The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 5238- 5245

Interleukin-23 as a Predictor of Activities in Inflammatory Bowel Disease

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ABSTRACT

Background: Crohn's disease and ulcerative colitis are both examples of inflammatory bowel diseases (IBDs) that are chronic GIT diseases of unknown etiology**.**

Aim: This research aimed to ascertain the interleukin-23 serum level in Crohn's disease and ulcerative colitis disease patients. **Patients and Methods:** The research was a case-control investigation involving 72 participants, subdivided into 48 patients who were either hospitalized in ICU or inpatient wards or outpatient clinics (IBD OPD) in Internal Medicine Department, (Zagazig University Hospitals). In addition, 24 healthy individuals who were age- and sex-matched were selected as a control.

Results: There were discernible contrasts between the groups with regard to the levels of IL-23. When the two groups are compared, it is clear that there was a considerable distinction between Crohn's disease (CD) in remission and moderate and severe ulcerative colitis. In addition, there was a significant difference between Crohn's disease, which is moderately severe, and ulcerative colitis, which is very severe. There is a large gap between having moderate Crohn's disease and having moderate ulcerative colitis.

Conclusion: The findings of this study lend support to the hypothesis that determining an individual's IL-23 levels may be helpful in determining the degree to which Crohn's disease or UC is present. It is possible to postulate that IL-23 is a reliable indicator of the eventual results of the patients. Therefore, it is possible for it to be evaluated with a lower amount of effort and cost compared to other markers and procedures.

Keywords: Interleukin 23, Predictor, Inflammatory bowel disease.

INTRODUCTION

Crohn's disease and ulcerative colitis are examples of IBDs, which are chronic illnesses of the GIT with an elusive root cause. Symptoms may develop gradually, starting with non-bloody diarrhea and low-weight growth. Extraintestinal symptoms impact more than a third of people with IBD [(1)]. Chronic IBD is most often shown in two diseases; Crohn's disease and ulcerative colitis. Both disorders are caused by an abnormal immune reaction of the gut microbiota [(2)]. Thus, understanding the components that contribute to susceptibility is crucial. Constant inflammation of the digestive system is what defines Crohn's disease, which is a kind of IBD that affects many people. The annual worldwide incidence of IBD has been rising steadily, with some estimates putting the number of Europeans with the disease at 2.2 million. Most damage occurs in the colon and terminal ileum, however, any region of the GI tract might be affected [(3)].

Genetic predisposition, environmental circumstances, and intestinal microbiota can all have a role in the development of Crohn's disease, which is characterized by a change in the mucosal immune response and the epithelial barrier function. The presence of symptoms like abdominal discomfort, diarrhea, rectal bleeding, fever, weight loss, and weariness can have a significant negative impact on a person's quality of life when they have CD. It is not uncommon for this severe disease to cause inflammation outside the intestines in the eyes, liver, skin, and joints. This highlights the disease's systemic character. In addition, the vast majority of patients experience penetrating or structuring difficulties, which need a great deal of surgical intervention and frequently leave them permanently incapacitated [(4)]. The mucosa that lines the colon is the only part of the body affected by ulcerative colitis (UC). Patients who suffer from IBD have a higher chance of developing cancer [(5)], and there appears to be a hereditary predisposition to the disease. The clinical signs of UC include diarrhea that does not go away, discomfort in the stomach, a lack of appetite, and stunted development. Many episodes of remission characterize the clinical history of UC and return in spite of treatment [(6)].

IL-23 is a heterodimer cytokine, and its p40 subunit, which is also present in IL-12, and its p19 subunit, which is also encoded by the IL-23 gene, are both components of the heterodimer. In contrast to IL-23, which belongs to the IL-12 cytokine family, human p19 is a protein composed of four alpha-helices and has a sequence that is 70% identical to that of its mouse orthologue. IL-23 was responsible for the activation of pSTAT3 in CD4+ mucosal T cells, which made these cells resistant to apoptotic signals. Significant quantities of cytokines belonging to the Th-1 and Th-17 subtypes are released when T cells are stimulated. Patients with Crohn's disease who have failed treatment with anti-TNF therapies have an excess of TNFR2+IL23R+T cells in the mucosa, which maintains chronic intestinal inflammation. It has long been hypothesized that the pro-inflammatory cytokine known as IL-23 plays a significant part in the pathogenesis of autoimmune diseases, and new research appears to lend credence to this speculation. Therefore, increased inflammation and autoimmunity, which have both been linked to UC, could be an explanation for why UC is associated with elevated IL-23 levels. The objective of this study was to determine the levels of interleukin-23 that are present in

Received: 01/12/2022
Accepted: 03/02/2023

the blood of patients suffering from inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis [(7)].

