Serum CXCL 9 as a Potential Biomarker for Patients with Ulcerative Colitis

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Abstract:

Background: Ulcerative colitis (UC) is an inflammatory bowel disease restricted to the large intestine, characterized by superficial ulceration. It is a progressive and chronic disease requiring long-term treatment. Although its etiology remains unknown, it is suggested that environmental factors influence genetically susceptible individuals, leading to the onset of the disease. (C-X-C) ligand 9 is a chemokine that belongs to the CXC chemokine family, it plays a role in the differentiation of immune cells such as cytotoxic lymphocytes, natural killer T cells, and macrophages. Its interaction with its corresponding receptor CXCR3 which is expressed by a variety of cells such as effector T cells, CD8+ cytotoxic T cells, and macrophage, leads to stimulation of the production of IFN-γ and TNF-α and in turn, stimulates the production of Th1 chemokines which results in promoting the inflammation.

Objectives: To assess the significance of serum chemokine (C-X-C) ligand 9 as a potential marker for identifying ulcerative colitis in adults with inflammatory bowel disease.

Patients and Methods: This is a case-control study that included 50 patients diagnosed with UC, aged between 18 and 75 years, compared to 50 apparently healthy controls, aged between 18 and 60 years. The study was conducted between November 2022 and March 2023, at the Gastroenterology and Hepatology Teaching Hospital at the Medical City Complex in Baghdad. The serum samples were analyzed using the Enzyme-Linked Immunosorbent Assay (ELISA) technique.

Results: The mean ± SD in pg/ml of serum CXCL9 in patient group was 26.9 ± 9.05 and in control group was 6.4 ± 2.37 ($p < 0.0001$) which indicates a highly significant difference.

Conclusion: CXCL 9 may be employed as a biomarker for identifying ulcerative colitis and it can be used as a tool for measuring disease activity, in addition to the possibility of being a potential therapeutic target.

Keywords: Inflammatory bowel disease (IBD), Ulcerative colitis (UC), T-Lymphocytes, Chronic inflammation, CXCL 9.

Introduction:

Ulcerative colitis (UC) is a chronic and recurrent inflammatory bowel disease (IBD) (1), restricted to the large intestine. It starts in the rectum and spreads all over the colon. The primary clinical manifestations of this condition include diarrhea, mucopurulent stools, and the presence of blood in the stool. Additionally, there may be systemic symptoms associated with the condition (2).

The precise etiology of IBD remains elusive despite ongoing research efforts (3–6). Symptoms vary from mild to severe during a relapse; however, they may decrease or disappear during disease remission (3). The inflammation is limited to the epithelial layer, continuous in the colonic mucosa and not interrupted by healthy areas (7,8).

Cytokines are soluble glycoproteins with low molecular weight in which they act in an endocrine, paracrine, or autocrine manner. The cytokine system is crucial in the body's immunological response to infection and inflammation. Immune cells produce different types of cytokines. These cytokines include chemokines, interleukins (ILs), adipokines,

interferons, colony-stimulating factors (CSFs), and tumor necrosis factor (TNF) (9). More than 200 Cytokines have been identified (10), with their physiological functions including division, apoptosis (programmed cell death), and tissue repair. However, their overproduction leads to unregulated inflammation that harms healthy cells (11). They modulate both the adaptive and innate immune responses to infections and antigens (12). The development and progression of inflammatory bowel disease are mediated by cytokines (13). Chemokine (C-X-C motif) ligand 9 or CXCL 9 is also known as monokine induced by gamma interferon (MIG). As other chemotactic chemokines, it acts to attract immune cells that have CXCR3+ (C-X-C motif chemokine receptor 3), such as effector T cells, regulatory T cells, CD8+ cytotoxic T cells, and macrophages (14).

T helper 1 cells express CXCR3 on their surfaces and thus they stimulate the secretion of interferon-γ (IFN-γ) locally in the inflamed tissues (15). IFN-γ and Tumor Necrosis Factor-α (TNF-α) secretion is enhanced by the recruited Th1 which in turn stimulates Th1 chemokines secretion by a variety of

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cells (16). CXCL9 is increased in many inflammatory diseases due to binding with its CXCR3 G protein-coupled receptor as it is highly expressed on different T cell subsets, which is mediated by IFN-γ (17).

