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Analysis of synovitis patterns in early RA supports the importance of joint-specific factors

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ABSTRACT

Background: Rheumatoid arthritis (RA) is classically considered a systemic disorder, but the role of local factors in driving synovial inflammation is increasingly being recognized. These joint-specific factors may consequently modulate disease phenotype.
Objectives: Our goal was to study the spatial distribution of swelling, tenderness and erosions in a large cohort of early RA (ERA) patients, to assess for patterns of simultaneously-involved joint clusters. We also aimed to investigate the link between arthritis localization and phenotypic features such as bone erosions and response to methotrexate therapy.
Methods: DMARD-naive patients from the ERA UCLouvain Brussels cohort were included. Forty-four joints were clinically assessed for swelling and tenderness before treatment, and 6 months later for methotrexate-treated patients. Clusters of joints were identified using Principal component analysis and Cramer's correlation coefficients. Frequency of bone erosions and joint-specific response to methotrexate were compared across different clusters.
Results: 452 ERA patients were included. Analysis of the spatial distribution of swelling and tenderness allowed for the identification of 3 joint clusters that showed significant simultaneous involvement: (i) MTP1–5 joints, (ii) hand joints (MCPs and PIPs), and (iii) larger joints. These clusters were associated with different susceptibility to bone erosions and distinct clinical features, but similar local response (joint swelling resolution) to methotrexate.
Conclusion: This is the first study investigating the spatial distribution of arthritis in a large cohort of early RA using an unbiased approach. We identify clusters of simultaneously involved joints, supporting the importance of local factors in driving synovitis in RA.

Key Messages

-What is already known on this topic

Rheumatoid Arthritis is considered a systemic immune disorder, yet susceptibility to arthritis differs across joint sites in RA. So far, the existence of simultaneously involved joints has never been assessed.

-What this study adds

Using unbiased approaches, we evidence the existence of 3 joint clusters, corresponding to different anatomical localizations: one with MTP joints, one with hand joints (MCPs and PIPs), and one with larger joints. These clusters exhibit distinct susceptibility for erosions but seemed to display similar response to therapy.

-How this study might affect research, practice or policy

Our data contribute to the phenotypic description of early RA and point to the existence of local drivers of synovitis in RA. Identification of such factors may provide important clues to pathogenesis.

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Introduction

Rheumatoid Arthritis (RA) is a chronic disease primarily presenting with symmetric polyarthritis, leading to joint pain, disability and destruction. Joint inflammation manifests clinically with swelling and/or tenderness, two features included in the standard assessment of disease activity [1]. RA may involve all synovial joints but preferentially small joints of the hands and feet, medium joint (wrists), and less frequently larger or axial joints [2], distinguishing RA from other inflammatory arthropathies. Bone erosions, a radiological hallmark of RA, are also more frequently identified in small and medium joints [3,4]. Mechanisms governing the susceptibility of a joint location to develop arthritis in the specific context of RA remain largely unknown.

From a pathophysiological point of view, RA is classically considered a primarily systemic disorder driven by the immune system [5], but the role of local factors in the development of synovial inflammation is increasingly being recognized [6,7]. These joint-specific factors may modulate disease phenotype: number and distribution of involved joints may vary greatly between individuals with RA, and specific sites have been associated with disease outcomes [8]. When describing disease phenotype in early RA, most studies have focused on disease activity, arthritis distribution, erosions or specific antibodies [9–11].

By contrast, whether arthritis "randomly" occurs across small joints, or whether some locations are more frequently affected simultaneously by RA synovitis, has not been explored. Here, we study the spatial distribution of swelling, tenderness and erosions in a large cohort of early RA (ERA) patients to assess for patterns of joint involvement and joint-specific responses to methotrexate.

