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Serum IL-22 as a Novel Non-Invasive Biomarker in Diagnosis and Assessment of Activity in Ulcerative Colitis Patients

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ABSTRACT

Background: A chronic inflammatory illness with a relapsing remitting course is ulcerative colitis (UC). The primary test for UC diagnosis is a colonoscopy, however there is a chance that anything could go wrong. Inflammation of the mucosa has a lower correlation with UC indicators than colonoscopy. Interleukin 22 (IL 22), a member of the IL-10 family of cytokines, has only lately been linked to the pathogenesis of UC.

Objective: The aim of this study was to evaluate the role of serum IL-22 as a novel non-invasive biomarker in diagnosis and assessment of activity in ulcerative colitis patients.

Patients and Methods: This was a case control study that was conducted on 40 UC patients and 15 healthy controls at Ain Shams University Hospitals, throughout 6 months. Patients with ulcerative colitis were divided into 20 patients in clinical, laboratory and endoscopic remission and 20 patients in clinical, laboratory and endoscopic activity.

Results: Statistical analysis revealed the following: For Interleukin 22, there was highly statistically significant difference found between the three groups. There was highly statistically significant correlation found between IL-22 (Pg/ml) and endoscopic activity, and there was statistically significant correlation found between IL-22 (Pg/ml) and Histological activity, and there was no statistically significant correlation found between IL-22 (Pg/ml) and Extent of the disease. IL 22 levels showed statistically significant correlations with erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and Mayo score of severity of UC. Receiver operating characteristic curve (ROC) showed that the best cut off point of IL-22 (Pg/ml) to detect Patients was found > 4.7 with sensitivity of 90.0%, specificity of 100%, PPV of 100.0%, NPV of 78.9% and total accuracy of 0.95%. (ROC) shows that the best cut off point of IL-22 to detect patients with activity was found > 10.2 pg/ml with sensitivity of 95.0%, specificity of 75.0%.

Conclusion: It is concluded that IL22 is an important marker of ulcerative colitis activity as it shows significant correlation with endoscopic and histological activity.

Keywords: Serum IL-22, Crohn's disease, Ulcerative colitis.

INTRODUCTION

Inflammatory bowel illnesses, such as Crohn's disease (CD) and ulcerative colitis (UC), are characterised by relapses and remissions over time. Its multifaceted aetiology includes genetic, environmental, gut microbiome, and improper immune response factors [(1)]. Affection of intestinal barrier integrity plays an important role in the pathogenesis of inflammatory bowel disease. As increasing barrier permeability leads to enhanced exposure to microbial and protein antigens and thus triggering immune system and causing marked mucosal inflammation [(2)].

The diagnosis and evaluation of severity of IBD is best confirmed by endoscopy. Valid and widely used scoring systems for endoscopy include Mayo endoscopic sub score for UC and the simple endoscopic score for Crohn's disease (CD) [(1)]. Although endoscopy is the standard investigation to diagnose and evaluate severity of IBD, it is costly and carries a risk of serious complications, so it is difficult to use it to monitor the disease activity [(3)].

Fecal calprotectin and CRP are used universally as clinical biological markers to monitor IBD activity but its correlation with mucosal inflammation is far less than endoscopy, so it is essential to discover a new biological marker that has the ability to differentiate between severe activity, subclinical activity and remission of the disease based on a better correlation with mucosal inflammation [(1)].

The ideal inflammatory marker would have a high predictive value, be sensitive and specific, simple to use, and not require invasive procedures. Additionally, it should be replicable in both individual and laboratory settings [(4)].

Interleukin 22 (IL 22) is a cytokine of interleukin 10 family. IL 22 is secreted by various immune cells especially T helper lymphocytes, it is also secreted by natural killer cells. Myeloid cell lineage (neutrophils) can also secrete IL 22. IL 22 is involved in various inflammatory diseases like psoriasis, rheumatoid arthritis and IBD [(2)].

The control of the expression of IL 22 is significantly influenced by T cells, transcription factors, and certain cytokines, such as IL 23 [(5)]. In animal models, IL-22 promotes proliferation, improves barrier performance, and protects against mucosal inflammation [(2)]. Patients with ulcerative colitis and Crohn's disease have elevated IL-22 levels [(2)].

IL 22 gene is proved to be involved in the pathogenesis of ulcerative colitis in many genetic studies. IL 22 appears to have a defensive role in UC by improving mucous production, preventing tissue damage and enhancing epithelial cell proliferation [(6)].