Material and Methods:

This is a case-control study that was conducted between November 2022 and March 2023, with the aim of investigating the potential association between UC and a serum CXCL 9. Participants were recruited from the Gastroenterology and Hepatology Teaching Hospital at the Medical City Complex in Baghdad.

A total of 100 participants were included in the study, consisting of 50 individuals with UC, along with 50 apparently healthy controls. The two study groups were age-matched, apart from one case who fell at the extreme age value of 75 years, for which no control of a similar age during the time of the study.

UC patients were evaluated under the supervision of a gastroenterologist. They were asked about the severity of their conditions using the disease activity index of UC (Truelove and Witts Severity Index) (18). No sub-groupings were made according to disease severity due to the small numbers in the severe subgroup, making meaningful comparisons difficult. Participants' consent was obtained, and participants provided information about their symptoms and complications, outlining risks and general information.

Apparently healthy controls were selected from the blood bank of the Gastroenterology and Hepatology Teaching Hospital, following a comprehensive medical history assessment.

Inclusion criteria for patients
• Males and females with UC,
• Age from 18 years to 75 years,
• Patients diagnosed with only UC who don't have other autoimmune disorders.

Exclusion criteria
• Those who refused to participate in this study,
• UC patients with other autoimmune disorders,
• Patients younger than 18 or older than 75 years.

Kits utilized in this study
The serum marker CXCL 9 was analyzed using human CXC-chemokine ligand 9 (CXCL 9) ELISA kits from Sunlong Biotech Co., LTD at the International Center for Training and Development, utilizing the Enzyme-Linked Immunosorbent Assay (ELISA) technique.

Statistical Analysis
Statistical analysis was performed using the IBM SPSS 27 (Statistical Package for the Social Sciences, version 27) for demographic parameters, the GraphPad Prism 9 was used to draw figures, in addition to the Receiver-operating characteristic (ROC) curve.

The data in both groups exhibited a normal distribution. The researcher employed the parametric Welch's t-test due to unequal variances between the two groups. For qualitative variables, the Chi square was used. Statistical significance was determined at P value < 0.05.

Results

Demographic parameters: In the UC group 23 (46%) were males and 27 (54%) were females Compared to 24 (48%) males and 26 (52%) females in the control group. The age range for UC cases was 18 - 75 years, compared to 18 - 60 years in the controls. The mean age was 36.4 ± 10.1 years for the UC cases and 36.4 ± 10.6 years for the controls. Nearly two thirds of the UC cases had a disease duration of five years or less, table 1.

Table 1: Demographic variables distribution between patient and control groups

Variables	Categories	Study Groups – No (%)		P-value
		Ulcerative Colitis	Controls	
Gender	Males	23 (46)	24 (48)	> 0.05
	females	27 (54)	26 (52)	
Age (Years)	/ Mean ± SD	36.4 ± 10.1	36.4 ± 10.6	> 0.05
Age groups	≤ 40 years	35 (70)	26 (52)	> 0.05
	> 40 years	15 (30)	24 (48)	
Disease Duration	≤ 5 years	31 (62)	N/A	
	> 5 years	19 (38)	N/A	

NA= not applicable / SD= standard deviation

Data Analysis: Welch's t-test results for the CXCL 9 show that the mean ± SD of CXCL9 was 26.9 ± 9.05 pg/ml in UC patients compared to 6.4 ± 2.37 pg/ml in controls, (p-value < 0.0001).