Material and methods

Patients

DMARD-naive patients with newly diagnosed Rheumatoid Arthritis from the ERA UCLouvain Brussels cohort were included in the study (inclusion period 2005–2020). Patients included between 2005 and 2010 met the ACR/EULAR 1987 RA criteria, patients included from 2010 on met the ACR/EULAR 2010 RA criteria. The study was approved by the ethics committee of the Université catholique de Louvain (n° 2013/24MAI/293). Patients provided informed consent for participation to the study. Patients were clinically assessed by an expert rheumatologist at baseline for the presence of joint swelling and joint tenderness in 44 sites: shoulder, sternoclavicular, acromioclavicular, elbow, wrist, knee, ankle, metacarpophalangeal (MCP), proximal interphalangeal (PIP) and metatarsophalangeal (MTP) joints. Other demographic data and indices of disease activity were collected at baseline. Systematic X-rays of wrists, hands, feet and ankles were taken at baseline for assessment of bone erosion by musculoskeletal radiologists; for large joints, X-rays were taken in case of clinical arthritis. Patients who were started on methotrexate monotherapy (without systemic or intra-articular steroids) were clinically evaluated after 3 and 6 months for resolution vs persistence of joint swelling.

Statistical analysis

Data on swelling/tenderness at each joint site were collected into binary data matrices. To increase clarity of the analysis of spatial distribution, data on joint swelling/tenderness/bone erosion were collapsed into a single binary value for each joint site ($n = 9944$ joint sites), not accounting for laterality (except for Supplementary Figure 2). Existence of joint clusters was first assessed using dimension-reduction approach (Principal component analysis), then confirmed using Cramer's correlation coefficient (φc) for binary values. Comparison of bone erosions across joint clusters was performed using Chi-square. Comparison of clinical data across patients' groups (patients with involvement of a specific joint site vs others; patients reaching DAS28 remission state vs others) were performed using Mann-Whitney tests, Chi-square, and/or Fischer's exact tests (when samples size <10). When applicable, correction for multiple comparison was performed using FDR-corrected p-value. Linear regression was performed with HAQ as dependent variable. Median number of swollen joints per individual at baseline, 3 months and 6 months after methotrexate monotherapy was compared using ANOVA. All statistical analyses were performed on SPSS (IBM) and GraphPad Prism v9.

Results

Patients characteristics

452 newly diagnosed, DMARD-naive RA patients from the ERA UCLouvain Brussels cohort were included in the analysis. Demographic and clinical characteristics of patients at baseline are shown in Table 1. Briefly, patients were mostly female (72.3 %), mean age was 47.5 years, ACPA and RF positivity occurred in 64.8 % and 63.3 % respectively, erosive disease was observed in 44 % and mean DAS28CRP was 4.6 (moderate disease activity). Median symptoms duration reported by the patients was 11.9 months [IQR 5.0–25.1] (data available for $n = 404$ patients).

Patterns of tender and swollen joint distribution in ERA

In total, 19,888 joints were clinically assessed for swelling and tenderness at baseline, of which 3685 (18.5 %) were swollen (SJ, mean per patient: 8.2) and 4982 (25.1 %) were tender (TJ, mean per patient: 11.2). The average spatial distribution of SJ and TJ is shown in Fig. 1. Wrist was by far the most frequently swollen and tender joint site (in 57 % and 50.8 % of patients, respectively), followed by PIP2 (38.8 %, and 37.4 %, respectively) and PIP3 (39.6 %, and 36.7 % respectively. No swelling or tenderness was observed in acromioclavicular and sternoclavicular joints; these were therefore removed from subsequent analysis. As expected, swelling and tenderness were well-correlated for most joints (Fig. 1); the shoulder and MTP1 joints were exceptions.

We postulated that dimension-reduction analytical approaches of such large dataset matrices would allow for the identification of joint pattern involvements, not previously recognized by clinicians. Thus, we applied principal component analysis (PCA) on SJ and TJ matrices to

Table 1
Clinical characteristics of $n = 452$ RA patients at inclusion.

