Journal of the Egyptian Society of Parasitology, Vol. 51, No. 3, December 2021
J. Egypt. Soc. Parasitol. (JESP), 51(3), 2021: 475- 484
(Online: 2090-2549)

CORRELATION OF CIRCULATING CATHELCIDIN LEVEL AND INFLAMMATORY BOWEL DISEASE ACTIVITY

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Abstract

Inflammatory bowel diseases (IBDs), which include Crohn's disease (CD) and ulcerative colitis (UC), are a group of idiopathic, chronic and relapsing inflammatory disorders of the gastrointestinal tract, whose incidence and prevalence has been increasing in the last decade. This study correlated the circulating cathelicidin levels with mucosal disease activity in patients with IBD.

This case control cross sectional study was conducted on 80 adults referred to Gastrointestinal Endoscopy and Liver Unit, El-Haram Hospital. Forty patients had IBD; the others were non IBD patients served as case control. All were submitted to complete medical history, physical examination, laboratory investigations, colonoscopic examination and cathelicidin serum level.

The results showed that there was no statistically significant difference between both studied groups regarding both age and sex distribution. In this study we found highly significant decrease in Hemoglobin level in cases group compared to control group ($P < 0.001$). Also, there was significant increase in platelets level among cases group compared to control ($P < 0.05$). Also, the serum albumin was decreased among IBD patients compared to control.

Keywords: Patients, Inflammatory bowel diseases, ulcerative colitis, Crohn's disease

Introduction

Inflammatory bowel diseases (IBDs), represented by Crohn's disease and ulcerative colitis, are associated with major morbidity in Western countries and with increasing incidence in the developing world. But, the genome analysis of IBD patients, especially through genome-wide association studies, has unraveled multiple pathways involved in IBD pathogenesis, only part of IBD heritability was explained by genetic studies (Ramos and Papadakis, 2019). Start of chronic mucosal inflammation resulted by immune dysregulation, changed intestinal microbiota, oxidative stress, abnormalities in the gastrointestinal mucosal barrier, and increased permeability (Larussa *et al,* 2017). Excess extracellular matrix deposition caused chronic CD patients to develop transmural luminal constriction and strictures. TGF-b1 levels are frequently greater in the mucosa covering CD, makes it a possible therapeutic target for IBD. This is predicated on the presence of strictures in gut as opposed to non-structured gut (Yoo *et al,* 2015).

The colonic epithelium of patients with ulcerative colitis frequently has a thinner mucus layer and fewer goblet cells. The mucus layer, which is mostly made up of mucins & trefoil peptides, serves as a physical barrier to protect epithelium from substances that may compromise its integrity, and prevent aberrant immune responses from being triggered by gut microbiota **(**Emily *et al,* 2013).

Antibacterial peptide cathelicidin is found on the surface of epithelial cells of stomach and colon as a key innate immune defence effector molecule. Membrane permeabilization was limited development of many microorganisms, including bacteria, fungi, some protozoa parasites, and viruses (Berjeaud *et al,* 2016). Besides, microorganisms, catholicidins showed a variety of roles in inflammation, wound healing, regulated immunological & inflammatory cell activity and aided in re-epithelialization of the human skin wounds **(**Emily *et al,* 2013). Ahluwalia and Tarnawski (2013) found that cathelicidins in neutrophils, macrophages, and epithelial cells of gastrointestinal tract, lungs, and skin to prevent pathogen overgrowth and invasion, stored as inactive precursor pro-peptides with a highly varied C-terminal antibacterial domain and a well conserved N-terminal ca-

thelin-like domain. Physiological active antimicrobial peptide was liberated by enzyme cleavage of the cathelin domain from propeptide. Peptides not only ecause wide antibacterial activity, but also control inflammation in sick tissues by changing cytokine response & inflammatory cell chemo-traction.

This study aimed to correlate circulating cathelicidin levels with mucosal disease activity in patient with inflammatory bowel disease.

Patients and Methods

Type of study: Case control prospective study held up on 80 Egyptian patients, 40 were control and 40 patients attended gastrointestinal endoescopy and liver unit at El-Haram Hospital, from December 2019 to August 2020.

Patients with inflammatory bowel disease diagnosed according to medical history, colonoscopy and biopsy result and assessment of severity of disease activity by partial mayo score for ulcerative colitis patients, Mayo endoscopic subscore to assess mucosal disease activity in UC patients and Harvey-Bradshaw index for Crohn's disease patients.

Ethical consideration: The Research Committee of thFaculty of Medicine, Ain-Shams University approval to this study. A written consent was obtained from patients and controls before the study. All had the right to withdraw at any time without any obligation.

Inclusion criteria: Patients with active inflammatory bowel disease according to PMS for UC and HBI for CD. Exclusion criteria: Patients with concurrent acute infection (CMV-*Clostridium difficile*, TB), malignancy, and autoimmune diseases.

