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Unmet Needs in Rheumatoid Arthritis: A Subgroup of Patients With High Levels of Pain, Fatigue, and Psychosocial Distress 3 Years After Diagnosis

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Objective. The study objective was to identify subgroups of patients with rheumatoid arthritis (RA) based on their health status 3 years after diagnosis and to assess potential associations to clinical presentation at diagnosis.

Methods. This observational study included patients with RA with 3-year follow-up data from the Swedish Epidemiological Investigation of RA study, collected from 2011 to 2018. Hierarchical agglomerative cluster analysis, based on symptoms of pain, fatigue, sleep quality, mood disturbances, and overall health-related quality of life (HRQoL), was used to identify subgroups 3 years after diagnosis. Modified Poisson regression was used to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for the associations between the subgroups and patient characteristics at diagnosis.

Results. A total of 1055 individuals constituted the study population, of whom 1011 had complete data on the clustering variables and were therefore eligible for analysis (73% women, median age 58 years). The following three clusters were identified: cluster 1 (466 patients with good health status), cluster 2 (398 patients in an intermediate group), and cluster 3 (147 patients with high levels of pain and fatigue together with markedly impaired HRQoL). Cluster 3 was associated to higher baseline pain (RR: 3.71 [95% CI: 2.14-6.41]), global health (RR: 6.60 [95% CI: 3.53-12.33]), and the Stanford Health Assessment Questionnaire (RR: 4.40 [95% CI: 2.46-7.87]), compared with cluster 1 (highest compared with lowest quartiles). An inverse association was seen for baseline swollen joint count (RR: 0.51 [95% CI: 0.34-0.85]).

Conclusion. A subgroup of patients with RA experience high levels of pain, fatigue, and psychosocial distress 3 years after diagnosis. This subgroup already displayed pronounced pain and functional disabilities at diagnosis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and pain, primarily affecting distal joints of the extremities in a symmetric manner (1). The primary goal in the clinical management of RA is to halt the inflammatory process and prevent inflammatory driven cartilage and bone erosions that could lead to irreversible damage of joint structures and subsequent functional impairment (2). During the last few decades, a wide range of new and effective antirheumatic treatments have been made available, making inflammatory remission and retardation of joint destruction feasible goals in the management of RA (3). In the wake of this development, however, other features than inflammatory disease activity have become increasingly important outcomes for many patients with RA (4). These features include the following: persistent pain, fatigue, and various other aspects of physical, emotional, and social well-being and are sometimes collectively referred to as "unmet needs" in RA (5). The importance of these health domains has been underlined in the Rheumatoid Arthritis Impact of Disease score, in which patient perspectives on health concerns in relationship to RA were

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SIGNIFICANCE & INNOVATIONS

- A subgroup of patients with rheumatoid arthritis (RA) experience high levels of pain, fatigue, and psychosocial distress 3 years after diagnosis.
- This subgroup already displayed characteristic features at diagnosis, with high levels of pain and functional disabilities but without a corresponding increase in inflammatory parameters.
- The display of characteristic features at diagnosis suggests that factors related to long-term pain and fatigue are already prevalent at this early stage of disease, which signals that the early identification of patients at risk and the adoption of targeted interventions should be a future priority in the management of these unmet needs in RA.

assessed to construct a patient-reported outcome measure (6). The health domains that received the highest importance among the patients were pain, physical function, fatigue, sleep, physical and emotional well-being, and coping abilities (7).

Pain is one of the cardinal signs of inflammation, and pain in RA can be a symptom of ongoing inflammation. During the course of the disease, however, pain seems to become uncoupled from inflammation for some patients, resulting in persistent pain in spite of resolved inflammation (8). Persistent pain is a major health concern for patients with RA, with negative consequences for physical and social functioning, emotional well-being, and sleep quality (9,10). Pain has also been reported to contribute more to functional disability than has structural joint damage (11). A sustained physical function has in turn been identified by patients with RA as fundamental for maintaining independence and quality of life (12).

Similarly to pain, fatigue is a common feature for patients with RA that can occur in relationship to ongoing inflammation but can also persist independent of inflammation (13). Severe fatigue has been reported in up to 41% of individuals with RA (14), and fatigue has been associated to impaired physical function, worse mental health, higher levels of stress, and increased health care consumption (15). Sleep disturbances, which have been associated to both disease activity and pain (16,17), are also a health concern for patients with RA (6,18). Impaired sleep is also known to pose detrimental effects on well-being and impact negatively on professional, social, and family life (19,20).

In all, health aspects other than inflammatory disease activity cause a substantial burden of illness for many patients with RA. These features often coexist, interact, and influence each other. Although the magnitude and significance of each individual symptom varies between individuals, there is a collective impact on overall health status. The objective of this observational study was to use cluster analysis as an unbiased approach for identifying subgroups of patients based on their health status 3 years after RA diagnosis and then to assess risk factors associated to the identified subgroups.

PATIENTS AND METHODS

Study population

Our study population consisted of participants from the Epidemiological Investigation of RA (EIRA) study, who had been followed up through a survey of clinical symptoms and lifestyle factors at 3 years after diagnosis. The case–control study EIRA started in 1996 has since been recruiting incident RA cases from the south and middle parts of Sweden (21). Since October 2011, participants in EIRA have also received a follow-up questionnaire 3 years after inclusion. The study population for the present study consisted of all EIRA participants who completed the 3-year questionnaire between October 2011 and August 2018. During this period, the overall response rate for the questionnaire was 76%. All patients in EIRA were diagnosed with RA according to the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European Alliance of Associations for Rheumatology criteria. Through the unique personal identity number given to Swedish residents, we linked the data from EIRA to the Swedish Rheumatology Quality Register (SRQ). The SRQ is used at most rheumatology clinics throughout Sweden for clinical follow-up and quality control and has an estimated coverage of greater than 85% of the prevalent RA cases in Sweden (22). The SRQ contains data on disease activity measures and medications, registered at diagnosis and follow-up visits. Virtually all patients included in EIRA also accepted participation in the SRQ.

