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Deficient Serum Levels of IL-10 and IL-37 in Treatment-Naïve Ulcerative Colitis: Diagnostic and Severity Biomarkers

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Abstract

Background: Ulcerative colitis (UC) is a chronic inflammatory disease characterized by abnormal immune responses in colonic tissues. Anti-inflammatory cytokines, such as IL-10 and IL-37, are critical regulators of intestinal immune homeostasis. However, their expression levels and their value as diagnostic markers in treatment-naive UC patients are still poorly understood, with limited data available from Middle Eastern countries. The study aims to evaluate IL-10 and IL-37 levels in sera as non-invasive biomarkers for UC diagnosis and disease severity.

Methods: This prospective case-control study recruited 40 treatment-naive UC patients and 40 healthy controls from Al-Diwaniyah Teaching Hospital, Iraq, from October 2025 to April 2026. Sera from UC patients and healthy controls were examined for IL-10 and IL-37 levels using enzyme-linked immunosorbent assay (ELISA). For assessing the severity of the disease, Endoscopic Mayo Sub-score was used. For assessing the diagnostic performance, Receiver Operating Characteristic curve analysis was used, and correlation analysis was used to see the relationship between cytokines and disease parameters.

Results: Significantly lower serum levels of interleukin-10 (IL-10) were found in patients with UC compared with healthy controls (8.33 ± 1.14 pg/mL vs. 12.31 ± 1.08 pg/mL; P = 0.001), representing a 32% decrease. Similarly, interleukin-37 (IL-37) levels were also found to be lower in patients with UC (24.79 ± 5.23 pg/mL) than healthy controls (40.90 ± 5.07 pg/mL; P = 0.001), representing a 39% decrease. ROC curve analysis for IL-10 showed an area under the curve (AUC) of 0.996 (95% CI, 0.988 to 1.000) with 95.0% sensitivity and 97.5% specificity for a cutoff < 10.47 pg/mL, while ROC curve analysis for IL-37 showed an area under the curve (AUC) of 0.973 (95% CI, 0.945 to 1.000) with 92.5% sensitivity and 95.0% specificity for a cutoff < 34.71 pg/mL. IL-10 levels were inversely correlated with endoscopic severity of disease (mild, 10.23 ± 1.4; moderate, 8.21 ± 1.3; severe, 7.69 ± 1.1 pg/mL; P < 0.001), but there was no correlation with severity (P = 0.668) for IL-37. There was a moderate positive

Conclusions: Treatment-naïve Ulcerative Colitis (UC) patients show significant deficiencies in serum Interleukin-10 (IL-10) and Interleukin-37 (IL-37), indicating compromised anti-inflammatory regulatory functions. These cytokines possess exceptional diagnostic potential, as their area under the receiver operating characteristic curve (AUC) is consistently higher than 0.97, outperforming existing markers. Moreover, IL-10 acts as a severity biomarker, showing an inverse correlation with endoscopic inflammation. These observations suggest potential non-invasive markers for Ulcerative Colitis diagnosis, which may be used for monitoring treatment response in the future.

Keywords: Ulcerative colitis, Interleukin-10, Interleukin-37, Inflammatory bowel diseases.

Introduction

Ulcerative colitis (UC) is a chronic, remitting-relapsing inflammatory bowel disease characterized by continuous inflammation of the colon's mucosa, which begins in the rectum and extends proximally to involve parts of the colon (Le Berre, Honap, & Peyrin-Biroulet, 2023). The incidence and prevalence rates of UC worldwide have been increasing steadily, showing marked geographic variation and posing significant healthcare and socioeconomic problems (R. Wang, Li, Liu, & Zhang, 2023). Although the pathogenesis of UC is still not clearly understood, existing evidence indicates that it involves multiple factors, including genetics, environment, intestinal microbiome, and immune response (Calvez et al., 2025). Among these factors, immune response imbalance, particularly cytokine balance, has been identified as one of the major factors that cause inflammation in UC. (Friedrich, Pohin, & Powrie, 2019). Regulatory cytokines play a critical role in the maintenance of immune homeostasis in the intestine by controlling excessive inflammatory responses to prevent tissue damage. Among these cytokines, interleukin-10 (IL-10), an anti-inflammatory cytokine with pleiotropic functions, has emerged as one of the key immunoregulatory cytokines in the gastrointestinal tract (Glocker et al., 2009). IL-10, mainly secreted by regulatory T cells, macrophages, and dendritic cells, possesses potent immunosuppressive activities against antigen-presenting cells and induces immune tolerance to the microbiota of the host.(Kühn, Löhler, Rennick, Rajewsky, & Müller, 1993). IL-10 and its receptor gene polymorphism has been strongly associated with increased susceptibility to IBD. Moreover, IL-10-deficient mice spontaneously develop severe chronic colitis, underscoring the importance of IL-10 in the regulation of immune homeostasis in the intestine(Franke et al., 2008; Glocker, Kotlarz, Klein, Shah, & Grimbacher, 2011) Studies suggest that IL-10 may play a key role in the regulation of intestinal inflammation by reducing the apoptosis of intestinal epithelial cells, suppressing the expression of pro-inflammatory cytokines including IL-6 and interferon-γ, and modulating the oxidative stress response. (He et al., 2025). Interleukin-37 (IL-37), a newly identified cytokine belonging to the interleukin-1 (IL-1) family, has been identified as a key player in limiting innate immunity (Nold et al., 2010). IL-37, produced by intestinal epithelial cells, regulatory T cells, and various other immune cells, plays a critical role in limiting the production of pro-inflammatory cytokines mediated through the action of IL-1 and Toll-like receptors(Jia, Liu, & Han, 2018) IL-37 has been shown to exert anti-inflammatory effects through the inhibition of the nuclear factor kappa-B (NF-κB) and the mitogen-activated protein kinase (MAPK) pathways, as well as the promotion of the proliferation of regulatory T cells(Lahimchi, Eslami, & Yousefi, 2023). Experimental data obtained from IL-10 knockout mouse models have demonstrated that transgenic overexpression of

