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Original Article

Clinical, hormonal and ınflammatory correlates of serum fractalkine (CX3CL1) in cyclic and non-cyclic mastalgia

Mehmet Zeki Ogut[1], Nizamettin Kutluer[2], Onur Ag[1], Bekir Saricik[1], Seyma Kurtoglu Ozer[1], Mehmet Bugra Bozan[2], Tamer Gundogdu[1], Hakan Ayyildiz[3], Harun Fener[3], Pinar Gundogan Bozdag[4]

[1]Elazığ Fethi Sekin City Hospital, Department of General Surgery, Elazığ, Türkiye
[2]Elazığ Training and Research Hospital, Department of General Surgery, Elazığ, Türkiye
[3]Elazığ Fethi Sekin City Hospital, Department of Clinical Biochemistry, Elazığ, Türkiye
[4]Elazığ Fethi Sekin City Hospital, Department of Radiology, Elazığ, Türkiye

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Corresponding Author: Mehmet Zeki Ogut, Elazığ Fethi Sekin City Hospital, Department of General Surgery, Elazığ, Türkiye
Email: drzeki44@gmail.com

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Abstract

Aim: Mastalgia is a common, predominantly benign breast complaint with a multifactorial etiology, but objective biomarkers reflecting its biological mechanisms remain undefined. The objective of this research was to assess the connection between serum fractalkine (CX3CL1) concentrations and the clinical and demographic features of patients experiencing mastalgia, as well as to explore the clinical, hormonal, and hematological factors linked to this condition.
Materials and Methods: This prospective, observational study conducted at a single center involved female patients experiencing mastalgia. The intensity of their pain was evaluated using a Visual Analog Scale (VAS). Serum fractalkine concentrations were determined through an enzyme-linked immunosorbent assay (ELISA). Clinical, hormonal, and inflammatory parameters were analyzed. The findings from breast ultrasound examinations were assessed using the BI-RADS classification system.
Results: There were no statistically significant differences found between the cyclic and non-cyclic mastalgia groups regarding age, body mass index, pain intensity, or hormonal and hematological parameters, with all p-values exceeding 0.05. Although serum fractalkine levels appeared to be elevated in the group with non-cyclic mastalgia, the difference was not statistically significant ($p = 0.107$). There were no notable correlations between serum fractalkine levels and the VAS score, WBC count, NLR, or PLR. However, within the cyclic mastalgia subgroup, serum fractalkine levels were significantly associated with both progesterone and prolactin ($p < 0.05$). A statistically significant positive correlation was also identified between the severity of pain and the WBC count ($r = 0.355$, $p = 0.007$).
Conclusion: This research indicates that the intensity of pain in mastalgia might be linked to cellular factors indicative of the body's inflammatory response. While no significant association was identified between serum fractalkine levels and clinical or inflammatory parameters, these findings warrant confirmation in larger, controlled prospective studies.

Keywords: Mastalgia, fractalkine, cyclic mastalgia, non-cyclic mastalgia, inflammatory markers

INTRODUCTION

Mastalgia is a common and predominantly benign form of breast discomfort, with an estimated lifetime prevalence of 50–70% in women (1,2). From a clinical perspective, mastalgia is divided into two primary categories: cyclic and non-cyclic. It is regarded as a diverse clinical condition that signifies different pathophysiological mechanisms. Cyclic mastalgia is linked to hormonal changes during the menstrual cycle and is usually marked by bilateral, widespread, and dull pain that becomes more severe in the premenstrual phase. In contrast, non-cyclic mastalgia is usually localized and presents as sharp or burning pain, often associated with different underlying mechanisms (3,4).

The complex and multifactorial etiology of mastalgia poses challenges in both diagnosis and management. Although hormonal imbalances, increased stromal sensitivity, and local inflammatory responses are frequently implicated in its pathogenesis, reliable biomarkers that objectively reflect these processes have not yet been identified. This limitation is particularly evident in non-cyclic mastalgia, where clinical heterogeneity is more pronounced and difficult to explain (3-6).

Fractalkine (CX3CL1) is a distinctive chemokine that functions as both an adhesion molecule and a chemotactic cytokine, contributing to the interaction between the immune and nervous systems (7,8). Acting through its receptor, CX3CR1, fractalkine has been shown to regulate microglial activation, neuronal sensitization, and chronic pain processes (9,10). Experimental and clinical studies have demonstrated the activation of the fractalkine–CX3CR1 axis in neuropathic pain and neuroinflammatory conditions (10,11).

