Subgrouping of Patients With Rheumatoid Arthritis Based on Pain, Fatigue, Inflammation, and Psychosocial Factors

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Objective. Among patients with rheumatoid arthritis (RA), pain may be attributed to peripheral inflammation or other causes, such as central pain mechanisms. The aim of this study was to use self-report measures and physical examination findings to identify clusters of RA patients who may have different causes of pain as well as different prognoses and treatment options.

Methods. Data from 169 RA patients with pain scores of >0 (on a 10-point numeric rating scale) in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study were analyzed. The patients completed questionnaires on pain, fatigue, and psychosocial factors. A hierarchical agglomerative clustering procedure with Ward's method was used to obtain subgroups. Multivariate analysis of variance was used to determine the contribution of each variable in a cluster. General linear regression models were used to examine differences in clinical characteristics across subgroups. Discriminant analyses were performed to determine coefficients for linear combinations of variables that assigned cluster membership to individual cases.

Results. Three clusters best fit these data. Cluster 1 consisted of 89 individuals with low levels of inflammation, pain, fatigue, and psychosocial distress. Cluster 2 consisted of 57 individuals with minimal inflammation but high levels of pain, fatigue, and psychosocial distress. Cluster 3 consisted of 23 individuals with active inflammatory disease, manifested by high swollen joint counts, high C-reactive protein levels, and high levels of pain and fatigue.

Conclusion. Although most patients had low levels of inflammation, pain, and fatigue, 47.3% continued to report having moderate to high levels of pain and fatigue. Most of these patients had minimal signs of inflammation but high levels of fatigue, pain catastrophizing, and sleep disturbance, indicative of a chronic widespread pain syndrome.

Rheumatoid arthritis (RA) is the most common systemic rheumatic disease, affecting ~1.5 million adults in the United States (1). Historically, physicians have focused on the inflammatory components of the disease (e.g., synovitis), whereas RA patients have cited pain, fatigue, sleep problems, and other quality of life outcomes as their main priorities (2). Both patients and physicians frequently assume that these symptoms are correlated with heightened systemic inflammation. However, many studies indicate that there is significant discordance between inflammation, pain, and fatigue among RA patients (3,4).

In a prospective observational cohort of patients with established RA whose inflammatory disease was in sustained remission, 12% continued to report experiencing clinically significant pain (pain score ≥4 on a 10-

point numeric rating scale) (5). A study that included 2,096 RA patients in a clinic setting and 14,607 RA patients from a survey-based cohort showed that the correlations between fatigue and measures of inflammation were weak (correlation coefficients 0.07–0.11) (6). Similarly, van Hoogmoed and colleagues found no association between fatigue and either the erythrocyte sedimentation rate or the C-reactive protein (CRP) level among 228 patients with RA in an outpatient setting in The Netherlands (7). These observations suggest that patient-reported outcomes, such as pain, fatigue, and sleep problems, should not be automatically attributed to inflammation in an inflammatory disease population such as RA.

Central, noninflammatory pain conditions, such as fibromyalgia, tend to be associated with high levels of pain, fatigue, and sleep problems (8,9). Compared to the general population (10,11), the prevalence of noninflammatory pain conditions is significantly higher in patients with RA, with 15–25% of RA patients also meeting the criteria for fibromyalgia, and an additional 7–15% of RA patients meeting the criteria for chronic widespread pain (12,13). Thus, although it is not debated that RA is an inflammatory condition, many patients with RA also have features (e.g., fatigue, sleep disturbances) that are characteristic of noninflammatory, centralized pain conditions.

The objective of this study was to determine whether subgroups of RA patients could be characterized by a latent construct, representing the involvement of central, noninflammatory pain processes. The latent construct was defined by grouping individuals based on the presence or absence of symptoms indicative of aberrant central nervous system involvement (e.g., fatigue, sleep problems, negative mood, catastrophic attributions, and perception of overall illness burden), using cluster analysis. Whereas factor analysis aggregates variables into patterns based on correlations, cluster analysis categorizes individuals into nonoverlapping subgroups (14). Cluster analysis is particularly valuable in identifying subgroups of patients who may differ in terms of their underlying pathogenic mechanisms and clinical outcomes (15). The identification of clinically distinct phenotypes within a heterogeneous population of RA patients would be the first step in understanding the pathogenic mechanisms underlying each symptom cluster and, ultimately, in identifying potential targets for treatment. The variables used in this cluster analysis were markers of central pain processes, similar to those included in a previous cluster analysis examining the role of central, noninflammatory pain in osteoarthritis (16).

