Estimation level of interleukin 8 in Iraqi patients have Crohn's disease under biological treatment

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المستخلص

الخلفية:
يُعد **داء كرون (Crohn's disease - CD)** أحد أمراض الأمعاء الالتهابية المزمنة، ويتميّز باضطراب في الاستجابة المناعية وارتفاع مستويات السيتوكينات الالتهابية، ومنها الإنترلوكين٨. تُستخدم العلاجات البيولوجية للسيطرة على الالتهاب، إلا أن تأثيرها في مستويات الإنترلوكين٨ في الدم ما يزال غير محدد بشكل كافٍ.

الهدف:
هدفت هذه الدراسة إلى قياس مستويات الإنترلوكين٨ في مصل الدم لدى المرضى العراقيين المصابين بداء كرون، ومقارنة هذه المستويات بين المرضى غير المعالجين، والمرضى الذين يتلقون علاجًا بيولوجيًا، والأشخاص الأصحاء.

الطرائق:
شملت الدراسة ٩٠ مشاركًا تتراوح أعمارهم بين ٢٠ و٦٨ سنة، وتم تقسيمهم إلى ثلاث مجموعات: مرضى داء كرون غير المعالجين (٣٠ مريضًا)، مرضى داء كرون الذين يتلقون علاجًا بيولوجيًا (٣٠ مريضًا)، مجموعة السيطرة من الأصحاء (٣٠ شخصًا)

تم قياس تركيز الإنترلوكين٨ في مصل الدم باستخدام تقنية **الاختبار المناعي المرتبط بالإنزيم (اليزا)** كما استُخدمت الاختبارات الإحصائية المعلمية المناسبة للمقارنة بين المجموعات، مع اعتبار مستوى الدلالة الإحصائية **$p < 0.05$**.

النتائج:
أظهرت النتائج أن مستويات الإنترلوكين٨ في المصل كانت أعلى بشكل معنوي لدى مرضى داء كرون غير المعالجين مقارنة بالمرضى المعالجين وبمجموعة الأصحاء (**$p < 0.01$**). كما أظهر المرضى الذين يتلقون العلاج البيولوجي انخفاضًا في مستويات الإنترلوكين٨ مقارنة بالمرضى غير المعالجين، إلا أن هذه المستويات بقيت أعلى مقارنة بمجموعة السيطرة.

الاستنتاج:
يرتبط داء كرون بارتفاع مستويات الإنترلوكين٨ في الدم، ويبدو أن العلاج البيولوجي يساهم في خفض هذا المؤشر الالتهابي، مما يشير إلى تأثيره في تقليل الالتهاب الجهازي.

الكلمات المفتاحية: داء كرون، الإنترلوكين٨، أمراض الأمعاء الالتهابية، اليزا.

Abstract

Background: Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by dysregulated immune responses and elevated levels of pro-inflammatory cytokines, including interleukin-8 (IL-8). Biological therapies are utilized to control inflammation; however, their effects on circulating IL-8 levels remain inadequately defined.

Objective: This study aimed to measure serum IL-8 levels in Iraqi patients with Crohn's disease and to compare levels among untreated patients, those undergoing biological therapy, and healthy controls.

Methods: Ninety participants aged 20 to 68 years were recruited and divided into three groups: untreated Crohn's disease patients (n = 30), Crohn's disease patients undergoing biological treatment (n = 30), and healthy controls (n = 30). We employed an enzyme-linked immunosorbent assay (ELISA) to assess the concentrations of IL-8 in serum. We employed appropriate parametric tests for statistical group comparisons, establishing a significance level of $p < 0.05$.

Results: Serum IL-8 levels were significantly higher in untreated Crohn's disease patients compared to treated patients and healthy controls ($p < 0.01$). Patients receiving biological therapy demonstrated diminished IL-8 levels in comparison to untreated individuals; however, these levels remained elevated when contrasted with controls.

Conclusion: Crohn's disease is linked to higher levels of IL-8 in the blood, and biological treatment appears to lower this inflammatory marker, suggesting that it has an effect on systemic inflammation.