Variables for cluster analysis, from the 3-year follow-up in EIRA

Health status was assessed in five domains (pain, fatigue, sleep status, mood, and health-related quality of life [HRQoL]) that included a total of 18 variables: joint pain intensity, joint pain disability, nonjoint pain intensity, nonjoint pain disability, painful nonjoint body areas, fatigue, sleep problems, nonrestorative sleep, the two Hospital Anxiety and Depression Scale (HADS), and eight domains of the Short Form (SF)-36. The variables are further described per category below.

Pain. We assessed five different aspects of pain: joint pain, nonjoint pain, pain intensity, pain disability, and the distribution of nonjoint pain. Pain intensity and pain disability were included as separate measures because a discrepancy between pain intensity and pain disability has previously been reported (23). Pain intensity and disability were assessed on visual analog scales (VASs)—0-100 mm—with higher scores indicating worse outcome. The patients were asked to rate their pain intensity from "No pain" to "Worst imaginable pain" and to state to what extent

the pain had interfered with their work or household chores during the preceding week, from "Not at all" to "Very much."

We included joint pain and nonjoint pain separately to distinguish symptoms of localized joint pain from symptoms of generalized pain. Joint pain intensity was compiled as the average of four individual VAS scores (0-100 mm, with higher scores indicating worse outcome), where the patients were asked to rate their a) pain at its minimum, b) pain at its maximum, c) current pain, and d) pain on average during the preceding week, in analogy with the Brief Pain Inventory "Pain Intensity" score (24). Nonjoint pain intensity and disability were assessed on a separate single VAS (0-100 mm). The number of painful nonjoint body areas (0-24) was assessed on a schematic pain mannequin, subdivided into 24 nonjoint regions. This mannequin has previously been used to assess widespread nonjoint pain in early RA (25).

Fatigue. Fatigue was assessed on a VAS (0-100 mm), in which the patients were asked "How much of a problem has fatigue been for you in the past week?" ranging from "No problem" (=0 mm) to "Worst imaginable problem" (=100 mm). Fatigue assessed on a VAS has been found to correlate at least as well to clinical variables and change over time as more lengthy fatigue questionnaires (26).

Sleep status. Sleep status was assessed for two domains, "sleep problems" and "nonrestorative sleep," derived from the Karolinska Sleep Questionnaire (27). The domain of "sleep problems" consisted of four questions assessing the extent of difficulty falling asleep, repeatedly waking up, having easily disturbed sleep, and waking up too early, depicted on a 6-level ordinal scale ranging from "1 = Never" to "6 = Always." The total sleep problems score was the arithmetic mean of the four questions. The domain of "nonrestorative sleep" consisted of two questions concerning difficulties waking up and waking up not well-rested, depicted on the same 6-level ordinal scale. The total nonrestorative sleep score was the arithmetic mean of the two questions.

Mood. Traits of anxiety and depression were assessed using HADS, a 14-item questionnaire validated in physically ill patients (28). The individual subscales for anxiety and depression range from 0 to 21, with higher scores indicating worse symptoms.

HRQoL. Overall HRQoL was assessed through the SF-36. The component scores were calculated according to instructions (29). The SF-36 measures physical and mental aspects of health in the following eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The semicontinuous scales range from 0 to 100, in which higher scores indicate more favorable health status.

Clinical characteristics at baseline and follow-up

We used clinical data from the SRQ to assess the patient's clinical features at diagnosis and potential associations to the subgroups at 3 years. The first visit in the SRQ, registered as the starting visit, was used as a baseline assessment, limited to visits occurring within −40 to +75 days of inclusion in EIRA as previously described (30). Data from the SRQ included the Disease Activity Score of 28 Joints (DAS28) and its individual components, together with VAS pain and the Stanford Health Assessment Questionnaire (HAQ). From the EIRA 3-year follow-up, we also included information on changes of diagnosis since baseline, as well as data on pain problems before onset of RA. Here, the patients were asked whether any headache, neck and shoulder pain, back pain, or other musculoskeletal pain had been a problem for them before onset of RA, assessed on four levels: "No," "Mild," "Moderate," and "Severe." From the baseline questionnaire in EIRA, we also included data on education level, smoking status, and body mass index (BMI).

Clinical follow-up data were obtained from the SRQ at 3, 6, 12, 24, and 36 months after diagnosis. More specifically, registered visits closest to target day between 76 and 152, 153 and 228, 229 and 547, 548 and 913, and 914 and 1278 days after baseline were used for the respective time-points, as previously described (30).

Statistical analysis

Patients with complete data on the 3-year health status variables were eligible for cluster analysis. We assessed the data for clustering tendency using the agglomerative coefficient (31) and the Hopkins statistic (32). The clustering data were standardized and subjected to a hierarchical agglomerative clustering procedure, using the Ward-D2 method of Euclidean distances. The dendrogram output of the cluster analysis was visually inspected, and to further guide the decision on the optimal number of clusters, a set of 30 internal clustering indices was applied, using the R package *NbClust* (33). The quality of the obtained clusters was assessed through a silhouette plot using the R package *factoextra* (34).

