EJMHR ISSN 2786-8524
EUROPEAN JOURNAL OF MEDICAL AND HEALTH RESEARCH
OPEN ACCESS
PEER REVIEWED

Anti-Carbamylated Protein Antibodies as Biomarkers in RA, SLE, and Primary Sjögren's Syndrome: Clinical Relevance and Diagnostic Utility

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Abstract

Background: Anti-carbamylated protein antibodies (Anti-CarPA) have been discovered to be useful as biomarkers for diagnosing systemic rheumatic disorders (RDs) and monitoring of disease activity. Nonetheless, they lack complete profiles on their occurrence, their value in the diagnosis, and clinical correlations in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and primary Sjögren syndrome (pSS).

Objective: In this study, the prevalence, diagnostic abilities, and clinical correlates of anti-CarPA in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and primary Sjögren syndrome (pSS) patients were investigated and determined as opposed to healthy controls (HC).

Methods: One hundred and thirty-one cases were employed in this retrospective study (40 with RA, 40 with SLE, 11 patients with pSS, and 40 healthy people were also used, and were matched with age and sex). The current international classification criteria were used in the diagnosis of all the patients (ACR/EULAR in RA and SLICC in SLE). The enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of serum anti-CarPA. The performance of the diagnosis was evaluated through sensitivity and specificity analysis. Connections with clinical and laboratory indicators of the disease activity were established.

Results: There was elevated serum Anti-CarPA concentration in RA (30.3 ± 22.9 ng/mL; $p < 0.001$), SLE (18.1 ± 11.1 ng/mL; $p = 0.005$), and pSS (14.6 ± 5.6 ng/mL; $p = 0.005$) when set alongside healthy control (3.2 ± 0.6 ng/mL). In RA, the Anti-CarPA positivity was correlated significantly with increased DAS28 scores (p = 0.041), rheumatoid factor detection (p = 0.003), and the volume of white blood cells (p = 0.045). The Anti-CarPA positivity was linked with a higher ESR (p = 0.002) and SLEDAI-2K (p = 0.025) in SLE. While in pSS patients, the anti-CarPA levels were also found to be significantly linked to elevated platelet counts (p = 0.001). Anti-CarPA sensitivity were 74.2 and 75.8 % in RA, 72.0 and 88.5 % in SLE, and 71.9 and 75.0 % in pSS, respectively.

Conclusion: Anti-CarPA antibodies are important in the diagnosis as well as in clinical evaluation of RA, SLE, and pSS. It is indicated by their close bonds to disease-related activity parameters and good diagnostic selectivity that they could be used as supporting biomarkers in the early detection of systemic rheumatic illnesses, their administration, and patient stratification.

More Information

How to cite this article: Khaleel ZK, Sultan NF, Mustafa MS. Anti-Carbamylated Protein Antibodies as Biomarkers in RA, SLE, and Primary Sjögren's Syndrome: Clinical Relevance and Diagnostic Utility. Eur J Med Health Res, 2025;3(5):4-10.

DOI: 10.59324/ejmhr.2025.3(5).01

Keywords:

Anti-carP Antibodies,
Systemic Lupus Erythematosus,
Rhumatoid Arthritis,
primary Sjögren syndrome,
Biomarkers.

Introduction

Etiology, pathogenesis, immunopathogenesis, and manifestation of patients with systemic rheumatoid diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and primary Sjögren syndrome (pSS) is variable but tends to be chronic which is attributed to the underlying autoimmune disorder, that is, a disease involving in its pathogenesis the production of autoantibodies and the result of widespread inflammation leading to the progressive destruction of tissue.[1-2]. Therefore, regardless of the developed immunology and improving diagnostic tools, the problem regarding the proper and timely identification of these diseases has not been solved, including seronegative patients who do not express classic disease-related autoantibodies. Improper diagnosis may lead to permanent damage to the organ, worsening long-term prognosis, and abnormal responsiveness to the treatment[3]. The autoantibodies that have already been well studied and are commonly used in the evaluation and diagnosis of RA include rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA)[4]. Nevertheless, some patients with RA test negative for these markers, and hence, there is a necessity to come up with new biomarkers that can be used to improve early detection and risk stratification[5]. Equally, in SLE and pSS, the disease heterogeneity and co-occurring clinical symptoms make it difficult to be diagnosed [6], and classical serological markers can be undefined or nonspecific in others. In that regard, anti-carbamylated protein antibodies (Anti-CarPA) have recently come to be a biomarker with possible prognostic and diagnostic potential in the scope of all systemic autoimmune illnesses [7]. Carbamylation is a non-enzymatic post-translational modification of proteins, resulting in the formation of homocitrulline residues, which may become neoantigens that may trigger autoimmune reactions[8]. Earlier forms of research have revealed that Anti-CarPA can be seen in many of RA patients, when focused on ACPA-negative RA patients, which has been linked to advanced joint destruction and inferior radiographic results[7]. Recent data indicate that Anti-CarPA could also be detected in other autoimmune rheumatic conditions, including SLE and pSS, but there was overall limited data and some inconsistent results[9].