Keywords: Crohn's disease, interleukin-8, inflammatory bowel disease, ELISA**.**

Introduction

inflammatory bowel disease (IBD) is a group of debilitating chronic inflammatory intestinal diseases that includes Crohn's disease (CD) and ulcerative colitis (UC) as subtypes, with different inflammatory dynamics (1). With recurrent and intermittent symptoms, Crohn's disease is a chronic inflammatory bowel disease (IBD) that over time may cause intestinal damage and disability. Thus, it is important to have an early diagnosis and appropriate treatment. CD can affect any portion of the

gastrointestinal tract, but the colon and terminal ileum are the most frequently afflicted (2). The CD is a chronic inflammatory disease, can affect any part of the gastrointestinal tract and is characterized by flare-ups and remissions. Because of a number of environmental factors, immune dysregulation, and genetic vulnerability, the exact etiology of CD is still unknown (3).

The importance of nutrition in Crohn's disease (CD) therapy has traditionally been minimal. The short duration of clinical appointments, the paucity of scientific evidence about the impact of diet on CD, and the lack of nutrition knowledge should all be blamed for the absence of dietary recommendations (4).

In recent years, however, there has been more interest in food as an important part of treating CD. A deeper awareness of the environment's potential influence on disease development and the microbiome's functional importance has initiated research investigations into the impact of nutrition on gut health. This narrative analysis examines the latest dietary guidelines for the nutritional management of Crohn's disease (CD) to enhance patient health and educate gastroenterologists, incorporating recent discoveries from advanced fields such as nutrigenomics (5).

Common symptoms that happen at the start of CD include diarrhea, stomach pain, rectal bleeding, fever, weight loss, and tiredness. The prevalence of CD is rising globally in both adults and children. The gold standard methods for determining a diagnosis and the severity of CD are endoscopy and cross-sectional imaging [8]. Additionally, several stool indicators, including as fecal calprotectin, C-reactive protein (CRP), and laboratory results like thrombocytosis are helpful screening tests to evaluate the illness [7].

Reducing inflammation and achieving clinical remission are the two main objectives of CD treatment; pharmacologic therapy based on 5-aminosalicylic acid/mesalazine and corticosteroids to alleviate symptoms varies according to the severity of the

disease. Biologics, with or without concurrent immunomodulators, are used to treat higher-risk patients in order to induce and sustain remission (5).

Cytokines, mainly made by monocytes and macrophages in the intestinal wall, are important to the disease's pathophysiology because they start and keep inflammatory processes going in the gut. This causes an imbalance between proinflammatory and anti-inflammatory cytokines and damage to the bowel over time (6).

It is clear that human heart attacks, heart failure, and perhaps many other forms of heart disease are influenced by interleukins or the cytokine. Interleukin-18 (IL-18) expression was shown to be higher in atherosclerotic plaques removed following carotid endarterectomy in humans, and the buildup of this protein has been connected to plaque instability (7).

Despite the fact that the majority of "IL-18 is soluble," certain macrophages might have it membrane-bound. When these cells are activated by lipopolysaccharide, they emit soluble IL-18 (LPS). This implies that "IL-18" may be released and activated by another "LPS-induced protease," most likely PR3.According to certain theories, PR3 may trigger proIL-1 and pro-IL-18, which are produced by dying cells (8).

Thus, the main role of interleukins in immunological and inflammatory responses is to regulate stimulation, development, and proliferation. Many protein molecules that have a high affinity for cell surfaces make up interleukins. The cells and tissues react in a variety of ways as a result. They have an autocrine role in addition to their paracrine one. Additionally, interleukins are employed in animal research to examine many clinical medicine domains (9).

Therefore, the present study aimed to evaluate serum interleukin-8 levels in Iraqi patients with Crohn’s disease and to assess the impact of biological therapy by comparing treated patients, untreated patients, and healthy controls.

Subjects and Methods

Ninety crohn's disease patients from Medical City Hospital in Iraq were included in the study between October 2024 to March 2025. The patients, who were of both sexes, ranged in age from 20 to 68. Three groups were created from the entire patient population: Thirty patients who tested positive for Crohn's disease were part of the first group. Group 2: Thirty individuals who appeared to be in good health were included as a control group. Thirty individuals with Crohn's disease were included as part of an under biological treatment.