Descriptive statistics were obtained for the clinical features at baseline for the whole sample and per cluster. The distributions for all variables were manually inspected, and (for normally distributed data) mean and SD were calculated, whereas (for nonnormally distributed data) median and first and third quartile (Q1, Q3) were calculated. Count data were reported as numbers and percentages. The potential associations between baseline characteristics and clusters were assessed with modified univariate Poisson regression (35) to obtain risk ratios (RRs) and 95% confidence intervals (95% CIs). We estimated RR for ending up in cluster 2 and cluster 3 respectively compared with cluster 1, for all baseline variables. The quantitative baseline variables were

categorized into quartiles to assess a potential dose–response relationship to the outcome. For C-reactive protein (CRP), we used less than 10 mg/L as reference level and three tertial levels above that because the lower detection level of CRP varied among the reporting clinics, from less than 1 to less than 10. Because the aim of the study was to assess association (not to investigate causation), the association for each baseline characteristic was assessed separately regardless of potential confounders.

As exploratory analyses, we assessed disease activity measures at 3, 6, 12, 24, and 36 months after diagnosis for all subjects with available clinical data as well as compared distributions of missing baseline data and changes in diagnosis since baseline between the clusters. Continuous variables were analyzed with the Kruskal-Wallis rank sum test, and count data were analyzed with Fisher's exact test if counts were below five—otherwise they were analyzed with the χ^2 test.

All analyses were performed using R statistical software, version 3.6.3 (36).

All participants gave informed consent, and the Ethics Review Board at Karolinska Institutet, Stockholm, Sweden, approved the study (960829; Dnr: 96-174; approved updates 2003-01-27 [96-174] and 2006/476-31/4). The study was conducted in accordance with the Helsinki Declaration.

RESULTS

At initiation of the current study in August 2018, 1386 participants in EIRA had been approached for the 3-year follow-up, of whom 1055 (76%) had completed the questionnaire and thereby constituted the study sample. A total of 44 (4%) individuals had incomplete data on the clustering variables and were therefore excluded, leaving 1011 individuals eligible for cluster analysis (see Figure 1 for flowchart). Mann–Whitney U tests revealed that excluded subjects were significantly older compared with the remaining sample (62 years at diagnosis [52-69] compared with 58 years [47-65]) and differed in the distribution of the "Role Physical" component of the SF-36 (100 [50-100] compared with 100 [25-100]). Otherwise, the demographical and clinical features of the excluded subjects were not significantly different from the remaining study sample. The number of women in the study sample was 742 (73%), and the median age at diagnosis was 58 years. Baseline characteristics are displayed in Table 1.

The agglomerative coefficient of the clustering variables was 0.98, and the Hopkins statistic was 0.29. Visual inspection of the dendrogram produced in the hierarchical agglomerative clustering procedure suggested a three-cluster solution (Figure 2A), which also found support in the applied clustering indices (10 indices suggested 3 clusters, 6 indices suggested 2 clusters, and other solutions were supported by 1-2 indices each). Cluster 1 consisted of 466 (46%) individuals with low levels of pain, fatigue, and functional disabilities, indicating a good health status

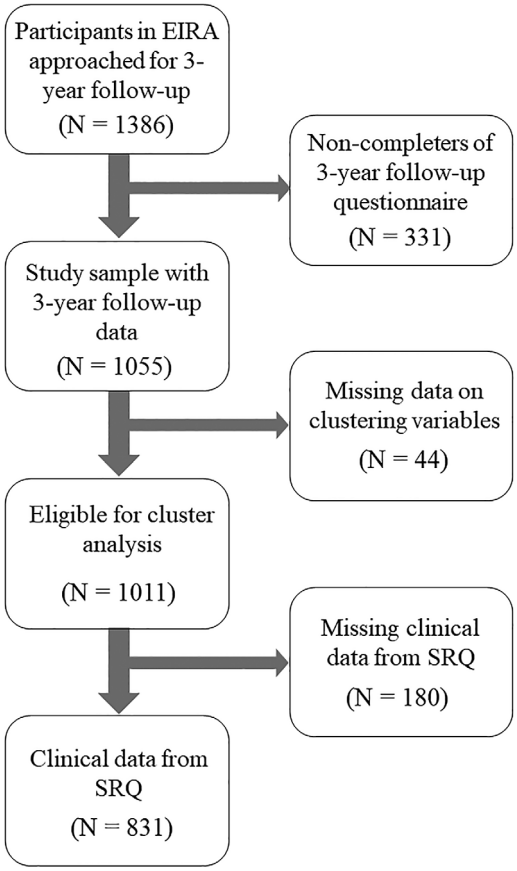

Figure 1. Flowchart depicting the enrollment of study participants. EIRA, Epidemiological Investigation of RA; RA, rheumatoid arthritis; SRQ, Swedish Rheumatology Quality Register.

(Table 2). Cluster 2 constituted an intermediate group of 398 (39%) individuals, and cluster 3 consisted of 147 (15%) individuals with high levels of pain and fatigue together with impaired physical and mental health (Table 2). The silhouette plot indicated that cluster 1 and cluster 3 were fairly cohesive, whereas cluster 2 was more disperse, rendering an average silhouette width of 0.20 (Figure 2B).

