JOURNAL LA LIFESCI
VOL. 07, ISSUE 03 (228-240), 2026
DOI: 10.37899/journallalifesci.v7i3.3301

Diagnostic Value of Serum Semaphorin-3A and Cartilage Oligomeric Matrix Protein in Rheumatoid Arthritis

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Article Info

Article history:
Received 11 April 2026
Received in revised from 15 May 2026
Accepted 4 July 2026

Keywords:
Rheumatoid arthritis
Semaphorin-3A
COMP
Biomarkers
ROC analysis

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder characterized by persistent synovial inflammation and progressive joint damage. The identification of reliable circulating markers could potentially improve early detection of the disease. To evaluate the diagnostic potential of circulating levels of Semaphorin-3A (SEMA3A) and Cartilage Oligomeric Matrix Protein (COMP) and their combined diagnostic potential in patients with Rheumatoid Arthritis. Comparative case-control study design was conducted in Division of Rheumatology, in Al-Najaf Teaching Hospital in Al-Najaf city of Iraq, for the period between July 2025 and January 2026, included 90 participants 45 of them patients with Rheumatoid Arthritis according to ACR/EULAR criteria and 45 apparently healthy controls. Blood samples were collected from all participants, and levels of circulating SEMA3A and COMP were estimated by Enzyme-Linked Immunosorbent Assay (ELISA). The serum concentration of both COMP and SEMA3A was significantly reduced ($P < 0.001$) in RA patients compared with controls (7.82 ± 2.31 pg/mL and 5.41 ± 1.62 ng/mL) vs. (11.96 ± 3.04 pg/mL and 8.73 ± 2.07 ng/mL). ROC analysis showed a good degree of discrimination for SEMA3A (84%, 80%, AUC = 0.88) and COMP (80%, 76%, AUC = 0.85) in RA patients. Combination of both biomarkers resulted in a better discrimination power (88.9%, 84.4%, AUC = 0.92). Serum SEMA3A and COMP show a good degree of discrimination for RA, and the combination of both biomarkers shows a better discrimination power for the diagnosis of RA.

Introduction

Rheumatoid arthritis is a chronic systemic autoimmune disorder characterized by the presence of chronic inflammation of the synovium, cartilage destruction, and irreparable joint damage. (Hasan et al., 2022; Jahid et al., 2023; Jang et al., 2022). RA is one of the most prevalent types of inflammatory arthritis worldwide and poses a great health risk since it significantly impacts patient life quality and increases the cost of healthcare provision (Finckh et al., 2022; Fazal et al., 2018; Weng et al., 2024). The epidemiology of rheumatoid arthritis demonstrates that the condition afflicts from 0.5% to 1% of the global population, predominantly female and middle-aged individuals (Di Matteo et al., 2023). Despite significant advances in treatment over the past few decades, the progressive nature of the disorder and its ability to cause irreversible joint damage have made it one of the most important causes of chronic musculoskeletal disability (Ali et al., 2023).

The pathology of rheumatoid arthritis arises from an interaction of several variables. They include the role played by genetics, the environment, and immunological dysregulation. It results in constant stimulation of the innate and adaptive immune systems (Alivernini et al., 2022; Saini et al., 2022; Merlo Pich et al., 2024). The process culminates in infiltration of T

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

lymphocytes, B lymphocytes, macrophages, and plasma cells into the joint synovium. The pro-inflammatory conditions in the synovium cause secretion of pro-inflammatory cytokines including TNF-alpha, IL-6, and IL-1. This contributes to synovial tissue proliferation, inflammation of synovial blood vessels, activation of osteoclasts, and degradation of cartilage components (Jonsson, 2024). All these processes culminate in joint destruction via the cytokine-mediated processes that damage cartilage matrix and bones (Deka, 2025; Hu et al., 2025; Umar et al., 2026).

In recent times, there has been an increase in the importance of biomarkers in terms of diagnosing and treating rheumatoid arthritis (Riaz et al., 2025; Biomarkers could play a crucial part in early diagnosis, assessing the degree of inflammation and studying the structural damage and progression of the disease (Sahin et al., 2025). Some of the most frequently used serological biomarkers for the treatment of rheumatoid arthritis include RF and anti-CCP antibodies. But they cannot fully cover the diversity of the disease and might not be found among people suffering from seronegative rheumatoid arthritis. That is why finding new biomarkers has become an important task (Bhamidipati & Wei, 2022; Eslami et al., 2025; Ravindran et al., 2025).

As for novel mediators in immunology, Semaphorin-3A (SEMA3A) has attracted researchers' interest because of its regulatory effect on immune responses (Lotfi *et al.*, 2025). Initially described as an axonal guide protein, SEMA3A was later found to be an important regulator of immune cells' functions including the modulation of T-cell activation, B-cell responses, the action of dendritic cells, and regulation of immune tolerance (Lotfi et al., 2025). There has been increasing evidence showing that SEMA3A plays an important role in autoimmune disorders due to its involvement in inflammatory pathways (Qamar et al., 2025). In relation to rheumatoid arthritis, changes in SEMA3A expression have been linked to inflammation, immune abnormalities, and metabolism in CD4+ T lymphocytes (Rosik et al., 2024; Yang et al., 2026; Xiao et al., 2025).