Patients in the biological treatment group were receiving biologic therapy according to standard clinical practice at Medical City Hospital. Details regarding the specific biologic agent, dosage, and treatment duration were not stratified in this study and represent a limitation.

Five milliliters of blood samples were collected and put in a vacuum gel plain tube, which was then allowed to sit at room temperature until the coagulant solidified. After that, the materials were centrifuged at 3000 rpm for 5 minutes. The serum samples were separated using Eppendorf tubes. Until the immunological tests were finished, the serum samples were stored at -20 C. by Using the enzyme-linked immunosorbent assay (ELISA) technique (10), the levels of Interleukin-8 (SUNLONG/ China) in all patient groups under study, patients without treatment, patients receiving biological treatment, and control groups.

Statistical Analysis

The Statistical Packages for the Social Sciences (SPSS) software (2019) was utilized to identify the impact of different groups on study parameters. Before employing parametric statistical tests, we used the Shapiro–Wilk test to see if the data was normally distributed. Because IL-8 data had a distribution that was close to normal, parametric tests were used. Pearson Correlation, Point-Biserial Correlation,

and Independent-Samples The t-Test was employed to compare means significantly. This study employed the LSD (Least Significant Difference) method for meaningful comparisons between means.

Groups	**Gender**	**Count**	**Means age ±SD**	**Min Age**	**Max Age**
Patients under treatment	Male	19	48.74±15.82	21	72
	Female	11	46.64±16.60	21	67
Patients without treatment	Male	16	46.81±15.52	17	72
	Female	14	35.07±12.23	20	59
Control	Male	18	39.72±14.34	18	68
	Female	12	42.42±15.25	19	65

3- Results

Demographic data of the study

Table 1 delineates the demographic attributes of the three study cohorts: treated patients, untreated patients, and healthy controls. Ninety individuals were enrolled: 30 patients undergoing therapy for Crohn's disease, 30 patients not yet getting treatment, and 30 age- and sex-matched healthy controls.

Table 1: shows the gender and age according to groups.

Comparing the level of IL-8 in different groups

Serum IL-8 levels (assessed via sandwich ELISA) exhibited substantial variation across the three research groups (Table 2). Untreated patients demonstrated the

highest mean IL-8 level (2.223 ± 0.340 pg/mL), followed by treated patients (1.850 ± 0.266 pg/mL) and healthy controls (1.303 ± 0.261 pg/mL) (figure 1).

Table 2:

Groups	**Means ±SD**
Patients under treatment	1.850 ± 0.266 a
Patients without treatment	2.223±0.340 b
control	1.303 ± 0.261 c
LSD	0.149
P-value	0.001
Means having with the different letters in same column differed significantly. ** (P≤0.01).	

comparing of different groups with IL-8

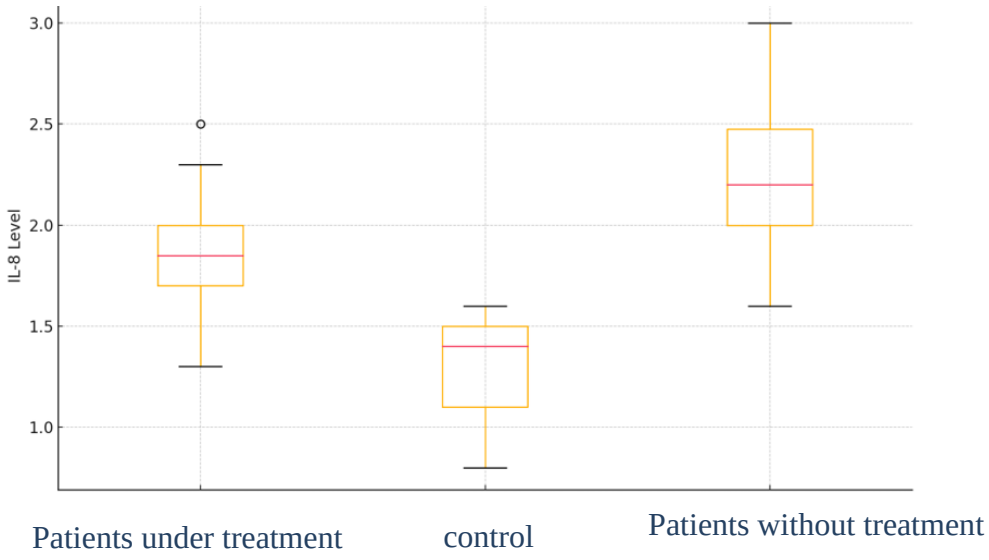

Figure 1: boxplot of IL-8 levels by groups.

