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## Research Article

# The Interplay of CX3CL1 and CX3CR1 Axis in the Pathogenesis of Systemic Lupus Erythematous

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**Abstract**

***Background***: Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are autoimmune diseases with multifactorial etiology. Both diseases are characterized by chronic inflammation and autoantibody production. ***Objective***: To investigate the role of Fractalkin***e*** (Fkn) and its receptor (CX3CL1-CX3CR1 axis) in the pathogenesis of these diseases. ***Methods***: The study was carried out on eighty-four SLE patients (classified into 77 with SLE and 7 with SLE associated with RA) and thirty-five healthy individuals as a control group. Levels of soluble Fkns axis were measured by enzyme-linked immunosorbent assay. Clinical parameter correlations were assessed. ROC curves explored CX3CL1 and CX3CR1 diagnostic potential for SLE. Serum levels of CX3CR1 and CX3CL1 were significantly elevated in both SLE and SLE-RA groups compared to controls. ***Results***: Demographic and clinical parameters showed significant differences in age distribution that were observed across SLE, SLE-RA, and control groups. WBC count was significantly elevated in SLE compared to controls. ESR was significantly increased in SLE compared to both controls and SLE-RA. No significant differences were observed in RBC and platelet counts between groups. The ROC analysis showed that ANA, CX3CL1, CX3CR1, and ESR were accurate for diagnosing SLE and SLE-RA in both groups. ***Conclusions***: The elevated concentrations of sFkn and its receptor in SLE are higher than in SLE-RA and the control group. They played a crucial role in the pathogenesis of the disease, which might serve as a serologic inflammatory marker of disease activity and tissue damage.

***Keywords***: ANA, *CX3CL1*, *CX3CR1*, SLE, SLE-RA.

**التفاعل بين محور CX3CL1 و CX3CR1 في التسبب في الذئبة الحمامية الجهازية**

**الخلاصة**

**الخلفية**: الذئبة الحمامية الجهازية والتهاب المفاصل الرثوي من أمراض المناعة الذاتية ذات المسببات المتعددة العوامل. يتميز كلا المرضين بالالتهاب المزمن وإنتاج الأجسام المضادة الذاتية. **الهدف**: التحقيق في دور Fractalkine (Fkn) ومستقبله (محور CX3CR1 -CX3CL1) في التسبب في هذه الأمراض. **الطرائق**: أجريت الدراسة على أربعة وثمانين مريضًا بالذئبة الحمامية الجهازية (مصنفين إلى 77 مريضًا بالذئبة الحمامية الجهازية و 7 مرضى بالذئبة الحمامية الجهازية المرتبطة بالتهاب المفاصل الرثوي)، وخمسة وثلاثين فردًا سليمًا كمجموعة تحكم. تم قياس مستويات محور Fkns القابل للذوبان بواسطة اختبار الممتز المناعي المرتبط بالإنزيم. تم تقييم ارتباطات المعايير السريرية. استكشفت منحنيات Roc إمكانات CX3CL1 و CX3CR1 التشخيصية للذئبة الحمامية الجهازية. **النتائج**: كانت مستويات CX3CR1 و CX3CL1 في المصل مرتفعة بشكل ملحوظ في كل من مجموعتي الذئبة الحمامية الجهازية والتهاب المفاصل الرثوي الجهازي مقارنة بالضوابط. أظهرت المعايير الديموغرافية والسريرية اختلافات كبيرة في توزيع الأعمار التي لوحظت عبر SLE و SLE-RA ومجموعات التحكم. ارتفع عدد خلايا الدم البيضاء بشكل ملحوظ في SLE مقارنة بالضوابط. زاد ESR بشكل ملحوظ في SLE مقارنة بكل من الضوابط و SLE-RA. لم يتم ملاحظة أي اختلافات كبيرة في عدد خلايا الدم الحمراء والصفائح الدموية بين المجموعات. أظهر تحليل ROC دقة تشخيصية كبيرة لـ ANA و CX3CL1 و CX3CR1 و ESR في كل من مجموعتي SLE و SLE-RA. **الأستنتاجات**: التركيز الأعلى لـ sFkn ومستقبله في SLE أكثر من SLE-RA ومجموعة التحكم يلعب دورًا حاسمًا في التسبب في المرض والذي قد يعمل كعلامة التهابية مصلية لنشاط المرض وتلف الأنسجة.