Table 2: CXCL9 serum concentrations in study groups

CXCL9	Ulcerative Colitis (50)	Controls (50)
mean ± SD (pg/ml)	26.9 ± 9.05	6.4 ± 2.37
Min – Max (pg/ml)	8.60 - 39.64	3.11 - 10.97
Welch's T-test		
P value <0.0001		

UC = Ulcerative colitis / CO = Control Validity of the test

The CXCL 9 demonstrates excellent validity in the diagnosis of patients with UC, with a cut-off point of ≥ 10.9 pg/ml, and an AUC of 99.2, signifying excellent discriminatory ability of the test. Sensitivity is 96%, specificity is 98%, PPV is 97.9%, NPV is 96%, and accuracy is 97% (P < 0.0001).
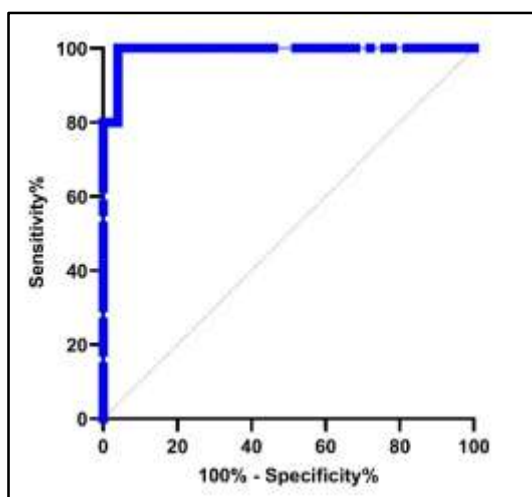
Figure 1: Receiver Operating Characteristic (ROC) Curve Analysis of CXCL 9 for Ulcerative Colitis Diagnosis

Discussion
This study found slightly more females than males within the the study group which is consistent findings of other studies from Iraq on the sex distribution of UC (19–21). However, these results are in contrast with the study from Saudi Arabia made by Alharbi, *et al.,* (22), as well as other studies from Iraq made by Abdul-Hussein, *et al.,* (23,24).
The reported difference in some studies between males and females in the occurrence of UC was explained by X-linked genetic factors and sex hormone signaling which may act together to trigger the sex-specific development of autoimmune disease (25). A study that is specifically designed to investigate this issue in depth is needed.
The majority of UC cases occur in the age group of 17-40 years (22), which is consistent with the results of the current study. the predominance of disease duration is less than 5 years among our cases, This result is consistent with that reported by Al-Khazraji, *et al.,* (26), where the majority of patients had a disease duration of less than 5 years.
It is possible that age-related changes in the immune system, diet, family history, genetic factors, or other physiological factors, in addition to the disease phenotype, may contribute to the differences in disease extent observed in patients of different age groups with UC as well as the disease duration. It is important to note that the Montreal classification of UC does not include age at diagnosis as a criterion, nor does the Truelove and Witts Severity Index.
Many studies indicated that CXCL9 and its receptor are highly expressed in the tissues of Crohn's disease (CD) patients in addition to the finding that same the elevation in the expression of CXCL9 and its receptor in IBD patients (27). CXCL9 and its receptor are highly expressed in lymphocytes, macrophages, and epithelial cells in patients with UC due to the overexpression of IFN-γ, as the first one plays a crucial role in the recruitment of mononuclear cells and granulocytes to the site of inflammation in UC (28). CXCR3 is expressed by epithelial, endothelial,

and lymphoid cells, and its ligands CXCL9, induced by IFN- and attract Th1 cells expressing high levels of CXCR3. Increased expression of CXCR3, especially in CD4 T lymphocytes, has been observed in the mucosa of IBD patients compared to controls (29). Serum levels of CXCL9 are elevated in CD and UC patients (30), which is in agreement with the results of the current study and this can be attributed to an overactive immune response that targets the colon tissues with overwhelming inflammation.
In response to inflammation, the IFN-γ stimulates the production of CXCL9, a chemokine that attracts immune cells like CD4+, CD8+, and natural killer cells to the inflamed site. This leads to increased CXCL9 levels in the blood.
The researcher suggests that CXCR3 and its ligand may be a therapeutic target for IBDs in general and for UC in particular which may result in reducing the activity of the disease due to the expression of CXCR3 by Th1, as it stimulates the secretion of IFN-γ which is a pro-inflammatory cytokine. IFN-γ and TNF-α secretion is enhanced by the recruited Th1, which enhances in synergism between IFN-γ and TNF-α and stimulates Th1 chemokines secretion by a variety of cells. Studies on a larger sample size may provide a clearer picture of this marker in UC and its association with disease severity.