IL-37 significantly reduces intestinal inflammation, ulcer formation, and carcinogenesis in chronic colitis, thus highlighting the anti-inflammatory potential of this cytokine(Mountford et al., 2019) . Moreover, the anti-inflammatory potential of IL-37 has been demonstrated to strengthen the intestinal epithelial barrier and regulate the innate immune response in organoid models(Kröhn et al., 2023). However, recent data suggest that the function of IL-37 may be dependent on various conditions, as some studies have reported the exacerbation of colitis in response to specific microbiomes, thus indicating a complex function of this cytokine, which was not previously considered.(Cong et al., 2022).

In spite of the established protective functions of interleukin-10 (IL-10) and interleukin-37 (IL-37), the expression and significance of the mentioned cytokines in ulcerative colitis (UC) patients are still the focus of research. The existing evidence points to the involvement of the mentioned regulatory cytokines in the maintenance of chronic intestinal inflammation. Thus, the mucosal IL-10 levels in UC patients were found to be increased, which is a sign of a compensatory anti-inflammatory response. The systemic levels of IL-10 and the correlation with the activity of the disease are characterized by inconsistency in different populations of UC patients (Guo & Lv, 2023). The role and significance of IL-37 in the pathogenesis of human UC are not elucidated yet. The recent studies on the subject are characterized by inconsistency in the expression levels and the anti-inflammatory or pro-inflammatory properties of the mentioned cytokine, depending on the composition of the intestinal microbiome. (Mohammed, Ghaloub, Risan, & Medicine, 2024). Such discrepancies may be attributed to the different phenotypes of disease, treatment, genetic backgrounds, and research methodologies. However, the majority of the studies concerning the regulation of cytokines in UC have been conducted in Western and Asian populations, with limited data available for Middle Eastern populations. Epidemiological studies have demonstrated that the incidence of inflammatory bowel disease (IBD), including UC, in the Middle East and newly industrialized regions is increasing, whereas region-specific immunology profiles have not been well characterized. (Tang, Huang, Zhu, Xu, & biology, 2025) Significant variations in genetic polymorphisms, dietary habits, environmental factors, and gut microbiomes have also been reported across different populations, which may affect the expression of cytokines and the manifestation of diseases (Porras et al., 2021). Furthermore, most of the earlier studies have recruited patients undergoing immunosuppressive or biological therapy, which may affect the results of cytokine analysis by interfering with the intrinsic immunological abnormalities in the pathogenesis of UC. Studying treatment-naïve patients is a unique approach to understanding immunological abnormalities at baseline, unaltered by any therapeutic interventions(D'Incà & Sturniolo, 2023).

Considering the aforementioned gaps in knowledge, the current study seeks to assess the levels of serum IL-10 and IL-37 in treatment-naive Iraqi patients with ulcerative colitis (UC) and healthy controls. The specific objectives of the proposed research are: (1) to determine and compare the levels of IL-10 and IL-37 in the sera of patients with UC and healthy controls; (2) to determine the accuracy of IL-10 and IL-37 as potential non-invasive biomarkers in the diagnosis of UC using the ROC curve; (3) to determine the relationship between IL-10 and IL-37 levels; and (4) to determine the relationship between the levels of IL-10 and IL-37 and the severity of the disease using endoscopic assessment. The proposed research will yield novel findings regarding the role of regulatory cytokines in the pathogenesis of UC in the Middle Eastern population and their potential role as biomarkers in the diagnosis of the disease.