PATIENTS AND METHODS

Seventy-two participants were included in the case-control research, subdivided into 48 Egyptian patients with IBD (24 patients U.C and 24 patients with Crohn's disease), who were either hospitalized in ICU or inpatient wards or outpatient clinic (IBD OPD) in the Internal Medicine Department, (Zagazig University Hospitals), Zagazig, Egypt, in addition to Twenty-four people of similar ages and sexes were selected as a control reference group. The studied group was divided into mild, moderate, and severe cases of ulcerative colitis, and IL-23 was compared between them.

All subjects were notified that blood samples withdrawn from them were for research purposes, and all had given their permission to take part in this investigation. Patients of both sexes were recruited for the research, and participation was contingent upon participants' informed agreement. Clinical, biochemical, stool, endoscopic, and histological examinations combined to identify patients with inflammatory bowel illnesses who presented for colonoscopy complaining of any lower GIT symptoms. The small intestine may need to be seen on a radiograph if Crohn's disease is suspected. Clostridium difficile and other infectious causes of colitis must be ruled out.

Exclusion criteria: pregnancy, acute or chronic renal failure, acute infections, congestive heart failure, thyroid anomalies, strokes, or simply those who refused to take part in the study.

For every patient shared in the study, detailed history and complete general examination personal history including age, name, gender, occupation, residence, and complete general and systemic examination were done.

Laboratory investigations as blood samples by venipuncture for CBC, ESR, CRP, urea, creatinine, total bilirubin, ALT, and AST for each patient. Blood was drawn in a BD vacutainer and measured to be 2 ml ® ESR tube, three ml of blood in ® plastic serum tube, BD vacutainer, and two ml of blood in ® EDTA tube (Becton, Dickinson and Company, NJ). The samples were allowed to clot for thirty minutes at room temperature before being centrifuged at 1200xg for 10 minutes to remove the serum. The serum was taken out and refrigerated at -80 degrees Celsius so that the IL-23 concentration could be measured by Elisa at a later time.

The following laboratory tests were performed for all patients: A fully automated cell counter (XS 500 Sysmex, Germany) was used for a complete blood count. (Gilmour and Sykes, 1951) The erythrocyte sedimentation rate (ESR; westergreen technique). C-reactive protein (CRP) assays were run using a Cobas 6000 from Roche Diagnostics in Mannheim, Germany, equipped with a c501 module. Serum urea, alanine aminotransferase, creatinine, total bilirubin, and aspartate aminotransferase using the Cobas 6000, c501 module (Roche Diagnostics, Mannheim, Germany). Fecal calprotectin ichroma™ Calprotectin Boditech Med Inc, Korea Catalog No. CFPC-83, the reference value was 50 mg/kg feces. Serum level of IL-23 by ELISA of Human Interleukin-23 p19 subunit (IL-23) (Innova Biotech Co, China) CAT NO: 201-12-0075 was performed according to manufacturer recommendation.

Colonoscopy: Colonoscopy is done if there is no contraindication. Colonoscopy was done by two senior experts and by OLYMPUS colonoscope, model /CV-190, serial NO 7336784.

Histopathological examination: The best transverse section may be achieved if tissue samples are promptly immersed in 10% buffered formalin, processed, and paraffin-embedded with a 90°-rotation by the technician. Multiple sections from each tissue sample should be analyzed, since certain lesions may be localized.

The Mayo Score for ulcerative colitis disease activity is a useful tool for gauging disease severity and tracking treatment progress. The scale goes from 0 to 12, with higher numbers signifying more severity. The Harvey-Bradshaw index [(11)] was developed in 1980 as a streamlined alternative to the Crohn's disease activity index (CDAI).

