

Correlation between IL-17 and inflammatory bowel disease

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The Egyptian Journal of Immunology,
E-ISSN (2090-2506)

Volume 32 (1), January, 2025

Pages: 56–62.

www.Ejimmunology.org

<https://doi.org/10.55133/eji.320106>

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Abstract

Inflammatory bowel disease (IBD) is a protracted, persistent gastrointestinal disease that is distinguished by recurring, persistent inflammation of the digestive tract. IBD, including Crohn's disease and ulcerative colitis, is characterized by persistent inflammation due to immune dysregulation. Interleukin -17 (IL-17) contributes significantly to the pathophysiology of IBD, as highlighted in the context of the provided research. There is a strong correlation between IL-17 inhibitors and the onset or exacerbation of IBD, with IL-17 inhibitor treatment being linked to gastrointestinal inflammatory events such as IBD and colitis. The goal of the current study was to determine the relationship between IBD disease activity and serum IL-17 levels in individuals with IBD. This case-control study included 102 IBD patients and 48 normal individuals as a control group. Blood samples were used for measuring IL-17 levels using the enzyme-linked immunosorbent assay. Levels of IL-17 were increased in patients compared with the control group ($p=0.0001$). IL-17 levels were significantly elevated in patients aged 1-15 years, 31-45 years and 16-30 years. IL-17 levels showed significant differences between two types of inflammatory bowel disease being elevated in Crohn's disease more than ulcerative colitis ($p=0.001$). IL-17 demonstrated significant differences in IL-17 levels between male and female in patients and controls groups ($p=0.0001$). In conclusion, patients with IBD have higher serum levels of IL-17, indicating that these cytokines may have a role in the development and pathophysiology of Crohn's disease and ulcerative colitis. Overall, monitoring IL-17 levels could serve as valuable biomarkers for assessing IBD severity and guiding treatment decisions.

Keywords: Inflammatory bowel disease, *E. coli*, Interleukin -17, Crohn's disease.

Date received: 23 August 2024; **accepted:** 04 December 2024

Introduction

Inflammatory bowel disease (IBD) is the collective term for a group of chronic inflammatory gastrointestinal illnesses that includes Crohn's disease and ulcerative colitis being the primary forms.¹ These conditions often manifest symptoms such as persistent diarrhea, abdominal pain, exhaustion, and

decreased body weight, impacting approximately 1% of the population.² Immunological, genetic, and environmental variables interact intricately in the etiology of IBD, leading to prolonged inflammation and potential complications such as impaired fetal growth in pregnant women with IBD.³ IBD is primarily caused by immunological effects,

specifically an immunological imbalance in the gut lining triggered by the response to adaptive immune system to self-antigens, leading to chronic inflammation.^{4,5} Abnormal gut microbiota, dysregulated immune response, genetic variations, and environmental variables are some of the components involved in the pathophysiology of IBD.^{6,7}

IBD patients typically exhibit dysbiosis, a common abnormality of the gut microbiome, underscoring the crucial role the gut microbiota plays in the onset of the illness. Furthermore, studies emphasize the involvement of T cell subsets, cytokines, and immune dysregulation in the gastrointestinal tract as key factors in the pathogenesis of IBD, underscoring the complex interplay between immunological factors and disease manifestation.⁸

Interleukin-17 (IL-17), a cytokine linked to Th17 cells, is essential to the etiology of (IBD). Studies have shown that IL-17 inhibitors, such as ixekizumab and secukinumab, can cause gastrointestinal inflammatory events and cause the onset or worsening of IBD.⁹ Th17 cells, regulated by gut microbiota and cytokines, contribute to the abnormal immune response in IBD, influencing inflammation and fibrosis progression.¹⁰ Understanding the intricate interplay between IL-17, Th17 cells, and cytokines is essential in elucidating the mechanisms underlying IBD development and progression, offering potential therapeutic targets for managing this complex inflammatory condition.¹¹ This research study aimed to investigate the relationship between IL-17 and IBD.