However, COMP is a structural biomarker strongly connected with the functioning of cartilage, cartilage turnover, and joint health (Smith and Melrose, 2025). COMP is an extracellular matrix glycoprotein, which is not made up of collagen. COMP is secreted into the blood when the turnover of cartilage occurs. Increased or abnormal levels of COMP have been associated with cartilage changes and tissue degradation within joints in several rheumatic conditions. Studies conducted in individuals suffering from rheumatoid arthritis have revealed that the serum concentration of COMP is indicative of structural joint damage in these individuals (Hussein et al., 2018).

In particular, SEMA3A and COMP are two complementary aspects of the biological dimension of rheumatoid arthritis (Yao et al., 2026; Galligos et al., 2026; Martínez-Ramos et al., 2024) On one hand, SEMA3A is an indicator of immunological regulation and inflammation (Lotfi et al., 2025). On the other hand, COMP shows cartilage degradation (Smith and Melrose, 2025). The simultaneous use of these biomarkers can lead to a deeper insight into disease processes through the combination of the activity of immunological processes and structural damage to the tissues. It should be noted that although these biomarkers have been studied separately before, little attention has been paid to the diagnostic significance of combining them in the case of rheumatoid arthritis. Thus, there is a necessity to conduct further research regarding whether such an approach would allow enhancing the accuracy of diagnosis.

Therefore, the current study aimed to estimate the diagnostic value of SEMA3A and COMP in serum of patients with RA and to determine whether their combined assessment could enhance diagnostic accuracy.

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Methods

Study Design and Setting

This is a comparative case control study carried out at the Division of Rheumatology, Al-Najaf Teaching Hospital, Najaf, Iraq between July 2025 to January 2026. The aim of this study to determine the role of Semaphorin-3A (SEMA3A) and Cartilage Oligomeric Matrix Protein (COMP) concentrations in the blood of patients with rheumatoid arthritis compared to healthy subjects.

Study Population

The study included 90 participants, the first group is composed of 45 patients diagnosed with rheumatoid arthritis by specialist rheumatologists according to the American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) classification criteria. The second group consisted of 45 apparently healthy individuals with no known history of autoimmune or inflammatory diseases.

Participants in both groups were matched as closely as possible in terms of age and sex in order to minimize potential confounding effects.

Inclusion Criteria

Participants were considered eligible to be included in the study if they met several criteria. The participants had to be adult subjects aged 18 years or older, clinically diagnosed with rheumatoid arthritis, and confirmed to have positive Anti-Cyclic Citrullinated Peptide Antibody (Anti-CCP) results. In addition, participants were required to express their willingness to take part in the study.

Exclusion Criteria

Participants were excluded from the study if they had any conditions that could potentially influence the study outcomes. These conditions included diabetes mellitus, ischemic heart disease, chronic kidney disease, pregnancy, other autoimmune diseases, and any acute or chronic inflammatory diseases other than rheumatoid arthritis.

Collection of Data

The demographic and clinical information was collected via a questionnaire prepared by the investigator. Variables recorded during data collection include age, sex, Body Mass Index (BMI), and selected clinical characteristics.

Body mass index was calculated using the following formula:

BMI= Weight (Kg)/Height (m^2)

Collection and Processing of Samples

Blood samples were drawn from all study participants under aseptic conditions via sterile disposable syringes. Collected blood samples were placed in both gel and EDTA tubes. The separation of serum was done through centrifugation of gel tubes at a speed of 2000–3000 rpm for 10–20 minutes. The separated serum was then divided into aliquots of Eppendorf tubes and stored at −20°C until analysis in the laboratory.

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Laboratory Analysis

Levels of SEMA3A and COMP in serum samples were determined via enzyme-linked immunosorbent assay (ELISA). The analysis was carried out by using commercial ELISA kits obtained from BT LAB.

Ethical Considerations

Ethical approval for the present study was obtained from the Scientific Committee of the College of Health and Medical Techniques/Kufa, as well as the administration of Al- Najaf Teaching Hospital. All participants were informed about the objectives and procedures of the study prior to participation, and written informed consent was obtained before sample collection. Participants' information was handled with strict confidentiality and used solely for research purposes.

Statistical Analysis

Data analysis were done using Statistical Package for the Social Sciences statistical software package version 27 (SPSS 27). Continuous variables were described by mean± standard deviation, whereas categorical variables were described by frequency and percentage.

For comparison of two groups, the independent samples t-test was employed, while Chi-square test was performed for categorical variables. Pearson correlation coefficients were calculated to determine the strength and direction of the correlation between the variables under study.

The ROC curve analysis was done to evaluate the performance of the selected biomarkers in diagnosing the outcome of interest. Maximum Youden index was employed to determine the optimal cut-off points. Binary logistic regression was employed to assess the combination diagnostic ability of the biomarkers selected.

