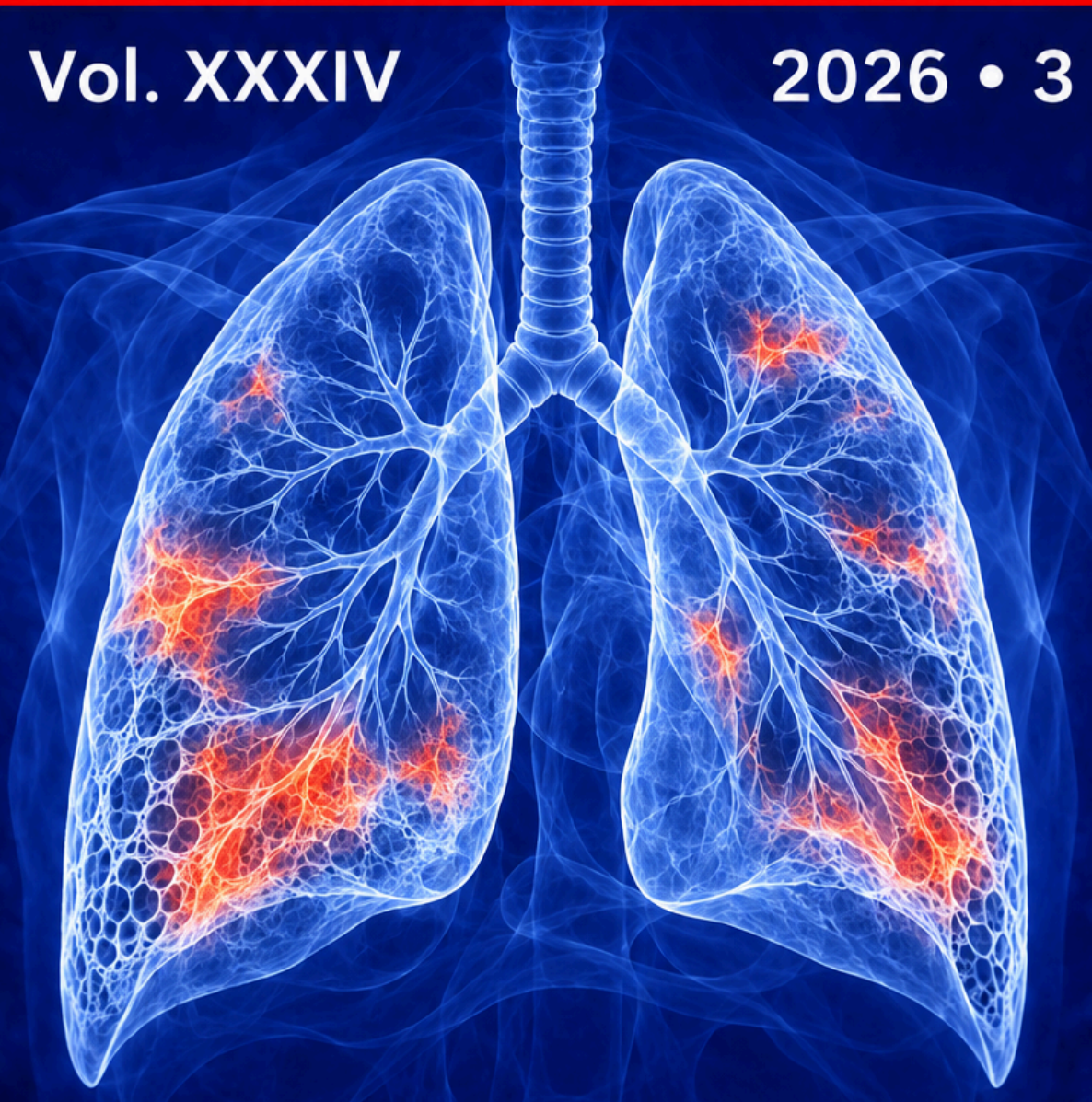
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Терапевтични показания: Ofev е показан при възрастни за лечение на идиопатична белодробна фиброза (ИБФ). Ofev е показан също при възрастни за лечение на други хронични фиброзиращи интерстициални белодробни болести (ИББ) с прогресивен фенотип. Ofev е показан при деца и юноши на възраст от 6 до 17 години за лечение на клинично значими прогресивни фиброзиращи интерстициални белодробни болести (ИББ). Ofev е показан при възрастни, юноши и деца на възраст 6 и повече години за лечение на свързана със системна склероза интерстициална белодробна болест (ССк-свързана ИББ). **Дозировка и начин на приложение:** Препоръчителната доза нинтеданиб при възрастни пациенти е 150 mg два пъти дневно, приложена приблизително през 12 часа. Дневна доза от два пъти по 100 mg се препоръчва за използване само при пациенти, които са показали непоносимост към дневна доза от два пъти по 150 mg. Не трябва да се надвишава препоръчителната дневна доза от 300 mg. Препоръчителната доза Ofev при педиатрични пациенти на възраст от 6 до 17 години е базирана на телото на пациента и се прилага два пъти дневно, през интервал от приблизително 12 часа. Дозата трябва да бъде коригирана спрямо телото в хода на лечението.
Специални популации: Пациенти в старческа възраст (≥ 65 год) - като цяло не са наблюдавани разлики в безопасността и ефикасността при пациенти в старческа възраст. Не се налага априори адаптиране на дозата в зависимост от възрастта на пациентите. Бъбречно увреждане: Не се налага корекция на началната доза при пациенти с леко до умерено бъбречно увреждане. Чернодробно увреждане: При пациенти с леко чернодробно увреждане(Child Pugh A) препоръчителната доза Ofev е 100 mg два пъти дневно с интервал приблизително 12 часа. Не се препоръчва лечение с Ofev при пациенти с умерено (Child PughB) и тежко (Child PughC) чернодробно увреждане. **Противопоказания:** Бременност. Свръхчувствителност към нинтеданиб, фъстъци или соя, или към някое от помощните вещества. **Специални предупреждения и предпазни мерки при употреба:** Стомашно-чревни нарушения: Диарията е най-честата стомашно-чревна нежелана реакция, за която се съобщава. Пациентите трябва да бъдат лекувани при първите прояви с адекватно хидратиране и антидиарични лекарствени продукти, като лоперамид, като може да се намаляване на дозата или прекъсване на лечението. Лечението с Ofev може да се поднови с намалена доза (100 mg два пъти дневно при възрастни пациенти) или с цялата доза (150 mg доза два пъти дневно при възрастни пациенти). Гадене и повръщане. Често съобщавани нежелани реакции от страна на стомашно-чревния тракт са гадене и повръщане. При повечето пациенти с гадене и повръщане съботието е леко до умерено. Чернодробна функция: Не са проучени безопасността и ефикасността на Ofev при пациенти с умерено (Child PughB) или тежко (Child PughC) чернодробно увреждане. По тази причина не се препоръчва лечение с Ofev при такива пациенти. Повишенията на чернодробните ензими (ALT, AST, алкална фосфатаза (ALKP) в кръвта,гамаглутамилтрансфераза (GGT)) и билирубина в повечето случаи са обратими след намаляване на дозата или прекъсване на лечението. Ако се установи повишаване на трансаминазите (AST или ALT) > 3 пъти ГГН, препоръчително е да се намали дозата или да се прекрати лечението с Ofev. Бъбречна функция: В случай на бъбречно увреждане/бъбречна недостатъчност, трябва да се обмисли корекция на терапията. Кръвоизлив: Потискането на рецепторите на съдовия ендотелен растежен фактор (VEGFR) може да е свързано с повишен риск от кървене. Пациентите с известен риск за кървене, включително пациентите с наследствено предразположение към кървене или пациентите, които получават антикоагулантно лечение цяла доза, не са включени в проучванията. Тези пациенти трябва да бъдат лекувани с Ofev само ако очакваната полза превишава потенциалния риск. Артериални тромбоемболични събития: Пациентите с анамнеза за скорошен инфаркт на миокарда или инсулт са били изключени от изпитванията. Бъдете внимателни, когато лекувате пациенти с по-висок сърдечносъдов риск, включително известна исхемична болест на сърцето. Венозна тромбоемболия: Не се наблюдава повишен риск от венозна тромбоемболия при лекуваните с нинтеданиб пациенти. Перфорации на стомашно-чревния тракт и исхемичен колит: Необходимо е особено внимание, когато се лекуват пациенти с предходна коремна операция, анамнеза за пептична язва, дивертикулна болест или получаващи съпътстващи кортикостероиди или НСПВС. Лечението с Ofev трябва да се започва най-малко 4 седмици след коремна операция. Хипертония: Прилагането на Ofev може да повиши кръвното налягане. Системното кръвно налягане трябва да се измерва периодично и според клиничните показания. **Бременност:** Няма информация относно употребата на Ofev при бременни жени, но предклиничните проучвания при животни са показали репродуктивна токсичност на това активно вещество. Ако пациентката забременее по време на приема на Ofev, лечението трябва да се преустанови и тя трябва да бъде информирана за потенциалния риск за плода. **Кърмене:** Няма информация за екскрецията на нинтеданиб и неговите метаболити в кърмата. Не може да се изключи риск за новороденте/кърмачетата. Кърменето трябва да се преустанови по време на лечение с Ofev. **Фертилитет:** На база на предклиничните проучвания няма данни за нарушение на фертилитета при мъжки животни. Ефекти върху способността за шофиране и работа с машини: Ofev повлиява в малка степен способността за шофиране и работа с машини. Пациентите трябва да бъдат посъветвани да бъдат внимателни, когато шофират или използват машини по време на лечението си с Ofev. **Педиатрична популация:** Данните относно употребата на нинтеданиб при педиатрични пациенти са ограничени до такива от малка подгрупа фиброзиращи интерстициални белодробни болести. Тази подгрупа не обхваща всички етиологии, свързани с прогресивна фиброзираща интерстициална белодробна болест при педиатрични пациенти. **Нежелани лекарствени реакции:** Най-често съобщаваните нежелани лекарствени реакции, свързани с употребата на нинтеданиб, включват диария; гадене и повръщане, болка в корема, намален апетит, загуба на тегло и повишаване на чернодробните ензими. *Диария:* В клиничните изпитвания диарията е най-честото събитие, за което се съобщава. При повечето пациенти събитието е с лека до умерена тежест. Повече от две трети от пациентите, които получават диария, съобщават за първа поява през първите три месеца на лечението. При повечето пациенти събитията се овладяват с противодиарийно лечение, намаляване на дозата или прекъсване на лечението. **Повишени чернодробни ензими:** В изпитванията INPULSIS повишаване на чернодробните ензими (вж. точка 4.4) се съобщава при 13,6 % спрямо 2,6 % от пациентите, лекуваните съответно с Ofev и плацебо. Повишенията на чернодробните ензими са обратими и не са свързани с клинично проявено чернодробно заболяване. Предозиране: Няма специфичен антидот или лечение при предозиране на Ofev. В случай на предозиране, лечението трябва да се преустанови и да се предприемат подходящи общи поддържащи мерки. **Срок на годност:** Да не се съхранява в оригиналната опаковка, за да се предпази от влага. По лекарско предписание. Преди да предпишете Ofev®, моля консултирайте се с актуалната Кратка характеристика на продукта (КХП), която е достъпна при сканиране на QR кода, както и на go.boehringer.com/OFV_SmPC. Пълната, актуална КХП може да Ви бъде предоставена и от медицинския представител на Boehringer Ingelheim.За пълна информация: Представителство за България Бьорингер Ингелхайм РЦВ ГмбХ и Ко КГ - клон България,София 1505, Сердика офиси, бул. Ситняково 48, ет. 8, тел.: 02/958 79 98.

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Original Article

Clinical and Serological Factors Associated with Radiographic Joint Damage Assessed by the Larsen Score in Egyptian Patients with Rheumatoid Arthritis: A Cross-Sectional Study

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Running title: Radiographic Damage in Egyptian RA

Abstract

Background: Radiographic joint damage is a primary determinant of long-term disability in rheumatoid arthritis (RA). This study aimed to identify the clinical and serological factors associated with structural damage, as quantified by the Larsen score, in a cohort of Egyptian patients with RA. Methods: This cross-sectional study enrolled 162 Egyptian patients with RA who fulfilled the 2010 ACR/EULAR classification criteria. Clinical manifestations, disease activity (DAS28-ESR), functional disability (HAQ), and serological profiles (RF and anti-CCP) were systematically recorded. Radiographic damage in the hands and feet was evaluated using the Larsen scoring method by two independent assessors. Multivariable linear regression, utilizing log-transformed Larsen scores, was conducted to determine factors independently associated with structural damage. Results: The cohort was predominantly female (91.4%), with a mean age of 38.1±9.2 years and a mean disease duration of 3.74±3.4 years. The median Larsen score was 5 (interquartile range [IQR], 2–14), demonstrating

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excellent inter-reader agreement (ICC=0.92). Univariate analysis revealed that patients with subcutaneous nodules and anti-CCP positivity exhibited significantly higher Larsen scores ($p<0.01$). Upon multivariable analysis, prolonged disease duration ($\beta=0.46$, $p<0.001$), the presence of subcutaneous nodules ($\beta=0.22$, $p=0.002$), and anti-CCP positivity ($\beta=0.14$, $p=0.035$) emerged as independent correlates of advanced radiographic damage, collectively explaining 34.2% of the variance (adjusted $R^2=0.342$, $p<0.001$). Conclusions: Prolonged disease duration, subcutaneous nodules, and anti-CCP positivity are independently associated with exacerbated radiographic joint damage in Egyptian patients with RA. Utilizing these accessible clinical markers can effectively stratify patients at elevated structural risk, thereby underscoring the critical need for prompt and sustained disease control.

Keywords: rheumatoid arthritis; Larsen score; radiographic damage; anti-CCP; disease duration; structural joint damage

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, which, if inadequately managed, leads to progressive joint destruction and functional decline [1]. The disease affects approximately 0.5% to 1% of the global adult population, with a higher predilection for women [2]. Despite substantial advancements in disease-modifying therapies, structural joint damage remains a critical clinical outcome, as it reflects the cumulative inflammatory burden and strongly correlates with long-term disability [3,4].

Radiographic assessment continues to be integral in evaluating structural joint damage in RA. Various scoring systems have been established for this purpose, notably the Sharp/van der Heijde method - which independently quantifies erosions and joint space narrowing - and the Larsen method, which offers a comprehensive global assessment of structural damage per joint [5,6]. The Larsen method is a robust, semiquantitative tool that grades individual joints on a scale from 0 to 5 based on the severity of erosive changes and joint space narrowing [5]. While the Sharp/van der Heijde method is predominantly utilized in clinical trials owing to its superior sensitivity to longitudinal change, the Larsen method provides distinct practical advantages in cross-sectional studies, including clinical efficiency and a strong correlation with functional outcomes and alternative scoring systems [5,7]. In resource-constrained settings where advanced imaging

modalities are not always accessible, the Larsen method offers a validated, time-efficient approach for the cross-sectional evaluation of cumulative structural damage. Consequently, the Larsen method was selected for the present study due to its proven reliability, feasibility, and suitability for assessing total structural burden in this cohort.

Several clinical and serological factors have been implicated in radiographic progression in RA, including longer disease duration, persistent inflammatory activity, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and extra-articular manifestations [8–10]. In particular, anti-CCP antibodies have been consistently associated with erosive disease and a more severe structural phenotype [10]. Identifying such factors is central to risk stratification and may inform treatment intensity under modern treat-to-target strategies [11,12].

While predictors of radiographic progression have been extensively investigated in Western and East Asian populations, data originating from the Middle East and North Africa (MENA) region remain sparse [13–15]. Specifically in Egypt, very few studies have explored the association between clinical or serological variables and radiographic damage utilizing a validated scoring system in patients with RA [13,16,17]. Furthermore, the relative contribution of these factors to structural damage has yet to be comprehensively elucidated within Egyptian RA cohorts.

Therefore, this study aimed to identify the clinical and serological factors associated with radiographic joint damage, as quantified by the Larsen score, in Egyptian patients with RA, and to delineate their relative contributions to structural deterioration.

2. Materials and Methods

2.1 Study design and setting

This cross-sectional observational study was conducted at the Rheumatology Department of a tertiary care university hospital in Cairo, Egypt, between January 2023 and December 2023. The study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cross-sectional studies [18].

2.2 Study population

The study enrolled 162 consecutive adult patients diagnosed with RA according to the 2010 American College of Rheumatology/European

League Against Rheumatism (ACR/EULAR) classification criteria [19]. Patients were recruited consecutively from all eligible attendees of the outpatient rheumatology clinic during the study period; no random sampling or convenience-based sub-selection was applied beyond the inclusion and exclusion criteria specified below.

2.3 Inclusion criteria

Inclusion criteria comprised: age ≥ 18 years, a confirmed diagnosis of RA based on the 2010 ACR/EULAR criteria, and the availability of hand and foot radiographs of sufficient quality for scoring.

2.4 Exclusion criteria

Patients were excluded if they presented with overlap connective tissue disease, psoriatic arthritis or alternative inflammatory arthropathies, were pregnant, or possessed incomplete clinical, laboratory, or radiographic records.

2.5 Sample size justification

The sample size was determined based on the established methodological guideline recommending a minimum of 10–20 observations per predictor variable for multivariable linear regression [20,21]. Anticipating a final model incorporating up to six candidate predictors, a minimum of 90–120 patients was mandated. The enrolled sample of 162 patients sufficiently exceeded this threshold, ensuring robust statistical power.

2.6 Ethical considerations

The study protocol was approved by the Institutional Ethics Committee of the Faculty of Medicine of our institution (Approval No: 0000126). Written informed consent was obtained from all participants prior to enrollment, in strict adherence to the principles of the Declaration of Helsinki.

2.7 Clinical assessment

All participants underwent a comprehensive clinical evaluation. Documented variables included age, sex, disease duration (defined as the time from symptom onset to the date of clinical assessment), morning stiffness duration, pain intensity (measured via a 100-mm visual analog scale [VAS]), 28-joint tender joint count (TJC28), and 28-joint swollen joint count (SJC28). The presence of subcutaneous nodules was determined through clinical examination.

2.8 Disease activity assessment

Disease activity was quantified utilizing the Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR), computed via the standard formula. Patients were stratified into four distinct categories: remission (< 2.6), low disease activity (2.6 to < 3.2), moderate disease activity (3.2 to ≤ 5.1), and high disease activity (> 5.1).

2.9 Functional assessment

Functional disability was appraised using the Health Assessment Questionnaire (HAQ), with scores ranging from 0 to 3; higher scores denote more severe functional impairment [22].

2.10 Laboratory assessment

Laboratory investigations encompassed: erythrocyte sedimentation rate (ESR) assessed via the Westergren method, rheumatoid factor (RF) testing, and anti-cyclic citrullinated peptide (anti-CCP) antibodies. RF and anti-CCP were determined qualitatively (positive/negative) as part of routine clinical care; quantitative titers were not available for this cohort. C-reactive protein (CRP) levels were not routinely available for the entire cohort and were consequently excluded from the analysis. The reliance on qualitative rather than quantitative data for RF and anti-CCP is acknowledged as a methodological limitation and is addressed in the discussion.

2.11 Radiographic assessment

Plain radiographs of both hands (posteroanterior view) and feet (anteroposterior view) were acquired for all participants. Radiographic joint damage was evaluated using the Larsen method [5], which grades the severity of structural abnormalities in each joint on a scale from 0 to 5:

Grade 0: Normal; Grade 1: Slight abnormality (periarticular soft tissue swelling or osteoporosis); Grade 2: Definite early abnormality (erosion and joint space narrowing); Grade 3: Medium destructive abnormality (marked erosion and joint space narrowing); Grade 4: Severe destructive abnormality (large erosions, joint deformity); Grade 5: Mutilating abnormality (original articular surfaces destroyed).

A total of 32 joints were assessed per patient (10 metacarpophalangeal joints, 8 proximal interphalangeal joints of the hands, both wrists [each evaluated as a single unit], 10 metatarsophalangeal joints, and both interphalangeal joints of the great toes), resulting in a potential total score range of 0–160. Radiographs were independently scored by two trained assessors who remained blinded to the clinical data. The mean of their

respective scores was utilized for the final analysis. Inter-reader agreement, evaluated using the two-way random, single-measures intraclass correlation coefficient (ICC), was 0.92 (95% CI 0.89–0.95), signifying excellent concordance.

2.12 Treatment data

Pharmacological therapies administered at the time of assessment were documented, encompassing methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, corticosteroids, and folic acid supplementation.

2.13 Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on distribution. Categorical variables were presented as frequencies and percentages.

Normality was assessed using the Shapiro–Wilk test. Because the Larsen score was positively skewed, non-parametric tests were used for univariate analyses. Spearman's rank correlation coefficient was used to assess associations between Larsen score and continuous variables, with 95% confidence intervals estimated using the bias-corrected and accelerated (BCa) bootstrap method (2000 resamples). Between-group comparisons were performed using the Mann–Whitney U test or Kruskal–Wallis test, as appropriate, with post hoc pairwise comparisons using Dunn's test with Bonferroni correction where indicated.

To address the positive skewness of the Larsen score, a log transformation [ln(Larsen score + 1)] was applied for multivariable linear regression analysis to better satisfy model assumptions of normality and homoscedasticity of residuals. Variables considered clinically relevant or statistically significant in univariate analyses were entered simultaneously into the regression model (forced entry method). Statistical significance for univariate screening was defined as $p < 0.10$. Joint deformities were not included as a predictor variable because they represent a clinical consequence of cumulative structural damage and their inclusion would introduce conceptual circularity with the outcome measure. The incremental contribution of each variable to explained variance (ΔR^2) was assessed using hierarchical entry based on the order of clinical plausibility (disease duration entered first, followed by clinical features, then serological markers). Collinearity was assessed using variance inflation

factors (VIF), and model assumptions were verified by examination of residual plots and the Shapiro–Wilk test of residuals. Results were back-transformed for clinical interpretation where appropriate. A two-sided p value < 0.05 was considered statistically significant.

3. Results

3.1 Patient characteristics

A total of 162 patients with RA were included. The cohort was predominantly female (148/162, 91.4%), with a mean age of 38.1 ± 9.2 years. Mean disease duration was 3.74 ± 3.4 years, and the median Larsen score was 5 (IQR 2–14), indicating substantial variability in structural damage across the cohort.

Subcutaneous nodules were present in 27 patients (16.7%), and joint deformities were observed in 52 (32.1%). Anti-CCP positivity was detected in 97 patients (59.9%), and RF positivity in 128 (79.0%). Double seropositivity (anti-CCP and RF positive) was present in 88 patients (54.3%), whereas 25 patients (15.4%) were seronegative for both markers. Nearly half of the cohort had high disease activity (46.3%), while only 6.2% were in DAS28-ESR remission. Methotrexate was the most frequently used treatment (72.8%), followed by corticosteroids (35.2%) and hydroxychloroquine (24.7%) (Table 1).

Table 1. Baseline demographic, clinical, laboratory, and treatment characteristics of the study population (N = 162)

Variable	Value
Age, years	38.1 ± 9.2
Female sex, n (%)	148 (91.4)
Disease duration, years	3.74 ± 3.4
Morning stiffness, min	34.7 ± 50.2
Pain VAS, mm	49.8 ± 26.1
Tender joint count (0–28)	8.3 ± 6.8
Swollen joint count (0–28)	5.9 ± 5.8
DAS28-ESR	4.93 ± 1.38
HAQ score	0.87 ± 0.76
ESR, mm/h	47.0 ± 26.3
Larsen score, median (IQR)	5 (2–14)
Subcutaneous nodules, n (%)	27 (16.7)
Joint deformities, n (%)	52 (32.1)

Anti-CCP positive, n (%)	97 (59.9)
RF positive, n (%)	128 (79.0)
Double seropositive, n (%)	88 (54.3)
Seronegative for both markers, n (%)	25 (15.4)
DAS28-ESR remission, n (%)	10 (6.2)
Low disease activity, n (%)	15 (9.3)
Moderate disease activity, n (%)	62 (38.3)
High disease activity, n (%)	75 (46.3)
Methotrexate use, n (%)	118 (72.8)
Hydroxychloroquine use, n (%)	40 (24.7)
Corticosteroid use, n (%)	57 (35.2)
Leflunomide use, n (%)	14 (8.6)
Sulfasalazine use, n (%)	10 (6.2)

Data are presented as mean ± SD unless otherwise indicated. Abbreviations: VAS, visual analog scale; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; IQR, interquartile range.

3.2 Correlation between Larsen score and continuous variables

Among continuous variables, disease duration showed the strongest association with radiographic damage, with a moderate positive correlation with Larsen score ($r_s = 0.52$, 95% CI 0.39–0.63; $p < 0.001$). Age showed a weak but statistically significant positive correlation ($r_s = 0.18$, 95% CI 0.03–0.32; $p = 0.022$).

No significant correlations were observed between Larsen score and morning stiffness duration, pain VAS, TJC28, SJC28, DAS28-ESR, HAQ score, or ESR (all $p > 0.05$) (Table 2).

Table 2. Correlation between Larsen score and continuous variables

Variable	Spearman's r_s	95% CI*	p value
Age (years)	0.18	0.03 to 0.32	0.022
Disease duration (years)	0.52	0.39 to 0.63	<0.001
Morning stiffness (min)	0.11	−0.05 to 0.26	0.162
Pain VAS (mm)	−0.02	−0.17 to 0.14	0.810
Tender joint count	0.08	−0.08 to 0.23	0.308
Swollen joint count	0.03	−0.13 to 0.18	0.712
DAS28-ESR	0.13	−0.03 to 0.28	0.098
HAQ score	0.09	−0.07 to 0.24	0.254
ESR (mm/h)	−0.04	−0.19 to 0.12	0.612

*95% confidence intervals estimated using the bias-corrected and accelerated (BCa) bootstrap method (2000 resamples). Abbreviations: VAS, visual analog scale; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate.

3.3 Univariate comparisons according to categorical variables

Patients with subcutaneous nodules had markedly higher Larsen scores than those without nodules (median 12 [IQR 8–22] vs 4 [IQR 1–10], $p < 0.001$).

Anti-CCP-positive patients had higher Larsen scores than anti-CCP-negative patients (median 8 [IQR 2–16] vs 4 [IQR 0–10], $p = 0.012$). RF positivity was associated with a numerical but non-significant increase in Larsen score (median 6 [IQR 2–14] vs 4 [IQR 0–8], $p = 0.068$). No significant difference in Larsen score was observed between female and male patients ($p = 0.724$).

When stratified by serological profile, double-seropositive patients had the highest radiographic burden, with significantly higher Larsen scores than seronegative patients (median 8 [IQR 3–16] vs 3 [IQR 0–6], $p = 0.012$). Larsen scores also increased significantly across disease-duration categories, from a median of 2 (IQR 0–6) in early disease (≤ 2 years) to 6 (IQR 3–12) in established disease (2–5 years) and 16 (IQR 10–25) in late disease (> 5 years) (overall $p < 0.001$). Post hoc analysis confirmed significant differences between all three disease-duration categories.

Although Larsen score differed across DAS28-ESR categories overall ($p = 0.020$), this association did not remain significant in multivariable analysis (Table 3).

Table 3. Univariate comparisons of Larsen score according to categorical clinical and serological variables

Variable	Group	n	Median Larsen score (IQR)	p value
Anti-CCP	Positive	97	8 (2–16)	0.012
	Negative	65	4 (0–10)	
RF	Positive	128	6 (2–14)	0.068
	Negative	34	4 (0–8)	
Subcutaneous nodules	Present	27	12 (8–22)	<0.001
	Absent	135	4 (1–10)	
Sex	Female	148	5 (2–13)	0.724
	Male	14	5 (2–12)	
	Remission	10	2 (0–3)	0.020

DAS28-ESR category	Low	15	3 (2–10)	
	Moderate	62	5 (2–10)	
	High	75	8 (2–16)	
Serostatus	Double	88	8 (3–16)	0.012
	Single	49	5 (2–10)	
	Seronegative	25	3 (0–6)	
Disease duration category	≤2 years	72	2 (0–6)	<0.001
	2–5 years	52	6 (3–12)	
	>5 years	38	16 (10–25)	

Post hoc Dunn's test with Bonferroni correction for disease duration categories: ≤2 vs 2–5 years, p = 0.008; ≤2 vs >5 years, p < 0.001; 2–5 vs >5 years, p = 0.002. Abbreviations: RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide antibodies; IQR, interquartile range; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate.

3.4 Current treatment and Larsen score

No significant differences in Larsen score were found according to current use of methotrexate, hydroxychloroquine, corticosteroids, leflunomide, or sulfasalazine (all $p > 0.05$). Because treatment choice in routine clinical practice is influenced by disease severity and duration, and because the cross-sectional design does not capture treatment history, delays, or adherence, these findings should be interpreted cautiously and are not reported in the multivariable model.

3.5 Multivariable analysis

Multivariable linear regression analysis using the log-transformed Larsen score [ln(Larsen score + 1)] as the dependent variable identified three variables independently associated with higher radiographic damage: longer disease duration (standardized $\beta = 0.46$, $p < 0.001$), the presence of subcutaneous nodules ($\beta = 0.22$, $p = 0.002$), and anti-CCP positivity ($\beta = 0.14$, $p = 0.035$).

The final model explained 34.2% of the variance in log-transformed Larsen score ($R^2 = 0.355$, adjusted $R^2 = 0.342$; $F = 29.0$; $p < 0.001$). Disease duration accounted for the largest incremental contribution to explained variance ($\Delta R^2 = 0.271$), followed by nodules ($\Delta R^2 = 0.051$) and anti-CCP positivity ($\Delta R^2 = 0.019$). Conversely, almost two-thirds of the variability in radiographic damage remained unexplained by the three identified factors, underscoring the multifactorial nature of structural progression in RA.

Of the six candidate variables entered into the multivariable model, age, RF positivity, and DAS28-ESR were not independently associated with

radiographic damage after adjustment (Table 4). Sex, morning stiffness duration, and ESR did not meet the univariate screening threshold ($p < 0.10$) and were therefore not entered into the multivariable model (Tables 2 and 3).

No relevant multicollinearity was detected (maximum VIF 1.34), and residual diagnostics (residual plots and Shapiro–Wilk test of residuals, $p = 0.14$) were satisfactory, confirming acceptable model fit after log transformation.

Table 4. Multivariable linear regression analysis of factors associated with higher Larsen score†

Predictor	B	SE	Standardized β	95% CI for B	p value
Disease duration (years)	0.14	0.02	0.46	0.10 to 0.18	<0.001
Subcutaneous nodules	0.62	0.20	0.22	0.23 to 1.01	0.002
Anti-CCP positivity	0.28	0.13	0.14	0.02 to 0.54	0.035

†Dependent variable: ln (Larsen score + 1). Model summary: $R = 0.596$; $R^2 = 0.355$; adjusted $R^2 = 0.342$; $F = 29.0$; $p < 0.001$. Incremental contribution to explained variance: disease duration, $\Delta R^2 = 0.271$; subcutaneous nodules, $\Delta R^2 = 0.051$; anti-CCP positivity, $\Delta R^2 = 0.019$. Maximum VIF = 1.34. Shapiro–Wilk test of residuals: $p = 0.14$ (acceptable normality). Age, RF positivity, and DAS28-ESR were also entered into the simultaneous model as candidate variables but did not reach statistical significance (all $p > 0.05$); their coefficients are omitted here for brevity and are available from the corresponding author upon request. Abbreviations: SE, standard error; CI, confidence interval; anti-CCP, anti-cyclic citrullinated peptide antibodies; VIF, variance inflation factor.

4. Discussion

In this cross-sectional study of 162 Egyptian patients with RA, radiographic joint damage as assessed by the Larsen score was independently associated with longer disease duration, subcutaneous nodules, and anti-CCP positivity. Among these variables, disease duration showed the strongest association with structural damage, whereas single-time-point measures of disease activity and inflammatory burden were not independently associated with Larsen score after adjustment.

The prominent role of disease duration observed in this analysis is both biologically and clinically sound. Structural joint damage in RA is fundamentally cumulative; it mirrors the long-term sequelae of persistent synovial inflammation rather than the acute inflammatory state captured during a single clinical encounter. The moderate positive correlation between disease duration and the Larsen score, paired with the substantial escalation of radiographic scores across successive duration strata,

reinforces the paradigm that joint destruction accrues progressively over the disease continuum. These findings align with pivotal longitudinal studies by Lindqvist et al. [23] and Kaarela and Kautiainen [24], which firmly established disease duration as a primary determinant of radiographic damage. Consequently, these observations amplify the critical need for early diagnosis and the aggressive initiation of disease-modifying therapies within the optimal therapeutic window of opportunity [25,26].

Subcutaneous nodules emerged as the second most impactful factor associated with higher Larsen scores. Rheumatoid nodules are universally acknowledged as hallmarks of a severe disease phenotype, frequently corresponding with extra-articular manifestations and entrenched, seropositive disease [27,28]. Their independent correlation with radiographic damage in this cohort suggests that nodular disease functions as a readily accessible clinical indicator for identifying patients facing heightened structural risk. Particularly in resource-constrained settings where access to advanced imaging or sophisticated prognostic assays is limited, the straightforward clinical detection of subcutaneous nodules can critically inform risk stratification.

Furthermore, anti-CCP positivity maintained its independent association with exacerbated Larsen scores within the multivariable model, an outcome not mirrored by RF positivity. This dichotomy is consistent with established literature asserting that anti-CCP antibodies are more intimately linked to erosive disease and structural progression than RF alone [10,29–32]. A plausible biological basis for this dichotomy lies in the direct osteoclastogenic potential of anti-citrullinated protein antibodies: these antibodies bind citrullinated vimentin expressed on the surface of osteoclast precursors, triggering osteoclast differentiation and bone resorption even in the absence of overt synovitis, whereas RF lacks this direct bone-resorptive mechanism [33]. This pathway offers a mechanistic explanation for why anti-CCP, rather than RF, retained independent prognostic value for structural damage in the present cohort. Meyer et al. [30] established that anti-CCP-positive patients suffer greater longitudinal radiographic progression, while Syversen et al. [31] confirmed that anti-CCP maintains prognostic relevance even after stringent adjustment for concurrent clinical variables. The markedly high Larsen scores observed among double-seropositive patients in our study further validate the notion that overlapping seropositivity defines a subgroup with a particularly aggressive structural phenotype. Contemporary data from expansive observational registries, including ESPOIR and METEOR, have consistently

corroborated the enduring prognostic utility of anti-CCP for structural damage, even within modern treat-to-target frameworks [34,35]. Importantly, because RF and anti-CCP were assessed qualitatively in this study, the findings likely underestimate the true strength of the association with antibody titers; quantitative serological measurements, which were not available, would have enabled a more refined analysis of the dose-response relationship between autoantibody levels and structural severity. In particular, RF titer rather than mere seropositivity may carry independent prognostic weight for radiographic progression that is obscured when RF is treated as a simple binary variable; quantitative titer data might therefore have unmasked an independent erosive effect of RF in this cohort that the dichotomous classification used here could not capture. This methodological constraint must be considered when interpreting the serological associations.