IL 22 appears to be beneficial in intestinal inflammation. It is proved to enhance regeneration of damaged epithelial layers and improve intestinal wound healing in mice and humans. Various genetic studies showed a correlation between IL 22 and major IBD

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susceptibility genes [5]. It has been shown that recombinant cytokine therapy or gene therapy using IL-22 can reduce the inflammatory response [7]. The aim of this study was to evaluate the role of serum IL-22 as a novel non-invasive biomarker in diagnosis and assessment of activity in ulcerative colitis patients.

PATIENTS AND METHODS

This case control study was conducted on 15 healthy controls and 40 ulcerative colitis patients from inpatient and outpatient settings of Ain shams university hospital throughout 6 months.

The patients in this study were divided into 3 groups: Group (1) includes 20 patients in clinical, laboratory and endoscopic activity confirmed by colonoscopy and histopathological examination of endoscopic biopsies, Group (2) includes 20 patients in clinical, laboratory and endoscopic remission confirmed by colonoscopy and histopathological examination of endoscopic biopsies. Group (3) includes 15 healthy controls.

Exclusion Criteria included Pregnancy, lactation, infections such as common cold, concurrent autoimmune diseases such as collagen diseases, age younger than 18 years old and patients who refuse a written consent after explanation the aim of the study.

All included participants had an informed written consent. After ethical committee approval, all participants were subjected to a detailed history taking, thorough clinical exam and laboratory tests including (complete blood count (CBC), alanine transaminase (ALT), aspartate transaminase (AST), Albumin, Total/Direct bilirubin, creatinine, urea, C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum IL-22). IL-22 serum levels were assessed using a standard sandwich ELISA kit (e-Bioscience, USA).

All patients were subjected to colonoscopy and histopathological examination of endoscopic biopsies of the gastrointestinal tract using the Simplified Geboes Score. Colonoscopy was done for every case with full comment on gross finding, extent of disease and Mayo classification. Mucosal appearance at endoscopy was graded to: 0 = Normal or inactive disease, 1 = Mild disease (erythema, decreased vascular pattern, mild friability), 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) and 3 = Severe disease (spontaneous bleeding, ulceration).
Remission and activity of UC were assessed using Mayo classification.

Mayo score for ulcerative colitis include 4 variables: stool pattern (0-3), rectal bleeding (0-3), endoscopic findings (0-3), physician global assessment (0-3) that are summed to give a total score that ranges from 0–12, interpreted as follows: clinical remission ≤ 2, mild activity (3-5), moderate activity (6-10), severe activity (11-12) [8].
Extent of the disease was assessed by Montreal classification.

The Montreal classification of ulcerative colitis severity: E1: Restrictive involvement to the rectum in ulcerative proctitis E2: UC on the left (distal UC) only a section of the colorectum distal to the splenic flexure is involved, and E3: Profound UC (pancolitis) The splenic flexure is close to where the involvement begins [8].

Ethical consent:

Ain Shams University Faculty of Medicine's ethics committee gave its approval for this study, which was carried out in accordance with the guidelines outlined in the Declaration of Helsinki. All study participants gave their informed consent.

Statistical Analysis

Data were gathered, reviewed, coded, and entered into IBM SPSS version 20 of the Statistical Package for Social Science. Quantitative data were presented as mean, standard deviations, and ranges when their distribution was found to be parametric, while qualitative data were given as numbers and percentages. When the predicted count in any cell was less than 5, the comparison between two groups utilising qualitative data was made using the Chi-square test or the Fisher exact test in place of the Chi-square test. The Independent t-test was used to compare two independent groups with quantitative data and parametric distribution. The One Way ANOVA test was used to compare more than two independent groups with quantitative data and a parametric distribution. Using quantitative data and a non-parametric distribution, the Mann- Whitney test was used to compare two independent groups. Krskal-Wallis was used to compare quantitative data from more than two independent groups with non-parametric distribution. The allowable margin of error was set at 5%, while the confidence interval was set at 95%. P value < 0.05 was considered significant.

RESULTS

Table 1 showed that there was no significant difference between patients and controls regarding age, sex or smoking status while there was a highly significant difference regarding number of motions.
There was a highly significant difference regarding systolic blood pressure (SBP) between controls (mean 123 mmHg), remission group (mean 110.75 mmHg) and activity group (mean 103.25 mmHg) and a highly significant difference between groups regarding temperature (T) ($p<0.002$) and pulse ($p<0.004$) while there was no significant relation regarding diastolic blood pressure (DBP) as shown in table 2.