Female	72.3 %
Age, years (mean ± SD)	47.5 ± 14.9
Smoking (active)	24.0 %
TJC total (mean ± SD) *	11.2 ± 9.5
SJC total (mean ± SD) *	8.2 ± 6.8
CRP mg/dL (mean ± SD)	2.2 ± 3.2
VAS physician (mean ± SD)	37.8 ± 23.9
VAS patient (mean ± SD)	56.9 ± 27.8
HAQ (mean ± SD)	1.23 ± 0.86
DAS28-CRP (mean ±SD)	4.6 ± 2.3
CDAI (mean ±SD)	21.0 ± 14.0
SDAI (mean ±SD)	23.2 ± 14.9
ACPA positivity	64.8 %
RF positivity	63.3 %
Erosive disease	44.0 %

ACPA: anti-citrullinated peptides antibody, CDAI: clinical disease activity index, HAQ: health assessment questionnaire, CRP: C-reactive protein, DAS28CRP: Disease activity score 28-CRP, RF: rheumatoid factor, SD: standard deviation, SDAI: simplified disease activity index, SJC: swollen joint count, TJC: tender joint count, VAS: Visual analog scale.
* : out of 44 assessed joints, see *Methods*.

	Total Swollen (N)	Total Tender (N)	Swollen *vs* Tender (φc)	Total Swollen (%)	Total Tender (%)
Shoulder	27	225	0.29	3.0	24.9
Elbow	74	139	0.49	8.2	15.4
Wrist	515	459	0.57	57.0	50.8
Knee	186	270	0.54	20.6	29.9
Ankle	209	266	0.62	23.1	29.4
MCP1	251	266	0.48	27.8	29.4
MCP2	311	303	0.53	34.4	33.5
MCP3	235	272	0.5	26.0	30.1
MCP4	75	161	0.36	8.3	17.8
MCP5	89	174	0.46	9.8	19.2
PIP1	89	96	0.64	9.8	10.6
PIP2	351	338	0.58	38.8	37.4
PIP3	358	332	0.56	39.6	36.7
PIP4	178	242	0.58	19.7	26.8
PIP5	151	221	0.49	16.7	24.4
MTP1	67	187	0.15	7.4	20.7
MTP2	166	281	0.54	18.4	31.1
MTP3	169	295	0.48	18.7	32.6
MTP4	114	263	0.47	12.6	29.1
MTP5	70	192	0.41	7.7	21.2

Fig. 1. Absolute number (N) and relative frequency (%) of joint swelling and tenderness for each joint site in $n = 452$ early untreated RA patients at baseline ($n = 19,888$ joints assessed clinically). Correlation between swelling and tenderness is shown for each joint in the 4th column, calculated with Cramer's coefficient (φc). All p-values <0.001.

assess for clusters of joints prone to be concurrently involved in individuals. We found a similar distribution for both SJ and TJ, clearly showing that some joints tended to be simultaneously inflamed (Fig. 2**A, B**). We found three apparent clusters, representing different anatomical sites: one with MTP1–5 joints, one with hand joints (MCPs and PIPs), and one with larger joints. The wrist joint seemed to be located at the boundary between the hand and large joint clusters. We replicated the same analysis separately for ACPA-positive and ACPA-negative patients and found very similar results (**Supplementary Figure 1A,B**), suggesting that the observed clustering is independent of ACPA status. To ensure that pooling left and right joints into a single value did not affect results (See Methods), PCA was also performed on all swollen joints with laterality taken into account and yielded comparable results (**Supplementary Figure 2**).

To further quantify this involvement of joints in specific clusters, we built a correlation matrix for SJ, which confirmed our initial observation (Fig. 2**C and Supplementary Figure 3**). Thus, swollen joint pairs showing the best correlations were MTP2 & MTP3, MTP3 & MTP4, PIP2 & PIP3, MCP2 & MCP3, MTP2 & MTP4 (Fig. 2**C**). Notably, large joints display low to no correlations, suggesting their clustering on PCA is mostly driven by lack of similarity with the other clusters.