A salient observation was the absence of an independent correlation between the Larsen score and concurrent disease activity, as indexed by DAS28-ESR. While univariate analysis indicated higher Larsen scores in patients with elevated disease activity, this relationship was attenuated in the multivariable model. This discrepancy elegantly highlights the conceptual divergence between acute inflammatory activity and cumulative structural detriment. The Larsen score synthesizes irreversible joint architecture damage accumulated over the entire disease trajectory, whereas DAS28-ESR and ESR merely provide a cross-sectional snapshot of the current inflammatory state. Analogous studies have similarly concluded that time-integrated inflammatory burden is a vastly superior predictor of structural progression compared to isolated, point-in-time measurements [36,37]. Therefore, this finding does not diminish the imperative of stringent disease control; rather, it underscores the inherent limitations of utilizing cross-sectional activity metrics to explain historically established radiographic damage.

The choice of the Larsen method over the Sharp/van der Heijde scoring system in the present study merits detailed discussion. The Sharp/van der Heijde method separately scores erosions and joint space narrowing at more joint sites and is considered more sensitive to longitudinal change and early erosive damage, making it the preferred tool in clinical trials evaluating treatment efficacy [6]. However, the Larsen method provides a reliable global assessment of cumulative damage per joint, is more time-efficient, and demonstrates strong correlations with functional outcomes and with the Sharp/van der Heijde method itself [5,7,38]. In the present cross-sectional design, where the objective was to assess the total

burden of structural damage rather than to detect subtle change over time, the Larsen method was considered appropriate and pragmatic. While we acknowledge that the Larsen method may be less sensitive to very small erosions, this limitation is mitigated by the study's focus on clinically evident cumulative joint destruction, which is the primary driver of functional disability. Future studies incorporating the Sharp/van der Heijde method could complement these findings, particularly in cohorts with very early disease.

No significant relationship was found between current treatment and Larsen score. This result should be interpreted cautiously, as observational cross-sectional studies are highly susceptible to confounding by indication. Patients with more severe or longstanding disease are more likely to receive more intensive treatment, and current treatment status does not capture treatment delays, prior therapeutic exposure, treatment adherence, or cumulative control of inflammation [39]. Consequently, residual confounding by unmeasured treatment-related factors - including the time elapsed between symptom onset and DMARD initiation, cumulative glucocorticoid exposure, and prior biologic use - cannot be excluded and may partly explain the associations observed between clinical/serological variables and radiographic damage.

Our results are highly concordant with the limited extant data from the MENA region. Abdel-Nasser et al. [16] previously reported that extended disease duration and seropositivity heralded poorer outcomes in Egyptian RA populations, while a Saudi Arabian cohort analyzed by Almoallim et al. [14] underscored the detrimental impact of diagnostic delays and high regional disease burdens. The present study substantively advances these observations by systematically quantifying the interplay between clinical/serological factors and radiographic damage using a rigorously validated scoring system supported by excellent inter-reader reliability. Nonetheless, the broad concordance between regional and Western cohorts should not obscure context-specific factors that may modulate the magnitude of these associations. Differences in shared epitope and other genetic susceptibility allele frequencies across ethnic groups, variable access to early diagnosis and biologic therapy within national healthcare systems, and disparities in time-to-treatment between MENA and Western settings could all influence the rate and severity of structural progression independently of the clinical and serological factors examined here, and may explain residual heterogeneity in effect sizes across studies.

The study has several clinical implications. First, it underscores the central importance of early recognition and timely treatment of RA to limit cumulative structural damage. Second, it highlights anti-CCP positivity and nodular disease as clinically relevant markers of patients at increased risk of severe radiographic involvement. Finally, it enriches the sparse epidemiological landscape of the MENA region by providing robust data on structural joint damage determinants from a well-characterized Egyptian cohort. In routine practice, these findings suggest that patients presenting with anti-CCP positivity, subcutaneous nodules, or longer disease duration at first assessment may warrant closer radiographic surveillance and a lower threshold for early, intensive treat-to-target strategies, rather than a watch-and-wait approach, even when current disease activity scores appear only moderately elevated.

Several limitations should be considered. First, the cross-sectional design precludes causal inference and does not allow assessment of true radiographic progression over time; accordingly, the identified associations should be viewed as correlates rather than predictors. Second, the study was conducted at a single tertiary center, which may limit generalizability to other populations or practice settings. Third, RF and anti-CCP were assessed qualitatively rather than quantitatively, which precluded evaluation of the dose-response relationship between antibody titers and structural severity; quantitative assessment would have added important prognostic information and might have revealed a significant independent role for RF. Fourth, CRP was not routinely available for all patients and therefore could not be included in the analysis; this is a relevant omission, as CRP is a recognized predictor of radiographic progression. Fifth, important variables such as smoking status, genetic susceptibility (e.g., shared epitope), baseline radiographic damage, and detailed treatment history were not available; in particular, the time elapsed between symptom onset and first conventional DMARD initiation was not systematically captured in this cohort, precluding quantification of treatment delay as a contributor to the structural damage observed. Sixth, the low proportion of male patients (8.6%) limited sex-specific analyses. Seventh, the Larsen method, while offering a validated global assessment of cumulative damage, may be less sensitive to small erosions compared to the Sharp/van der Heijde method; however, given the cross-sectional design and the aim to capture overall structural burden, this limitation is acceptable. Finally, although the model explained approximately one-third of the variance in radiographic damage, a substantial proportion of the variance remained unexplained, likely reflecting unmeasured factors such

as cumulative inflammatory burden, treatment adequacy over time, and genetic determinants.

Despite these limitations, the study has important strengths, including a well-characterized RA cohort, use of standardized 2010 ACR/EULAR classification criteria, radiographic assessment using the validated Larsen method with documented inter-reader reliability, log transformation of the skewed outcome variable, exclusion of conceptually circular predictors, and multivariable modeling of both clinical and serological variables.

5. Conclusions

Within this cross-sectional cohort of Egyptian patients with RA, exacerbated radiographic joint damage - assessed via the Larsen score - was independently and significantly associated with prolonged disease duration, the manifestation of subcutaneous nodules, and anti-CCP positivity. Disease duration emerged as the factor most strongly associated with structural damage. These findings underscore the cumulative nature of structural joint injury in RA and support the importance of early diagnosis and rigorous risk stratification, particularly among patients presenting with anti-CCP seropositivity or a nodular clinical phenotype. Future longitudinal investigations, integrating serial radiographic evaluations and quantitative serological profiling, are essential to validate the predictive capacity of these factors regarding future radiographic progression within this specific demographic.

Declarations

Author Contributions

A.I.A. conceived and designed the study and drafted the manuscript. H.G.I. collected the data and performed radiographic scoring. A.S.E. contributed to data analysis and interpretation. All authors critically revised the manuscript and approved the final version.

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Institutional Review Board Statement

The study protocol was approved by the Institutional Ethics Committee of the Faculty of Medicine of our institution (Approval No: 0000126).

Informed Consent Statement

Written informed consent was obtained from all participants included in the study.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Declaration of generative AI use

During the preparation of this work, the author(s) used an AI-based language model to assist with literature organization, language editing, and critical methodological review of successive manuscript drafts. The tool was not used for data collection, statistical analysis, or generation of the reported scientific findings or interpretations. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Review

Rheumatoid Arthritis Interstitial Lung Disease: Treating the Trajectory, Not the Pattern

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Abstract

Rheumatoid arthritis-associated interstitial lung disease [RA-ILD] requires more than a radiological diagnosis. A usual interstitial pneumonia pattern describes pulmonary architecture, but does not by itself establish whether disease is progressing, which component is modifiable, or how safely treatment can be deferred. This narrative review revisits the disease-behaviour approach and distinguishes susceptibility to ILD, prognosis after ILD develops, and prediction of treatment benefit. It integrates contemporary classification and guidance with evidence from immunomodulatory cohorts, INBUILD, TRAIL1 and FIBRONEER-ILD. We propose a reserve-aware interpretation of trajectory: structural burden and the pace of deterioration should be considered alongside remaining physiological reserve, competing hazards and the likely cost of waiting. This is a clinical reasoning framework, not a validated score. Progressive

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pulmonary fibrosis provides a useful operational definition, but should neither be mistaken for proof of an exclusively fibrotic mechanism nor become a prerequisite for treating already consequential lung disease. Molecular advances, including MUC5B, telomere length and protein signatures, illustrate the distance between biological plausibility and treatment selection. Antifibrotic evidence supports slowing functional loss; newer survival analyses require careful separation of overall pulmonary fibrosis populations from RA-specific inference. The therapeutic objective is therefore not to treat an imaging label or normalise an isolated measurement, but to preserve useful lung function while controlling systemic disease and limiting treatment-related harm.

Keywords: rheumatoid arthritis, interstitial lung disease, pulmonary fibrosis, disease progression, antirheumatic agents, precision medicine

1. Introduction

Associated with rheumatoid arthritis (RA) interstitial lung disease (RA-ILD) is among the most severe extra-articular manifestations of RA, encompassing a heterogeneous spectrum of inflammatory and fibrotic parenchymal lung disease with markedly variable clinical trajectories [1,2]. Although high-resolution computed tomography (HRCT) patterns, particularly usual interstitial pneumonia (UIP), retain diagnostic and prognostic importance, morphology alone does not define disease behaviour. This distinction is formalized by the concept of progressive pulmonary fibrosis (PPF), which describes progression in an ILD other than idiopathic pulmonary fibrosis by the development, within one year and without an alternative explanation, of at least two of three domains: worsening respiratory symptoms, physiological progression, and radiological progression [3].

The central challenge in RA-ILD is therefore no longer simply to identify and name an imaging pattern, but to determine which patient is at risk, which lung is truly progressing, and when that trajectory warrants therapeutic intervention. The historical association between RA-ILD and excess mortality established the importance of pulmonary involvement; it did not establish that every interstitial abnormality has the same prognosis or requires the same intervention [4].

A useful starting point predates the current enthusiasm for progressive pulmonary fibrosis. The 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) classification already incorporated disease behaviour, recognising that management sometimes depends on observed

course when a diagnostic label is insufficient. The 2025 ERS/ATS update extends classification beyond idiopathic disease, distinguishes fibrotic from non-fibrotic interstitial disorders and explicitly incorporates diagnostic confidence. These developments refine morphology rather than displace it. A pattern remains indispensable for understanding the lung; it becomes misleading when asked to function as a complete treatment algorithm [5,6].

Three questions must therefore remain separate: what disease is present, what is likely to happen, and what a particular treatment is likely to change. Neither a poor prognostic marker nor a plausible pathogenic mechanism automatically predicts treatment benefit. Current guidance from the American College of Rheumatology/American College of Chest Physicians (ACR/CHEST) and the ERS/European Alliance of Associations for Rheumatology (EULAR) provides a necessary clinical scaffold, but much RA-specific treatment evidence remains conditional and of low or very low certainty. The absence of a simple hierarchy reflects the evidence, not a failure to recognise the correct radiological pattern [7,8].

We use 'treating the trajectory' in a deliberately qualified sense. It means interpreting change in the context of baseline burden, remaining reserve and treatment risk, not waiting for every patient to deteriorate before acting. A severely impaired patient should not have to lose additional lung function merely to make the need for treatment easier to document. Conversely, a fibrotic image in a patient with preserved function and a convincingly stable course is not, by itself, proof that immediate escalation will offer net benefit. The central task is to identify clinically consequential, potentially modifiable disease without confusing vigilance with overtreatment.

2. Beyond UIP and NSIP: What Actually Defines Risk?

Non-specific interstitial pneumonia (NSIP) and UIP describe different morphological organisations of injury, not self-sufficient risk categories. In a cohort of 137 patients with RA-ILD, baseline forced vital capacity (FVC) and its subsequent decline were important mortality predictors, whereas the HRCT pattern did not retain independent prognostic significance in the adjusted model. This does not render UIP unimportant; it shows why physiology and change can substantially modify the information contained in a pattern [9].

The same distinction is essential when interpreting molecular data. The mucin 5B (MUC5B) promoter variant is strongly associated with susceptibility to RA-ILD, particularly UIP, yet a subsequent RA-ILD cohort

did not establish an association with survival or progression. A susceptibility allele should not quietly become a progression biomarker, still less an indication for antifibrotic therapy. The relevant denominator changes once every patient in the clinic already has ILD [10,11].

Recent biomarkers sharpen, rather than solve, this problem. In a 2025 prospective study of 101 patients, short leukocyte telomeres were associated with more progression events, but the adjusted estimate was imprecise and its confidence interval included unity (odds ratio 2.80; 95% confidence interval 0.99-8.29). A 2026 blood-protein study reported diagnostic discrimination using CXCL9, CXCL13 and TIMP-1, not prospective prediction of progression or treatment response. Neither observation currently supplies a validated molecular rule for choosing immunomodulation over an antifibrotic [12,13].

Disease activity requires equally careful interpretation. Prospective evidence associates greater rheumatoid arthritis activity with incident clinically apparent ILD. This supports attention to systemic inflammation, but it is not equivalent to demonstrating that lowering an articular activity score will reverse established pulmonary fibrosis. Susceptibility, prognosis and treatment responsiveness are related research questions; their endpoints are not interchangeable [14].

2.1 Burden, tempo and reserve

For clinical decisions, the most useful distinction is between the amount of lung already affected, the speed of change and the patient's capacity to tolerate further loss. HRCT defines distribution and structural extent; serial physiology describes functional consequences; symptoms and exercise-related limitations place these measurements in the patient's life. None is sufficient in isolation. We propose considering these domains alongside plausible treatment responsiveness and competing harms (Figure 1). This is an explicit reasoning framework, not a new prognostic score or validated treatment threshold.

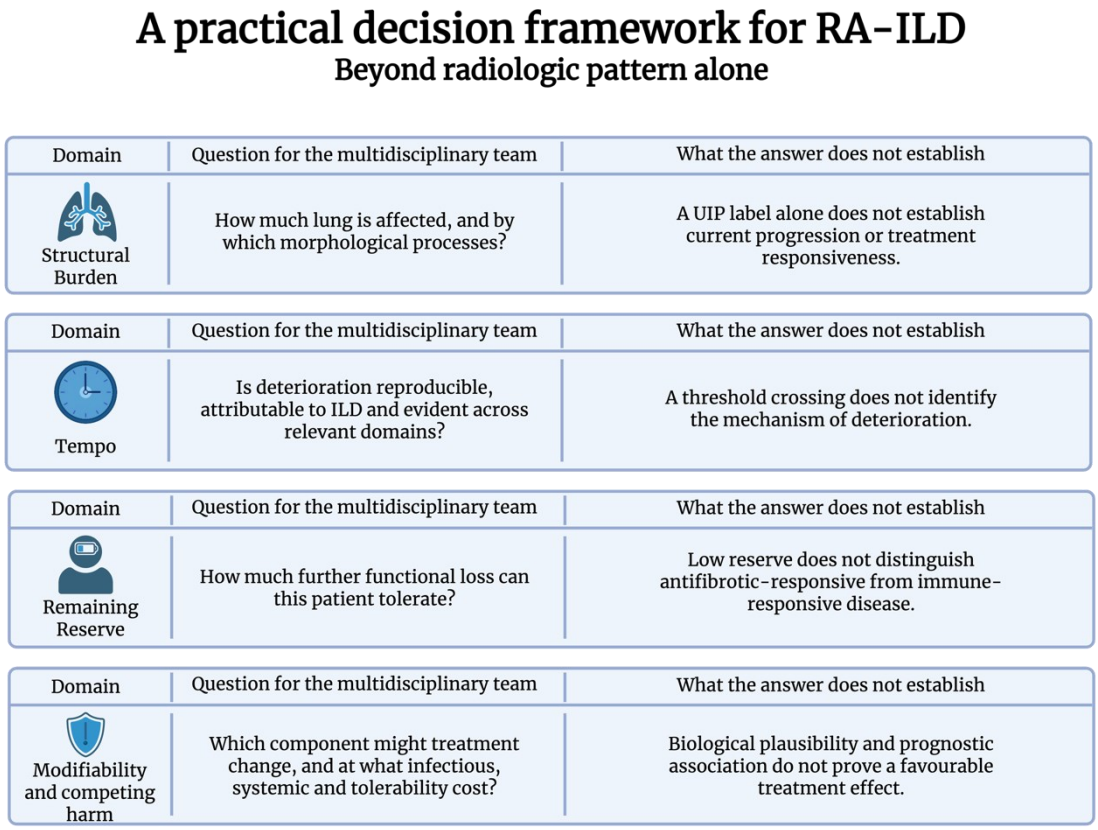


Figure 1. A trajectory-based multidisciplinary decision framework for Rheumatoid Arthritis-Associated Interstitial Lung Disease [RA-ILD]. Moving beyond static radiologic classifications, this approach redirects clinical evaluation toward four dynamic domains: structural burden, tempo of disease progression, remaining physiologic reserve, and modifiability versus competing harms. The framework outlines key questions for multidisciplinary teams while explicitly defining the clinical limitations of each domain's assessment, emphasizing that comprehensive disease trajectory - rather than an isolated histopathologic or radiologic pattern - must drive therapeutic decision-making. Abbreviations: RA-ILD, Rheumatoid Arthritis-Associated Interstitial Lung Disease; ILD, Interstitial Lung Disease; UIP, Usual Interstitial Pneumonia; NSIP, Non-Specific Interstitial Pneumonia. Created in BioRender. Dimitrov, S. [2026] https://BioRender.com/c5xllss.

A hypothetical comparison illustrates the point. Two patients may both have UIP and the same recent FVC decline, yet the cost of another small loss may differ substantially when one has preserved gas exchange and the other has little functional reserve. Conversely, extensive but stable fibrosis does not prove that additional immunosuppression can recover the missing reserve. Low reserve increases urgency; it does not identify the correct drug. Decisions must address both what is dangerous and what is plausibly modifiable.

Preserved reserve does not justify deferral once progression is objectively documented and not attributable to infection, airway disease or measurement variability (Sections 2.2 and 6.2). Its principal role in timing is confined to marginal, single-domain or technically uncertain change, in which preserved reserve may permit a short, prespecified confirmatory interval and limited reserve favours earlier intervention. Reserve additionally informs treatment intensity and the acceptable level of treatment-related risk.

2.2 Progression is a definition, not a mechanism

The 2022 ATS/ERS/JRS/ALAT definition of progressive PPF, in fibrotic ILD other than idiopathic pulmonary fibrosis (IPF), requires at least two of three domains within the preceding year, without another explanation: worsening respiratory symptoms, physiological progression or radiological progression. The physiological component is an absolute FVC decline of at least 5 percentage points predicted or an absolute decline in haemoglobin-corrected diffusing capacity for carbon monoxide (DLCO) of at least 10 percentage points predicted. A decrease from 80% to 75% predicted is five percentage points, not a 5% relative decline. Two physiological abnormalities still constitute one domain, not two [3].

The one-year interval is an observation window, not a requirement to postpone a decision for twelve months. Nor should the PPF definition be confused with every trial's entry criterion: INBUILD used a different, 24-month progression framework. Validation studies show that deterioration, particularly a relative FVC decline of at least 10%, identifies a poor-prognosis population across non-IPF fibrotic ILDs [15]. Prognostic discrimination, however, is not the same as demonstrating that a threshold uniquely predicts response to a given drug. PPF describes behaviour; it does not establish that inflammation has disappeared or that every competing cause of deterioration is fibrotic [3,16].

2.3 Stability needs a denominator and a time horizon

The 2026 BERTHA cohort provides a useful warning against equating stable average physiology with an event-free course. Among 95 patients with predominantly mild RA-ILD, group-level function and quantitative imaging remained broadly stable over 24 months, yet eight patients died; pulmonary infections accounted for four deaths. These data cannot establish that a particular therapy caused those events, and group averages should not be read as individual trajectories. They do show why infection, hospitalisation and survival must remain visible when a treatment appears successful by FVC alone [17].

Observation should consequently specify both the next assessment and the event that would bring it forward. ACR/CHEST suggests pulmonary function testing every 3-12 months in RA-ILD during the first year, with subsequent frequency tailored to stability; HRCT is appropriate when clinically indicated. Within that range, uncertain or changing disease and limited reserve argue for closer review. An unexpected result should prompt assessment of measurement quality and alternative explanations, not automatic acceptance or dismissal. 'Stable' should mean stable across a defined period and relevant domains, not simply no complaint at the last appointment [18].

3. The Silent Lung: Whom Should We Screen?

ILD represents one of the most frequent and severe extra-articular manifestations of RA, yet it remains notoriously subclinical and insidious during its early stages [19]. A substantial proportion of patients with RA - ranging from 15% in early-onset cohorts up to 50% in established disease - harbor subclinical ILD or interstitial lung abnormalities (ILAs) detectable on HRCT, despite reporting no overt respiratory symptoms [20,21]. This "silent" nature is further compounded by joint pain and functional physical impairment, which frequently mask exertional dyspnea and lead to marked diagnostic delays [22]. Given that established RA-ILD carries a three-fold increase in overall mortality and constitutes a leading cause of non-articular death [23,24], identifying pulmonary involvement before extensive, irreversible fibrotic remodeling occurs has become a paramount clinical goal.

3.1 The Case Against Universal Screening

Despite the high prevalence and substantial prognostic impact of subclinical pulmonary involvement, universal HRCT screening for all unselected RA patients is currently not recommended by international consensus guidelines [25–27]. As emphasized by the French Society of Rheumatology (SFR) guidelines, RA-ILD does not currently fulfill the classical World Health Organization (WHO) criteria for universal screening programs, as there is a lack of high-level evidence demonstrating that early therapeutic intervention in asymptomatic, unselected cohorts improves long-term survival or alters overall disease trajectory [26]. This conservative stance is strongly reinforced by the joint ERS and EULAR clinical practice guidelines, which refrain from universal radiological screening and suggest instead that screening be considered only in RA patients exhibiting specific risk profiles [25]. Longitudinal studies demonstrate that a significant proportion of subclinical ILDs or ILAs remain stationary over extended

follow-up without requiring immediate immunomodulatory or antifibrotic management [20]. Furthermore, unselected radiological screening carries significant drawbacks, including the overdiagnosis of non-progressive or clinically trivial lesions, increased patient anxiety, unnecessary downstream procedures for incidental findings, and substantial economic and radiation burdens on healthcare systems [26].

3.2 Targeted Screening and Risk Stratification

Consequently, current clinical consensus advocates for a risk-stratified, targeted screening approach focused on identifying RA patients at the highest risk for developing progressive ILD [28]. The 2023 ACR]/ CHEST guidelines as well as the joint ERS/EULAR guidelines conditionally recommend screening high-risk individuals, highlighting that screening decisions should be tailored through shared decision-making between rheumatologists and patients [25,27]. This enriched risk profile for RA-ILD encompasses a complex interplay of demographic, clinical, serological, and genetic predictors. Demographically, older age at RA onset (60 years), male sex, and a significant history of cigarette smoking (10-13 pack-years) constitute established non-modifiable and environmental vulnerability factors [20,29]. From a clinical and serological standpoint, risk is strongly driven by high articular disease activity [marked by sustained elevations in DAS28 or CDAI scores, elevated acute-phase reactants (CRP and ESR), high-titer rheumatoid factor (RF), high-titer anti-citrullinated protein antibodies (anti-CCP/ACPA), and the presence of severe extra-articular manifestations such as rheumatoid nodules [30,31]. At the molecular level, genetic predisposition plays a pivotal role, particularly the *MUC5B* promoter gain-of-function variant (rs35705950) - which markedly increases the odds of subclinical ILD and a usual interstitial pneumonia (UIP) pattern - alongside short leukocyte telomeres and elevated serum biomarkers such as Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), and matrix metalloproteinase-7 (MMP-7) [32,33].

3.3 Evaluation Modalities: Roles and Limitations

When implementing targeted screening in high-risk or clinically suspicious patients, a multimodal diagnostic strategy is essential to overcome the limitations inherent to any single modality. Clinicians must maintain a high index of suspicion for subtle respiratory complaints, such as dry cough, unexplained exertional dyspnea, or exercise intolerance [19,22]. On physical examination, the presence of fine, dry, inspiratory "Velcro-like" crackles at the lung bases serves as a classic diagnostic clue; however, while highly specific, lung auscultation alone lacks sufficient sensitivity for early

detection [34]. Baseline pulmonary function tests (PFTs) - comprising spirometry, plethysmographic lung volumes, and DLCO - provide vital objective measurements [28]. However, ERS/EULAR guidelines explicitly recommend against replacing HRCT with PFTs alone for screening, as physiological testing frequently misses early subclinical ILD when FVC and DLCO values remain within normal predicted limits despite visible parenchymal involvement on imaging [25].

To address these diagnostic gaps, HRCT stands as the gold-standard modality for detecting, quantifying, and pattern-categorizing RA-ILD [35]. Accordingly, the ACR/CHEST guidelines conditionally recommend combining HRCT with full PFTs over PFTs or clinical examination alone to maximize diagnostic sensitivity in high-risk individuals [27], with low-dose volumetric HRCT protocols increasingly advocated to minimize radiation exposure while preserving diagnostic quality. Furthermore, ERS/EULAR conditionally recommends against replacing HRCT with lung ultrasound (LUS), noting that point-of-care sonography remains highly operator-dependent and non-specific for ILD [25]. Conventional modalities and invasive procedures offer minimal screening value: standard chest radiography exhibits poor sensitivity for early interstitial changes, while routine screening using the 6-minute walk distance (6MWD), ambulatory desaturation testing, bronchoscopy, or invasive lung biopsy is strongly or conditionally discouraged across international guidelines. Indeed, both ACR/CHEST and ERS/EULAR explicitly suggest that lung biopsy has no diagnostic role for routine screening, and restrict bronchoalveolar lavage (BAL) strictly to scenarios where infection, malignancy, or alternative etiologies must be excluded [25,27].

4. When Does RA-ILD Need Treatment?

The decision to initiate, defer, or escalate pharmacological therapy for RA-ILD represents a complex clinical challenge, primarily due to the heterogeneous disease trajectory and a historical lack of dedicated randomized controlled trials. Recently, however, expert consensuses and the first joint ERS and EULAR clinical practice guidelines have provided a more structured framework for therapeutic triage [25,36]. Treatment decisions must be highly individualized through multidisciplinary discussion, balancing the severity and progression rate of the pulmonary involvement against the activity of the articular disease, while remaining cognizant of the potential pulmonary toxicity or immunosuppressive risks associated with systemic therapies [37]. In contemporary practice, patient

management can be broadly conceptualized into three distinct clinical paradigms: observation, immunomodulation, and antifibrotic escalation.

For a substantial subset of patients with subclinical, mild, or non-progressive RA-ILD, a strategy of watchful observation is considered appropriate. Current guidelines suggest that in the absence of respiratory symptoms, significant physiological impairment, or documented radiological progression, specific pulmonary-targeted interventions may be deferred [25–27]. In these scenarios, the primary therapeutic objective is the strict control of the underlying rheumatoid arthritis, as sustained articular inflammation is an independent predictor of ILD progression [38]. During this observation phase, routine surveillance with pulmonary function tests is mandated, and conventional or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) should be optimized. Notably, historical concerns regarding methotrexate-induced pneumonitis have been largely re-evaluated; recent evidence indicates that methotrexate does not inherently increase the risk of ILD progression and may safely be continued in stable disease [37].

When patients exhibit clinically significant, symptomatic ILD, or manifest a predominantly inflammatory radiological phenotype (such as non-specific interstitial pneumonia or organizing pneumonia), immunomodulatory therapy constitutes the first-line approach [39]. The ERS/EULAR guidelines conditionally recommend immunosuppressive treatment for RA-ILD, though it is explicitly noted that this recommendation rests on a very low certainty of evidence derived mostly from retrospective cohorts and extrapolation from other connective tissue diseases [25]. Glucocorticoids are frequently utilized to induce initial disease control, but their long-term use must be strictly minimized to avert cumulative toxicity and increased infection risk [37]. As a steroid-sparing strategy, biological DMARDs - particularly rituximab and abatacept - are increasingly preferred. Retrospective data and indirect trial evidence suggest these agents can stabilize or modestly improve lung function with an acceptable safety profile, whereas tumor necrosis factor inhibitors (TNFi) are generally approached with caution due to conflicting reports regarding potential pulmonary exacerbations [40]. The role of targeted synthetic DMARDs, such as Janus kinase (JAK) inhibitors, remains an area of active investigation [41]. Conversely, the novel phosphodiesterase-4B (PDE4B) inhibitor nerandomilast has recently demonstrated robust Phase III prospective clinical efficacy in autoimmune disease-related progressive pulmonary fibrosis (autoimmune ILD/PPF) - with RA-ILD as the largest subgroup - significantly slowing FVC decline and reducing mortality risk [42,43].

A critical paradigm shift in the management of RA-ILD involves the recognition and targeted treatment of the PPF phenotype, which closely mimics the relentless trajectory of idiopathic pulmonary fibrosis [44]. For patients demonstrating objective functional or radiological decline despite optimal immunomodulation, or for those presenting with a severe usual interstitial pneumonia (UIP) pattern, the escalation to antifibrotic therapy is warranted [45]. Nintedanib is conditionally recommended by ERS/EULAR for any connective tissue disease exhibiting PPF, largely based on the INBUILD trial which demonstrated a significant 59% reduction in the annual rate of forced vital capacity decline in the RA-ILD subgroup [46]. Similarly, pirfenidone may be considered, particularly for RA-ILD patients with a UIP pattern, drawing upon conditional recommendations and data from the prematurely terminated TRAIL1 study [47]. However, clinical expectations must be managed objectively: antifibrotics serve to decelerate disease progression rather than halt or reverse fibrosis, and their efficacy is frequently compromised by dose-limiting gastrointestinal toxicities [48]. While the concomitant use of antifibrotics and immunomodulators appears safe and is increasingly adopted for severe PPF, the optimal timing for initiation - whether sequentially after immunosuppressant failure or as upfront combination therapy in high-risk UIP - remains a subject of ongoing debate and underscores the critical need for further precision-medicine research.

5. Treating the Joint and the Lung as One Disease

Historically, the clinical management of RA-ILD has been hampered by an artificial and counterproductive dichotomy between "rheumatoid arthritis treatment" and "ILD treatment." Contemporary pathobiological insights and clinical evidence demonstrate that articular inflammation and pulmonary interstitial remodeling are systemic manifestations of a singular autoimmune disease process driven by shared immunological drivers [49]. Consequently, effective management requires a unified approach, where systemic rheumatic disease control is viewed as essential for pulmonary stability.

5.1 Re-evaluating Methotrexate: Dismantling Historical Dogma

For decades, MTX was routinely withheld or discontinued in patients with RA-ILD due to persistent concerns regarding drug-induced pneumonitis and purported fibrogenic pulmonary toxicity [50]. However, rigorous modern epidemiological evidence and prospective cohort studies have comprehensively overturned this long-standing dogma [51]. Current data indicate that MTX use is not associated with an increased risk of incident

RA-ILD; in fact, several large-scale longitudinal analyses suggest that MTX exposure may be linked to a lower incidence of ILD and a delayed onset of pulmonary symptoms [52]. Clinicians must carefully distinguish between rare, acute, hypersensitivity-driven methotrexate pneumonitis (MTX-P) and chronic, progressive RA-ILD, as MTX remains a safe and foundational anchor therapy for the majority of stable RA-ILD patients [53].

5.2 Immunomodulatory Hierarchy: Biologics and Targeted Synthetic DMARDs

Because adaptive immunity and autoantibody-mediated pathways - such as ACPA-driven neutrophil activation and local iBALT formation - fuel both synovial destruction and alveolar remodeling, selecting immunomodulatory agents with targeted pulmonary safety profiles is critical [49,54].

Observational data and systematic reviews consistently position non-TNF biologic agents - specifically the T-cell co-stimulation modulator abatacept and the anti-CD20 B-cell depleting agent rituximab - as superior therapeutic options for RA-ILD [55]. Studies have demonstrated that abatacept, in particular, is associated with stable or improved pulmonary function and radiological markers, and may confer a survival advantage compared to other biologics [56,57]. Rituximab similarly demonstrates efficacy in slowing pulmonary function decline in refractory cases, serving as a pivotal agent in complex management scenarios [58]. In contrast, the role of TNFi in RA-ILD remains a subject of clinical caution. Several observational studies have reported associations between TNFi use and disease exacerbation or higher mortality rates, leading many experts to favor switching to abatacept or rituximab in patients with established or progressive ILD [50,58,59]. Emerging evidence for targeted synthetic DMARDs (tsDMARDs) suggests that JAK inhibitors may possess both anti-inflammatory and potential anti-fibrotic properties [60,61]. Recent comparative data indicate a lower incidence of incident ILD with tofacitinib compared to other biologic classes, and in vitro models suggest an additive effect when combined with MTX in modulating fibrotic pathways like epithelial-mesenchymal transition (EMT) [60–62].

5.3 Integrating Antifibrotic Therapy

When pulmonary fibrosis acquires autonomous momentum and progresses despite optimal immunomodulation, treatment must incorporate targeted antifibrotic therapy [63,64]. Nintedanib has demonstrated robust efficacy in decelerating the annual decline of FVC in patients with PPF, including a distinct subgroup of RA-ILD patients [53,64,65]. Antifibrotics should be

utilized not solely based on a radiological UIP label, but rather as a strategy to arrest an objectively progressive fibrotic trajectory in patients failing first-line immunomodulation [53,66]. Future management strategies will likely rely on a personalized, multidisciplinary framework where the intensity of immunomodulation is calibrated to systemic articular activity, while antifibrotic escalation is triggered by the functional and radiological behavior of the lung.

6. The Clinical Traps

6.1 Not Every Ground-Glass Opacity Is Inflammation

A pervasive clinical misconception in RA-ILD is the automatic conflation of ground-glass opacity (GGO) on high-resolution computed tomography (HRCT) with active, steroid-responsive inflammation. While pure GGO in a non-specific interstitial pneumonia (NSIP) pattern can represent cellular alveolar infiltration, GGO is fundamentally an attenuation marker reflecting non-specific volume averaging of alveolar septal thickening and partial alveolar filling [67]. In patients with pre-existing fibrotic architecture, GGO may represent fine intralobular fibrosis below the threshold of macroscopic resolution, microatelectasis, or traction-induced alveolar collapse rather than active alveolitis [67].