Ethical Approval: The study was approved by the Ethics Board of Zagazig University IRB (ZU-IRB9600 #/20-6-2022). Patients were given all the information they needed about the trial. Informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 26 was utilized in order to carry out the analysis of the collected data. Absolute frequencies were used to construct the categorical variables, and chi-square and Monte Carlo tests were utilized to make comparisons between the categorical variables. In order to validate the hypotheses that the parametric test was based on, the Shapiro-Wilk test was carried out. When comparing quantitative data from two distinct groups, either the independent sample t-test or the Mann-Whitney test was applied, depending on whether or not the data followed a normal distribution. If the data did not follow a normal distribution, the independent sample t-test was used.

RESULT

There was no noticeable difference between the two groups in terms of gender, age, or geography (Table 1).

Table (1): A comparison of the groups analyzed with respect to the parameters studied

		Ulcerative colitis group	Crohn's disease group	Control group	χ^2	p
		N=24 (%)	N=24(%)	N=24(%)		
Gender:	Female	17 (70.8%)	10 (41.7%)	10 (41.7%)		
	Male	7 (29.2%)	14 (58.3%)	14 (58.3%)	5.449	0.066
Residence:	Rural	13 (54.2%)	11 (45.8%)	-		
	Urban	11 (45.8%)	13 (54.2%)		0.333	0.564
		Mean ± SD	**Mean ± SD**	**Mean ± SD**	F	p
	Age (year)	27.83 ± 8.9	28.88 ± 6.78	28.67 ± 7.47	0.12	0.887

χ^2 chi-square test F One way ANOVA test

In terms of IL-23, A statistically significant split may be seen between the studied groups. There was a statistically significant variance between ulcerative colitis patients and other patients (With UC patients ranking highest) (Table 2).

Table (2): Analyzing the IL-23 differences between the groups

	Ulcerative colitis group	Crohn's disease group	Control group	KW	p
	Median (IQR)	**Median (IQR)**	**Median (IQR)**		
IL-23	35.15(26.63 – 53.6)	26.34(22.28 – 50.54)	22.5(21 – 24.2)	21.226	<0.001**
Pairwise	P_1 <0.001**	P_2 0.387	P_3 0.008*		

With a cutoff of ≥ 22.8, IL-23 has the highest area under the curve was 0.748, sensitivity was 75%, and specificity was 54.2%, positive predictive value was 62.1%, negative predictive value was 68.4%, and total accuracy was 64.6%, (p=0.003) for diagnosing Crohn's disease (Table 3).

Table (3): Performance of IL-23 in diagnosis of Crohn's disease

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥22.8	0.748	75%	54.2%	62.1%	68.4%	64.6%	0.003*

When diagnosing ulcerative colitis disease, the optimal cutoff of IL-23 was ≥ 23.75. The cutoff has an area under the curve of 0.884, sensitivity of 87.5%, specificity of 70.8%, positive predictive value of 75%, negative predictive value of 85%, and overall accuracy of 79.2% (p 0.001) (Table 4).

Table (4): Performance of IL-23 in diagnosis of UC disease

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥23.75	0.884	87.5%	70.8%	75%	85%	79.2%	<0.001**

There was a statistically significant inverse association between the level of IL-23 that was present in ulcerative colitis patients and their hemoglobin levels. There was a statistically significant positive connection between IL-23 and the Mayo score in the group of people with ulcerative colitis. The connection between IL-23 in people with ulcerative colitis and either age or other laboratory markers was statistically insignificant (Table 5).