Table (1): Comparison between Control group (no. =15) and Patient group (no. =40) regarding Age, Sex, Smoking status and Number of motions

		Control	Patient	Test value	P-value	Sig
		No.= 15	No.= 40			
Age (years)	Mean ± SD Range	38.20 ± 6.27 27 – 48	35.53 ± 7.72 20 – 47	1.199•	0.236	NS
Sex	Female Male	7 (46.7%) 8 (53.3%)	23 (57.5%) 17 (42.5%)	0.516*	0.472	NS
Smoking status	No Yes	12 (80.0%) 3 (20.0%)	31 (77.5%) 9 (22.5%)	0.040*	0.842	NS
Number of motions	Mean ± SD Range	0.53 ± 0.12 0 – 2	2.98 ± 0.62 1 – 7	-5.058•	0.000	HS

Table (2): Comparison between Control group (no. =15), Activity group (no. =20) and Remission group (no. =20) regarding SBP, DBP, Pulse and Temperature

		Control	Activity	Remission	Test value ß	P-value
		No.= 15	No.= 20	No.= 20		
SBP (mmHg)	Mean ± SD	123.00 ± 11.46	103.25 ± 9.50	110.75 ± 10.04	15.955	0.000
DBP (mmHg)	Mean ± SD	76.67 ± 6.17	72.50 ± 4.44	75.00 ± 6.07	2.511	0.091
Pulse	Mean ± SD	83.60 ± 4.05	87.35 ± 3.91	83.50 ± 3.79	6.050	0.004
Temperature	Mean ± SD	36.94 ± 0.22	37.23 ± 0.32	37.00 ± 0.18	6.977	0.002

There was a highly significant difference between controls, remission group and activity group regarding the levels of CRP, ESR, serum albumin, ALT and total leucocytic count (TLC). ($p<0.01$) and a significant difference between the groups regarding platlets count and AST as shown in table 3.

Table (3): Comparison between Control group (no. =15), Activity group (no. =20) and Remission group (no. =20) regarding Laboratory investigations

Laboratory investigations		Control	Activity	Remission	Test value	P-value
		No.= 15	No.= 20	No.= 20		
HB (g/dL)	Mean ± SD	10.32 ± 0.85	10.48 ± 1.89	10.53 ± 1.83	0.070 ß	0.933
TLC (mcL)	Mean ± SD	6.39 ± 1.54	8.55 ± 2.08	14.36 ± 3.42	30.048 ß	0.000
Platelets (mcL)	Mean ± SD	141.80 ± 33.32	189.85 ± 46.12	214.05 ± 52.21	4.239 ß	0.020
ALT (U/L)	Mean ± SD	19.93 ± 4.81	47.73 ± 11.32	34.45 ± 7.42	13.190 ß	0.000
AST (U/L)	Mean ± SD	25.67 ± 6.31	42.10 ± 10.22	34.10 ± 8.12	4.407 ß	0.017
Total bilirubin (µmol/L)	Mean ± SD	1.04 ± 0.18	1.24 ± 0.27	1.12 ± 0.27	2.734 ß	0.074
ESR (mm/hr)	Mean ± SD	20 ± 4.72	45 ± 11.21	9.5 ± 2.71	32.567¥	0.000
CRP (mg/L)	Mean ± SD	1.9 ± 0.31	4.55 ± 1.01	2.95 ± 0.41	19.384¥	0.000
Creatinine (mg/dl)	Mean ± SD	1.01 ± 0.22	0.96 ± 0.20	0.97 ± 0.21	0.060 ß	0.942
Urea (mg/dL)	Mean ± SD	16.27 ± 3.78	14.60 ± 3.60	13.05 ± 3.21	1.590 ß	0.214
Albumin (g/L)	Mean ± SD	3.60 ± 0.50	3.86 ± 0.48	3.40 ± 0.31	5.498 ß	0.007

As regard clinical manifestations through our patient population. The most common symptoms were abdominal pain (55%), diarrhea (42.5%) and bleeding per rectum (40%) as shown in table 4.