Correlation of IL-8 with treatments

In the cohort of Crohn's disease patients undergoing therapy (n = 30), blood IL-8 levels quantified using ELISA exhibited a robust, statistically significant inverse correlation with age (Pearson's r = –0.8461, p < 0.0001). In summary, younger patients had elevated IL-8 levels, while older patients demonstrated reduced quantities of this pro-inflammatory chemokine (figure 2). A significant connection between gender and IL-8 was not observed (figure 3). The Pearson correlation between gender (coded 0 = male, 1 = female) and IL-8 was r = –0.0661 (p = 0.7287), and an independent-samples t-test indicated that mean IL-8 levels were not significantly different between males and females (t = 0.3504, p = 0.7287; 19 males, 11 females).

Table 3: the correlation of age and gender with IL-8 levels in the patients under treatment.

Analysis	**Statistic**	**p-value**	**Sample Size**
Age vs IL-8	r = -0.8461	p < 0.0001	30
Gender vs IL-8	r = -0.0661	p = 0.7287	19 / 11 (M / F)
Gender IL-8 t-test	t = 0.3504	p = 0.7287	30
r= personal correlation, M= male, F= female			

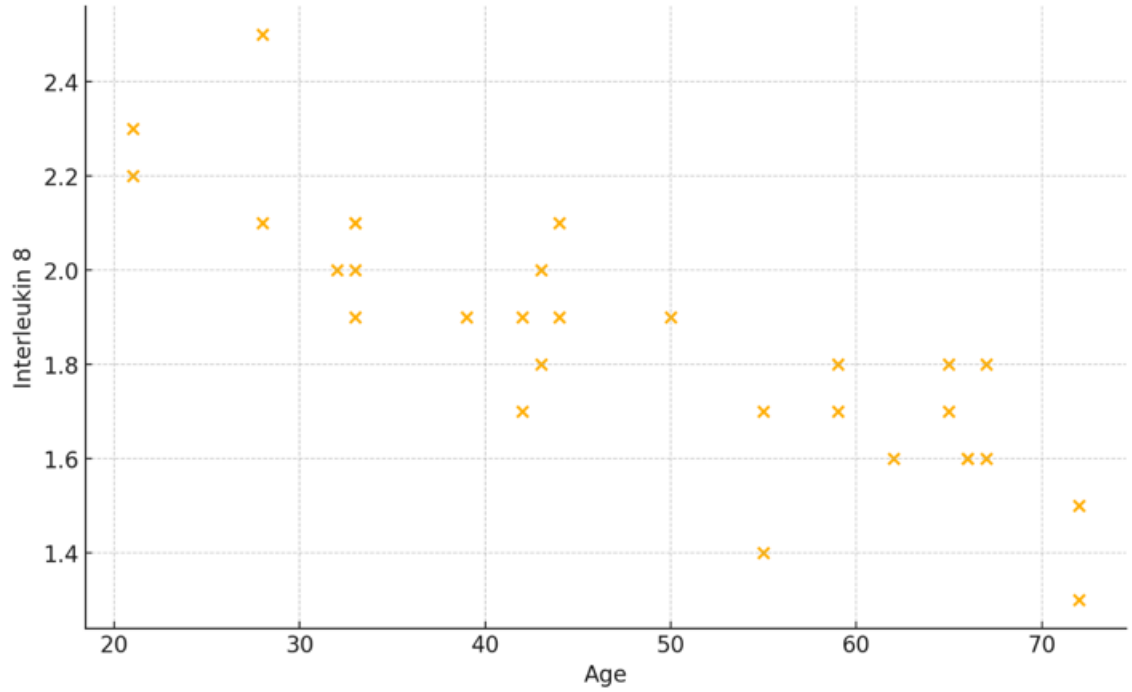

Figure 2: age vs IL-8 scattered plot.

