3 mg)) while 21 were new starts (mean new dose was 14.3 mg (14.1 mg)). Out of the 22 subjects who made modifications to their DMARDs, 12 increased their current dose and 10 added one or more DMARDs. Of the DMARDs modified, 14 were non-biologics, all of which were methotrexate. Twelve of the DMARDs modified were biologics (9 were TNF-alpha inhibitors in addition to 1 each of tofacitinib, tocilizumab, abatacept). Only 3 participants added a new narcotic (2 oxycodone, 1 tramadol) and none increased their existing dose for their flare management. Overall, the average duration of an increased dosage of any medication for flare management was 33.2 (47.6) days. Those who used a new medication did so for an average of 39.5 (59.3) days. Notably, 72 (70%) of those who made any medication change did so without consulting a physician and 32% of the changes to DMARDs were also made without physician consultation (Table 3). All medication changes described here were made to manage the most recent flare.

A comparison was done of the demographic and clinical variables in Table 1 comparing those who initiated home management with those who did not. No differences were found between the 2 groups, other than a higher number of women utilized home management strategies (122 (92%) vs. 37 (71%), p = 0.0003). Similarly, in a comparison of demographic and clinical variables (Table 1) of those who initiated medication management versus those who did not, no significant differences were found. There were 69 (37%) patients who did both home management and medication changes for their flares.

Table 4 illustrates the univariate comparisons among the flare outcome groups (worse, unchanged, better) by clinical and demographic variables. Among all the variables, lower flare

pain severity (p = 0.03) and making a medication change (p < .0001) were significantly associated with better flare outcomes at the p-value < 0.05 level.

An analysis was done to compare those who did and those who did not have a flare in the preceding 6 months. Participants who flared in the last 6 months were younger (58.5 (13.5) vs. 63.3 (12.6) years, p = 0.0004), had a higher median DAS28-CRP3 score (2.1 (1.7, 2.8) vs. 1.8 (1.5, 2.4), p = 0.001), and were more likely to be seropositive (76% vs. 64%, p = 0.0114). There were some differences in medication use as well. Participants who flared in the last 6 months were more likely to use narcotics (11% vs. 4%, p = 0.0066) and had a higher median methotrexate dosage (20 (15, 25) vs. 17.5 (15, 25) mg per week, p = 0.0227) (Supplementary Table).

A proportional odds logistic regression analysis was performed to determine which factors were associated with a better flare outcome (Figure 2A). In the adjusted model, only flare pain severity and making a medication change to manage a flare were associated with a better flare outcome. Participants with higher pain severity during their most recent flare had lower odds of having a better flare outcome (OR = 0.8, p = 0.02). Those who made any medication change had higher odds of having a better flare outcome (OR = 3.5, p = 0.0008). This result was further reinforced by a backward selection model using the same predictors, flare pain severity (OR = 0.9, p = 0.03) and making a medication change (OR = 3.7, p = 0.0002) remained in the model.

A similar logistic regression model was performed separating out the medication change variable by category. The different medication categories (NSAIDs, corticosteroids, and

DMARDs) showed similar results, where the type of medication changed predicted a better flare outcome compared with no medication change (Figure 2B). A model that made comparisons between the medication categories did not find that any one category was more likely to predict better outcomes.

An additional proportional odds logistic regression analysis was run that included a subset of subjects with a prior DAS28-CRP3 score (n=110) to evaluate whether previous disease activity affected post flare RA symptoms. Making any medication change was still the strongest factor affecting post flare RA symptoms (OR 4.0, 95% CI [1.5,10.6]). Adding this variable did not alter the findings of the main model. Additionally, among the 110 patients who had consecutive DAS28-CRP3 scores, there was little within patient difference of scores (mean 0.11 (1.12), p = 0.33 Wilcoxon signed rank test for paired data).

Discussion:

In this study, flares occurred frequently, and most patients who experienced a flare had more than one in the last 6 months. Nearly three quarters of the patients who flared used home-based interventions (such as rest, heat or cold) to manage their symptoms; however, only making a medication change was associated with a better flare outcome. More than half of the participants in this cohort modified their medications to manage their flare symptoms; interestingly, most participants who made medication changes did so without seeking clinician input. While most of the medication changes were to NSAID or corticosteroid use, many also modified DMARDs on their own. Having a milder flare also contributed to a better flare

outcome indicating that it is both management and clinical factors that contribute to an improved flare resolution.