Table (5): Correlation between IL-23 and the studied parameters among patients with ulcerative colitis

	R	P
Age (year)	-0.333	0.12
Calprotectin	0.245	0.248
ALT	-0.141	0.512
AST	-0.304	0.149
Total bilirubin (mg/dl)	-0.088	0.683
Creatinine (mg/dl)	-0.346	0.125
Urea (mg/dl)	0.02	0.93
Glucose (mg/dl)	0.269	0.238
ESR (mm/hr)	-0.056	0.795
CRP (mg/L)	0.204	0.34
Platelet count (10^3/mm^3)	0.288	0.172
Hemoglobin (g/dl)	-0.426	**0.038***
TLC (10^3/mm^3)	0.383	0.063
Mayo	0.727	**<0.001****

There was a correlation between IL-23 and blood creatinine that was statistically significant. Within the Crohn's disease group, there was a correlation that can be considered statistically significant between IL-23 and all of the Calprotectin, ESR, and Mayo scores. In patients with Crohn's disease, the correlation between IL-23 and age or any of the other parameters measured in the lab was not statistically significant (Table 6).

Table (6): A correlation was found between IL-23 and the parameters that were being evaluated in patients with Crohn's disease

	r	p
Age (year)	-0.367	0.078
Calprotectin	0.558	**0.002***
ALT (U/L)	-0.302	0.161
AST (U/L)	-0.124	0.572
Total bilirubin (mg/dl)	-0.317	0.14
Creatinine (mg/dl)	-0.686	**<0.001****
Urea (mg/dl)	-0.358	0.094
Glucose (mg/dl)	0.196	0.407
ESR (mm/hr)	0.409	**0.047***
CRP (mg/L)	0.35	0.093
Platelet count (10^3/mm^3)	0.173	0.42
Hemoglobin (g/dl)	-0.098	0.648
TLC (10^3/mm^3)	0.235	0.292
Mayo	0.69	**<0.001****

When it comes to IL-23, there was a difference that was statistically significant between the populations of persons who have ulcerative colitis and those who have Crohn's disease. When both mild and serious ulcerative colitis and CD that has gone into remission are compared. It is clear that there was a big difference between the two groups. Also, there was a big difference between Crohn's disease that was mild and ulcerative colitis that was serious. Between moderate Crohn's disease and weak ulcerative colitis, there was a big difference (Table 7).

Table (7): Comparison between different severities of Crohn's and ulcerative colitis diseases regarding IL-23

	Median (IQR)	KW	p	Pairwise comparison	
CD on remission	25(21.73 – 27)	26.909	<0.001**	P1 0.289	P7 0.004*
Mild CD	24.5(21.84 – 60.36)			P2 <0.001**	P8 0.056
Moderate CD	66.7(46.41 – 89.05)			P3 <0.001**	P9 0.845
Mild UC	30(23.35 – 34.5)			P4 0.913	
Moderate UC	35.3(26.95 – 47.05)			P5 0.242	
Severe UC	73.35(64.53 – 76.25)			P6 0.002*	

KW Kruskal Wallis test p1 difference between CD on remission and mild UC p2 difference between CD on remission and moderate UC p3 difference between CD on remission and severe UC p4 difference between mild CD and mild UC p5 difference between mild CD and moderate UC p6 difference between mild CD and severe UC p7 difference between moderate CD and mild UC p8 difference between moderate CD and moderate UC p9 difference between moderate CD and severe UC *p<0.05 is statistically significant **p≤0.001 is statistically highly significant.

Table (8) and figure (1) showed that there was a statistically significant difference among the groups of persons who have Crohn's disease in terms of Mayo. There was a significant difference when comparing patients with mild CD to each other category.

Table (8): Comparison between the studied groups regarding laboratory parameters

	Remission	Mild Crohn's	Moderate Crohn's	KW	p
	Median (IQR)	Median (IQR)	Median (IQR)		
IL-23	25(21.73 – 27)	24.5(21.84–50.36)	66.7(46.41 – 89.05)	10.95	0.004*
Pairwise	P1 0.494	P2 0.029*	P3 0.001**		

