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PII: S0049-0172(20)30004-4
DOI: https://doi.org/10.1016/j.semarthrit.2020.01.004
Reference: YSARH 51575

To appear in: *Seminars in Arthritis & Rheumatism*

Please cite this article as: Dewi Guellec , Servane Cozien , Adeline Ruyssen-Witrand , Philippe Dieudé , Alain Saraux , Prevalence and Clinical Significance of Extra-Articular Manifestations at Diagnosis in the ESPOIR Cohort with Recent-Onset Arthritis, *Seminars in Arthritis & Rheumatism* (2020), doi: https://doi.org/10.1016/j.semarthrit.2020.01.004

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Prevalence and Clinical Significance of Extra-Articular Manifestations at Diagnosis in the ESPOIR Cohort with Recent-Onset Arthritis

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ABSTRACT

Objectives: The aim of this study was to determine the prevalence and clinical significance of extra-articular manifestations (EAMs) at inclusion into a cohort of patients with recent-onset arthritis consistent with rheumatoid arthritis (RA).

Methods: The ESPOIR cohort included patients aged 18 to 70 years who had a definitive or probable diagnosis of RA. Symptoms consistent with EAMs were collected at baseline. We divided the patients into two groups, with vs. without baseline EAMs. We looked for associations linking the presence of EAMs at baseline to patient and disease characteristics at baseline and 5 years later, as well as to diagnostic certainty after 2 years. The analyses were adjusted for multiple comparisons using the Benjamini-Hochberg procedure to control the false discovery rate.

Results: Of 798 patients, 330 (41.4%) had at least one symptom consistent with EAM at baseline, with the most common being sicca syndrome (28.4%) and Raynaud's phenomenon (17.3%). The EAM+ group had a higher mean baseline DAS-28 value (5.3±1.3 versus 5.0±1.3; corrected *p* value =0.005) compared to the EAM- group. The final diagnosis did not differ between the two groups. After 5 years, the EAM+ group had significantly higher values for the tender joint count (3.9±6.4 versus 1.8±3.3, corrected *p* value =0.005) and swollen joint count (1.3±2.8 versus 1.1±2.3, corrected *p* value =0.0005) compared to the EAM- group.

Conclusion: EAMs, particularly sicca syndrome and Raynaud's phenomenon, are very common in patients with early arthritis consistent with RA. In this population, several parameters reflecting disease activity were higher among patients with EAMs, at baseline and after 5 years.

Keywords: Rheumatoid arthritis, Extra-articular manifestations, Cohort study.

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INTRODUCTION

Extra-articular manifestations (EAMs) are common in rheumatoid arthritis (RA), with occurrence rates over time ranging from 18% to 41% (1,2). EAMs, according to its classical definition, must be distinguished from other multifactorial conditions associated with RA such as osteoporosis, cardiovascular disease, hemopathies, and solid malignancies (3). To date, there is no consensual definition or classification of EAMs. The modified Malmö criteria can be used to categorise EAMs based on their severity and on the affected tissue or organ (1,4).

Rheumatoid nodules, Raynaud's phenomenon, and sicca syndrome are the most frequently reported EAMs among patients with established RA. Rheumatoid nodules affected up to 30% of patients in the past but have become less common due to improvements in the treatment of RA (5,6). Raynaud's phenomenon has been reported in 5% to 17% of patients with RA, but RA-related and idiopathic forms are difficult to distinguish in young females (7). Sicca syndrome can range from isolated subjective dryness to disabling secondary Sjögren's syndrome (sSS) (8). In the CORRONA registry, the prevalence of sSS was 30% (95% confidence interval, 29%-31%) and increased with disease duration (9). Interestingly, patients with sSS were characterized by higher disease activity and a heavier burden of comorbidities. Severe EAMs are rare, affecting only about 2% of patients with established RA (10), with variations according to the definition used. Interstitial lung disease (ILD), serositis, vasculitis, and ocular complications are the most common severe EAMs.