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## INTRODUCTION

Systemic lupus erythematosus is an autoimmune disease characterized by chronic multi-organ damage in which the immune cell attacks healthy cells [1]. It is a connective tissue disease with evident formation of autoantibodies and immune complexes leading to complement system activation [2]. Its prevalence is higher in women of childbearing age [3]. The exact cause of this disease is not well known. However, it has been shown that genetic and environmental factors work together to cause immune responses, resulting in an overproduction of pathogenic autoantibodies by the B cells and cytokine dysregulation [4], which causes damage to tissues and organs [5]. SLE is characterized by an inflammatory immune response mediated by cytokines and chemokines produced by antigen-presenting cells (APCs) and other immune cells,

contributing to disease development and progression. Cytokines are a diverse group of low-molecular-weight glycoproteins that include monokines, lymphokines, interleukins, interferons (IFNs), colony-stimulating factors (CSFs), and chemokines. Cytokines are generated during both adaptive and innate immune responses [6], and an imbalance in their production may give rise to inflammation, autoimmunity, and subsequent tissue damage. They are produced by nearly every cell, including lymphocytes, macrophages, natural killer (NK) cells, and mast cells [7]. They also play a vital role in regulation and influencing the immune response [8,9] Cytokines are responsible for the dynamic regulation of the maturation, growth, and responsiveness of immune cells and are important determinants of health. Cytokine levels may vary in various cellular fluids such as serum, blood, stool, saliva, and sweat, giving important information regarding the diagnosis, stage, and prognosis of many diseases, such as abnormal or increased production of cytokines, such as during a cytokine storm that can lead to organ failure and death [10]. Chemokines play crucial functions in recruitment as well as retention of inflammatory immune cells at sites of inflammation [11]. Comprehending the function of chemokines in the etiology of autoimmune disorders leads to future targeted therapeutic strategies. The chemokine CX3CL1 is the only member of the CX3C chemokine subclass [12]; the soluble form of fractalkine (Fkn; CX3CL1) exerts a chemotactic effect on inflammatory/immune cells [13]. CX3CL1 and its receptor CX3CR1 are associated with the pathogenesis of multiple autoimmune rheumatic diseases, such as rheumatoid arthritis, Sjögren's syndrome, scleroderma, and systemic lupus erythematosus [14]. Furthermore, Fkn and its receptors have been identified as potential therapeutic targets in inflammatory diseases [9,15]. Inflamed endothelium may play a role as a vascular gateway for cytotoxic effector cells (CX3CR1-expressing cells) by rapidly capturing them from the blood and promoting migration into tissue [16]. The current study hypothesized to investigate the serum level of Fkn/CX3CL1 and its receptor CX3CR1 in the patients of SLE and SLE with rheumatoid arthritis. As well as correlating these levels with biological indices of patients.

## METHODS

### *Study design and sampling*

Eighty-four female patients with SLE were recruited for the study with ages between 18 and 55 years with a mean age of 32.73±1.072, and 35 volunteers as healthy controls with ages between 19 and 53 years with a mean age of 29.57±1.703. SLE patients were allocated into two distinct groups: Group 1: 77 females with SLE only. Group 2: 7 females with SLE-RA "rheumatoid arthritis." Healthy controls were filtered into thirty-five healthy volunteers comparable to the patients regarding age and gender and were clinically or laboratory-free. Patients who have a family history of other connective tissue diseases that might be associated with SLE, like primary Sjogren's syndrome and systemic sclerosis, were excluded from this study group. However, it included patients with SLE affected by rheumatoid arthritis. However, it included patients with SLE who were also affected by rheumatoid arthritis.

### *Samples collection*

In this study, 119 blood samples were collected from SLE patients and healthy control groups from the Department of Rheumatology, Baghdad Teaching Hospital, Medical City in Baghdad, Iraq, from the period of November 2023 to April 2024. All samples were divided into two 2-mL EDTA tubes, 2.5 mL in the gel tube, and 0.5 mL in the Triazole tube for RT-qPCR analysis. And all the samples were subjected to the following tests: CBC, ESR, ANA (using ELISA kits), and the targeted chemokines CX3CR1 and CX3CL1, also through ELISA kits. A small group was subjected to mRNA expression of CD47, CX3CR1, and its receptor "CX3CL1 using q-PCR. Another 2 ml of blood was centrifuged for 5 min at 1107g for serum collection. All samples were kept at -20 °C for further analysis.