All tests of significance in the current study were two-tailed tests. P-value <0.05 was considered statistically significant.

Results and Discussion

The demographic details of the study subjects are shown in Table (1). Ninety people participated in the study, of whom half belonged to each group, 45 rheumatoid arthritis patients and 45 apparently healthy controls.

The average age of the rheumatoid arthritis patients was 44.8 ± 11.6 years, while that of the control group was 43.1 ± 10.9 years. Statistically, no significant difference existed in terms of age between the two groups (P = 0.48).

As far as the distribution of gender is concerned, both study groups had a higher number of females. Amongst the rheumatoid arthritis patients, 33 subjects (73.3%) were females and 12 (26.7%) males, while amongst the control group 31 subjects (68.9%) were females and 14 (31.1%) males. No significant difference existed between the two groups in terms of gender distribution (P = 0.64).

Table 1. Baseline Demographic Characteristics of the Study Participants

Variable	RA patients (n=45)	Controls (n=45)	P-value
Age (years), mean ± SD	44.8 ± 11.6	43.1 ± 10.9	0.48
Sex, n (%)			0.64
Female	33 (73.3%)	31 (68.9%)	
Male	12 (26.7%)	14 (31.1%)	

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Table 2 present the comparison of anthropometrical parameters between patients having rheumatoid arthritis and control subjects. The average body weight of the patients having rheumatoid arthritis is 72.6 ± 11.2 kg, while the average body weight of the control subjects is 74.3 ± 10.8 kg. Using independent samples t-test there was found no statistically significant difference between the studied populations (P = 0.46).

As for height, the average height of the patients was 165.2 ± 7.4 cm, while the average height of the control subjects was 166.8 ± 6.9 cm. There was no statistically significant difference between the heights of the studied groups of individuals (P = 0.31).

With respect to body mass index (BMI), this parameter was also similar in both groups; the average BMI was 26.7 ± 3.8 kg/m² in the first group of individuals, while it was 26.3 ± 3.5 kg/m² in the second one. Again there was no statistically significant difference between the groups (P = 0.59).

Table 2. Comparison of Anthropometric Characteristics Between Rheumatoid Arthritis Patients and Controls

Variable	RA patients (n=45)	Controls (n=45)	P-value
Weight (kg), mean ± SD	72.6 ± 11.2	74.3 ± 10.8	0.46
Height (cm), mean ± SD	165.2 ± 7.4	166.8 ± 6.9	0.31
BMI (kg/m²), mean ± SD	26.7 ± 3.8	26.3 ± 3.5	0.59

Table 3, shows the results of the distribution of body mass index (BMI) category among the study sample (rheumatoid arthritis patients) and the control sample.
For the case of rheumatoid arthritis patients, the number of patients falling under normal BMI category was 17 (37.8%), under overweight category was 19 (42.2%), and under obese category was 9 (20.0%). In the control sample, 19 (42.2%) patients fell under normal BMI category, 18 (40.0%) patients were overweight, and 8 (17.8%) patients were considered to be obese.

No statistically significant difference was observed between the distribution of BMI category between the study and control groups (P = 0.71).

Table 3. Distribution of Body Mass Index Categories Among Study Groups

BMI Category	RA patients (n=45)	Controls (n=45)	P-value
Normal (18.5–24.9)	17 (37.8%)	19 (42.2%)	0.71
Overweight (25–29.9)	19 (42.2%)	18 (40.0%)	
Obesity (≥30)	9 (20.0%)	8 (17.8%)	

Table 4 present the comparison of serum concentrations of Cartilage Oligomeric Matrix Protein (COMP) and Semaphorin-3A (SEMA3A) among patients with rheumatoid arthritis compared to the control group. The serum concentration of Cartilage Oligomeric Matrix Protein (COMP) was significantly lower in the patients with rheumatoid arthritis (7.82 ± 2.31 pg/mL) than the control group (11.96 ± 3.04 pg/mL). Using an independent samples t-test, statistical analysis confirmed the significant difference between the two groups (P < 0.001). On the other hand, the serum concentration of SEMA3A in the rheumatoid arthritis patients group was significantly lower (5.41 ± 1.62 ng/mL) than the controls (8.73 ± 2.07 ng/mL). The difference in the mean values of the two groups was –3.32 ng/mL. There was a significant difference between the two groups (P < 0.001).

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Table 4. Comparison of Serum COMP and SEMA3A Levels Between Rheumatoid Arthritis Patients and Controls

Biomarker	RA patients (n=45) Mean ± SD	Controls (n=45) Mean ± SD	P-value
COMP (pg/mL)	7.82 ± 2.31	11.96 ± 3.04	<0.001
SEMA3A(ng/mL)	5.41 ± 1.62	8.73 ± 2.07	<0.001

Table 5 shows the results of receiver operating characteristic (ROC) curve analysis of serum SEMA3A and COMP for diagnosing rheumatoid arthritis.
It was shown that ROC analysis for SEMA3A indicated an area under the curve (AUC) of 0.88 with a 95% confidence interval (CI) of 0.81–0.95. Optimal cut-off value was ≤6.7 ng/mL with sensitivity of 84%, and specificity of 80%, while Youden Index was 0.64 with statistically significant results (P < 0.001).
As regards ROC curve analysis for serum COMP, it was shown that its AUC was 0.85 with 95% CI being of 0.77–0.93. Optimal cut-off value was ≤9.2 pg/mL, and sensitivity and specificity were 80% and 76% respectively. In addition, the obtained Youden Index was 0.56, and result was statistically significant (P < 0.001).