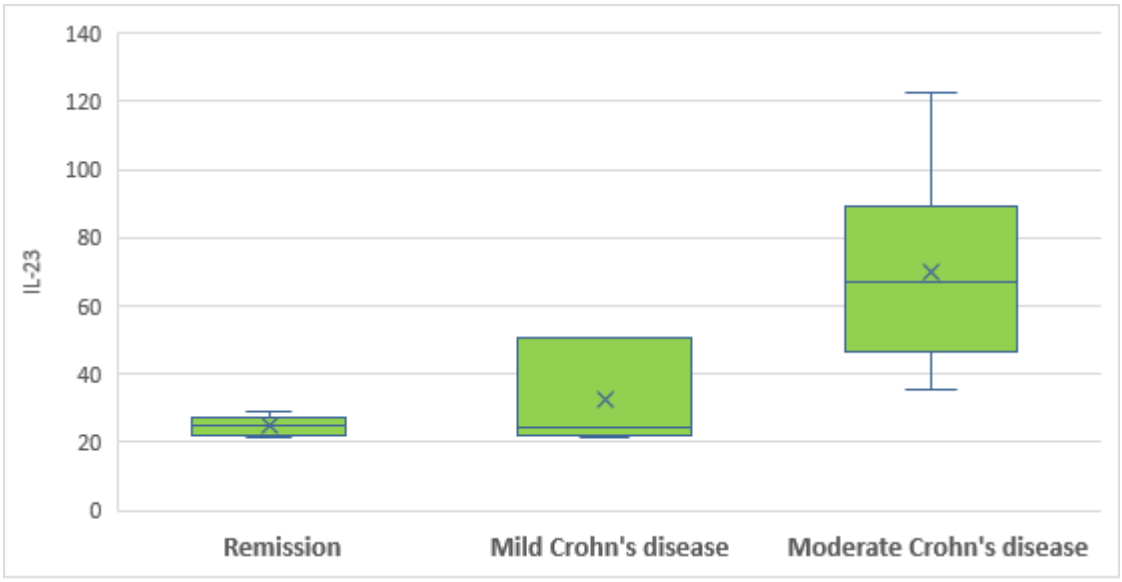

Figure (1): Boxplot showing comparison between groups of CD regarding IL-23

According to table (9) and figure (2), the value of 42.82 was the optimal threshold for measuring IL-23 when attempting to diagnose moderate Crohn's disease. This cutoff had a positive predictive value of 83.3%, a negative predictive value of 83.3%, an overall accuracy of 83.3% (p 0.001), an area under the curve of 0.949, a sensitivity of 83.3%, a specificity of 83.3%, a positive predictive value of 83.3%, and a negative predictive value of 83.3%.

Table (9): Performance of IL-23 in diagnosis of moderate Crohn's disease

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥42.82	0.949	83.3%	83.3%	83.3%	83.3%	83.3%	<0.001**

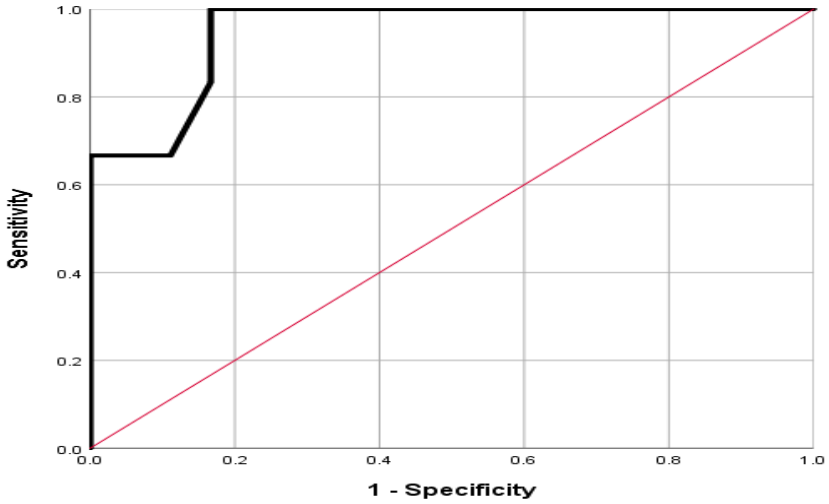

Figure (2): ROC curve showing performance of IL-23 in diagnosis of moderate Crohn's disease

As shown in table (10) and figure (3) there was a statistically significant difference between the groups of people with ulcerative colitis considering the Mayo (on pairwise comparison, there is a significant difference between patients who had severe UC and each other group).