### *Serum CX3CL1 and CX3CR1 analysis*

The manufacturer's instructions were followed to determine the concentration of chemokines CX3CL1 and CX3CR1 using an ELISA kit (Ylbiont, catalog numbers YLA0591HU, YLA0601HU, and YLA0042HU). In summary, the standards, samples, and controls were pipetted into wells that had been pre-coated with a monoclonal antibody that was specific for the targeted chemokine. The immobilized antibody binds to any targeted chemokine that is present. Subsequently, the enzyme-linked polyclonal antibody that is specific for the same chemokine is added to the wells after any unbound material has been washed away. The substrate solution was introduced to the wells after rinsing to eliminate the free antibody-enzyme reagent. Subsequently, color development occurred in accordance with the quantity of targeted chemokines bound in the initial step. The microtiter plate was read at a wavelength of 450 nm, and the reaction was halted by the addition of a stop solution. The standard curve was used to calculate the chemokine levels in relation to the measured optical density. The results were reported in pg/ml.

### *Ethical considerations*

This study was approved by the ethical committee of the Biotechnology Department, College of Science/University of Baghdad, according to the reference number CSEC/1024/0067.

### Statistical analysis

Statistical analysis was performed using Microsoft Excel 2023 and GraphPad Prism 8. Descriptive statistics, including means and standard deviations, were calculated in Excel (17). A one-way analysis of variance (ANOVA) has been done on the variables to analyze their differences, followed by Tukey's post-hoc analysis to identify specific differences among each group. GraphPad Prism was utilized for its robustness in handling statistical analyses and graphical representation. A one-way ANOVA was chosen due to the independent nature of the experimental groups, and the homogeneity of variances assumption was confirmed using Prism's diagnostic tools.

## RESULTS

The samples were collected from one hundred and twenty-one samples: seventy-seven from SLE patients, seven from SLE-RA patients, and thirty-seven from apparently healthy volunteers as a control group. The age range of samples was between 18 and 55 years old, results shown in Table 1.

**Table 1:** Distribution of study groups according to age

| Groups | Ages group (year) n(%) | | | | | Total |
|---|---|---|---|---|---|---|
| | ≤20 | 21-30 | 31-40 | 41-50 | >50 | |
| SLE | 6(7.8) | 37(48.1) | 22(28.6) | 7(9.1) | 5(6.5) | 77 |
| SLE-RA | 0(0.0) | 0(0.0) | 2(28.6) | 3(42.9) | 2(28.6) | 7 |
| Control | 6(16.2) | 17(51.4) | 5(13.5) | 6(16.2) | 1(2.7) | 35 |
| Total | 12(9.9) | 54(46.3) | 29(24) | 16(13.2) | 8(6.6) | 119 |
| *p*-value | | | 0.009 | | | |

Data presented as frequency and percentage. Chi-square ($\chi^2$) independence test is used at $p < 0.05$ to characterize significant differences.

The hematological parameters of each group were presented in Table 2. Some of the hematological parameters were found to be significantly different between the control group and the SLE group. There was a *p*-value of 0.004 for the difference between the WBC count in the SLE cases (8.5±0.24) and the control group (7.8±0.25). However, the difference was not significant in the SLE+RA cases (63.8±9.1). Also, ESR was significantly higher in people with SLE (45.7±3.2) compared to those without SLE (18.41±1.01) and in people with SLE and EA (6.09±0.85), with a *p*-value of <0.0001.

**Table 2:** Hematological profile analysis

| Groups | Results | | | |
|---|---|---|---|---|
| | RBC | WBC | PLT | ESR |
| Control | 4.7±0.12 | 7.8±0.25 | 281.6±10.6 | 18.41±1.01 |
| SLE | 4.42±0.1 | 8.5±0.24 | 260.05±6.7 | 45.7±3.2 |
| SLE-RA | 4.41±0.31 | 6.09±0.85 | 227.86±21.6 | 63.8±9.1 |
| *p*-value | 0.123 | 0.004 | 0.055 | <0.0001 |

Data presented as mean±SD. One-way ANOVA test is used to characterize significant differences at *p*<005.