We hypothesized that we could identify at least 3 subgroups of RA patients based on cluster analyses, with the first group comprising RA patients with well-controlled disease, minimal fatigue, and low psychosocial distress, the second group comprising RA patients with active inflammatory joint pain and moderate levels of psychosocial distress, and the third group comprising RA patients with low swollen joint counts and high levels of pain, fatigue, and other symptoms characteristic of a chronic, noninflammatory pain syndrome. This hypothesis was based on clinical observations, as well as on studies in patients with other painful chronic conditions. In these prior studies, similar subgroups were identified, consisting of 1) participants predominantly affected by peripheral pain generators (e.g., joint inflammation and/or mechanical and structural markers), and 2) participants in whom inflammation and/or mechanical factors appear to have minimal impact compared to the influence of central, noninflammatory pain processes (16,17). Additional subgroups may also exist. For example, other reports have described a group of patients with high levels of depression but low levels of other symptoms (16,17). However, given the low levels of depression in our patient population (18), we did not expect to identify this particular subgroup in our cluster analysis.

PATIENTS AND METHODS

Study population. The study population was derived from a subgroup of the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS). The BRASS involves a prospective observational cohort of >1,300 participants over the age of 18 years whose diagnosis of RA was confirmed by a board-certified rheumatologist (19). Of these participants, 208 participated in a substudy to examine the effects of widespread pain on functional status. Exclusion criteria for the current study included the following: 1) absence of pain (average pain severity score of 0 on the Brief Pain Inventory [BPI]), and 2) incomplete data for any of the clustering variables. Written informed consent was obtained from all participants for both the BRASS study and for the substudy on widespread pain and functional status. This study was approved by the Partners Institutional Review Board.

Measures. *Inflammation.* Board-certified rheumatologists performed 28-joint counts to assess tenderness and swelling. Both the physicians and the patients also provided global assessments of disease activity (on 0–100 numeric rating scales). Samples of blood were collected for a standard laboratory panel, including measurement of the CRP level. Based on these measures, the Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) was calculated (20).

Pain. To quantify pain intensity, we used the average pain severity score on the short form version of the BPI (BPI-sf). The BPI-sf is a validated, 9-question survey that

assesses the sensory and reactive aspects of clinical pain. The sensory portion includes questions regarding the severity of pain on average (the average BPI-sf pain severity score) as well as the severity of pain "at its worst," "at its least," and "right now" (21). We also measured the distribution of nonjoint pain using the Widespread Pain Index (WPI), which assesses pain in 19 areas (22). The distribution of joint pain was quantified using the joint score from the Rheumatoid Arthritis Disease Activity Index (RADAI) (23,24).

Mood. Depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item questionnaire validated in physically ill patients (25).

Fatigue. The fatigue numeric rating scale on the Multidimensional Health Assessment Questionnaire (MD-HAQ) was used to assess fatigue. Specifically, the MD-HAQ presents the question, "How much of a problem has fatigue or tiredness been for you in the past week?" (26).

Illness burden. We quantified illness burden using a count of patient-reported symptoms of headaches, migraines, poor concentration, poor memory, and poor word-finding. This measure was based on the concept of illness burden described by Murphy et al in a similar cluster analysis of symptoms in osteoarthritis patients (16).

Sleep problems. Sleep problems were measured using the Medical Outcomes Study (MOS) Sleep Problems Index II, a validated, 12-item questionnaire that assesses sleep problems in chronically ill populations (27).

Catastrophizing. The Pain Catastrophizing Scale (PCS), a validated 13-item scale that assesses negative emotional and cognitive processes (e.g., helplessness, rumination, pessimism, and magnification of symptoms), was used to evaluate catastrophizing (28).

Polysymptomatic features of chronic widespread pain. Polysymptomatic features of chronic widespread pain (e.g., fatigue, somatic symptoms, cognitive and sleep problems, decreased pain threshold, etc.), referred to by Wolfe as "fibromyalgianess" (29), were measured by summing the WPI and the Symptom Severity Score, a measure that also assesses the presence of headaches, abdominal pain, and depression. Both the WPI and the Symptom Severity Score are components of the American College of Rheumatology 2010 diagnostic criteria for fibromyalgia (22).

