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BRIEF REPORT

Elevated Serum Proadrenomedullin Levels in Rheumatoid Arthritis Versus Spondyloarthritis: Insights From a Biobank Cohort

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Objective. Proadrenomedullin (pro-ADM) is a peptide implicated in immunomodulation, with higher levels observed in inflammatory conditions, cardiovascular impairment, and sepsis. Although extensively studied in acute disorders, its potential as a biomarker in inflammatory arthritis remains underexplored. This study aims to examine serum pro-ADM levels across different types of inflammatory arthritis and to investigate correlations with disease characteristics.

Methods. We included 163 patients with inflammatory arthritis who were prospectively enrolled in our institutional Biobank. Among them, 99 patients had rheumatoid arthritis (RA), 36 patients had psoriatic arthritis (PsA), 22 patients had axial spondyloarthritis (axSpA), and 6 patients had undifferentiated spondyloarthritis (uSpA). Serum pro-ADM levels were measured using enzyme-linked immunosorbent assay, with cross-sectional assessment at baseline in all patients and longitudinal follow-up in a subset of 31 patients with RA.

Results. At baseline, patients with RA exhibited significantly higher serum pro-ADM levels (median 51.7 pg/mL) in comparison to PsA, axSpA, and uSpA (median values between 33.9 and 35.6 pg/mL; all $P < 0.001$). Pro-ADM showed good discriminative ability in distinguishing RA from SpA but had no correlation with markers of inflammation, disease duration, or disease activity indices. In patients with RA with follow-up data, pro-ADM levels exhibited a significant decrease from 52.5 to 30.1 pg/mL after six months ($P = 0.023$). However, changes in pro-ADM did not correlate with changes in the Disease Activity Score in 28 joints using the C-reactive protein level.

Conclusion. Serum pro-ADM levels are markedly elevated in RA relative to SpA, although they do not correlate with inflammatory burden or disease activity. In RA, pro-ADM levels decrease following treatment initiation or modification; nonetheless, they lack predictive value for treatment response. These findings suggest that pro-ADM reflects disease-specific pathophysiologic differences rather than representing a dynamic biomarker.

INTRODUCTION

Inflammatory arthritides represent a group of chronic diseases characterized by immune-mediated joint inflammation and variable systemic involvement. Among them, rheumatoid arthritis (RA) is the prototypical autoimmune disease, marked by systemic inflammation, persistent synovitis, and increasing joint and bone damage.[1,2] In contrast, spondyloarthritis (SpA) encompasses a group of diseases that include psoriatic arthritis (PsA), axial SpA (axSpA), and undifferentiated SpA (uSpA). These conditions are mechanistically linked with the interleukin-23(IL-23)/IL-17 axis, share clinical and radiologic characteristics, and are strongly associated with the presence of HLA-B27.[3,4] Although there is some clinical overlap, the immunopathogenic pathways of RA and SpA are considerably different, thus reinforcing the need for disease-specific biomarkers.[5,6]

Currently available biomarkers in rheumatology lack both sensitivity and disease specificity.[5,6] Even when there is active synovitis, acute-phase reactants like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) might remain within normal

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ranges.[7] Autoantibodies, including rheumatoid factor (RF) and anticitrullinated peptide antibody (ACPA), can be absent in RA or yield false positives, and are not useful for disease monitoring.[8]

Composite indices like the Disease Activity Score in 28 joints (DAS28) and the Bath Ankylosing Spondylitis Disease Activity Index may underestimate the amount of residual inflammation.[7] These limitations highlight the need for new biomarkers that more accurately describe disease activity, estimate response to treatment, and assist in differential diagnosis.