Materials and Methods

2.1 Study Design and Participants

The study was a prospective case–control study conducted at the Gastroenterology Unit of Al-Diwaniyah Teaching Hospital in Al-Diwaniyah, Iraq. The study was conducted between October 1st, 2025, and April 1st, 2026. The study was designed to investigate the levels of interleukin-10 (IL-10) and interleukin-37 (IL-37) in treatment-naive ulcerative colitis patients and healthy controls. A total of 80 participants were included in the study. Among the participants, there were 40 healthy controls and 40 ulcerative colitis patients. All the patients with ulcerative colitis were treatment-naive. This meant that the patients with ulcerative colitis were not previously treated with any immunosuppressive agents, biological agents, or corticosteroids. In addition, the study was approved by the Institutional Review Board of the University of Al-Qadisiyah. Informed consent was obtained from all the participants before the study.

2.2 Inclusion and Exclusion Criteria

For patients with ulcerative colitis (UC), the inclusion criteria were: (1) a diagnosed case of UC according to clinical evaluation, endoscopic examination, and histopathological results in accordance with established guidelines; (2) the patient's age ranged from 18 to 60 years; (3) the patient was treatment-naïve, meaning the patient was not previously subjected to treatment with corticosteroids, immunosuppressive agents, or biologic agents; and (4) the patient's clinical and endoscopic data were complete. The exclusion criteria were: (1) the presence of other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, or other inflammatory bowel diseases except ulcerative colitis; (2) the presence of chronic infections such as hepatitis B, hepatitis C, tuberculosis, or HIV; (3) the presence of malignancies or a history of malignancies within the past five years; (4) the patient was either pregnant or lactating; (5) the patient declined to participate in the research; and (6) the patient's condition was ambiguous with regard to the conclusions drawn from the diagnosis.

Healthy controls were collected from the population of attendees at the hospital for routine health checks or to accompany patients. The inclusion criteria for the healthy controls were as follows: (1) the controls had to be between the ages of 18 and 60; (2) the controls had to have no history of inflammatory bowel disease, gastrointestinal symptoms, or other chronic inflammatory conditions; (3) the controls had to have no history of autoimmune or chronic infectious diseases; and (4) the controls had to be willing to participate in the study. The healthy controls were matched to the ulcerative colitis (UC) patients based on age, within ±5 years, and gender to control for potential confounding variables.

2.3 Assessment of Disease Severity

Disease severity in the participants with ulcerative colitis (UC) was determined using the Endoscopic Mayo Sub-score. This scoring system has been validated for assessing the endoscopic severity of ulcerative colitis. The range for the Endoscopic Mayo Sub-score is between 0 and 3. A higher score reflects a higher disease activity. The scoring for the endoscopic severity of ulcerative colitis is as follows: a score of 0 reflects normal or inactive disease (normal vascular pattern and absence of friability), a score of 1 reflects mild disease (erythema, diminished vascular pattern, and mild friability), a score of 2 reflects moderate disease (moderate erythema, absent vascular pattern, friability, and erosions), and a score of 3 reflects severe disease (spontaneous bleeding and ulceration). Experienced gastroenterologists endoscopically examined the participants and categorized the participants based on the endoscopic severity of ulcerative colitis as mild (0-1), moderate (2), and severe (3).

2.4 Blood Sample Collection and Processing

Peripheral venous blood (5 ml) from each participant was collected under sterile conditions using standard phlebotomy techniques. Blood was drawn into plain tubes without an anticoagulant to ensure the separation of the serum from the sample. The blood clotted at room temperature for 30 minutes and then centrifuged at 3,000 g for 15 minutes at 4°C to separate the serum from the sample. The serum was then separated into sterile microcentrifuge tubes and stored at -80°C prior to analysis. The sample processing was completed within 2 hours of sample collection to ensure the stability of cytokines and the absence of freeze-thaw cycles.

2.5 Measurement of Serum IL-10 and IL-37 Concentrations

The levels of IL-10 and IL-37 in the sera were estimated by sandwich enzyme-linked immunosorbent assay (ELISA) technique. All the procedures were done strictly according to the manufacturer's guidelines. In brief, the assay was done by employing a 96-well plate coated with anti-IL-10 and anti-IL-37 antibodies. Serum samples were added to the wells in duplicate and incubated at 37°C for 90 minutes. After incubation, the wells were washed four times with wash buffer to remove any unbound materials. Biotin-conjugated anti-IL-10 and anti-IL-37 were added to the wells and incubated at 37°C for 60 minutes. After the incubation period, the wells were washed four times with wash buffer. Then, horseradish peroxidase-streptavidin was added to the wells and incubated at 37°C for 30 minutes. A final wash was done to remove any unbound materials. Tetramethylbenzidine substrate was added to the wells and incubated in the dark at room temperature for 15 minutes. After the addition of the substrate, the plate was stopped by adding the stop solution. Finally, the plates were read at 450 nm with a microplate reader (BioTek Instruments, USA). Intra-assay and inter-assay variations were less than 10%.