The RR and 95% CI for the association between baseline characteristics and clusters are displayed in Figure 3 (cluster 2 vs. 1) and Figure 4 (cluster 3 vs. 1) for a selection of baseline variables. The results for all baseline variables are listed in Supplementary Table S1. Cluster 2 displayed an inverse association to higher education level compared with cluster 1 (RR: 0.78 [95% CI: 0.62-0.99]), as well as an inverse association to occasional smoking compared with never smoking (RR: 0.68 [95% CI: 0.46-0.99]). Cluster 3 displayed a positive association to female sex (RR: 2.19 [95% CI: 1.42-3.38]) and higher tender joint count (RR: 1.73 [95% CI: 1.07-2.80]), as well as an inverse association to swollen joint count (RR: 0.51 [95% CI: 0.34-0.85]) compared with cluster 1. Both cluster 2 and cluster 3 were associated with higher BMI at baseline; higher DAS28, DAS28-CRP, VAS pain, patient global assessment (PGA), and HAQ scores; and pain

Table 1. Baseline characteristics of all included subjects stratified by cluster

Baseline characteristics	All patients N = 1011	Cluster 1 n = 466	Cluster 2 n = 398	Cluster 3 n = 147
Age, y	58 (47, 65)	58 (46, 65)	58 (47, 65)	57 (49, 63)
Female sex, n (%)	742 (73)	329 (71)	286 (72)	127 (86)
Education level, n (%)				
Elementary school	174 (17)	76 (16)	71 (18)	27 (18)
High school/vocational school	506 (50)	211 (45)	220 (55)	75 (51)
University degree	281 (28)	153 (33)	93 (23)	35 (24)
BMI (kg/m^2)	25.1 (22.5, 28.4)	24.8 (22.1, 27.2)	25.2 (22.8, 29.4)	26.1 (23.1, 29.4)
Smoking status, n (%)				
Never	341 (34)	162 (35)	132 (33)	47 (32)
Occasional	76 (8)	48 (10)	21 (5)	7 (5)
Past	338 (33)	154 (33)	137 (34)	47 (32)
Current	199 (20)	75 (16)	88 (22)	36 (25)
ACPA-positive, n (%)	647 (64)	302 (65)	257 (65)	88 (60)
DAS28, mean (SD)	5.13 (1.28)	5.0 (1.3)	5.2 (1.3)	5.4 (1.1)
DAS28-CRP, mean (SD)	4.69 (1.22)	4.5 (1.2)	4.8 (1.2)	4.9 (1.0)
ESR (mm)	26 (14, 42)	26 (14, 42)	27 (15, 44)	23 (12, 39)
CRP (mg/L)	8 (3, 23)	8 (3, 22)	10 (3, 27)	6 (3, 16)
Swollen joint count (0-28)	8 (4, 12)	8 (5, 13)	8 (4, 12)	7 (4, 10)
Tender joint count (0-28)	7 (3, 11)	6 (3, 10)	7 (3, 12)	8 (4, 12)
Pain (VAS score 0-100 mm)	53 (32, 72)	46 (26, 66)	55 (36, 73)	64 (50, 80)
PGA (VAS score 0-100 mm)	50 (30, 68)	42 (21, 60)	52 (35, 70)	66 (49, 80)
HAQ (0-3)	0.9 (0.5, 1.4)	0.9 (0.4, 1.2)	1.0 (0.6, 1.5)	1.2 (0.8, 1.6)
Pain problems before onset of RA				
Headache, n (%)				
No	704 (70)	366 (79)	269 (68)	69 (47)
Mild	136 (14)	55 (12)	58 (15)	23 (16)
Moderate	110 (11)	32 (7)	41 (10)	37 (25)
Severe	56 (6)	11 (2)	28 (7)	17 (12)
Back pain, n (%)				
No	536 (53)	306 (66)	199 (50)	31 (21)
Mild	217 (22)	102 (22)	86 (22)	29 (20)
Moderate	163 (16)	41 (9)	74 (19)	48 (33)
Severe	93 (9)	16 (3)	39 (10)	38 (26)
Neck/shoulder pain, n (%)				
No	501 (50)	287 (62)	179 (45)	35 (24)
Mild	225 (22)	106 (23)	101 (25)	18 (12)
Moderate	181 (18)	53 (11)	85 (21)	43 (29)
Severe	99 (10)	17 (4)	32 (8)	50 (34)
Other joint or muscle pain, n (%)				
No	534 (53)	314 (67)	185 (47)	35 (24)
Mild	195 (19)	79 (17)	95 (24)	21 (14)
Moderate	178 (18)	47 (10)	81 (20)	50 (34)
Severe	99 (10)	23 (5)	36 (9)	40 (27)

Abbreviations: ACPA, anticitrullinated protein antibody; BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; HAQ, Stanford Health Assessment Questionnaire; PGA, patient global assessment; Q, quartile; RA, rheumatoid arthritis; VAS, visual analog scale.
Note: The values are reported as median (Q1, Q3) unless otherwise noted.

problems before onset of RA compared with cluster 1, with generally stronger associations displayed by cluster 3. The strongest associations comparing cluster 2 with cluster 1 were seen for PGA, in which the highest compared with lowest quartile implied an RR of 1.79 (95% CI: 1.42-2.27), and for having severe problems with back pain compared with no problems with back pain before onset of RA (RR 1.80 [95% CI: 1.47-2.20]). The corresponding RR (95% CI) for cluster 3 compared with cluster 1 was 6.60 (3.53-12.33) and 7.65 (5.25-11.16), respectively. The variables DAS28-CRP score, VAS pain score, PGA score, HAQ score, BMI at baseline, and pain problems before onset of RA displayed a strong dose–response association for both clusters 2 and 3 (P for trend < 0.001).