The multifunctional peptide known as adrenomedullin (ADM), which is produced from its precursor pro-ADM, has strong immunomodulatory, angiogenic, and vasodilatory effects.[9] It is well established that systemic inflammation causes a significant increase in ADM levels, especially in response to IL-1β and tumor necrosis factor α (TNFα), two cytokines essential to the pathophysiology of RA.[10]

Although pro-ADM has been extensively studied in cardiovascular and infectious diseases, its role in rheumatology remains less explored.[11] Remarkably, in patients with RA, synovial tissue has been found to express ADM, implying local production in involved joints.[10] Experimental studies have shown that ADM actively modulates rheumatoid synovial biology by promoting fibroblast-like synoviocyte adhesion to extracellular matrix proteins through integrin activation, suggesting a role in synovial tissue organization and cell–matrix interactions.[12] ADM has been shown to modulate inflammatory responses and cellular interactions within the synovial microenvironment, reducing inflammation and preserving endothelium integrity, thus suggesting a regulatory role within the inflammatory cascade.[13,14]

However, the potential diagnostic utility of pro-ADM in differentiating RA from other inflammatory arthritides, together with its longitudinal dynamics during treatment, is insufficiently explored.

The objective of this study is three-fold: (1) to evaluate the differences in baseline serum pro-ADM levels among RA, PsA, axSpA, and uSpA; (2) to examine the relationships between pro-ADM and conventional clinical and laboratory indicators of disease activity; and (3) to investigate whether pro-ADM levels correlate with changes in clinical status or treatment response over time in RA.

PATIENTS AND METHODS

Study population and design. This research used data and biologic specimens from the Arthritis Biobank (RheumaBank) of the Rizzoli Orthopedic Institute (IOR), Bologna, Italy.[15] The RheumaBank enrolls adult patients diagnosed with RA, PsA, axSpA, or uSpA, whether newly diagnosed or initiating therapy with a biologic or targeted synthetic disease-modifying antirheumatic drug (bDMARD/tsDMARD). Patients are enrolled in a consecutive manner and monitored longitudinally during standard clinical care. The RheumaBank gathers and preserves biologic samples, such as serum, urine, and synovial fluid, along with extensive demographic and clinical information, encompassing disease activity indices, laboratory parameters, and treatment history.

For this study, we selected a cohort of consecutive patients from the RheumaBank whose serum pro-ADM levels were evaluated. The inclusion criteria were (1) a verified diagnosis of RA, PsA, axSpA, or uSpA and (2) the availability of a baseline (T0) serum sample. No exclusion criteria were applied, because the study was conceived as an exploratory analysis in a real-world inflammatory arthritis population. Although this approach may introduce clinical heterogeneity, it minimizes selection bias and reflects routine clinical practice. Potential sources of confounding were therefore addressed through detailed clinical characterization and multivariable analyses, as described subsequently. For contextual reference, serum pro-ADM levels were also available for a group of individuals without inflammatory rheumatic diseases, evaluated in the rheumatology outpatient setting for noninflammatory conditions (eg, osteoporosis) or as accompanying relatives. These subjects were not included as a formal control group and were not used for inferential comparisons but served as a frame of reference for the interpretation of pro-ADM values. Serum pro-ADM levels were quantified with a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) technique after a 1:2 dilution, adhering to the manufacturer's guidelines. All assays were conducted in the IOR central laboratory. Owing to the restricted availability of ELISA kits, the follow-up assessment of pro-ADM at six months (T6) was performed exclusively in a subset of consecutive patients with RA.

Ethical approval. The research was conducted in accordance with the Declaration of Helsinki and its latest amendments.[16] The study was approved by the Area Vasta Emilia Centro Ethics Committee (CE AVEC: EM9/2025_206/2023/Sper/IOR_EM1; date of approval: 27/01/2025). All participants provided written informed consent at the time of enrollment.

Statistical analysis. Because of the nonnormal distribution of pro-ADM values, this variable was summarized using the median and interquartile range (IQR), and nonparametric tests were employed for related analyses. For regression analyses, serum pro-ADM concentrations were log-transformed to approximate normality and improve model fit. The Kruskal–Wallis test was used to assess variations in baseline pro-ADM levels among diagnostic groups, with Bonferroni correction for multiple comparisons. For additional analysis, patients with PsA, axSpA, and uSpA were categorized as SpA and compared to RA using the Mann–Whitney U test.