Moreover, earlier studies have come up with valuable knowledge, there is still some lack in the knowledge where a considerable number of investigations have been devoted to RA only, and a comparatively small number of investigations are devoted to the study of prevalence and clinical significance of Anti-CarPA in other autoimmune rheumatic diseases[10-11]. There is a need to investigate Anti-CarPA systematically in a variety of autoimmune disorders where the cohorts are precisely defined and the methods used are thoroughly documented. Thus, the present study is a systematic analysis of Anti-CarPA immunoreactivities. In addition, this study could present a comprehensive view of the prevalence and clinical associations of Anti-CarPA beyond RDs. The study adds evidence towards the integration of the Anti-CarPA test into the standard clinical practice and identifies the areas of future longitudinal studies that would further clarify its pathophysiological significance and clinical applicability.

Related Studies

Various high-impact studies have been conducted on anti-carbamylated protein antibodies (Anti-CarPA) in the prevalence, diagnostic utility, and clinical significance of systemic, autoimmune diseases in recent years, with one of its studies conducted by Shi et al. (2024) regarding the prevalence of Anti-CarPA in patients with early rheumatoid arthritis (RA), and the results showed that about 40 per cent of tested patients were positive, on the other hand, Anti-CarPA-positivity was related to more advanced progression of patients with a systemic lupus erythematosus (SLE)[12]. Romero-Diaz et al. (2022) study evaluated the level of Anti-CarPA and significant correlations between the titers of Anti-CarPA, which implies the utility of Anti-CarPA as a marker of the disease manifestations leading to the risk of organ failure. As their analysis pointed towards the existence of significant heterogeneity of prevalence levels between studies, findings suggest the possible value of Anti-CarPA as a tool to increase the accuracy of diagnosing pSS in seronegative situations[13]. This knowledge was further extended by Mohamed et al. (2022), who measured the Anti-CarPA value in connective tissue diseases other than RA and found that antibody levels tend to be lower than in RA but may help distinguish between overlap syndromes and abnormal disease presentations [14]. The final contribution was made by Derksen et al. (2024) who showed that carbamylated proteins induce divergent immune responses (like promoting local inflammation and tissue damage pathways) in the synovium that forms the basis of a proposed mechanism under Overall these studies demonstrate emerging importance of Anti-CarPA but also indicate the necessity of future, large scale studies to clarify its clinical practice[15]. All these studies emphasize the emerging suitability of Anti-CarPA as a cross-disease biomarker. It is on this basis that the current research develops the findings and incorporates new information that supports the idea of using Anti-CarPA from a well-documented multidisease cohort and considers the need to continue with the theories to enable the application of testing Anti-CarPA as a daily clinical practice.

Materials and Methods

Design and Population of Studies

This study used a retrospective approach conducted on 131 patients at the Rheumatology Department of Al-Yarmouk Teaching Hospital, Baghdad, Iraq, between October 2024 and June 2025. They included 40 patients with rheumatoid arthritis (RA), 40 patients with systemic lupus erythematosus (SLE), 11 patients with primary Sjögren's syndrome (pSS), and 40 matched healthy controls (HC). Confirmation of RD's diagnoses was performed following the criteria of the international classification, which are the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria in RA and the Systemic Lupus International Collaborating Clinics (SLICC) 2012 in SLE. The study did not include any patients with a previous history of diabetes, cardiovascular diseases (angina, myocardial infarction, stroke, transient ischemic attack, heart failure, and peripheral vascular disease), or obesity. Prior written consent was obtained from each participant in order to publish the results of this work.