Subjects and Methods

This study was carried out at the Departments of Gastrointestinal and Liver Disease and Surgery, Al-Hakim General Hospital, and from Private Outpatient Clinics in Al-Najaf during the period between December 2022 till May 2023. The case-control study involved 150 participants. Of these, 102 were patients with IBD and 48 individuals as normal controls. Patients were aged between 2 and 90 years and of both sexes. Their diagnoses were made based on clinical symptoms (e.g., diarrhea, anemia, abdominal pain, blood in stool, bowel

abstraction, etc.,) and endoscopy. The age range of the control group was between 15 and 68 years.

We collected 102 clinical specimens (3 ml serum) in Eppendorf tubes from patients with IBD (cases), while the remaining specimens were from the normal controls. An aliquot blood sample (3 ml) was placed into a gel tube for serum separation, used for measuring IL-17 level and immediately stored at -80 °C. Assessment of IL-17 level was performed by enzyme linked immunosorbent assay (ELISA) kits (CAT. NO: EKHU-0082, MELSIN, China), according to the manufacturer's instructions.

Statistical Analysis

The Statistical Package for Social Science (SPSS) program version 20 was used for data analysis. Experimental data are presented as number and percentage frequencies. Data are expressed as means $\pm$ standard deviation (SD). Statistical analyses were performed using an independent T-test and one-way ANOVA. A p -value ≤ 0.05 was considered significant. The Receiver operating characteristic (ROC) curve was used to assess the best cutoff point to determine the sensitivity, specificity, and to differentiate patients from normal controls.

Results

Estimation the level of IL-17 in IBD patients and controls

The serum level of IL-17 was significantly increased in the serum of IBD patients to 4.47 ± 2.36 pg/ml compared with the normal controls (0.69 ± 0.41 pg/ml) ($p = 0.0001$), as shown in Figure 1.

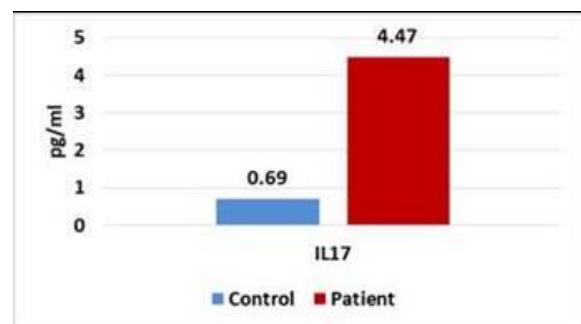


Figure 1. Comparison of interleukin-17 (IL -17) in patient and control groups.

Estimation the level of IL-17 in patients according to their sex

The level of IL-17 demonstrated significant differences between males and females in the patients and the control groups. It was

increased in female patients more than males ($p=0.0001$). The mean values for IL-17 in male patients and controls were 4.18 ± 2.58 pg/ml and 0.66 ± 0.29 pg/ml as shown below in Figure 2.

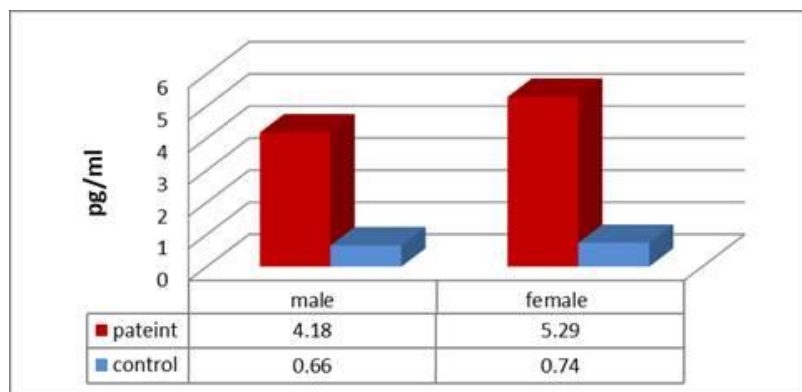


Figure 2. Comparison of interleukin-17 (IL-17) according to sex in patients and controls.

Evaluation of the IL-17 level in patients according to the type of disease

There were significant differences in IL-17 levels between the two types of inflammatory bowel disease (Crohn's disease and Ulcerative colitis)

($p=0.001$). The mean values for IL-17 in Crohn's disease and Ulcerative colitis patients were 5.09 ± 2.68 pg/ml and 3.33 ± 0.59 pg/ml, respectively (Figure 3).