Prospective and retrospective cohort studies of patients with RA patients have identified several parameters associated with benign and/or severe EAMs. Rheumatoid vasculitis was associated with male sex (11) and rheumatoid nodules with smoking (6). Patients with EAMs more often had positive markers for inflammation, anti-nuclear antibodies, rheumatoid

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factors, and anti-cyclic citrullinated peptide (CCP) antibodies (12). Among genetic factors, the shared epitope and *PTPN22* variants were associated with EAMs in patients with RA (13,14). The *MUC5B* promoter variant was recently shown to be associated with ILD, and more specifically with usual interstitial pneumonia, in patients with RA (15). Both cardiovascular events and death were more common among patients with EAMs, notably those with severe forms (16,17). However, these findings may be biased by a number of confounding factors.

Despite the extensive data available on EAMs in patients with RA, the clinical significance of EAMs early in the course of the disease is unclear, as most studies focussed on patients with established RA. An important issue is whether the early presence of EAMs in patients with recent-onset arthritis is associated with the clinical outcomes and/or final diagnosis. To assess this issue, we used the French prospective multicentre ESPOIR cohort (18). Our approach should be viewed as pragmatic, since patients in the ESPOIR cohort did not routinely undergo extensive investigations for EAMs.

The primary objective of this study was to determine the prevalence and clinical significance of EAMs at inclusion into the French ESPOIR cohort of patients with recent-onset arthritis consistent with RA. The secondary objective was to assess potential associations linking the immunological profile, shared epitope, and presence of EAMs at baseline.

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METHODS

Study population

The French prospective multicentre ESPOIR cohort (NCT03666091) was established to monitor the clinical, laboratory, and radiographic data from patients with recent-onset

inflammatory arthritis affecting more than one joint (18). It was approved by the institutional review board of the Montpellier University Hospital, which was the coordinating centre. All patients gave their written informed consent before inclusion. General practitioners and rheumatologists referred patients to 14 sites in 10 regions throughout France. Patient inclusion occurred from December 2002 to March 2005.

Inclusion criteria in the ESPOIR cohort were age 18 to 70 years; recent-onset arthritis defined as swelling of at least two joints for 6 weeks to 6 months; and a definitive or probable diagnosis of RA or of polyarthritis not better explained by another aetiology. Patients who had taken disease-modifying antirheumatic drugs (DMARDs) or substantial glucocorticoid dosages were excluded. Patients given glucocorticoid therapy in a dosage ≤20 mg/day for ≤2 weeks were eligible for inclusion if the treatment had been discontinued for at least 2 weeks.

Study design

Demographic and clinical variables assessed at baseline included body mass index (BMI), tobacco consumption, disease duration, patient global assessment of disease, total tender joint count (TJC), total swollen joint count (SJC), and the Disease Activity Score on 28 joints (DAS-28). Laboratory tests included the erythrocyte sedimentation rate (mm/h), centralised C-reactive protein assay (mg/L), IgM/IgA rheumatoid factors, anti-CCP antibodies, anti-nuclear antibodies, and HLA-DR typing. A chest radiograph and radiographs of the hands and feet were obtained routinely. Clinical, laboratory, and radiological abnormalities consistent with EAMs were sought at baseline and described using a standardised form. No consensus exists about the classification of EAMs in RA. We used a list of manifestations corresponding to the modified Malmö criteria to classify EAMs based on organ system involved and severity (1). Systematic sicca syndrome assessment was limited

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to a subjective evaluation of xerostomia and xerophtalmia. For interstitial lung disease, systematic evauation was limited to clinical judgement and chest X-ray.

Follow-up visits were performed after 6 and 12 months then once a year. Each visit included clinical, laboratory, and radiographic evaluations for RA. Glucocorticoid and DMARD prescriptions were recorded at each visit.

Radiographic damage was assessed at baseline and at each follow-up visit by determining the modified Sharp-van der Heijde score (19,20). Radiographs were read by trained investigators who were blinded to the clinical data. Patients were excluded at any time during follow-up if RA was ruled out and another condition diagnosed.

The final diagnosis was determined after 2 years based on the ACR/EULAR criteria (21), whether the treating rheumatologist had made an alternative diagnosis, and methotrexate exposure.

We assessed associations linking the presence of EAMs at baseline to the clinical, laboratory, and radiographic outcomes after 5 years.