To account for potential confounding, multivariable linear regression models were additionally constructed including age and sex as covariates in analyses comparing RA and SpA groups. In exploratory adjusted models, clinically relevant comorbidities and concomitant therapies potentially influencing pro-ADM levels were included using composite indicators, specifically a

cardiometabolic or renal comorbidity burden (including hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, or established cardiovascular disease) as well as ongoing glucocorticoid use and DMARD therapy (conventional synthetic DMARD [csDMARD], bDMARD, or tsDMARD). Chronic kidney disease and established cardiovascular disease (defined as a history of myocardial infarction, stroke or transient ischemic attack, or heart failure) were therefore not entered separately as individual covariates, given their low prevalence in the study population.

To evaluate the discriminative ability of baseline serum pro-ADM in distinguishing RA from SpA, receiver operating characteristic (ROC) curve analyses were performed. ROC curves were first generated using baseline pro-ADM alone.[17] Subsequently, a multivariable logistic regression model including log-transformed pro-ADM, age, and sex was fitted, and predicted probabilities from the adjusted model were used to construct an adjusted ROC curve. Discriminative performance was quantified by the area under the curve (AUC) with 95% confidence intervals (CIs) calculated using the DeLong method.[18]

Correlations between serum pro-ADM and clinical or demographic variables were evaluated across the entire study population using Spearman's rank correlation coefficient (Spearman's rho). In the RA subgroup having follow-up data, linear regression was employed to assess whether baseline pro-ADM levels or their variation over six months (Δ-pro-ADM) were associated with clinical improvement, quantified as the change in DAS28-CRP (Δ-DAS28). Given the limited sample size, these analyses were conducted in an exploratory manner, with adjustment restricted to age and sex.

The association between Δ-pro-ADM and EULAR response categories (responders vs nonresponders) was further examined using the Mann–Whitney U test, logistic regression, and ROC curve analysis. The threshold for statistical significance was established at $P < 0.05$. All analyses were performed using R Studio (R Foundation for Statistical Computing).

Data availability. Data are available from the corresponding author upon reasonable request.

RESULTS

Patient characteristics and baseline pro-ADM levels by diagnosis. A total of 163 patients were enrolled: 99 patients with RA and 64 patients with SpA, including 36 patients with

Table 1. Patients' characteristics at the baseline visit*

	RA (n = 99)	PsA (n = 36)	axSpA (n = 22)	uSpA (n = 6)
Age, mean (SD), y	57.8 (17.5)	54.0 (13.7)	43.2 (14.4)	47.2 (11.1)
Newly diagnosed patients, n (%)	50 (51)	15 (42)	12 (55)	5 (83)
Disease duration, mean (SD), mo	75.5 (92.1)	103.4 (90.3)	117.0 (108.2)	87.1 (107.1)
Female, n (%)	69 (70)	15 (42)	6 (27)	2 (33)
BMI, mean (SD)	25.4 (5.8)	26.4 (4.3)	25.6 (5.2)	27 (3)
CRP, mean (SD), mg/dL	1.29 (2.0)	1.91 (4.5)	1.07 (2.2)	3.12 (4.8)
Hypertension, n (%)	17 (17)	8 (22)	1 (5)	1 (17)
Diabetes, n (%)	4 (4)	7 (19)	1 (5)	0
Dyslipidemia, n (%)	7 (7)	7 (19)	1 (5)	0
Established cardiovascular disease, n (%)	0	2 (6)	0	1 (17)
Chronic kidney disease, n (%)	1 (1)	1 (3)	0	0
TJC, mean (SD)[a]	4.2 (5.2)	3.4 (4.2)	1.7 (2)	3.5 (4.8)
SJC, mean (SD)[a]	3.5 (4.5)	2.5 (3.4)	0.7 (1)	2.1 (2)
DAS28-CRP, mean (SD)[b]	3.5 (1.47)	–	–	–
DAPSA, mean (SD)[b]	–	21.3 (13.9)	–	20.3 (5.0)
ASDAS (CRP), mean (SD)[b]	–	–	2.4 (1.1)	–
BASDAI, mean (SD)[b]	–	–	3.7 (1.7)	–
Ongoing therapy with glucocorticoids, n (%)	24 (24)	6 (17)	1 (5)	2 (33)
Ongoing therapy with csDMARD, n (%)	31 (31)	14 (39)	5 (23)	0
Ongoing therapy with bDMARD or tsDMARD, n (%)	29 (29)	10 (28)	7 (32)	1 (17)
RF positivity, n (%)	59 (60)	–	–	–
ACPA positivity, n (%)	60 (61)	–	–	–
HLA-B27 positivity, n (%)	–	–	10 (45)	–
pro-ADM at baseline, median (IQR), pg/mL	51.7 (37.6–60.1)	35.6 (33.5–40.8)	35.0 (34.4–37.6)	33.9 (32.5–35.1)