Clinical Evaluation

All the patients were examined with thorough clinical tests that determined the complete medical history, physical tests, and analysis of the degree of disease activity. The disease activity in rheumatoid arthritis (RA) was quantified using disease activity score in 28 joints with erythrocyte sedimentation rate (DAS28-ESR) that involves the number of swollen and tender joints (out of 28 in total) and worldwide the score of the health of the patient along with erythrocyte sedimentation rate (ESR). DAS28-ESR was compared by interpretable categories where 2.6 or lower resulted in remission, 2.7 to 3.2 indicated low disease activity, 3.3 to 5.1 indicated moderate disease activity, and greater than 5.1 indicated high disease activity. Moreover, the Systemic Lupus Erythematosus Disease Activity Index 200 was used, having a list of 24 clinical and laboratory descriptions to measure the disease in the nine organ systems during the past 30 days before the observation. The weight of all the descriptors is pre-determined, and the total SLEDAI-2K score is 0-105, with the higher score, the more organ involved/the more active it is.

Sample Collection

Collected blood samples were taken to serum separator tubes and left to clot at room temperature and centrifuged at 1000 x g for 20 minutes. The serum was frozen in aliquots at -20 °C until testing. The measurement of anti-CarPA was based on the commercial enzyme-linked immunosorbent assay (ELISA) kit (ELK Biotechnology) as provided by the manufacturer. The serum samples or control solution were also incubated, after which they were washed, the biotinylated antibody was placed, then streptavidin-HRP conjugate, and the substrate solution (TMB). A stop solution was added to stop the reaction, and optical densities (OD) of 450 nm were measured. Anti-CarPA was measured in ng/mL, and the assay CV was 0.523 ng/mL with an intra-assay coefficient of variation (CV) of 9.1%. The cut-off point was stipulated by calculating the mean of Anti-CarPA in healthy controls + 2 standard deviations (SD). The detection of anti-CCP antibodies was performed by the MESACUP-2 test CCP kit (O/N) (Medical and Biological Laboratories), followed by the manufacturer's instructions. The results were classified as positive when the level was greater >25 U/mL.

Statistical Analysis

Data were statistically analysed with the help of IBM SPSS Statistics for Windows, Version 20. Normal distribution of continuous variables was gauged via the Kolmogorov-Smirnov test of normality, and homogeneity of variances was determined through the utilization of the Levene test. Since the criteria of parametric ANOVA were not entirely met, the analysis of differences in Anti-CarPA serum levels was carried out using Welch ANOVA and Games-Howell post-hoc tests (the latter are insensitive to unequal sample sizes and variances). Serum Anti-CarPA levels are reported as means SD. The asterisk was used on figures to show between-group statistical significance ($p < 0.05$, $p < 0.01$, and $p < 0.001$). The chi-squared test was used to analyse qualitative variables. The diagnostic performance of Anti-CarPA was evaluated through the Receiver Operating Characteristic (ROC) curve, and the Area Under the Curve (AUC) was calculated to measure diagnostic accuracy in each group of diseases. All the tests involved using a p-value of less than 0.05 as statistically significant.

Results

Demographic and Clinical Characteristics

In total, 131 subjects participated in our study, the group of persons with rheumatoid arthritis (RA) consisted of 40 patients, the systemic lupus erythematosus (SLE) group was also 40 patients, primary Sjogren syndrome (pSS) was presented by 11 patients, and an age- and sex-matched healthy control group (HC) consisted of 40 individuals. In all the participants of the patients, who included 70 percent of patients in the rheumatoid arthritis (RA), 77.5 percent in systemic lupus erythematosus (SLE), and 90.9 percent of the patients in Primary Sjögren syndrome (pSS), the females dominated. The age of the patients was 46.6 ± 12.9 years with RA, 27.4 ± 10.9 years with SLE, and 51.0 ± 13.2 years with pSS patients. RA was more common in joint involvement (77.5 percent) in comparison with SLE (52.5 percent) and pSS (36.4 percent), as illustrated in Table 1.

Table 1: Clinical Characteristics of RA, SLE, and pSS

Characteristic	RA (n=40)	SLE (n=40)	pSS (n=11)
Age, mean ± SD (years)	46.6 ± 12.9	27.4 ± 10.9	51.0 ± 13.2
Sex (female), n (%)	28 (70.0%)	31 (77.5%)	10 (90.9%)
Joint involvement, n (%)	31 (77.5%)	21 (52.5%)	4 (36.4%)

Serum Anti-CarPA levels

The rheumatoid arthritis (RA) (30.3 ± 22.9 ng/ml; p < 0.001), systemic lupus erythematosus (SLE) (18.1 ± 11.1 ng/ml; p = 0.005) and Primary Sjögren syndrome (pSS) (14.6 ± 5.6 ng/ml; p = 0.005) groups had significant levels of anti-CarPA serum as compared to healthy controls (3.2 ± 0.6 ng/ml) as shown in Table 2 while Figure 1 shows Anti-CarPA serum concentrations in RA, SLE, pSS, and healthy controls (HC) with their mean, standard deviations, and their p-values.