2.6 Statistical Analysis

Statistical analysis was performed using the statistical software program SPSS 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe the demographic and clinical characteristics of the sample. Continuous data were expressed as the mean and standard deviation if the data were normally distributed or as the median and interquartile range if not normally distributed. For the categorical data, the results were expressed as frequency and percentage. The normality of the data was tested using the Kolmogorov-Smirnov test.

For the comparison between the levels of interleukin-10 (IL-10) and interleukin-37 (IL-37) in UC patients and healthy controls, a two-sample t-test was applied for those data sets that met the criteria for a normal distribution. Otherwise, the Mann-Whitney U test was used. To compare the levels of IL-10 and IL-37 between mild, moderate, and severe UC cases, a one-way ANOVA test followed by a post-hoc test using Tukey's test was applied for those data sets that met the criteria for a normal distribution. Otherwise, a Kruskal Wallis test followed by a post-hoc test using Dunn's test was applied.

In this study, receiver operating characteristic curve analysis was used to evaluate the diagnostic potential of interleukin-10 and interleukin-37 as potential markers for ulcerative colitis. The area under the curve, sensitivity, specificity, positive and negative predictive values were calculated. The cutoff points for the markers were determined using the Youden index. The correlation between the levels of interleukin-10 and interleukin-37 and the disease severity score was determined using the Pearson correlation coefficient. The significance level was set at a two-tailed p-value < 0.05.

2.7 Ethical Considerations

The research was carried out with the ethical considerations as per the Declaration of Helsinki. The research was approved by the Institutional Review Board of the University of Al-Qadisiyah with the ethical committee's approval number: IRB-2025-UC-10. The research participants were fully informed about the research objectives, procedures, risks, and benefits before the data collection process. The research participants were assured confidentiality and the right to withdraw from the research at any stage without any consequences.

Results

3.5.1. Interleukin-10 (IL-10) level in patients and healthy controls.

The comparison of Interleukin-10 (IL-10) level between patients and control groups has been carried out and the results were demonstrated in table (3-3). Mean levels of IL-10 were 8.33± 1.14 and 12.31± 1.08, in UC disease patients and healthy control group respectively; the mean levels was lower in UC patients in compared to healthy control and the difference was significant (P= 0.001).

Table (3-3): Interleukin-10 (IL-10) level in patients and healthy control.

Groups		**Interleukin-10 (IL-10) level**
UC patients	**Mean ± SD**	**8.33 ± 1.14**
	Range	7.12-10.70
Healthy control	**Mean ± SD**	**12.31** ± 1.08
	Range	10.18-13.83
p-value		**0.001**** †

n: number of cases; **SE**: standard error; †: Independent T test; **: significant at $P < 0.05$

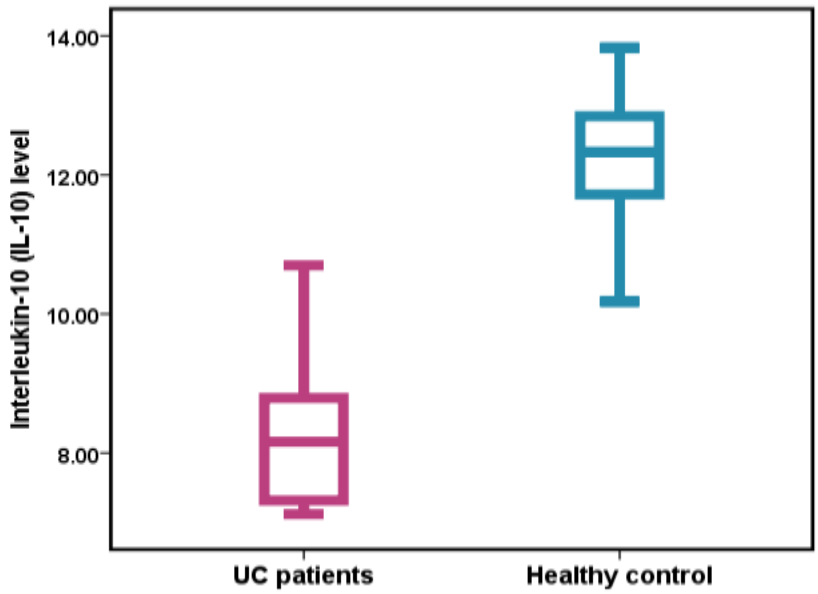

Figure (3-4): The means level of IL-10 in patients and control groups

3.5.1.1 Diagnostic accuracy of Interleukin-10 (IL-10) level

Receiver operating characteristic (ROC) analysis was performed to reveal the diagnostic accuracy of using IL-10 concentrations to UC patients from healthy control subjects and the results are shown in table (3-4), and figure (3-5). The IL-10 cutoff value was less than 10.47-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 95.0%, 97.5%, 97.4%, 95.1% and 0.996 (0.988- 1.000). The present results indicates IL-10 is considered as excellent diagnostic marker.