*ACPA, anticitrullinated peptide antibody; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity Index for Psoriatic Arthritis; DAS28, Disease Activity Score in 28 joints; IQR, interquartile range; pro-ADM, proadrenomedullin; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; SpA, spondyloarthritis; TJC, tender joint count; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; uSpA, undifferentiated spondyloarthritis.
[a]TJC and SJC were calculated on 28 joints for RA and in 44 joints for PsA, uSpA, and axSpA.
[b]DAS28-CRP was calculated only for RA, ASDAS (CRP) was calculated only for axSpA, DAPSA was calculated for PsA and uSpA, and BASDAI was calculated only for axSpA.

PsA, 22 patients with axSpA, and 6 patients with uSpA. Patients with RA were older than patients with SpA and predominantly female (Table 1). Patients with RA had the highest median serum pro-ADM levels, with a broader distribution compared to the other groups (51.7 pg/mL; IQR 37.6–60.1). In contrast, pro-ADM levels were significantly lower and more homogeneous among patients with PsA (median 35.6 pg/mL; IQR 33.5–40.8), axSpA (median 35.0 pg/mL; IQR 34.4–37.6), and uSpA (median 33.9 pg/mL; IQR 32.5–35.1). A Kruskal–Wallis test showed a significant overall difference across diagnostic groups ($P < 0.001$). Post hoc Bonferroni correction confirmed that patients with RA had significantly higher pro-ADM levels than each of the SpA subtypes (all $P < 0.001$), whereas no significant differences were observed among the SpA groups themselves. When SpA was considered as a unified category encompassing PsA, axSpA, and uSpA, baseline pro-ADM levels remained significantly higher in patients with RA compared to patients with SpA (median 51.7 pg/mL [IQR 37.6–60.1] vs 35.1 pg/mL [IQR 33.5–40.4], respectively; $P < 0.001$; Figure 1). As illustrated in Figure 1, pro-ADM values showed a wider dispersion in RA compared with SpA, with all extreme values observed in the RA group.

For contextual interpretation, serum pro-ADM levels were also available in a noninflammatory reference population evaluated in the rheumatology outpatient setting (n = 41; mean age 59.8 years; 68% female), with a median pro-ADM concentration of 35.9 pg/mL (IQR 34.2–43.2), overlapping with values observed in SpA subtypes.