A previous study of the BRASS registry by Bykerk et al. (11) reported that a similar percentage of participants modified DMARDs during a flare, and these changes were more likely to have been made by those with longer duration flares. In this analysis, a higher flare pain severity diminished the likelihood of a better flare outcome while medication changes increased that likelihood. Flare duration was influential in Bykerk et al., however, it did not have an influence on flare outcome in this study. It is possible that it, indirectly, had an impact on flare outcome by triggering patients to make a change in pharmacologic therapy. Similar to findings in this analysis, in Bykerk's analysis nearly three-fourths of the patients used either home-based or pharmacologic strategies to manage their flares. They were unable to provide data on whether patients consulted physicians for help managing their flare, but hypothesized that patients often self-manage flares. This study was initiated to address those questions and better understand which strategies contributed to improved flare outcomes, postulating that this might be associated with better long term clinical and functional outcomes.

This analysis found that the majority of individuals who made a medication change to manage their flare symptoms did so without seeking clinical advice. This is similar to findings reported by Hewlett et al. (10) which found that flares were frequently self-managed, and that increasing medication use also commonly occurred without clinical advice. In that study, patients sought help when symptoms could not be contained, or were described as complex whole body experiences. In this analysis, patients were not specifically queried as to why they

may or may not have consulted their physician. More patients made changes to NSAIDs without clinical advice than to DMARDs. Conversely, more patients who changed their DMARDs sought clinical advice compared with those who made NSAID or corticosteroid changes. Nevertheless, all medications have possible adverse effects and clinical input may improve patient safety. This illustrates the need to understand whether accessibility issues or self-efficacy factor into patients' decision making process when modifying medications. Given how frequently patients self-manage their flares, it could be beneficial for clinicians to consider a prespecified plan with their patients on how to better manage their symptoms and when to call for clinical advice.

Even though there has been some research on flare management strategies (11), little is known about predictors of better flare outcomes. Flares occur frequently in RA, and research has demonstrated that they are associated with worse long-term clinical outcomes, such as lower functional status and radiographic progression (3, 4). There is a need for additional research on how patients manage their flares and which strategies contribute to improved long term outcomes. The results of this study support the finding that, in the short term, individualized drug therapy adjustments may be an effective way to manage flares.

This study has several limitations. This cohort is mostly composed of patients in remission or with low disease activity, thus it is difficult to extend these findings to newly diagnosed RA or moderate to high disease activity groups. Similarly, the cohort is predominantly white and highly educated (college or graduate school degree). These findings may not be generalizable to less educated or non-Caucasian populations. Additionally, the long-term effects of patients making self-initiated medication changes cannot be assessed due to the

cross-sectional design. Another limitation of this analysis is that it is based on patients' recall of their flare(s) in the last 6 months, which is less reliable than real time reporting of flare intensity or having DAS28-CRP3 scores before and after the flare. Furthermore, having had some information about an individual's immediate pre-flare pain level may have helped shed light on their choice of management strategies. Nevertheless, a strength of this analysis is its ability to detail the most effective patient-initiated strategies for flare management, which has not been previously studied in depth.

In conclusion, this study demonstrates that patients, even those in low disease activity, can experience several flares in a 6-month time period. Patients implemented home-based and/or pharmacological interventions to manage their flares and patients who managed their flare symptoms with a medication change often did so without clinician input. Better flare outcomes were associated with making a medication change, of any type, and having lower pain severity during the flare. These findings help explain how a patient's self-management of flares contribute to better flare outcomes and inform future initiatives on flare management. Future studies should focus on the reasons why patients initiate medication changes for flare management without contacting their rheumatologist and whether doing so is associated with any long term adverse events. This would illuminate the best methods to maximize patient safety through more proactive clinical engagement or an education module to optimize patients self-initiated flare management strategies.

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Disclosures/Conflict of Interest Statement:

- Taysir Mahmoud has no conflicts of interest to report.
- Jie Huang has no conflicts of interest to report.
- Michelle Frits has no conflicts of interest to report.
- Christine Iannaccone has no conflicts of interest to report.
- Dr. Bykerk received <$10,000 in consultancies from Amgen, Pfizer, Bristol-Myers Squibb, and UCB.
- Dr. Bingham has no conflicts of interest to report.
- Dr. Weinblatt receives <$10,000 in consultancies from AbbVie, Amgen, Novartis, Roche, GlaxoSmithKline, Merck, Samsung, Crescendo Bioscience, Gilead, Pfizer, and UCB. Also, receives >$10,000 in consultancies from Lilly and Bristol-Myers Squibb.
- Dr. Shadick receives <$10,000 in consultancies from Bristol-Myers Squibb.