Table (3-5): Sensitivity and specificity of IL-10 level (<10.47-fold) in UC disease

IL-10 level	**UC patients** ***n*** **= 40**	**Healthy control** ***n*** **= 40**
< 10.47	38 (%)	1(%)
> 10.47	2 (%)	39 (%)
Sensitivity %	95.0 %	
Specificity %	97.5 %	
PPV %	97.4 %	
NPV %	95.1%	
AUC (95% CI)	0.996 (0.988- 1.000)	

CI: Confidence interval, AUC: Area under curve.

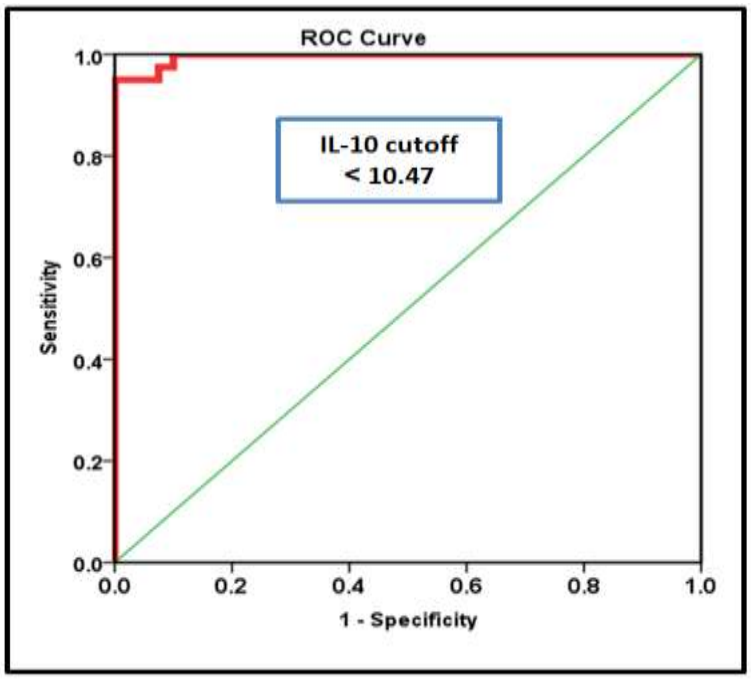

Figure (3-5): Receiver operator characteristic curve analysis of IL-10 for the calculation of possible diagnostic cutoff value.

IL-10 levels as a function of multiple attributes

An analysis of IL-10 levels as a function of multiple attributes is shown in Table 3. The results indicate that IL-10 levels were significantly lower in patients with severe disease than in patients with moderate and mild disease, respectively (7.69 ± 1.10 vs. 8.21 ± 1.30 and 10.23 ± 1.40, P = 0.001). In addition, the results indicate a non-significant tendency toward increased IL-10 levels in patients with disease duration of less than 5 years than in patients with disease duration of 5 years or more (8.46 ± 1.16 vs. 7.81 ± 1.02, P = 0.083). Furthermore, when compared with patients who do not have a positive family history, patients with a positive family history have a non-significantly increased level of IL-10 (8.59 ± 1.21 vs. 8.25 ± 1.18), P = 0.444.

Table 3: Range of IL-10 levels by frequency across specific attributes.

Characteristics		n	Mean ± SD	Range	P
Severity of disease					
Severity of disease	Mild n=9	9	10.23 ± 1.40	7.22 – 12.50	0.001 A HS
	Moderate n=13	13	8.21 ± 1.30	6.10 – 10.20	
	Severe n=19	19	7.69 ± 1.10	5.80 – 9.80	
Duration of disease					
Duration of disease	< 5 years	25	8.46 ± 1.16	7.12 – 10.70	0.083 † NS
	≥ 5 years	15	7.81 ± 1.02	6.20 – 9.90	
Family history					
Family history	Positive n=9	9	8.59 ± 1.21	7.12 – 10.50	0.444 † NS
	Negative n=31	31	8.25 ± 1.18	6.10 – 10.70	

n: number of cases; SD: standard deviation; †: Mann–Whitney test; A: One-way ANOVA; K: Kruskal–Wallis test; HS: highly significant at P ≤ 0.001; NS: not significant at P > 0.05.