Statistical analysis. Descriptive measures, including median values, interquartile ranges (IQRs), and frequencies, were determined. Based on Formann's method (30), which states that the maximum number of clustering variables should be *m*, where sample size = 2^m, the number of clustering variables was limited to 7 (31,32). Clustering variables were chosen based on those reported in previous studies, in which the presence of depression–pain–fatigue clusters and fatigue–insomnia–pain clusters has been described in populations of patients with chronic disease, such as cancer and osteoarthritis (16). In addition, catastrophizing was included as a measure of negative cognitive and emotional processes, in accordance with a study examining psychological subgrouping of patients with low back pain (33).

The swollen joint count was included as a measure of joint inflammation. The swollen joint count was chosen to represent RA-related inflammation because 1) the number of swollen joints is considered to be an objective measure of inflammation, whereas the tender joint count and physician's global assessment of disease activity may be influenced by other factors, such as widespread pain sensitivity, and 2) the number of swollen joints directly reflects the presence of active inflammation at joint sites, whereas the CRP level is a marker of overall systemic inflammation and the Sharp/van der Heijde radiographic erosion score (34) reflects the extent of cumulative damage, but not acute inflammation.

A hierarchical agglomerative clustering procedure with Ward's method, incorporating squared Euclidian distances, was used to obtain the clusters. To determine the optimal number of clusters, we used the cubic clustering criterion (35) and constructed a dendrogram to visually inspect the distances between clusters.

To determine the relative contribution of each clustering variable, all variables were included in a multivariate analysis of variance (MANOVA) model with the cluster assignment as the independent variable. The clustering variables were standardized by subtracting each data point from the mean and dividing by the standard deviation. This standardization process minimized deviations from normality, but some variables, particularly the swollen joint count, illness burden, and pain catastrophizing, continued to have a skewed distribution. In general, the F-test, which is the basis of the MANOVA, is robust to non-normal distributions, particularly when the sample size is large, because the sampling distribution of the mean value approximates the normal distribution (central limit theorem) (36,37). We used the Wilks' λ as an evaluation of the dissimilarity measure between clusters. Unadjusted general linear regression models were used to identify differences in clustering variables and in sociodemographic and clinical characteristics across clusters.

A discriminant analysis was performed to examine cluster groupings. To define the discriminant functions, a constant value and 7 coefficients (one for each clustering variable) were calculated for each cluster. To determine the relative contribution of each clustering variable to the discriminant functions, the total canonical structure was analyzed. The proportion of misclassified observations in each group was assessed. All statistical analyses were performed using the SAS software package version 9.2 (SAS Institute).

RESULTS

Characteristics of the patients. Among the >1,300 RA patients in the BRASS, 208 completed baseline questionnaires for the substudy examining the effects of widespread pain on functional status. Of these 208 patients, 13 (6.3%) were excluded because they did not report any pain, and 26 (12.5%) were excluded due to incomplete data for at least one clustering variable. The majority of missing data were from participants who did not complete the PCS, the MD-HAQ fatigue scale, or questions used to calculate illness burden. These 26 participants did not differ from those who had complete data for any of the clustering variables assessed (swollen joint count, BPI-sf average pain intensity, HADS de-

Table 1. Clinical characteristics of the rheumatoid arthritis study population (n = 169)*

Age, median (IQR) years	58.0 (50.0–65.0)
Female, no. (%)	136 (80.5)
White, no. (%)	157 (94.6)†
BMI, median (IQR) kg/m²	26.1 (23.4–29.8)
Disease duration, median (IQR) years	13.0 (7.0–23.0)
Rheumatoid factor positive, no. (%)	104 (62.7)†
DAS28-CRP, median (IQR)	2.6 (2.0–3.8)
BPI-sf pain intensity score, median (IQR)	3.0 (2.0–5.0)
Fatigue score, median (IQR)	35.0 (15.0–65.0)
Current DMARD use, no. (%)	149 (88.2)
Current biologic DMARD use, no. (%)	98 (58.0)
Current synthetic DMARD use, no. (%)	108 (63.9)

* IQR = interquartile range; BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; BPI-sf = short form version of the Brief Pain Inventory; DMARD = disease-modifying antirheumatic drug.
† Percentages of patients are derived from a denominator of 166, due to missing data.

pression score, MD-HAQ fatigue score, illness burden, MOS Sleep Problems Index II score, or PCS score).