The diagnostic stakes are highest during acute or subacute respiratory worsening, where the emergence of new bilateral GGOs superimposed on chronic reticulation or honeycombing typically heralds an acute exacerbation (AE) of RA-ILD [68]. Pathobiologically characterized by diffuse alveolar damage (DAD) rather than benign inflammatory progression, AE carries a catastrophic in-hospital mortality rates [69]. Because international diagnostic criteria mandate that AE is a diagnosis of exclusion, clinicians must not reflexively treat new GGOs with intensified immunosuppression without first systematically ruling out competing etiologies. In immunocompromised RA cohorts, opportunistic infections - particularly *Pneumocystis jirovecii* pneumonia and respiratory viral infections - present with identical diffuse GGO patterns [49]. Similarly, cardiogenic pulmonary edema, aspiration pneumonitis, and hypersensitivity-driven drug toxicity [such as acute methotrexate pneumonitis] can closely mimic acute interstitial exacerbation [67]. Furthermore, patients with an underlying UIP pattern exhibit a substantially higher vulnerability to developing superimposed DAD and GGO-associated acute deterioration compared to non-UIP phenotypes [68,69]. Consequently, interpreting GGO demands a rigorous multi-tier

evaluation incorporating microbiology, cardiac function assessment, and chronological trajectory rather than an immediate assumption of treatable parenchymal inflammation.

6.2 Not Every FVC Decline Is ILD Progression

FVC is widely regarded as the cornerstone physiological metric for tracking disease behavior and defining PPF [70]. However, in rheumatoid arthritis, reflexively equating a declining FVC with accelerating interstitial parenchymal fibrosis represents a major diagnostic trap [71]. Because RA is a multicompartmental pulmonary disorder, spirometric volume loss is frequently driven by airway pathology, extraparenchymal mechanics, or mixed ventilatory defects rather than pure interstitial fibrotic remodeling [72].

Airway disease is exceptionally prevalent in RA, affecting between 30% and 60% of patients across large series [72]. Distal airway complications - most notably follicular bronchiolitis, constrictive (obliterative) bronchiolitis, and bronchiectasis - cause severe peripheral airflow obstruction, inflammatory luminal plugging, and dynamic hyperinflation [71]. In these scenarios, air trapping and premature airway closure at low lung volumes compress vital capacity, resulting in a spurious FVC decline that masquerades as restrictive disease progression. Similarly, in patients with a history of tobacco exposure, the syndrome of combined pulmonary fibrosis and emphysema (CPFE) introduces complex physiological antagonism: hyperinflation from emphysematous upper lobes counterbalances the volume loss of basilar fibrosis, causing FVC to remain spuriously preserved or to fluctuate unpredictably even as gas exchange (DLCO) deteriorates precipitously [70,72,73].

Extraparenchymal RA manifestations further compromise spirometric reliability. Recurrent rheumatoid pleural effusions, pleural thickening, chest wall restriction from costochondral and thoracic joint involvement, and cricoarytenoid arthritis can each depress FVC independently of parenchymal status [19,72]. Moreover, recent prospective findings from the multicenter BERTHA cohort demonstrate that in mild RA-ILD, group-level FVC and quantitative CT densitometry can remain completely stable over 24 months despite significant mortality from acute pulmonary infections and systemic comorbidities, confirming that fatal events often occur without preceding measurable FVC loss [74]. Conversely, meta-analytic data across targeted therapies (b/tsDMARDs) show overall functional stabilization across broad cohorts [75]. Therefore, an isolated drop in FVC should never trigger an uncritical escalation of antifibrotic or

immunosuppressive therapy; clinicians must first perform plethysmographic lung volume measurements, assess DLCO, and evaluate serial HRCT scans to isolate true parenchymal fibrosis progression from confounding airway or extraparenchymal derangements.

6.3 Stable Arthritis Does Not Imply Stable Lung Disease

In clinical practice, achieving articular remission is often falsely equated with complete disease quiescence. However, articular and pulmonary trajectories frequently decouple; patients with mild or oligosymptomatic joint involvement can still harbor significant pleuropulmonary disease [76].

While high systemic inflammatory activity strongly predisposes to interstitial lung involvement in both early and established disease [77], pulmonary damage often develops insidiously within the initial years of arthritis [78]. Longitudinal cohorts show that approximately 50% of RA-ILD patients exhibit progressive fibrotic remodeling on HRCT over 1.5 to 3 years, frequently despite quiescent arthritis [79,80]. This occurs because established pulmonary fibrosis often transitions from an immune-driven phase into an autonomous, self-sustaining fibroproliferative process governed by baseline structural extent and a UIP pattern rather than ongoing joint inflammation [79,80]. Consequently, while controlling synovitis is essential, articular remission alone does not guarantee pulmonary stability, making structured lung surveillance mandatory regardless of joint control.

6.4 UIP in RA Is Not Simply IPF with Arthritis

The radiological and histopathological appearance of UIP in RA has frequently led to the reductionist view that RA-UIP is merely IPF occurring in a patient who happens to have joint disease [81,82]. While both entities share demographic vulnerabilities [older age, male sex, smoking], fibrotic pattern, and specific genetic risks - most notably the *MUC5B* promoter variant [rs35705950] and telomere shortening [83,84] - treating them as biological equivalents ignores fundamental immunopathological divergence.

Histopathologically, RA-UIP exhibits prominent autoimmune features that are absent in IPF, including dense lymphocytic infiltration within myofibroblastic foci, extensive bronchus-associated lymphoid tissue (BALT) hyperplasia, and local immune complex deposition [81,85]. Genome-wide pleiotropy and proteomic profiling confirm that RA-UIP is uniquely driven by shared immune-regulatory loci (such as *IRF5*, *ANKRD55*, and *ALDH2*) and molecular signatures enriched in $CD4^+$ effector T-cell

programs and neutrophil-mediated tissue damage [84,86]. Although localized anti-modified protein antibodies (AMPA) and anti-CCP can be detected in the bronchoalveolar lavage of some IPF patients - where they paradoxically delineate a younger, less progressive subgroup [87,88] - RA-UIP is characterized by broad, multivalent systemic autoimmunity [89]. Furthermore, Mendelian randomization demonstrates that alveolar injury in UIP-susceptible lungs actively promotes the breakdown of mucosal immune tolerance to citrullinated antigens, establishing a causal pathogenic link between pulmonary damage and seropositive RA rather than a coincidental overlap [82].

Prognostically, the apparent survival advantage of RA-UIP over IPF is largely driven by earlier diagnostic capture; once adjusted for age and baseline DLCO, fibrotic progression and acute exacerbation risks become comparable [90,91]. Crucially, the therapeutic paradigms remain distinct: while immunosuppression increases mortality in IPF, targeted immunomodulation remains a viable first-line approach in inflammatory or early RA-UIP, with antifibrotics reserved or added sequentially when an autonomous, progressive fibrosing phenotype emerges [81,90]. Equating the two conditions risks withholding effective immunomodulatory therapy in early disease or inappropriately applying IPF-specific treatment algorithms to an autoimmune disorder.

6.5 Observation Without Predefined Follow-Up Is Not a Strategy

Observation or "watchful waiting" is an established and rational clinical approach in patients with mild, subclinical, or seemingly stable RA-ILD, designed to avoid unnecessary or premature therapeutic escalation [92]. However, the clinical challenge arises when observation becomes purely passive - relying solely on the emergence of patient-reported respiratory symptoms or routine physical examination before re-evaluating disease status [93]. Because subclinical interstitial lung changes occur in up to 35% of RA patients, symptom-based questionnaires (such as mMRC or VAS cough) exhibit modest sensitivity (40% to 60%), and conventional chest radiographs miss the vast majority of early fibrotic changes [92,94,95]. Consequently, passive waiting risks undetected functional and anatomical decline before clinical deterioration is recognized.

Because approximately 40% to 55% of RA-ILD patients may eventually develop PPF over their disease course [93,96], recent international recommendations (including ACR/CHEST, SER/SEPAR, and Austrian Delphi consensus statements) emphasize transitioning from passive waiting to structured active surveillance [97–99]. To remain safe and

effective, observation must follow predefined timelines: in confirmed or high-risk RA-ILD, complete PFT - specifically FVC and diffusing capacity DLCO - should be performed every 3 to 12 months during the initial evaluation period and at regular, prespecified intervals thereafter [97]. Furthermore, accessible, radiation-free modalities such as lung ultrasound (which achieves negative predictive values >95%) and low-dose CT protocols are increasingly viable tools to support routine, longitudinal monitoring [94,95].

Most importantly, structured surveillance is only actionable when anchored to predefined progression thresholds. A documented relative decline in FVC of 10% or more, a 5% to 10% FVC decrease accompanied by a declining DLCO, or expanding fibrotic changes on HRCT should systematically trigger a multidisciplinary team (MDT) reassessment to consider adjusting immunomodulatory therapy or introducing antifibrotic agents [96,100]. In this framework, observation is not the absence of management, but a proactive, protocolized monitoring strategy designed to preserve lung function and identify the therapeutic window before irreversible parenchymal loss occurs.

7. When Fibrosis Becomes the Therapeutic Target

The rationale for targeting fibrosis is not that autoimmunity becomes irrelevant, but that extracellular-matrix remodelling may cease to track systemic inflammatory activity closely. Experimental work on lung fibroblasts demonstrates persistence of an activated phenotype after mechanical priming and implicates matrix stiffness-sensitive YAP/TAZ signalling in a profibrotic feedback loop. This provides a plausible account of continuing fibrosis despite improved arthritis. It is mechanistic evidence from experimental systems, not proof that an individual patient's RA-ILD has crossed a measurable boundary into an autonomous phase [101,102].

The therapeutic implication is coexistence rather than an obligatory sequence of inflammation followed by fibrosis. In a multisite observational study of 212 patients treated with mycophenolate, azathioprine or rituximab, post-treatment pulmonary function was better than the trajectory projected from pretreatment measurements; UIP did not show a statistically significant differential treatment association. The study cannot supply an untreated randomised counterfactual or prove equal efficacy across patterns. It does, however, argue against using UIP as a reason to dismiss the possibility of an immunomodulatory benefit [103].

7.1 Nintedanib: a defensible indication and a defined evidence boundary

INBUILD enrolled patients with fibrotic ILD affecting more than 10% of lung volume and evidence of progression within the previous 24 months despite management considered appropriate in clinical practice. Its results therefore concern an enriched progressive population, not all CT-detected fibrosis. In the overall trial, nintedanib reduced the annual rate of FVC loss. The study was not a randomised comparison of an antifibrotic-first strategy against an immunomodulation-first strategy [15].

The RA-ILD subgroup comprised 89 patients. Annual FVC decline was -82.6 mL with nintedanib and -199.3 mL with placebo, a difference of 116.7 mL/year (95% confidence interval 7.4-226.1; nominal p=0.037). This is the basis of the frequently quoted 59% relative reduction in decline. It is not a 59% reduction in death, and it does not demonstrate restoration of lost lung. As a subgroup estimate, its precision and ability to address mortality are limited [104].

The most directly supported candidate is consequently a patient with established fibrotic RA-ILD and attributable, objectively documented progression despite otherwise appropriate management. ACR/CHEST includes nintedanib among options after progression on first-line ILD treatment, but did not reach consensus on its first-line use in RA-ILD [7]. 'Appropriate management' should not be interpreted as a requirement to expose every patient to several ineffective or contraindicated immunosuppressants before considering an antifibrotic. The decision should instead document disease tempo, fibrotic burden, plausible inflammatory activity, previous treatment and why further waiting is acceptable or hazardous [7].

7.2 Pirfenidone and the limits of a pattern-independent argument

TRAIL1 is particularly relevant because it was a dedicated RA-ILD trial. Recruitment stopped early, with 123 participants, and the primary composite of FVC decline of at least 10% or death was not significantly different between groups: 7 of 63 versus 9 of 60 participants (p=0.48). The estimated annual FVC decline nevertheless favoured pirfenidone (-66 versus -146 mL; p=0.0082). The positive secondary result is clinically informative, but does not erase the unsuccessful primary endpoint or the consequences of under-recruitment [105].

A strictly pattern-blind interpretation would also misrepresent current guidance. ERS/EULAR conditionally suggests pirfenidone in RA-ILD with

UIP, while ACR/CHEST conditionally supports adding it in RA-ILD progressing despite first-line treatment. Morphology therefore remains relevant to the discussion. A conditional recommendation resting on limited evidence should not be transformed into proof that every stable RA-UIP patient benefits, or that UIP is a validated predictive biomarker. The defensible principle is not to ignore pattern, but to resist allowing it to decide alone [7,8].

7.3 Nerandomilast: new evidence without subgroup inflation

FIBRONEER-ILD extends treatment evidence beyond conventional antifibrotic agents. In 1176 patients with PPF, the preferential phosphodiesterase-4B inhibitor nerandomilast reduced 52-week FVC loss; 43.5% were receiving background nintedanib. At 18 mg twice daily, the adjusted difference from placebo was 67.2 mL (95% confidence interval 31.9-102.5); at 9 mg twice daily it was 81.1 mL (46.0-116.3). These results establish an effect in the trial's PPF population, not superiority of the lower dose or comparative superiority over nintedanib [106].

The subsequent survival evidence deserves inclusion, not dismissal. Whole-trial follow-up reported a mortality hazard ratio of 0.51 (95% confidence interval 0.34-0.78) for each nerandomilast dose versus placebo. A later pooled analysis of FIBRONEER-IPF and FIBRONEER-ILD also supported a survival signal [107]. These analyses extend beyond the primary 52-week FVC endpoint; the original trials had not met their key secondary composite endpoints, and the hierarchy and multiplicity of later analyses matter. Neither analysis establishes a separately powered, RA-specific mortality benefit. Evidence for the broad progressive phenotype must not be relabelled as definitive evidence for every constituent autoimmune disease [107,108].

The broader lesson is methodological. A drug can act on overlapping inflammatory and fibrotic pathways without the trial demonstrating control of rheumatoid synovitis, permitting withdrawal of an effective disease-modifying antirheumatic drug, or defining the optimum sequence of combined therapy. RA-specific treatment decisions still require attention to the underlying trial population and concomitant-treatment restrictions. The size of a subgroup is not a substitute for its estimate and uncertainty.

7.4 Add, switch or combine?

In mixed inflammatory-fibrotic disease, adding a lung-directed agent may be more coherent than replacing treatment that is successfully controlling systemic autoimmunity. Conversely, apparent progression during poorly

tolerated or inadequately delivered immunomodulation warrants reassessment of the whole regimen. These are different problems, and neither is solved by a universal 'antifibrotic next' rule. For a patient without progression on mycophenolate, ACR/CHEST conditionally recommends against routine antifibrotic addition; its recommendations should not be read as endorsing indiscriminate upfront combination therapy [7].

New combination reports have not closed the RA-specific evidence gap. A 2026 pooled real-world study of nintedanib with dual immunosuppression included 28 patients with RA-ILD and 36 with systemic sclerosis-ILD, but longitudinal pulmonary function was unavailable for the RA subgroup. Functional findings from the systemic sclerosis participants cannot therefore be presented as evidence of efficacy for triple therapy in RA-ILD. Feasibility, tolerability, efficacy and optimal sequencing remain separate claims [109].

7.5 The endpoint is preserved function, not a motionless FVC

A patient may continue to lose FVC while benefiting from a treatment that makes the decline slower than it would otherwise have been (Table 1). Because that untreated individual trajectory is unobservable, residual decline is neither proof of failure nor permission to disregard worsening disease. It should trigger review of adherence, adverse effects, alternative causes, radiological change and the need for additional intervention. Clinical success should include useful activity, symptoms, oxygen requirements, hospitalisations and treatment burden, rather than a forced choice between 'stable FVC' and 'no benefit'.

Tolerability is part of effectiveness. In the RA-ILD INBUILD analysis, diarrhoea occurred in 61.9% with nintedanib and 27.7% with placebo over the whole trial; adverse events led to permanent discontinuation in 23.8% and 17.0%, respectively. Shared planning for gastrointestinal symptoms, liver-function monitoring, dose adjustment or interruption, and competing comorbidities is therefore essential. A treatment that cannot be sustained may offer little practical protection, however persuasive the average trial effect [15, 104].

Nintedanib should therefore be viewed not as a treatment for the radiological label of RA-UIP, but as a strategy to slow an objectively progressive fibrotic trajectory.

Table 1. Three treatment programmes: the supported inference and its boundary.

Evidence	What was demonstrated	What should not be inferred
INBUILD: RA-ILD subgroup; 89 patients [20]	Nintedanib reduced annual FVC loss by 116.7 mL versus placebo; 95% CI 7.4-226.1.	No demonstrated reversal of fibrosis or adequately powered RA-specific survival benefit.
TRAIL1: dedicated RA-ILD trial; 123 patients [21]	Primary composite not significant; a secondary FVC slope analysis favoured pirfenidone.	Not a positive primary-endpoint trial; no mandate to treat all stable UIP.
FIBRONEER-ILD: PPF; 1176 treated patients [22, 23, 24]	Reduced 52-week FVC loss; subsequent broader-population analyses support a survival signal.	Not a separately powered RA-ILD trial, a head-to-head comparison or proof of arthritis control.

The populations, entry criteria and endpoints differ. The numerical results must not be used for an indirect ranking of the drugs. FVC, forced vital capacity; PPF, progressive pulmonary fibrosis; UIP, usual interstitial pneumonia; CI, confidence interval.

8. Strengths and Limitations

This is a critical narrative review, and the proposed reserve-aware framework should be viewed as a clinically oriented synthesis rather than a validated decision tool. Its interpretation is constrained by the underlying RA-ILD literature, particularly the predominance of observational data for immunomodulatory therapy and the limited size and generalisability of RA-specific subgroups in antifibrotic trials [103,110]. Prospective validation is therefore needed before such a framework - or any molecular stratification strategy - can be used to guide treatment allocation. For now, “precision” in RA-ILD should refer to the quality of the clinical decision rather than to a level of biological certainty the evidence does not yet support.

9. Conclusion

The practical objective is to preserve usable lung while controlling rheumatoid disease and avoiding preventable harm. That requires separate attention to systemic immune activity, pulmonary progression, competing causes of deterioration and treatment tolerability. When fibrosis is demonstrably progressing, antifibrotic treatment has a defensible role; when mechanisms overlap, combination may be reasonable without being assumed optimal. The decision to observe, add or switch should have an explicit target and a scheduled test of whether that target is being met.

The pattern is where the discussion begins. The trajectory, interpreted in the context of reserve and modifiability, is what should keep changing the decision.

Declarations

Author Contributions

TG, AB conceived the article and its overarching conceptual framework, developed the trajectory- and reserve-based approach to RA-ILD, drafted the Introduction and the sections on risk stratification, antifibrotic therapy, strengths and limitations, and conclusions, and integrated and critically revised the final manuscript. SD drafted the sections on screening, indications for treatment, integrated articular and pulmonary management, and major clinical pitfalls, and contributed to the interpretation and critical revision of the manuscript. AB contributed to the conceptual development and clinical interpretation of the review and critically revised the manuscript for important intellectual content. R.K., K.B. and Z.B. contributed to the appraisal and interpretation of the evidence and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. Generative AI (Claude, Opus 5, Anthropic Inc.) was used as a language-editing and formatting assistant during manuscript preparation. It helped refine English phrasing, improve clarity, and align the structure with Rheumatology (Bulgaria) formatting requirements. No AI tools were used for data generation, analysis, interpretation, or reference fabrication. All scientific content, interpretation, and conclusions are entirely the authors' own. The authors take full responsibility for the accuracy and integrity of the submitted work.

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The authors declare no conflict of interest.

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Интерстициална белодробна болест, асоциирана с ревматоиден артрит: лечение, насочено към траекторията, а не към модела на засягане

Резюме

Интерстициалната белодробна болест, асоциирана с ревматоиден артрит (РА-ИББ), изисква повече от рентгенологична диагноза. Моделът на обичайна интерстициална пневмония описва белодробната архитектура. Сам по себе си обаче той не показва дали заболяването прогресира, кой компонент е модифицируем и доколко безопасно може да се отложи лечението. Настоящият наративен обзор преразглежда подхода, основан на поведението на заболяването, и разграничава три въпроса: предразположението към ИББ, прогнозата след развитието на ИББ и предвиждането на ползата от лечението. Обзорът интегрира съвременните класификации и препоръки с доказателства от кохорти, лекувани с имуномодулиращи средства, и от проучванията INBUILD, TRAIL1 и FIBRONEER-ILD. Предлагаме тълкуване на траекторията, съобразено с белодробния резерв. Структурната тежест и темпът на влошаване трябва да се преценяват заедно с оставащия физиологичен резерв, конкуриращите рискове и вероятната цена на изчакването. Това е рамка за клинично мислене, а не валидиран скор. Прогресиращата белодробна фиброза е полезна операционална дефиниция. Тя обаче не бива да се приема като доказателство за изцяло фибротичен механизъм, нито да се превръща в предварително условие за лечение на вече клинично значимо белодробно заболяване. Молекулярните постижения, включително MUC5B, дължината на теломерите и протеиновите профили, показват колко голяма е дистанцията между биологичната правдоподобност и избора на лечение. Доказателствата подкрепят ролята на антифибротичната терапия за забавяне на функционалната загуба. По-новите анализи на преживяемостта обаче изискват внимателно разграничаване между данните от общите популации с белодробна фиброза и изводите, специфични за РА. Следователно терапевтичната цел не е да се лекува образен етикет или да се нормализира отделен показател. Целта е да се запази полезната белодробна функция, като едновременно се контролира системното заболяване и се ограничава вредата, свързана с лечението.

Ключови думи: ревматоиден артрит, интерстициална белодробна болест, белодробна фиброза, прогресия на заболяването; антиревматични средства, прецизна медицина

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Review

Adhesion Molecules in Psoriatic Arthritis: Linking Inflammation, Endothelial Dysfunction, and Cardiovascular Disease

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Abstract

Psoriatic arthritis (PsA) is associated with increased cardiovascular morbidity and mortality that cannot be fully explained by traditional cardiovascular risk factors. Adhesion molecules, particularly intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), have emerged as important mediators linking chronic

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inflammation with endothelial dysfunction and atherosclerosis. To review current evidence regarding the role of adhesion molecules in endothelial dysfunction and cardiovascular disease in patients with psoriatic arthritis. A narrative literature review was conducted using PubMed, Scopus, and Web of Science databases. Studies evaluating ICAM-1, VCAM-1, endothelial dysfunction, subclinical atherosclerosis, and cardiovascular risk in PsA were identified and analyzed. Available evidence demonstrates that elevated adhesion molecule levels are associated with endothelial dysfunction, increased carotid intima-media thickness, inflammatory activity, and cardiovascular risk in PsA. Histopathological studies further support their involvement in synovial and vascular inflammation. Recent data suggest that VCAM-1 may be more closely associated with inflammatory burden and endothelial activation than ICAM-1. Emerging evidence also indicates that modern biologic and targeted therapies may influence adhesion molecule expression. Adhesion molecules play an important role in the pathogenesis of endothelial dysfunction and atherosclerosis in PsA. VCAM-1 appears to be a promising candidate biomarker of endothelial activation, although its prognostic value remains to be established.

Keywords: psoriatic arthritis, adhesion molecules, ICAM-1, VCAM-1, endothelial dysfunction, atherosclerosis.

1. Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease associated with an increased risk of cardiovascular morbidity and mortality. Numerous studies have demonstrated that patients with PsA exhibit accelerated atherosclerosis and increased prevalence of subclinical vascular damage compared with the general population [1–3]. Although traditional cardiovascular risk factors contribute substantially to this increased burden, chronic systemic inflammation is now recognized as an independent driver of endothelial dysfunction and atherogenesis.

Endothelial dysfunction represents one of the earliest stages of vascular injury and precedes the development of clinically overt atherosclerosis. Persistent inflammatory activation promotes leukocyte recruitment, oxidative stress, lipid oxidation, and vascular remodeling, creating a proatherogenic environment. Among the molecular mediators involved in these processes, adhesion molecules have emerged as key regulators of endothelial activation and leukocyte trafficking. In particular, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1

(VCAM-1) have attracted considerable attention because of their central role in linking chronic inflammation with cardiovascular damage [4,5].

The aim of this review is to summarize current evidence regarding the role of adhesion molecules in endothelial dysfunction, atherosclerosis, and cardiovascular risk in patients with psoriatic arthritis.

2. Materials and Methods

A narrative literature review was conducted to summarize current evidence regarding the role of adhesion molecules in endothelial dysfunction, atherosclerosis, and cardiovascular disease in patients with psoriatic arthritis. Relevant publications were identified through searches of PubMed, Scopus, and Web of Science from database inception to June 2026. Search terms included combinations of “psoriatic arthritis”, “adhesion molecules”, “ICAM-1”, “VCAM-1”, “endothelial dysfunction”, “atherosclerosis”, “cardiovascular disease”, “subclinical atherosclerosis”, and “vascular inflammation”.

Original studies involving patients with PsA were prioritized, particularly those evaluating circulating or tissue expression of adhesion molecules in relation to disease activity, endothelial dysfunction, vascular imaging, cardiovascular risk, or treatment exposure. Systematic reviews, meta-analyses, experimental studies, and studies conducted in other inflammatory diseases or the general cardiovascular population were included when relevant to the biological or pathophysiological context. Non-English publications, conference abstracts with insufficient methodological information, and studies without relevance to adhesion molecules or vascular involvement were excluded. Reference lists of selected articles were additionally screened to identify relevant publications.

Given the narrative design and the limited and heterogeneous PsA-specific literature, no formal risk-of-bias assessment or quantitative evidence synthesis was performed. Evidence derived directly from PsA populations was distinguished from mechanistic or contextual evidence extrapolated from other inflammatory diseases and the general cardiovascular literature.

3. Adhesion Molecules and Endothelial Dysfunction

The presence of accelerated atherosclerosis has been well documented in several chronic inflammatory rheumatic diseases, including rheumatoid

arthritis and systemic lupus erythematosus [6–10]. One of the earliest pathophysiological events associated with atherosclerotic development is endothelial dysfunction [11–13], which represents the response of the vascular endothelium to traditional cardiovascular risk factors and precedes clinically apparent atherosclerosis (Figure 1).

Endothelial dysfunction contributes to atherosclerotic lesion formation through multiple mechanisms, including increased expression of adhesion molecules, secretion of chemokines, enhanced leukocyte adhesion to the vascular wall, increased endothelial permeability, oxidation of low-density lipoproteins, platelet activation, production of pro-inflammatory cytokines, and migration and proliferation of vascular smooth muscle cells [14]. A central component of this process is the impairment of nitric oxide (NO) production and bioavailability, leading to the loss of endothelium-dependent vasodilation and the development of a proatherogenic vascular environment [15,16].

Inflammatory cytokines further amplify endothelial injury, with tumor necrosis factor-alpha (TNF-α) playing a particularly important role through activation of signaling pathways involved in vascular inflammation, oxidative stress, and atherogenesis [17–19].

In addition to disturbances in endothelial vasoactive mediators, several molecular mechanisms may contribute to endothelial injury and atherogenesis during chronic inflammation. One such mechanism involves cholesterol 27-hydroxylase, an enzyme expressed by endothelial cells and macrophages that participates in cholesterol homeostasis by converting cholesterol into the more soluble metabolite 27-hydroxycholesterol. Experimental studies have demonstrated that circulating immune complexes containing C1q suppress the expression of cholesterol 27-hydroxylase, thereby potentially impairing cholesterol efflux from the arterial wall [20]. Reduced enzyme activity may favor lipid retention within vascular tissues and contribute to the development of a proatherogenic environment.

Interferon-gamma (IFN-γ) exerts a similar inhibitory effect on cholesterol 27-hydroxylase, further linking immune activation with disturbances in vascular lipid metabolism [20]. At the same time, pro-inflammatory cytokines including interleukin-1 (IL-1), TNF-α, and IFN-γ induce profound changes in endothelial cell function [21]. These mediators suppress the expression of endothelial anticoagulant receptors such as the endothelial protein C receptor (EPCR) while simultaneously promoting the expression

of adhesion molecules and chemokines, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) [22]. The resulting endothelial phenotype is characterized by enhanced leukocyte recruitment, increased vascular inflammation, and a greater propensity for atherosclerotic lesion development.

Atherosclerosis is currently regarded as a chronic inflammatory disease characterized by a complex cascade of cellular and molecular events. One of the earliest stages of atherogenesis involves increased endothelial permeability and disruption of endothelial integrity, facilitating the migration of inflammatory cells from the circulation into the subendothelial space [23,24]. This process depends on activation of cell adhesion molecules expressed on both endothelial cells and circulating leukocytes [25,26].

Selectins (P-selectin, E-selectin, and L-selectin) initiate leukocyte rolling and transient adhesion to activated endothelium [27–29]. These early interactions are subsequently stabilized by ICAM-1 and VCAM-1, together with leukocyte integrins, resulting in firm adhesion to the endothelial surface. Platelet endothelial cell adhesion molecule-1 (PECAM-1) facilitates transendothelial migration of leukocytes into the vascular intima [30]. ICAM-1 and VCAM-1 exist in both membrane-bound and soluble forms. Whereas membrane-bound molecules mediate leukocyte adhesion and transendothelial migration, circulating sICAM-1 and sVCAM-1 are commonly assessed as indirect markers of endothelial and inflammatory activation.

Oxidized low-density lipoproteins (OxLDL) further amplify these mechanisms by stimulating endothelial expression of adhesion molecules and chemokines such as MCP-1 [31]. This promotes monocyte recruitment into the arterial wall, where they differentiate into macrophages and internalize OxLDL, forming foam cells that represent a hallmark of early atherosclerotic lesions [32].

Activated foam cells release cytokines, chemokines, growth factors, and matrix metalloproteinases, promoting vascular inflammation, extracellular matrix remodeling, and smooth muscle cell proliferation. Additional recruitment of monocytes, T lymphocytes, and B lymphocytes further amplifies local inflammation through enhanced production of TNF-α and IL-1β, contributing to plaque progression and instability [33]. Mast cells located within the vascular adventitia also participate in these processes

through secretion of IL-8 and MCP-1, facilitating recruitment of additional inflammatory cells [34].

Beyond their pathogenic role, adhesion molecules possess important diagnostic and prognostic value. Increased expression of VCAM-1, ICAM-1, and L-selectin has been identified within atherosclerotic plaques, while elevated circulating concentrations of soluble VCAM-1 and soluble ICAM-1 have been associated with increased cardiovascular risk [35–38]. Elevated sICAM-1 levels have been reported in asymptomatic individuals, whereas sVCAM-1 appears to be more closely associated with clinically manifest coronary artery disease [39,40].

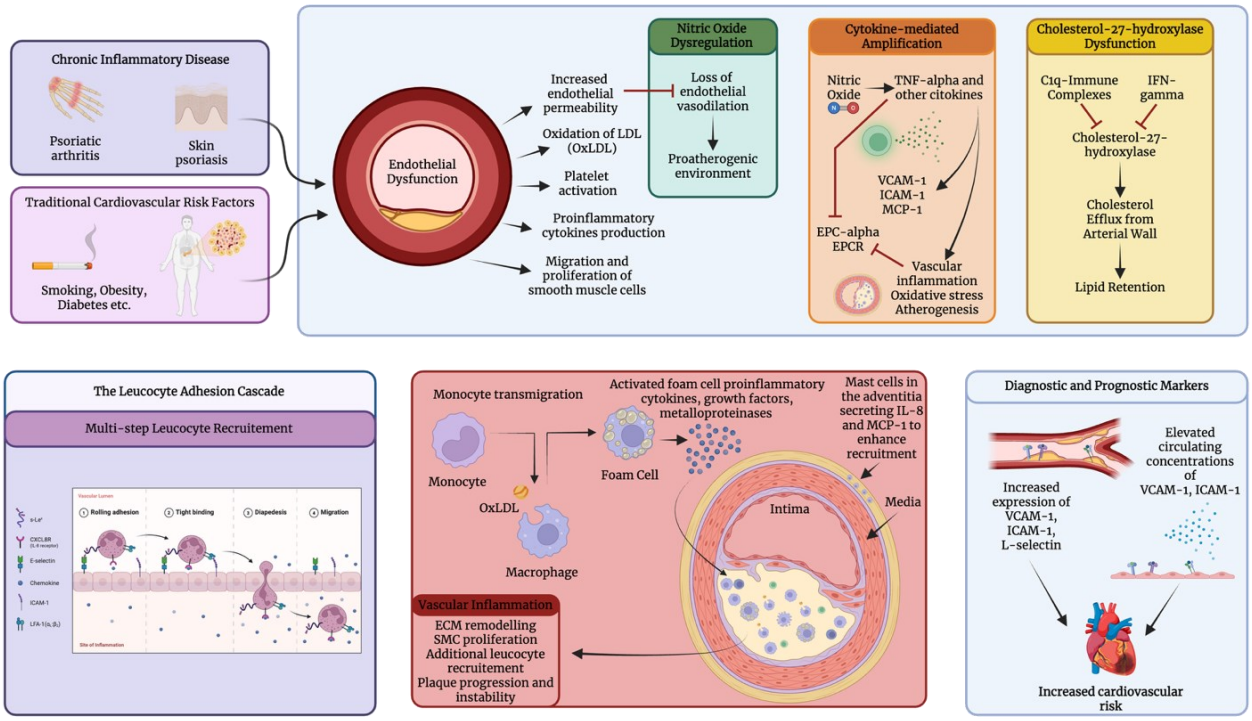


Figure 1. Integrated pathophysiological pathways linking chronic inflammation to endothelial dysfunction, leukocyte recruitment, and atherogenesis. This diagram integrates the cellular and molecular pathways linking chronic inflammation and traditional cardiovascular risk factors to endothelial dysfunction. Pro-inflammatory cytokines trigger a cascade involving altered nitric oxide bioavailability, reduced cholesterol efflux, and the multi-step recruitment of leukocytes via adhesion molecules, ultimately leading to foam cell formation, plaque progression, and instability. Abbreviations: C1q, complement component 1q; ECM, extracellular matrix; EPCR, endothelial protein C receptor; ICAM-1, intercellular adhesion molecule-1; IFN-gamma, interferon-gamma; IL-8, interleukin-8; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; OxLDL, oxidized low-density lipoprotein; SMC, smooth muscle cell; TNF-alpha, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1. Created in BioRender. Dimitrov, S. [2026] https://BioRender.com/nb17sty.

4. Adhesion Molecules, Lipid Abnormalities and Cardiovascular Risk

In addition to promoting leukocyte recruitment, oxidized low-density lipoproteins (OxLDL) establish an important mechanistic link between inflammation, endothelial activation, and atherosclerosis. OxLDL activates endothelial cells through nuclear factor-kappa B (NF-κB)-dependent signaling pathways, resulting in increased expression of adhesion molecules, including VCAM-1 and ICAM-1, as well as pro-inflammatory chemokines such as monocyte chemoattractant protein-1 (MCP-1). These changes facilitate monocyte adhesion to the vascular endothelium and subsequent migration into the arterial wall, thereby accelerating the development of atherosclerotic lesions [25,31,41].