Table 1. Demographics and Clinical Characteristics of Study Cohort (n=185)

Baseline Characteristics	Values
Age (years), mean (SD)	58.5 (13.5)
Female, n (%)	159 (86)
White, n (%)	171 (93)
Education, n (%) High school degree College degree Graduate degree	 51 (28) 88 (48) 46 (25)
Disease duration (years), median (IQR)	15 (9, 24)
DAS-CRP3, median (IQR)	2.1 (1.7, 2.8)
Seropositive, n (%)	119 (76)
Anti-CCP positive, n (%)	104 (68)
RF positive, n (%)	106 (72)
Oral Corticosteroids, n (%) Prednisone dose (mg/day), median (IQR)	42 (23) 5 (2.5, 6.5)
NSAIDs, n (%)	68 (37)

Narcotics, n (%)	20 (11)
Biologics, n (%)	117 (63)
TNF inhibitor, n (%)	80 (68)
Methotrexate, n (%)	105 (57)
Methotrexate dose (mg/week), median (IQR)	20 (15, 25)

Table 2. Description of Flares and Flare Management Strategies (n=185)

Characteristics	Value
Number of flares in last 6 months, median (IQR)	2 (1, 4)[a]
Severity of most recent flare (0-10 scale, 10 severe pain), median (IQR)	7 (5, 8)[a]
Duration of most recent flare, n (%)	
Less than 1 day	24 (13%)
1-3 days	86 (47%)
4-6 days	20 (11%)
1-2 weeks	23 (12%)
More than 2 weeks	32 (17%)
Medication change (new or increased) for flare, n (%)	103 (56%)
NSAIDs	50 (49%)
Oral Corticosteroids	28 (27%)
DMARDs	22 (21%)
Narcotics	3 (3%)
Home management, n (%)	133 (72%)
Rest	81 (61%)
Applied heat and/or cold	80 (60%)

Assistive device (splint/brace/bandage)	26 (20%)
Massage	17 (13%)
Exercise	16 (12%)
Herbal supplement/vitamin	9 (7%)
Physical therapy exercises	6 (5%)
Other	7 (5%)
Clinical consultation, n (%)	43 (23%)
Rheumatologist	36 (84%)
Primary Care Physician	3 (7%)
Chiropractor	3 (7%)
Inpatient	1 (2%)
Occupational therapist	1 (2%)
Physical therapist	1 (2%)
Urgent care/emergency room	1 (2%)
Pain management specialist	1 (2%)
Acupuncture	1 (2%)
Psychologist	1 (2%)

a Total number is n=183

Table 3. Type of Medication Change for Flare Management According to Type of Consultation (n=103)

Medication Category	With Clinical Consult n (%)	Without Clinical Consult n (%)	Medication Type Total (n)
NSAIDs	7 (14%)	43 (86%)	50
Oral Corticosteroids	13 (46%)	15 (54%)	28
DMARDs	15 (68%)	7 (32%)	22
Biologics	9 (75%)	3 (25%)	12
Non-Biologics	10 (71%)	4 (29%)	14
Narcotics	1 (33%)	2 (67%)	3
Consultation Type Total	31 (30%)	72 (70%)	

Medication Categories not mutually exclusive

Table 4. Univariate Comparisons of Flare Outcomes by Clinical and Demographic Variables

	Worse (n=22)	Unchanged (n=125)	Better (n=38)	p-value
Age[a]	55.0 (13.7)	58.5 (13.2)	60.5 (14.5)	0.32
Female[b]	21 (95%)	103 (82%)	35 (92%)	1.00
Number of flares[c]	1.5 (1, 3)	2 (1, 4)	2 (1, 4.5)[d]	0.19
Flare pain severity[c]	8 (7, 9)	7 (5, 8)	7 (5, 8)[d]	**0.03**
With home management[b]	21 (95%)	85 (68%)	27 (71%)	0.11
With clinical consultation[b]	5 (23%)	24 (19%)	13 (34%)	0.21
With medication change[b]	5 (23%)	69 (55%)	29 (76%)	**< .0001**
Flare duration less than a week[b]	11 (50%)	100 (80%)	19 (50%)	0.39
Previous DAS-CRP3[c,e,f]	2.3 (1.6, 2.8)	2.1 (1.7, 3.0)	2.2 (1.6, 2.9)	0.80
Seropositive[b]	13 (72%)	78 (76%)	28 (80%)	0.80
Education[b]				
High school degree	8 (36%)	29 (23%)	14 (37%)	0.29
College degree	8 (36%)	62 (50%)	18 (47%)	
Graduate degree	6 (27%)	34 (27%)	6 (16%)	
RA duration[b]	15.5 (11 29)	16 (9 24)	13 (9 25)	0.70

a Variables that are normally distributed are represented by mean (SD); ANOVA was used.

b Categorical variables are represented as n (%); Exact Mantel-Haenszel Chi-square test was used.

c Variables that are not normally distributed are represented by median (IQR); Kruskal-Wallis test was used.

d Total number is n=36.

e Total numbers are Worse (n=15), Unchanged (n=78) and Better (n=18).