Of the 169 RA patients included in this analysis, 136 (80.5%) were female and 157 (94.6%) of 166 (3 patients did not provide information on race) were white (Table 1). The median disease duration was 13.0 years (IQR 7.0–23.0 years). Of 166 patients (3 were missing data regarding rheumatoid factor status), 104 (62.7%) were rheumatoid factor positive. The median DAS28-CRP score was 2.6 (IQR 2.0–3.8), and the median MD-HAQ fatigue score was 35 (IQR 15.0–65.0). The median BPI-sf pain score was 3.0 (IQR 2.0–5.0).

Cluster analysis. The cluster analyses identified 3 subgroups of RA patients (Figure 1). Cluster 1 consisted of the largest number of patients (n = 89; 52.7%) and was characterized by the lowest swollen joint counts (median 0.0, IQR 0.0–1.0; each $P < 0.0001$ versus cluster 2 or cluster 3) (Table 2). Patients in cluster 1 also had the lowest levels of fatigue (each $P < 0.0001$ versus cluster 2 or cluster 3) and lowest levels of depression ($P = 0.01$ versus cluster 2 and $P = 0.004$ versus cluster 3). Cluster 2 consisted of 57 patients (33.7%) and was characterized by low swollen joint counts (median 2.0, IQR 0.0–4.0) and high levels of fatigue, pain catastrophizing, and sleep problems. Cluster 3 consisted of 23 patients (13.6%) and was characterized by high swollen joint counts and moderate levels of fatigue, pain catastrophizing, and sleep problems.

MANOVA confirmed that the clustering variables were significantly different between the 3 groups (Wilks' λ = 0.08, F[df 14, 320] = 60.0, $P < 0.0001$). These differences were confirmed in unadjusted general linear regression models, which showed statistically significant differences in all clustering variables ($P < 0.03$), except for illness burden ($P = 0.06$), between the groups.

Clinical variables among subgroups. *Cluster 1.* Compared to clusters 2 and 3, patients in cluster 1 had the lowest WPI scores (median 2 in cluster 1 versus median 5 in clusters 2 and 3; $P = 0.0006$ versus cluster 2 and $P = 0.005$ versus cluster 3), consistent with the localized distribution of pain in these patients. Measures of inflammatory disease activity were also significantly lower in cluster 1 than in clusters 2 and 3 (Table 3). The median DAS28-CRP score was 2.4 in cluster 1, compared to a median score of 2.9 in cluster 2 ($P = 0.0005$) and a median score of 5.1 in cluster 3 ($P \leq 0.0001$), and the median physician's global assessment of disease activity score was 10 in cluster 1, compared to a median score of 20 in cluster 2 ($P = 0.02$) and a median score of 40 in cluster 3 ($P \leq 0.0001$). Similarly, the median patient's global assessment of disease activity score was 15 in cluster 1, compared to a median score of 30 in clusters 2 and 3 ($P \leq 0.0001$ versus cluster 2 and $P = 0.001$ versus cluster 3). Patients in cluster 1 also had low CRP levels (median level 1.7 mg/liter), low Sharp/van der Heijde radiographic erosion scores (median score 1), and low Sharp/van der Heijde radiographic joint space narrowing scores (median score 2), although these values were not significantly different from those in cluster 2.
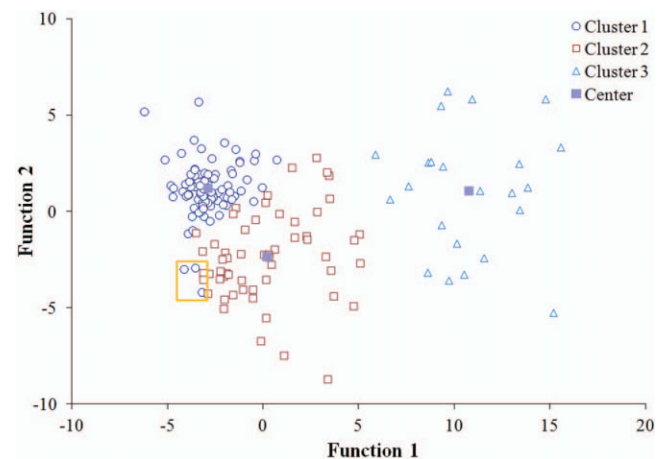

Figure 1. Canonical discriminant functions used to differentiate clusters of patients with established rheumatoid arthritis based on clustering analyses. Two discriminant functions significantly distinguished the 3 clusters, accounting for 88.3% and 11.7% of the variance (each $P < 0.0001$). Three potential outliers (designated in the orange square) were noted.