Table 2: Anti-CarPA Serum Levels Among RA, SLE, pSS, and Healthy Controls

Group	Mean ± SD (ng/ml)	p-value*
RA	30.3 ± 22.9	<0.001
SLE	18.1 ± 11.1	0.005
pSS	14.6 ± 5.6	0.005
HC	3.2 ± 0.6	-

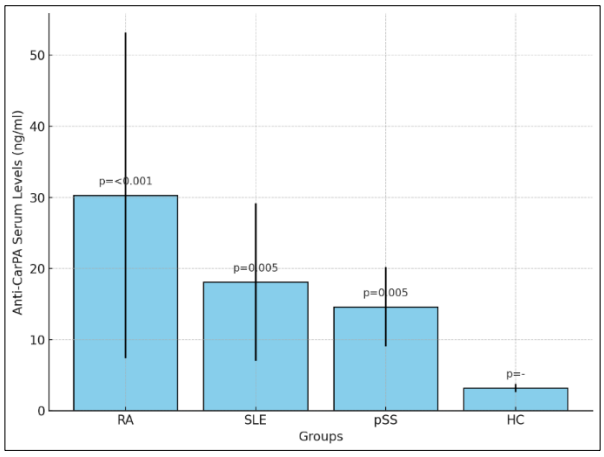

Figure 1: Anti-CarPA Serum Concentrations

Clinical and Laboratory Correlates of Anti-CarPA in RA

The clinical characteristics of individuals with rheumatic diseases (RDs) were compared according to their anti-CarPA status. Patients who tested positive for anti-CarPA had considerably higher values in various parameters than anti-CarPA-negative patients. Anti-CarPA positive people exhibited higher white blood cell counts (6.75 $\times 10^9$/L vs. 5.87 $\times 10^9$/L, p = 0.045), higher ESR value (51.72 vs. 44.31, p = 0.25), CRP also showed greater level (16.51 g/L vs. 7.92 g/L, p = 0.079), greater rheumatoid factor levels (147 g/L vs. 61 g/L, p = 0.003), higher CCP levels (200.00 (72.00,200.00) vs 168.00 (28.00,200.00), p = 0.21) and higher disease effect as shown with the scores (6.00 vs. 5.03, p = 0.041). This study found a significant favorable connection between anti-carP Ab, clinical and laboratory data, including DAS 28-ESR, among RA patients. Table 3 shows the clinical and laboratory characteristics.

Table 3: Clinical and Laboratory Characteristics by Anti-CarPA Status in RA

Variable	Anti-CarPA (+)	Anti-CarPA (–)	p-value
WBC ($\times 10^9$/L), median (IQR)	6.75 (4.95–8.68)	5.87 (3.88–6.85)	0.045
ESR (mm/h), mean ± SD	51.7 ± 33.6	44.3 ± 28.2	0.25
CRP (g/L), median (IQR)	16.5 (4.50–61.7)	7.9 (2.01–24.6)	0.079
RF (U/mL), median (IQR)	147 (53–451)	61 (3–200)	0.003
CCP (U/mL), median (IQR)	200 (72–200)	168 (28–200)	0.21
DAS28, mean ± SD	6.00 ± 0.90	5.03 ± 1.18	0.041

Clinical and Laboratory Correlates of Anti-CarPA in SLE

Many indicators were used to identify significantly elevated patients with systemic lupus erythematosus (SLE) compared to those of anti-CarPA-negative patients. They presented with high erythrocyte sedimentation rate (ESR) (54.90 vs. 35.66mm/h, p = 0.002), elevated CRP (8.56vs. 3.54 g/L, p = 0.087), higher rates of arthritis (13/21(61.9)%) vs. 10/19(52.63)%, p = 0.4) and greater disease activity scores according to SLEDAI [No significant association was found between anti-carPAbs and the SLEDAI-2K in clinical aspects as well as laboratory aspects. Table 4 shows the laboratory Characteristics comparisons.