Table 5: Receiver Operating Characteristic (ROC) Analysis of COMP and SEMA3A for Detection of Rheumatoid Arthritis

Biomarker	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	Youden Index	P-value
SEMA3A (ng/mL)	≤6.7	84	80	0.88	0.81–0.95	0.64	<0.001
COMP (pg/mL)	≤9.2	80	76	0.85	0.77–0.93	0.56	<0.001

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the studied biomarkers.
The optimal cut-off values were determined using the maximum Youden Index.
An AUC value >0.80 indicates good diagnostic performance.

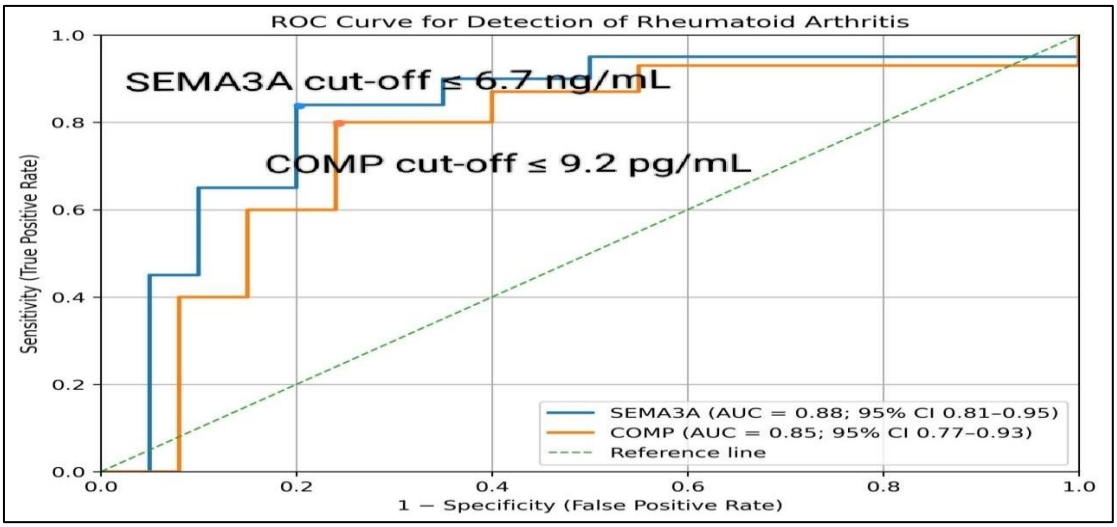

Figure 1 illustrates the receiver operating characteristic (ROC) curves of SEMA3A and COMP for the diagnosis of rheumatoid arthritis.

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Figure 1 illustrating the diagnostic accuracy of serum SEMA3A and COMP in discriminating between rheumatoid arthritis subjects and control individuals. SEMA3A showed somewhat superior diagnostic accuracy (AUC = 0.88; 95% CI 0.81-0.95) to that of COMP (AUC = 0.85; 95% CI 0.77-0.93). Optimal cut-off points of SEMA3A and COMP.

Table (6) presents the classification of the subjects in the study according to the cut-off values of the biomarkers obtained from the ROC curve.

According to the cut-off point ≤ 9.2 pg/mL of COMP, 36 rheumatoid arthritis subjects (80.0%) were classified positive while 9 rheumatoid arthritis subjects (20.0%) were classified negative. For the control group, 11 subjects (24.4%) were classified positive while 34 subjects (75.6%) were classified negative. There was a statistical significant difference between the two groups ($P < 0.001$) according to the Chi-square test.

According to the cut-off point ≤ 6.7 ng/mL of SEMA3A, 38 rheumatoid arthritis subjects (84.4%) were classified positive while 7 rheumatoid arthritis subjects (15.6%) were classified negative. For the control group, 9 subjects (20.0%) were classified positive while 36 subjects (80.0%) were classified negative. There was a highly statistical significant difference between the two groups ($P < 0.001$) according to the Chi-square test.

Table 6. Diagnostic Classification of Study Participants Based on ROC-Derived Cut-off Values

Biomarker	Test result	RA patients n (%)	Controls n (%)	P-value
COMP (≤9.2 pg/mL)	Positive test	36 (80.0%)	11 (24.4%)	<0.001
	Negative test	9 (20.0%)	34 (75.6%)	
SEMA3A (≤6.7 ng/mL)	Positive test	38 (84.4%)	9 (20.0%)	<0.001
	Negative test	7 (15.6%)	36 (80.0%)	

Cut-off values were obtained from ROC curve analysis. Categorical comparisons were performed using the Chi-square test. Percentages represent proportions within each study group.