Beyond the effects of modified LDL particles, chronic inflammation may profoundly alter the structure and function of high-density lipoprotein cholesterol (HDL-C). Under physiological conditions, HDL exerts anti-inflammatory, antioxidant, antithrombotic, and endothelial-protective effects through promotion of reverse cholesterol transport and inhibition of LDL oxidation. However, persistent inflammatory activity can transform HDL into a dysfunctional particle with reduced atheroprotective capacity. Dysfunctional HDL exhibits impaired cholesterol efflux capacity, diminished antioxidant activity, and a reduced ability to suppress endothelial activation and adhesion molecule expression, thereby contributing to sustained vascular inflammation and endothelial dysfunction [42,43].

Inflammatory cytokines that play a central role in psoriatic arthritis, particularly TNF-α, IL-6, and IL-17, further influence lipid metabolism and lipoprotein composition. Consequently, patients may develop a proatherogenic vascular phenotype despite apparently normal conventional lipid parameters. This phenomenon, often referred to as the “lipid paradox” of chronic inflammatory diseases, suggests that qualitative changes in lipoprotein function may be more important than absolute cholesterol concentrations alone. In parallel, ongoing endothelial activation promotes persistent expression of VCAM-1 and ICAM-1, creating a self-perpetuating cycle linking inflammation, dyslipidemia, and atherosclerosis [41,44,45].

Collectively, these findings indicate that adhesion molecules occupy a central position at the intersection of inflammatory and metabolic pathways involved in atherogenesis. Through their interactions with modified lipoproteins, activated endothelial cells, and circulating

leukocytes, ICAM-1 and VCAM-1 may represent important mechanistic mediators linking chronic inflammation with accelerated cardiovascular disease in patients with psoriatic arthritis.

5. VCAM-1 versus ICAM-1: Are all adhesion molecules equally informative?

Although most studies have evaluated ICAM-1 and VCAM-1 simultaneously, accumulating evidence suggests that these molecules may not provide equivalent information regarding cardiovascular risk in PsA. Elevated concentrations of both adhesion molecules have been reported in association with endothelial dysfunction and subclinical atherosclerosis [46–48] However, VCAM-1 appears to demonstrate a more consistent relationship with inflammatory activity and vascular involvement. In the study by Gündüz et al., both ICAM-1 and VCAM-1 correlated with CIMT, whereas recent data from Markov et al. showed that only VCAM-1 remained associated with CRP, ESR, disease activity, and treatment exposure [48,49]. Similar observations have been reported in cardiovascular populations, where circulating VCAM-1 concentrations correlate more closely with atherosclerotic burden than ICAM-1 [35,36]. These findings suggest that VCAM-1 may more closely reflect persistent endothelial activation and inflammatory activity in PsA, although its independent prognostic value remains to be established.

6. Heterogeneity of Published Findings

Despite the overall consistency of evidence linking adhesion molecules with cardiovascular involvement in PsA, considerable heterogeneity exists across studies. Earlier investigations consistently reported significantly elevated ICAM-1 and VCAM-1 concentrations compared with healthy controls [46–48]. In contrast, Markov et al. observed comparable adhesion molecule concentrations among PsA patients, ankylosing spondylitis patients, and controls despite significant associations between VCAM-1 and inflammatory activity [49]. Several factors may account for these discrepancies, including differences in disease duration, sample size, cardiovascular risk profile, laboratory methodology, and treatment exposure. The increasing use of biologic and targeted synthetic therapies in contemporary cohorts may attenuate endothelial activation and partially normalize circulating adhesion molecule levels, thereby reducing differences between patients and healthy individuals.

Additional methodological factors may also contribute to the observed variability. Studies have employed different laboratory assays, evaluated heterogeneous patient populations, and used varying definitions of disease activity and cardiovascular risk. Moreover, disease duration differed substantially across cohorts, ranging from recent-onset PsA to long-standing disease. Such differences may influence circulating adhesion molecule concentrations and complicate direct comparisons between studies. Therefore, the absence of significant between-group differences should not necessarily be interpreted as evidence against endothelial involvement but rather as a reflection of the complex interaction between inflammation, treatment, and vascular biology.

7. Therapeutic Implications

The association between adhesion molecule concentrations and treatment exposure raises the possibility that these biomarkers may reflect changes related to inflammatory control. Markov et al. reported higher VCAM-1 concentrations among biologic-naïve patients, whereas lower levels were observed in patients receiving biologic therapies and particularly in those treated with JAK inhibitors [49]. However, the cross-sectional design does not allow these differences to be attributed directly to treatment effects. Longitudinal studies are needed to determine whether changes in ICAM-1 and VCAM-1 parallel treatment response and whether they are accompanied by measurable improvement in vascular function or cardiovascular outcomes.

8. Limitations and Future Directions

Several limitations of the current evidence should be acknowledged. Direct evidence on adhesion molecules in PsA remains limited, and much of the current understanding of their role in vascular inflammation is derived from studies in other inflammatory diseases and the broader atherosclerosis literature. These data provide a useful mechanistic framework but should be interpreted separately from findings obtained directly in PsA populations. Most available studies are cross-sectional and involve relatively small patient populations, limiting the ability to establish causal relationships between adhesion molecules and cardiovascular outcomes. Furthermore, the majority of investigations rely on surrogate markers such as CIMT, FMD, or circulating biomarker concentrations rather than hard cardiovascular endpoints. Future prospective longitudinal studies are required to determine whether ICAM-1 and VCAM-1 independently predict cardiovascular events and whether therapeutic

modulation of endothelial activation translates into meaningful cardiovascular benefit.

The available literature supports a model in which adhesion molecules occupy a central position at the interface between chronic inflammation, endothelial dysfunction, and atherosclerosis. While significant progress has been made in understanding their biological and clinical relevance, further studies are required to clarify their prognostic value and potential role as therapeutic targets in psoriatic arthritis.

9. Conclusions

Adhesion molecules represent an important mechanistic link between chronic inflammation, endothelial dysfunction, and accelerated atherosclerosis in psoriatic arthritis. Experimental and clinical studies consistently demonstrate that ICAM-1 and VCAM-1 participate in leukocyte recruitment, vascular inflammation, and early atherogenic processes. Available evidence further suggests that elevated adhesion molecule levels are associated with markers of endothelial dysfunction and subclinical vascular involvement in patients with PsA.

Among the investigated biomarkers, VCAM-1 appears to show a more consistent relationship with inflammatory activity and vascular abnormalities, suggesting that it may better reflect ongoing endothelial activation. Although recent therapeutic advances may influence adhesion molecule expression, their precise role in cardiovascular risk stratification remains incompletely defined. Further longitudinal studies are required to determine whether adhesion molecules can identify patients at increased cardiovascular risk and whether changes in their circulating concentrations translate into improved vascular outcomes.

Declarations

Author Contributions

M.M.: Conceptualization, literature search, data interpretation, writing – original draft preparation. S.B.: Literature review, data interpretation, writing – review and editing. S.D.: Visualization, figure preparation, writing – review and editing. T.G. & M.D.: Supervision, critical revision of the manuscript, writing – review and editing. All authors have read and approved the final version of the manuscript. Generative AI (Claude, Opus 5, Anthropic Inc.) was used as a language-editing and formatting assistant

during manuscript preparation. It helped refine English phrasing, improve clarity, and align the structure with Rheumatology (Bulgaria) formatting requirements. No AI tools were used for data generation, analysis, interpretation, or reference fabrication. All scientific content, interpretation, and conclusions are entirely the authors' own. The authors take full responsibility for the accuracy and integrity of the submitted work.

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Conflicts of Interest

The authors declare no conflict of interest.

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Адхезионни молекули при псориатичен артрит: връзка между възпалението, ендотелната дисфункция и сърдечно-съдовите заболявания

Резюме

Псориатичният артрит (PsA) е свързан с повишена сърдечно-съдова заболеваемост и смъртност, които не могат да бъдат напълно обяснени с традиционните сърдечно-съдови рискови фактори. Адхезионните молекули, особено междуклетъчната адхезионна молекула-1 (ICAM-1) и съдовата клетъчна адхезионна молекула-1 (VCAM-1), се утвърждават като важни медиатори, свързващи хроничното възпаление с ендотелната дисфункция и атеросклерозата. Да се направи обзор на наличните доказателства относно ролята на адхезионните молекули в развитието на ендотелна дисфункция и сърдечно-съдови заболявания при пациенти с псориатичен артрит. Проведен е наративен литературен обзор чрез търсене в базите данни PubMed, Scopus и Web of Science. Анализирани са проучвания, оценяващи ICAM-1, VCAM-1, ендотелната дисфункция, субклиничната атеросклероза и сърдечно-съдовия риск при пациенти с PsA. Наличните данни показват, че повишените нива на адхезионните молекули са свързани с ендотелна дисфункция, увеличена дебелина на комплекса интима–медия на каротидните артерии, по-висока възпалителна активност и повишен сърдечно-съдов риск при PsA. Хистопатологичните изследвания допълнително потвърждават тяхното участие в синовиалното и съдовото възпаление. Последните данни предполагат, че VCAM-1 е по-тясно свързана с възпалителната активност и ендотелната активация в сравнение с ICAM-1. Натрупват се и доказателства, че съвременните биологични и таргетни терапии могат да повлияят експресията на адхезионните молекули. Адхезионните молекули играят важна роля в патогенезата на ендотелната дисфункция и атеросклерозата при псориатичен артрит. VCAM-1 се очертава като особено обещаващ биомаркер на съдовото възпаление. Необходими са допълнителни проспективни проучвания, за да се изяснят прогностичната и терапевтичната стойност на адхезионните молекули при оценката на сърдечно-съдовия риск.

Ключови думи: псориатичен артрит, адхезионни молекули, ICAM-1, VCAM-1, ендотелна дисфункция, атеросклероза.

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Review

Hyperuricemia Destroying the Heart: Are Tophaceous Valves that Rare?

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Running title: Tophaceous Valves in Hyperuricemia

Abstract

While the extraarticular deposition of urate crystals and its general cardiovascular impact are well recognized, the specific association between hyperuricemia and heart valve disease remains under-documented. Currently, only isolated cases of tophaceous valves have been reported, highlighting a significant gap in the literature. This narrative review aims to investigate the available data on monosodium urate (MSU) deposition on heart valves, assessing its prevalence, detection via advanced imaging modalities, and potential contribution to structural valve dysfunction. A literature search was conducted in the PubMed (MEDLINE) database for records published up to April 2026. The search strategy utilized Boolean operators to combine terms for specific heart valves with "gout," "urate crystals," "tophi," and imaging modalities relevant to extraarticular gout. Relevant case reports, imaging studies, and primary references were curated and analyzed. The search identified 10 historical case reports and one systematic review detailing histologically proven tophaceous valves,

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predominantly affecting the mitral and aortic valves. Historically, valvular tophi were considered exceedingly rare, often manifesting as incidental postmortem or postoperative findings. However, recent data utilizing Dual-Energy Computed Tomography (DECT) contrasts this paradigm. A prominent DECT study revealed cardiovascular MSU deposition in 86.4% of gout patients, with 18.2% specifically exhibiting urate deposits within the heart valves. These imaging findings were histologically validated, demonstrating DECT's accuracy in differentiating MSU from typical degenerative calcinosis, which may macroscopically mask urate deposits during routine histopathological examinations. Although isolated case reports suggest valvular tophi are rare, advanced imaging reveals a significantly higher prevalence of MSU deposits in cardiac valves. This discrepancy highlights the necessity for increased clinical vigilance regarding valvular involvement in hyperuricemic individuals and warrants further investigation into its precise role in structural heart disease.

Keywords: gout, hyperuricemia, heart valves, extraarticular urate deposits, tophaceus valve, X-Ray computed tomography

1. Introduction

Gout is one of the most common metabolic diseases of our times [1-3] and the extraarticular effects of hyperuricemia and especially its contribution to the cardiovascular risk are well recognized [4-6]. Even though treating isolated hyperuricemia even in the absence of other cardiovascular risk is not recommended [5, 7], there is an ongoing debate as data accrues on even isolated hyperuricemia leading to both articular and extraarticular deposition of precipitated crystals of monosodium urate (MSU) [8]. Especially in untreated or poorly managed gout MSU deposition takes form of gouty tophi with well-known typical histological structure [9]. Apart from the joints and their surrounding tissues, tophi have been found in different loci in head and neck, around nerves, in the axial skeleton etc. [10]. Over time, tophi can lead to erosion of the articular cartilage and periarticular fibrosis of the surrounding soft tissues [11, 12]; similar changes have been found in kidney, nerves and vessels [13, 14]. However, data on particular association of gout or hyperuricemia with heart valve disease seem to be insufficient. Only a few cases of tophaceus valves can be found in the literature [13].

In this review we aim to investigate further the data available on MSU deposition on heart valves specifically both by case reports and imaging modalities, its prevalence as well as its contribution on valve dysfunction.

Throughout this review, we distinguish between histologically confirmed tophi, as reported in the case-report literature, and imaging-detected urate deposits, as identified by DECT, recognizing that these represent related but non-equivalent findings.

2. Search Methodology and Results

To construct this biomedical review, we employed a systematic methodology adapted from the framework proposed by Gasparyan et al. [16]. A literature search was executed across the PubMed (MEDLINE) database, covering all available records up to April 2026 in two directions – capturing case reports on tophaceous heart valves on the one hand, and looking up the relevant imaging modality for visualizing those. Furthermore, the discussion incorporates insights derived from primary references, auxiliary database searches, and the authors' clinical expertise and professional judgment [16].

2.1. Case Reports

Our search strategy utilized Boolean operators to combine the terms “valve,” “mitral valve,” “aortic valve,” and “tricuspid valve” with (AND) “gout,” “urate crystals,” and “tophi.” The initial inquiry yielded 399 records. Following the removal of duplicates, review papers, and non-pertinent entries, the primary data were curated and are detailed in the subsequent section.

As a result of our search, 10 case reports of tophaceous valves—predominantly histologically confirmed—were identified, along with one 2019 review summarizing eight of these cases [15, 17-26]. Table 1 summarizes the demographic, clinical, and diagnostic characteristics of these 10 cases, together with the reviewing authors' judgment on whether the valvular tophus was likely to have contributed causally to valve dysfunction or represented an incidental, non-causal finding. The earliest published report in the medical literature is attributed to Coupland (referenced by Bunim and McEwen [18]) and dates back to 1873. The author described "tophi in a calcified aortic valve based on a positive murexide test, [which] merely represented incidental urate deposition in an old calcareous deposit" [18].

In 1940, Bunim and McEwen reported a patient with clinically diagnosed chronic tophaceous gout who lacked any evidence of cardiac disease. However, postmortem histological analysis revealed a typical tophus on the posterior mitral leaflet, composed primarily of urates and cholesterol. In

1982, Dennstedt and Weilbaecher reported another incidental finding of a gouty tophus in a surgically excised mitral valve. Histological examination showed birefringent, dichroic crystals consistent with uric acid [19].

The first case linking chronic tophaceous gout to the aortic valve was reported in Australia in 1983 by Jaworski and Gibson. An autopsy revealed tophi on the aortic valve leaflets containing birefringent, dichroic uric acid crystals [20]. That same year, Curtiss et al. described a 31-year-old man with congenital heart disease (Taussig-Bing anomaly) and tophaceous gouty arthritis [21]. The patient was treated for suspected infective endocarditis due to clinical signs of a brain abscess and a newly developed regurgitant heart murmur. An autopsy revealed that the valvular dysfunction was caused by sterile tophi located along the coaptation line of the pulmonary valve, with similar deposits noted on the mitral valve.

In 1984, Scalapino et al. presented the case of a 68-year-old woman with chronic tophaceous gout, a history of rheumatic heart disease, and signs of heart failure. Echocardiography revealed thickened, immobile mitral leaflets and a dilated left atrium containing a dense thrombus [22]. Surgical intervention included two aortocoronary bypasses, mitral valve replacement, and the removal of the atrial thrombus. The authors concluded that subannular tophi prevented proper leaflet opening and contributed to leaflet rigidity.

The majority of these cases were summarized in a 2019 systematic review by LaMoreaux and Chandrasekaran [13]. In their review, the average patient age was 60.9 years, with a strong male predominance (89%). The mitral valve was most frequently affected, followed by the aortic and pulmonary valves; notably, no tricuspid valve involvement was reported. Diagnosis across these cases was typically established through histopathological examination.

Table 1. Summary of the 10 historical case reports of histologically or clinically identified tophaceous heart valves.

#	Author, Year [Ref]	Age/ Sex	Valves Affected	Clinical Presentation	Diagnostic Confirmation	Clinician's Judgment on Causality
1	Coupland, 1873 [17]	NR	Aortic	Incidental finding on a calcified aortic valve	Murexide test	Incidental - original author described it as “merely...incidental urate deposition in an old

						calcareous deposit"
2	Bunim & McEwen, 1940 [18]	NR	Mitral (posterior leaflet)	Clinically diagnosed chronic tophaceous gout; no clinical evidence of cardiac disease during life	Postmortem histology (urate + cholesterol)	Incidental - postmortem finding with no antemortem cardiac disease
3	Dennstedt & Weilbaecher, 1982 [19]	NR	Mitral	Found in a surgically excised mitral valve	Histology / polarized light (birefringent, dichroic crystals)	Incidental - explicitly reported as an incidental finding
4	Jaworski & Gibson, 1983 [20]	NR (adult)	Aortic	Chronic tophaceous gout; aortic valve stenosis found at autopsy	Postmortem histology (birefringent, dichroic crystals)	Not explicitly stated - tophi and stenosis co-existed; authors did not assert causation
5	Curtiss et al., 1983 [21]	31y, M	Pulmonary (primary); mitral (also involved)	Congenital heart disease (Taussig-Bing anomaly); new regurgitant murmur and brain abscess, suspected endocarditis	Autopsy/histology (sterile tophi)	Causal - authors stated dysfunction "was caused by" the tophi
6	Scalapino et al., 1984 [22]	68y, F	Mitral	Chronic tophaceous gout, rheumatic heart disease history, heart failure, mitral stenosis, LA thrombus	Echocardiography + surgical histology (MVR specimen)	Causal - subannular tophi held to prevent leaflet opening/cause rigidity
7	Gawoski et al., 1985 [23]	Elderly, M	Aortic	Long-standing gout; valve surgically resected (calcified)	Histology + X-ray diffraction (confirmed MSU + hydroxyapatite/ whitlockite)	Incidental - tophus found alongside dystrophic calcification, the presumed primary pathology
8	Iacobellis &	NR	Mitral	Asymptomatic cardiac finding;	NR (full text not accessible)	Incidental - title reports it as "rare

	Iacobellis, 2004 [24]			severe gouty tophaceous arthritis elsewhere		and asymptomatic"
9	Koffi et al., 2010 [25]	NR	NR	NR (full text paywalled)	NR	NR
10	Rohani et al., 2012 [26]	75y, M	Mitral (posterior leaflet)	10 yr history of tophaceous gout, acute flare; incidental echo finding during HF screening	Echocardiography only (TTE+TEE) - not histologically confirmed	Incidental - authors state "without significant valve dysfunction"; diagnosis was presumptive

Abbreviations: NR: not reported / not available in the accessible source. MVR: mitral valve replacement; MSU: monosodium urate; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; HF: heart failure; LA: left atrium.

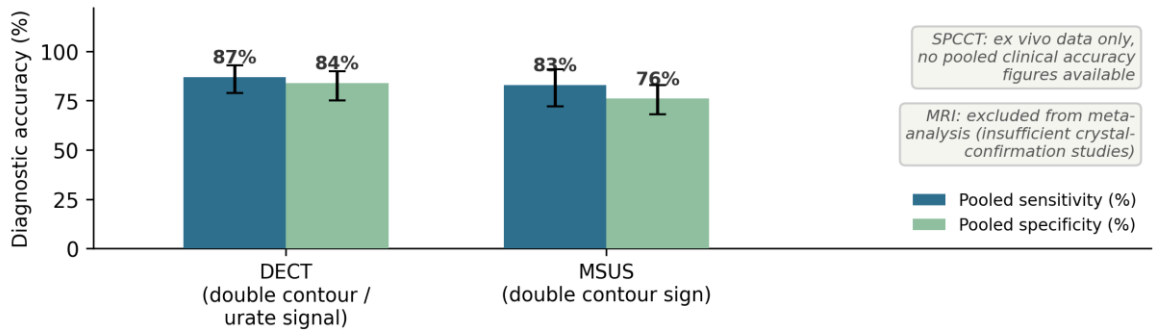
2.2. Imaging Modalities for Detecting MSU Deposits in the Heart Valves

A structured literature search was conducted to evaluate imaging modalities relevant to extraarticular monosodium urate (MSU) deposits. The primary search utilized the exact Boolean string: ("extraarticular gout" AND "imaging"). Additional scoping queries were executed using the search strings ("MSU deposits" OR "tophi" OR "heart valves" OR "tophaceous valves") AND "imaging".

Articles were filtered based on their direct relevance to the imaging of extraarticular MSU deposition. The primary search string yielded 35 records that met this inclusion criterion. Upon abstract review, it was noted that none of these initial 35 records directly addressed deposition within the heart valves. However, subsequent citation tracking of this literature cohort identified a recurrent and highly relevant article [27]. This specific study, which compared Dual-Energy Computed Tomography (DECT) with histopathology, explicitly described valve crystal deposition and was subsequently included in the review.

2.2.1. Imaging Modalities for the Detection of Extra-Musculoskeletal Monosodium Urate Deposits

A. Pooled diagnostic accuracy vs. microscopic crystal identification (95% CI)



B. Comparative features of imaging modalities for extra-articular / valvular MSU deposits

	DECT	MSUS	SPCCT	MRI	Conventional CT
Detects heart-valve MSU deposits (published evidence)	✓	✗	✗	✗	✗
Differentiates MSU from calcification	✓	~	✓	✗	~
Radiation-free	✗	✓	✗	✓	✗
Current clinical availability	✓	✓	✗	~	✓

✓ established / yes ~ partial or indirect ✗ not established / no

Figure 1. Comparison of imaging modalities for detecting extra-articular and valvular monosodium urate (MSU) deposits. (A) Pooled sensitivity and specificity of DECT and MSUS against microscopic crystal identification, with 95% confidence intervals [29]; SPCCT accuracy has only been reported in ex vivo studies, and MRI was excluded from the pooled meta-analysis due to insufficient crystal-confirmation studies. (B) Comparative features of the five modalities discussed in the text, based on the evidence summarized above.

Dual-Energy CT (DECT) is currently the most robustly investigated modality for detecting both intra- and extra-articular MSU deposits [28]. The technique exploits the differential X-ray attenuation of MSU crystals at varying energy levels to generate color-coded maps of crystal deposition. When compared to microscopic crystal identification, DECT demonstrates a pooled sensitivity of 87% (95% CI 0.79-0.93) and a specificity of 84% (95% CI 0.75-0.90) [29]. In the context of extra-musculoskeletal applications, DECT has been successfully utilized to visualize MSU deposits in cardiovascular structures, as well as in deep soft tissues, tendons, and bursae [28]. The technology has evolved significantly; third-generation scanners offer improved spectral separation, resulting in fewer equivocal interpretations (a reduction from 33% in 2013 to 16% in 2019) [30].

Musculoskeletal Ultrasound (MSUS) identifies MSU deposits through characteristic features such as the double contour sign (a hyperechoic band overlying the cartilage), soft tissue tophi, and microaggregates [31]. The double contour sign exhibits a pooled sensitivity of 83% (95% CI 0.72-0.91) and a specificity of 76% (95% CI 0.68-0.83) [29]. Although ultrasound is a widely accessible, cost-effective, and radiation-free modality highly valuable for periarticular soft tissues, its utility for extra-musculoskeletal applications is limited. It is highly operator-dependent and lacks the physical capability to evaluate deep internal structures or provide a whole-body assessment of the crystal burden. [28] Nevertheless, recent advancements, including superb microvascular imaging and AI-based deep learning algorithms, continue to enhance its diagnostic accuracy [32].

Multi-energy spectral photon-counting CT (SPCCT) is an advanced technology that uses energy-resolving photon-counting detectors, providing superior spectral separation compared to conventional systems [33]. In ex vivo studies, SPCCT has demonstrated the ability to detect MSU deposits with significantly finer detail than standard DECT [34]. It can also differentiate between distinct crystal types based on their elemental composition, successfully distinguishing MSU from calcium pyrophosphate (CPP) and hydroxyapatite (HA) within calcified tissues [34]. Despite its potential for detailed whole-body crystal assessment, SPCCT remains primarily a research tool with limited clinical availability [33, 34].

Magnetic Resonance Imaging (MRI) effectively visualizes soft tissue abnormalities, tophi, synovial inflammation, and bone marrow edema; however, its images are nonspecific for MSU crystals [35, 36]. On both T1- and T2-weighted sequences, tophi typically present with low to intermediate signal intensity that may also be feature of variety of other pathological structures [37]. Contrast enhancement also lacks diagnostic specificity for gout [37]. Due to an insufficient number of studies utilizing microscopic crystal confirmation (the gold standard), MRI was excluded from the meta-analysis on diagnostic accuracy conducted by Ogdie et al [29].

Conventional CT is capable of visualizing tophi as soft tissue masses with a density of approximately 160 Hounsfield units (HU), thus yielding a relative degree of specificity for MSU [36]. However, its primary limitation is that it cannot reliably differentiate MSU deposits from other crystal types or calcifications in extra-musculoskeletal tissues [35, 37].

2.2.2. Emerging Technologies

The application of deep learning reconstruction techniques to DECT shows significant promise. These algorithms enhance the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), improving MSU detection while potentially allowing for a reduction in patient radiation exposure [38].

As mentioned above, the only study dealing with MSU deposits in valves is the one by Klauser et al. [27]. The team conducted a prospective case-control study aiming "to compare coronary calcium score and cardiovascular MSU deposits detected by DECT". Among the 157 participants, 110 had gout (according to the 2015 ACR/EULAR criteria) and the remaining 47 were age- and sex-matched controls. The imaging protocol featured a cardiovascular-optimized software with a density threshold of 150 Hounsfield units aiming to minimize artifacts from tissue calcifications. There was a significantly higher prevalence of cardiovascular MSU deposition in the gout group (86.4%) compared to only 14.9% of the controls. Apart from deposits in the aorta (77.3%) and coronary arteries (33.6%), DECT specifically identified urate deposits within the heart valves - the mitral and tricuspid valves - in 18.2% of the studied group. Analysis of 10 cadavers that displayed positive DECT signals was also performed with histological examination including polarized light microscopy and confirmed the presence of negatively birefringent, needle-shaped MSU crystals in 70% of the cases. Thus, a main conclusion of the study was that DECT accurately discriminates MSU (urate) deposits from calcium in valvular and vascular structures. The authors acknowledge several limitations of their work: its cross-sectional design, the relatively small control group, along with technical challenges such as calcifications masking smaller neighboring urate deposits due to strong signal.

4. Discussion

4.1. Strengths and Limitations

In this narrative review, we aimed to present data available in the scientific literature concerning MSU deposits on cardiac valves. Although the isolated case reports form the last century would suggest that valve involvement is exceedingly rare, the sole study using imaging modality reveals quite a contrasting picture. This is the main limitation of this review and, in fact, of the data available - its scarcity, relying on a single database: a limited number of cases and only one, even though well-designed, case-control study. The second limitation of the data compared is that the case reports presented refer to tophi, while the DECT study discriminated urate deposits

only. This distinction is not merely semantic: a histologically confirmed tophus reflects an organized, chronic deposit accompanied by a characteristic granulomatous tissue reaction, whereas DECT identifies the presence of urate crystals based on their dual-energy attenuation profile alone, without providing direct information on the surrounding tissue response or the maturity of the deposit. Accordingly, DECT-detected valvular urate deposits and histologically confirmed tophaceous valves should be regarded as related but non-equivalent findings, and the higher prevalence reported by DECT cannot be directly equated with a comparable prevalence of true tophi. Notably, although our literature search extended through April 2026, no additional independent imaging studies were identified that replicated or disputed the findings of Klauser et al.; the DECT-based prevalence estimates therefore remain unconfirmed by any second dataset.

Despite these limitations, this review offers several strengths. To our knowledge, it is the first work to systematically juxtapose the historical case-report literature on tophaceous heart valves with the emerging imaging-based evidence on valvular urate deposition, applying a structured search methodology adapted from established narrative-review guidance. By compiling the demographic, clinical, and diagnostic characteristics of all 10 published case reports (Table 1) alongside a critical appraisal of the available imaging modalities (Figure 1), this review provides a practical reference for clinicians and a clear framework for future investigation, while explicitly flagging the non-equivalence between imaging-detected and histologically confirmed findings discussed above.

4.2. Clinical Implications and Future Directions

However, the data presented still suggest that routine postoperative histopathological examinations may frequently fail to identify MSU deposits as the macroscopic appearance of the valve may resemble a typical degenerative calcinosis and thus easily be overlooked. The discrepancy suggests that closer scrutiny of structural valve damage is warranted, particularly in patients with hyperuricemia.

The precise degree to which valvular tophi contribute to structural - and consequently functional - valvular damage remains unclear. In several of the previously discussed reports, tophi were documented as incidental findings, whereas other authors explicitly argued for a causal relationship. Given the current evidence base, this causal relationship should be regarded as unproven, and prospective studies with systematic histological and functional assessment are needed before valvular tophi can be

considered a definitive contributor to structural heart disease. Further studies are required to systematically classify the sites of deposition, investigate the underlying tissue alterations, and account for the impact of concomitant comorbidities.

It is well established that hyperuricemia (serum urate ≥ 6.8 mg/dL) is independently linked to hypertension, chronic kidney disease (CKD), metabolic syndrome, diabetes, and cardiovascular disease [5, 39, 40] via inflammasome activation, oxidative stress, endothelial dysfunction, and reduced nitric oxide bioavailability [40, 41]. Furthermore, epidemiological studies have shown that elevated uric acid levels are predictive of coronary artery disease, left ventricular hypertrophy, atrial fibrillation, stroke, and CKD progression [40-43]. Moreover, approximately 25% of individuals with hyperuricemia exhibit MSU crystal deposition detectable by specialized imaging, even prior to the development of clinical gout [27]. Nevertheless, randomized trials have inconsistently demonstrated clinical benefits from treating asymptomatic cases, although urate-lowering therapy may offer advantages for specific high-risk populations [5, 43]. Given these facts, alongside the data presented in this review, further investigation into cardiac valve involvement in asymptomatic hyperuricemic patients is highly warranted.

4. Conclusions

The growing number of histologically confirmed case reports, combined with DECT data revealing a significant percentage of imaging-detected MSU deposits in cardiac valves - two related but non-equivalent lines of evidence - warrants increased clinical and scientific attention to valvular involvement in both overtly gouty and hyperuricemic individuals, although these observations remain preliminary and should be interpreted with caution given the limited and heterogeneous evidence base.

Declarations

Author Contributions

All authors contributed to the study conception and design. BP performed the literature review and was responsible for drafting, editing, and revising the manuscript, as well as participating in the clinical management of the patient. GS and VG contributed to the editing and critical revision of the manuscript at all stages of production. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author used LLM Gemini (Google Inc.) to improve the overall language and readability of the manuscript. Additionally, generative AI was used to draft the initial versions of the abstract and the section summarizing the article "Dual-Energy Computed Tomography Detection of Cardiovascular Monosodium Urate Deposits in Patients With Gout". After using these tools, the authors carefully reviewed, edited, and verified all content, and take full responsibility for the accuracy, originality, and final content of the publication.

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Institutional Review Board Statement

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Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Review

Synovial Fluid Biomarkers: Current Applications and Future Perspectives

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Running title: Synovial Fluid Biomarkers: Overview

Abstract

Synovial fluid offers a direct window into the intra-articular environment, but individual biomarkers rarely separate arthritis subtypes reliably. This narrative review compares conventional tests with cytokines, proteomic markers, extracellular vesicles, microRNAs, metabolomics, and machine-learning-assisted multi-omics across rheumatoid arthritis, osteoarthritis, psoriatic arthritis, septic arthritis, periprosthetic joint infection, crystal-induced arthritis, connective tissue disease-associated arthritis, and Lyme arthritis. Relevant publications from 2017–2026 were identified through structured searches of PubMed, Scopus, Web of Science, and Google Scholar, supplemented by manual screening of reference lists; selection prioritized systematic and narrative reviews, translational studies, and clinically relevant biomarker investigations, and reporting followed the SANRA framework for narrative reviews.

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The most clinically mature applications remain conventional cell count, crystal analysis, microbiological testing, and alpha-defensin assessment for periprosthetic joint infection, whereas extracellular vesicles, microRNAs, and multi-omics remain largely translational.

Keywords: synovial fluid, biomarkers, cytokines, proteomics, metabolomics, extracellular vesicles

1. Introduction

Arthritis remains a major cause of pain and disability worldwide. Although synovial fluid (SF) analysis is already essential in determining cell counts, crystal identification, and microbiology, its molecular content is still underused in routine care worldwide[1,2,3] .

Compared with blood, synovial fluid better reflects local inflammatory activity, matrix turnover, and tissue remodeling [4]. The challenge is not whether the fluid is informative, but which measurements are specific, reproducible, and likely to change management.

Traditionally, synovial fluid analysis has focused on leukocyte count, differential cell analysis, crystal identification, Gram staining, glucose levels, and microbiological cultures[5,6]. These techniques remain fundamental for distinguishing inflammatory, septic, and crystal-induced arthritis; however, they provide limited insight into molecular disease mechanisms and prognostic heterogeneity.

SF represents a direct biochemical reflection of the intra-articular microenvironment and therefore provides unique information regarding local inflammatory activity, cartilage degradation, angiogenesis, oxidative stress, and immune activation [7,8].

Compared with serum biomarkers, SF-derived biomarkers are less influenced by systemic physiological variation and may therefore provide greater specificity regarding local joint pathology [4].

Recent developments in proteomics, metabolomics, transcriptomics, extracellular vesicle research, and machine learning-assisted molecular analysis have transformed SF into a promising source of diagnostic and prognostic biomarkers. Emerging evidence suggests that integrated biomarker panels may distinguish inflammatory from degenerative arthritis, identify aggressive disease phenotypes, predict radiographic progression, and monitor therapeutic response.

This narrative review summarizes current evidence regarding conventional and emerging SF biomarkers across major diseases, discusses recent methodological advances, evaluates limitations of current research, and highlights future directions toward precision rheumatology.