On the other hand, the study showed non-statistically significant differences in RBC and PLT between the groups. There was no statistically significant difference in RBC count between the control group (4.7±0.12), SLE cases (4.42±0.1), and SLE+RA group cases (4.41±0.31), with *a p*-value of 0.123. The PLT counts showed the same pattern. There is no significant difference between the controls (281.6±10.6), the SLE cases (260.05±6.7), and the SLE+RA group cases (227.86±21.6), with a *p*-value of 0.253. Antinuclear antibody results revealed significant difference (*p*= 0.001) between the patients and the control group, as shown in Figure 1. The ANA levels are significantly higher in SLE patients (0.54±0.02) when compared to the control group (0.2±0.006), as well as SLE+EA patients (0.79±0.08) as shown in Figure 1.

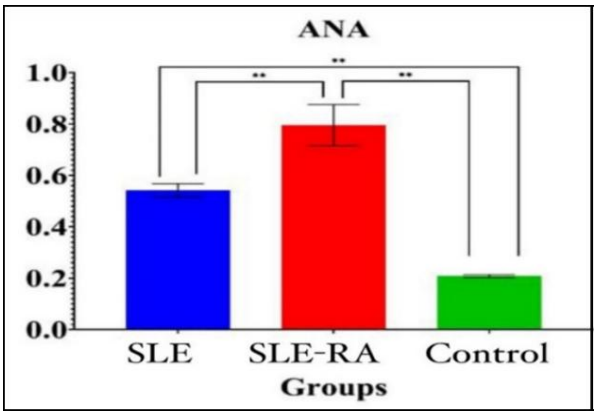


**Figure 1:** levels of ANA in patients and control groups. ** Significantly different (*p*<0.01).

Figure 2 shows that there was a significant difference (*p*= 0.001) between the patients and the control group regarding the levels of the chemokine fractalkine and its receptor.

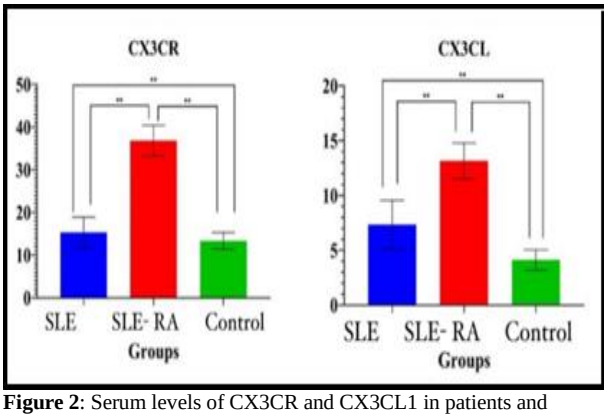


**Figure 2**: Serum levels of CX3CR and CX3CL1 in patients and control groups. ** Significantly different (*p*<0.01).

The levels of CX3CR1 and CX3CL1 are much higher in people with SLE (15.36±0.4 and 7.34±0.25, respectively) compared to those in the control group

(13.36±0.32 and 4.11±0.15) and also in people with SLE and RA (36.85±1.3 and 13.16±0.61). as shown in Figure 2. The study of ROC curves for ANA in SLE group showed that it was significant in the SLE group, with a sensitivity of 87.01%, a specificity of 91.89%, an AUC of 0.963±0.01, a cutoff value of 0.269, and a *p*-value of 0.0001. ROC analysis showed that CX3CL was very accurate, with a sensitivity of 88.31% and a specificity of 86.49%. The confidence interval was between 0.878 and 0.975, and the AUC was 939±0.02. The cutoff value was 4.88, and the *p*-value was <0.0001. ROC analysis revealed that CX3CR sensitivity was 54.55%, specificity was 86.49%, the confidence interval was 0.612 to 0.786, AUC was 0.704±0.04, the cutoff value was 14.89, and *p*<0.0001. In ESR, the sensitivity was 85.71%, the specificity was 67.57%, the confidence interval was 0.762 to 0.903, AUC = 0.842 ± 0.03, the cutoff value was 18, and *p* < 0.0001. However, in RBC the sensitivity was 38.96, specificity was 97.3%, confidence interval was 0.569 to 0.75, AUC was 0.664±0.05, cutoff value was 4.12, and *p*=0.001. Additionally, PLT demonstrated sensitivity of 67.53%, specificity of 56.76%, a confidence interval of 0.51 to 0.696, an AUC of 0.606±0.05, a cutoff value of 277, and a *p*-value of 0.06. ROC analysis of WBS recorded sensitivity of 35.06%, specificity of 91.89%, confidence interval of 0.503 to 0.69, AUC = 0.599 ± 0.05, cutoff value of 9.2, and *p*= 0.06, as shown in Table 3.