The results in Table (7) shows the diagnostic accuracy measures of biomarkers, serum (COMP and SEMA3A), in the detection of rheumatoid arthritis according to their cut-off levels obtained by ROC.

For COMP, with the cut-off level of ≤9.2 pg/mL, the PPV was found to be 76.6%, NPV at 79.1%, and diagnostic accuracy at 77.8%. The COMP test diagnosis is associated with the condition significantly ($P<0.001$).

For SEMA3A, with the cut-off level of ≤6.7 ng/mL, the PPV was found to be 80.9%, NPV at 83.7%, and diagnostic accuracy at 82.2%. SEMA3A diagnosis is also significant statistically ($P<0.001$).

Table 7. Diagnostic Accuracy Indices of Serum COMP and SEMA3A in the Detection of Rheumatoid Arthritis

Biomarker	Cut-off value	PPV (%)	NPV (%)	Accuracy (%)	P-value
COMP (pg/mL)	≤9.2	76.6	79.1	77.8	<0.001
SEMA3A (ng/mL)	≤6.7	80.9	83.7	82.2	<0.001

PPV = Positive Predictive Value

NPV = Negative Predictive Value

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

Accuracy was calculated as the proportion of correctly classified cases among the total study population.

Cut-off values were determined according to ROC curve analysis

The results in Table (8), shows that the diagnostic performance of each individual biomarker (COMP and SEMA3A) and the combination of both biomarkers (COMP + SEMA3A) for detecting rheumatoid arthritis through the ROC analysis has been presented.

According to the ROC analysis results, it has been observed that for COMP, the AUC value obtained is 0.85 with 95% CI being 0.77 – 0.93 with a sensitivity of 80.0% and specificity of 76.0%. Whereas for SEMA3A, the ROC analysis result shows that the AUC value obtained is 0.88 with 95% CI being 0.81 – 0.95 with sensitivity of 84.0% and specificity of 80.0%.

For the model where both biomarkers were combined (COMP + SEMA3A), the ROC analysis shows that the AUC value obtained is 0.92 with 95% CI being 0.86 - 0.97 with sensitivity of 88.9% and specificity of 84.4%.

Table 8. Receiver Operating Characteristic (ROC) Analysis of Single and Combined Biomarker Models for Detection of Rheumatoid Arthritis (n = 90)

Biomarker / Model	AUC	95% CI	Sensitivity (%)	Specificity (%)	P-value
COMP	0.85	0.77 – 0.93	80.0	76.0	<0.001
SEMA3A	0.88	0.81 – 0.95	84.0	80.0	<0.001
Combined COMP + SEMA3A	0.92	0.86 – 0.97	88.9	84.4	<0.001

ROC curve analysis was performed to evaluate the diagnostic performance of the studied biomarkers.

The combined biomarker model was generated using binary logistic regression analysis.

AUC = Area Under the Curve
CI = Confidence Interval

This current study aimed to identify the diagnostic utility of two different biological biomarkers, SEMA3A and COMP, in RA patients. The main results showed that the serum levels of both biomarkers were significantly lower in RA patients than in the control group. In addition, the ROC curve analysis confirmed that the diagnostic efficiency of both biomarkers was relatively high with AUC equaling 0.88 in SEMA3A and 0.85 in COMP, but when used together, their diagnostic ability was the highest (AUC = 0.92). Thus, the use of biomarkers with diverse pathology pathways could improve the diagnosis of RA and prove the idea of the multi-biomarker approach in autoimmunity.

The demographic and anthropometric data of the baseline assessment did not show any statistical difference between the RA patients and the control group in terms of their age, gender composition, or body mass index. The similarity of the research groups is essential from the methodological perspective since it decreases the impact of the possible confounding factors that might have an effect on the biomarker levels in circulation. In the case of biomarker research where the cases and controls are compared, matching participants for demographic factors is a common practice (Smolen *et al.*, 2018).

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

The reduction in the level of SEMA3A in the blood sera of RA patients may be rationalized with regard to the immunological imbalance typical of this condition. This autoimmune disorder occurs as a result of complex interactions between the innate and adaptive immune responses leading to the development of inflammation in the synovial tissues, activation of T-cells, and damage to joints. SEMA3A is protein belongs to the immunomodulators known to regulate T-cells activity, facilitate immune tolerance, and inhibit excessive inflammatory reactions. As indicated by the experimental findings, SEMA3A might be involved in the suppression of T-cell proliferation and immune cell migration processes, thereby ensuring the maintenance of immune balance (Iragavarapu-Charyulu *et al.*, 2020). Thus, a lower level of SEMA3A in RA patients can be associated with a lack of a physiologic immunomodulator responsible for restraining inflammation within the synovium.