f Values within the past 15 months

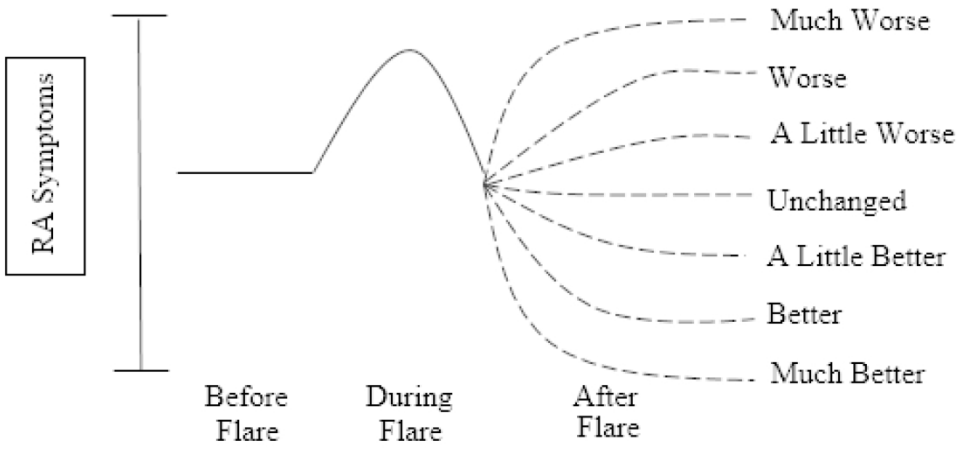

Figure 1: Likert Scale Assessing Post Flare Outcomes

137x69mm (600 x 600 DPI)

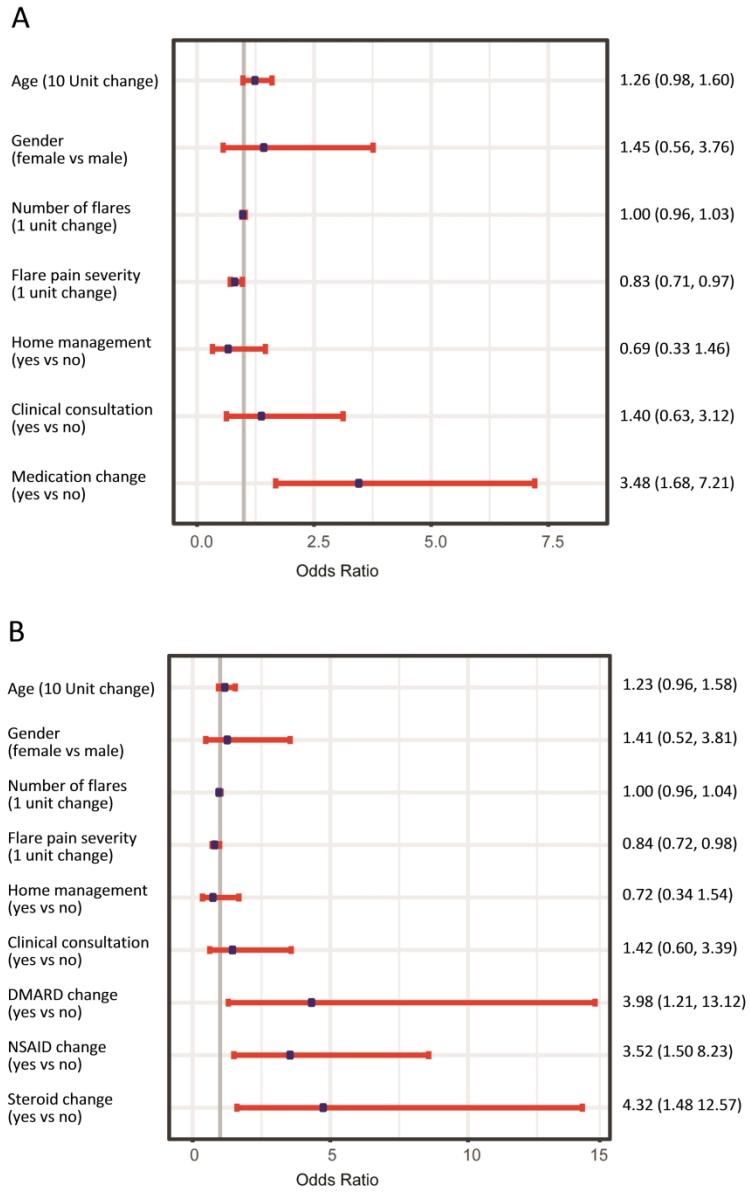

Figure 2: Adjusted Odds Ratios Estimating Better Post Flare Symptoms
A. Adjusted Odds Ratios Estimating Better Post Flare Symptoms (n=181)
B. Adjusted Odds Ratios Estimating Better Post Flare Symptoms by Medication Category (n=169)