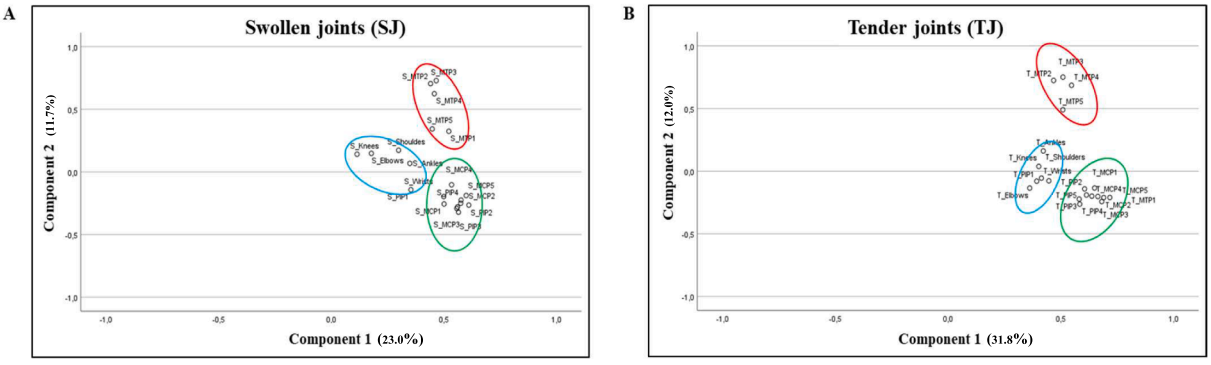
Site-specific baseline erosions in ERA

We next set out to analyze the presence of baseline erosions at the anatomical site level. Higher rates of bone erosion were observed in the MTP cluster (especially MTP5), followed by the wrist (Fig. 3). This contrasts with the lower frequency of swelling and tenderness in the feet joints (Fig. 1**).** Erosions were less frequent in the MCP+PIP group, contrasting with a higher rate of swelling and tenderness at these locations. Erosions was almost absent in large joints.

Association between joint location and clinical characteristics

Next, we investigated the link between joint swelling location and clinical features (age, smoking status, ACPA/RF positivity, erosive disease, Health Assessment Questionnaire (HAQ), and disease activity). We built a PCA plot including SJ distribution and these parameters. No specific clinical feature seemed to strongly segregate with particular joint clusters (**Supplementary Figure 4A**).

In a complementary approach, we divided patients into 2 subgroups according to presence/absence of swelling for each joint location and compared clinical characteristics between these groups (**Supplementary Table 1**). As expected, swelling of most joints (shoulder, elbow,



C

Swelling correlation across different joint sites

	Sh.	Elbow	Wrist	Knee	Ankle	MCP1	MCP2	MCP3	MCP4	MCP5	PIP1	PIP2	PIP3	PIP4	PIP5	MTP1	MTP2	MTP3	MTP4	MTP5
Shoulder																				
Elbow	0.228																			
Wrist	0.046	0.056																		
Knee	0.101	0.137	0.067																	
Ankle	0.184	0.085	0.17	0.134																
MCP1	0.07	0.065	0.215	-0.04	0.094															
MCP2	0.153	0.011	0.269	0	0.124	0.366														
MCP3	0.148	0.058	0.194	0.002	0.185	0.315	0.541													
MCP4	0.269	0.106	0.158	0.083	0.18	0.185	0.295	0.393												
MCP5	0.183	0.091	0.198	0.13	0.165	0.29	0.339	0.324	0.497											
PIP1	0.055	0.041	0.134	0.038	0.127	0.297	0.214	0.242	0.162	0.269										
PIP2	0.049	0.022	0.191	-0.03	0.18	0.304	0.354	0.25	0.154	0.259	0.344									
PIP3	0.016	-0.021	0.191	-0.013	0.093	0.26	0.303	0.298	0.194	0.24	0.251	0.567								
PIP4	0.044	0.102	0.157	0.033	0.142	0.211	0.224	0.254	0.263	0.288	0.235	0.435	0.448							
PIP5	0.034	0.007	0.122	0.013	0.125	0.276	0.178	0.212	0.174	0.366	0.398	0.393	0.41	0.478						
MTP1	0.269	0.168	0.041	0.11	0.15	0.17	0.168	0.208	0.314	0.221	0.231	0.139	0.109	0.198	0.198					
MTP2	0.12	0.058	0.073	0.05	0.197	0.088	0.1	0.098	0.095	0.081	0.122	0.117	0.093	0.119	0.048	0.326				
MTP3	0.115	0.05	0.108	0.069	0.147	0.092	0.11	0.049	0.086	0.114	0.112	0.147	0.122	0.14	0.084	0.316	0.842			
MTP4	0.111	0.083	0.087	0.063	0.072	0.073	0.124	0.069	0.106	0.144	0.071	0.188	0.121	0.164	0.123	0.274	0.523	0.662		
MTP5	0.176	0.154	0.038	0.06	0.115	0.117	0.172	0.108	0.204	0.205	0.132	0.186	0.112	0.112	0.162	0.428	0.235	0.242	0.416	