3.5.2. Interleukin-37 (IL-37) level in patients and healthy controls.

The comparison of Interleukin-37 (IL-37) level between patients and control groups has been carried out and the results were demonstrated in table (3-5). Mean levels of IL-37 were 24.79 ± 5.23 and 40.90 ± 5.07, in UC disease patients and healthy control group respectively; the mean levels was lower in UC patients in compared to healthy control and the difference was significant (P= 0.001).

Table (3-5): Interleukin-37 (IL-37) level in patients and healthy control.

Groups		Interleukin-37 (IL-37) level
UC patients	**Mean ± SD**	**24.79 ± 5.23**
	Range	10.86-37.70

Healthy control	**Mean ± SD**	**40.90** ± 5.07
	Range	29.78-52.20
p-value		**0.001**** †

n: number of cases; **SE**: standard error; †: Independent T test; **: significant at $P < 0.05$

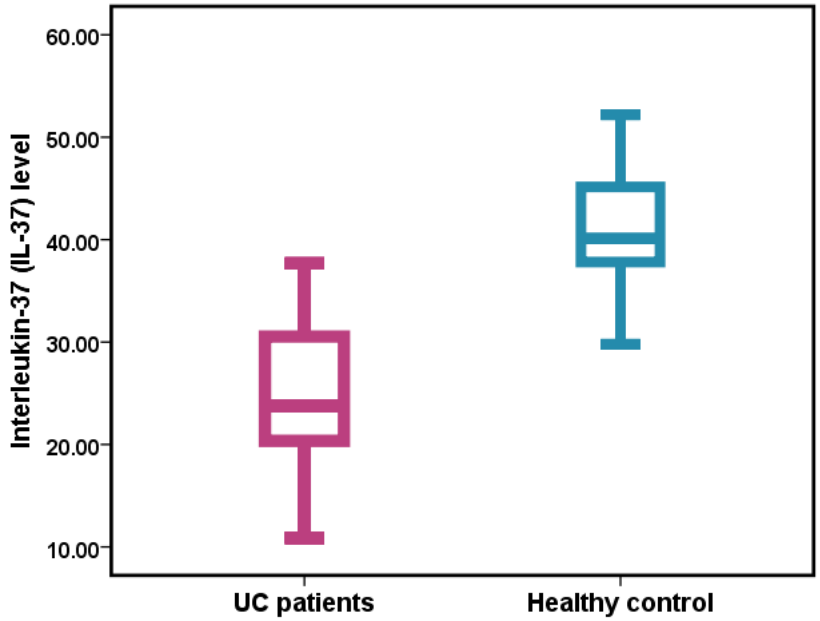

Figure (3-6): The means level of IL-37 in patients and control groups

3.5.2.1 Diagnostic accuracy of Interleukin-37 (IL-37) level

Receiver operating characteristic (ROC) analysis was performed to reveal the diagnostic accuracy of using IL-37 concentrations to UC patients from healthy control subjects and the results are shown in table (3-6), and figure (3-7). The IL-37 cutoff value was less than 34.71-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 92.5%, 95.0%, 94.9%, 92.7% and 0.973 (0.945- 1.000). The present results indicates IL-37 is considered as excellent diagnostic marker.

Table (3-6): Sensitivity and specificity of IL-37 level (<34.71-fold) in UC disease

IL-37 level	**UC patients** ***n* = 40**	**Healthy control** ***n* = 40**
< 34.71	37 (%)	2 (%)
> 34.71	3 (%)	38 (%)
Sensitivity %	92.5 %	
Specificity %	95.0 %	
PPV %	94.9 %	
NPV %	92.7%	
AUC (95% CI)	0.973 (0.945- 1.000)	

CI: Confidence interval, AUC: Area under curve.

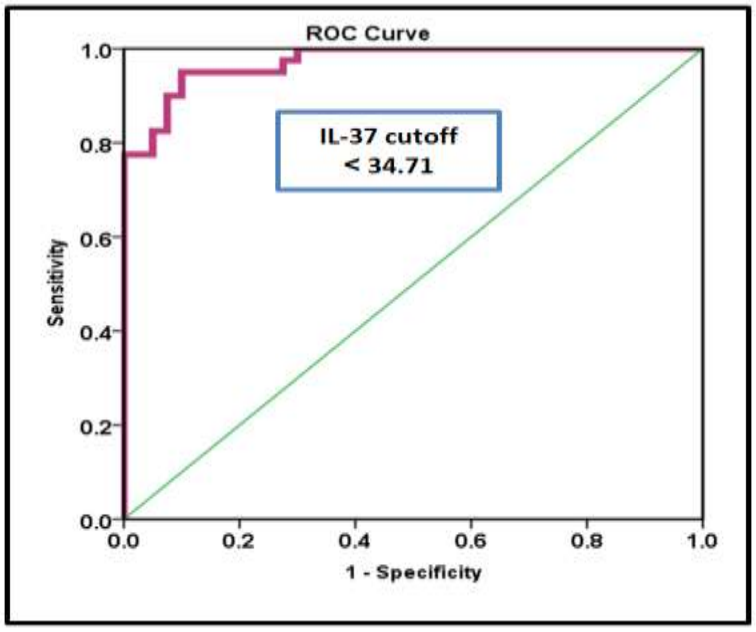

Figure (3-7): Receiver operator characteristic curve analysis of IL-37 for the calculation of possible diagnostic cutoff value.