Table 2. Clinical characteristics of the patients, used as variables to define the clusters*

Characteristic	Cluster 1 (n = 89)	Cluster 2 (n = 57)	Cluster 3 (n = 23)	P†
Swollen joint count	0.0 (0.0–1.0)	2.0 (0.0–4.0)‡	12.0 (10.0–14.0)‡§	<0.0001
BPI-sf pain intensity	3.0 (2.0–4.0)	3.0 (2.0–5.0)‡	3.0 (2.0–5.0)	0.03
Fatigue	20.0 (10.0–30.0)	70.0 (50.0–80.0)‡	60.0 (25.0–80.0)‡§	<0.0001
Sleep problems	27.2 (16.1–41.1)	38.3 (27.2–46.7)‡	35.6 (17.5–47.8)	0.009
HADS depression	3.0 (1.0–5.0)	4.0 (1.0–7.0)‡	5.0 (2.0–8.0)‡§	0.004
Illness burden	1.0 (0.0–3.0)	2.0 (1.0–3.0)‡	1.0 (0.0–2.0)§	0.06
Pain catastrophizing	6.0 (1.0–12.0)	12.0 (5.0–21.0)‡	9.0 (3.0–18.0)	<0.0001

* Values are the median (interquartile range). BPI-sf = short form version of the Brief Pain Inventory; HADS = Hospital Anxiety and Depression Scale.
† P value for overall difference, signifying any one cluster is different from the others.
‡ Significantly different from cluster 1 ($P \leq 0.05$).
§ Significantly different from cluster 2 ($P \leq 0.05$).

Table 3. Sociodemographic and clinical characteristics of the rheumatoid arthritis patients based on clusters*

Characteristic	Cluster 1 (n = 89)	Cluster 2 (n = 57)	Cluster 3 (n = 23)	P†
Sociodemographic				
Age, years	58.0 (50.0–65.0)	56.0 (49.0–64.0)	60.0 (52.0–70.0)	0.23
Female, no. (%)	70 (78.7)	47 (82.5)	19 (82.6)	0.82
White, no. (%)‡	84 (95.5)	51 (91.1)	22 (100)	0.25
BMI, kg/m^2	26.2 (22.9–29.6)	25.7 (23.3–29.1)	28.3 (24.8–31.1)	0.14
Clinical				
Disease duration, years	12.0 (7.0–21.0)	13.0 (8.0–22.0)	22.0 (13.0–27.0)§	0.006
Rheumatoid factor positive, no. (%)¶	51 (58.0)	34 (61.8)	19 (82.6)	0.09
DAS28-CRP	2.4 (1.7–3.0)	2.9 (2.2–3.8)#	5.1 (4.5–5.9)§	<0.0001
CRP, mg/liter	1.7 (0.6–2.9)	1.7 (0.6–4.8)	2.6 (1.5–22.2)§	0.0003
Tender joint count (of 28 joints)	1.0 (0.0–3.0)	2.0 (0.0–6.0)	14.0 (12.0–16.0)§	<0.0001
Patient's global assessment of disease activity (scale 0–100)	15.0 (5.0–25.0)	30.0 (15.0–60.0)#	30.0 (20.0–50.0)#	<0.0001
Physician's global assessment of disease activity (scale 0–100)	10.0 (10.0–30.0)	20.0 (10.0–30.0)#	40.0 (30.0–50.0)§	<0.0001
Sharp/van der Heijde erosion score (scale 0–160)	1.0 (0.0–10.0)	1.0 (0.0–4.0)	12.0 (1.0–31.0)§	0.03
Sharp/van der Heijde joint space narrowing score (scale 0–120)	2.0 (0.0–23.0)	2.0 (0.0–18.5)	26.0 (2.0–53.0)§	0.002
RADAI joint count (scale 0–10)	1.0 (0.4–1.9)	1.7 (0.8–2.9)#	2.7 (1.0–3.3)#	0.0007
Widespread Pain Index (scale 0–19)	2.0 (1.0–5.0)	5.0 (2.0–7.0)#	5.0 (2.0–8.0)#	0.0004
Polysymptomatic features of chronic widespread pain (scale 0–31)	7.0 (4.0–9.0)	10.0 (7.0–14.0)#	11.0 (6.0–15.0)#	<0.0001
Medications, no. (%)				
Current use				
DMARDs	85 (95.5)	47 (82.5)#	17 (73.9)#	0.004
Biologic DMARDs	54 (60.7)	33 (57.9)	11 (47.8)	0.54
Synthetic DMARDs	64 (71.9)	32 (56.1)#	12 (52.2)#	0.07
Corticosteroids	14 (15.7)	8 (14.0)	5 (21.7)	0.69
Past use				
DMARDs	89 (100)	57 (100)	23 (100)	–
Biologic DMARDs	61 (68.5)	44 (77.2)	20 (87.0)	0.16
Synthetic DMARDs	89 (100)	57 (100)	23 (100)	–