2. Search Strategy

A narrative literature review was conducted using PubMed, Scopus, Web of Science, and Google Scholar to identify relevant publications on SF biomarkers in arthritis. Articles published between 2017 and 2026 were prioritized to capture contemporary work in proteomics, metabolomics, transcriptomics, extracellular vesicles, and machine learning-assisted biomarker research, while landmark older studies were retained when necessary to contextualize major concepts or historically important discoveries. Search terms included combinations of "synovial fluid biomarkers", "rheumatoid arthritis", "osteoarthritis", "psoriatic arthritis", "gout", "septic arthritis", "periprosthetic joint infection", "proteomics", "metabolomics", "microRNA", "extracellular vesicles", "cytokines", and "machine learning". Boolean operators and MeSH terms were used to broaden retrieval and improve precision. Priority was given to systematic reviews, narrative reviews, translational studies, observational cohort studies, and clinically relevant biomarker investigations. Particular emphasis was placed on inflammatory cytokines, matrix-degrading enzymes, extracellular vesicle-derived biomarkers, metabolomic profiles, transcriptomic signatures, and integrated multi-marker approaches. Studies focusing exclusively on serum biomarkers without SF analysis were generally excluded unless directly relevant to local intra-articular inflammatory mechanisms. Reference lists of selected articles were also screened manually to identify additional relevant studies not captured in the initial search. Because this is a narrative review, the methodology is inherently subject to selection bias and does not have the same level of reproducibility as a formal systematic review. This narrative review was prepared with consideration of the SANRA (Scale for the Assessment of Narrative Review Articles) recommendations in order to improve methodological transparency, literature selection, and overall reporting quality.

3. Synovial Fluid as a Diagnostic Tool

SF is a viscous ultrafiltrate of plasma produced by type A and type B synoviocytes within the synovial membrane. Under physiological

conditions, SF provides lubrication, nutrient transport, shock absorption, and maintenance of cartilage homeostasis [8].

Normal SF contains hyaluronic acid, lubricin, electrolytes, proteins, and small numbers of mononuclear cells. During inflammatory and degenerative joint diseases, substantial alterations occur in SF composition due to increased vascular permeability, infiltration of inflammatory cells, synovial hyperplasia, cartilage matrix degradation, oxidative stress, and cytokine release [7,9].

In rheumatoid arthritis (RA), SF becomes highly inflammatory and enriched with neutrophils, macrophages, cytokines, proteolytic enzymes, and autoantibodies [10]. In osteoarthritis (OA), although inflammation is generally less pronounced, elevated inflammatory mediators and degradative enzymes contribute significantly to cartilage destruction and pain generation [11,12].

Routine SF analysis traditionally includes macroscopic appearance and viscosity, leukocyte count and differential, crystal analysis using polarized microscopy, Gram stain and microbial culture, and protein and glucose measurements [5,6]. These conventional methods remain clinically indispensable. For example, neutrophil predominance strongly suggests inflammatory or septic arthritis, while monosodium urate and calcium pyrophosphate crystals establish the diagnosis of gout and pseudogout.

However, conventional cytological analysis alone cannot fully characterize the molecular pathways driving disease progression. As a result, high-throughput molecular technologies have emerged as valuable tools for detailed characterization of SF proteins, metabolites, lipids, nucleic acids, and extracellular vesicles [13-16]. Conventional SF testing remains essential for acute diagnostic assessment, whereas most molecular biomarkers remain investigational.

4. Cytokines and Inflammatory Biomarkers

Inflammatory cytokines are among the most extensively studied SF biomarkers because they directly reflect immune activation and synovial inflammation. Cytokine networks regulate leukocyte recruitment, angiogenesis, osteoclast activation, pannus formation, and extracellular matrix degradation [10,17].

IL-6 plays a central role in inflammatory arthritis and is strongly associated with synovial inflammation, disease activity, and radiographic progression

in RA [18,19]. SF IL-6 concentrations correlate with DAS28 and inflammatory markers and remain elevated, although typically to a lesser degree, in OA [11,12]. Despite its pathogenic and therapeutic relevance, IL-6 lacks sufficient specificity as an isolated diagnostic biomarker.

TNF-α is a central cytokine in RA and psoriatic arthritis (PsA) pathogenesis and contributes to chronic synovial inflammation, leukocyte recruitment, angiogenesis, cartilage destruction, and bone erosion [20,21,22]. Elevated SF TNF-α concentrations correlate with synovitis severity and radiographic progression in inflammatory arthritis. However, variable therapeutic response highlights the molecular heterogeneity of inflammatory arthritis and limits the utility of TNF-α as a standalone biomarker.

IL-1β is a major pro-inflammatory cytokine involved in cartilage degradation, synovial inflammation, and activation of catabolic pathways in arthritis [12,23]. Elevated SF IL-1β concentrations are observed in RA, OA, PsA, gout, and septic arthritis [23,24]. In gout, monosodium urate crystals activate the NLRP3 inflammasome, resulting in IL-1β-driven neutrophilic inflammation [41]. Although biologically important, IL-1β lacks disease specificity, and therapeutic targeting has produced mixed clinical results in OA and RA.

Elevated SF IL-8 levels are associated with increased neutrophil infiltration and synovial inflammation in RA, PsA, and septic arthritis [10,24].

CSF-1 is associated with macrophage activation, synovitis, cartilage degeneration, and structural progression in OA [12,25]. Because macrophage-driven inflammation is increasingly recognized as an important component of OA pathogenesis, CSF-1 has attracted interest as both a prognostic biomarker and potential therapeutic target. However, its clinical utility remains insufficiently validated.

Cytokines are sensitive markers of local inflammation but demonstrate substantial overlap across inflammatory, degenerative, and infectious arthritides. Their greatest potential clinical value lies in integrated biomarker panels and therapeutic-response stratification rather than standalone diagnosis. Measurement of inflammatory cytokines provides important information regarding disease activity, severity of synovial inflammation, risk of disease flare, therapeutic response, and prognostic stratification [17,19].

5. Proteomics and Matrix-Degrading Enzymes

Proteomics enables comprehensive evaluation of proteins involved in inflammation, extracellular matrix remodeling, cartilage degradation, oxidative stress, angiogenesis, and tissue repair [13,26]. Recent advances in liquid chromatography-tandem mass spectrometry (LC-MS/MS) have significantly expanded understanding of SF protein composition.

Matrix metalloproteinases (MMP) are key mediators of extracellular matrix degradation and structural joint damage in arthritis [12,27]. Among them, MMP-3 and MMP-13 are the most extensively studied SF biomarkers.

MMP-3 reflects synovial fibroblast activation and inflammatory activity and correlates with synovitis severity, radiographic progression, and treatment response in RA [27,28]. In OA, elevated MMP-3 levels are also associated with cartilage degradation, although concentrations are generally lower than in RA.

MMP-13 plays a more direct role in degradation of type II collagen and is strongly associated with cartilage destruction and OA progression [29]. Because MMP-13 expression may occur early in disease, it has attracted interest as a potential marker of early cartilage degeneration.

TIMP-1 is a natural inhibitor of MMP and contributes to regulation of extracellular matrix turnover. Altered MMP/TIMP balance is associated with progressive structural damage in both RA and OA [30]. Elevated SF TIMP-1 concentrations likely represent a compensatory response to increased matrix degradation; however, TIMP-1 alone lacks sufficient specificity for routine clinical use.

VEGF promotes synovial angiogenesis and correlates with inflammatory activity, pannus formation, and disease severity in RA and PsA [20,21]. Although biologically informative, VEGF lacks disease specificity and remains primarily investigational.

Among proteomic markers, MMP-3 currently demonstrates the clearest association with active synovitis and treatment monitoring, whereas MMP-13 is more closely linked to cartilage degradation. VEGF and TIMP-1 are biologically informative but demonstrate limited disease specificity.

Recent advances in proteomics have shifted attention from isolated biomarkers toward integrated multi-protein signatures capable of reflecting the biological heterogeneity underlying arthritis. Proteomic analyses have also shown that inflammatory OA phenotypes may resemble

RA more closely than previously recognized, particularly regarding cytokine activation and neutrophil-associated pathways [11].

High-throughput mass spectrometry has further enabled identification of candidate biomarkers associated with complement activation, lipid metabolism, extracellular matrix remodeling, oxidative stress, and synovial angiogenesis.

Integrated proteomic profiling may improve molecular characterization of arthritis; however, current applications remain primarily investigational and lack sufficient standardization for routine clinical use.

6. Extracellular Vesicles and Exosome Biomarkers

Exosomes isolated from OA SF contain proteins associated with cartilage degradation, oxidative stress, and extracellular matrix remodeling. Additionally, exosome-derived microRNAs regulate inflammatory signaling pathways and cartilage metabolism [16,31]. In inflammatory arthritis, SF EVs arise from multiple cellular sources, including fibroblast-like and macrophage-like synoviocytes, chondrocytes, activated T cells and monocytes, and platelets; their surface tetraspanins (CD9, CD63, CD81) and vesicular cargo—non-coding RNAs (including miR-146a and miR-155), heat shock proteins, complement components, and matrix-degrading enzymes—broadly reflect this cell of origin and the local inflammatory state, with synoviocyte-derived EVs predominating in rheumatoid synovitis and chondrocyte-derived EVs more prominent in osteoarthritic cartilage turnover [32]. Isolating EVs from SF is technically demanding because of the fluid's high viscosity, which stems from its dense hyaluronic acid and lubricin content. Differential ultracentrifugation, the most widely used isolation method, co-purifies substantial non-vesicular contaminants—serum albumin, immunoglobulins, high-density lipoproteins, and extracellular matrix fragments—that can confound downstream proteomic and functional analyses; size-exclusion chromatography improves purity but adds cost, processing time, and inter-laboratory variability, and no isolation protocol has yet been standardized specifically for SF [44]. Although extracellular vesicles-derived biomarkers demonstrate diagnostic and mechanistic potential, this methodological variability and limited standardization currently restrict clinical implementation.

7. MicroRNAs and Genetic Biomarkers

MicroRNAs (miRNAs) are short non-coding RNAs involved in post-transcriptional regulation of gene expression. Because miRNAs remain

relatively stable in biological fluids, they have emerged as attractive biomarker candidates in rheumatologic diseases [16,32].

miR-146a is one of the best-characterized microRNAs in inflammatory arthritis and regulates NF-κB-associated inflammatory signaling pathways [32]. Elevated SF miR-146a levels correlate with inflammatory activity, synovial hyperplasia, and cytokine expression in RA. Although increased expression may represent a compensatory anti-inflammatory response, it appears insufficient to suppress chronic inflammation fully.

miR-155 is a pro-inflammatory microRNA associated with macrophage activation, cytokine production, and persistent synovitis [32,33]. Increased expression has been reported in RA and PsA and correlates with inflammatory activity and cytokine release. Experimental studies suggest that miR-155 contributes to osteoclast activation and structural damage.

miR-140 is strongly associated with cartilage homeostasis and extracellular matrix regulation in OA [33]. Reduced SF miR-140 expression correlates with cartilage degeneration and disease progression and may occur early in OA development. Although miR-140 has attracted interest as a potential biomarker and therapeutic target, current evidence remains largely experimental.

8. Metabolomics and Multi-Omics Approaches

Metabolomics involves large-scale analysis of small molecules generated during cellular metabolism [7,14]. Because inflammatory and degenerative joint diseases alter metabolic activity inside the intra-articular environment, metabolomic profiling provides valuable insight into disease mechanisms. Altered SF concentrations of lactate, amino acids, lipid metabolites, and oxidative stress markers have been identified in both OA and RA [7,14].

8.1 Lactate

Elevated SF lactate concentrations reflect anaerobic metabolism and hypoxic synovial environments associated with intense inflammatory activity [34]. During severe synovial inflammation, increased leukocyte infiltration and local tissue hypoxia stimulate anaerobic glycolysis, resulting in lactate accumulation within the joint cavity. Increased lactate levels are commonly observed in septic arthritis and severe inflammatory synovitis. Because bacterial infection additionally contributes to metabolic dysregulation and neutrophil activation, lactate levels may assist in the differentiation between infectious and noninfectious arthritis. Several

studies suggest that markedly elevated SF lactate concentrations demonstrate favorable sensitivity for septic arthritis, particularly when interpreted together with leukocyte count and microbiological findings. D-lactate has attracted additional interest because it is produced predominantly through bacterial metabolism rather than host cellular activity. As a result, D-lactate may potentially provide greater specificity for bacterial infection compared with total lactate alone. Elevated lactate concentrations are not exclusive to septic arthritis and may additionally occur in severe inflammatory arthritides such as RA or crystal-induced arthritis. Despite this promise, lactate and D-lactate measurement is not yet incorporated into most routine SF diagnostic panels, and proposed cut-off values vary across studies depending on the analytical platform and patient population, underscoring the need for assay standardization before broader clinical adoption.

8.2 Lipid Metabolites

Changes in lipid metabolism contribute to inflammatory signaling, membrane instability, oxidative stress, and cellular dysfunction within arthritic joints [12,35]. Altered phospholipid, sphingolipid, cholesterol, and fatty acid profiles have been identified in both OA and RA. Certain phospholipid and sphingolipid species have been associated with cartilage degeneration, synovitis severity, and pain burden. Specific lysophosphatidylcholine, lysophosphatidic acid, ceramide, and sphingosine-1-phosphate species have been implicated in pain signaling and catabolic chondrocyte responses, while cholesterol accumulation within synoviocytes contributes to activation of inflammatory pathways such as the NLRP3 inflammasome. Altered lipidomic profiles have been associated with synovitis severity, cartilage degeneration, and inflammatory activity in both OA and RA [12,35]. Because lipidomic assays require specialized mass spectrometry infrastructure and standardized pre-analytical handling to prevent lipid degradation, these markers remain confined largely to research settings.

8.3 Amino Acid Profiles

Altered amino acid metabolism reflects inflammatory activation, oxidative stress, and tissue remodeling within arthritic joints [7]. Changes in glutamine, arginine, tryptophan, and branched-chain amino acid metabolism have been described in both RA and OA. These alterations may reflect immune-cell activation, cartilage catabolism, and metabolic stress; for example, glutamine depletion has been linked to heightened synovial lymphocyte and macrophage activity, while reduced branched-chain amino

acid concentrations parallel cartilage catabolic turnover in OA. However, amino acid profiles are strongly influenced by obesity, diet, medication exposure, and systemic metabolic factors, limiting current clinical applicability.

8.4 Multi-Omics Integration and Machine Learning

Integrated multi-omics approaches combine cytokine profiling, proteomics, metabolomics, transcriptomics, imaging findings, and clinical data to better characterize the biological heterogeneity underlying arthritis [14,15,16,30,36]. Early studies suggest that machine learning-assisted analyses can improve arthritis classification, identification of inflammatory phenotypes, and prediction of disease progression or therapeutic response compared with conventional biomarker assessment [30,36]. Although current applications remain largely investigational, integrated multi-omics approaches represent one of the most promising future directions in precision rheumatology.

Table 1 summarizes the major synovial fluid biomarker categories in inflammatory arthritis, including cytokines, matrix remodeling enzymes, microRNAs, metabolites, extracellular vesicles, and multi-protein signatures, together with their principal pathophysiological roles and potential clinical applications.

Table 1. Major Synovial Fluid Biomarkers and Their Clinical Relevance in Arthritis.

Biomarker Category	Examples	Main Pathophysiological Role	Diseases Associated	Potential Clinical Utility	References
Cytokines/Chemokines	IL-6, TNF-α, IL-1β, IL-17, IL-8	Immune activation, synovitis, cytokine amplification	RA, PsA, OA, septic arthritis, gout	Disease activity assessment, prognosis, therapeutic monitoring	[17,18,20,23]
Matrix remodeling enzymes	MMP-3, MMP-13, ADAMTS-5	Extracellular matrix degradation, cartilage destruction	RA, OA, PsA	Prediction of structural progression, monitoring cartilage damage	[26,27,29,35]
Matrix inhibitors	TIMP-1	Regulation of extracellular matrix turnover	RA, OA	Evaluation of MMP/TIMP balance and tissue remodeling	[26,27]

Angiogenic mediators	VEGF	Synovial angiogenesis, vascular proliferation	RA, PsA, OA	Assessment of inflammatory severity and pannus formation	[20,21]
Macrophage-associated markers	CSF-1, calprotectin	Macrophage activation, innate immune signaling	OA, RA, septic arthritis	Identification of inflammatory phenotypes	[9,12,25]
MicroRNAs	miR-146a, miR-155, miR-140	Post-transcriptional immune and cartilage regulation	RA, OA, PsA	Disease stratification, treatment response prediction	[16,32,33]
Metabolites	Lactate, lipid metabolites, amino acids	Metabolic reprogramming, oxidative stress	Septic arthritis, RA, OA, gout	Diagnostic support and metabolomic profiling	[7,34,35]
Extracellular vesicle biomarkers	Exosomal proteins and miRNAs	Intercellular signaling and inflammatory regulation	RA, OA, PsA	Precision medicine and molecular phenotyping	[15,31,32]
Multi-protein signatures	Integrated cytokine/proteomic panels	Complex inflammatory and degradative pathways	RA, OA, PsA	Improved diagnostic and prognostic accuracy	[26,30,36]
Genetic/Epigenetic markers	HLA alleles, DNA methylation patterns	Genetic susceptibility and immune dysregulation	RA, PsA, CTD-associated arthritis	Molecular stratification and personalized medicine	[16,33]

Abbreviations: ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs 5; CSF-1, colony-stimulating factor 1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-8, interleukin-8; IL-17, interleukin-17; miRNAs (incl. miR-146a, miR-155, miR-140), microRNAs; MMP-3, matrix metalloproteinase-3; MMP-13, matrix metalloproteinase-13; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TIMP-1, tissue inhibitor of metalloproteinases-1; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

9. Biomarkers in Specific Arthritides

9.1 Rheumatoid Arthritis

RA demonstrates one of the most extensively characterized synovial fluid biomarker profiles among inflammatory arthritides [10,18]. Elevated SF concentrations of IL-6, TNF-α, IL-1β, MMP-3, RF, and anti-CCP antibodies

correlate with active synovitis, radiographic progression, and disease severity [18,19,27].

MMP-3 is considered one of the most clinically relevant SF biomarkers in RA because it reflects synovial fibroblast activation and extracellular matrix degradation. Elevated MMP-3 levels correlate with radiographic progression and may decrease following successful biologic therapy, supporting its potential role in treatment monitoring [27,28].

Autoantibody analysis within SF may provide insight into local autoimmune activation. Anti-CCP antibodies detected in SF may reflect intra-articular immune activity, while local immune complex formation and synovial B-cell activation contribute to persistent inflammation [10,18]. Recent transcriptomic studies suggest substantial molecular heterogeneity in RA inflammatory pathways [15,16,31].

9.2 Osteoarthritis

Synovial inflammation, macrophage activation, oxidative stress, metabolic dysregulation, and extracellular matrix degradation all contribute to disease progression. Elevated SF concentrations of IL-6, IL-1β, MMP-13, ADAMTS-5, CSF-1, and exosome-derived proteins reflect cartilage degradation and synovial inflammation and have been associated with structural damage, pain severity, synovitis, and functional limitation [11,12,29]. MMP-13 and ADAMTS-5 contribute to cartilage degradation and structural progression in OA [29]. Macrophage-driven inflammation has also emerged as an important pathogenic component of OA. Elevated CSF-1 concentrations correlate with macrophage activation and synovial hypertrophy, supporting the contribution of innate immune mechanisms to disease progression [25]. Several studies have identified inflammatory OA phenotypes characterized by elevated IL-6, TNF-α, and neutrophil-associated biomarkers resembling inflammatory arthritis [9,11]. Current evidence also suggests that metabolic inflammation associated with obesity contributes to distinct inflammatory OA phenotypes characterized by increased synovial expression of pro-inflammatory cytokines and matrix-degrading enzymes, further supporting the potential use of SF inflammatory biomarkers for patient stratification and monitoring disease progression [37,38].

9.3 Psoriatic Arthritis

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by synovitis, enthesitis, dactylitis, axial inflammation, and pathological bone remodeling. Available data indicate that SF biomarker

profiles in PsA differ from both RA and OA, although overlap exists [10,21]. Elevated concentrations of TNF-α, IL-17, IL-23, IL-22, and IL-8 have been consistently identified within PsA SF and contribute to synovial inflammation, osteoclast activation, angiogenesis, and enthesial pathology. Elevated SF IL-17 concentrations have additionally been associated with active enthesitis and erosive disease. Increased VEGF concentrations may contribute to synovial vascular proliferation and persistence of chronic inflammation. Proteomic studies have identified disease-specific exosomal and protein signatures in PsA synovial fluid. Certain inflammatory proteins and extracellular vesicle-associated molecules may assist differentiation between PsA and RA, particularly in seronegative patients with overlapping clinical manifestations [15,31].

9.4 Septic Arthritis and Periprosthetic Joint Infection (PJI)

Distinguishing septic arthritis from inflammatory or crystal-induced arthritis may be clinically challenging, particularly during early disease stages. Traditional diagnostic methods include leukocyte count, Gram stain, glucose measurement, and microbiological culture; however, these approaches demonstrate important limitations. Culture results may be delayed or falsely negative, while elevated leukocyte counts may occur in both infectious and noninfectious inflammatory arthritides. Among the emerging SF biomarkers proposed to address these gaps—including alpha-defensin, presepsin, lactate, D-lactate, calprotectin, procalcitonin, and synovial CRP—alpha-defensin has become one of the most extensively investigated in PJI diagnosis [39,40]. Alpha-defensins are antimicrobial peptides released by activated neutrophils in response to bacterial pathogens. Multiple investigations have demonstrated high specificity for PJI, particularly when combined with leukocyte esterase testing and synovial CRP. Despite this, alpha-defensin does not achieve perfect diagnostic accuracy. False-positive results may occur in severe inflammatory arthritis, metallosis, or crystal-induced inflammation. As a result, current evidence supports interpretation of alpha-defensin within broader diagnostic algorithms rather than as an isolated definitive test. D-lactate additionally represents a promising biomarker because it is produced primarily by bacterial metabolism rather than host tissues [46]. Elevated SF D-lactate concentrations may therefore assist differentiation between septic and noninfectious inflammatory arthritis. Presepsin, a soluble CD14 subtype released during bacterial activation of monocytes and macrophages, has also attracted interest as a rapid biomarker for septic arthritis. Preliminary studies suggest potentially favorable sensitivity and specificity; however, validation continues to be restricted. In native septic

arthritis, neutrophil-associated cytokines and inflammatory mediators such as IL-8 and calprotectin may additionally correlate with infection severity and inflammatory burden. Despite substantial progress, no single SF biomarker currently replaces conventional microbiological analysis and clinical assessment. Therefore, multimodal diagnostic approaches integrating biomarkers, culture results, imaging findings, and clinical presentation remain essential.

9.5 Crystal-Induced Arthritis

Crystal-induced arthritides, including gout and calcium pyrophosphate deposition disease (CPPD), continue to be diagnosed primarily through the detection of monosodium urate or calcium pyrophosphate crystals by polarized light microscopy [5,6]. Nevertheless, analysis of synovial fluid biomarkers may provide complementary information regarding the intensity of local inflammation and may be useful when distinguishing crystal-induced flares from septic arthritis is challenging. In gout, deposition of monosodium urate crystals triggers activation of the NLRP3 inflammasome, resulting in increased IL-1β production and a predominantly neutrophil-driven inflammatory response [41]. Acute attacks are also associated with increased levels of pro-inflammatory mediators such as IL-6, TNF-α, IL-8, and calprotectin, reflecting activation of innate immune pathways within the joint [10,24,41]. Comparable inflammatory mechanisms have been described in CPPD, although the available evidence regarding specific synovial fluid biomarkers is considerably less extensive [10]. Despite growing interest in these molecular markers, none currently demonstrate sufficient diagnostic specificity to replace crystal identification, and their principal role remains the assessment of inflammatory activity rather than establishing a definitive diagnosis [5,6,41].

9.6 Connective Tissue Disease-Associated Arthritis

Emerging evidence suggests that SF biomarkers may also contribute to characterization of connective tissue disease-associated arthritis [42,43]. In systemic lupus erythematosus (SLE) and related connective tissue diseases, SF biomarkers are less validated than in RA or PsA, but IL-17A, IL-6, and immune-complex-related signatures suggest local inflammatory activity that should be interpreted alongside systemic serology and phenotype [43]. Cellular studies of SLE synovial fluid have additionally identified an expansion of CCR6-expressing CD4+ T cells with a Th17-skewed phenotype, together with elevated frequencies of granzyme A- and Eomes-expressing CD8+ T cells, suggesting that lupus arthritis reflects a systemic Th17-

associated immune deviation rather than a joint-specific autoimmune process analogous to RA [43]. Because SLE arthritis is typically non-erosive and clinically less destructive than RA, and because comparably sized SF cohorts are difficult to assemble given the low frequency of arthrocentesis in SLE, biomarker signatures for other connective tissue disease-associated arthritides, including Sjögren's syndrome and systemic sclerosis, remain considerably less characterized and represent an area requiring dedicated prospective study.

9.7 Lyme Arthritis

Lyme arthritis, a late manifestation of infection with *Borrelia burgdorferi*, most commonly presents as monoarthritis or oligoarthritis of the knee and can mimic septic or crystal-induced arthritis both clinically and on conventional SF analysis. Direct detection of *B. burgdorferi* DNA by polymerase chain reaction in SF supports diagnosis in a substantial proportion of patients and remains more sensitive than culture, although a negative result does not exclude the diagnosis, particularly after antibiotic exposure [45]. Serum and SF anti-borrelial antibody testing (two-tier serology) remains the diagnostic mainstay, but SF biomarkers may assist when serology is equivocal or when distinguishing Lyme arthritis from septic arthritis is clinically urgent. Elevated SF alpha-defensin (human neutrophil peptides 1–3) concentrations have been reported in Lyme arthritis, reflecting neutrophil activation in response to spirochetal infection; because these levels can overlap with those seen in bacterial PJI and severe inflammatory arthritis, alpha-defensin elevation in Lyme arthritis should be interpreted together with epidemiological exposure, serology, and PCR findings rather than in isolation [42]. Compared with RA, OA, and PJI, the SF biomarker literature specific to Lyme arthritis remains limited, and further studies are needed to define its cytokine and proteomic signature relative to other inflammatory and infectious arthritides.

Although these biomarkers are not yet routinely used clinically, they highlight disease-specific inflammatory pathways and may contribute to future molecular stratification. Figure 1 shows the evolution of synovial fluid biomarkers.

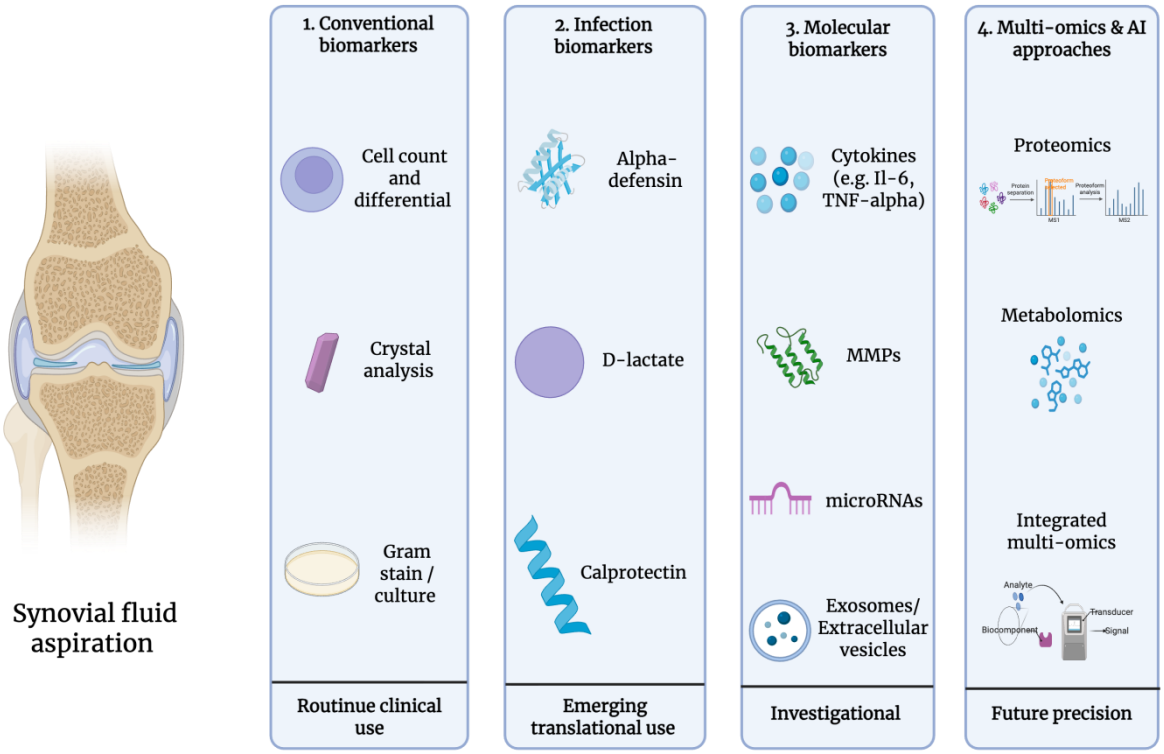


Figure 1. Evolution of Synovial Fluid Biomarkers.

10. Clinical Applications and Future Perspectives

The central shift in synovial fluid biomarker research is no longer whether SF is biologically informative, but which biomarkers provide clinically actionable information beyond conventional assessment. The clearest near-term clinical utility is in infection-oriented applications, particularly septic arthritis and PJI, where biomarkers such as D-lactate and alpha-defensin may complement leukocyte count, microbiological culture, and conventional synovial fluid analysis to improve diagnostic triage and early therapeutic decision-making [34,40,39,46].

Viewed comparatively, biomarker readiness for clinical use varies substantially across the diagnostic performance, prognostic utility, and validation dimensions summarized in Table 1. Alpha-defensin has the strongest evidence base of any single SF biomarker, with high reported specificity for PJI in multiple cohorts, though its diagnostic performance falls short of a stand-alone test because of false positives in metallosis and severe inflammatory arthritis; it is best regarded as validated for a narrow,

well-defined clinical question (infection versus aseptic loosening) rather than as a general-purpose marker. D-lactate, calprotectin, and presepsin occupy an intermediate tier: mechanistically plausible and consistent across smaller cohorts, but lacking the multicenter validation and standardized cut-offs needed for routine adoption. Cytokines (IL-6, TNF-α, IL-1β, IL-17) and matrix-degrading enzymes (MMP-3, MMP-13) have the deepest mechanistic literature and clear prognostic associations with radiographic progression, but their limited disease specificity means they function better as components of composite activity or treatment-response panels than as diagnostic tests in isolation; IL-6 and MMP-3 in particular are shared across RA, PsA, and OA and therefore discriminate inflammatory intensity rather than diagnosis. Extracellular vesicles, microRNAs, and metabolomic and lipidomic panels remain the least clinically mature tier: individually informative and mechanistically rich, but constrained by methodological variability (Section 6), absence of standardized isolation and reporting protocols, and a near-total lack of prospective validation cohorts, which are the principal factors currently limiting their transition from investigational tool to clinical assay. This tiered picture - one validated infection-specific test, several intermediate infection and inflammation markers awaiting standardization, a mechanistically rich but non-specific cytokine/protease layer, and an investigational omics layer—frames the translational priorities discussed below.

In contrast, for RA, PsA, and OA, most cytokines, proteases, and molecular biomarkers improve inflammatory phenotyping and prognostic stratification rather than providing disease-specific diagnostic certainty. Multi-omics integration and machine learning-assisted analyses remain particularly promising because they may capture the biological heterogeneity underlying clinically similar arthritis phenotypes [14,15,16,30,36]. For instance, in a patient with established RA, such an approach might in principle help distinguish a flare of uncontrolled inflammatory disease activity from superimposed secondary OA, though this specific application has not yet been directly validated and remains a hypothesis for future study rather than an established capability.

At present, the most practical translational strategy is a stepwise multimodal approach: conventional SF analysis for initial triage, selective incorporation of targeted biomarkers when clinically relevant questions arise, and future integration of validated multi-omics models for molecular stratification and rheumatology applications.

Translating this stepwise strategy into routine hospital practice, however, requires an honest appraisal of cost and infrastructure. Mature markers such as alpha-defensin, lactate, and calprotectin are compatible with existing lateral-flow, ELISA, or automated chemistry platforms already present in most clinical laboratories, and their per-sample cost and turnaround time are comparable to routine inflammatory markers. In contrast, high-throughput mass spectrometry-based proteomics and RNA sequencing require substantial capital investment in instrumentation, specialized bioinformatics support, and quality-control infrastructure that remain concentrated in a small number of academic or reference centers [13,36]. Within European healthcare systems, and particularly in Bulgaria and other countries with more limited public laboratory budgets, this translates into restricted geographic access, longer turnaround times, and reimbursement pathways that are not yet defined for omics-based SF testing. Consequently, mature biomarkers are likely to remain the pragmatic first-line tools for the foreseeable future, while omics panels are best positioned as centralized reference-laboratory or research tools for complex or diagnostically ambiguous cases, with eventual broader adoption contingent on falling sequencing and instrumentation costs, simplified sample-to-answer workflows, and formal cost-effectiveness data relative to conventional testing.

11. Limitations and Challenges

Despite substantial progress, most SF biomarkers remain insufficiently validated for routine clinical use. Major limitations include biological overlap between arthritides, variability in sample handling and analytical methods, limited reproducibility across studies, and the high cost and technical complexity of omics-based approaches [4,14,15,16,30,36]. Future progress will depend on multicenter validation, assay standardization, and demonstration of incremental clinical value beyond conventional SF analysis.

A principal strength of this narrative review is its broad disease scope, spanning not only the major inflammatory and degenerative arthritides but also less commonly reviewed entities such as Lyme arthritis and connective tissue disease-associated arthritis, together with an integrated treatment of conventional, proteomic, metabolomic, extracellular vesicle, microRNA, and multi-omics biomarkers within a single framework. This breadth allows direct comparison of biomarker maturity across diseases, which is rarely attempted in narrower disease-specific reviews. The principal limitations are inherent to the narrative format: literature selection was not conducted

according to a pre-registered systematic protocol and is therefore susceptible to selection bias; searches were restricted to English-language databases, which may have excluded relevant regional or non-English literature; and the qualitative synthesis of heterogeneous study designs, patient populations, and analytical platforms does not permit formal quantitative pooling of diagnostic accuracy across studies.