Table (10): Comparison between the studied groups regarding laboratory parameters

	Mild ulcerative colitis	Moderate ulcerative colitis	Severe ulcerative colitis	KW	p
	Median (IQR)	**Median (IQR)**	**Median (IQR)**		
IL-23	30(23.35 – 34.5)	35.3(26.95 – 35.3)	73.35(64.25 – 76.25)	19.932	0.002*
Pairwise	P_1 0.243	P_2 0.012*	P_3 <0.001**		

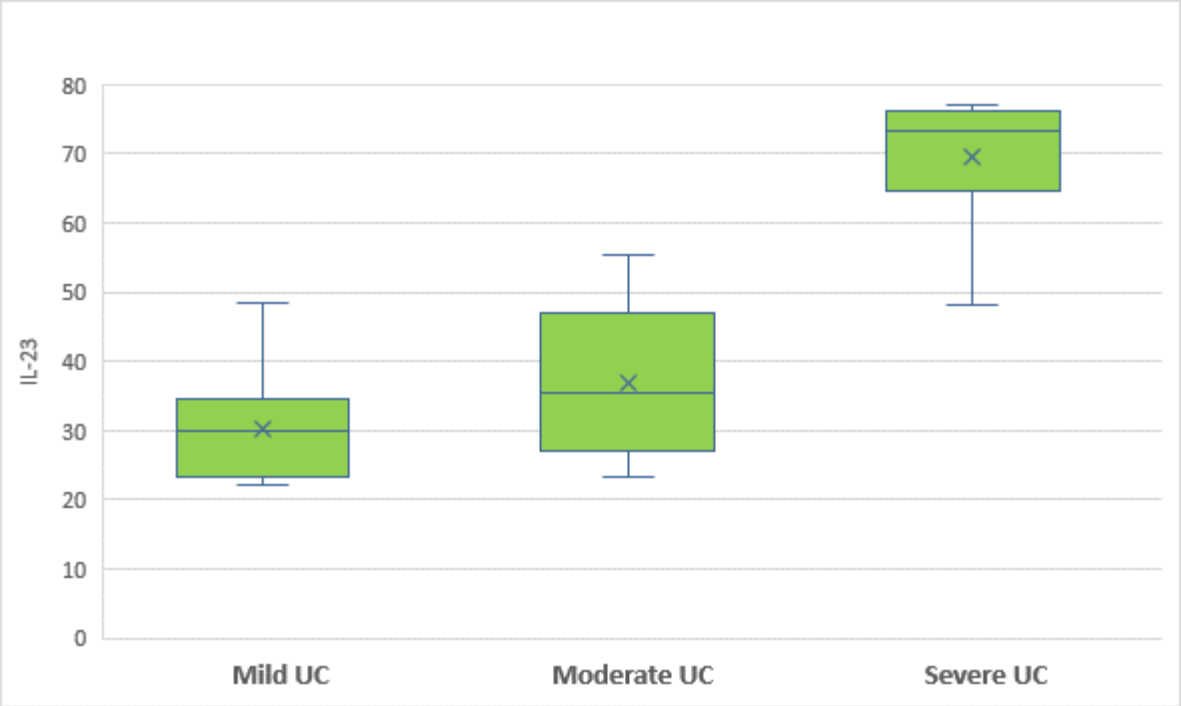

Figure (3): Boxplot showing comparison between groups of ulcerative colitis regarding IL-23

A cutoff of 48.3 for IL-23 had been shown to have the highest area under the curve, the highest sensitivity, the best specificity, the highest positive predictive value, the highest negative predictive value, and the highest overall accuracy, as shown in table (11) and figure (4) ($p<0.001$).