Table 4. Clinical and Laboratory Features Comparisons in Anti-carPA-positive and Anti-carPA-negative SLE Patients

Variable	Anti-CarPA (+)	Anti-CarPA (–)	p-value
ESR (mm/h), mean ± SD	54.9 ± 27.9	35.7 ± 21.4	0.002
CRP (g/L), median (IQR)	8.56 (2.53–25.5)	3.54 (0.67–20.0)	0.087
SLEDAI-2K, median (IQR)	7.0 (5.0–9.0)	4.6 (3.1–6.8)	0.025
Joint involvement, n (%)	13/21 (61.9%)	10/19 (52.6%)	0.40

Clinical and Laboratory Correlates of Anti-CarPA in pSS

In anti-CarPA-positive pSS, there was also a significant increase in platelet count (300.9 ± 91.4 vs. 185.2 ± 83.5 x 109/L, p = 0.001). Differences with no statistical significance concerned ESR, CRP, involvement of the joints, and anti-SSA antibodies, as shown in Table 5.

Table 5. Clinical and Laboratory Characteristics by Anti-CarPA Status in pSS

Variable	Anti-CarPA (+)	Anti-CarPA (–)	p-value
PLT (×10^9/L), mean ± SD	300.9 ± 91.4	185.2 ± 83.5	0.001
Joint involvement, n (%)	2/4 (50.0%)	2/7 (28.6%)	0.10
ESR (mm/h), median (IQR)	35 (10–95)	22 (9–45.6)	0.11
CRP (g/L), median (IQR)	1.50 (0.7–3.0)	1.00 (0.5–1.8)	0.13

Diagnostic Performance of Anti-CarPA

Anti-carbamylated protein antibodies (Anti-CarPA) diagnostic performance differed among the systemic rheumatic illnesses under investigation. Anti-CarPA in RA had a sensitivity of 74.2 percent and a specificity of 75.8 percent, whereas in SLE, sensitivity and specificity were 72.0 percent and 88.5 percent, respectively. The sensitivity and specificity of Anti-CarPA in the primary Sjögren syndrome (pSS) were 71.9 and 75.0 %, respectively. This is in line with the fact that such findings point to the potential utility of Anti-CarPA as an attractive biomarker towards the differential diagnosis and clinical assessment of patients within the context of the systemic rheumatic disorders.

Clinical Context of Anti-CarPA Serum Levels in RA, SLE, and pSS

The clinically meaningful implications are that the differences in serum Anti-CarPA levels between the RA, SLE, and pSS groups and the healthy controls have been observed. High Anti-CarPA level, especially in RA patients (30.3 ± 22.9 ng/ml), is a notable finding, indicating its possible application as a diagnostic and prognostic biomarker, especially in those seronegative cases that do not show classical indicators, RF and anti-CCP. This is vital in early detection and stratification of patients whose phenotype of RA is aggressive or atypical, wherein normal autoantibodies are not present.

In SLE, the Anti-CarPA levels are rather high in the moderate case (18.1 ± 11.1 ng/ml) and have a significant correlation with the SLEDAI-2K score and ESR, which helps to believe in its role of measuring the inflammatory burden and disease activity. As SLE may be characterized by heterogeneous symptoms, and verifying disease activity may be characterized by a changeable disease course, Anti-CarPA may help clinicians track the risk of a flare or even determine response to intervention in situations with ambiguous serologic status.

In pSS patients, despite the small number of samples, the Anti-CarPA concentration (14.6 ± 5.6 ng/ml) was considerably higher than in the control. Its relationship with increased platelets also indicates that it may be associated with inapparent inflammation or increased immune response. The presence of Anti-CarPA could be used to detect pSS patients with additional autoimmune characteristics or that who develop secondary autoimmune diseases.

Moreover, this specificity of the marker, represented by comparatively low levels of Anti-CarPA in healthy controls (3.2 +/- 0.6 ng/ml), gives new value to the use of such a marker as a supplement to the current serological panels. The integration of Anti-CarPA testing to standard autoimmune investigations can enhance early detection, treatment resolutions, and prolonged care in systemic rheumatic failures.