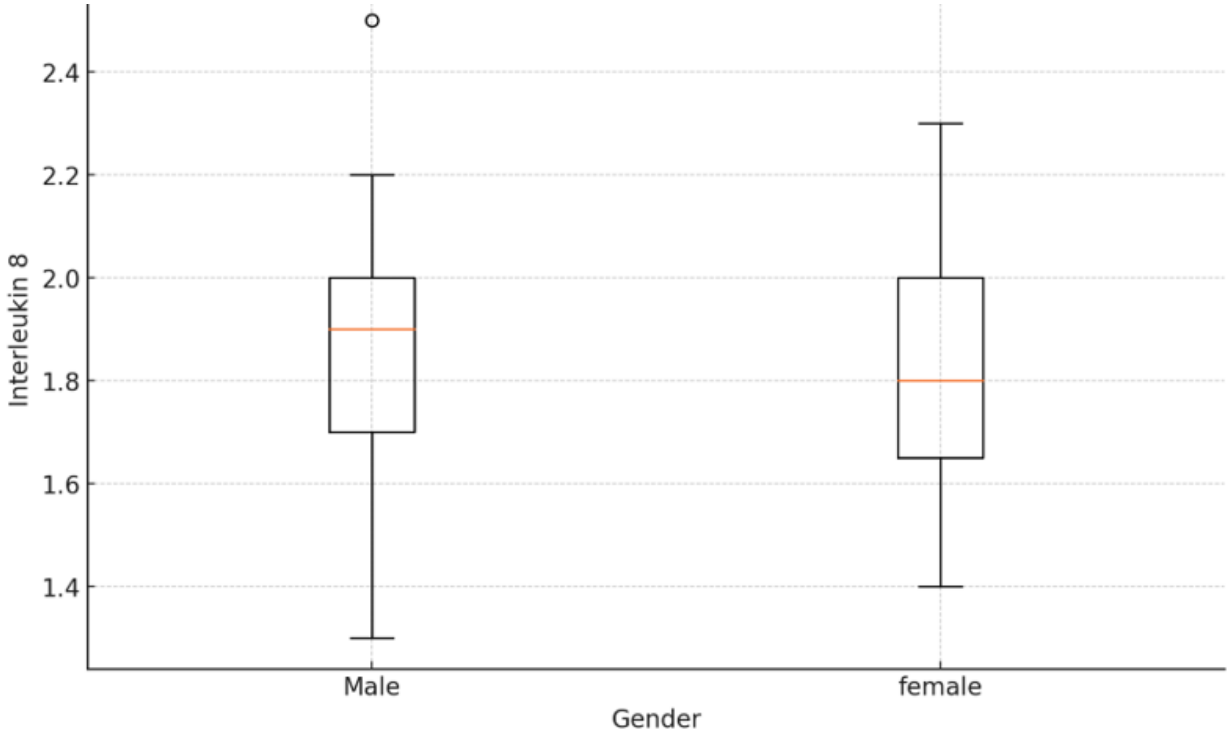

Figure 3: IL-8 by gender

Patients without treatment

In the cohort of 30 treatment-naïve Iraqi Crohn's patients, serum IL-8 concentrations showed no statistically significant association with either age or gender. Specifically, Pearson's correlation between age and IL-8 yielded $r = –0.203$ ($p = 0.283$; $n = 30$) (figure 4), indicating a small, non-significant inverse trend whereby older patients tended to have marginally lower IL-8 levels (Table 3). Similarly, gender was not associated with IL-8 levels: the correlation coefficient for male versus female was $r = 0.035$ ($p = 0.856$; $n = 30$)(figure 5), and an independent-samples t-test comparing IL-8 between the 16 male and 14 female patients produced $t = –0.183$ ($p = 0.856$).

Table 3: The correlation of age and gender with IL-8 levels in the patients without treatment.