Fig. 2. **A-B:** Principal component analysis on swollen joint (A) and tender joint (B) matrices of 20 × 452 = 9040 individual anatomical joint location. Percentage of variation explained by each principal component is shown on the graph. Identified clusters are circled in red (MTP cluster), green (MTP-PIP cluster) and blue (large joints cluster). **C:** Cramer's coefficient (φc) matrix showing correlation of joint swelling between all anatomical sites. Joint clusters are circled as in **A-B**.

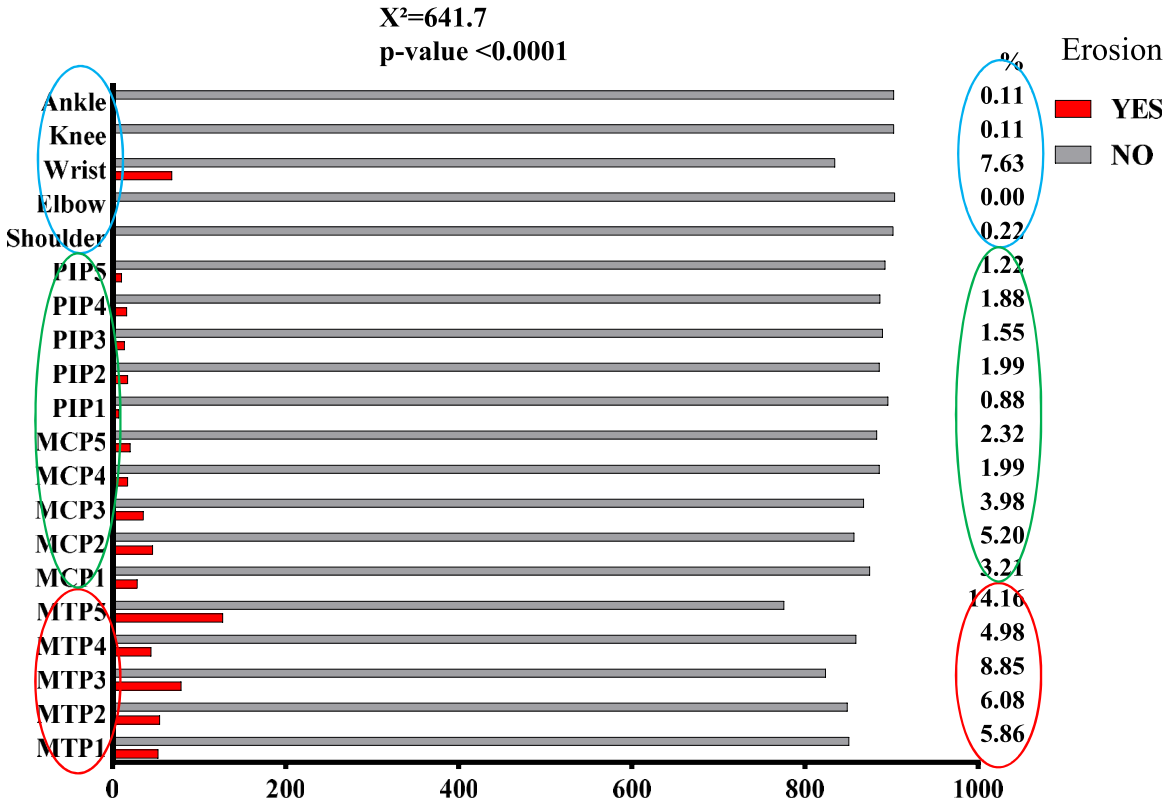


Fig. 3. Frequency of baseline erosions for each joint site in $n = 452$ early untreated RA patients. The fraction of joint with bone erosion is shown for each anatomical site on the right of the figure. Joint clusters are circled as in Fig. 2. X^2 and p-values from chi-square test are shown above the panel.