* Except where indicated otherwise, values are the median (interquartile range). BMI = body mass index; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; RADAI = Rheumatoid Arthritis Disease Activity Index; DMARDs = disease-modifying antirheumatic drugs.
† P value for overall difference, signifying any one cluster is different from the others.
‡ Percentages of patients are derived from denominators of 88, 56, and 22 for clusters 1, 2, and 3, respectively, due to missing data.
§ Significantly different from clusters 1 and 2 ($P \leq 0.05$).
¶ Percentages of patients are derived from denominators of 88, 55, and 23 for clusters 1, 2, and 3, respectively, due to missing data.
# Significantly different from cluster 1 ($P \leq 0.05$).

Cluster 2. Similar to cluster 1, patients in cluster 2 had low CRP levels (median 1.7 mg/liter), low tender joint counts (median 2), low Sharp/van der Heijde radiographic erosion scores (median 1), and low Sharp/ van der Heijde radiographic joint space narrowing scores (median 2). However, patients in cluster 2 had significantly higher DAS28-CRP scores than did patients in cluster 1 ($P = 0.0005$), likely because the patient's global assessment of disease activity scores were higher in cluster 2 ($P < 0.0001$). Patients in cluster 2 also had significantly higher physician's global assessment of disease activity scores ($P = 0.02$) and more widespread distribution of pain, as assessed by the WPI score ($P = 0.0006$), as compared to cluster 1.

Cluster 3. Compared to clusters 1 and 2, patients in cluster 3 had significantly higher levels of inflammatory disease activity, as assessed by the DAS28-CRP score ($P < 0.0001$), the CRP level ($P = 0.0001$), the tender joint count ($P < 0.0001$), and the physician's global assessment of disease activity ($P < 0.0001$). Although the patient's global assessment of disease activity scores were significantly higher in cluster 3 compared to cluster 1 ($P = 0.001$), the patient's global assessment of disease activity scores were not higher in cluster 3 compared to cluster 2. Measures of joint destruction were consistently higher in cluster 3 compared to clusters 1 and 2 ($P = 0.009$ for erosions and $P = 0.0005$ for joint space narrowing). Moreover, patients in cluster 3 had a significantly longer disease duration ($P = 0.002$) and significantly more patients in cluster 3 were currently taking disease-modifying antirheumatic drugs (DMARDs) ($P = 0.04$) when compared to patients in clusters 1 and 2. Past DMARD use did not differ across the groups.

Discriminant functions. The clusters were distinguished by 2 discriminant functions, corresponding to 88.3% and 11.7% of the variance (each $P < 0.0001$). The coefficients for the discriminant functions for each cluster are reported in Table 4. Function 1 was mostly influenced by the swollen joint count and fatigue, whereas function 2 was mostly influenced by fatigue and pain catastrophizing. Function 1 was primarily responsible for distinguishing clusters 1 and 2 from cluster 3, whereas function 2 was required to distinguish between clusters 1 and 2. Using discriminant function analysis, we were able to correctly categorize 95.9% of the participants into the groups determined by cluster analysis.

Outliers. Three potential outliers were noted. Each was grouped into cluster 1, although, based on graphic presentation, the characteristics of these 3 patients who were outliers appeared more similar to those

Table 4. Discriminative analysis of cluster characteristics*

Variable	Cluster 1	Cluster 2	Cluster 3
Constant	−2.31	−1.95	−18.8
Swollen joint count	−3.74†	0.09	14.26†
BPI-sf pain intensity	0.59	−0.47	−1.11
Fatigue	−2.57†	2.35†	4.13†
Sleep problems	1.18	−0.92†	−2.28
HADS depression	0.12	−0.12	−0.16
Illness burden	−0.03	0.14	−0.24
Pain catastrophizing	−0.69	0.62	1.14

* Values are the coefficients for discriminant functions for each cluster. BPI-sf = short form version of the Brief Pain Inventory; HADS = Hospital Anxiety and Depression Scale.
† Highest variable loads for each cluster.

of patients in cluster 2 (Figure 1). These individuals had no swollen joints but had high levels of pain catastrophizing, sleep problems, and fatigue. Using discriminant analyses, 2 of these 3 patients were ultimately recategorized into cluster 2.