Analysis	**Statistic**	**p-value**	**Sample Size**
Age vs IL-8	r = −0.2028	p = 0.2825	30
Gender vs IL-8	r = 0.0346	p = 0.8558	16 / 14 (M / F)
Gender IL-8 t-test	t = −0.1834	p = 0.8558	30
r= personal correlation, M= male, F= female			

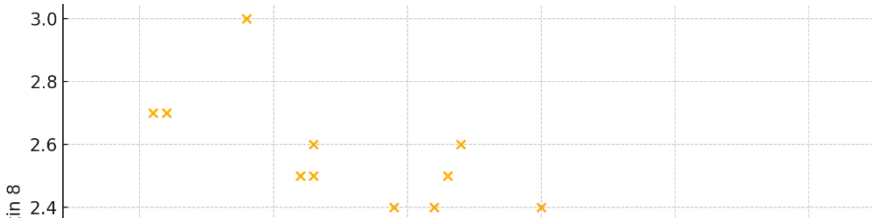

Figure 4: age vs IL-8 scattered plot.

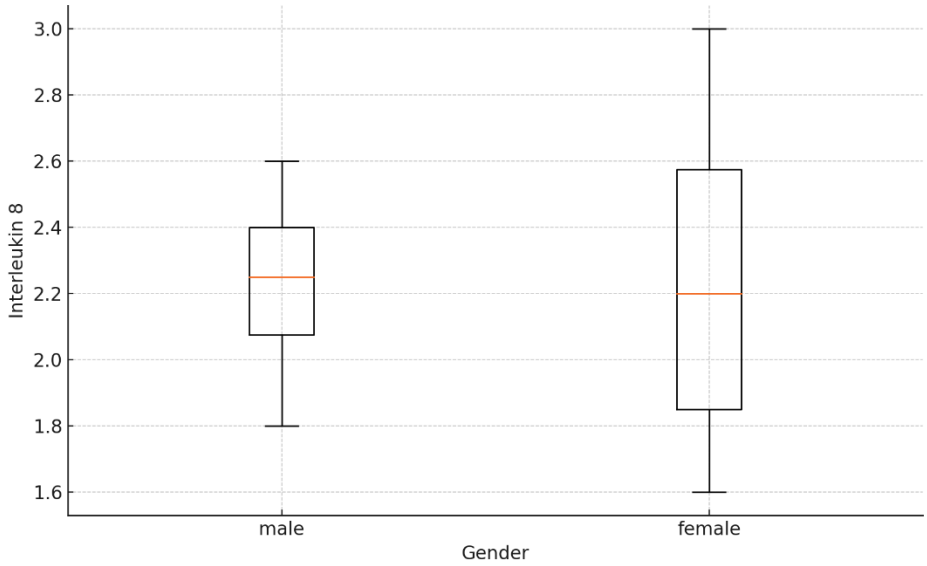

Figure 5**:** IL-8 by gender.

Control

In the healthy control group (n = 30), serum IL-8 levels measured by ELISA demonstrated no significant correlation with age ($r = 0.247$, $p = 0.188$) (figure 6) or gender ($r = 0.281$, $p = 0.132$; $t = –1.643$, $p = 0.132$) (figure 7). Thus, within this cohort of 18 males and 12 females, IL-8 concentrations did not vary meaningfully across demographic subgroups (Table 4).

Table 4: the correlation of age and gender with IL-8 levels in the control group.

Analysis	**Statistic**	**p-value**	**Sample Size**
Age vs IL-8	r = 0.247	p = 0.188	30
Gender vs IL-8	r = 0.281	p = 0.132	18 / 12 (M / F)
Gender IL-8 t-test	t = –1.643	p = 0.132	30
r= personal correlation, M= male, F= female			