The exploratory analysis of disease activity measures during follow-up visits, at 3, 6, 12, 24, and 36 months, displayed generally higher measures for cluster 3, primarily regarding the pain-related features and—to a lesser extent—the inflammatory features. The level of missing data was high (24%-60%). The results are displayed in Supplementary Table S2. Missing baseline data were nondifferentially distributed across clusters, except for HAQ, for which the proportion of missing data were significantly higher in cluster 1 (Supplementary Table S3). The total number

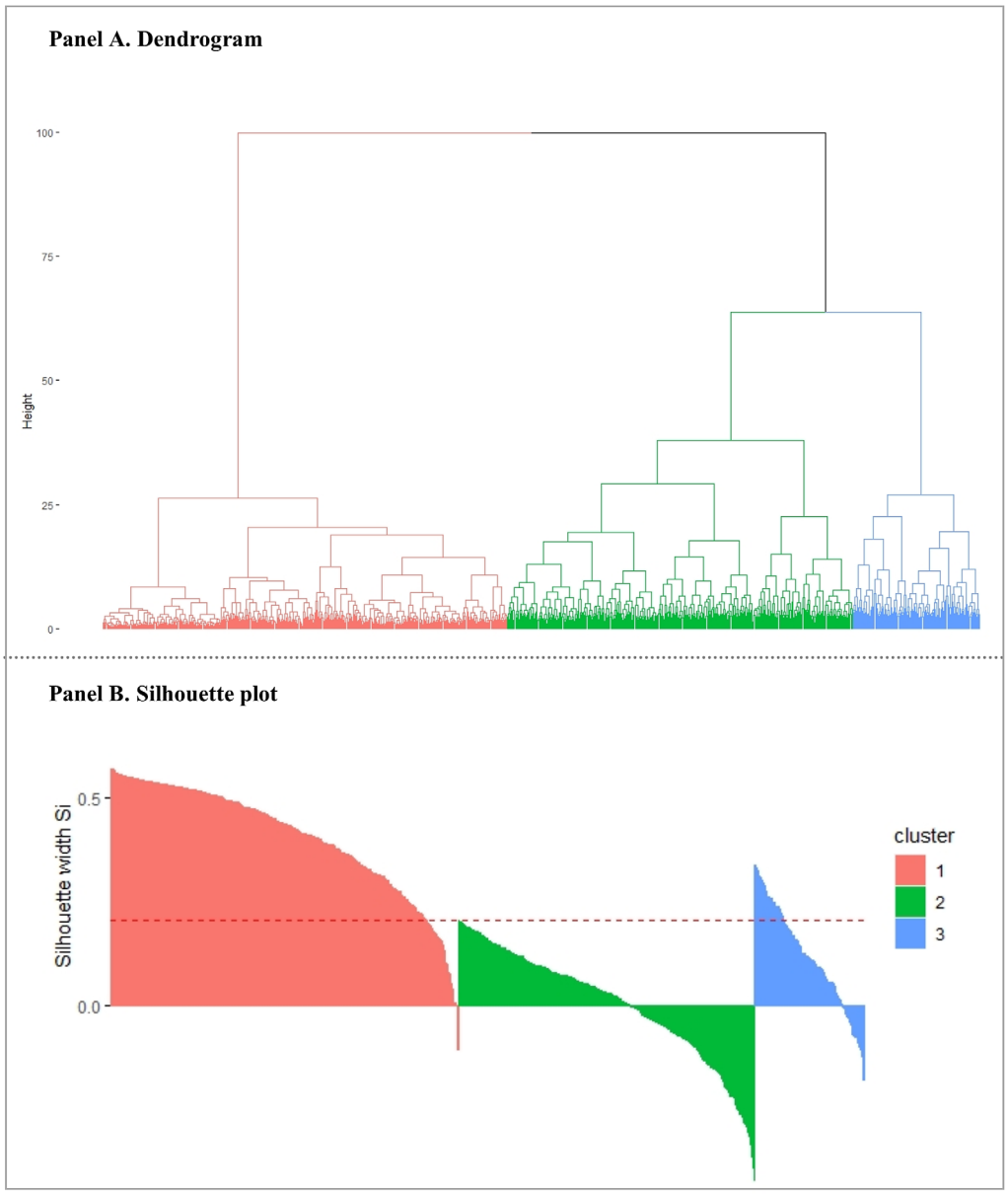

Figure 2. (**A**) Shows the dendrogram produced in the hierarchical agglomerative clustering procedure and (**B**) shows the silhouette plot for the three clusters. The silhouette plot shows that cluster 1 (red) and 3 (blue) are fairly cohesive, whereas cluster 2 (green) is more disperse, rendering an average silhouette width of 0.2 (red dashed line).

of patients who reported having had their diagnosis changed since baseline was 14 (1.4%). The distribution among clusters were six (1.3%) in cluster 1, four (1.0%) in cluster 2, and four (2.7%) in cluster 3. The differences were not statistically significant.

DISCUSSION

Through cluster analysis, we identified a subgroup of patients with high levels of pain, fatigue, and psychosocial distress 3 years after RA diagnosis. These patients already displayed high levels of pain and pain-related features at diagnosis without correspondingly elevated inflammatory parameters. Patients who were doing well at 3 years had less pain and pain-related features at diagnosis but displayed a higher level of inflammation as assessed by swollen joint count.