DISCUSSION

The theory underlying this study is that symptoms such as pain, fatigue, and sleep problems may be predominantly associated with either 1) active inflammatory disease or 2) a chronic, noninflammatory pain syndrome. Our results characterized 3 distinct subgroups of RA patients on the basis of inflammatory disease activity (swollen joints), co-occurring symptoms (e.g., pain, fatigue, sleep problems), cognitive and emotional factors (e.g., catastrophizing and depression), and functional illness burden. Although the majority of the RA patients in this cohort were doing well (cluster 1), a significant number continued to have multiple areas of pain and difficulties with fatigue, sleep, and catastrophizing. Of the 80 patients who had significant problems in these areas, 23 (28.8%) had active inflammatory disease, manifested by elevated swollen joint counts, elevated tender joint counts, and increased serum levels of CRP (cluster 3). In contrast, the remaining 71.2% (cluster 2; n = 57) had low levels of inflammatory disease activity, despite having the worst patient's global assessment of disease activity scores and the highest levels of fatigue and pain catastrophizing of all 3 groups. These patients also had low Sharp/van der Heijde radiographic erosion and joint space narrowing scores, indicating that joint damage was not a major cause of the pain and mood disturbances. Taken together, these results suggest that cluster 2 represents a subgroup of RA patients who likely have a more centralized chronic widespread pain syndrome, such as fibromyalgia, in addition to RA.

Several other studies have used cluster analysis to identify subgroups of RA patients, but, within each study, the clustering variables were limited to one dimension (e.g., pain behaviors or psychosocial measures) (38,39). To our knowledge, none of those prior studies have included a wide assessment of clinical factors, such as inflammatory disease activity, cognitive and emotional factors, and functional illness burden, as we did in our study. The study most similar to ours was a cluster analysis of 104 RA patients that was based on observed pain behaviors (guarding, bracing, active rubbing, grimacing, sighing, and rigidity) (38). That study yielded 5 subgroups with varying behavior patterns, ranging from those with very few pain behaviors to those with multiple distressing behaviors. Although the subgroups differed in behavior patterns, all 5 subgroups of patients reported having a similar intensity of pain, highlighting that there may be a disconnect between physical responses to pain and verbal reports of pain.

In a large longitudinal study, cluster analysis was used to classify 561 RA patients based on 5 psychosocial measures (ability to cope, RA impact, health satisfaction, adequacy of social support, psychological mastery) (39). Those authors identified 3 subgroups of psychosocial risk, which were predictive of the development of depression, poor functional status, and global pain over an 8-year period. These results showcase the ability of cluster analysis to identify clinically meaningful subgroups. Notably, no previous studies have used cluster analysis to identify subgroups with similar sources and patterns of pain in an inflammatory arthritis population, such as RA.

However, in populations of patients with chronic, noninflammatory pain, researchers have frequently identified subgroups of patients with widespread pain and psychosocial impairment in the absence of inflammation and the absence of other obvious causes of pain. A cluster analysis of 104 older women identified 3 distinct groups, which were strikingly similar to the clusters defined in this study: 1) a "healthy" group, 2) a group with high levels of psychosocial distress and illness burden, and 3) a group with poor physical health and moderate levels of psychosocial distress (40). Similarly, in a cohort of 121 patients with chronic neck pain, 3 distinct subgroups were noted, which varied in the severity of psychosocial distress, sleep disorder, and disability (41). In a longitudinal study of 843 pediatric patients with functional abdominal pain, Walker and colleagues used a variety of clustering variables, including pain intensity, gastrointestinal symptoms, coping abilities, catastrophizing, negative affection, and physical

activity, to categorize patients into 3 subgroups, including a "high pain dysfunctional" group of patients in whom there was an associated high risk of functional abdominal pain disorder in adolescence/adulthood (42).