Table (11): Performance of IL-23 in diagnosis of severe ulcerative colitis

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥48.3	0.972	83.3%	83.3%	83.3%	83.3%	83.3%	0.001**

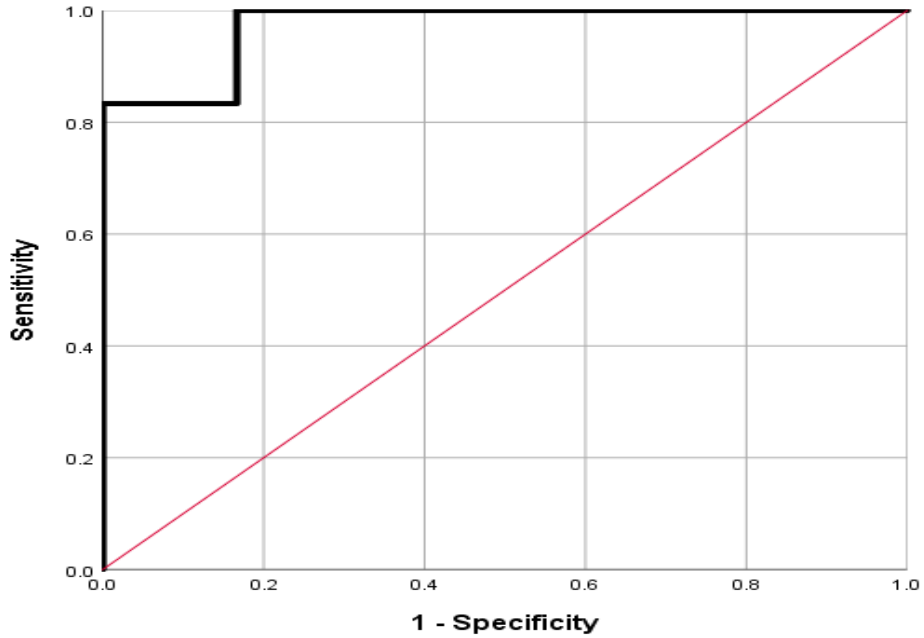

Figure (4): ROC curve showing performance of IL-23 in diagnosis of severe ulcerative colitis

DISCUSSION

Most of the time, IL-23 is thought to be a cytokine that causes CD disease. However, **Kobayashi *et al.*** [8] found that IL-23 expression was higher in both inflamed and non-inflamed mucosa of UC patients. But it's not clear yet what part IL-23 plays in how UC gets worse. Research on the role of IL-23 in inflammatory bowel disease (IBD) has therefore informed us about the complexity and variety of the disease. Additionally, it has begun to show how genetic and risk variables interact in the development of IBD. However, we do not yet have a complete understanding of the intricate genetic background that paves the way for the development of IBD when IL-23 is activated [9].

According to the findings of our study, 24 individuals were found to have ulcerative colitis, and 24 patients were found to have Crohn's disease. We observed that UC is more common in women, whereas CD is more common in males, despite the fact that there was no statistically significant difference between the two groups in regard to sex. In contrary to our finding, **Cosnes *et al.*** [10] reported that UC occurs slightly more frequently in men, whereas CD occurs more in women.

Our results showed that IBD was slightly more frequent in women. **Esmat *et al.*** [11] showed that male to female ratio was 1:1.15. This slightly raise in the female incidence means that there are more women who are affected than in other parts of the world. Inflammatory bowel disease (IBD) is characterized by a considerable difference in prevalence, etiology, and outcomes between men and women. The delicate interplay of well-described components of pathogenesis, including as immunological dysfunction, exposure to the environment, and intestinal dysbiosis, may be altered by sex-dependent variables, as indicated by varying degrees of evidence. These components include genetic predisposition, immunological dysregulation, environmental exposures and intestinal dysbiosis.

Patients with UC averaged 27.83 ± 8.9 years old, whereas those with CD averaged 28.88 ± 6.78 years old. The difference of age between both groups was not statistically significant. For CD, the peak age is between 20 and 30 years old, whereas for UC it is between 30 and 40 years old, with a second peak occurring between 60 and 70 years old [10].

There is a statistically significant difference between the groups regarding IL-23. Pairwise comparisons showed a statistically significant difference between the ulcerative colitis group and the other groups. In addition, **Mirsattari *et al.*** [12] found that the average serum IL-23 level in people who had ulcerative colitis was significantly higher than in the group that served as a control. In certain populations in Europe, IL-23 was shown to have no effect on ulcerative colitis vulnerability. Perhaps there is genetic diversity between the two groups at additional risk loci for ulcerative colitis that accounts for the observed variations in the occurrence of other instances of ulcerative colitis. CD patients had median IL-23 levels of 937.4 (interquartile range: 773.3-1477.4) pg/mL, whereas controls had levels of 371.5 (interquartile range: 362.8-380.1) pg/mL ($p < 0.001$). Patients diagnosed with ulcerative colitis showed higher amounts of the cytokine IL-23 compared to healthy control subjects: 1365.1 (751.7-1512) pg/mL vs. 371.5 (362.8; 380.1) pg/mL, $p < 0.001$ [13].