Statistical analysis

Analysis were conducted in all patients included in the ESPOIR cohort and available data regarding EAMs at baseline. To determine the prevalence of EAMs at baseline, we considered overall EAMs, EAMs according to site of involvement, and EAMs according to severity. We looked for associations linking the presence of EAMs at baseline to the clinical, laboratory, and radiographic features at baseline and after 5 years, as well as to the diagnostic certainty after 2 years. The same analyses were performed in the sub-group of patients with severe EAMs at baseline. Associations linking the immunological profile and shared epitope to the various EAMs categories were sought. Groups were compared using the χ^2 test or Fisher's exact test, as appropriate, if variable distribution was normal and the Mann-Whitney

test otherwise. The analyses were adjusted for multiple comparisons using the Benjamini-Hochberg procedure to control the false discovery rate (22). Benjamini-Hochberg adjusted *p* values <0.05 were considered significant. All statistical analyses were performed using R software version 3.4.2.

RESULTS

Figure 1 is the study flow chart.

Baseline findings

Of 798 patients, 330 (41.4%) had clinical manifestations consistent with EAMs at baseline (Table 1). EAMs were more prevalent in females than in males (44.8% and 29.9%, respectively). Sicca syndrome was the most common EAM and was also more common, together with Raynaud's phenomenon, in females than in males. Severe EAMs were present at baseline in 30/798 (3.8%) patients, consisting in cutaneous vasculitis in 9 patients, severe ocular manifestations in 9 patients, peripheral neuropathy in 6 patients, pleuritis in 4 patients and pericarditis in 4 patients. None had a diagnosis of ILD at inclusion but 8 patients had a previous diagnosis of pneumonia, 5 a diagnosis of chronic obstructive pulmonary disease and 2 a diagnosis of bronchiectasis. However, misdiagnosis could not be ruled out for these patients as chest CT-scan was not performed systematically.

After correction for multiple comparisons, SJC, TJC, the visual analogue scale (VAS) score for pain, and the DAS-28 were significantly higher in the group with EAMs, but not in the sub-group with severe EAMs, compared to the group without EAMs (Table 2).

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Diagnosis at 2 years according to baseline extra-articular manifestation (EAM) status (Table 3)

The groups with and without EAMs at baseline were not significantly different for the proportion of patients satisfying ACR/EULAR criteria, proportion of patients given a plausible differential diagnosis by the treating rheumatologist, or proportion of patients given methotrexate therapy. In the sub-group of patients with severe EAMs, there was a non-significant trend toward greater confidence in a diagnosis of RA. There was also a trend towards less Methotrexate exposure in these patients.

Clinical outcomes at 5 years according to baseline extra-articular manifestation (EAM) status (Table 4)

After 5 years, the TJC and SJC remained higher in the group with EAMs at baseline. Neither the VAS pain score nor the DAS-28 were significantly different between the groups with and without EAMs at baseline. Presence of EAMs at baseline was not associated with subsequent exposure to glucocorticoids, methotrexate, or biologic DMARDs.

Shared epitope distribution and immunological status according to baseline extra-articular manifestation (EAM) status (supplementary table 1)

No significant associations between EAM types and immunological status at baseline were found. Shared epitope positivity was less prevalent in patients with EAMs at baseline (50.3% versus 56.3%), especially in men (42.3% versus 62.9%), although the differences were not statistically significant after adjustment.

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DISCUSSION

In a large cohort with recent-onset inflammatory arthritis consistent with RA**,** EAMs were present at baseline in 41.4% of patients overall and in 44.8% of female patients. Presence of EAMs at baseline was associated with female sex and with higher baseline values of the VAS pain score, SJC, TJC, and DAS-28. After 5 years, disease activity remained higher in the patients with EAMs at baseline. However, the groups with and without EAMs at baseline did not differ regarding the diagnosis after 2 years, the treatments used, or the 5-year radiographic outcomes.