The results obtained in the present study compatible with one research showing that low levels of SEMA3A in autoimmune diseases such as rheumatoid arthritis. According to Darwish *et al.*, (2020), the SEMA3A concentration was significantly lower in RA subjects compared to controls, and an AUC of around 0.85 was noted. This observation has been made in other studies focused on the role of semaphorins in inflammatory/autoimmune disease processes, implying that reduced SEMA3A might be involved in continuous immune activation and inflammation of the joint (Lotfi *et al.*, 2025). Hence, the current findings are in agreement with existing data on the regulation of autoimmune disease pathogenesis by SEMA3A.

The interpretation of the COMP results needs further elucidation. COMP is an extracellular matrix protein that does not contain collagen and is primarily synthesized in cartilage. It plays an important role in the formation of collagen fibers and the stability of cartilage. Inflammatory joint disorders are accompanied by cartilage degeneration and changes in the composition of the extracellular matrix. As a result, the levels of fragments of COMP in the blood increase. Multiple previous studies have reported elevated levels of COMP in RA patients. The authors argued that elevated levels of COMP indicate ongoing cartilage destruction (Idriss *et al.*, 2020). Nevertheless, the present investigation found significantly lower levels of COMP in RA patients than those in healthy subjects. Several reasons can explain this inconsistency. First, it may relate to the difference between the stages of the disease. Second, the samples were taken after receiving certain drugs. Moreover, the number of observations could affect the results. It is likely that low levels of COMP are due to changes in cartilage metabolism and reduced production of full-length COMP (Lambova *et al.*, 2024).

Analysis of the ROC curve for the studied biomarkers also confirms their diagnostic significance. Both SEMA3A and COMP have an area under the curve higher than 0.80, which usually reflects good discriminative power of biomarkers in their studies. It should be noted that SEMA3A was somewhat more informative in its diagnosis compared to COMP, meaning that markers of immunoregulation might be more sensitive as diagnostic factors in comparison with structural cartilage biomarkers in RA patients. These results confirm modern views on the importance of immunoregulation disturbance as the main cause of RA development and the structural changes in joints as its secondary outcome (Di Matteo *et al.*, 2023).

A notable finding of the present study is that the addition of SEMA3A and COMP lead to better diagnostic outcomes than the individual biomarkers alone. The combination of both biomarkers raised the AUC to 0.92, which shows that there is a good discriminating power between patients and healthy subjects. This demonstrates the benefit of combining two biomarkers from different pathophysiological pathways.Thus, the combination of such biomarkers yields a more accurate understanding of the underlying disease. Indeed, recent literature on rheumatology

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

reveals that a potential way forward in RA diagnostics would be based on a panel of biomarkers that would account for RA biological heterogeneity (Neto *et al.*, 2025).

From a clinical point of view, it can be concluded that SEMA3A and COMP can be regarded as reliable non-invasive biomarkers to detect rheumatoid arthritis. Despite the importance of traditional serologic biomarkers like RF and anti-CCP in diagnosing rheumatoid arthritis, more biomarkers can help increase the sensitivity of diagnosis. Moreover, some biomarkers associated with immune regulation and cartilage metabolism may play roles in monitoring disease progression and prognosis in further clinical studies (Sahin *et al.*, 2025).

There are multiple advantages to the current study. First, the use of the case-control design allows comparing patients and healthy control subjects directly. Second, the patients were diagnosed by the internationally recognized ACR/EULAR criteria. Third, biomarkers were measured by applying ELISA technology, which is common in the field of biomarker research. Lastly, ROC curves and logistic regression models are adopted to examine the diagnostic power of biomarkers.

There are some limitations despite the strengths of the study, including firstly, the small sample size may compromise the external validity of the study. Secondly, only one clinical center participated in the research, and, thus, population bias may play a role here as well. Third, utilized a cross-sectional design and, thus, failed to examine how biomarker levels may change over time. Fourth, disease activity indices such as DAS28 were not used, and, consequently, no correlations could be assessed in this regard.

Therefore, future research in this area should be based on multicenter studies with large and heterogeneous samples that will be used to confirm the effectiveness of SEMA3A and COMP as diagnostic biomarkers. In addition, longitudinal research may also contribute to this area of study since biomarker dynamics may be investigated during disease progression and treatment.

Conclusion

The finding of this study show that the concentration of Semaphorin-3A (SEMA3A) and Cartilage Oligomeric Matrix Protein (COMP) is considerably reduced in the serum of patients with rheumatoid arthritis when compared to healthy subjects, which implies the role of these biomarkers in the pathophysiological processes involved in this disease. The discriminatory power of both markers was proven sufficient in diagnosing rheumatoid arthritis, and SEMA3A had a slightly higher performance than COMP in this process. Importantly, when assessing SEMA3A and COMP together, there was a significant increase in diagnostic efficiency when compared to testing for each marker individually. Therefore, assessing both biomarkers together can be used as an additional, non-invasive diagnostic tool for detecting rheumatoid arthritis.

References

Ali, S., Ali, S. A., Kondrapu, P., Tripathi, N., Kumar, P. B., Prasad, P. D., ... & Saha, A. (2023). A brief review of pathophysiology and management of different types of arthritis. *Eur. Chem. Bull*, *12*(12), 199-230.