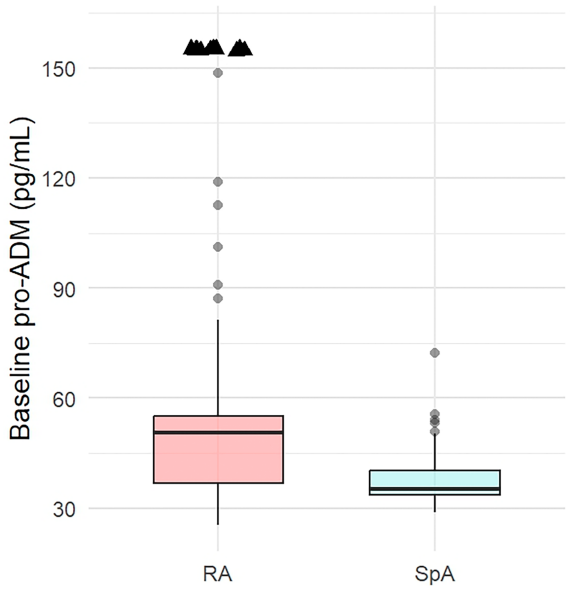

Figure 1. Box-and-whisker plot comparing baseline serum pro-ADM levels between patients with RA and SpA. Pro-ADM levels were significantly higher in RA compared to SpA ($P < 0.001$, Mann–Whitney U test). For clarity, extreme outliers above 150 pg/mL (n = 9, all in the RA group) are shown as black triangles placed at the plot's upper bound (y = 150). Other outliers are shown individually as points. pro-ADM, proadrenomedullin; RA, rheumatoid arthritis; SpA, spondyloarthritis.

Within the RA cohort, baseline pro-ADM levels did not significantly differ across serologic subgroups defined by RF and ACPA status (Kruskal–Wallis $P = 0.212$). Median pro-ADM concentrations were 52.2 pg/mL (IQR 40.0–76.7) in ACPA+/RF+ patients (n = 45), 53.2 pg/mL (IQR 37.8–65.4) in ACPA+/RF– patients (n = 15), 52.2 pg/mL (IQR 34.8–58.5) in ACPA–/RF+ patients (n = 14), and 40.8 pg/mL (IQR 35.1–54.2) in patients with seronegative RA (ACPA–/RF–, n = 25).

In multivariable linear regression models with log-transformed pro-ADM as the dependent variable, RA remained independently associated with higher pro-ADM levels compared with SpA after adjustment for cardiometabolic and renal comorbidity burden (β = 0.53, 95% CI 0.31–0.76; $P < 0.001$).

Further adjustment for ongoing DMARD therapy and glucocorticoid use did not materially change the association between RA and pro-ADM, whereas neither comorbidities nor treatments were independently associated with pro-ADM levels.

Discriminative analysis showed that baseline serum pro-ADM had good ability to distinguish RA from SpA, with an AUC of 0.79 (95% CI 0.72–0.86). When a multivariable logistic regression model including log-transformed pro-ADM, age, and sex was applied, discriminative performance further improved, yielding an adjusted AUC of 0.82 (95% CI 0.73–0.91).

Correlation between pro-ADM and clinical variables. When analyzing all 163 patients collectively, no significant correlations were identified between pro-ADM and CRP ($\rho = -0.029$, $P = 0.780$), ESR ($\rho = 0.019$, $P = 0.862$), age ($\rho = 0.123$, $P = 0.226$), disease duration ($\rho = -0.094$, $P = 0.357$), or body mass index (BMI; $\rho = -0.207$, $P = 0.062$). Furthermore, pro-ADM levels showed no correlation with composite disease activity indices such as DAS28-CRP in RA ($\rho = 0.205$, $P = 0.187$) or Disease Activity Index for Psoriatic Arthritis ($\rho = -0.198$, $P = 0.285$).

Longitudinal analysis in RA. A group of 31 patients with RA had available follow-up pro-ADM levels determined at T6. Median pro-ADM concentrations significantly decreased from 52.5 pg/mL (IQR 38.7–115.8) at baseline to 30.1 pg/mL (IQR 26.2–48.7) at follow-up ($P = 0.023$). Among the 31 patients with RA with available follow-up, 14 patients started a csDMARD, 9 patients initiated a bDMARD or tsDMARD, and 8 patients switched or swapped between bDMARDs or tsDMARDs. Median changes in pro-ADM levels were –11.4 pg/mL (IQR –100.8 to 3.7) in patients initiating a csDMARD, –5.7 pg/mL (IQR –33.5 to 49.8) in those starting a bDMARD or tsDMARD, and –25.0 pg/mL (IQR –35.5 to –8.3) in patients switching between bDMARDs or tsDMARDs. Comparison using the Kruskal–Wallis test did not reveal statistically significant differences across treatment categories ($P = 0.470$).