**Table 3**: ROC curve analysis (Wilson/Brown method) of SLE group

| Group | Sensitivity (%) | Specificity (%) | 95% CI | AUC mean±SE | Cut-off | *p*-value |
|---|---|---|---|---|---|---|
| ANA | 87.01 | 91.89 | 0.91 to 0.989 | 0.963±0.01 | 0.269 | <0.0001 |
| CX3CL | 88.31 | 86.49 | 0.878 to 0.975 | 0.939±0.02 | 4.88 | <0.0001 |
| CX3CR | 54.55 | 86.49 | 0.612 to 0.786 | 0.704±0.04 | 14.89 | <0.0001 |
| ESR | 85.71 | 67.57 | 0.762 to 0.903 | 0.842±0.03 | 18 | <0.0001 |
| PLT | 67.53 | 56.76 | 0.51 to 0.696 | 0.606±0.05 | 277 | 0.06 |
| RBC | 38.96 | 97.3 | 0.569 to 0.75 | 0.664±0.05 | 4.12 | 0.001 |
| WBS | 35.06 | 91.89 | 0.503 to 0.69 | 0.599±0.05 | 9.2 | 0.06 |

*p*-value of < 0.05 is considered for significance.

We found that the ANA test was very accurate in the SLE group. The confidence range was 0.92 to 1, the area under the curve (AUC) was 0.1 ± 0, the cutoff value was 0.324, and the *p*-value was less than 0.0001. The ROC analysis of the data in the SLE-RA group showed that CX3CL was very accurate, with a sensitivity of 100%, a specificity of 100%, an AUC of 0.10, a cutoff value of 7.16, a confidence interval of 0.92 to 1.0, and a *p*-value of less than 0.0001. ROC analysis recorded that CX3CR sensitivity was 100%, specificity was 100%, the confidence interval was 0.92 to 1.0, AUC was 0.10, the cutoff value was 17.9, and *p* < 0.0001 (Table 4).

**Table 4:** ROC curve analysis (Wilson/Brown method) of SLE-RA group

| Group | Sensitivity (%) | Specificity (%) | 95% CI | AUC mean±SE | Cut-off | *p*-value |
|---|---|---|---|---|---|---|
| ANA | 100 | 100 | 0.92 to 1.0 | 1.0±0.0 | 0.324 | <0.0001 |
| CX3CL | 100 | 100 | 0.92 to 1.0 | 1.0±0.0 | 7.16 | <0.0001 |
| CX3CR | 100 | 100 | 0.92 to 1.0 | 1.0±0.0 | 17.9 | <0.0001 |
| ESR | 85.71 | 100 | 0.864 to 0.998 | 0.967±0.03 | 34 | <0.0001 |
| PLT | 85.71 | 70.27 | 0.585 to 0.86 | 0.739±0.1 | 250 | 0.017 |
| RBC | 42.86 | 97.3 | 0.478 to 0.777 | 0.637±0.13 | 4.13 | 0.32 |
| WBS | 42.86 | 97.3 | 0.581 to 0.857 | 0.736±0.11 | 5.34 | 0.04 |

*p*-value of < 0.05 is considered for significance.