Alivernini, S., Firestein, G. S., & McInnes, I. B. (2022). The pathogenesis of rheumatoid arthritis. *Immunity*, *55*(12), 2255-2270.

Alivernini, S., Firestein, G. S., & McInnes, I. B. (2022). The pathogenesis of rheumatoid arthritis. *Immunity*, 55(12), 2255–2270.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

Bhamidipati, K., & Wei, K. (2022). Precision medicine in rheumatoid arthritis. *Best Practice & Research Clinical Rheumatology*, 36(1), 101742.

Darwish, N. F., Hablas, S. A., Baiomy, N. N., & Rageh, E. S. M. H. (2020). Evaluation of serum 14-3-3η protein and Semaphorin-3A levels in rheumatoid arthritis: Diagnostic and prognostic value. *Egyptian Rheumatology and Rehabilitation*, 47, 43.

Deka, D. (2025). Pathogenesis and current treatment strategies in rheumatoid arthritis: a systematic review article. *Annals of African Medicine*, *24*(3), 532-539.

Di Matteo, A., Bathon, J. M., & Emery, P. (2023). Rheumatoid arthritis. *The Lancet*, 402(10416), 2019–2033.

Eslami, M., Naderian, R., Bahar, A., Babaeizad, A., Rezanavaz Gheshlagh, S., Oksenych, V., & Tahmasebi, H. (2025). Microbiota as diagnostic biomarkers: Advancing early cancer detection and personalized therapeutic approaches through microbiome profiling. *Frontiers in Immunology*, *16*, 1559480. https://doi.org/10.3389/fimmu.2025.1559480

Fazal, S. A., Khan, M., Nishi, S. E., Alam, F., Zarin, N., Bari, M. T., & Ashraf, G. M. (2018). A clinical update and global economic burden of rheumatoid arthritis. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *18*(2), 98-109. https://doi.org/10.2174/1871530317666171114122417

Finckh, A., Gilbert, B., Hodkinson, B., Bae, S. C., Thomas, R., Deane, K. D., ... & Lauper, K. (2022). Global epidemiology of rheumatoid arthritis. *Nature Reviews Rheumatology*, *18*(10), 591-602.

Galligos, A., Varberg, J. M., Yueh, W. T., Converse, A., Malloy, S., Aljubran, F., ... & Gerton, J. L. (2026). Multicellular origins of murine ovarian inflammaging. *Communications Biology*. https://doi.org/10.1038/s42003-026-09826-1

Hasan, A. A., Khudhur, H. R., & Hameed, A. K. (2022). Rheumatic autoimmune diseases (focus on RA): prevalence, types, causes and diagnosis. *Karbala Journal of Pharmaceutical Sciences*, *1*(20).

Hu, K., Song, M., Song, T., Jia, X., & Song, Y. (2025). Osteoimmunology in osteoarthritis: unraveling the interplay of immunity, inflammation, and joint degeneration. *Journal of Inflammation Research*, 4121-4142. https://doi.org/10.2147/JIR.S514002

Hussein, D. A., El Bakry, S. A., Morshedy, N. A., Ibrahim, S. E., Sakr, H. M., & Abo-Shady, R. A. (2018). Role of cartilage oligomeric matrix protein (COMP) as a prognostic biomarker in early rheumatoid arthritis. *The Egyptian Rheumatologist*, 40(4), 221–226.

Idriss, N. K., Gamal, R. M., Gaber, M. A., El-Hakeim, E. H., Hammam, N., Ghandour, A. M., Abdelaziz, M. M., & Goma, S. H. (2020). Joint remodeling outcome of serum levels of Dickkopf-1, cartilage oligomeric matrix protein, and C-telopeptide of type II collagen in rheumatoid arthritis. *Central European Journal of Immunology*, 45(1), 73–79.

Iragavarapu-Charyulu, V., Wojcikiewicz, E., & Urdaneta, A. (2020). Semaphorins in angiogenesis and autoimmune diseases: Therapeutic targets. *Frontiers in Immunology*, 11, 346.

Jahid, M., Khan, K. U., & Ahmed, R. S. (2023). Overview of rheumatoid arthritis and scientific understanding of the disease. *Mediterranean journal of rheumatology*, *34*(3), 284-291.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

Jang, S., Kwon, E. J., & Lee, J. J. (2022). Rheumatoid arthritis: pathogenic roles of diverse immune cells. *International journal of molecular sciences*, *23*(2), 905. https://doi.org/10.3390/ijms23020905

Jonsson, A. H. (2024). Synovial tissue insights into heterogeneity of rheumatoid arthritis. *Current Rheumatology Reports*, 26(3), 81–88.

Lambova, S. N., Batsalova, T., Moten, D., & Dzhambazov, B. (2024). Cartilage oligomeric matrix protein in osteoarthritis and obesity: Emerging perspectives. *International Journal of Molecular Sciences*, 25(10), 5263.