Table (4): Distribution of the Patient group according to Abdominal pain, Diarrhea, Bleeding per rectum, Weight loss, Urgency and Extra intestinal manifestations

	Patient Group
	No.= 40
Abdominal pain	22 (55.0%)
Diarrhea	17 (42.5%)
Bleeding per rectum	16 (40.0%)
Weight loss	9 (22.5%)
Urgency	8 (20.0%)
Extra intestinal manifestations	8 (20.0%)
Arthritis	5 (12.5%)
Stomatitis	2 (5.0%)
Apthous ulcer	1 (2.5%)

As regard findings of colonoscopy in our patients, the most common finding was erythema and decreased vascular pattern (42.5%) followed by marked erythema and erosions (37.5%) and ulceration and spontaneous bleeding (12.5%). As shown in table 5.

Table (5): Distribution of the Patient group according to Colonoscopy

Colonoscopy	**Patient Group**	
	No.	**%**
Eryhtema - Decreased vascular pattern	17	42.5%
Marked erythema - Abscent vascular pattern - Erosions	15	37.5%
Spontaneous bleeding – Ulceration	5	12.5%
Normal mucosa	3	7.5%

As regard the findings of histological examination of endoscopic biopsies from our patients, the most common finding was moderate increase in neutrophils infiltration with erosions (22.5%) while the most severe finding was marked increase in neutrophils infiltration with cryptitis and ulceration (12.5%) as shown in table 6.

Table (6): Distribution of the Patient group according to Histological examination

Histological examination	**Patient Group**	
	No.	**%**
Moderate increase in neutrophils infiltration – Erosions	9	22.5%
Mild increase in chronic inflammatory cells - Mild architexture changes	8	20.0%
Moderate increase in chronic inflammatory cells - Mild architexture changes	7	17.0%
Marked increase in neutrophils infiltration - Cryptitis - Ulceration	5	12.5%
Mild increase in chronic inflammatory cells - No architexture changes	4	10.0%
Mild increase in neutrophils infiltration - Mild crypt injury	4	10.0%
Normal biopsy	3	7.5%

There was a highly significant difference between controls and patients regarding IL 22 level as the median in controls was 3.4 Pg/ml and the median in patients was 22.85 Pg/ml. as shown in table 7

Table (7): Comparison between Control group (no. =15) and Patient group (no. =40) regarding IL-22 (Pg/ml)

IL-22 (Pg/ml)	**Control**	**Patient**	**Test value μ**	**P-value**	**Sig.**
	No.= 15	**No.= 40**			
Median (IQR)	3.4 (2.4 – 4.2)	22.85 (6.15 – 45.5)	-5.151	0.000	HS
Range	1.9 – 4.7	2.5 – 86.5			

Median (IQR) and range: fore non- parametric data.

There was a highly significant difference between controls, activity group and remission group regarding IL 22 levels as the median in controls was 3.4 Pg/ml while the median in activity group was 43.9 Pg/ml and the median in remission group was 6.15 Pg/ml. as shown in table 8.

Table (8): Comparison between Control group (no. =15), Activity group (no. =20) and Remission group (no. =20) regarding IL-22 (Pg/ml)

IL-22 (Pg/ml)	Control	Activity	Remission	Test value ¥	P-value
	No.= 15	No.= 20	No.= 20		
Median (IQR) Range	3.4 (2.4 – 4.2) 1.9 – 4.7	43.9 (25 – 63.3) 8.7 – 86.5	6.15 (5.35 – 16.8) 2.5 – 76.5	37.243	0.000
Post hoc analysis				–	–
P1	0.000			–	–
P2	0.046			–	–
P3	0.000			–	–

Median (IQR) and range: fore non- parametric data.

There was a highly significant correlation between IL 22 and some laboratory investigations of the patients including ESR and TLC and a significant correlation with CRP. In the patient groups there was a highly significant correlation between IL 22 and (SBP), temperature, number of motions and Mayo score and a significant correlation with pulse as shown in table 9.

Table (9): Correlation between IL-22 (Pg/ml) With Age, Number of motions, Examination, Laboratory investigations and Mayo Score in all patients.