wrist, knee, ankle, MCP1–5, PIP 1–5, and MTP1) is associated with higher DAS28CRP, as with higher HAQ scores (wrist, knee, ankle, MCP 2,4–5, and PIP1,4). Notably, the association with increased HAQ was most pronounced for wrist and MCP4-5 involvement, whereas MTP joints were not associated with higher HAQ. This tendency was not confirmed after correction for confounding factors: in multiple linear regression analysis with HAQ as dependent variable, only DAS28CRP, baseline erosions and female gender significantly predicted HAQ values (and not joint location) (**Supplementary Table 2**). Furthermore, we found that MTP4,5 are more often swollen in younger patients, and wrist and MCP2-4 in older patients. The elbow seemed more frequently swollen in females, and PIP4 in males. Swelling in MCP1 is associated with erosive disease, whereas swelling of small joints (MCP1-3, PIP3 and MTP2) is associated with the presence of ACPA/RF. By contrast, knee swelling more frequently manifests in non-erosive and seronegative disease. We found no association between specific joint location and smoking status.

Joint-specific response to therapy

Finally, we analyzed the impact of methotrexate (MTX) therapy on joint swelling across the different anatomical sites. We focused on a homogenously treated group (n = 101 patients, started under MTX monotherapy 15 mg increased to 20 mg weekly, without systemic or intra-articular steroids). As expected, the number of swollen joints decreased significantly after 6 months (Fig. 4**A),** but response to methotrexate was only partial: out of the 606 SJ at baseline, swelling persisted in 220 joints (36.3 %). Having shown that specific sites are associated with distinct arthritis distribution patterns and erosion susceptibility, we wondered whether some locations are more resistant to treatment. We found no significant difference in joint swelling persistence across joint sites after 6 months of methotrexate therapy (Fig. 4**B**). The joint with most persistent swelling was the wrist, followed by the MCP2. To increase statistical power, we grouped all joints into the previously identified clusters, but no statistical difference in resolution of joint swelling was observed (Fig. 4**C**). This may suggest that joint-specific response to therapy is not dependent on joint location, at least with MTX monotherapy.

We also investigated whether certain joint locations or clinical features may be predictive of treatment response to MTX, but found no association between these features and remission (defined by DAS28CRP<2.6) (**Supplementary Table 3**).