Cluster analysis has previously been used to identify subgroups of patients with RA based on patient-reported health status (37–39). One study involved 561 patients (mean disease duration 18 years) recruited for interviews in 1995 with 8 years of follow-up. The study identified three subgroups with high, median, or low levels of psychosocial risk factors and found that high levels of psychosocial risk factors was associated with long-term depression and functional disability but not to pain

Table 2. Variables included in cluster analysis at 3 years for all 1011 subjects stratified by cluster

Variables	All patients N = 1011	Cluster 1 n = 466	Cluster 2 n = 398	Cluster 3 n = 147
Pain intensity (VAS score 0-100 mm)	22 (8, 38)	9 (2, 20)	29 (20, 43)	48 (37, 63)
Pain disability (VAS score 0-100 mm)	7 (0, 31)	0 (0, 5)	19 (4, 40)	52 (28, 75)
Nonjoint pain intensity (VAS score 0-100 mm)	0 (0, 26)	0 (0, 0)	0 (0, 27)	54 (35, 71)
Nonjoint pain disability (VAS score 0-100 mm)	0 (0, 17)	0 (0, 0)	0 (0, 21)	51 (32, 74)
Painful body areas (0-24)	0 (0, 2)	0 (0, 0)	0 (0, 2)	5 (3, 8)
Fatigue (VAS score 0-100 mm)	17 (1, 46)	3 (0, 14)	29 (12, 51)	68 (48, 83)
Sleep problems (1–6)	2.5 (1.8, 3.3)	2.0 (1.8, 2.8)	2.5 (2.0, 3.2)	3.8 (3.0, 4.8)
Nonrestorative sleep (1–6)	2.0 (1.5, 3.0)	2.0 (1.5, 2.5)	2.5 (1.5, 3.0)	3.0 (2.5, 4.2)
HADS Anxiety score (0-21)	4 (1, 6)	2 (1, 4)	4 (2, 7)	8 (5, 11)
HADS Depression score (0-21)	2 (1, 5)	1 (1, 2)	3 (1, 6)	6 (4, 9)
SF-36 (0-100)				
Physical functioning	80 (60, 95)	90 (80, 100)	65 (50, 85)	50 (30, 65)
Role physical	100 (25, 100)	100 (100, 100)	50 (25, 100)	0 (0, 38)
Bodily pain	62 (42, 84)	84 (72, 100)	52 (42, 62)	32 (22, 42)
General health	60 (40, 77)	77 (62, 87)	50 (40, 62)	32 (23, 45)
Vitality	55 (40, 75)	75 (60, 85)	50 (35, 60)	25 (15, 40)
Social functioning	88 (68, 100)	100 (100, 100)	75 (63, 100)	50 (38, 63)
Role emotional	100 (67, 100)	100 (100, 100)	100 (33, 100)	33 (0,100)
Mental health	80 (64, 92)	88 (80, 96)	72 (60, 84)	56 (40, 68)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; Q, quartile; SF-36, Short Form-36; VAS, visual analog scale. The values are reported as median (Q1, Q3).

and number of annual doctoral visits (37). Another study identified subgroups of patients based on pain-related characteristics in 169 patients with remaining pain and a median disease duration of 13 years (38). This study also identified the following three subgroups: one with low levels of pain, fatigue, and psychosocial distress; a second with low inflammation but high levels of pain, fatigue, and psychosocial distress; and a third group with active inflammation and high levels of pain and fatigue. A third study on a total of 4046 patients with severe fatigue, recruited to two different cohorts between the years 2000 and 2008 (median disease durations of 7 and 12 years, respectively), identified four fatigue subtypes, described as "basic," "affective," "inflammatory," and "global" (39). All clusters experienced severe pain and disability and were distinguished on the presence or absence of poor mental health and inflammation. The findings of these studies show that cluster analysis can be used to identify clinically relevant subgroups in populations of patients with RA, further supported in the present analysis. The present study contributes with a structured longitudinal assessment early in the course of disease, showing that subgroups of patients experiencing worse health status can be distinguished already 3 years after diagnosis. We also demonstrate that factors associated to health status at 3 years are already prevalent at diagnosis.

Previously proposed cut points for the current clustering variables highlight the affected health status in cluster 3 and support the clinical relevance of the identified subgroups. The median pain rating in cluster 3 (48 mm) exceeds the "patient acceptable symptom state" for pain (40 of 100 mm), and the difference between the clusters touches on the minimal clinically important difference (20 of 100 mm) previously described by Tubach et al (40). The median VAS fatigue score in cluster 3 (68 mm) is well above 50 mm, which previously has been defined as a high level of fatigue in patients with RA (41). The high level of fatigue is also supported by the SF-36 Vitality score of 25, where scores of 35 or less have been proposed as severe fatigue (14). The corresponding fatigue ratings for cluster 1 were 3 and 75, respectively, and for cluster 2 were 29 and 50, indicating a distinction between the clusters. The HADS scores were generally below threshold across clusters, except for the anxiety score in cluster 3 (8 of 21), which was in the range of 8-10 considered as "possible anxiety disorder" (28). For the SF-36, there are no validated cut points for symptom severity, but the scores of cluster 3 were all—except for physical functioning—well below the pooled mean scores of 22,335 patients with RA described in a systematic review and meta-analysis (42), whereas the scores in cluster 1 are in line with previously reported scores from the general Swedish population (43). Taken together, our findings indicate that cluster 3 constitutes a group of patients with high levels of pain and fatigue together with clearly impaired HRQoL 3 years after diagnosis. On the contrary, cluster 1 constitutes a group of patients who display a health status comparable to the general population.