In ESR, the sensitivity was 85.71%, the specificity was 100%, the confidence interval was 0.864 to 0.998, AUC = 0.967 ± 0.03, the cutoff value was 34, and *p*< 0.0001. ROC analysis of PLT recorded sensitivity of 85.71%, specificity of 70.27%, confidence interval of 0.585 to 0.86, AUC of 0.739±0.1, cutoff value of 250, and *p of* 0.017. While in WBC, the sensitivity was 42.86%, specificity of 97.3%, confidence interval of 0.581 to 857, AUC = 0.736 ± 0.11, cutoff value of 5.34, and *p*= 0.04. It has been shown that the RBC test has a sensitivity of 42.86%, a specificity of 97.3%, an AUC of 0.637 ± 0.13, a cutoff value of 4.13, a *p* value of 0.32, and a confidence interval of 0.478 to 0.777. In people with SLE, there is no significant association between the amount of ANA and the amounts of CX3CR1 and CX3CL1, as shown in Figures 3A and B (r= 0.007, *p*= 0.953 for CX3CR1 and -0.007 for CX3CL1). On the other hand, there was a significant negative correlation between the CX3CR1 and CX3CL (r= -0.665, *p*< 0.0001), as shown in Figure 3C. There is no significant association between the level of ANA in patients with SLE-RA and that of CX3CR and CX3CL (r= 0.5, *p*= 0.25) and (r= 0.07, *p*= 0.88), as shown in Figures 4A and B. Also, there was a non-significant correlation between the CX3CR1 and CX3CL1 (r= 0.21; *p*= 0.65), as shown in Figure 4C.

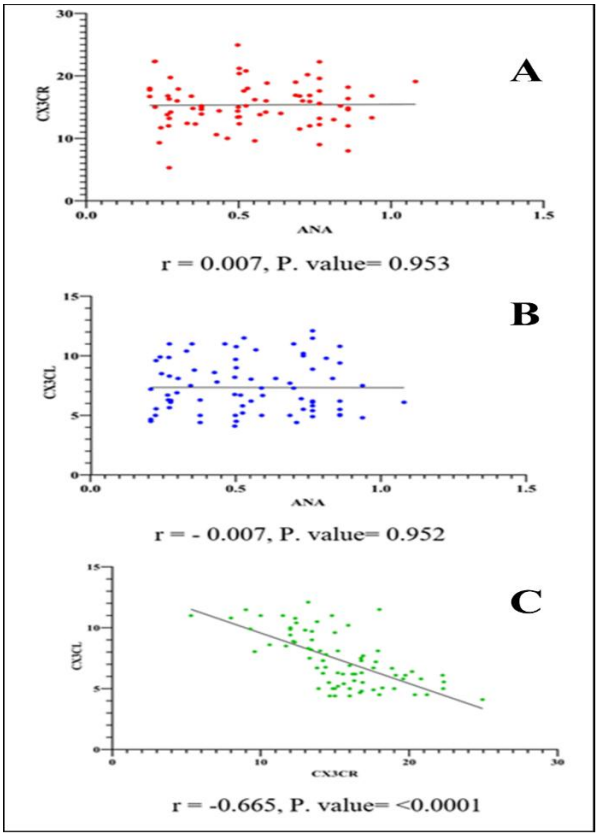


**Figure 3:** Correlation coefficient in SLE Patients between (A) ANA, and CX3CR, (B) ANA, and CX3CL, (C) CX3CR, and CX3CL.

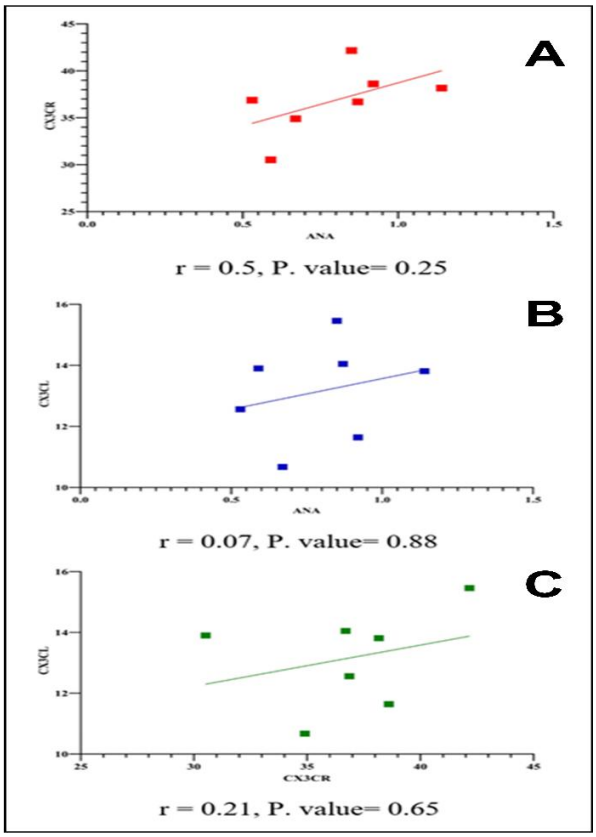


**Figure 4:** Correlation coefficient in SLE+RA Patients between: (a) ANA, and CX3CR, (b)ANA, and CX3CL and (c) CX3CR, and CX3CL.