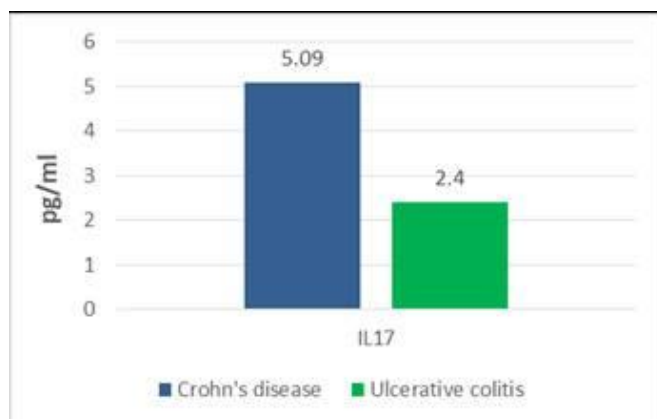


Figure 3. Comparison of interleukin-17 (IL-17) between patients with Crohn's disease and ulcerative colitis.

Estimation the level of IL-17 in IBD patients according to age

This study showed elevated IL-17 levels in the sea of younger patients. The mean concentration level of IL-17 in serum of patients of 1-15 years old, 31-45 years old and 16-30 years old were $7.66A \pm 2.33$ pg/ml, $5.97A \pm 2.99$ pg/ml and $5.58A \pm 2.99$ pg/ml, respectively,

($p=0.001$). On the other hand, the mean IL-17 concentration in serum of elder patients 46-60 years and >60 years were 2.64 ± 1.29 pg/ml and 0.81 ± 0.27 pg/ml and the differences were significant. However, there was no significant difference in IL-17 concentration in sera of younger patients in comparison with elder patients (Figure 4).

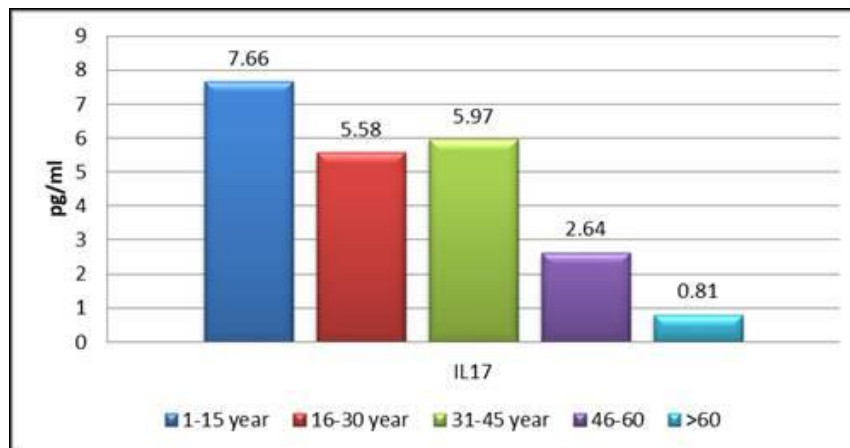


Figure 4. Levels of sera interleukin -17 (IL-17) of different age groups.

The ROC curve analysis was performed to compare the expression efficiency of IL-17. The current results show that in an area under the curve of 1.00 and cutoff value of 1.60045, there was a high sensitivity and specificity (Figure 5),

$p = 0.0001$ (95% CI 1-1). The association between specificity and sensitivity demonstrated a positive correlation (100%, 100%, respectively) as shown in Figure 5 and Table 1.

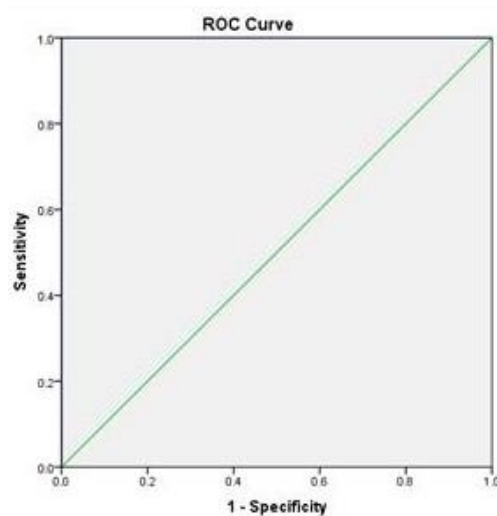


Figure 5. Interleukin 17 (IL-17) receiver operating characteristic (ROC) curve analysis comparing patients with inflammatory bowel illness to controls.