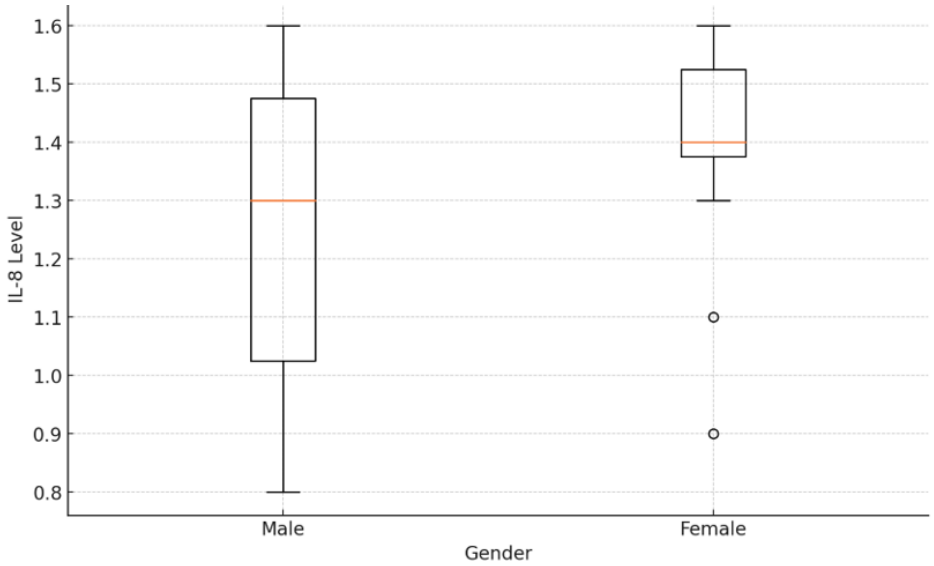

Figure 6: boxplot of IL-8 levels by gender.

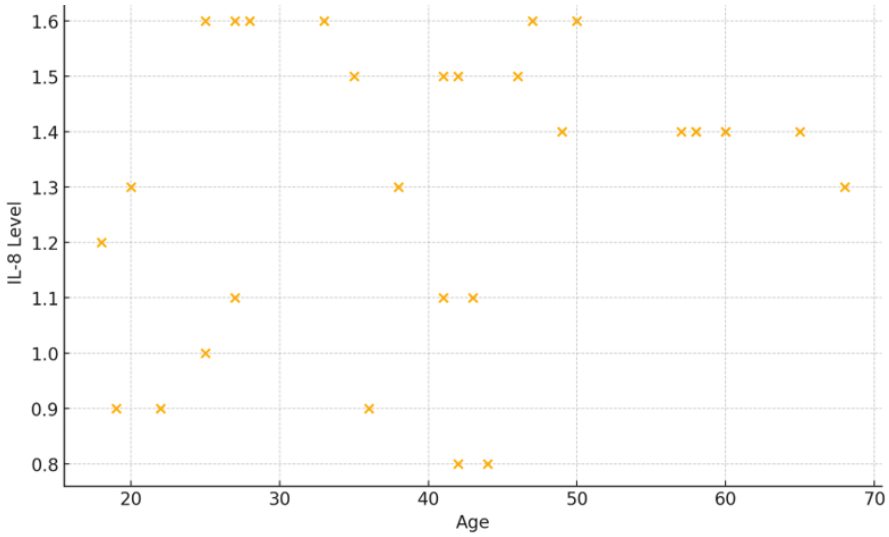

Figure 7: scatter plot of age vs IL-8

Discussion

The cohorts of Crohn's patients, both treated and untreated, as well as healthy controls, were meticulously matched for age and sex, therefore reducing demographic confounding in IL-8 comparisons (11). While IL-8 may exhibit a slight rise with age, the overlapping age ranges and non-significant differences among groups indicate that the observed variations in IL-8 are attributable to disease and therapy effects rather than age-related bias (12). Equitable male-to-female ratios (~60:40) within each group further diminish the impact of sex hormones on cytokine levels (13). The demographic uniformity enhances the dependability of our ELISA assessments of serum IL-8 in Iraqi Crohn’s patients. Future studies should also consider additional potential confounders, including BMI and smoking.

The observation that untreated Crohn's patients exhibit significantly higher IL-8 levels (2.223 pg/mL) compared to controls (1.303 pg/mL) aligns with IL-8's pivotal function in neutrophil recruitment and mucosal inflammation in inflammatory bowel disease (IBD). A study by (14) found that intestinal samples

from individuals with active Crohn's disease release elevated levels of IL-8, which promotes transmural neutrophil infiltration and tissue destruction. A (15) also showed elevated serum IL-8 levels related with endoscopic disease activity. Patients on standard anti-inflammatory treatment (e.g., corticosteroids or anti-TNF drugs) exhibited a notable decrease in blood IL-8 levels (1.850 pg/mL) compared to untreated individuals ($p < 0.01$). This decrease likely indicates the downstream inhibition of NF-κB–mediated chemokine production by these drugs. In a randomised experiment, (16) found that infliximab therapy decreased serum IL-8 by around 20% within 8 weeks, coinciding with clinical remission. Our Iraqi cohort exhibits a comparable degree of IL-8 suppression, indicating analogous pharmacodynamics within this group.