Patients were categorized based on EULAR response criteria: 12 (39%) patients had no response, 7 (23%) patients demonstrated a moderate response, and 12 (39%) patients had a good response. No significant difference in Δ-pro-ADM was observed between moderate or good responders (–13.9; IQR –66.9 to –6.57) and nonresponders (–11.6; IQR –30.2 to 12.9) ($P = 0.346$).

Linear regression analysis using Δ-DAS28 as the dependent variable and Δ-pro-ADM as the predictor indicated no significant correlation (β = 0.00039, $P = 0.400$). Logistic regression employing EULAR response as a binary outcome (responder vs nonresponder), adjusted for baseline pro-ADM, further substantiated the lack of predictive ability of Δ-pro-ADM (odds ratio [OR] = 0.993, $P = 0.155$) and baseline pro-ADM (OR = 1.004, $P = 0.184$). As shown in Figure 2, ROC analysis yielded an AUC of 0.61, demonstrating only limited discriminative performance of pro-ADM for predicting EULAR response at follow-up.

DISCUSSION

Motivated by the need for more specific and biologically informative biomarkers, in this study we investigated the role of pro-ADM in inflammatory arthritides. Our data suggest that pro-ADM levels may differ between inflammatory arthritis subtypes, particularly showing higher values in RA, although its role as a disease-specific biomarker requires further confirmation. We detected substantially higher baseline serum pro-ADM levels in RA compared to PsA, axSpA, and uSpA, which presented lower and more homogenous levels. Importantly, this difference remained evident after adjustment for age, sex, and major cardiometabolic comorbidities and concomitant therapies, supporting an association between RA and higher pro-ADM levels that appears largely independent of these potential confounders. The selective increase of pro-ADM in RA may be related to disease-specific inflammatory pathways, which differ substantially from those characterizing SpA.[2,19] Experimental studies in RA synovial fibroblasts have demonstrated that ADM is biologically active within the synovial compartment, where it inhibits IL-1β–induced cell proliferation and downregulates the production of matrix metalloproteinases, COX-2, and prostaglandin E2, supporting a regulatory role of the ADM pathway in synovial inflammation and tissue damage.[20] Pro-ADM expression can be induced by proinflammatory cytokines such as TNFα and IL-1β, both central to RA pathogenesis, and may be associated with vascular stress or the dysregulation of adaptive immunity.[21,22] In this scenario, increased pro-ADM could reflect underlying endothelial activation or tissue hypoxia more distinctly in RA than in other types of inflammatory arthritis. However, because no direct markers of endothelial activation or tissue hypoxia were assessed in the present study, no mechanistic inferences can be drawn from the present data. These interpretations should be regarded as speculative and hypothesis-generating.

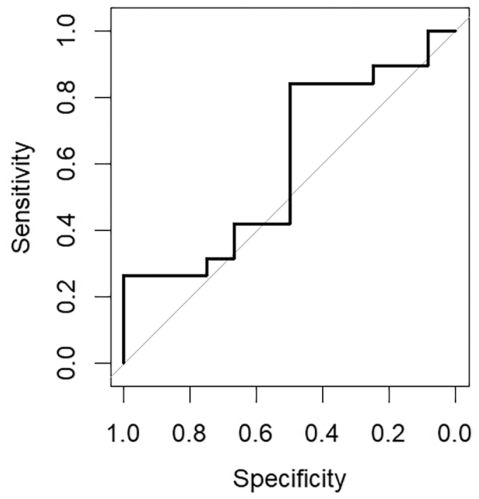

Figure 2. Receiver operating characteristic curve for baseline delta proadrenomedullin as a predictor of EULAR response at follow-up in patients with rheumatoid arthritis. The area under the curve was 0.61, indicating limited discriminative ability. The model was based on 31 patients with available follow-up data.