The dense innervation of breast tissue and its sensitivity to hormonal fluctuations suggest that neuroimmune interactions may be particularly relevant in this tissue (12). In this context, neuroinflammatory processes mediated by fractalkine have been proposed to contribute to the pathophysiology of mastalgia. Nonetheless, there is a scarcity of research directly assessing the connection between serum fractalkine levels and either clinical characteristics or the intensity of pain in individuals suffering from mastalgia (13-15). This gap highlights the need for targeted clinical investigations to better elucidate fractalkine-related mechanisms in mastalgia.

Our research aimed to investigate the association between serum fractalkine concentrations and various clinical, demographic, hormonal, and inflammatory factors in individuals experiencing mastalgia, while also exploring its possible involvement in the condition's underlying mechanisms.

MATERIALS AND METHODS

Study Design and Ethical Approval

This observational clinical study, conducted at a single center, took place in the General Surgery Clinic, Radiology Clinic, and Biochemistry Laboratory of Elazığ Fethi Sekin City Hospital. Approval for the study protocol was granted by the Non-Interventional Clinical Research Ethics Committee of Elazığ Fethi Sekin City Hospital (Date: December 04, 2025; Decision No: 2025/20-25). All procedures adhered to the principles outlined in the Declaration of Helsinki, and written informed consent was obtained from each participant before they were enrolled in the study.

Study Population and Patient Selection

Women experiencing breast pain (mastalgia) who attended the general surgery outpatient clinic were evaluated consecutively.

Inclusion Criteria

- Age ≥ 18 years,
- Premenopausal status,
- Presentation with mastalgia,
- Provision of written informed consent.

Exclusion Criteria

- Postmenopausal status,
- History of breast malignancy, metastatic cancer, or prior breast cancer surgery,
- Presence of active infectious, rheumatologic, autoimmune, or systemic inflammatory disease,
- Uncontrolled thyroid disease,
- Pregnancy, assisted reproductive treatment, or hormone replacement therapy,
- Consistent use of systemic steroids, nonsteroidal anti-inflammatory medications, or immunosuppressive drugs,
- Known musculoskeletal or neurological disorders.

Clinical Assessment and Mastalgia Classification

Each participant underwent a standardized clinical evaluation. Information on demographics, including age and body mass index, as well as smoking habits, caffeine intake, and the use of hormonal or contraceptive drugs, was documented. The menopausal status of all participants was determined, and those who were postmenopausal were not included in the study.

Clinical characteristics associated with mastalgia were examined using a structured data-collection form. Data collection was conducted through in-person interviews with a general surgery specialist. Questions were directed to the participants individually. Responses such as "unknown" or unanswered items were recorded as missing data for the relevant variables.

The Visual Analog Scale (VAS; 0–10) was utilized to evaluate the intensity of pain (16). Breast pain that began before menstruation, persisted for at least two consecutive months, and decreased after menstruation was classified as cyclic mastalgia; cases that did not meet these criteria were classified as non-cyclic mastalgia (1). No separate healthy control group was included in this study, and comparisons were primarily performed between mastalgia subtypes (cyclic vs. non-cyclic).

Imaging Assessment

All participants underwent radiological evaluation using breast ultrasonography. Imaging reports were generated as part of routine clinical practice by experienced radiologists at our institution.

All imaging results were documented and categorized following the guidelines of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) Atlas, 5th Edition (2013) (17).

Blood Sampling and Laboratory Analysis

Venous blood samples were obtained from all participants for complete blood count, hormonal analyses (estradiol, progesterone, prolactin), and serum fractalkine measurement. Blood samples were obtained according to the menstrual status at presentation; however, hormonal measurements were not standardized according to the menstrual cycle phase, which may have introduced variability in the results.

Blood samples for hemogram and hormonal analyses were processed immediately within the routine laboratory workflow and analyzed on the same day. These analyses were performed in the Biochemistry Laboratory of Elazığ Fethi Sekin City Hospital under the supervision of a biochemistry specialist and in accordance with the routine quality control procedures. All laboratory analyses were conducted under blinded conditions, with laboratory personnel unaware of the participants' clinical and radiological data.

Blood count parameters were assessed using a Beckman Coulter DXH 800 Hematology Analyzer (Beckman Coulter, California, USA). The variables recorded included counts of white blood cells (WBC), neutrophils, lymphocytes, and platelets. From these data, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were derived.

Hormonal analyses, specifically for estradiol, progesterone, and prolactin, were conducted using a Beckman Coulter AU5800 analyzer (Beckman Coulter, California, USA).