The symptoms displayed in cluster 3 correspond to the characteristic features of fibromyalgia, a condition characterized by widespread nociplastic pain, fatigue, sleep problems, and cognitive symptoms (44). Predictors of secondary fibromyalgia have previously been studied in a cohort of established patients with RA, with a mean disease duration of 12 years, in which it was found that factors such as psychosocial distress, comorbidities and severity of pain, fatigue, and sleep problems were predictive of future development of fibromyalgia (45). In analogy with that study, we found that patients in cluster 3 had a higher BMI, higher levels of pain, and higher HAQ and PGA scores at the time of

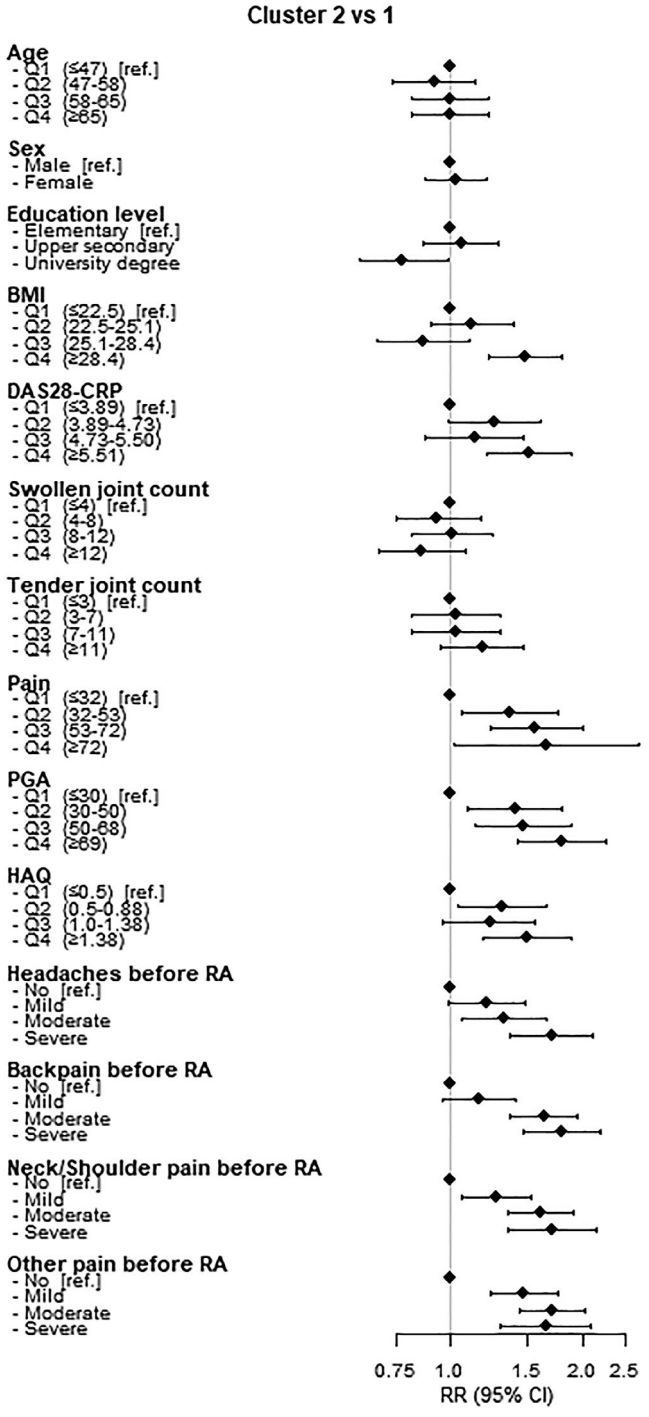

Figure 3. Forest plot displaying RRs and 95% CIs for the association between baseline characteristics for cluster 2 with cluster 1 as reference. BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; HAQ, Stanford Health Assessment Questionnaire; PGA, patient global assessment; Q, quartile; RA, rheumatoid arthritis; RR, risk ratio.

diagnosis. In contrast to the same study, we found no association between cluster 3 and smoking status, nor educational level. We did, however, find an association of lower educational level in cluster 2 compared with cluster 1 and, somewhat surprisingly, a decreased risk of ending up in cluster 2 compared with cluster 1 for occasional smokers compared with never-smokers.

Predictors for secondary fibromyalgia have also been examined in an early arthritis cohort, in which associations were found