IL-37 levels in different attributes

An examination of the levels of IL-37 in different attributes was performed, and the results are depicted in Table 4. The data show that there was no statistical variation in the levels of IL-37 in different categories of disease severity, including mild (25.61 ± 4.78), moderate (25.58 ± 5.52), and severe (23.49 ± 4.95) disease (P = 0.668). The levels of IL-37 in the disease duration of less than 5 years and over 5 years were not significantly different (25.41 ± 6.87 and 23.22 ± 6.99, respectively; P = 0.371). The levels of IL-37 in the presence or absence of a positive family history were compared, and the data show that the levels of IL-37 in the presence of a positive family history were significantly elevated but not significantly different (28.29 ± 6.15 and 23.14 ± 5.72, P = 0.151).

Table (4) shows the level of IL-37 across a range of frequency ranges, which are defined based on specific attributes.

Characteristics		n	Mean ± SD	Range	P
Severity of disease					
Severity of disease	Mild n=9	9	25.61 ± 4.78	17.20 – 33.40	0.668 A NS
	Moderate n=13	13	25.58 ± 5.52	15.10 – 35.20	
	Severe n=19	19	23.49 ± 4.95	12.50 – 33.80	
Duration of disease					
Duration of disease	< 5 years	25	25.41 ± 6.87	10.86 – 37.70	0.371 † NS
	≥ 5 years	15	23.22 ± 6.99	11.20 – 35.90	
Family history					

Characteristics		n	Mean ± SD	Range	P
Family history	Positive n=9	9	28.29 ± 6.15	18.40 – 37.70	0.151 † NS
	Negative n=31	31	23.14 ± 5.72	10.86 – 35.20	

Note: n represents the number of cases; SD represents standard deviation; † represents the Mann-Whitney test; A represents One-way ANOVA; K represents Kruskal-Wallis test; NS represents not significant at P > 0.05.

Discussion

Ulcerative colitis indeed poses a considerable health risk to the global population, as the worldwide prevalence of the disease in the year 2023 has been estimated to be about 5 million cases (Kobayashi et al., 2020). Incidence of the disease has been reported to have risen at a rapid rate in newly industrialized countries, including the Middle East (Ng et al., 2017). The aim of the present study was to evaluate and compare the serum levels of IL-10 and IL-37 in 40 treatment-naïve ulcerative colitis patients and 40 healthy controls. The mean age of the patient group was found to be 36.95 ± 7.24 years, whereas the mean age of the healthy controls was found to be 35.67 ± 6.56 years. There were no significant differences in the mean age and gender of the study subjects (P = 0.479 and P = 0.370, respectively), indicating that the study subjects were well-matched.

In the present study, the mean serum levels of IL-10 in ulcerative colitis patients were found to be significantly lower compared to healthy controls (8.33 ± 1.14 pg/mL vs. 12.31 ± 1.08 pg/mL, P = 0.001). The anti-inflammatory cytokine IL-10 has been considered to be one of the most important regulatory mediators of the immune system (Godala, Gaszyńska, Walczak, & Małecka-Wojciesko, 2023).

However, there are inconsistencies in the literature regarding the level of interleukin-10 (IL-10) in patients with ulcerative colitis (UC) (Pavel et al., 2025; Yamamoto-Furusho, Fonseca-Camarillo, Barrera-Ochoa, & Furuzawa-Carballeda, 2020). Some studies found that IL-10 was raised in patients with UC, whereas others found that IL-10 was decreased during active disease (Aghamohamadi et al., 2022; Cui et al., 2024) The reason for these inconsistencies may be related to disease activity and treatment status. In this study, we specifically recruited treatment-naïve patients with active disease, which may explain our findings. Recent studies on the mechanisms of IL-10 showed that IL-10 controls cellular metabolism in macrophages and that it has several mechanisms to control intestinal inflammation (Marlow, van Gent, & Ferguson, 2013; Rosnev et al., 2025)

IL-10 gene polymorphisms were found to increase susceptibility to UC (Krawiec, Lejman, & Pac-Kożuchowska, 2025; Liu, Yuan, & Park, 2022).Similar to that of IL-10, the serum level of IL-37 in patients with ulcerative colitis (UC) was significantly decreased compared to healthy controls (24.79 ± 5.23 pg/mL vs 40.90 ± 5.07 pg/mL, P = 0.001). IL-37, a member of the IL-1 superfamily, is known to play a significant role in the regulation of inflammatory bowel diseases and autoimmune diseases as an anti-inflammatory cytokine (Mohammed et al., 2024).