Beyond these methodological considerations, several clinical limitations intrinsic to SF sampling itself constrain biomarker research and its translation. Non-effusive or minimally effusive joints frequently yield a "dry tap," precluding SF collection altogether and biasing available samples toward more severely inflamed joints. Obtaining genuinely healthy control SF for baseline omics comparisons is ethically and logistically difficult, since arthrocentesis is not performed on asymptomatic joints without clinical indication; consequently, many "control" samples are in fact derived from patients undergoing joint surgery or arthroscopy for unrelated mechanical indications, which may not fully represent a biomarker-naïve baseline. Finally, systemic comorbidities—including obesity, diabetes, and chronic kidney disease—can alter local joint metabolism and inflammatory tone independently of the primary articular disease, potentially confounding SF biomarker interpretation unless these factors are explicitly accounted for in study design and analysis.

12. Conclusion

SF biomarkers are increasingly recognized as useful adjuncts for diagnosis, inflammatory phenotyping, and therapeutic monitoring in arthritis. Among currently available biomarkers, alpha-defensin demonstrates the strongest clinical utility, particularly in PJI, while D-lactate, calprotectin, MMP-3 and MMP-13 show emerging translational relevance. Most proteomic, metabolomic, extracellular vesicle, and microRNA-based biomarkers remain investigational because of limited validation and standardization. Future progress will likely depend on integrated multimodal approaches combining molecular biomarkers with imaging and clinical assessment rather than reliance on isolated analytes.

Declarations

Author Contributions

Author Contributions: Conceptualization: V.T.; Methodology: M.I., V.T.; Writing - original draft preparation: V.T.; Visualisation: V.T., S.T.; Writing - review and editing: M.I., G.K., V.T.

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Conflicts of Interest

The authors declare no conflict of interest.

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Биомаркери в синовиалната течност: настоящи приложения и бъдещи перспективи

Резюме

Синовиалната течност предоставя директен поглед към вътреставната среда, но отделните биомаркери рядко разграничават надеждно подтиповете артрит. Настоящият наративен обзор сравнява конвенционалните изследвания с цитокини, протеомични маркери, извънклетъчни везикули, микроРНК, метаболомика и мултиомика, подпомогната от машинно обучение, при ревматоиден артрит, остеоартрит, псориатичен артрит, септичен артрит, перипротезна ставна инфекция, кристал-индуциран артрит, артрит, свързан със заболявания на съединителната тъкан, и Лаймски артрит. Релевантните публикации от периода 2017–2026 г. бяха идентифицирани чрез структурирани търсения в базите данни PubMed, Scopus, Web of Science и Google Scholar, допълнени от ръчен преглед на библиографските списъци; при селекцията бяха приоритизирани систематични и наративни обзори, транслационни проучвания и клинично значими изследвания на биомаркери, като докладването следва рамката SANRA за наративни обзори. Най-утвърдените в клиничната практика приложения остават конвенционалното определяне на клетъчния брой, анализът на кристали, микробиологичното изследване и оценката на алфа-дефензин при перипротезни ставни инфекции, докато изследването на извънклетъчните везикули, микроРНК и мултиомиката запазват предимно транслационния си характер.

Ключови думи: синовиална течност, биомаркери, цитокини, протеомика, метаболомика, извънклетъчни везикули

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Review

Problems within the SpA group – diagnostic versus classification criteria; differential diagnosis within the SpA group; the issue of axial psoriatic arthritis

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Running title: Diagnostic Challenges in SpA

Abstract

Diagnostic delay in spondyloarthritis (SpA) results in the occurrence and progression of structural damage, which is irreversible and presented by a unique combination of inflammation-induced bone loss (erosions, periarticular and systemic osteoporosis), together with new bone formation and extraosseous ossification (ligaments/entheses). The most significant opponent of diagnostic delay is misdiagnosis, leading to incorrect treatment with its complications, together with the consequences of an untreated but present disease. In the second part of the review, the problems of early diagnosis in axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) will be considered - related to the available criteria, the accessible diagnostic methods, or arising from other factors (related to the patient or the systems for specialized medical care).

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Keywords: axial spondyloarthritis, psoriatic arthritis, diagnosis, classification, criteria

1. Introduction

In the context of early diagnosis, it is important to bear in mind that the ASAS criteria for axSpA [1], pSpA, and the combined set (axSpA + pSpA) - shown in Figure 1 [2] and including the revised ASAS-SPARTAN 2025 classification criteria [3] (Table 1). They are applicable in patients with an already established diagnosis and are intended to define homogeneous groups of patients with the same pathology, necessary for the development of strategies for monitoring and management of this pathology, as well as for contemporary clinical studies [4].

In the diagnostic approach, the physician is faced with a patient without an established diagnosis, presenting with complaints (symptoms) suggestive of a particular disease (or group of diseases), known as "main symptoms." Each main symptom is associated with a certain probability, the so-called "pre-test probability" (pre-test probability /P-pre/) for the presence of the respective disease in a patient presenting with the given main symptom. For example, in the general population of patients with chronic back pain (CBP), the P-pre for axSpA is 5% [5]. The use of the definitions (Calin/Berlin/ASAS) [5-7] for inflammatory back pain (IBP) increases the P-pre from 5% to 30–40%, depending on the definition used [8]. In the course of the diagnostic process, the physician identifies objective findings (signs) using various diagnostic tests (physical, laboratory, imaging). The different tests applied in this process have varying sensitivity and specificity, which determine their diagnostic value [9] (Table 1).

Table 1. Classification table of main definitions.

	Population groups			
Test results	Disease /Condition present	Disease /Condition absent	**Total (sum)**	
Test is positive	(True Positive) (A)	(False Positive) (B)	Total positive tests (A + B)	Positive Predictive Value (PPV) = A/(A + B)
Test is negative	(False Negative) (C)	(True Negative) (D)	Total negative tests (C + D)	Negative Predictive Value (NPV) =D /(C + D)
Total (sum)	Total number of people with disease / condition	Total number of people without disease /condition	Total number of people (A + B + C + D)	Accuracy = (A+D)/(A+B+C+D)

	(A + C)	(B + D)		
	Sensitivity A /(A+C)	Specificity D /(B+D)		
	Prevalence /Pretest Probability (P-pre) (A + C) /(A + B + C + D)			
Sensitivity = True Positive Rate (TPR) = A / (A + C) i.e., the proportion of patients with disease who will have positive test results. The high-sensitivity tests provide us with a high TPR while minimizing false negative rates (FNR), making it useful for ruling out the disease when the result is negative.				
Specificity = True Negative Rate (TNR) = D /(D + B) i.e., the proportion of people without the disease who will have a negative result. The high-specificity tests have very few false positives, making it useful for ruling in the disease when the result is positive.				
Positive predictive value (PPV) = Precision = A /(A + B) i.e., the proportion of people with a positive test result who actually have the disease. PPV is, sometimes, also referred to as the 'post-test probability of disease given a positive test.' PPV = sensitivity x prevalence / sensitivity x prevalence + (1 – specificity) x (1 – prevalence)				
Negative predictive value (NPV) = D /(C+D) i.e. the proportion of people with a negative test result who do not have the disease, or 'the probability of not having disease given a negative test'. NPV =Specificity x (1 – Prevalence) / (1 – Sensitivity) x Prevalence + Specificity x (1 – Prevalence).				
Prevalence = Pretest probability (P-pre) = (A+C)/(A+B+C+D) i.e. proportion of population with specific disease at given point in time, calculated by dividing the total number of cases (A+C) by the total population (A+B+C+D). The Prevalence (P-pre) of the same disease is different in different populations!				
Positive Likelihood Ratio (LR+) = TPR / FPR = Sensitivity / (1-Specificity). The higher the value of LR+, the higher the probability of diagnosis if the parameter is positive.				
Negative Likelihood Ratio (LR-) = FNR / TNR = (1-Sensitivity) / Specificity. The lower the value of LR-, the lower the probability of diagnosis if the parameter is negative.				
Diagnostic Odds Ratio (DOR) = LR+ / LR-				
False Positive Rate (FPR) = (1-Specificity) = B/(B+D)				
False Negative Rate (FNR) = (1-Sensitivity) = C/(A+C)				
False Omission Rate (FOR) = C/(C+D)				
False Discovery Rate (FDR) = B/(A+B)				
Proportion Correctly Classified = Accuracy = (A+D)/(A+B+C+D)				
Proportion Incorrectly Classified = (B+C)/(A+B+C+D).				

Sensitivity reflects the ability of a test to identify individuals who have a specific disease. By definition (Table 9), Sensitivity = True Positive Rate (TPR) = A / (A + C). Tests with high sensitivity provide a high proportion of true positive results (TPR), while at the same time minimizing false negative results (FNR), thereby reducing missed diagnoses [10-15].

Specificity reflects the ability of a test to identify individuals who do not have the disease, that is, to yield a true negative result (TNR) for those who are healthy or without the respective disease. By definition (Table 1), Specificity = TNR = D / (B + D). Tests with high specificity have very few

false positive results (FPR), which makes them useful for confirming disease when the result is positive [10-15].

The **predictive value** of each test is determined by its sensitivity and specificity, as well as by the prevalence of the disease (for which the test is used) in the respective population. The prevalence of the disease in a given population is equivalent to the pre-test probability (P-pre) that a given symptom (or finding) is associated with the presence of the specific disease [10-15].

Each test additionally has its own likelihood ratio (LR), which summarizes how many times it is more likely (positive likelihood ratio /LR+/) or less likely (negative likelihood ratio /LR-/) for a patient with a given disease to have the respective result (a positive test in the case of LR+ / a negative test in the case of LR-), compared to a patient without the disease [10-15]. For example, the parameter IBP, according to Rudwaleit and colleagues [16-18], has a positive likelihood ratio (LR+) of 3.1 (when present as a symptom) and a negative likelihood ratio (LR-) of 0.33 (when absent as a symptom). This means that the presence of the symptom IBP increases the probability of the presence of axSpA by 31%, whereas the absence of the symptom IBP decreases the probability of axSpA by 33% (the calculations are presented below). The positive (LR+) and negative (LR-) likelihood ratios can be obtained from the sensitivity and specificity of each test using the following formulas: (LR+) = Sensitivity / (1 - Specificity); (LR-) = (1 - Sensitivity) / Specificity. These coefficients (LR+ / LR-) represent probability ratios and are treated in the same way as risk ratios in the calculation of confidence intervals (Odds Ratio /OR/): OR = 1 indicates that there is no association between exposure (risk); a result OR > 1 indicates a higher probability of the outcome in relation to the exposure, whereas OR < 1 indicates a lower probability. In the same way, LR > 1 indicates that the test result is associated with the presence of the disease, whereas LR < 1 indicates that the test result is associated with the absence of the disease, regardless of whether it is a positive test (presence of the symptom, LR+) or a negative test (absence of the symptom, LR-). Accordingly, the higher the value of LR, the greater the probability of the presence of a diagnosis if the parameter is positive, and correspondingly, the lower the value of LR-, the lower the probability of a diagnosis if the parameter is negative [10-15]. The probability of the presence of disease after a positive or negative diagnostic test is referred to as the post-test probability (post-test probability /P-post/) and is calculated using Bayes' theorem [18], by applying the "post-test odds," the "pre-test odds," and the likelihood ratio (LR) of the respective test, in combination with the prevalence of the disease in the population (P-

pre) [16-18]: P-pre (pre-test probability) = disease prevalence (for the specific population of interest); Pre-test odds = P-pre / (1 – P-pre); For a single test, Post-test odds = pre-test odds × LR; For multiple tests, Post-test odds = pre-test odds × likelihood ratios (product), where the likelihood ratios (product) /LRP/ = LR1 × LR2 × LR3 × … × LRn; Post-test probability (P-post) = post-test odds / (post-test odds + 1).

The use of probabilities (LRs – likelihood ratios), rather than risks (OR), makes the calculation somewhat more complex, but already developed nomograms by Rudwaleit et al. [16-18] - Table 2 and Figure 1; the nomograms of Fagan T.J., which are freely available [19,20]; or the summation of the logarithms of the likelihood ratios (LR+ / LR-) using the method proposed by Feldtkeller E and colleagues [21], can be applied.

Table 2. Representative values of sensitivity and specificity for SpA features along with the resulting LR+ and LR- [16].

Parameter	Sensitivity (%)	Specificity (%)	Likelihood Ratio	
			LR+	LR-
Inflammatory back pain	75	76	3.1	0.33
Heel pain (enthesitis)	37	89	3.4	0.71†
Peripheral arthritis	40	90	4.0	0.67†
Dactylitis	18	96	4.5	0.85†
Iritis or AAU	22	97	7.3	0.80†
Psoriasis	10	96	2.5	0.94†
IBD	4	99	4.0	0.97†
Positive family history for axial SpA, reactive arthritis, psoriasis, IBD or anterior uveitis	32	95	6.4	0.72
Good response to NSAIDs	77	85	5.1	0.27
Raised acute-phase reactants (CRP/ESR)	50	80	2.5	0.63
HLA-B27ǂ	90	90	9.0	0.11
Sacroiliitis shown by magnetic resonance imaging	90	90	9.0	0.11

Legend: LR+ = sensitivity/ (1 – specificity); LR- = (1 – sensitivity)/specificity; CRP, C-reactive protein; ESR- erythrocyte sedimentation rate; HLA- human leucocyte antigen; IBD, inflammatory bowel disease; NSAIDs- non-steroidal anti-inflammatory drugs. † As enthesitis, dactylitis, uveitis, peripheral arthritis, psoriasis and IBD may not be present at disease onset but may develop later, it is recommended to ignore a negative test result of these tests in an early state of possible axial SpA. ǂThe figures for sensitivity and specificity of HLA-B27 refer to a European Caucasian population. In European Caucasian patients with psoriasis or IBD, a sensitivity of 50%, a specificity of 90%, an LR+ of 5.0 and an LR- of 0.56 for HLA-B27 should be applied. In other ethnic populations, sensitivity and specificity of HLA-B27 may be different, resulting in different LR+/-.

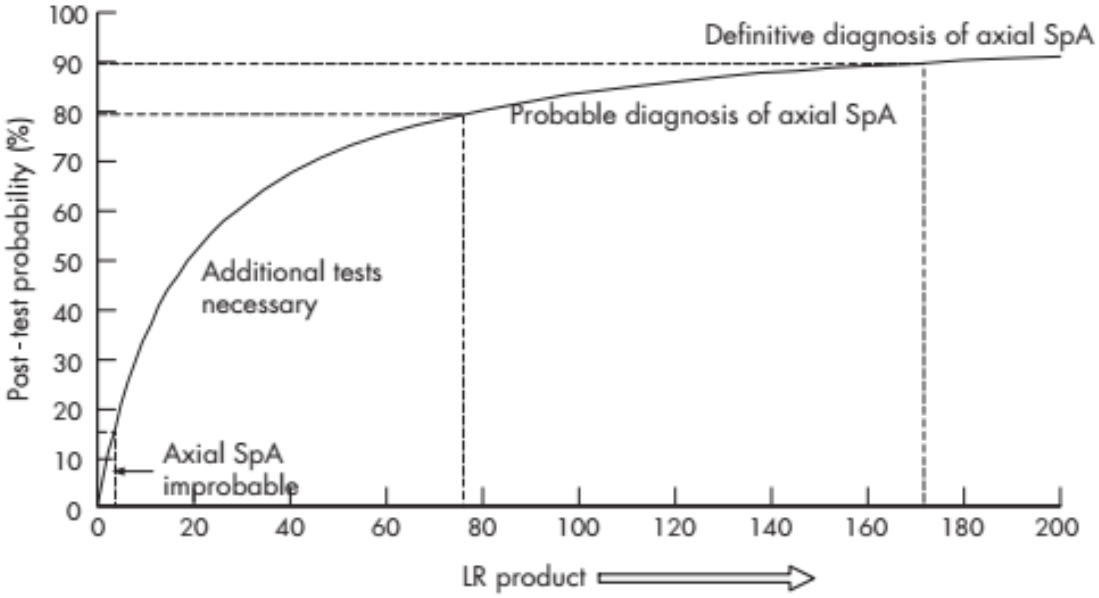


Figure 1. Dependency of the post-test probability of axial spondyloarthritis (SpA) on the resulting likelihood ratio (LR) product for an assumed pretest probability of 5%. This probability curve is meant to be applied in patients with chronic back pain suspected to have axial SpA. Image taken with permission from [18].

The diagnosis can be considered definite if the post-test probability (P-post) is >90%; the diagnosis is probable if P-post is between 80 and 90%, and unlikely if P-post <20% [15–20]. Based on this principle (a system combining the positive and negative likelihoods of individual signs and symptoms to calculate P-post), diagnostic algorithms for axSpA have also been developed, for example - the Berlin 2004 algorithm and its modification - ASAS 2013 (sensitivity 78.5%; specificity 79.6%) [22]. However, regardless of the method chosen for determining P-post, it should be remembered that the diagnostic value of SpA characteristics varies among different patient populations (i.e., Caucasian vs. Asian vs. African-American) [23]. Furthermore, the specificity and positive likelihood ratio for diagnosis (LR+) of these tests vary depending on the clinical setting (primary versus secondary/tertiary care) in which they are applied, as well as on whether they have already served as selection criteria for referral to

a rheumatologist. This phenomenon is clearly demonstrated by the findings of the DIVERS study, discussed in the first part of this review [24].

2. Problems related to the use of the CASPAR criteria

The separation of psoriatic arthritis (PsA) from other arthritides began with the fundamental works of Verna Wright (1956–1959 – "Psoriasis and arthritis" [25-27]) and Baker H. (1963 – "Psoriasis and arthritis" [28]), which led to the inclusion of PsA as a distinct clinical entity in the classification of rheumatic diseases of the ARA (American Rheumatism Association) [28]. The first developed criteria (Moll & Wright 1973) [29] included: (1) presence or personal history of psoriasis or nail involvement; (2) presence of inflammatory involvement of the skeleton (peripheral arthritis and/or sacroiliitis or spondylitis); (3) absence of positive serological tests for rheumatoid arthritis (RA). These criteria, although not validated, are maximally simplified and objective, and form the basis of all subsequent definitions and attempts at classification of PsA (Table 3).

Table 3. Different criteria used to define psoriatic arthritis, with their sensitivity and specificity according to their authors [30-36] and the comparisons made [37,39,40].

Authors; Conditions for defining PsA; Sensitivity and Specificity	Criteria Sets
Moll & Wright 1973†‡ [28] **DDg = (1) + (2) + one of (3)** **Sensitivity -91%;** **Specificity -94%**	(1) Current psoriasis, history of psoriasis or nail disease. (2) NOT Rheumatoid Factor positive. (3) Plus one of 5 distinct clinical subset: 3.1. Oligoarticular arthritis; 3.2. Polyarticular arthritis; 3.3. DIP predominant; 3.4. Spondylitis predominant; 3.5. Arthritis Mutilans.
Bennett et al 1979 ‡ [29]; **DDg = Mandatory criteria (2 of 2) + 6 of Supportive criteria (not of these in italic);** **Sensitivity -69%;** **Specificity -98%**	Mandatory criteria: Clinically apparent psoriasis (skin or nails); Pain and soft tissue swelling and/or limitation of motion in at least one joint observed by a physician for six weeks or longer; Supportive criteria: Pain and soft tissue swelling and/or limitation of motion in one or more other joints observed by a physician; Presence of an inflammatory arthritis in a distal interphalangeal joint. Specific exclusions: Bouchard's or Heberden's nodes; Presence of 'sausage' fingers or toes; An asymmetrical distribution of arthritis in the hands and feet;

	Absence of subcutaneous nodules; A negative test for rheumatoid factor in the serum; An inflammatory synovial fluid with a normal or increased C3 or C4 level and an absence of infection (including acid fast bacilli) and crystals of monosodium urate or pyrophosphate A synovial biopsy showing hypertrophy of the synovial lining with a predominantly mononuclear cell infiltration and an absence of granuloma or tumour Peripheral radiographs showing erosive arthritis of small joints with a relative lack of osteoporosis. Specific exclusion: erosive osteoarthritis; Axial radiographs showing any of the following: sacroiliitis, syndesmo-phytes, paravertebral ossification
Vasey & Espinosa 1984 † [30]; **DDg = Criterion I + one from either –Criterion II or III** **Sensitivity -97%;** **Specificity -96%**	Criterion I: Psoriatic skin or nail involvement; Criterion II: Peripheral pattern (1) Pain and soft tissue swelling with or without limitation of movement of the distal interphalangeal joint for over four weeks; (2) Pain and soft tissue swelling with or without limitation of motion of the peripheral joints involved in an asymmetrical peripheral pattern for over four weeks. This includes a sausage digit; (3) Symmetrical peripheral arthritis for over four weeks, in the absence of rheumatoid factor or subcutaneous nodules; (4) Pencil in cup deformity, whittling of terminal phalanges, fluffy periostitis and bony ankylosis; Criterion III: Central pattern (1) Spinal pain and stiffness with the restriction of motion present for over four weeks; (2) Grade 2 symmetric sacroiliitis according to the New York criteria (3) Grade 3 or 4 unilateral sacroiliitis;
Gladman et al 1987 ‡ [31]; **DDg = 'A' + one of 'B' + <u>absence of</u>: rheumatoid nodules, grade 4-osteoarthritis, reactive arthritis, enteropathic arthritis, gout, SLE;** **Sensitivity -91%;** **Specificity -98%**	Mandatory criterion - history of or current psoriasis, psoriatic onychopathy; Supportive criteria: Arthritis; Inflammatory spinal disease; Sacroiliitis;
ESSEG 1991† [32]; **DDG = One criterion from – 'A' and One or Two criteria from –'B';** **Sensitivity -74%;** **Specificity -98%**	IBP or Synovitis (either asymmetrical or predominantly lower limb); One or more of the following: Positive family history of psoriasis; Psoriasis;
McGonagle et al 1999 ‡ [33]; **DDG = 'A' + one of 'B';** **Sensitivity -98%;**	Mandatory criterion –psoriasis or family history of psoriasis; Supportive criteria: Enthesitis (clinical or radiographic); DIP arthritis;

Specificity -97%	Sacroiliitis /Spinal inflammation; Dactylitis; Monoarthritis; Oligoarthritis (≤4 swollen joints); SAPHO; Arthritis mutilans; Onycho-pachydermo-periostitis; Chronic multifocal recurrent osteomyelitis.
Fournie´ et al 1999*‡ [34]; DDg ≥11 points; Sensitivity -99%; Specificity -88%	Psoriasis antedating or concomitant with joint symptom onset – 6 points; Family history of psoriasis (if criterion 1 negative) or psoriasis post dating joint symptom onset – 3 points; Arthritis of a distal interphalangeal joint – 3 points; Asymmetrical monarthritis or oligoarthritis – 1 points; Buttock pain, heel pain, spontaneous anterior chest wall pain, or diffuse inflammatory pain in the entheses – 2 points; Radiological criterion (if any one criterion present) – 5 points: Erosion of distal interphalangeal joint; Osteolysis; Ankylosis; Juxta-articular periostitis; Phalangeal tuft resorption; Human leucocyte antigen (HLA)-B16 (38, 39) or B17 – 6 points; Negative rheumatoid factor – 4 points
CASPAR*† criteria 2006 [36]; Differential diagnosis – patient must have inflammatory articular disease (joint, spine, or entheseal) as a mandatory criterion and a total score of 3 or more points from the 5 categories listed in opposite column: Sensitivity and Specificity: For established disease [106]: Sensitivity - 91.4%; Specificity - 98.7% For early PsA [107, 108]: Sensitivity - 87.4%; Specificity - 99%	(1) Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis: 1.1. Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist (Score = 2) 1.2. A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider (Score = 1) 1.3. A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report (Score = 1) (2) Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (Score = 1). (3) A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range (Score = 1). (4) Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (Score = 1). (5) Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint

	margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (Score = 1).

Legend: *, validated definition; †, easy to use definition; ‡, difficult to use definition; ǂ, presence of implied but undeclared characteristics/methods; DD, definite diagnosis.

It is worth noting that among all subsequent definitions [31-36], only that of Fournie and colleagues [36] has been validated. The sensitivity and specificity of all of them have been compared and evaluated [37]. The most sensitive for defining PsA (≥97%) were the criteria of Vasey & Espinosa [32], McGonagle [35], and Fournie [36], whereas the others had lower sensitivity, ranging between 56% and 94%. The specificity of all criteria was significant and statistically similar, ranging between 88% and 98%. The criteria of Bennett and Fournie were the most difficult to use, whereas those of Vasey & Espinosa and Moll & Wright were the easiest to use [37].

The CASPAR criteria (ClASsification of Psoriatic ARthritis /CASPAR/ study group) [38] have also been validated and tested, both in patients with established PsA [39-41] and in patients with early PsA [42,43]. The criteria have been compared with all existing ones [39-43], with consistent conclusions-CASPAR criteria have the highest sensitivity among all previous ones (due to the inclusion of family history of PSO), while their specificity (98.7%) is equal to or higher than that of the criteria with the highest specificity (≥98%) [39-41].

The reported limitations (by the authors themselves [44]) and by other groups [45,47] are:

The CASPAR criteria are classification, not diagnostic criteria. That is, they are applicable to patients with an established diagnosis of PsA, who have undergone a differential diagnostic process addressing the key disease characteristics (skin/nail psoriasis/dactylitis) - see differential diagnosis of the main features.

The placement of the data on “current PSO, personal or family history of PSO, and/or nail involvement” after the mandatory condition “presence of inflammatory involvement of the skeleton (spinal, peripheral, or entheseal)” makes it possible to classify a patient with axSpA presenting with dactylitis (1 point) and juxta-articular new bone formation (1 point) and negative RF (1 point) as PsA (3 points), in the absence of any evidence of PSO at present, including personal or family history of PSO.

The problem of the possibility of classifying axSpA as PsA in the absence of PSO (PsA sine PSO), as well as personal and family history of PSO, was

discussed as early as 2003 (Scarpa R, et al. [44]), and subsequently in 2007–2009 by the creators of the criteria [44] and other authors [45,47]. However, none of the proposed solutions: (a) inclusion of HLA-Cw6+ as a condition [46,47]; (b) inclusion of imaging biomarkers (MSUS/MRI) as a condition - was not approved [45].

The inclusion of the genetic marker HLA-Cw6 as a condition [46,47] is associated, on the one hand, with 100% development of PSO within 10 years, but on the other hand, only 36–76% of patients with PSO are positive for it, that is, there is a real possibility of missing approximately one-third of patients with PSO (those who are negative for HLA-Cw6 but at the same time develop cutaneous and/or nail PSO) [44]. Thus, the introduction of HLA-Cw6 as a mandatory criterion in the absence of PSO/history of PSO would significantly reduce the sensitivity of the criteria, with a non-significant (1.3%) increase in specificity [44].

The inclusion of a mandatory imaging biomarker (MSUS/MRI - mini-enthesitis and paratenonitis) [45] as a condition in addition to the presence of inflammatory involvement of the skeleton, although highly specific for PsA, would also lead to missing approximately one-third of patients (those with purely axial disease, for which enthesitis of the axial skeleton is characteristic). Thus, we would again significantly reduce sensitivity at the expense of a non-significant increase in specificity [44].

On the other hand, allowing the classification of axSpA as PsA in the absence of personal and family history of PSO is associated with a real probability of developing PSO, similar to that of the axSpA group (≈10% at 5 years; ≈20% at 10 years and ≈35% at 20 years) [48]. This fact, together with the low prevalence of the condition (Table 4), combined with the more destructive nature of arthritis in rPsA compared to that in axSpA, makes the significance of misclassification (axSpA as PsA) much lower compared to the alternative misclassification (PsA as axSpA) [48].

Table 4. Peripheral spondyloarthritis versus Psoriatic arthritis sine psoriasis [46]

Variables	PsA sine PSO†	PsA sine PSO‡
Prevalence	5.5% of all SpA-continuum (studies without overlapping SpA features –COMPOSA; PerSpA); 15% of all cases of PsA / 0.15% of population	2.5% of all SpA-continuum (studies without overlapping SpA features – COMPOSA; PerSpA); 5% of all cases of PsA /0.05% of population
Dactylitis	60-70%	36-40%
Enthesitis	36-40%	60-70%

Arthritis pattern	DIP 50-70%	Large joints of lower limbs 50-70%
HLA-B27 (+)	18%	36-66%
HLA-Cw6 (+)	36-76%	<1%

Legend: † – PsA with family history of PSO or HLA-Cw6 (+), included in CASPAR criteria as a separate entity (15±5%), 100% progression toward PSO within 2-12 years; ‡ – PsA without any features of PSO (family history, HLA-Cw6+) = pSpA with dactylitis, enthesitis and juxtra-articular new-bone formation on plain radiographs. The probability of developing PSO in this condition (10% over 5 years, 20% over 10 years, and 35% over 20 years of follow-up) is the same as in pSpA.

Differential diagnosis (DD) represents another way of transforming classification criteria into diagnostic criteria, through assessment of the probability that other conditions may be the cause of the respective symptom or finding and their justified, stepwise exclusion.

The problem with DD in PsA within the SpA continuum has two directions: a) Misinterpretation of a rash - the greatest risk here concerns mycosis fungoides vs. PSO. Fortunately, 99% of the problem is avoided by combining dermatological examination with histopathological examination [49,50]; b) Misinterpretation of nail changes (onychomycosis/onychodystrophy vs. PSO) - again, dermatological consultation, staining and fungal culture, and histology solve the problem [51].

DD of the key characteristics for axSpA/PsA - dactylitis and enthesitis (Table 5 and Figure 2) [52-55].

2.1. Dactylitis

Dactylitis is detected clinically in up to 50% of patients with PsA, and as an asymptomatic finding on MSUS (Musculoskeletal Ultrasound) in up to 66% of patients. Dactylitis is a frequent finding at the onset of the disease (as an initial symptom), and recurrent dactylitis (very often in the same digit) may be the only manifestation of PsA for months to years. Dactylitis is usually asymmetrical, with more frequent involvement of the dominant compared to the non-dominant side, and with more frequent involvement of the feet - 66% (fourth toe, usually bilaterally), than of the hands - 44% (second and third fingers, usually unilaterally), while several digits may be affected simultaneously. When dactylitis occurs in a digit with synovial sheaths communicating with the ulnar palmar carpal sheaths, the swelling may extend to the palm (ulnar and/or radial bursae) [52]. Dactylitis may present as acute dactylitis (tender, tense, painful, often erythematous and warm digit) or as chronic (swollen but asymptomatic digit). Whether a chronically swollen but asymptomatic digit represents low-grade acute dactylitis or a resolving one can be determined only by MRI or MSUS, when performed in

combination using gray scale and power Doppler (GSUS/PDUS) [53,54]. MSUS examination, in addition to clinical assessment, is strongly recommended during the initial screening of a SpA patient, precisely because of the risk of missing subclinical dactylitis and enthesitis. The most recent validated MSUS index for the assessment of dactylitis is GLOUDAS (Global OMERACT Ultrasound Dactylitis Score), the validation of which also included participation of our experts. The instructions for scanning, definitions of primary lesions, and the scoring methodology are presented, together with detailed illustration, turning the article into a guide for the assessment of dactylitis with MSUS [55]. Early diagnosis of dactylitis in the course of PsO is essential, both for establishing the diagnosis of PsA and in the context of its role as an unfavorable prognostic factor - acute, "warm" (PDUS+) dactylitis is associated with active disease and predisposes to the development of local erosions/acral osteolysis and radiographic progression (Figure 2). It is therefore not surprising that dactylitis is a component of composite indices for the assessment of PsA, such as the Composite Psoriatic Disease Activity Index (CPDAI) and the Psoriatic Arthritis Disease Activity Score (PASDAS) [56]. The direct relationship between the nail unit and the DIP joint through the enthesis of the DIP extensor supports the link between enthesitis, dactylitis, and psoriatic nail disease, and their typical co-occurrence. This co-occurrence (dactylitis, enthesitis, DIP arthritis, and nail involvement) also shows a genetic association with specific "B" and "C" alleles of the HLA system: the allele B27:05:02–C02:02:02 is associated with all of them and additionally with the presence of symmetrical sacroiliitis; B08:01:01–C07:01:01 with dactylitis, enthesitis, asymmetrical sacroiliitis, nail involvement, and DIP arthritis; B37:01:01–C06:02:01 with enthesitis, dactylitis, nail involvement, and DIP arthritis [57]. The differential diagnosis of dactylitis is presented in Table 5 and illustrated for the rare cases (sarcoid/tuberculous dactylitis) in Figure 3 [56].

2.2 Enthesitis

Enthesitis in peripheral arthritis - is a hallmark of the SpA group and is only sporadically encountered in the course of the other destructive peripheral polyarthritis. That is, MSUS findings of mini-enthesitis/paratenonitis practically resolve the differential diagnosis - RA vs. pSpA/pPsA [51–53] (Figure 2). In the same way, the presence of dactylitis, combined with dermatological consultation and histological findings from a punch biopsy, resolves the differential diagnosis pSpA/pPsA, usually without the need for HLA-Cw6 genotyping.

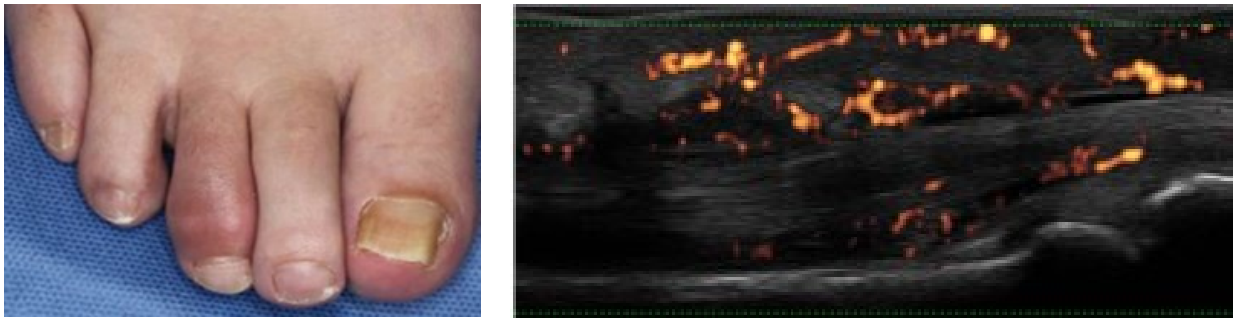


Figure 2. 'Hot dactylitis' –swollen and tender (sausage digit), as a result of soft-tissue oedema, related to the inflammation of the digital entheseal structures, including the fibrous skeleton of the digit (pulleys) also known as 'pseudotenosynovitis' or 'paratenonitis. The flexor tenosynovitis is also present, while the 'true' synovitis of MCPs /PIPs /DIPs are usually absent, but may be found in the subacute stage when the 'paratenonitis' begins to resolve.

Table 5. Differential diagnosis of dactylitis [50, 56].