For the measurement of fractalkine, blood samples were left to clot at room temperature for about 10 minutes before being centrifuged at 3000 rpm for 10 minutes to separate the serum. The serum samples were then stored at -20°C until analysis day, following the manufacturer's guidelines for short- to medium-term storage. To reduce inter-assay variability, fractalkine measurements were conducted in batches. Serum fractalkine levels were determined using a commercially available human-specific sandwich ELISA kit (YLbiont, Shanghai YL Biotech Co., Ltd., Shanghai, China; Catalog No: YLA0591HU), following the manufacturer's instructions. According to the manufacturer, the intra-assay and inter-assay coefficients of variation were < 8% and < 10%, respectively.

Outcome Measures

The main focus was to assess the connection between serum fractalkine concentrations and the intensity of mastalgia, measured through the VAS.

Secondary outcomes included the evaluation of associations between serum fractalkine levels and mastalgia type (cyclic/non-cyclic), hormonal parameters (estradiol, progesterone, prolactin), inflammatory and hematological markers [WBC, NLR, PLR], demographic characteristics, lifestyle factors, and breast imaging findings.

Sample Size Calculation

The sample size was determined using G*Power 3.1 software, focusing on the comparison of serum fractalkine levels between groups experiencing cyclic and non-cyclic mastalgia. Due to insufficient literature data, a medium effect size (Cohen's d = 0.7), an α level of 0.05, and a power of 80% were assumed, leading to a minimum required sample size of 26 participants for each group.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was utilized to evaluate the distribution of continuous variables. Variables with a normal distribution are shown as mean ± standard deviation, while those not normally distributed are represented as median (interquartile range).

To compare the cyclic and non-cyclic mastalgia groups, the independent samples t-test or Mann–Whitney U test was employed, depending on suitability. Categorical variables were examined using the chi-square or Fisher's exact test.

The relationships between serum fractalkine levels and clinical, hormonal, and inflammatory parameters were assessed through Pearson or Spearman's correlation analysis, based on the distribution of the data.

Estradiol, progesterone, and prolactin were entered into the multivariate model based on a priori biological rationale (their established roles in mastalgia pathophysiology), regardless of univariate p-values. Model assumptions were checked before conducting the analysis. Statistical significance was defined as $p < 0.05$. No imputation method was used for missing data; analyses were carried out using the available data.

RESULTS

During the study period, 62 female patients visited the general surgery outpatient clinic with mastalgia complaints. Fifteen patients were excluded due to postmenopausal status (n = 6), active autoimmune or systemic inflammatory disease (n = 3), use of systemic steroids/nonsteroidal anti-inflammatory drugs/immunosuppressive agents (n = 2), declined participation (n = 2), and incomplete clinical data (n = 2). The final analysis included 47 patients. Of those included, 32 patients (68.1%) were diagnosed with non-cyclic mastalgia, while 15 patients (31.9%) had cyclic mastalgia.

All participants underwent breast ultrasonography, and the imaging results were assessed using the BI-RADS classification. The findings showed that 4 patients were categorized as BI-RADS 0 (8.5%), 8 as BI-RADS 1 (17%), 17 as BI-RADS 2 (36.2%), 16 as BI-RADS 3 (34%), and 2 as BI-RADS 4 (4.3%).

Breast biopsy was performed in two patients, and no malignancy was detected on histopathological examination. The BI-RADS classifications of these cases were 4A and 4, respectively; histopathological findings included complex fibroadenomatous breast tissue and fibroadenomatous changes.

Table 1 presents a summary of the demographic and clinical features of the groups experiencing cyclic and non-cyclic mastalgia. The only statistically significant differences between these groups were found in menstrual regularity and smoking habits (Table 1).

No significant differences were noted in terms of age, body mass index (BMI), parity, VAS score, WBC count, NLR, PLR, or serum fractalkine levels, as all p-values exceeded 0.05 (Table 2). Specifically, serum fractalkine levels showed no significant variation between the groups (p = 0.107).

A significant positive correlation was identified between the severity of pain (VAS score) and WBC count (r = 0.355, p = 0.007).

Multivariate linear regression analysis demonstrated that progesterone (B = 4.5, p = 0.002) and prolactin (B = 12.281, p < 0.001) were independently associated with serum fractalkine levels in the cyclic mastalgia group, whereas estradiol was not a significant predictor (B = 83.281, p = 0.51) (Table 3).