Discussion

In this study, we confirm a large diversity of involved joint locations

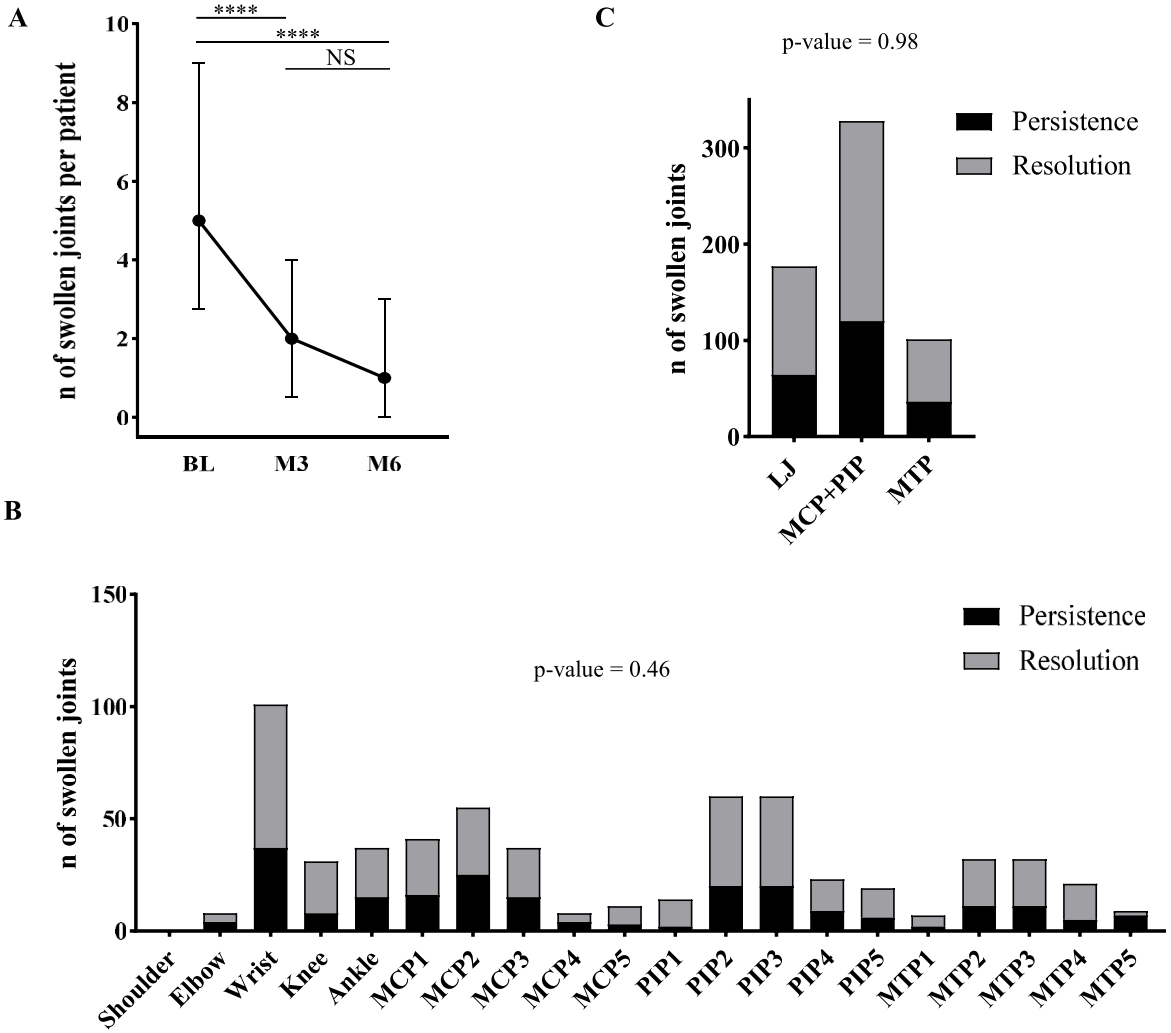


Fig. 4. Evolution of joint swelling after 6 months in n = 101 patients under methotrexate monotherapy. The median and interquartile range of swollen joint per patient at baseline (BL), 3, and 6 months is shown on panel (**A**). The proportion of joints with persistent swelling (black) and swelling resolution at 6 months (grey) are shown for each joint location (**B**) and for each joint cluster (**C**). Of note, analyzing wrist as a separate cluster did not significantly change results. Adjusted p-values of ANOVA with Tukey's multiple comparison with are shown on panel A. p-values of chi-square test are shown on panels B and C. ****: $p < 0.0001$.

in ERA. We leverage unsupervised analysis methods to analyze spatial distribution of joint swelling, tenderness, and bone erosions in a large cohort of early untreated RA patients. We highlight that particular clusters of joints are more likely to be simultaneously involved in RA, particularly an MTP cluster and a hand cluster (PIPs and MCPs). Previous data already suggested the existence of an MTP cluster, also more frequently involved in younger RA patients [12]. Altogether, we show that joint involvement in ERA does not occur "at random" across small joints in ERA. We also confirm that bone erosions are more likely to be present in specific joint sites at baseline in ERA, especially MTP5 (as previously shown by others [3,8,9]), and the wrist (the most frequently tender/swollen joint in our cohort).

Overall, our analysis of site-specific joint involvement strongly points toward the existence of local factors in driving synovial inflammation in ERA. Mechanistic explanations for the simultaneous involvement of specific joint clusters may be multiple [6]. The most intuitive hypothesis would be the existence of "arthritogenic" neo/-autoantigens, differently expressed across joint types, hence inducing preferential recognition by autoreactive T cells in certain locations. In opposition with this hypothesis, we and others have shown that synovial TCR repertoires are largely similar between pairs of joints from the same patients [13,14]. However, these studies have only been performed on inflamed joints, in patients with chronic RA. Another potentially important local player could be joint-resident stromal cells. Thus, we and others have shown that specific transcription factors (particularly HOX genes) are differentially expressed between fibroblasts from large and small joints of RA patients [7,14]. Next, biomechanical constraints are differentially distributed across anatomical sites and likely play a role, especially in the development of bone erosions in MTPs, but also in triggering joint inflammation [6,15,16]. The potential role of lymph nodes in orchestrating local joint inflammation could also contribute to the observed anatomical clustering [17]. Finally, more "systematic factors " driven by ethnicity and/or environment may also influence arthritis pattern, as joint swelling distribution was found to be different between Dutch and Indian RA patients [9].