IL-37 exerts its regulatory effects by interacting with IL-18Rα or by entering the nucleus along with Smad3 (Rusiñol & Puig, 2024). Studies involving transgenic mice expressing human IL-37 have demonstrated reduced intestinal inflammation compared to wild-type mice (Q. Wang, Zhang, An, Hambly, & Bao, 2024).Several clinical studies have documented the inverse relationship between IL-37

expression in the intestine and mucosal inflammation in IBD patients (Andoh & Nishida, 2023; Dang et al., 2022).

From the present study, the simultaneous decrease in the expression of IL-10 and IL-37 indicates the involvement of various anti-inflammatory pathways in the development of ulcerative colitis. ROC analysis was conducted to assess the diagnostic potential of IL-10 and IL-37. IL-10 showed excellent diagnostic potential with an optimal cutoff value (<10.47 pg/mL), which resulted in a sensitivity of 95.0%, specificity of 97.5%, and AUC of 0.996 (95% CI: 0.988-1.000). IL-37 also showed excellent diagnostic potential with an optimal cutoff value (<34.71 pg/mL), which resulted in a sensitivity of 92.5%, specificity of 95.0%, and AUC of 0.973 (95% CI: 0.945-1.000). This indicates the superior diagnostic potential of these cytokines as non-invasive markers of ulcerative colitis. Moreover, the diagnostic potential of these cytokines was superior to the other markers of ulcerative colitis, including C-reactive protein and calprotectin (Dulai et al., 2023; Kawashima et al., 2023).

IL-10 levels were inversely correlated with the severity of the disease ($P < 0.001$), while IL-37 levels were not correlated with the severity of the disease as reflected by endoscopy ($P = 0.668$), suggesting the involvement of these cytokines in the pathogenesis of ulcerative colitis (UC). A moderate positive correlation was observed between IL-10 and IL-37 levels by Pearson's correlation analysis ($r = 0.531$, $P = 0.001$), suggesting the involvement of these cytokines in the regulation of the immune response. The treatment of UC has evolved with the introduction of IL-23 inhibitors, JAK inhibitors, and S1P modulators (Shehab et al., 2025; Vieujean et al., 2025). However, despite such advances, the outcome still remains suboptimal, and the lack of regulatory cytokines may be one of the reasons for this problem (Friedrich et al., 2019).

Therapeutic strategies for the treatment of the IL-10 system have been investigated, including the use of recombinant IL-10 and cell-based therapy (Neurath, 2024; Tian et al., 2025). The detection of patients who show low levels of regulatory cytokines may help in the practice of precision medicine. There are various strengths associated with the study. However, the limitations include a cross-sectional design, a single-center study, and the lack of tissue expression. Overall, the serum levels of interleukin-10 (IL-10) and interleukin-37 (IL-37) show a marked decrease in treatment-naïve patients with ulcerative colitis (UC). Moreover, the diagnostic accuracy for these two cytokines is excellent, as the area under the curve (AUC) > 0.97. The regulation of the pathways for regulatory cytokines may play a significant role in the pathogenesis of the disease. These two biomarkers may prove to be useful for the diagnosis and treatment of UC.

Conclusion

This study clearly indicates that in the serum of treatment-naïve patients with ulcerative colitis, the level of IL-10 and IL-37 is significantly lower compared to healthy controls. In the serum of patients with ulcerative colitis, the level of IL-10 is 8.33 ± 1.14 pg/mL, while in healthy controls, the level of IL-10 is 12.31 ± 1.08 pg/mL, showing significant differences between the two groups at $P = 0.001$. Similarly, the level of IL-37 in patients with ulcerative colitis is 24.79 ± 5.23 pg/mL, while in healthy controls, the level of IL-37 is 40.90 ± 5.07 pg/mL, showing significant differences between the two groups at $P = 0.001$. Both these cytokines show good diagnostic potential, as indicated by the high area under the ROC curve, i.e., 0.996 (95% CI = 0.988-1.000) for IL-10, while the area under the ROC curve is 0.973 (95% CI = 0.945-1.000) for IL-37. Thus, the low level of these regulatory cytokines indicates that these regulatory

pathways are of critical importance in the pathogenesis of ulcerative colitis, which is in accordance with the concept that the low level of regulatory cytokines is responsible for the persistence of intestinal inflammation in ulcerative colitis.

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Conflict of Interest

The authors declare that they have no competing interests or conflicts of interest.

Ethical Approval

Informed consent was obtained from all participants before the study.

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