Table 1. Demographic and clinical characteristics of patients with cyclic and non-cyclic mastalgia

Variable		Cyclic (n = 15)	Non-cyclic (n = 32)	Total (n = 47)	p value
Parity	**Yes**	10 (21.3%)	24 (51.1%)	34 (72.3%)	
	No	5 (10.6%)	8 (17%)	13 (27.7%)	.40
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
Lactation history	**Yes**	9 (19.1%)	24 (51.1%)	33 (70.2%)	
	No	6 (12.8%)	8 (17%)	14 (29.8%)	.24
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
Menstrual regularity‡	**Regular**	9 (19.1%)	29 (61.7%)	38 (80.9%)	
	Irregular	6 (12.8%)	3 (6.4%)	9 (19.1%)	.02*
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
Smoking status‡	**Yes**	9 (19.1%)	7 (14.9%)	16 (34%)	
	No	6 (12.8%)	25 (53.2%)	31 (66%)	.01*
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
Contraceptive use	**Yes**	3 (6.4%)	5 (10.6%)	8 (17%)	
	No	12 (25.5%)	27 (57.4%)	39 (83%)	.70
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
History of breast surgery	**Yes**	1 (2.1%)	5 (10.6%)	6 (12.8%)	
	No	14 (29.8%)	27 (57.4%)	41 (87.2%)	.37
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
Cervical disc herniation	**Yes**	4 (8.5%)	13 (27.7%)	17 (36.2%)	
	No	11 (23.4%)	19 (40.4%)	30 (63.8%)	.28
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	
Coffee consumption	**Yes**	12 (25.5%)	21 (44.7%)	33 (70.2%)	
	No	3 (6.4%)	11 (23.4%)	14 (29.8%)	.26
Total (n%)		15 (31.9%)	32 (68.1%)	47 (100%)	

Values are presented as n (%); Categorical variables were analyzed using the chi-square test, with Fisher's exact test applied when expected cell counts were below 5; ‡ Fisher's exact test was used; *p < .05

Table 2. Comparison of anthropometric and clinical parameters between cyclic and non-cyclic mastalgia groups

Variable	Cyclic (Median [IQR])	Non-cyclic (Median [IQR])	p value
Age (years)	38 (30 – 42)	38 (30.5 – 41)	.97
Parity	2 (0 – 3)	2 (0.5 – 2.5)	.93
Height (cm)	160 (155.5 – 165.5)	162.5 (158 – 169)	.77
Weight (kg)	70 (65 – 75)	67.5 (60 – 78.5)	.95
BMI (kg/m²)	27 (22 – 28.5)	26 (24.5 – 28)	.72
VAS score	5 (3 – 6)	6 (4.5 – 7.5)	.41
WBC (×10⁹/L)	8 (5.5 – 9.5)	8 (7 – 9)	.74
Neutrophils (×10⁹/L)	3 (2 – 3)	2 (1.5 – 3)	.76
Lymphocytes (×10⁹/L)	2 (2 – 2)	2 (2 – 3)	.45
Platelets (×10⁹/L)	304 (257.5 – 326.5)	290 (250.50 – 341)	.94
Estradiol (pg/mL)	90 (62.5 – 140.5)	67 (41 – 100)	.17
Progesterone (ng/mL)	1 (1 – 4.5)	1.5 (0 – 6)	.72
Prolactin (ng/mL)	10 (9 – 13.5)	10 (6 – 14)	.20
Fractalkine (ng/mL)	5 (4 – 6.5)	6 (5 – 20)	.11
NLR	3 (2 – 3)	2 (1.5 – 3)	.07
PLR	153 (129 – 174)	137.5 (101.5 – 166.5)	.30

*Values are presented as median (interquartile range); $p < 0.05$, Continuous variables were analyzed using the independent samples t-test or Mann–Whitney U test, as appropriate; BMI: body mass index, VAS: visual analog scale, WBC: white blood cell count, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio

Table 3. Multivariate linear regression analysis of hormonal predictors of serum fractalkine levels in the cyclic mastalgia group

Variable	B coefficient	t value	p value	95% confidence interval		Partial eta squared
				Lower bound	Upper bound	
Estradiol	83.281	0.67	.51	-167.129	333.692	0.010
Progesterone	4.5	3.319	.002	1.770	7.230	0.197
Prolactin	12.281	4.725	< .001	7.046	17.516	0.332

B: unstandardized regression coefficient; Dependent variable: serum fractalkine (CX3CL1) level; $p < 0.05$ was considered statistically significant

DISCUSSION

Mastalgia is a common benign breast complaint in women, and its pathophysiology remains incompletely understood. It is primarily associated with estradiol–progesterone imbalance, ductal distension, and increased stromal sensitivity (18,19). However, reliance on subjective pain scores in clinical practice limits the objective characterization of the underlying biological mechanisms. This constraint is especially noticeable in non-cyclic mastalgia, where various pathophysiological mechanisms may occur simultaneously, highlighting the condition's diverse nature. This diversity emphasizes the necessity for dependable and objective biomarkers to assess mastalgia (20,21).