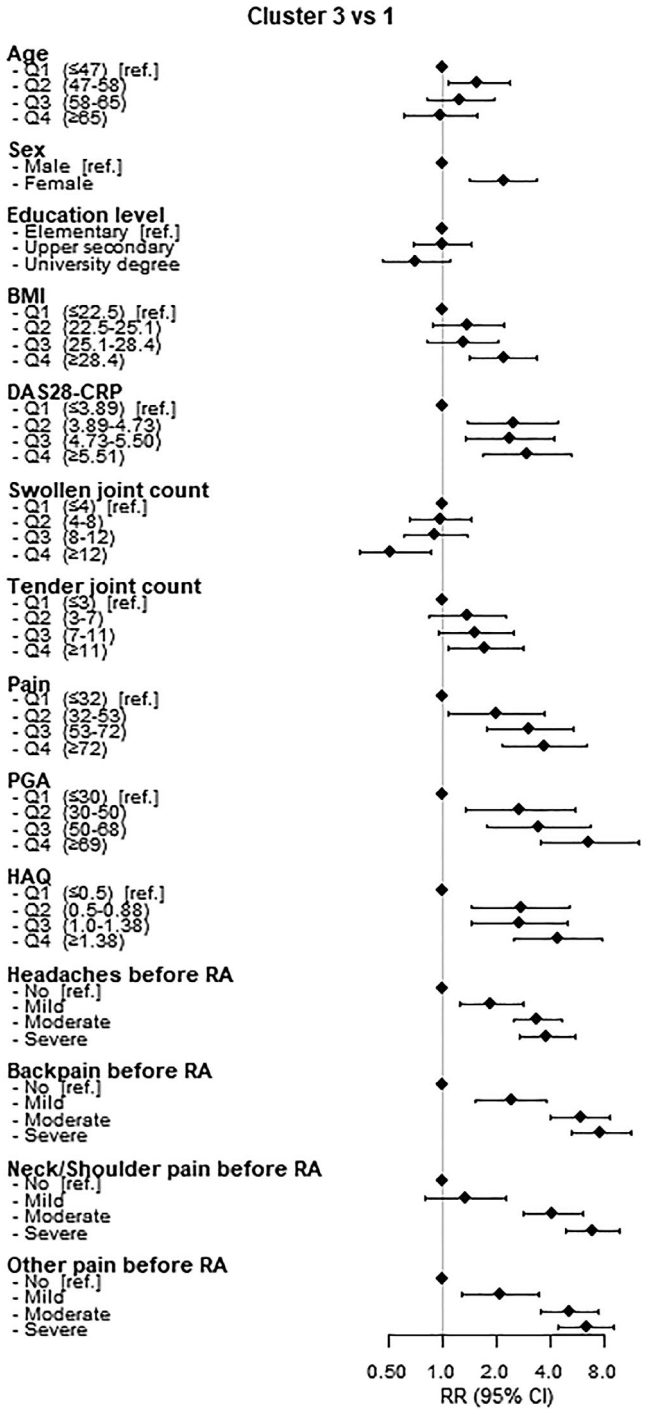

Figure 4. Forest plot displaying RRs and 95% CIs for the association between baseline characteristics for cluster 3 with cluster 1 as reference. BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; HAQ, Stanford Health Assessment Questionnaire; PGA, patient global assessment; Q, quartile; RA, rheumatoid arthritis; RR, risk ratio.

to tender joint count and pain as well as corticosteroid use, SF-36 mental component summary, and sleep disturbances, whereas an inverse association was found for anticitrullinated protein antibody (ACPA) positivity (46). Similarly to this study, we found higher baseline pain and tender joint count in cluster 3 compared with cluster 1. However, we found no associations between clusters and ACPA status.

It is also notable that both cluster 2 and cluster 3 were strongly associated with the presence of pain problems before the onset of RA compared with cluster 1. It should be borne in mind that these pain problems are reported retrospectively and might be influenced by recall bias; however, this is an interesting finding that corroborates the notion that factors influencing pain sensitization may precede the rheumatic disease, as discussed earlier (47). Moreover, the inflammatory status at diagnosis may be important for the ability to decrease pain in response to antirheumatic drugs. We showed earlier that higher inflammatory load at diagnosis is associated with a lower risk of having longstanding high levels of pain (48). This was also supported in the present study, in which cluster 1 was associated with higher baseline swollen joint count, suggesting that an inflammatory phenotype at diagnosis is associated with a more favorable long-term outcome.

The notion that patients at risk of developing long-term pain and fatigue already display distinguishing features at diagnosis provides ground for the early identification and adoption of preventive measures, which has been discussed as a feasible and highly warranted goal for the management of unmet needs in RA (49). Current guidelines for pain management in RA advocates for a patient-centered approach, which acknowledges the biopsychosocial underpinnings of the pain condition, and suggests a stepped-care approach that may include educational activities, physical activity, and psychological interventions (50).

The exploratory assessment of disease activity measures during follow-up suggested generally higher DAS28 scores in cluster 3, which is in line with earlier reports of patients with increased pain having higher DAS28 scores during the first years after diagnosis, dominated by the subjective components of the DAS28, such as tender joint count and global health (51). However, in the present study, the proportion of missing data were high, and the relationship between inflammatory disease activity and the features of ill health displayed in cluster 3 cannot be clarified.

Strengths of the study include the comprehensive assessment of patient characteristics at the time of diagnosis and the combination of register- and survey-based data sources linking early clinical features to long-term patient health status, with low levels of loss to follow-up and high participation rates of patients from a large geographic area in Sweden, favoring the generalizability of the findings.

Limitations to the study include the conflicting results between the two indices of clustering tendency—the agglomerative coefficient and the Hopkins statistic—in which the former suggested high clustering tendency in the data and the latter suggested more uniformly distributed data. In addition, cluster 2 constituted a disperse subgroup of patients who did not form a coherent cluster. However, we reasoned that the more coherent clusters 1 and 3 were the two subgroups of primary interest in this study and that subgroups identified along a gradient of symptom severity, as suggested by the Hopkins statistic, would also constitute clinically relevant subgroups, albeit not forming clusters in several dimensions. Other limitations include potential recall bias of retroactively reported pain problems before RA and that we could not fully assess to what extent inflammatory disease activity contributed to the observed health status at 3 years; however, that was also not an aim of this project.

In conclusion, we identified three subgroups of patients with differing levels of health status 3 years after RA diagnosis. Although a large subgroup of patients was doing well at 3 years, a smaller subgroup of patients displayed high levels of pain, fatigue, and psychosocial distress at this stage of the disease. Furthermore, these patients already displayed characteristic features at diagnosis, with high levels of pain and pain-related features together with low or average inflammatory parameters, which suggests that factors influencing the long-term course of the disease are already present at diagnosis. Early identification and targeted interventions should therefore be both feasible and warranted measures for these patients.

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AUTHOR CONTRIBUTIONS

Dr. Lindqvist drafted the article, and all authors critically revised the article for important intellectual content and approved the final version to be published. Dr. Lindqvist had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study conception and design. Lindqvist, Lampa, Westerlind.
Acquisition of data. Alfredsson, Klareskog, Westerlind.
Analysis and interpretation of data. Lindqvist, Lampa, Westerlind.

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