Compared to the cluster analyses done in patients with noninflammatory chronic pain conditions, our results are most similar to those in a study that used cluster analysis to characterize patients with symptomatic osteoarthritis of the knee or hip (16). Both our current study and that prior study identified a group of patients with high levels of pain, fatigue, sleep problems, and mood disturbances, comprising approximately one-third of the study population. In the osteoarthritis study, the chronic widespread pain group also had significantly higher levels of illness burden, assessed by MANOVA. In our study, illness burden was not significantly different between the groups based on MANOVA ($P = 0.06$). The lack of a difference may partially be attributed to our measure of illness burden, which was assessed based on 5 common somatic symptoms, as opposed to the 41 symptoms used in the previous study. Thus, we may not have captured the full spectrum of illness burden. We do note, however, that when the clusters were separately compared with each other using a general linear model, the differences in illness burden between cluster 2 and clusters 1 and 3 were both statistically significant at $P = 0.04$ (Table 2).

Post hoc analyses highlighted key differences between pain measures. Although the BPI-sf average pain severity scores did not differ between groups, clinical pain measures that incorporated the distribution of pain (e.g., the RADAI joint count and the WPI) significantly distinguished cluster 1 from clusters 2 and 3, with patients in cluster 1 having RADAI and WPI scores that were significantly lower than those in patients in the other 2 clusters. However, neither the RADAI joint count nor the WPI significantly differentiated cluster 2 from cluster 3, even though the RADAI and WPI are designed to focus on joint pain and nonjoint pain, respectively. Interestingly, the tender joint count was significantly lower among patients in cluster 2 compared to patients in cluster 3, suggesting that, despite previous reports of flaws in its specificity for assessing arthritis pain (43), the tender joint count may offer greater discriminating capacity compared to either the RADAI or the WPI.

The results of this study have important theoretical and clinical implications. Specifically, our results indicate that, in a population of patients with established RA, many continue to have widespread pain, despite relatively low levels of inflammation. Thus, physicians

should carefully assess symptoms such as fatigue, sleep problems, depression, and pain catastrophizing when evaluating RA patients, particularly if these patients provide high scores of disease activity in the face of low scores for objective measures of inflammation. In theory, this group may be more likely to respond to psychological interventions (e.g., cognitive behavioral therapy, pain-coping skills training) (44) or to medications aimed at treating chronic widespread pain syndromes, such as serotonin norepinephrine reuptake inhibitors and neuroleptic pain medications. Studies are currently underway to examine whether similar medications may be effective for RA patients with stable inflammatory disease activity who continue to have widespread pain and fatigue.

This study does have limitations. Specifically, the generalizability of these findings is limited by the study population, a cohort of patients with established RA (median disease duration 13 years) treated at a single academic medical institution. Among this population, 88% of patients were treated with a DMARD, including 58.0% who were taking biologic DMARDs. The proportion of patients with active inflammatory disease would likely be much higher in a population of patients who are not as intensively treated. Although patients in cluster 3 were significantly less likely than patients in clusters 1 and 2 to be taking a DMARD at the time of the study, all of the patients had been treated with DMARDs in the past. Past biologic DMARD use was not significantly different between the clusters, with 87% of the patients in cluster 3 reporting past use of biologic DMARDs. These results suggest that cluster 3 may consist of patients whose disease was particularly resistant to treatment.

Other limitations include the use of a hierarchical agglomerative clustering technique, which may be influenced by outliers, and the lack of quantitative information about pain mechanisms. Future studies are needed to replicate these findings and to further characterize these patients using quantitative sensory testing techniques. Quantitative sensory testing may help determine whether patients in cluster 2 have measurable differences in central pain regulatory mechanisms, such as loss of conditioned pain modulation, which are associated with chronic widespread pain conditions. The identification of different subgroups of RA patients may lead to a better understanding of the mechanisms causing pain and fatigue in RA, which can facilitate the identification of appropriate treatment targets.

In conclusion, a clustering algorithm based on the swollen joint count, co-occurring symptoms (e.g., pain,

fatigue, sleep problems), psychological distress (pain catastrophizing and depression), and functional illness burden identified 3 groups of patients with established RA. Although most patients were doing well, 47.3% continued to have moderate to high levels of pain, fatigue, and sleep problems. The majority of these patients had low markers of inflammation but high levels of catastrophizing, consistent with the characteristics of a chronic widespread pain syndrome. These results are poignant because they indicate that 1) chronic widespread pain syndromes are common among patients with established RA, 2) active inflammatory disease may account for problems with pain, fatigue, and mood disturbance in only a minority of patients, and 3) chronic widespread pain syndromes are associated with significantly diminished quality of life, even compared to that in patients with active inflammatory disease.

AUTHOR CONTRIBUTIONS

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