All Cases	IL-22 (Pg/ml)	
	R	P-value
Age (years)	-0.171	0.291
Number of motions	**0.665****	**0.000**
SBP (mmHg)	**-0.472****	**0.002**
DBP (mmHg)	-0.289	0.071
Pulse	**0.345***	**0.029**
Temperature	**0.483****	**0.002**
HB (g/dL)	-0.066	0.686
TLC	**-0.501****	**0.001**
Platelets (mcL)	-0.225	0.164
ALT (U/L)	0.305	0.055
AST (U/L)	0.163	0.315
Total bilirubin (U/L)	0.033	0.838
ESR (mm/hr)	**0.545****	**0.000**
CRP (mg/L)	**0.385***	**0.014**
Creatinine (mg/dl)	0.104	0.521
Urea (mg/dL)	-0.057	0.726
Albumin (g/L)	0.071	0.665
Mayo Score	**0.475****	**0.002**

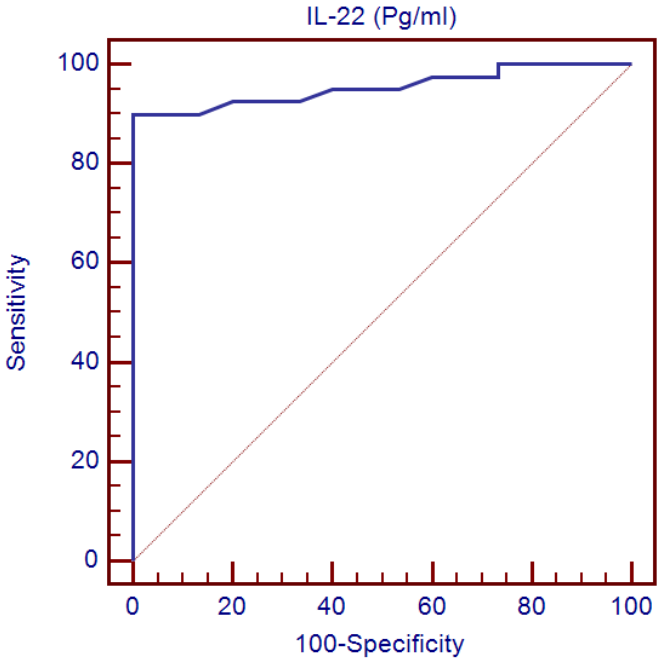
There was a highly significant correlation between IL 22 and colonoscopy findings as the highest levels of IL 22 was associated with the severest colonscopic finding (mucosal ulceration and spontaneous bleeding) with the median 53.2 pg/ml and range (43.2 –64.4)pg/ml and the lowest levels of IL22 was associated with normal mucosa with the median 7.5 pg/ml and range (5.4 – 23.4) pg/ml. and there was a significant correlation between IL 22 and the degree of severity of histological examination with the highest levels of IL 22 associated with marked increase in neutrophils infiltration, Cryptitis and Ulceration.
($P<0.021$), while there was no significant relation between IL 22 and extent of the disease as shown in table 10.

Table (10): Relation between IL-22 (Pg/ml) With Colonoscopy, Histological examination and Extent of disease in all patients

All Cases		IL-22 (Pg/ml)		Test value ß	P-value	Sig.
		Median (IQR)	Range			
Colonoscopy	**Eryhtema - Decreased vascular pattern**	10.2 (5.7 – 22.3)	3.2 – 76.5	4.969¥	0.005	HS
	Marked erythema – Abscent vascular pattern – Erosions	43.2 (5.6 – 62.2)	2.5 – 86.5			
	Spontaneous bleeding - Ulceration	53.2 (43.2 – 64.4)	35.4 – 86.3			
	Normal mucosa	7.5 (5.4 – 23.4)	5.4 – 23.4			
Histological examination	**Moderate increase in neutrophils infiltration – Erosions**	45.6 (44.6 – 65.4)	27.7 – 86.5	3.686¥	0.021	S
	Mild increase in chronic inflammatory cells - Mild architexture changes	6.65 (4.8 – 22.35)	2.5 – 45.5			
	Moderate increase in chronic inflammatory cells - Mild architexture changes	5.6 (5.4 – 8.7)	3.5 – 11.3			
	Marked increase in neutrophils infiltration - Cryptitis – Ulceration	53.2 (43.2 – 64.4)	35.4 – 86.3			
	Mild increase in chronic inflammatory cells - No architexture changes	15 (4.9 – 49.95)	3.2 – 76.5			
	Mild increase in neutrophils infiltration - Mild crypt injury	20.45 (17.6 – 32.75)	16.5 – 43.2			
	Normal biopsy	7.5 (5.4 – 23.4)	5.4 – 23.4			
Extent	**Pancolitis**	20.45 (5.7 – 43.2)	2.5 – 86.3	0.868¥	0.467	NS
	Left sided colitis	25.55 (8.7 – 75.3)	3.5 – 86.5			
	Extensive colitis	34.5 (8.7 – 45.5)	4.3 – 64.4			
	Normal	7.5 (5.4 – 23.4)	5.4 – 23.4			

Median (IQR) and range: fore non- parametric data.