## DISCUSSION

The results of this study show that the CX3CL1-CX3CR1 axis plays a role in the development of SLE and, more specifically, in the condition where SLE and RA overlap. CX3CR1 and CX3CL1 levels were significantly higher in the SLE and SLE-RA groups compared to healthy controls. This suggests that this chemokine system may play a part in the inflammatory processes that cause these autoimmune diseases [18]. The observed increase in WBC count and ESR in the SLE group aligns with previous findings, indicating active inflammation in these patients. The fact that these markers were higher in the SLE-RA group suggests a highly severe inflammatory state, which fits with the fact that this overlapping condition tends to have a worse disease course [19,20]. ROC curve analysis shows that ANA, CX3CL1, CX3CR1, and ESR are accurate at diagnosing SLE and SLE-RA. This means they might be useful as biomarkers for these conditions. However, further validation in larger cohorts is necessary to establish their clinical significance. The lack of a significant correlation between ANA levels and CX3CR1/CX3CL1 in both SLE and SLE-RA groups suggests that these chemokines may contribute to disease pathogenesis through mechanisms independent of autoantibody production [21]. The negative correlation between CX3CR1 and CX3CL1 in the SLE group is intriguing and warrants further investigation to elucidate its underlying mechanisms. Different sorts of reports have been published indicating the levels of the chemokine fractalkine in SLE patients [9,15]. To the best of our knowledge, all of these reports demonstrate increased serum levels of the soluble form of Fkn. Our results are consistent with these observations. An Fkn/CX3CL1 antagonist may halt the progress of human SLE. Many reports have discussed the pathological role of Fkn/CX3CL1 and its receptor in rheumatic diseases. In their review, they stated that these two molecules mediate the mechanism of leukocyte adhesion in an unusual way. The chemokine domain sticks to the top of the mucin-like stalk that is attached to the membrane. This is where it works as an adhesion molecule, so it's not needed to connect with proteoglycans or other adhesion molecules [22]. When Fkn/CX3CL1 and CX3CR1 interact, it can greatly raise the affinity of integrins, which helps leukocytes move out during the early steps of tethering and transmigration. Intercellular adhesion molecule ICAM-1 and vascular cell adhesion molecule VCAM-1 were co-expressed on inflamed endothelium. This greatly improved cell adhesion function by attracting CX3CR1-expressing cells from the blood and helping them move into tissue. Many reports suggested that Fkn/CX3CL1 expression at the inflammatory location can attract and activate NK cells [7,23] and consequently cause the lysis of neighboring endothelial cells. Inciting factors such as viral or bacterial

infections, ischemia, or cytokine induction with IL-1, TNF-α, or IL-6 can increase Fkn/CX3CL1, ICAM-1, and VCAM-1 expression on endothelial cell membranes. The expression of adhesion molecules and Fkn/CX3CL1 favors NK cell adhesion and transmigration across endothelial cell layers, thereby setting up inflammation.

## Conclusion

Plasma levels of Fkn/CX3CL1 and CX3CL1 increased in SLE patients more than in SLE-RA patients. The current study suggests that the Fkn/CX3CL1-CX3CL1 axis plays a role in the disease process and its pathogenesis in SLE, such as inflammation and leukocyte adhesion. More research needs to be done to compare CX3CL1/Fkn and other chemokines in SLE and to find out what role they play in SLE and related disorders that are different from the inflammatory diseases they have been studied for. Further research is warranted to elucidate the precise mechanisms underlying the dysregulation of this chemokine system and to explore its potential as a prognostic biomarker.

### Conflict of interests

The authors declared no conflict of interest.

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The authors did not receive any source of funds.

### Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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