The significant negative correlation between age and IL-8 in treated Crohn's patients ($r = –0.8461$, $p < 0.0001$) indicates that younger individuals exhibit a more vigorous IL-8–mediated inflammatory response, even while undergoing treatment, compared to older persons. This discovery corresponds with earlier observations that age might influence chemokine dynamics in inflammatory bowel disease, possibly indicating age-related alterations in immune cell functionality and cytokine generation capability (17, 18). In practical terms, our observations suggest that younger patients may necessitate more vigilant monitoring of IL-8 as a biomarker for residual inflammation despite treatment. The absence of a gender influence on IL-8 levels aligns with several population studies in IBD, which have indicated negligible or no sex disparities in circulating IL-8 when considering disease activity and treatment (19, 20). The study establishes that male and female patients receiving identical treatment regimens demonstrate analogous IL-8 patterns. Collectively, these findings underscore age—rather than gender—as a significant factor influencing IL-8 dynamics in Crohn's disease during treatment.

Age-related changes in cytokine production are well established; however, studies on IL-8 are inconsistent. In whole-blood assays, LPS-induced IL-8 production may increase with age, although isolated PBMCs from older individuals produce less IL-8 than those from younger persons (21). Senescent stromal cells, such as fibroblasts, acquire a pro-inflammatory secretory phenotype characterised by increased IL-8 levels, hence contributing to the "inflamm-aging" environment (22). This supports the idea that systemic IL-8 levels represent a complicated equilibrium among several cellular sources and stressors, rather than a straightforward linear increase with age. Sex variations in IL-8 secretion have been seen in old populations: senior males demonstrate reduced spontaneous IL-8 release compared to elderly females or young controls; nevertheless, upon LPS stimulation, male monocytes may "over-produce" IL-8 in relation to their young counterparts (23). Conversely, our cross-sectional investigation of untreated Crohn's patients revealed no initial sex discrepancies, indicating that disease-driven inflammatory signalling may supersede minor hormone-mediated influences on IL-8 in this context. IL-8 is pivotal in the pathogenesis of Crohn's disease, as evidenced by mucosal biopsy ELISA and in situ hybridisation, which reveal significantly elevated levels of IL-8 in both inflamed and uninflamed ileocolonic segments of Crohn's patients relative to healthy controls (24). The results of this demographic analysis bolster IL-8's potential as a widely applicable inflammatory biomarker, however it may necessitate mucosal sample or sensitive multiplex assays to detect disease-relevant alterations.

The lack of an age effect on systemic IL-8 in our control subjects corresponds with previous studies indicating consistent IL-8 levels throughout adult age ranges. No significant variations in serum IL-8 levels were identified between the young cohort (< 65 years) and the elderly cohort (≥ 65 years) (25). Similarly, certain studies

indicate increased levels of IL-8 in cognitively impaired elderly persons (26). The majority of research indicates that baseline circulating IL-8 levels stay rather stable with chronological ageing in healthy persons. This stability contrasts with the more significant age-related alterations observed in other "inflamm-aging" indicators, such as IL-6 and TNF-α, highlighting IL-8's potential as a demographic-independent reference analyte. Our observation of no significant gender differences in IL-8 among controls aligns with extensive biomarker studies in healthy individuals. In a research including 80 smokers without COPD (40 males and 40 females), plasma IL-8 levels exhibited no significant differences between sexes after controlling for confounding variables (27). While sex hormones can influence certain cytokines, IL-8 seems to be less responsive to hormonal variations in basal states. The demographic neutrality in healthy individuals increases the applicability of IL-8 as a reference point when evaluating pathological upregulation in Crohn's disease or other inflammatory conditions.

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