With a sensitivity of 75%, specificity of 54.2%, positive predictive value of 62.1%, negative predictive value of 68.4%, and overall accuracy of 64.6% ($p = 0.003$), a cutoff for IL-23 of 22.8 is optimal for diagnosing Crohn's disease (differentiating Crohn's disease from the control group). This value has the ability to differentiate Crohn's disease from the control group. This is due to the fact that this figure has a positive predictive power of 62.1% while simultaneously having a negative predictive power of 68.4%. Using a cutoff for IL-23 of 23.75 in the process of diagnosing ulcerative colitis disease may result in an area under the curve of 0.884, sensitivity of 87.5%, specificity of 70.8%, positive predictive value of 75%, negative predictive value of 85%, and overall accuracy of 79.2% (p 0.001) in some cases.

There was a significant inverse association between the amount of IL-23 and hemoglobin that was evaluated in the group of persons with ulcerative colitis. The correlation between these two variables was statistically significant. It has been proven that there is a link between the positive relationship of IL-23 and Mayo score that carries with it a statistically meaningful level of connection. Serum levels of IL-23 were found to have a positive link with the length of illness, as discovered by **Mirsattari *et al.*** [12]. This was determined to be the case when the researchers analyzed the data.

Although there was a correlation between age and serum IL-23 levels in individuals diagnosed with ulcerative colitis, the link was not statistically significant. **Mohammadi *et al.*** [9] compared the blood IL-23 level of patients with ulcerative colitis to that of healthy controls and found that patients with UC had a strong inverse connection between serum IL-23 and age. On the other hand, it was found that with age comes increasing expression of the p19 component of IL-23. Only Mayo is independently connected with IL-23 at a statistically significant level ($p < 0.001$). Patients' demographic information was used by **Mirsattari *et al.*** [12] to show that there is a statistically significant difference in the levels of blood IL-23 between the patients and healthy people.

We discovered that people suffering from Crohn's disease and ulcerative colitis had considerably varied amounts of IL-23 in their bodies. Those who had Crohn's disease who reached remission have a dramatically different experience than those who have moderate or severe types of ulcerative colitis. This is especially noticeable when comparing their condition to others who have moderate or severe ulcerative colitis. The difference between Crohn's disease in its mild form and ulcerative colitis in its severe form is significant.

Comparing mild ulcerative colitis to moderate Crohn's disease revealed a significant difference.

In spite of the fact that IL-23 region has been linked to a number of different illnesses in a number of different reports, the functional evidence for the participation of IL-23 variants remains sparse. The connection of multiple SNPs (single nucleotide polymorphisms) across the IL23R gene with UC provided evidence in support of a major involvement of the IL-23 pathway in the pathogenesis of IBD. This provided evidence is in support of the hypothesis of **McGovern and Powrie, [(14)]** that IL-23 plays an important role in the development of GI mucosal inflammation. **Zheng *et al*. [(15)]** shown that serum IL-23 has a role in the development of ulcerative colitis, which is consistent with our results. They hypothesized that IL-23, through stimulating the synthesis of IL-17, was a crucial factor in the development of UC. Increased expression of IL-23 in intraepithelial tissue also causes inflammation, as shown by **De Nitto *et al*. [(16)]**. Therefore, it is hypothesized that IL-23 targeted treatment may have therapeutic benefits in UC patients.

CONCLUSION

Our results added credence to the concept that measuring IL-23 levels may be useful for gauging disease severity in those with Crohn's disease or UC. It might be hypothesized that IL-23 is a good predictor of the patients' outcomes. So, it might be evaluated with less effort and cost than other markers and procedures.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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