Lotfi, R., Rahmani, H., & Nasirifar, A. (2025). Semaphorin-3A in autoimmune rheumatic diseases: immunological and pathological aspects. *Inflammopharmacology*, *33*(8), 4369-4376.

Martínez-Ramos, S., Rafael-Vidal, C., Malvar-Fernández, B., Pérez, N., Mouriño, C., Pérez, S. G., ... & García, S. (2024). Semaphorin3B promotes an anti-inflammatory and pro-resolving phenotype in macrophages from rheumatoid arthritis patients in a MerTK-dependent manner. *Frontiers in Immunology*, *14*, 1268144. https://doi.org/10.3389/fimmu.2023.1268144

Merlo Pich, L. M., Ziogas, A., & Netea, M. G. (2024). Genetic and epigenetic dysregulation of innate immune mechanisms in autoinflammatory diseases. *The FEBS Journal*, *291*(20), 4414-4432. https://doi.org/10.1111/febs.17116

Neto, M., Mendes, B., Albuquerque, F., & da Silva, J. A. P. (2025). Novel biomarkers in rheumatoid arthritis: Implications for diagnosis, prognosis, and personalised treatment. *Best Practice & Research Clinical Rheumatology*, 39(1), 102021.

Qamar, T., Misra, D. P., & Kar, S. (2025). Semaphorins and its receptors: Emerging cellular biomarkers and therapeutic targets in autoimmune and inflammatory disorders. *Life Sciences*, 361, 123281.

Ravindran, S., Ranganathan, S., Kannan, S. K., & Marri, J. (2025). The role of molecular biomarkers in the diagnosis, prognosis, and treatment stratification of oral squamous cell carcinoma: A comprehensive review. *The Journal of Liquid Biopsy*, *7*, 100285.

Riaz, M., Rasool, G., Yousaf, R., Fatima, H., Munir, N., & Ejaz, H. (2025). Anti-Rheumatic potential of biological DMARDS and protagonistic role of bio-markers in early detection and management of rheumatoid arthritis. *Innate Immunity*, *31*, 17534259251324820. https://doi.org/10.1177/17534259251324820

Rosik, J., Kulpa, J., Szczepanik, M., & Pawlik, A. (2024). The role of semaphorins in the pathogenesis of rheumatoid arthritis. *Cells*, 13(7), 618.

Sahin, D., Di Matteo, A., & Emery, P. (2025). Biomarkers in the diagnosis, prognosis and management of rheumatoid arthritis: A comprehensive review. *Annals of Clinical Biochemistry*, *62*(1), 3-21.

Saini, A., Ghoneim, H. E., Lio, C. W. J., Collins, P. L., & Oltz, E. M. (2022). Gene regulatory circuits in innate and adaptive immune cells. *Annual review of immunology*, *40*, 387-411. https://doi.org/10.1146/annurev-immunol-101320-025949

Smith, M. M., & Melrose, J. (2025). COMP is a biomarker of cartilage destruction, extracellular matrix and vascular remodeling and tissue repair. *International Journal of Molecular Sciences*, *26*(18), 9182.

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)

Smolen, J. S., Aletaha, D., Barton, A., Burmester, G. R., Emery, P., Firestein, G. S., Kavanaugh, A., McInnes, I. B., Solomon, D. H., Strand, V., & Yamamoto, K. (2018). Rheumatoid arthritis. *Nature Reviews Disease Primers*, 4, 18001.

Umar, M., Wang, Z., Li, J., Li, Z., Li, G., Tong, L., & Chen, D. (2026). Novel therapeutic strategies for osteoarthritis: from mechanistic insights to precision medicine. *Bone Research*, *14*(1), 64. https://doi.org/10.1038/s41413-026-00540-6

Weng, Q., Chen, Q., Jiang, T., Zhang, Y., Zhang, W., Doherty, M., ... & Zeng, C. (2024). Global burden of early-onset osteoarthritis, 1990–2019: results from the Global Burden of Disease Study 2019. *Annals of the Rheumatic Diseases*, *83*(7), 915-925. https://doi.org/10.1136/ard-2023-225324

Xiao, J., Qin, X., Chen, W., Que, X., Ma, Y., Huang, W., ... & Shan, S. (2025). Immunoinflammation and post-translational modifications in the aging process. *Journal of Translational Medicine*, *23*(1), 910. https://doi.org/10.1186/s12967-025-06892-7

Yang, Y., Zhang, Y., Liu, K., Zhang, H., Zuo, X., & Guo, M. (2026). Lactate and lactylation in immune cell function and autoimmune diseases: mechanisms and therapeutic potential. *Immunology*, *177*(4), 643-661.

Yao, C., Yu, J., Xie, D., Zhang, S., Tao, J., Kong, L., ... & Fang, M. (2026). Source-Specific Extracellular Vesicle Functions and Engineering Strategies for Chronic Pain Management: A Comprehensive Review. *International Journal of Nanomedicine*, 598699. https://doi.org/10.2147/IJN.S598699

ISSN 2721-1304 (Print), ISSN 2721-1207 (online)