Type of dactylitis	Clinical picture	Structures involved	Diagnostic finding	Imaging findings
PsA	Generally asymmetrical swelling of entire digit that is discernibly different than adjacent digits; tenderness; pain, mostly along flexor tendons. May be presenting and only feature for some time	Few fingers and/or toes; sometimes simultaneous involvement of most fingers. May extend below digit to ulnar bursa	US features of 'hot dactylitis' (PDUS+); paratenonitis and flexor tenosynovitis	MRI: subcutaneous soft-tissue edema, tenosynovitis, synovitis, osteitis, and bone marrow edema
Sarcoid (figure 3-a)	Focal or diffuse spongy soft-tissue swelling over affected digit from granuloma formation; pain may be absent; overlying skin may be erythematous. Mostly observed in chronic sarcoidosis. May be presenting and only feature for some time	Phalanges and adjacent soft tissue. May involve single or multiple digits. Distal and middle phalanges involved more than proximal phalanges, metacarpals, and meta-tarsals	HRCT-Noncaseating granulomas	Radiographic: incidental bone lesions (diffuse trabecular changes leading to a honeycomb or lattice-like configuration)
Syphilitic	Mostly hands.	Mostly hands	Osteomyelitis	Radiographic: mimics

	Bone changes – osteomyelitis.		(X-Ray; CT; MRI; microbiology)	tuberculous dactylitis, but involvement is bilateral and symmetric; periostitis is more exuberant; soft-tissue swelling less prominent.
Tuberculous (figure 3-b)	Painful soft-tissue swelling around diaphysis of involved bone. Trauma may precede disease onset	Tuberculous dactylitis affects the short tubular bone of the hands and feet. Osteomyelitis extending to digit soft tissue. Hand bones involved more than feet bones. Phalanges affected more often than metacarpals. Proximal phalanges of index and middle fingers most common sites of infection.	Specific granulomatous inflammation with caseous necrosis and positive PPD skin test.	Radiographic: spina ventosa; periostitis. MRI: sinus tract (caused by lesion extending to soft tissue through cortical defects)
Blistering Distal Dactylitis	Tense bullae; Typically, no constitutional symptoms	Anterior fat pad of distal portion of finger or thumb; blister may extend dorsally and involve proximal and lateral nail folds	Infection of anterior fat pad of volar surface of distal part of digit. Mostly caused by group A β-hemolytic streptococci	Not applicable
Sickle cell disease	Sudden onset of very painful, warm, tender global swelling of hands and/or feet lasting 1–3 weeks; fever and leukocytosis may be present.	Carpal and tarsal bones and phalanges	Bone marrow infarction	Radiographic: soft-tissue swelling (first few days); radiolucent areas of the shaft, with surrounding periostitis intermingled with lytic areas and focal osteo-

				sclerosis giving a moth-eaten appearance (within weeks; resembles osteomyelitis)

Legend: MRI, magnetic resonance imaging; US, ultrasound imaging; PPD, purified protein derivate.



Figure 3. Differential diagnosis of dactylitis: (A) Image of sarcoid pseudodactylitis (left image) and plain x-ray of the right hand (right image), showing intra-osseous bone lesions –the 4th metacarpal displays lattice changes typical of osseous sarcoidosis. Image taken with permission of courtesy of Dr Gurjit Kaeley. (B) Image of osteoarticular tuberculosis dactylitis affecting the right thumb (left image), index and fourth fingers (right image). The X-rays of the affected thumb and fingers showing osteolytic lesions of the second phalanges. Reproduced with permission of [56].

2.3. DD of axSpA from imitators of chronic back pain

The present DD in the context of fibromyalgia with concomitant degenerative disc disease (DDD) and/or osteoporosis, and/or biomechanical problems (scoliosis). This DD, as well as the use of the above-

mentioned (P-pre / P-post / LR±) in the Dg/DD process, is discussed in detail by Philip Mease and Atul Deodar. [57].

Table 6. Differentiating axSpA from mimickers presenting with chronic back pain [57].

Condition and its characteristics	Differentiating clinical features	Key DD methodologies and findings
Fibromyalgia (central sensitization): **CBP not IBP;** **Tenderness mimicking enthesitis;** **Possibly co-occurring;**	CBP has no inflammatory features (better with rest and worse with activity, no / minimal relief with NSAIDs); No objective inflammatory disease in the musculoskeletal system or in the eyes, gut or skin; If observed as a comorbidity - very high patient-reported disease activity after treatment of nr-axSpA is reported	MRI –No objective inflammatory disease [109-114]; MSUS (GSUS and PDUS) examination of entheseal sites [107,108]
Degenerative disc disease: **Symptoms of nerve root compression (NRC) in the corresponding dermatome;** **Possibly co-occurring in younger adults**	CBP has no inflammatory features (better with rest and worse with activity); Characteristic of pain – sharp or burning pain, numbness that spreads along a corresponding dermatome; Symptoms of NRC along a correspon-ding dermatome;	Plain radiographs -disc space narrowing; subchondral sclerosis; CTE -changes in the context of DDD (disc height loss; vacuum phenomenon; bulging /herniation; spondylolisthesis; foraminal or central spinal stenosis. MRI –No sacroiliitis [109-114]; Changes are concentrated in one segment, typically in the lumbar spine, rather than distributed across the whole spine; Spinal bone marrow edema and fatty lesions across the whole endplate rather than just the anterior or posterior corners of the vertebrae on MRI
Spinal osteoarthritis/ Vertebral fractures **Older patients;** **Possibly co-occurring in older patients**	CBP has no inflammatory features (better with rest and worse with activity);	Plain radiographs – Degenerative changes; Osteoporosiss; Vertebral fractures; MRI – No inflammatory changes; No sacroiliitis [109-114]

DISH (diffuse idiopathic skeletal hyperostosis)/ Forestier disaese	Older patients; Metabolic syndrome; CBP with stiffness but no inflammatory features, weather-related – worsens in damp or cold weather	Plain radiographs/CTE – preserved disc height; pronounced bony bridging over at least four vertebral bodies; right-sided predilection with cervical and lumbar symmetry; pronounced pelvic enthesopathy without sacroiliitis; pronounced peripheral enthesophytes (bony spurs) and ossification of ALL; Osteophytes are largely paraspinal with a linear lucency often seen between the anterior vertebral body cortex and the osteophyte. MRI - fatty metaplasia in the vertebral corners, without or to a lesser extent bone marrow edema [109-114].

Legend: MRI, magnetic resonance imaging; MSUS, musculoskeletal ultrasound; GSUS, grey scale ultrasound; PDUS, power doppler ultrasound; CTE, computer tomography examination.

3. The problem of axial involvement in PsA (axPsA)

The questions asked here are: Is it present and what is it – a combination of r/nr-axSpA with PSO or a different phenotype of PsA? Where, when and how should we look for it? How should we treat it (role of IL-23 inhibitors in the two types of axial involvement during the course of axPsA)?

A categorical answer to the first part of the first question is given by Dafna D. Gladman [58] – 'Axial involvement is present in 20 up to 45% of patients with PsA. The variation in reported rates is due to the different tools used (definitions; patient cohorts; diagnostic screening tools; imaging modalities, i.e. MRI vs. X-ray) and the disease duration – because the axial involvement develops and progresses over time.' The answer to the second part of the question comes several years later, with the definition of the 2 types of axial involvement in PsA, based on many analyses including the follow-up of PsA cohorts, analyses of radiographic / MRI changes, genotyping and the phenotypes in PsA [59-65].

3.1 AxPsA with symmetric involvement of the axis

AxPsA with symmetric involvement of the axis (AxPsA-SAI) is directly associated with carriage of HLA-B27 and its distribution in populations

(different even within one continent – for example, Norwegians 16% [66] and Greeks 6% [67]), explaining the different frequency of this phenotype, even between European countries. The involvement of the axis here is analogous to that in r-axSpA (former AS): 99% presence of IBP /IBP (Inflammatory Back or Buttock Pain) as an initial symptom; the presence of symmetric sacroiliitis in ≥90% of cases and symmetric involvement of the spine by marginal syndesmophytes. It is observed approximately in 26–33% of axPsA cases. In addition, in this phenotype there are the highest associations within the PsA group with AAU (25%) and IBD (6%) [68, 69].

3.2 AxPsA with asymmetric involvement of the axis

AxPsA with asymmetric involvement of the axis (axPsA-AAI), observed ≈66% of axPsA, is not associated with HLA-B27 (+); IBP/IB*P are present in no more than 50% of cases, and their presence in another 50% of cases is not associated with the presence of sacroiliitis /spondylitis on imaging studies (including MRI). Conversely, ≈50% of imaging findings of sacroiliitis /spondylitis (X-ray /MRI) identified in patients with axPsA are in asymptomatic patients [58–64]. The characteristic findings here are asymmetric and/or unilateral sacroiliitis, uneven (zonal or 'patchy') involvement of the spine (skipping individual vertebrae or even entire segments), preference for the cervical spine, as well as asymmetric, coarse and non-marginal (not growing from the edge of the vertebra) osteophytes [58–64].

4. Where, when and how should we look for axPsA?

In early PsA (E-PsA), covering the transition from subclinical PsA to classifiable PsA and the first 12 months of the development of classifiable PsA (review part one) [70, 71], – 3 large studies attempt to define the presence of the individual phenotypes in E-PsA [72–74]. Unfortunately, however – they only show us the influence of selection bias of the patients on the final result. All three studies use dermatological cohorts with PSO of similar size (384 [72] vs. 355 [73] vs. 365 [74]). The dermatological patients were screened for the presence of symptoms of subclinical /classifiable PsA by dermatologists, however using different DCS (dermatologist-centred screening tool). After the screening, the 'suspected' patients were referred to a rheumatologist for the decision – PsA present or absent. The rheumatologist, for making this decision, performed an examination and could order extended investigations (including HLA typing, MSUS /MRI). Zabotti A, and colleagues [72], use a DCS – centred on the search for arthralgia /synovitis – 'Have you recently had pain in the joints of your arms (from your shoulders to your fingers) or legs (from your hips to your toes)

for no apparent reason?' and obtain a result that 56 of 384 dermatological patients (15%) have classifiable PsA, of which 82% had peripheral arthritis versus 3.6% with axial disease and 12.5% with entheseal (axial + peripheral) involvement or, in total – 16% for axis involvement [72]. A German study [73], uses the same methodology, but with a DCS – centred on the search for IBP /IB*P – 'Have you recently had back or buttock pain after resting or that wakes you up in the morning and makes you move or stretch to make it go away?' with a result – 19 /350 (6%) presence of classifiable PsA among patients with PSO. Of these: 5/19 (26%) have isolated peripheral PsA; 3/19 (16%) have mixed (peripheral + axial involvement) and 14/19 (74%) have axial involvement. An Italian study [74], uses a DCS with a combined questionnaire – PURE-4 [75] (covering both the peripheral – arthralgia /synovitis and the axial – IBP/IB*P, inflammatory pain). Of 365 screened with DCS, 265 were referred to a rheumatologist (73%), of whom 124 (47%) were assessed as subclinical PsA and were subjected to the extended investigations mentioned above. In 21/124 (17%) isolated pPsA was established; in 36/124 (29.0%) mixed involvement (axial + peripheral) was present, and in 43/124 (46%), PsA remained subclinical (non-classifiable) [74]. What do these numbers mean?

Centred DCS (directed only towards IBP /IB*P or only towards arthralgia /synovitis) might miss real patients with PsA among dermatological cohorts with PSO, generating a lower percentage of the PSO – PsA transition: 15% [72] vs. 6% [73] vs. 46% [74]. On the other hand, axPsA exists already at the E-PsA stage, and it is reasonable to accept a frequency among E-PsA of 20-24% (intermediate relative to the data of Proft F, and colleagues – 64% [73] and Zabotti A, and colleagues – 16% [72]) with a pPsA/axPsA ratio (in E-PsA) ≈ 4-5/1. Of this percentage in E-axPsA, 2/3 are HLA-B27 (+) patients (axPsA-SAI phenotype), in whom the axial symptoms start early, may precede the skin manifestations in up to 1/4 of cases and are clinically expressed. In the stage of established axial psoriatic arthritis (axPsA), more and more patients with the axPsA-AAI phenotype are added to the axPsA-SAI phenotype over time. These patients are HLA-B27 negative (-), and their axial symptoms develop slowly [58]. This gradual progression results in approximately 45% axial disease involvement in long-standing PsA, which includes the combined "axial + peripheral" phenotype. Accordingly, the pPsA to axPsA ratio in long-standing established disease is 3:2 (58% vs. 42%) [58]. This 40–45% prevalence correlates excellently with the findings reported by Xabier Michelena and colleagues, who identified 20% "pure axial" and 25% "axial + peripheral" phenotypes in patients with long-duration PsA [76].

The answer to the question – when should we look for axPsA? (which we have just given) is directly related to the question – where and how should we look for axPsA?

Here the answer is screening and we can propose the one used by us: 1) Personal and family history – with great weight in making a decision for extended MSUS/genetic screening/MRI investigations, in young men with PSO and 'unclear' clinical findings; 2) Precise physical examination directed towards the enthesal involvement (table 7), on the principle – 'the more entheses we assess – the better': MASES – created and validated for the assessment of enthesitis in r-axSpA (AS) – assesses mainly axial entheses and only one peripheral; LEI – created and validated for the assessment of enthesitis in PsA, assesses 6 peripheral entheses; SPARCC and its modification – SPARCC plus One (including all zones from LEI) are created for axSpA [77]. In our practice, the SPARCC plus One index is used due to the inclusion of a greater number of peripheral entheses.

Table 7. Enthesal sites assessed by the most commonly used enthesitis indices [77]

Entheseal sites assessed	MASES	LEI	SPARCC*
First costochondral	R, L		
Seventh costochondral	R, L		
Supraspinatus insertion			
Lateral epicondyle humerus		R, L	R, L
Medial epicondyle humerus		R, L	R, L
Posterior superior iliac spine	R, L		
Anterior superior iliac spine	R, L		
Iliac crest	R, L		
Fifth lumbar spinous process	X		
Achilles tendon	R, L	R, L	R, L
Greater trochanter			R, L
Medial condyle femur			SPARCC plus One‡
Insertion plantar fascia			R, L
Quadriceps insertion patella			R, L
Inferior pole patella			(R, L)*
Tibial tubercle			(R, L)*

Legend: MASES, Maastricht Ankylosing Spondylitis Enthesis Score, developed and validated in patients with AS [148]; SPARC, Spondyloarthritis Research Consortium of Canada, developed and validated in patients with AS [149]; ‡, include one more site (medial femoral condyle – SPARCC plus One, which then

allows calculation of both the SPARCC and Leeds indices, because the other four sites of the LEI are included in the SPARCC); LEI, Leeds Enthesitis Index, developed and validated in patients with PsA [150]; X, single site present, not bilateral; *, The total score of SPARCC is 16, because the distal patella and tibial tuberosity, in close proximity, are considered as one site;R, right; L, left.

Genetic screening (extended screening for alleles associated with axial involvement: B27:05:02–C02:02:02; B08:01:01–C07:01:01; B37:01:01–C06:02:01; HLA-B38; HLA-B39; HLA-Cw07:02 [54, 78]) has a slightly lower cost than the combination: MRI of the whole spine (WS - whole spine) with MRI of the sacroiliac joints (SIJ-MRI). In our setting, genetic screening is usually performed after extended MSUS screening and before WS accompanied by SIJ-MRI.

MSUS assessment of entheses is mandatory, because relying only on history and physical examination (using the enthesitis indices mentioned in table 7), we miss 16–20% of existing subclinical enthesitis [79]. In addition to the assessed peripheral entheses (Table 8) [80–85], an assessment is also performed of all accessible axial and axially-related entheses (A /AR-E – axial /axially related entheses). Three groups of enthesis are assessed (Figures 3 and 4) [86–106].

Table 8. Comparison of existed ultrasound (US) enthesal indices –GUESS [80], MASEI [81], OMERACT US-working group (WG) [82], GRAPPA US-WG [83, 84], DEUS Enthesitis Index (DEI) [85].

Enthesal Site	GUESS	EI	OMERACT	MASEI	GRAPPA
Achilles enthesis (superior pole of the calcaneus)	+	+	+	+	(+)
Plantar fascia (inferior pole of the calcaneus)	+	+	–	+	(+)
Tibialis posterior insertion on navicular bone tubercule	–	–	–		+
Distal patellar ligament attachment (tibial tuberosity)	–	–	–	+	(+)
Proximal patellar ligament attachment (inferior pole of the patella)	+	+	+	+	(+)
Quadriceps insertion (superior pole of the patella)	+	+	+	+	+
Triceps insertion (olecranon tuberosity)	–	–	–	+	+
Lateral epicondyle (common extensor tendon attachment)	–	–	–	–	(+)
Medial epicondyle (common flexor tendon attachment)	–	–	–	–	+
Deltoid muscle insertion on the deltoid tuberosity of the humerus	–	–	–	–	+

Supraspinatus tendon attachment (superior facet of the greater tubercle of the humerus)	–	–	–	–	(+)
Doppler within 2 mm of the cortex of the enthesis	–	+	+	+	+
Doppler >2 mm from the cortex of the enthesis	–	+	–	+	+
Doppler at bursa	–	+	–	+	+

Legend: GUESS, Glasgow Ultrasound Enthesitis Score; DEI, Defining enthesitis on Ultrasound in Spondyloarthritis (DEUS) Enthesitis Index; OMERACT, proposed entheseal sites and scores by the OMERACT Ultrasound Enthesitis Working Group; MASEI, Madrid Sonography Enthesitis Index; GRAPPA, proposed entheseal sites and scores by the GRAPPA Ultrasound Working Group; (+), selected entheseal sites in the GRAPPA-DUET project to distinguish PSA from age- and sex-matched healthy individuals.

4.1 Entheses of the anterior chest wall

Entheses of the anterior chest wall (ACWE) are often involved in axSpA and are accessible to musculoskeletal ultrasound (MSUS). These encompass the entheses of the sternoclavicular joint (SCJ), the costochondral joints and entheses (CCJ) - where the sites at which the ribs meet the cartilage frequently exhibit inflammatory changes - and the manubriosternal joint and its entheses.

4.2 Spinal entheses

Among the spinal ligaments suitable for MSUS evaluation is the iliolumbar ligament (ILL). Notably, one of the first publications regarding this structure originated from a Bulgarian research group [92], and it was subsequently included in the protocol for the MSUS scanning of spinal entheses, again developed with Bulgarian participation (Figure 4) [93]. Other evaluable structures include the lateral costotransverse ligaments (LCTL), which connect the costal tubercle on the posterior aspect of the rib to the lateral border of the transverse process of the corresponding thoracic vertebra (Figure 4) [93], and the supraspinous ligaments (SSL) (Figure 4). Furthermore, the erector spinae muscles, which originate from the common tendon of the thoracolumbar fascia, course upward to attach to the posterior part of the ribs and the spinous processes of the thoracic and cervical vertebrae. These insertions are typical sites of enthesitis in axSpA that are accessible for MSUS evaluation and have already been incorporated into established assessment protocols [93].

4.3 Pelvic and hip joint entheses (Axial/Axial-related)

Pelvic and hip joint entheses represent significant sites of axial and axial-related involvement. In the lumbosacral region, accessible structures include the insertions of the iliocostalis lumborum muscle (which originates from the pelvis and sacrum and primarily inserts into the lower ribs and the transverse processes of the lumbar vertebrae) and the longissimus thoracis muscle (originating from the sacrum, iliac crest, and lumbar vertebrae, and inserting into the thoracic vertebrae and lower ribs) onto the posterior and lateral iliac crests [88]. This region also encompasses the insertions of the thoracolumbar fascia, where the erector spinae muscles converge into a common tendon - the thoracolumbar aponeurosis - that attaches to the iliac crests, posterior sacrum, and spinous processes of the lumbar vertebrae, serving as a key site for the accumulation of mechanical stress and inflammation in axSpA [88]. Other relevant sites involve the greater trochanter, specifically the attachment sites of the gluteus medius and gluteus minimus tendons, which are frequently affected in axSpA [94–96], and the iliac crest at the attachment sites of the abdominal muscles and fascia [97, 98]. Additionally, at the sacroiliac joints (SIJ), the attachments of the posterior longitudinal ligament along the posterior wall and the joint itself are accessible for evaluation by an experienced operator [99-106]. A methodological issue arises here, as the ASAS–MRI definitions of sacroiliitis, which require the presence of osteitis with bone marrow edema and/or erosions [109-114], cannot be visualized by MSUS. Conversely, the pathologies visualizable by MSUS (such as enthesitis, synovitis, and ligamentitis) do not meet the ASAS (MRI) criteria for sacroiliitis. Consequently, the two imaging modalities rely on different pathologies to define the presence of inflammatory changes in the SIJ [99-106] vs. [109-114]. Nevertheless, this discrepancy inherently supports their complementarity, suggesting a diagnostic approach where MSUS screening precedes SIJ and whole-spine (WS) MRI, culminating in a comprehensive assessment of the combined findings.

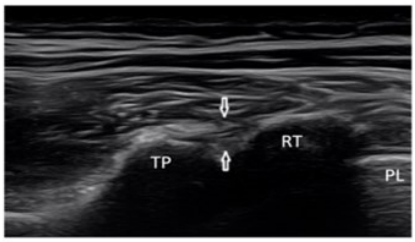
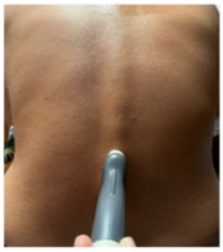
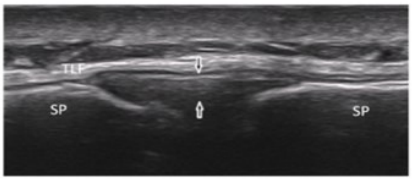
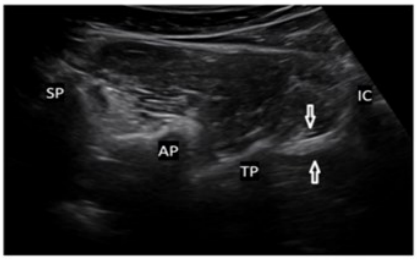
Structure	Patient position	Transducer position	Landmarks	US image
Lateral costotransverse ligament	Seated position with slight anterior flexion of the spine		Vertebral transverse process Rib tubercle	
Supraspinous ligament	Seated position with anterior flexion of the spine		Vertebral spinous process	
Iliolumbar ligament	Lateral decubitus		Transverse process of L5 Posterior Iliac crest	

Figure 3. Available for MSUS examination axially related entheses in axSpA [88]

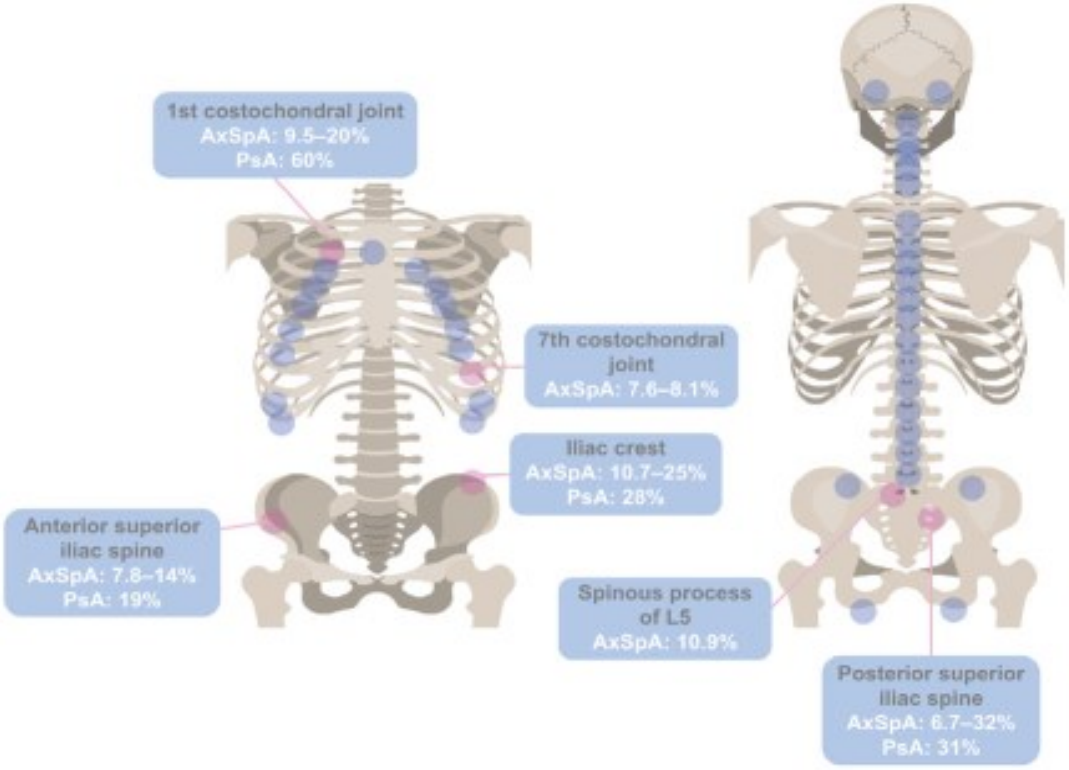


Figure 4. US scanning protocol of the three ligaments studied developed in healthy controls. Arrow: Ligament; AP, articular process; IC, iliac crest; PL, pleural line; RT, rib tubercle; SP, spinous process; TLF, thoracolumbar fascia; TP, transverse process; MSUS, Musculoskeletal Ultrasound.

As can be seen from Table 8, all ultrasound indices for enthesitis assessment cover the key entheses relevant to axSpA (plantar fascia and Achilles tendon insertion to the calcaneus; superior and inferior poles of the patella (quadriceps tendon and patellar tendon)). However, only one of them – GRAPPA-DUET (diagnostic ultrasound enthesitis tool) – was developed specifically for PsA, which is reflected in the greater number of peripheral entheses included in it, with similar US definitions of the primary lesions detected at enthesis sites (GRAPPA-DUET vs. MASEI vs. DEI vs. GUESS vs. OMERACT) [80–85]. Here again, the rule applies – "the more, the better", especially when it comes to entheses in axPsA – peripheral [80–85] + axial or axial-related [88-106]. In our practice, MASEI [81] is used for the assessment of axSpA, and GRAPPA-DUET [83, 84] – for the assessment of PsA. Available data (history, enthesitis indices) are an indication for performing MSUS – A/AR, as mentioned above [88–106]. The role of MSUS/PDUS in evaluation and decision-making (biomechanical vs. inflammation-driven lesions) [87] is crucial in differentiating enthesitis from mimickers associated with chronic back pain. Such conditions include those mentioned in Table 6, fibromyalgia [105], and others, especially considering that all of them may also coexist with true axSpA.

In contrast to r-axSpA (100% involvement of the sacroiliac joints (SIJ)) and nr-axSpA (≥75% involvement of the SIJ), where a diagnostic MRI-SIJ is sufficient, in axPsA – in order to capture the focal involvement of the spine, a WS-MRI (whole spine) in addition to SIJ-MRI is required [109-114]. This combination (WS-MRI + SIJ-MRI), as a method for objectifying early (non-radiographic) axial involvement in axPsA, has been used in clinical studies since 2017 [115-120].

However, the examination is expensive and burdensome for the patient (long duration of the examination), therefore the decision to perform it is made after careful assessment of the risk of its presence during the course of PsA (in our practice, after clinical and MSUS evaluations, before or after extended genetic screening).

4. Conclusions

Having classification rather than diagnostic criteria, our path to an accurate, early diagnosis is thorny. None of the widely adopted diagnostic modalities

– (MSUS, including PDUS); MRI (including the new criteria for assessing the nature of lesions), as well as genetic typing – are capable on their own of providing a categorical and final answer (definitive diagnosis). For example, the typically described MRI bone marrow edema of the SIJ was identified in 3131 (30.8%) of 10,165 patients with a mean age of 53 years, during whole-body MRI (WB-MRI) performed in the German NAKO cohort – established to investigate the causes and risk factors for common chronic diseases in Germany [120]. This percentage is ≈50 times higher than the reported 0.6% prevalence of axSpA in Germany [120]. That is, each of the new modalities has its strengths and weaknesses, and their results must be carefully weighed when making decisions. This weighing is still only within the capabilities of an experienced physician, because it involves the assessment of many factors: (1) Anamnestic data (ethnicity, sex, age, family history), characteristics of the main symptoms (inflammation vs. biomechanics), their course over time, and the influence of environmental factors (climate, lifestyle, work) or prior interventions (physical or pharmacological) on them. All of these help us calculate the pre-test and post-test probabilities and the likelihood ratio (LR±) of the main symptoms in the specific patient; (2) Proper selection of tools for physical examination (so that key findings for the group are not missed (enthesitis indices)); **(**3) Proper selection of laboratory investigations: a) biochemical (lower LR± values and respectively Dg/DD values of acute-phase proteins /CRP/ in the nr-axSpA /PsA group), b) serological (the presence of RF /ACPA antibodies in p-PsA with a corresponding impact on LR± and Dg/DD value of the findings), c) genetic investigations (HLA-B27, etc.), which also have their LR± and corresponding Dg/DD value in decision-making; (4) Proper selection of imaging modalities (conventional X-ray vs. CT vs. MRI vs. MSUM) and assessment of their LR± (Dg/DD) values in the specific patient. Careful assessment of post-test probabilities and LR± values (the calculations, nomograms, diagnostic algorithms mentioned at the beginning), accompanied by precise DD of the present main characteristics (enthesitis, dactylitis, rashes, nail changes, presence of eye involvement – AAU and bowel involvement – IBD), is our path to the definitive diagnosis. The authors hope that recalling all these details will be useful for correct decision-making by rheumatologists in their daily practice.

Declarations

Author Contributions

Conceptualization: L.S.; Methodology: L.S., T.S.; Formal analysis: M.M & K.B.; Investigation: all authors; Writing - original draft: L.S. & M.M.; Writing – review & editing: all authors. The authors take full responsibility for the content of this manuscript, including all figures and tables.

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Conflicts of Interest

The authors declare no conflict of interest.

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Case Report

Lupus Enteritis as the Initial Presentation of Systemic Lupus Erythematosus: A Diagnostic Challenge Case Report

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Running title: Diagnostic Challenge: Lupus Enteritis

Abstract

Background: Gastrointestinal (GI) involvement in systemic lupus erythematosus (SLE) is uncommon and often presents with nonspecific symptoms that mimic primary gastrointestinal disorders or postoperative complications, resulting in delayed diagnosis and inappropriate management. Lupus enteritis is a rare but potentially life-threatening manifestation of SLE and may occasionally represent its initial presentation, further complicating the diagnostic process. Case Presentation: A 27-year-old woman presented with a one-year history of persistent nausea, vomiting, and progressive weight loss leading to severe malnutrition. She had previously undergone abdominal surgery for presumed gastrointestinal disease without clinical improvement. During

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hospitalization, she developed systemic manifestations including alopecia, pancytopenia, hypocomplementemia, and positive antinuclear antibodies, raising suspicion for active SLE. Contrast-enhanced abdominal computed tomography demonstrated small-bowel wall thickening with a target sign and mesenteric vessel engorgement, findings consistent with lupus enteritis. Endoscopic evaluation excluded structural obstruction and malignancy. Based on the integration of clinical, serological, and radiological findings, a diagnosis of lupus enteritis as the initial presentation of SLE was established. Treatment with high-dose corticosteroids followed by cyclophosphamide resulted in rapid clinical, nutritional, and hematologic improvement. Conclusion: Lupus enteritis should be considered in patients with persistent unexplained gastrointestinal symptoms, particularly when accompanied by systemic autoimmune features. Recognition of characteristic radiologic findings together with serologic evidence of disease activity is crucial for timely diagnosis. Early immunosuppressive therapy may prevent unnecessary surgical interventions and reduce the risk of serious complications.

Keywords: systemic lupus erythematosus, lupus enteritis, mesenteric vasculitis, immunosuppressive therapy, diagnostic challenge

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by autoantibody production and immune complex deposition, leading to diverse clinical manifestations [1]. Approximately 40–60% of patients with SLE experience gastrointestinal symptoms; however, only a minority of these manifestations are directly attributable to active lupus-related gastrointestinal disease [2]. These manifestations often pose significant diagnostic challenges, as they may mimic primary GI disorders or adverse drug reactions [3].

Lupus enteritis represents one of the rare but clinically important GI manifestations of SLE [4]. It is characterized by immune-mediated inflammation and vasculopathy affecting the mesentery and intestinal wall [5]. Recent studies highlight that although its incidence is low, lupus enteritis can lead to severe complications such as bowel ischemia, perforation, pseudo-obstruction, and malnutrition if not recognized promptly. The nonspecific nature of its clinical presentation frequently results in delayed diagnosis and, in some cases, unnecessary surgical interventions [6].

Contrast-enhanced abdominal computed tomography (CT) has become the imaging modality of choice for diagnosing lupus enteritis. Typical findings include small-bowel wall thickening with a “target sign” and engorgement of mesenteric vessels, which help distinguish lupus enteritis from infectious or mechanical causes of abdominal pain. Nevertheless, radiologic findings must be interpreted in conjunction with systemic features of lupus, such as cytopenia, hypocomplementemia, and positive autoantibody serology, to establish a comprehensive diagnosis [7].

This case report aims to highlight the diagnostic challenges of lupus enteritis as a manifestation of SLE, particularly in patients with chronic GI symptoms unresponsive to surgical intervention. By presenting this case, we seek to raise clinical awareness of lupus enteritis, emphasize the importance of recognizing characteristic imaging findings, and underscore the role of timely immunosuppressive therapy in preventing morbidity and unnecessary surgical procedures.

2. Case Presentation

A 27-year-old woman presented with a one-year history of persistent daily vomiting and progressive weight loss. Her symptoms began in 2024 with abdominal pain initially treated as gastritis without improvement. She was later hospitalized for abdominal pain, low-grade fever, and black vomitus, and diagnosed with a GI infection. In October 2024, she underwent an appendectomy with partial bowel resection; however, nausea and vomiting persisted postoperatively despite preserved appetite and swallowing. She also reported alopecia and intermittent arthralgia. The patient had no previous history of blood transfusion apart from perioperative transfusion during abdominal surgery. She reported normal bowel habits and denied fever, seizures, or other neurological symptoms.

On admission, the patient appeared weak and severely undernourished (weight 35 kg, height 157 cm, BMI 14.2 kg/m^2). Vital signs were stable with blood pressure 97/58 mmHg, heart rate 89 beats/min, respiratory rate 20 breaths/min, temperature 36.3°C, and oxygen saturation 99% on room air. Conjunctival pallor was noted without scleral icterus. Cardiorespiratory examination was unremarkable. Abdominal examination revealed increased bowel sounds, diffuse tenderness, and ascites without shifting dullness. Bilateral lower limb edema was present.