Previous studies have reported increased circulating levels of ADM-related peptides in RA.[23–25] However, available evidence is limited to RA cohorts and does not include direct comparisons with SpA subtypes. Moreover, previous investigations predominantly assessed different fragments of the ADM precursor, such as pro-ADM N-terminal peptide or mature ADM, using heterogeneous analytical methods and units of measurement.[23–25] These methodologic differences preclude direct numerical comparison with serum pro-ADM concentrations. Our study extends existing evidence by providing a direct comparative evaluation of pro-ADM across RA and SpA subtypes within the same analytical framework. In addition, the availability of a reference group without inflammatory rheumatic disease in our cohort provides contextual information on the distribution of pro-ADM levels, although this group was not intended for formal hypothesis testing.

Pro-ADM, despite its increased levels in RA, did not exhibit a correlation with traditional systemic inflammatory indicators such as CRP or ESR, nor with clinical factors including age, disease duration, or BMI. This pattern differs from previous findings in established RA cohorts, where pro-ADM has been shown to increase along with systemic inflammation.[25] Conversely, our findings are more consistent with observations in early RA populations, in which circulating ADM-related markers were increased compared with controls but showed limited or no association with conventional systemic inflammatory indices such as CRP or disease activity scores.[24] In that context, ADM levels correlated more closely with markers of synovial involvement, including IL-6 and matrix metalloprotease 3, rather than with global inflammatory measures.[24] However, direct comparisons remain limited by

differences in study design, disease stage, and biomarker assessment. Pro-ADM levels did not predict clinical response as defined by EULAR criteria or significantly correlate with changes in disease activity in the longitudinal part of our study. Respondents' pro-ADM levels revealed a small numerical decline, but this was not statistically significant and had weak discriminatory capacity. Consistently, ROC analyses demonstrated poor prognostic discrimination for treatment response. These results suggest that pro-ADM may have limited utility as an indicator of clinical improvement or treatment response over time. This observation may have several explanations. Rather than representing transient variations in disease activity, pro-ADM could represent a relatively stable systemic inflammatory or vascular-related state. This interpretation is consistent with experimental evidence showing that the ADM pathway is regulated by cytokines involved in chronic inflammatory signaling.[26] Nonetheless, the present study does not allow conclusions regarding vascular remodeling, hypoxia, or tissue-level expression of ADM, and the lack of longitudinal association should be interpreted with caution.

Even though we were the first to compare ADM levels across different types of inflammatory arthritides, it is important to recognize the limitations of this study. The sample size was limited, especially within the longitudinal RA cohort and individual SpA subgroups, which could have decreased the ability to identify subgroup-specific trends or minor effects. Furthermore, due to logistical constraints we had to restrict the longitudinal analysis to patients with RA, hindering the capacity to assess dynamic changes in pro-ADM across the SpA subtypes. Although exploratory multivariable models were applied, residual confounding cannot be excluded, particularly for factors not captured or insufficiently powered in the present data set. Finally, we are unable to properly contextualize the observed differences in pro-ADM levels or demonstrate a clear pathophysiologic relationship due to the lack of mechanistic indicators. These limitations highlight the necessity of more extensive, mechanistically focused research with more comparator groups and consistent procedures.

In summary, our results may indicate that pro-ADM may help distinguish RA from SpA but does not correlate with systemic inflammation or disease activity, nor does it predict treatment response over time. Pro-ADM may have diagnostic relevance, especially in cases of seronegative RA or unclear clinical presentations, even though it has limited utility for monitoring purposes. The biologic role of pro-ADM and its potential as a disease-specific biomarker in inflammatory arthritis require more research with larger cohorts, mechanistic insights, and broader control groups.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Ciaffi confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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