The considerably higher overall prevalence of baseline EAMs in our cohort compared to data from previous observational studies is chiefly ascribable to higher prevalences of sicca syndrome and Raynaud's phenomenon (1). This finding may be due in part to the wording of the questionnaire on EAMs completed by the physicians at baseline, which did not include rigorously defined subjective or objective findings suggestive of EAMs. In addition, no distinction was made between Raynaud's phenomenon antedating versus coinciding with the onset of arthritis symptoms. Thus, we cannot rule out overestimation of the prevalence of EAMs. However, the baseline prevalence of sicca syndrome was consistent with data from the CORRONA registry showing true sSS in 30% of patients with RA (9). Severe EAMs as defined using the Malmö criteria were identified in 3.8% of patients at baseline, a prevalence slightly higher than expected based on previous work in established RA (10). Possible explanations to this higher prevalence include overestimation of EAMs, as indicated above, and differences between recent-onset arthritis and established RA. The baseline prevalence of rheumatoid nodules was only 1.2%, with no difference between males and females.

EAMs were more common at baseline in females, as expected from the major contribution of sicca syndrome and Raynaud's phenomenon to these EAMs. EAMs at

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baseline were not associated with age at disease onset or smoking. The group with EAMs at baseline had greater disease activity at baseline and after 5 years. However, the groups with and without baseline EAMs were not different regarding laboratory markers for inflammation, rheumatoid serology, or ANAs; long-term treatments used; or radiographic outcomes. Similarly, in the large recent CORRONA registry, the disease was more severe in patients with sSS (9). Thus, EAMs at baseline may be a marker for a more severe disease phenotype.

Another important issue is whether the presence of EAMs at baseline predicts a diagnosis other than RA. Our data suggest that, in general, EAMs in patients with recent-onset arthritis consistent with RA are not associated with subsequent attribution of the arthritis to a condition other than RA. Among patients with severe EAMs, there was a non-significant trend toward greater confidence in a diagnosis of RA but lesser Methotrexate exposure at 2 years. These conflicting results could be partially explained by a prescription bias in patients with atypical clinical presentation at baseline.

We investigated potential associations linking the immunological profile and shared epitope to the various EAM categories. In contradiction to data from patients with established RA, our results suggest a negative association between baseline EAMs and presence of the shared epitope, especially in men. However, the observed differences in the present study did not reach statistical significance after adjustment for multiple comparisons. The lack of association between EAMs and the shared epitope seems surprising, but may reflect the distribution of baseline EAMs in the ESPOIR cohort, as associations may vary for different manifestations (23, 24).

A major limitation of our study is that EAMs were not sought at baseline using a standardised set of routine investigations. Thus, interstitial lung disease was investigated through clinical judgement and chest X-ray but patients did not undergo systematic CT-scan in order to precisely assess lung involvement. The absence of ILD cases identified at baseline

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in the present study is consistent with the data previously obtained in larger cohorts assessing pulmonary involvement as part of standard clinical practice, on the basis of pulmonary symptoms or abnormal clinical features (25). Consequently, the results of the present study cannot be applied to patients with clinical or subclinical lung involvement identified at disease onset. Similarly, sicca syndrome assessment at baseline did not include a systematic objective evaluation of dryness. In addition, standardised definitions of EAMs were not used. Future studies should use strict definitions, particularly for the most common EAMs and for EAMs involving the lungs. Similarly, the proportion of patients with severe EAMs at baseline was probably too small to identify statistical associations linking this condition to long-term outcome.

To conclude, EAMs are very common in patients with early arthritis suggesting RA and most often consist in sicca syndrome and/or Raynaud's phenomenon. Early EAMs are associated with female sex and with parameters reflecting disease activity at baseline and 5 years later. In general, the early presence of EAMs was not a predictor of the final diagnosis or treatment strategy. Future prospective studies should use rigorous definitions of baseline EAMs to better assess their associations with long-term outcomes, with the final aim of developing personalized therapeutic and/or monitoring strategies (26).

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Acknowledgements

An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from the INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Pfizer, Abbvie, Lilly, and Sanofi also supported the ESPOIR cohort study.

We are grateful to Nathalie Rincheval (CHU Montpellier and EA 2415) for their expert monitoring and data management and to the the investigators who recruited and followed the patients (F. Berenbaum, Paris-Saint Antoine; MC. Boissier, Paris-Bobigny; A. Cantagrel, Toulouse; B. Combe , Montpellier; M. Dougados, Paris-Cochin; P. Fardellone and P. Boumier, Amiens; B. Fautrel, Paris-La Pitié; RM. Flipo, Lille; Ph. Goupille, Tours; F. Liote, Paris- Lariboisière; O. Vittecoq, Rouen; X. Mariette, Paris-Bicêtre; P. Dieude, Paris Bichat; A. Saraux, Brest; T. Schaeverbeke, Bordeaux; and J. Sibilia, Strasbourg).