By contrast with the presence of swelling/tenderness or erosion susceptibility, local response to treatment (resolution of clinical joint swelling) did not seem to be affected by joint site. This may suggest that, although joints have different susceptibility to develop inflammation, similar mechanisms operate in all joints once synovitis has been triggered [14,18]. Nevertheless, swelling at different joint sites is associated with different erosive risk and functional impacts . The latter observation was also found by previous work showing that synovitis at distinct MCPs site associates with different impact on the grip force [19]. Altogether, this raises the question whether arthritis location should also be taken into account when defining the therapeutic targets [20].

The strength of correlations observed within joint clusters is low to moderate, not perhaps surprising given these patterns have not been previously recognized by clinicians. This illustrates the power of applying unbiased analytic approaches to large clinical datasets, to provide clinically and pathologically relevant insights [21–24]. In this regard, the monocentric design of our study is certainly an advantage, ensuring more uniform clinical and radiological assessment. Interestingly, a similar approach in Juvenile Idiopathic Arthritis (a group of heterogenous immune-mediated chronic arthritis with pediatric onset) also highlighted the correlated involvement of MTP joints, and MCP-PIP joints [24].

Besides their pathophysiological value, our data also highlight clinically-relevant information. Joint count (not location) is a major component of disease activity monitoring in RA. The original DAS (assessment of 44 joints swelling/tenderness) was replaced by the DAS28 and the clinical disease activity index (CDAI) or simplified clinical disease activity index (SDAI) score, excluding MTP evaluation from standard disease activity assessment tools [25,26]. However, our finding of an MTP cluster in ERA indicates that at least 40 joints should be evaluated in both clinical practice and research trials, as suggested by others [27].

We acknowledge several limitations in our study: first, while we have mostly focused on clinical joint swelling as an indicator of synovial inflammation, other sensitive radiologic modalities (ultra-sound, MRI) would be of interest to investigate synovitis distribution, and to differentiate between synovitis and tenosynovitis [28]. In addition, analysis of infrequently involved joints (such as cervical spine or temporo-mandibular joint) was not performed. Next, response to treatment was only analyzed in a subset of patients with homogenous therapy. Our study is therefore possibly underpowered for the discovery of outcome predictors. The association of joint distribution pattern with occupational factors such as profession, sport, hobbies, etc. would be interesting but challenging to assess (e.g. MTPs and mechanical stress). Finally, swelling of previously uninvolved joints may occur during disease course [29]; consequently, the long-term persistence of joint patterns remains to be to assessed.

In conclusion, we identify patterns of involved joint clusters using unsupervised analysis of arthritis spatial distribution in a large cohort of ERA patients. These joint clusters correspond to different anatomical locations (MTPs, hands and large joints). Joints in each cluster are more frequently simultaneously involved, and have different susceptibilities to bone erosions. Our observations strongly support an important role for joint-specific factors in driving synovitis and erosions in ERA. Further research is needed to gain better insights into joint-specific RA synovitis susceptibility.

CRediT authorship contribution statement

Laura Bricman: Investigation, Data curation, Writing – original draft. **Clément Triaille:** Formal analysis, Conceptualization, Methodology, Writing – original draft. **Emilie Sapart:** Investigation, Data curation. **Tatiana Sokolova:** Investigation, Data curation, Formal analysis, Methodology, Software. **Aleksandra Avramovska:** Investigation, Data curation. **Francesco Natalucci:** Formal analysis, Methodology, Software. **Thomas Kirchgesner:** Investigation, Data curation. **Patrick Durez:** Investigation, Data curation, Formal analysis, Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Durez Patrick reports financial support was provided by CAP48 (RTBF). Triaille Clement reports financial support was provided by Fund for Scientific Research. Triaille Clement reports financial support was provided by WBI World. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152524.

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