Diagnostic Performance of Anti-CarPA

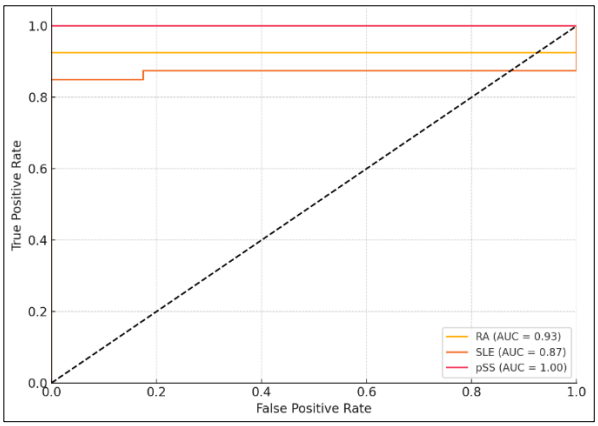

Figure 2: ROC Curves for Anti-CarPA Diagnostic Performance

ROC (Receiver Operating Characteristic) curve analyses were also used to evaluate the diagnostic capacity of Anti-CarPA across disease groups further. The reference unit discrimination was 0.87 in RA, 0.83 in SLE, and 0.82 in pSS, which reported great discriminative ability of each condition in the area under the curve, as shown in Figure 2.

Discussion

The research gives convincing evidence concerning the clinical usefulness of anti-carbamylated protein indicators (Anti-CarPA) in systemic rheumatic disorders with special reference to Rheumatoid arthritis (RA), SLE, and pSS. Based on our findings, it is observed that the concentration of Anti-CarPA significantly elevates among patients with such diseases compared to healthy people, thereby could be considered as a helpful diagnostic examination material and disease follow-up determination indicator. This study has realized that the incidence of Anti-CarPA is so high in RA disorders, and in the other cases in SLE and pSS. More specifically, anti-CarPA was highly sensitive and specific of RA (74.2% and 75.8%, respectively), and it was comparable with other research with regards to its possible diagnostic capability among seronegative RA patients as do not match the classical markers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies[16- 17]. In addition, this study shows that the Anti-CarPA is an even better diagnostic tool, particularly in the hard-to-diagnose seronegative RA. Therefore, the sensitivity of (72%) and an outstanding high specificity (88.5%) of the Anti-CarPA on SLE patients support the previous contradictions in literature anti-CarPA was highly sensitive and specific of RA (74.2% and 75.8%, respectively), and it was comparable to the other research regarding its potential diagrammatic potential among seronegative RA patients as they do not fall to the classical biomarkers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies[7,18].

Furthermore, the two factors are linked to the Anti-CarPA positive group as they increase the disease activity of RA patients in terms of the high Disease Activity Scores (DAS28) and the level of rheumatoid factor. These correlations emphasize some precarious prognostic significance of anti-CarPA and its possible use in the detection of patients with a high risk of aggressive behavior and poor clinical outcome, because it has already been suggested by other researchers[7, 19-20].Anti-CarPA was highly associated with high ESR and high scores of disease activity (scores of SLEDAI-2K) in SLE. Although a significant correlation with the level of complement expression or engagement of the joints could not be found, these data reinforce prior findings suggesting that Anti-CarPA could be applied in the context of supplying the inflammatory load or predisposing to erosive arthritis in SLE patients [21]. The results showed that the occurrence of Anti-CarPA was found in patients with RA, SLE, and pSS has been indicating to demonstrate how Anti-CarPA can be employed together with the already existing biomarkers. Therefore, it would be clinically possible to diagnose earlier with the help of Anti-CarPA, particularly in seronegative patients, so that treatment may be provided earlier.

Conclusion

This study showed that there are correlations between Anti-CarPA positivity, markers of disease activity, and inflammatory markers, especially evident when these traditional autoantibodies are absent. The introduction of Anti-CarPA detection into clinical work might improve the early diagnosis, stratification of patients, and control of disease development. This work had clear cohorts, exact diagnostic criteria, and well-matched healthy controls. Various indicators of the clinical and laboratory considerations are evaluated to depict in full detail the clinical significance of Anti-CarPA. Nonetheless, the research is limited in several respects. It has a retrospective design that is bound with such biases as completeness and accuracy of data. The small sample size, especially in the pSS group, could reduce the generalizability and statistical strength to find marginal links. In addition, due to its cross-sectional character, it is impossible to pose the causal relationships and determine temporal fluctuations in Anti-CarPA levels, the dynamics of the disease progression, and response to the treatment. Therefore, to confirm these results, future studies need to involve prospective longitudinal studies with a large cohort size to have the write answer on the real meaning of Anti-CarPA in the pathogenesis and clinical management of the disease. The research on its predictive effect on long-term outcomes, response to therapy, and death or complications of the disease, together with mechanistic research to build up on its pathophysiological role in autoimmune inflammation, may help expand the body of knowledge and enhance the use of Anti-CarPA as a stratifying biomarker favoring personalized therapeutic interventions.

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