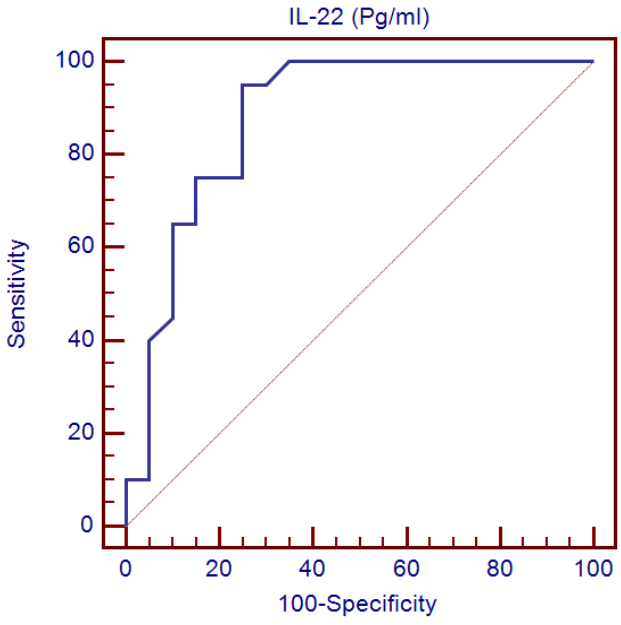
Receiver operating characteristic curve (ROC) shows that the best cut off point of IL-22 to detect Patient group was found > 4.7 pg/ml with sensitivity of 90.0%, specificity of 100% as shown in figure 1.



	Cut of point	AUC	Sensitivity	Specificity	+PV	-PV
IL-22 (Pg/ml)	>4.7 *	0.95	90.0	100.0	100.0	78.9

Figure (1): ROC curve (Patient and Control) group regarding IL-22 (Pg/ml).

Receiver operating characteristic curve (ROC) shows that the best cut off point of IL-22 to detect Activity group was found > 10.2 pg/ml with sensitivity of 95.0%, specificity of 75.0% as shown in figure 2.



	Cut of point	AUC	Sensitivity	Specificity	+PV	-PV
IL-22 (Pg/ml)	>10.2 *	0.88	95.0	75.0	79.2	93.7

Figure (2): ROC curve (Activity and Remission) group regarding IL-22 (Pg/ml).

DISCUSSION

This is the first study to evaluate the level of serum IL-22 in ulcerative colitis and its effect in diagnosis and assessment of activity in ulcerative colitis patients.

In this study, we observed a high significant difference regarding IL 22 levels between controls and UC patients and a high significant difference between control group, remission group and activity group. This shows the importance of IL 22 as a potential marker in diagnosing cases and differentiating between activity and remission of the disease.

This was supported by increased expression and upregulation of IL 22 in Crohn's disease and ulcerative colitis proved by various studies as in **Brand *et al.*** [(9)] who showed an increased expression of IL 22 in inflamed intestinal samples from Crohn's disease patients and **Sekikawa *et al.*** [(10)] who showed increased expression of IL 22 in colonic biopsy samples from ulcerative colitis patients.

In this study, there was a highly significant negative correlation between IL 22 and systolic blood pressure and a highly significant positive correlation between IL 22 and temperature, number of motions and Mayo score of severity for UC.

The highly significant relation observed in our patients between IL 22 and both of Mayo score and number of motions highlights the importance of IL 22 as a potential marker for clinical severity for ulcerative colitis.

In a pilot study, the relationship between IL22 and the activity of Crohn's disease was verified [(11)]. IL-22 levels and disease activity as measured by the Crohn's disease activity index were shown to be strongly correlated in a study of 242 Crohn's disease patients. A predictor of Crohn's disease activity was serum IL-22 [(12)].

In ulcerative colitis, CRP and ESR levels were found to be connected with disease activity. Either CRP or ESR may be sufficient on its own, with CRP having a slight edge [(13)].

IL 22 was found to be correlated to ESR and CRP in our patients providing multiple evidences for the correlation between IL22 and activity of ulcerative colitis.