Table 1. Cutoff between patients and controls in normal and diseased subjects.

			Cutoff: 1.60045		Total
			Control	Disease	
IL-17	Patient	Count	0	45	45
		% within	0%	100%	67.2%
	Control	Count	22	0	22
		% within	100%	0%	32.8%

Discussion

IBD and IL-17 have a complicated relationship that includes IL-17's function in disease pathophysiology as well as the potential therapeutic uses of IL-17 inhibitors.¹² Research indicates that IL-17 levels are elevated in IBD patients, they do not correlate with disease activity, suggesting a nuanced role in inflammation rather than direct causation.^{13,14} Patients with Crohn's disease and ulcerative colitis have considerably higher serum IL-17 levels than controls, indicating its involvement in the inflammatory process.¹⁵

The significance of IL-17 was highlighted in eosinophilic gastrointestinal disorders, where elevated IL-17 and other pro-inflammatory cytokine levels were observed. This observation agreed with the findings of previous research that showed elevated IL-17 serum levels in IBD patients and can provide valuable insights into disease severity, potential complications, and aid in the development of targeted therapeutic strategies.^{16,17}

According to sex, sex-specific immune responses are responsible for the higher level of IL-17 in males with IBD than in females. Researchers found that male patients with IBD had considerably higher levels of IL-17 compared to females, suggesting a potential sex-based difference in cytokine regulation.¹⁸ Whereas the mean values for IL-17 in female patients and controls. This may be related to estrogen receptor dysregulation in female IBD patients and may lead to increased IL-17 levels, impacting inflammation. Sex-specific estrogen signaling alterations could contribute to elevated IL-17 in females with IBD.¹⁹

Estrogen exposure is linked to increased risk of CD and UC in women, particularly during reproductive years.²⁰ Hormonal contraceptives and hormone replacement therapy have been associated with heightened IBD risk, while post-menopausal estrogen deprivation appears to reduce disease activity.²¹

A previous research study indicated that the inflamed mucosal tissue of patients with Crohn's disease and ulcerative colitis has much higher levels of IL-17 than that of healthy

controls.²² Notably, IL-17 is present in CD3+ T cells and CD68+ monocytes/macrophages in patients with active IBD patients.²³ Furthermore, a possible genetic influence on IL-17 expression in IBD was suggested by the association between genetic polymorphisms in IL-17A and autoimmune susceptibility and Specifically, some IL-17A genotypes were connected to raised IL-17 levels in ulcerative colitis patients and greater disease severity.²⁴

The increased levels of IL-17 in younger patients with IBD compared to older individuals can be attributed to several factors related to immune response and disease characteristics.²⁵ Research indicates that pediatric patients exhibit a striking overexpression of IL-17A, particularly in ulcerative colitis (UC), suggesting a distinct immune profile in younger populations.²⁶ Younger patients may have a more robust activation of Th17 cells, which produce IL-17, Genetic predispositions and environmental triggers may also play a role in the heightened immune response observed in younger individuals.²⁷

Furthermore, investigations into the immunological parameters of IBD patients have revealed significant differences in proinflammatory cytokine IL-17A and IL-17F levels compared to controls, emphasizing the importance of these cytokines in IBD pathogenesis.²⁸ Overall, evaluating IL-17 serum levels in IBD patients can provide valuable insights into disease severity, potential complications, and aid in the development of targeted therapeutic strategies.²⁹⁻³¹

In this study, we found a complex interplay between various biomarkers, immune cells, and genetic factors in the context of IBD. The precise processes behind the association between higher IL-17 levels and IBD require more investigation, as well as to identify novel biomarkers for improved diagnosis and management of the disease.

Acknowledgements

The authors express their gratitude to the staff members of Departments of Gastrointestinal and Liver Disease and Surgery, Al-Hakim General Hospital in AL-Najaf Al-Ashraf.

Author Contributions

HTM, collected the data and wrote the draft of the manuscript. ZYM, proposed the topic of this research and designed the study, and revised draft of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, University of Kufa (reference no. HK/1059, dated 2/11/2022).

Informed consent

An informed written consent was obtained from each study subject before included in the study.

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