Declarations of interest

none

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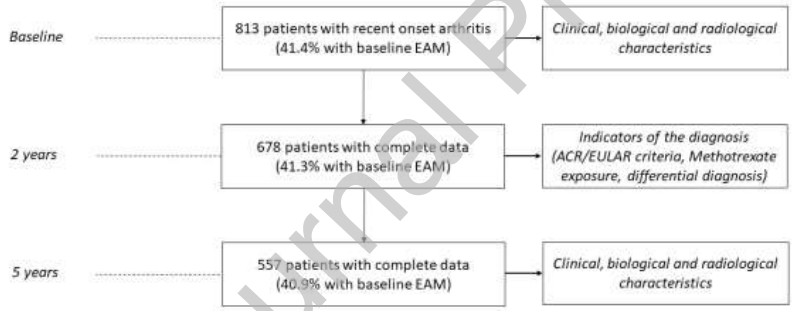

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Figure 1. Study flow chart

EAMs: extra-articular manifestations

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	All patients	Women	Men
EAMs	41.4% (330/798)	44.8% (274/611)	29.9% (56/187)
Severe EAMs	3.8% (30/798)	3.9% (24/611)	3.2% (6/187)
Sicca syndrome	28.4% (230/811)	31.0% (193/622)	19.6% (37/189)
Raynaud's phenomenon	17.3% (137/794)	18.9% (115/610)	12.0% (22/184)
Rheumatoid nodules	1.2% (10/812)	1.3% (8/623)	1.1% (2/189)
Purpura	1.1% (9/811)	1.3% (8/622)	0.5% (1/189)
Other ocular manifestations	1.1% (9/809)	1.0% (6/620)	1.6% (3/189)
Peripheral neuropathy	0.7% (6/807)	0.8% (5/619)	0.5% (1/188)
Pleuritis	0.5% (4/809)	0.5% (3/620)	0.5% (1/189)
Pericarditis	0.5% (4/811)	0.6% (4/622)	0.0%(0/189)
Interstitial lung disease	0..0% (0/811)	0.0% (0/622)	0.0%(0/189)

Table 1. Extra-articular manifestations (EAMs) at baseline in the ESPOIR cohort

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	EAMs	*p* value*	Adjusted *p* value *	Severe EAM	*p* value **	Adjusted *p* value **	No EAMs
Age, y, mean±SD	47.7±12.2	0.34	0.64	46.3±11.8	0.35	0.63	48.4±12.7
BMI, kg/m², mean±SD	25.2±4.8	0.59	0.83	25.2±4.5	0.69	0.85	24.92±4.3
Female sex, n (%)	274/330, 83.0%	0.0003	**0.006**	24/30, (80.0%)	0.34	0.67	337/468 (72.0%)
Current smoking, n (%)	165/330 (50.0%)	0.31	0.68	15/30 (50.0%)	0.70	0.84	217/468 (46.4%)
Disease duration, days, mean±SD	76.7±69.4	0.21	0.60	53.7±37.8	0.29	0.68	73.6±82.0
VAS pain score, on100, mean±SD	64.1±24.8	0.0001	**0.002**	64.1±28.9	0.50	0.78	57.1±25.6
SJC, mean±SD	9.7±7.5	0.00005	**0.002**	9.2±7.7	0.29	0.66	7.5±6.5
TJC, mean±SD	8.0±5.4	0.00001	**0.0009**	7.2±4.8	0.36	0.64	6.64±5.3
ESR, mm, mean±SD	28.40±24.6	0.12	0.45	37.6±27.1	0.12	0.42	30.3±24.6
CRP, mg/L, mean±SD	21.4±30.7	0.20	0.59	29.1±31.1	0.31	0.66	22.8±35.8
DAS-28, mean±SD	5.3±1.3	0.0003	**0.005**	5.4±1.4	0.16	0.50	5.0±1.3
RF positivity, n (%)	142/330 (43.0%)	0.81	0.94	12/30 (40.0%)	0.81	0.93	197/467 (42.2%)
Anti-CCP positivity, n (%)	114/330 (34.5%)	0.04	0.20	11/30 (36.7%)	0.58	0.87	195/467 (41.8%)
ANA positivity, n (%)	165/328 (50.3%)	0.36	0.63	14/30 (46.7%)	0.97	1	218/464 (47.0%)
Sharp score, mean±SD	3.5±4.9	0.02	0.14	4.7±7.2	0.34	0.65	2.9±5.2