In this study, there was a significant correlation between levels of IL 22 and ulcerative colitis on both a macroscopic and microscopic level represented in our UC patients through the significant correlation of IL 22 levels with both colonoscopy and histopathological findings. As regard colonoscopy, normal mucosa was associated with the lowest levels of IL 22 while mucosal ulceration was associated with the highest levels of IL 22. This highlights the importance of IL 22 as a potential marker for endoscopic activity. The highest levels of IL22 in our patients were significantly associated with marked increase in neutrophils infiltration, Cryptitis and Ulceration.

It was discovered that serological biomarkers like CRP and ESR are not very accurate at spotting endoscopic activity in post-operative Crohn's disease and ulcerative colitis [(14)].

Fecal calprotectin (FC) level was found to be related to both endoscopic and histological activity in a study of 61 UC patients, and it can be used to measure mucosal healing in UC [(15)].

Theede *et al.* [(16)] found that the level of FC is associated with endoscopic and histologic features of mucosal healing in UC and is correlated with endoscopic and histologic inflammatory activity.

Neutrophils are the main source of calprotectin but it was found that ectopic secretion of calprotectin can be induced by IL22 in colonic epithelial cells [(17)].

IL 22 in our study and FC in various studies showed a correlation with endoscopic and histologic activity of UC. This can be partially explained by the participation of IL 22 in ectopic production of FC.

IL 22 is secreted mainly from CD4 T lymphocytes, it binds to IL 22 receptors in intestinal epithelial cells.IL 22 mediates many beneficial actions, it induces epithelial cell proliferation and an increase in mucin production. it inhibits apoptosis and maintains integrity of intestinal barrier [(2)].

These beneficial actions of IL22 may appear to contradict the significant association of high levels of IL22 with the endoscopic and histological severity of ulcerative colitis observed in our patient population.

IL 22 binding protein (BP) is a natural inhibitor of IL 22. It is produced from dendritic cells and binds to IL 22 and inhibits its actions on intestinal epithelial cells [(14)].

Martin *et al.* [(14)] found upregulation of expression of IL 22 binding proteins in endoscopic samples of inflamed intestinal and colonic mucosa from patients with Crohn's disease and ulcerative colitis. They found also abundant eosinophils in inflamed tissues which were suggested as the source of elevated IL 22 binding protein

In a murine model of induced colitis, it was found that rats deficient in IL 22 binding protein gene showed an improvement and attenuation of the colitis[(14)].

Martin *et al.* [(14)] results remove any contradiction between the beneficial actions of IL 22 and its significant correlation with endoscopic and histologic severity observed in our patients.

Another evidence to support our results comes from a murine model of anti-CD40-induced colitis, as IL 22 was found to be the only mediator for inflammation suggesting a pathological role of IL 22 in colitis [(18)].

In this study, the best cut off point of IL-22 to detect patients was found to be more than 4.7 pg/ml with sensitivity of 90.0%, specificity of 100% and the best cut off point of IL-22 to detect patients with activity was found to be more than 10.2 pg/ml with sensitivity of 95.0%, specificity of 75.0%.

In a study included 451 patients with ulcerative colitis, The best cutoff points to distinguish between remission, mild, moderate, and severe disease activity were found to be 23, 23-29, 30-37, > 37 mm/h for ESR, and 2.5, 2.5-5, 5.01-9, > 9 mg/L for CRP, with sensitivity (69%- 72%), specificity (67%- 70%) for ESR, and (68%-72%) for CRP [(13)].

Regarding fecal calprotectin (FC) role in UC, the best cut off point to differentiate between active and inactive disease according to mayo score of disease activity was > 21.4 ng/ml with 72.3% sensitivity and 73.1% specificity. FC levels were correlated to CRP and ESR levels in UC patients [(19)].

Based on this study, IL 22 appears to be more sensitive and specific in diagnosis of UC than CRP, ESR and FC, and more correlated to the activity of the disease. However, more studies with larger patient population are needed to confirm the excellent results of IL 22 observed in this study.

There are some limitations to this study, the small number of patients may cause analytical bias. Fecal calprotectin was not tested in this study. Addition of fecal calprotectin can be beneficial when combining it with IL 22 in diagnosis of UC.

CONCLUSION

It is concluded that IL22 is an important marker of ulcerative colitis as it shows significant correlation with endoscopic and histological activity.

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