Previous studies exploring the link between inflammatory markers and breast pain have not yielded consistent or clinically applicable results. Current findings indicate that inflammatory indices derived from blood tests, especially the NLR and PLR, might be elevated in a range of chronic inflammatory and pain-related conditions; however, they do not demonstrate a strong or consistent association with pain severity. Accordingly, their utility as reliable biomarkers for mastalgia appears limited

(22,23). In line with these results, the current study found no notable link between NLR, PLR, and mastalgia. However, the observed positive correlation between the VAS score and WBC count (r = 0.355) suggests a weak-to-moderate association between pain severity and systemic inflammatory cellularity. While this is consistent with the hypothesis that mastalgia may have a systemic inflammatory component, the strength of the correlation is modest and the finding requires confirmation in larger, controlled cohorts before firm conclusions can be drawn.

Fractalkine is a chemokine that plays a role in neuroinflammatory and chronic pain pathways by interacting with the CX3CR1 receptor, and it has been found to be activated in conditions of neuropathic pain (9,24). In this study, researchers did not find a meaningful correlation between serum fractalkine levels and the various mastalgia subtypes, the severity of pain, or inflammatory indicators. Although the non-cyclic mastalgia group exhibited higher fractalkine levels, this difference was not statistically significant. These findings suggest that fractalkine may not function as a direct biomarker for mastalgia but may represent a component of more complex pathophysiological mechanisms.

Numerous studies have consistently demonstrated that the risk of cancer in patients suffering from mastalgia is quite low (25). In our study, the absence of malignancy on imaging and histopathological evaluations confirmed that the study population consisted of patients with benign mastalgia. This minimizes the potential confounding effect of malignancy and allows for a more specific evaluation of fractalkine levels in the context of benign breast pain.

The clinical and lifestyle factors evaluated in this study further support the multifactorial and heterogeneous nature of mastalgia. The diversity of obstetric history, lifestyle habits, and clinical variables indicates that mastalgia cannot be explained solely by hormonal mechanisms (26,27). These findings suggest that mastalgia represents a complex clinical condition involving the interplay of neuroinflammatory, hormonal, and environmental factors.

This study is subject to several limitations. It was performed at a single center with a relatively small participant pool, and hormone levels were not standardized according to the menstrual cycle phase. Because estradiol and progesterone concentrations vary by approximately one order of magnitude across the menstrual cycle, this design choice introduces substantial within-group variability and limits the interpretability of the multivariate associations observed within the cyclic subgroup. Future studies should obtain blood samples at a fixed cycle day (e.g., day 21) or stratify analyses by cycle phase. In particular, the cyclic mastalgia subgroup (n = 15) did not reach the a priori target of 26 participants per group, leaving the comparison underpowered. This limitation may explain, at least in part, the borderline non-significance observed for the between-group comparison of serum fractalkine and may also constrain the precision of the multivariate analysis performed within this subgroup. The wide confidence interval observed for estradiol in the multivariate model may reflect the limited sample size of the cyclic mastalgia subgroup and variability in hormonal measurements across the menstrual cycle. Additionally, serum fractalkine levels were measured only once, which limits the ability to assess temporal changes and their association with pain. The absence of a healthy control group is another important limitation that affects the interpretation of the findings.

Of note, the proportion of non-cyclic mastalgia in our cohort (68.1%) was higher than that reported in most population-based series, in which cyclic mastalgia predominates. This may reflect a referral pattern at our tertiary center, where women with persistent or atypical pain are more likely to be evaluated, and should be taken into account when extrapolating our findings to primary-care or community settings.

CONCLUSION

In this study, two key findings emerged. First, serum fractalkine levels did not significantly differ between cyclic and non-cyclic mastalgia, although a non-significant trend toward higher levels in the non-cyclic subgroup warrants further investigation. Second, pain severity correlated weakly but significantly with WBC count, suggesting a possible — though modest — link between mastalgia and systemic inflammatory activity. Because no healthy control group was included and the cyclic subgroup was underpowered, these findings should be regarded as hypothesis-generating. Larger, controlled prospective studies with standardized hormonal sampling are needed to clarify the role of fractalkine and other neuroimmune mediators in mastalgia.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that there is no financial support.

Ethical Approval
The Non-Interventional Clinical Research Ethics Committee at Elazığ Fethi Sekin City Hospital granted approval for this study (Date: 04 December 2025; Decision No: 2025/20-25).

Informed Consent
All participants provided written informed consent.

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