Initial laboratory evaluation (16/09/2025) revealed normocytic normochromic anemia with bicytopenia and marked inflammatory markers. Hypoalbuminemia and mild transaminase elevation were

observed, while renal function remained preserved despite mild albuminuria. Immunologic testing showed low complement C3 with normal C4 and positive ANA, supporting immune-mediated disease activity. Tumor markers and viral hepatitis serology were negative. Detailed laboratory results are presented in Table 1.

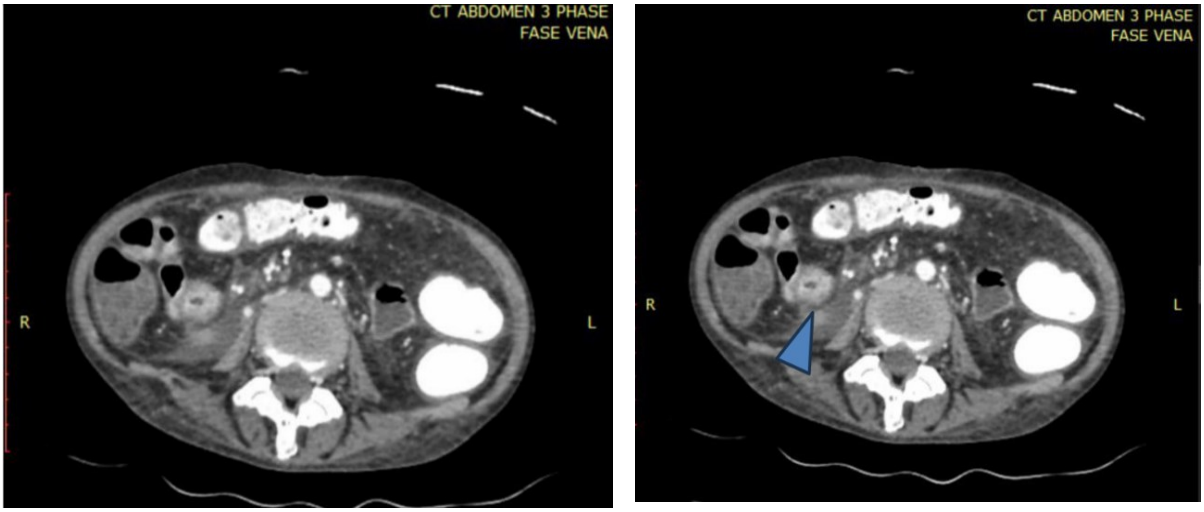
Table 1. Laboratory Findings.

Type	Parameter	Result	Reference range
Hematology	Hemoglobin	9.2 g/dL	12.0–16.0 g/dL
	Hematocrit	25.8 %	36–46 %
	Erythrocytes	3.02 $\times 10^6$/μL	3.8–5.2 $\times 10^6$/μL
	Leukocytes	3.52 $\times 10^3$/μL	4.0–10.0 $\times 10^3$/μL
	Platelets	115 $\times 10^3$/μL	150–400 $\times 10^3$/μL
	MCV	85.4 fL	80–100 fL
	MCH	30.5 pg	27–33 pg
	MCHC	35.7 g/dL	32–36 g/dL
	RDW-CV	16.0 %	11.5–14.5 %
	ESR	>140 mm/h	<20 mm/h
Differential count	Neutrophils	62.5 %	40–70 %
	Lymphocytes	31.5 %	20–40 %
	Monocytes	5.7 %	2–8 %
	Eosinophils	0.3 %	1–4 %
	Basophils	0 %	0–1 %
Clinical chemistry	Albumin	2.78 g/dL	3.5–5.0 g/dL
	AST	48 U/L	<35 U/L
	ALT	37 U/L	<35 U/L
	BUN	12.0 mg/dL	7–20 mg/dL
	Creatinine	0.17 mg/dL	0.6–1.1 mg/dL
	CRP	0.78 mg/dL	<0.3 mg/dL
	Electrolytes	Within normal limits	—
Immunology	Complement C3	49.0 mg/dL	90–180 mg/dL
	Complement C4	20.8 mg/dL	10–40 mg/dL
	ANA	43.5 (positive)	Negative
Tumor markers / serology	CEA	Within normal range	<5.0 ng/mL
	CA 15-3	Within normal range	<30 U/mL
	Anti-HCV	Non-reactive	Non-reactive
Urinalysis	Urine albumin	30 mg/L	<30 mg/L

Abbreviations: MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RDW-CV, red cell distribution width – coefficient of variation; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; C3, complement component 3; C4,

complement component 4; ANA, antinuclear antibodies; CEA, carcinoembryonic antigen; CA 15-3, cancer antigen 15-3; anti-HCV, antibodies against hepatitis C virus.

Contrast-enhanced abdominal CT demonstrated a characteristic target sign in the mid-jejunum, suggestive of lupus enteritis, along with multiple strictures in the duodenum (pars II–III) and jejunum causing proximal dilatation. Multiple enlarged lymph nodes were observed in para-aortic and mesenteric regions. The CT findings are shown in Figure 1.



(A) **(B)**

Figure 1. (A) Patient's Abdominal CT scan; (B) Blue arrow shows bowel wall thickening seen in Patient's Abdominal CT scan.

Based on the integration of clinical, laboratory, and radiologic findings, the patient was diagnosed with SLE with gastrointestinal involvement consistent with lupus enteritis. According to the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria, the patient fulfilled the entry criterion of positive antinuclear antibodies (ANA) and accumulated a total score of 12 points (2 points for non-scarring alopecia, 3 points for leukopenia, 4 points for thrombocytopenia, and 3 points for low complement C3), thereby meeting the classification criteria for SLE. Additional clinical problems included severe malnutrition, suspected gastric outlet obstruction, chronic wound dehiscence, anemia, and hypoalbuminemia-related edema [8].

Given the patient's prolonged history of persistent nausea, vomiting, severe weight loss, previous abdominal surgery, and bowel wall thickening on CT imaging, several differential diagnoses were considered before establishing the diagnosis of lupus enteritis. Histopathological records from the

previous appendectomy were unavailable for review, precluding retrospective assessment of the initial pathological diagnosis. These diagnoses and the rationale for their exclusion are summarized in Table 2.

Table 2. Differential Diagnosis of Lupus Enteritis and the Clinical Findings Supporting or Excluding Each Diagnosis

Differential diagnosis	Findings supporting the diagnosis	Findings leading to exclusion
Mechanical bowel obstruction	Persistent vomiting, history of abdominal surgery	No obstructive lesion on endoscopy; CT favored inflammatory bowel wall thickening rather than transition point
Intestinal tuberculosis	Chronic symptoms, weight loss, mesenteric lymphadenopathy	No microbiological, histopathological, or radiological evidence suggestive of tuberculosis
Crohn's disease	Small bowel wall thickening	Endoscopy showed no characteristic inflammatory lesions; clinical and laboratory findings favored SLE
Gastrointestinal malignancy	Severe weight loss and anemia	Endoscopy showed no evidence of malignancy; imaging did not demonstrate a mass lesion
Chronic intestinal pseudo-obstruction	Persistent nausea and vomiting without clear mechanical obstruction	Characteristic CT findings, positive ANA, hypocomplementemia, and favorable response to immunosuppressive therapy supported lupus enteritis
Lupus enteritis	Positive ANA, hypocomplementemia, bowel wall thickening with target sign, systemic manifestations of SLE	Final diagnosis

Abbreviations: CT, computed tomography; SLE, systemic lupus erythematosus; ANA, antinuclear antibodies.

Initial management consisted of intravenous fluids (1,000 mL/24 h), intravenous lipid emulsion every 48 hours, and intravenous methylprednisolone 62.5 mg daily. Symptomatic therapy included metoclopramide, sucralfate, and omeprazole. One unit of packed red blood

cells (PRC) was transfused. Esophagogastroduodenoscopy (EGD) was planned for further evaluation.

On Day 4 (19/09/2025), the patient experienced one episode of postprandial vomiting and persistent weakness. Laboratory evaluation revealed progression to severe pancytopenia (hemoglobin 7.9 g/dL, leukocytes 2.57×10^3/µL, platelets 62×10^3/µL). A central venous catheter was inserted due to difficult access. Two additional PRC units were transfused, and corticosteroid therapy was escalated to high-dose intravenous methylprednisolone 500 mg/day.

By Day 8 (23/09/2025), clinical improvement was noted with reduced edema and fewer vomiting episodes. Laboratory results showed significant hemoglobin and leukocyte recovery (14.0 g/dL and 5.23×10^3/µL, respectively), although thrombocytopenia persisted (60×10^3/µL). Serum albumin improved to 3.28 g/dL. Steroids were tapered to intravenous methylprednisolone 31.25 mg/day.

On Day 10 (25/09/2025), EGD revealed gastroesophageal reflux disease with Los Angeles grade C esophagitis, erosive pangastritis, and duodenitis without mechanical obstruction. Histopathology showed non-specific inflammatory changes and was negative for Helicobacter pylori. Endoscopic findings are presented in Figure 2. Follow-up laboratory tests showed recurrent leukopenia and thrombocytopenia, suggesting ongoing immune-mediated marrow suppression. Intravenous cyclophosphamide 250 mg was administered.

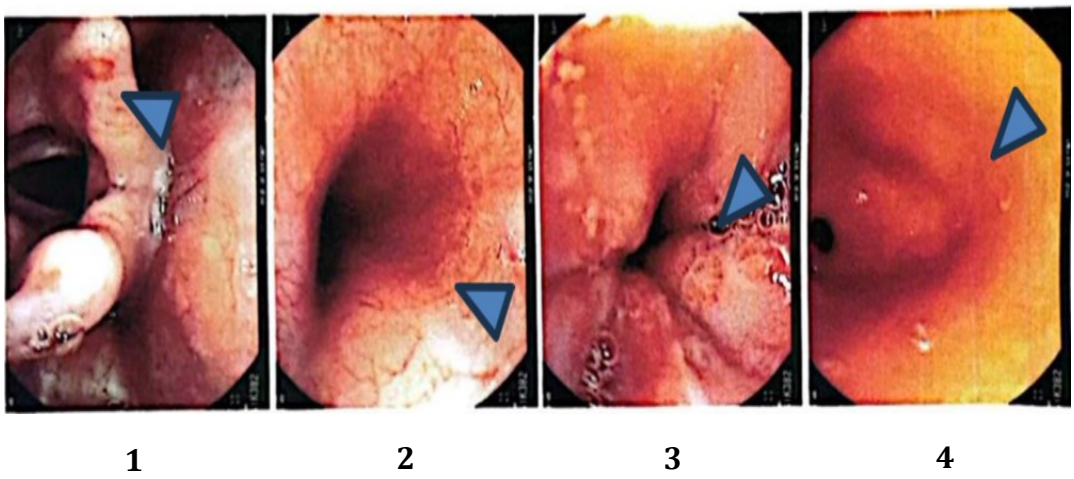


Figure 2. Patient's EGD Result (1) Larynx: Hyperemic, edematous mucosa with prominent vascularity; (2) and (3) Esophagus: Diffuse hyperemia from proximal

to distal segments with erosions in the middle to distal third; EGJ showed a mucosal break with granular changes; (4) Stomach (Antrum) The mucosa appeared hyperemic, edematous, and erosive.

The patient was discharged on oral methylprednisolone 16 mg twice daily, sucralfate, omeprazole, ondansetron, and domperidone. At outpatient follow-up (7/10/2025), GI symptoms had markedly improved with better oral intake. Hematologic parameters showed recovery (hemoglobin 13.5 g/dL, leukocytes $5.71\times10^3/\mu L$, platelets $87\times10^3/\mu L$), and albumin normalized to 4.34 g/dL. The patient was scheduled to receive six monthly intravenous cyclophosphamide 250mg pulses followed by maintenance therapy with hydroxychloroquine 200mg daily and tapering corticosteroids.

3. Discussion

Chronic recurrent nausea and vomiting with progressive weight loss require a structured diagnostic approach prioritizing common GI etiologies before systemic autoimmune causes are considered [9,10]. Mechanical obstruction including peptic ulcer–related stenosis or postoperative adhesions must be excluded, particularly in patients with prior abdominal surgery [11]. Functional disorders such as gastroparesis or intestinal pseudo-obstruction may clinically mimic obstruction without structural blockage [12]. In this case, persistence of symptoms despite prior surgery, combined with severe malnutrition and systemic manifestations, prompted reassessment beyond mechanical pathology toward inflammatory systemic disease.

Although gastrointestinal manifestations are relatively uncommon in SLE, they may occasionally represent the earliest manifestation of the disease. Research reported that gastrointestinal complaints were frequently recalled as prodromal symptoms preceding the diagnosis of SLE [13]. This observation is consistent with our case, in which persistent nausea and vomiting preceded the diagnosis of SLE by approximately one year and initially led to an alternative surgical diagnosis. Therefore, persistent unexplained gastrointestinal symptoms, particularly when accompanied by systemic abnormalities such as cytopenia or hypocomplementemia, should prompt consideration of underlying autoimmune disease even in the absence of classic lupus manifestations.

Gastrointestinal involvement occurs in 40–60% of patients with SLE, although only a minority of cases are directly attributable to active lupus [3]. Lupus enteritis represents a rare but potentially life-threatening

manifestation characterized by immune-mediated small-bowel inflammation. Because GI manifestations are not incorporated into SLEDAI scoring, disease activity may be underestimated [2,3]. In this patient, chronic vomiting, severe malnutrition (BMI 14.2 kg/m^2), alopecia, anemia, and progressive pancytopenia indicated multisystem disease. Positive ANA and low complement C3 supported active immune complex–mediated activity, while hematologic abnormalities reinforced systemic involvement rather than isolated GI pathology.

The pathogenesis of lupus enteritis is driven by immune complex deposition and complement activation within mesenteric vessels, resulting in submucosal edema, vascular congestion, and segmental ischemia. Complement consumption correlates with disease activity, consistent with the low C3 level observed in this patient [7]. In addition to vasculitis, enteric neuropathy and smooth muscle dysfunction may contribute to reversible dysmotility, explaining chronic vomiting in the absence of complete obstruction [14]. The absence of perforation or hemorrhage suggests inflammatory involvement without transmural necrosis.

Contrast-enhanced abdominal CT remains the diagnostic cornerstone for lupus enteritis. Typical findings include bowel wall thickening with a “target sign” and mesenteric vascular engorgement (“comb sign”) [7]. In patients with prior abdominal surgery, distinguishing inflammatory vasculitic changes from mechanical obstruction represents a significant diagnostic challenge [14]. In this case, integration of imaging findings with serologic activity and systemic features favored active lupus enteritis over postoperative obstruction.

Endoscopy plays a complementary role primarily to exclude structural obstruction or malignancy, as superficial biopsies often fail to detect submucosal vascular lesions characteristic of lupus enteritis [15]. In this patient, erosive gastritis and nonspecific duodenitis were observed without obstructive pathology. The discordance between persistent vomiting and minimal mucosal abnormalities further supported a motility-dominant autoimmune process.

Hematologic involvement complicated the clinical course. Pancytopenia in SLE may result from immune-mediated destruction or inflammation-related marrow suppression [16]. The temporal association between high-dose corticosteroid and cyclophosphamide therapy and hematologic recovery supports immune-mediated suppression rather than drug toxicity. The coexistence of lupus enteritis and pancytopenia likely reflects

heightened systemic immune activation and may indicate more severe disease.

The management of lupus enteritis depends on disease severity, the presence of systemic involvement, and the patient's clinical response. High-dose corticosteroids remain the first-line treatment, while additional immunosuppressive agents are recommended for severe, recurrent, or refractory disease. The currently available therapeutic options and their clinical indications are summarized in Table 3.

Table 3. Therapeutic options for lupus enteritis and their clinical indications

Treatment	Clinical indication	Role in management
High-dose corticosteroids	First-line treatment for active lupus enteritis	Rapid control of intestinal inflammation
Intravenous cyclophosphamide	Severe disease, recurrent lupus enteritis, or major organ involvement	Induction therapy in severe SLE
Mycophenolate mofetil	Steroid-sparing agent or refractory disease	Maintenance or alternative immunosuppression
Azathioprine	Maintenance therapy after remission	Prevention of relapse
Rituximab	Refractory or relapsing disease	Rescue therapy in selected patients
Hydroxychloroquine	All patients with SLE unless contraindicated	Long-term disease control and relapse prevention
Nutritional support	Malnutrition or prolonged gastrointestinal symptoms	Supportive management

In the present case, high-dose intravenous methylprednisolone was initiated as first-line therapy because of active lupus enteritis. Intravenous cyclophosphamide was subsequently administered due to the severity of gastrointestinal involvement, prolonged disease course, marked malnutrition, pancytopenia, and active systemic disease. The patient demonstrated rapid clinical improvement following immunosuppressive therapy, supporting the diagnosis of lupus enteritis. The patient remained clinically stable during outpatient follow-up and was scheduled to complete six monthly intravenous cyclophosphamide pulses, followed by maintenance therapy with hydroxychloroquine and tapering corticosteroids.

High-dose corticosteroids constitute first-line therapy for lupus enteritis, with response rates approaching 70–90% [7]. Additional

immunosuppressive agents, including cyclophosphamide, are recommended in severe or refractory cases. Although standardized treatment algorithms are lacking, early immunosuppression is associated with improved outcomes [2,3]. In this patient, pulse methylprednisolone followed by cyclophosphamide resulted in rapid symptom resolution and hematologic recovery, supporting inflammatory rather than structural etiology.

Nutritional optimization is critical, as prolonged vomiting and intestinal inflammation frequently result in severe protein-calorie malnutrition [14]. Temporary parenteral support facilitates intestinal recovery and stabilization. Following immunosuppressive therapy, this patient demonstrated restored oral intake and normalization of albumin levels.

Although prognosis is generally favourable with prompt treatment, relapse occurs in 20–30% of cases, particularly in the presence of persistent hypocomplementemia [3]. Ongoing serologic monitoring and maintenance therapy are therefore essential. Given the initial complement consumption observed in this patient, continued hydroxychloroquine therapy and gradual steroid tapering are warranted to reduce recurrence risk.

Strengths and Limitations

This case illustrates the diagnostic challenge of lupus enteritis presenting as the initial manifestation of SLE. However, several limitations should be acknowledged. Extended autoantibody profiling, including anti-dsDNA, anti-Sm, anti-Ro/SSA, anti-La/SSB, and antiphospholipid antibodies, was not available in this case. In addition, histopathological findings from the previous appendectomy were unavailable, and long-term follow-up after cyclophosphamide therapy was limited. Nevertheless, the diagnosis was supported by fulfilment of the 2019 EULAR/ACR classification criteria, characteristic clinical manifestations, hypocomplementemia, positive ANA, typical radiologic findings, and a favourable response to immunosuppressive therapy. The ANA immunofluorescence pattern using HEp-2 cells was not available because the test was reported only qualitatively at our institution. Direct antiglobulin testing (Coombs test) was not performed because autoimmune hemolytic anemia was not clinically suspected.

4. Conclusions

Gastrointestinal involvement in SLE remains a diagnostic challenge due to its nonspecific presentation and frequent misclassification as functional or

mechanical disease. Persistent GI symptoms accompanied by serologic evidence of active lupus and characteristic radiologic findings should prompt early suspicion of lupus enteritis. A rapid response to immunosuppressive therapy further supports an inflammatory rather than structural etiology. Timely recognition of mesenteric vasculitis–related pathophysiology and implementation of a multidisciplinary diagnostic strategy are essential to prevent catastrophic complications, including intestinal ischemia and perforation.

Declarations

Author Contributions

Conceptualization: F.V., A.A.; Methodology: F.V., A.A.; Formal analysis: F.V; Investigation: F.V., A.A.; Writing—original draft: F.V.; Writing—review & editing: F.V., A.A.

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Informed consent was obtained from the patient prior to the publication of this case report and accompanying clinical data/images. The case report was conducted in accordance with the Declaration of Helsinki.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Case Report

Hidradenitis Suppurativa, Spondyloarthritis, and Demyelinating Lesions: A Case Report of a Complex Clinical Association

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Running title: Complex Triad: HS, SpA, and Demyelinating Lesions

Abstract

Background: Hidradenitis suppurativa (HS) is an inflammatory skin disease primarily affecting large folds, which can be associated with spondyloarthritis (SpA). However, the rare coexistence of HS, SpA, and demyelinating lesions presents significant challenges in therapeutic decision-making, especially when resistant to first-line therapies. Case Presentation: We report the case of a 17-year-old boy with a three-year history of stage III hidradenitis suppurativa (HS) who presented with chronic inflammatory back pain for three months and a two-month history of a waddling gait. Initial treatments, including topical and oral antibiotics, failed to control his skin lesions. Physical examination revealed lumbar stiffness, positive sacroiliac tests, and brisk lower limb reflexes. Pelvic X-ray revealed bilateral stage III sacroiliitis, and brain MRI showed T2 and FLAIR hyperintensities suggestive of demyelinating lesions. Extensive workup, including cerebrospinal fluid analysis and normal levels of ANA, anti-DNA, anti-NMO, anti-MOG antibodies, syphilitic and HIV serologies, vitamin B12, and folate, concluded to non-specific demyelinating lesions. A diagnosis of radiographic axial SpA and peripheral enthesitis associated with HS was

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established. Worsening skin condition prompted initiation of anti-TNF-α therapy (adalimumab) after multidisciplinary consultation. His gait disturbances improved with physiotherapy, with neurological evaluation favoring a functional origin. Conclusion: Managing concurrent HS and SpA with demyelinating lesions is challenging. Although anti-TNF-α therapy is effective for HS and SpA, its link to demyelinating diseases demands caution. Further research is needed to refine treatment strategies and improve patient outcomes.

Keywords: hidradenitis suppurativa, spondyloarthritis, demyelinating lesions, anti-TNF-α therapy

1. Introduction

Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil's disease, is a chronic inflammatory skin condition that occurs in flare-ups. It primarily affects large skin folds, such as the axilla, submammary, inguinal, and perianal regions [1]. HS has a prevalence of 1% to 4% and predominantly affects young women [2,3]. HS can be associated with other inflammatory diseases, either cutaneous such as psoriasis, acne conglobata, and skin cancers [4–6], or extra-cutaneous such as chronic inflammatory bowel diseases and spondyloarthropathies [7–9]. Spondyloarthritis (SpA) is a chronic inflammatory rheumatic disease that affects the entheses and primarily involves the axial skeleton, potentially progressing to ankylosis. The association of HS and SpA has been reported in the literature [8–11], presenting a therapeutic challenge requiring multidisciplinary management. We report the case of a 17-year-old boy with severe hidradenitis suppurativa (HS) associated with axial SpA, resistant to antibiotics and requiring initiation of anti-Tumor necrosis factor-α (anti-TNF-α) biologic therapy. The patient also presented with gait disturbances and demyelinating lesions on MRI, complicating therapeutic decision-making. A thorough evaluation and multidisciplinary consultation were conducted to guide management.

2. Case Presentation

We report the case of a 17-year-old boy who presented to our rheumatology department in 2023 with chronic inflammatory low back pain persisting for three months before admission. The pain was associated with morning stiffness lasting 20 minutes, improving with activity. The patient had a three-year history of HS classified as stage III according to the Hurley classification [4], initially treated with topical and oral antibiotics, including

tetracyclines, clindamycin-rifampicin, and acitretin with no improvement and worsening of the skin lesions over time. Subsequently, he experienced gait disturbances characterized by a waddling gait for 2 months. Physical examination revealed lumbar stiffness with positive sacroiliac tests and brisk osteotendinous reflexes in the lower limbs with no motor deficits. His skin lesions were characterized by painful nodules, abscesses which progressed to pus discharge, pustules, and subsequent healing with hypertrophic scars mainly located in major folds such as the armpits, buttocks, and intergluteal fold. The pelvic X-ray revealed bilateral stage 3 sacroiliitis. In the presence of neurologic abnormalities, brain MRI was performed and revealed T2 and FLAIR hypersignals in the white matter and in the subcortical occipital region bilaterally, as well as adjacent to the right and left frontal horns, suggestive of demyelinating lesions. There was no evidence of spinal myelitis. Additionally, inflammatory sacroiliitis with involvement of the manubriosternal joint and vertebral enthesis at T10 and T11 was observed. Laboratory tests revealed a CRP level of 53 mg/L and a normal complete blood count. A diagnosis of radiographic axial spondyloarthritis and peripheral enthesitis associated with Hidradenitis Suppurativa was made. To investigate the gait disturbances and demyelinating lesions on brain MRI, a lumbar puncture was performed. Chemical, cytological, and bacteriological analysis of the cerebrospinal fluid (CSF) revealed no abnormalities. Isoelectric focusing of CSF and serum showed a normal profile with a IgG index of 0.42. Levels of ANA, anti-DNA, anti-NMO, anti-MOG antibodies, syphilitic and HIV serologies, as well as vitamin B12 and folate levels, were all within normal ranges. The diagnosis of demyelinating disease was ruled out and the lesions were considered nonspecific. The patient was started on NSAIDs with improvement in rheumatic symptoms. However, he continued to be bothered by his skin disease, for which anti-TNF-α therapy was indicated. Adalimumab is the biologic therapy of choice for resistant HS [12–14]. After a multidisciplinary discussion involving rheumatologists, neurologists and dermatologists, the benefit-risk balance favored initiation of anti-TNF-α therapy, despite the presence of demyelinating lesions. Under adalimumab therapy, the patient showed a marked improvement in articular symptoms, with the BASDAI decreasing from 6.3 to 2. However, no improvement in cutaneous lesions was observed after 12 weeks of treatment, and C-reactive protein (CRP) remained elevated at 30 mg/L.

In view of the persistent dermatological lesions, an intra-class switch to infliximab was performed. This resulted in a favorable clinico-biological response, with significant improvement in both cutaneous and articular

manifestations. At 8 weeks of treatment, CRP had decreased to 3 mg/L and the BASDAI to 1.9, with sustained clinical remission thereafter.

Regarding the gait disorder, the neurological assessment favored considering it a functional gait disorder due to the absence of an organic cause. The patient began physiotherapy sessions, leading to a gradual recovery of normal walking. Summary of the patient's history is provided in Table 1.

Table 1. Summary of Clinical, Radiological, and Therapeutic Features of Hidradenitis Suppurativa, Spondyloarthritis, and Demyelinating Lesions

	Hidradenitis suppurativa	Spondyloarthritis	Demyelinating lesions
Duration at presentation	3 years	3 months	2 months (gait disturbance)
Symptoms	Painful nodules and abscesses Pus discharge, pustules Hypertrophic scarring Axillae, buttocks, intergluteal fold	Chronic inflammatory low back pain Morning stiffness (~20 min), improving with activity Lumbar stiffness, positive sacroiliac tests Peripheral enthesitis BASDAI: 6.3 at baseline	Waddling gait (2 months) Brisk lower limb reflexes No motor deficit
Key investigations	Clinical diagnosis — Hurley stage III	Pelvic X-ray: bilateral sacroiliitis stage III MRI: sacroiliitis, manubriosternal joint involvement, enthesis T10–T11 CRP: 53 mg/L	MRI: T2/FLAIR hyperintensities — subcortical occipital (bilateral) and adjacent to frontal horns; no spinal myelitis CSF: normal (chemistry, cytology, bacteriology) IgG index: 0.42 (normal) ANA, anti-DNA, anti-NMO, anti-MOG: normal HIV, syphilis: negative; B12, folate: normal
Diagnosis retained	Hurley stage III HS — refractory to systemic antibiotics and acitretin	Radiographic axial SpA + peripheral enthesitis	Non specific demyelinating lesions — demyelinating disease ruled out

Prior treatments & response	Topical antibiotics — failure Tetracyclines — failure Clindamycin-rifampicin — failure Acitretin — failure, worsening	NSAIDs — improvement of rheumatic symptoms	
1st biologic: Adalimumab	No improvement in skin lesions at 12 weeks	Marked improvement — BASDAI decreased from 6.3 to 2.0	Multidisciplinary discussion: Rheumatology / Neurology / Dermatology Benefit-risk balance favored anti-TNF-α initiation despite demyelinating lesions No worsening of neurological status under anti-TNF-α treatment
Intra-class switch: Infliximab	Significant improvement of cutaneous lesions; sustained remission	Sustained remission — BASDAI: 1.9; CRP: 3 mg/L at week 8	
Gait disorder outcome	Neurological assessment: **functional gait disorder** (no organic cause identified) — Progressive recovery of normal walking after physiotherapy		

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; MRI, magnetic resonance imaging; CRP, C-reactive protein; T2, T2-weighted; FLAIR, fluid-attenuated inversion recovery; CSF, cerebrospinal fluid; IgG, immunoglobulin G; ANA, antinuclear antibodies; anti-DNA, anti-deoxyribonucleic acid antibodies; anti-NMO, anti-neuromyelitis optica (anti-aquaporin-4) antibodies; anti-MOG, anti-myelin oligodendrocyte glycoprotein antibodies; HIV, human immunodeficiency virus; HS, hidradenitis suppurativa; SpA, spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; TNF-α, tumor necrosis factor alpha.

3. Discussion

We report a case of an association of HS and SpA treated with anti-TNF-α therapy evolving in a context of demyelinating lesions. The association between SpA and HS has been documented in several studies. In a prospective study involving 640 cases of HS, 3.7% of patients had an associated SpA, with skin involvement preceding joint involvement in 90% of cases [8]. A monocentric cross-sectional study with 39 HS patients reported an association with SpA in 28.2% of cases (11 patients) [9]. Additionally, in a study of 449 patients with axial SpA, HS was diagnosed in 41 patients (9.1%), with those having HS showing higher ASDAS scores

[10]. In a retrospective study reevaluating pelvic MRIs of 46 patients, performed as part of the surgical excision preparation for HS, 56.5% of these MRIs showed typical changes indicative of SpA [15]. The pathogenesis of HS remains insufficiently clear [16]. An aberrant innate and adaptive immune response plays a key role in the disease. Notably, both these two diseases share commonalities in their pathogenesis, such as the involvement of TNF-α and interleukins (IL)-23/IL-17 pathways. This shared mechanism explains why anti-TNF-α agents are effective for both conditions [13,16,17]. International guidelines recommend biologic therapy for moderate to severe HS in cases of resistance to systemic antibiotics. Adalimumab is the only approved biologic in adolescents for HS and serves as the first-line biologic treatment in all guidelines [14]. Its efficacy and safety in Hurley stage II/III HS have been demonstrated in randomized controlled trials [18–20]. It is administered subcutaneously, starting with a 160 mg loading dose at week 0, followed by 80 mg at week 2, and then 40 mg weekly [21]. Infliximab is generally considered a second-line biologic therapy, administered using the same dosing regimen as in SpA: 5 mg/kg intravenously at weeks 0, 2, and 6, followed by infusions every 8 weeks.

If anti-TNF-α therapy fails, anakinra and ustekinumab may be alternative options, though supporting evidence for their efficacy in HS remains limited [14]. For SpA, biologic therapy is recommended when at least two classes of NSAIDs fail to provide improvement after four weeks of treatment. Available options include anti-TNF-α, IL-17 inhibitors (IL-17i), and JAK inhibitors, with no clear evidence favoring one class over another in axial SpA [22]. For our patient, the resistance of HS to local and oral antibiotics and acitretin, as well as the recurrence and severity of flare-ups, indicated the need for anti-TNF-α biologic therapy, despite his SpA responding well to NSAIDs. However, the presence of T2 and FLAIR hypersignals in the white matter on cerebral MRI, frequently found in older subjects [23,24], required further investigation into demyelinating diseases such as multiple sclerosis (MS) or neuromyelitis optica.

Few studies have investigated the prevalence and clinical relevance of white matter hyperintensities (WMH) in young individuals.

A study involving individuals younger than 45 years reported a WMH prevalence of 25.9% (324/1249), excluding participants with a history of stroke, traumatic brain injury, neoplasm, psychiatric disorders, demyelinating diseases, metabolic disorders, or substance abuse. In this study, WMH were associated with a history of cardiovascular disease, including hypertension, diabetes mellitus, and hyperlipidemia [25].

Other risk factors for WMH in young adults reported in the literature include female sex, headaches and syncope, sleep disturbances[26], migraine[27], and bipolar disorder [28].

Furthermore, WMH in young adults have been associated with poorer working memory performance[29].

The association between demyelination and SpA has been reported. However, it remains unclear whether these events are coincidental, driven by a shared pathophysiological mechanism, or linked to anti-TNF therapy. A longitudinal observational study of 2,268 SpA cases identified 26 cases (1.14%) of demyelinating disease, including eight patients who were anti-TNF-naïve. This corresponds to an incidence of 31 demyelinating events per 100,000 person-years, which, although low, remains higher than the general population's incidence of multiple sclerosis (2.1 per 100,000 person-years) [30]. Demyelination of the central nervous system following anti-TNF-α treatment is a rare event [31]. However, cases of demyelinating diseases, including MS and neuromyelitis optica, have been observed in patients treated with these agents [32–35]. Exposure to anti-TNF-α has been associated with an increased risk of inflammatory central nervous system events, with a similar risk for both demyelinating and non-demyelinating events [36]. In MS, anti-TNF-α therapy has been associated with the potential to exacerbate demyelination and worsen symptoms [37,38]. Genetic susceptibility may predispose certain patients to demyelination when treated with these agents [39]. However, It remains unclear whether these events are coincidental or represent a treatment side effect [35,40]. Given the severity of his skin disease and the absence of an absolute contraindication to anti-TNF-α therapy, this treatment was indicated after a multidisciplinary consultation meeting. The patient was initially treated with adalimumab and experienced a marked improvement in joint symptoms; however, no improvement was observed in the cutaneous lesions. Although adalimumab is considered the first-line biologic therapy for HS, suboptimal responses have been reported, with an overall therapeutic response rate of approximately 40% [41]. Given the absence of cutaneous improvement, treatment was switched to infliximab, a second-line biologic option for HS. This therapeutic change resulted in a favorable clinical and biological outcome, with significant improvement in both the articular and cutaneous manifestations.

4. Conclusions

This case highlights the challenges of managing concomitant HS and SpA in the presence of demyelinating lesions. Anti-TNF-α agents are effective for HS and SpA but require caution due to their possible neurological risks. Awareness of these associations is crucial to guide therapeutic decisions.

Declarations

Author Contributions

Conceptualization: Yasmine Makhlouf, Wassim Tekaya.; Methodology: Yasmine Makhlouf, Wassim Tekaya.; Formal analysis: Yasmine Makhlouf, Wassim Tekaya.; Investigation: Yasmine Makhlouf, Wassim Tekaya.; Writing—original draft: Wassim Tekaya; Writing—review & editing: all authors.

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Informed consent for publication was obtained from the patient's legal guardian. No identifying information is included in the report. The study was conducted in accordance with the Declaration of Helsinki.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

Artificial Intelligence Statement

During the preparation of this manuscript, artificial intelligence tools were used solely for language editing and grammatical correction. The authors take full responsibility for the content of the manuscript.

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