Conclusion
CXCL 9 may be employed as a biomarker for identifying ulcerative colitis. It can be used as a tool for measuring disease activity, in addition to the possibility of being a potential therapeutic target.

Authors declaration:
We confirm that all figures and tables presented in the manuscript are our original work.
Ethical Approval: Ethical approval for this study was obtained from the University of Baghdad, College of Medicine. All participants provided written informed consent before sample collection. The study protocol, subject information sheet, and consent form were reviewed and approved by a local ethics committee according to document number 0230, dated November 7, 2023.
Conflict of interest: None
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Author Contributions:
Study conception & design: (*Mohammed A. Qusay, Sarmad M.H. Zeiny, Haider J.M. Al-Maraashi*). Literature search: (*Mohammed A. Qusay*). Data acquisition: (*Mohammed A. Qusay*). Data analysis & interpretation: (*Mohammed A. Qusay*). Manuscript preparation: (*Mohammed A. Qusay*). Manuscript editing & review: (*Mohammed A. Qusay, Sarmad M.H. Zeiny, Haider J.M. Al-Maraashi*).

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CXCL9 في المصل كعلامة بيولوجية محتملة لمرضى التهاب القولون التقرحي

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الخلاصة:

الخلفية: التهاب القولون التقرحي هو مرض التهابي معوي يقتصر على الأمعاء الغليظة، ويتميز بتقرح سطحي. إنه مرض متفاقم ومزمن يتطلب علاجا طويل الأمد. على الرغم من أن سببه لا يزال مجهولا، يقترح أن العوامل البيئية تؤثر على الأفراد ذوي القابلية الوراثية، مما يؤدي إلى ظهور المرض.

عامل الجذب (C-X-C)9 هو عامل جذب ينتمي إلى عائلة عوامل الجذب CXC، ويلعب دورا في تمايز خلايا المناعة مثل الخلايا الليمفاوية السامة وغيرها، ويتفاعل مع مستقبله المناظر CXCR3 الموجود على خلايا مختلفة مثل الخلايا التائية الفعالة والبلعمة، مما يحفز إنتاج إنترفيرون غاما وعامل نخر الورم ألفا، اللذان بدورهما يحفزان إنتاج عوامل جذب الخلايا التائية المساعده 1 التي تؤدي إلى تعزيز الالتهاب.

الأهداف: الهدف الرئيسي لهذه الدراسة هو تقييم أهمية مصل عامل الجذب (C-X-C)9 كعلامة محتملة لتحديد التهاب القولون التقرحي عند البالغين الذين يعانون من مرض التهاب الأمعاء.

المرضى والطرق: هذه دراسة الحالات والشواهد، شملت 50 مريضا تم تشخيص إصابتهم بالتهاب القولون التقرحي، تتراوح أعمارهم بين 18 و75 عاما، مقارنة بـ 50 فردا سليما ، تتراوح أعمارهم بين 18 و60 عاما. أجريت الدراسة بين نوفمبر 2022 ومارس 2023، في المستشفى التعليمي لأمراض الجهاز الهضمي والكبد في مجمع مدينة الطب في بغداد. تم تحليل عينات المصل باستخدام تقنية المقايسة المناعية المرتبطة بالإنزيم (ELISA).

النتائج: أظهرت الدراسة اختلافا كبيرا في الأهمية الإحصائية بين مستوى عامل الجذب (C-X-C) 9 في مجموعتي الحالات والشواهد (بمتوسط ± انحراف معياري 9.05 ± 26.9 مقابل2.37 ± 6.4، وقيمة p أقل من (0.0001) مما يشير إلى قيمة تشخيصية عالية للكشف عن التهاب القولون التقرحي.

الخاتمة: تشير نتائج هذه الدراسة إلى إمكانية استخدام عامل الجذب 9 (C-X-C) كعلامة حيوية لتشخيص التهاب القولون التقرحي وكمقياس لنشاط المرض، بالإضافة إلى إمكانية استخدامه كهدف علاجي محتمل.

الكلمات المفتاحية: مرض التهاب الأمعاء، التهاب القولون التقرحي، الخلايا التائية اللمفاوية، التهاب مزمن، CXCL 9.