Table 2. Baseline characteristics of patients according to the presence of extra-articular manifestations (EAMs)

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*groups with versus without EAMs

**group with severe EAMs versus group without EAMs

Benjamini-Hochberg adjusted *p* values <0.05 (in bold font) were considered significant.

EAMs, extra-articular manifestations; BMI: body mass index; VAS: visual analogue scale; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS-28, Disease Activity Score on 28 joints; RF: rheumatoid factor; CCP, cyclic citrullinated peptides; ANA: anti-nuclear antibodies

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	EAMs	*p* value*	Adjusted *p* value *	Severe EAMs	*p* value**	Adjusted *p* value**	No EAMs
ACR/EULAR criteria	288/316 (91.1%)	0.41	0.66	27/29 (93.1%)	0.52	0.80	393/440 (89.3%)
Other diagnosis[1]	110/280 (39.3%)	0.66	0.86	7/29 (24.1%)	0.074	0.33	163/398 (41.0%)
Methotrexate exposure	148/280 (52.9%)	0.24	0.64	10/29 (34.5%)	0.016	0.15	229/399 (57.4%)

Table 3: Indicators of the diagnosis after 2 years according to baseline extra-articular manifestation (EAM) status

*groups with versus without EAMs

**group with severe EAMs versus group without EAMs

Benjamini-Hochberg adjusted *p* values <0.05 were considered significant.

[1]: Considered plausible by the treating rheumatologist at the 2-year visit

	EAMs	*p* value*	Adjusted *p* value *	Severe EAMs	*p* value **	Adjusted *p* value **	No EAMs
VAS pain score, mean±SD	29.5±27.1	0.02	0.13	37.4±30.1	0.02	0.17	23.4±23.7
SJC, mean±SD	3.9±6.4	0.0004	**0.005**	5.0±8.1	0.08	0.34	1.8±3.3
TJC, mean±SD	1.3±2.8	0.00001	**0.0005**	1.3±3.1	0.36	0.60	1.1±2.3
ESR, mm, mean±SD	13.8±11.7	0.87	0.95	12.6±11.0	0.43	0.69	15.0±14.4
CRP, mg/L, mean±SD	7.2±11.7	0.12	0.40	7.4±15.2	0.59	0.84	6.6±11.7

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DAS-28, mean±SD	2.9±1.5	0.009	0.11	3.0±1.6	0.28	0.69	2.6±1.2
Current glucocorticoid therapy, n (%)	57/228 (25.0%)	0.59	0.82	5/23 (21.7%)	0.58	0.85	89/329 (27.1%)
Current methotrexate therapy, n (%)	107/228 (47.9%)	0.41	0.68	9/23 (39.1%)	0.29	0.65	166/329 (50.5%)
Current bDMARD use, n (%)	36/228 (15.8%)	0.99	1	4/23 (17.4%)	0.84	0.94	52/329 (15.8%)
Sharp score, mean±SD	8.7±11.6)	0.86	0.95	12.7±16.7)	0.32	0.67	9.1±11.8
Death, n (%)	2/330 (0.6%)	0.34	0.68	1/29 (3.4%)	0.35	0.65	6/468 (1.2%)

Table 4. Five-year outcomes according to baseline extra-articular manifestations (EAMs) status

*groups with versus without EAMs

**group with severe EAMs versus group without EAMs

Benjamini-Hochberg adjusted *p* values <0.05 (in bold font) were considered significant.

EAMs, extra-articular manifestations; VAS: visual analogue scale; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS-28, Disease Activity Score on 28 joints; bDMARD, biologic disease-modifying anti-rheumatic drug

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