All were subjected to full medical history including disease duration, progression with especial stress on IBD symptoms and complete clinical examination. IBD activity was assessed after partial Mayo score (PMS) for ulcerative colitis patients, Harvey-Bradshaw Index for Crohn's patient and Mayo endoscopic subscore (MES) assessed mucosal activity of UC patients, on the same day of blood sample collection for LL-37 CRP and other tools (Walsham and Sherwood, 2016):

Table 1: Mayo Endoscopic Sub-score to assess mucosal disease activity in UC patients (MES) range (0-3).

Score	Disease activity	Endoscopic features
0	Normal (inactive)	None
1	Mild	Erythema, decreased vascular pattern, mild friability
2	Moderate	Marked erythema, absent vascular pattern, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

Laboratory examinations: Complete blood picture (CBC) and ESR. Liver function tests: AST, ALT, Alkaline phosphatase, Serum albumin, Total and direct bilirubin, Serum urea & creatinine, C-reactive protein (CRP) and Colonoscopy and terminal ileoscopy.

Patients preparation for colonoscopy: They was asked not to take any solid foods for 3 days before the procedure only fluids water and clear juices, The day before the colonoscopy, patients were given a laxative preparation (polyethylene glycol 3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate, and ascorbic acid) for oral solution which were tolerable and effective in the majority of them.

Sedation of patients before colonoscopy: During procedure patients were often given intravenous sedation, employing agents such as fentanyl or midazolam, in an average of combined of both drugs, usually between 25 to 100µg fentanyl and 5-10mg midazolam.

Procedure: First step was a digital rectal examination, to detect anal stricture or any rectal mass and to determine if preparation has been inadequate. Endoscope was then sent up the rectum, the colon (sigmoid, descending, transverse, and ascending colons, the cecum), and finally the terminal ileum into anus. Histopathology was done on several samples collected from pathologic lesion.

Colonoscopic biopsy (descending colon): Biopsies were referred to an expert pathologist for processing, embedding, sectioning and staining with H & E (Abdel-Bary *et al,* 2012). Diagnosis of IBD had to satisfy ac-

cepted clinical and endoscopic criteria with histological confirmation.

Serum cathelicidin level: Cathelicidin was detected by ELISA. Kit Glory Science used a double-antibody sandwich ELISA to assay human level (cathelicidin LL-37) in samples. Add (cathelicidin LL-37) to monoclonal antibody Enzyme well was pre-coated with human (cathelicidin) monoclonal antibody, incubation and (cathelicidin LL-37) antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add chromogenic solution A, B, the color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. Chroma of color and concentration of human (LL-37) were positively correlated. Color change was measured spectrophotometric at a wave length 450nm. LL-37 was compared to OD to standard curve, and data were expressed as ng/ml, & kit was 0.5ng/ml→ 200ng/ml, sensitivity, 2.68ng/ mL

Statistical analysis: Data were collected, and computerized by IBM SPSS version 23, and quantitatively presented as M±SD and when distribution found parametric and median with interquartile range (IQR), or when distribution found non-parametric. Qualitative variables were presented as No. and %. Qualitative comparison between groups was done using Chi-square test. Comparison between 2 independent ones with quantitative data and parametric distribution were done by using Independent t-test, but comparison between 2 independent groups with quantitative data & non-parametric distribution were done by using Mann-Whitney test. Comparison between >2 independent groups with quantitative data and parametric distribution were done by One Way ANOVA test. Spearman correlation coefficients assessed correlation between 2 quantitative parameters in same group. ROC assessed predictors of IBD cases with best cut off point of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under curve (AUC). Confidence interval was 95% & accepted error was 5%. P-value was significant at <0.05. A negative correlation between LL-37 & CRP among patients was compared with diagnostic alone accuracies of LL-37, CRP, combined LL-37 & CRP for clinical and mucosal disease activity. LL-37=sensitivity (82.5%), specificity (87.5%) PPV (86.8%) & AUC (84.1%), CRP sensitivity was (52.5%), specificity (92.5%), PPV (87.5%) & AUC (78.9%).

Details were in tables (2, 3, 4, 5, 6, 7, 8 & 9), and figures (1, 2 & 3).

Results

Table 2: Demographic data of cases (n=40).

Variants		No. = 40
Age	M±SD	35.67 ± 7.69
	Range	18 – 45
Sex	Female	30 (75%)
	Male	10 (25%)

Table 3: LL-37 level among cases (n = 40).

LL-37(ng/ml)	Cases
M±SD	57.27±19.70
Range	5.9 -95.1

Table 4: Severity in 40 IBD patients as to PMS for UC patients and HBI for CD.

Variants		Cases (n=40)
Partial mayo score	Median(IQR)	4 (3 – 6)
	Range	2 – 6
Severity of Partial mayo score	Mild	18 (52.9%)
	Moderate	14 (41.2%)
	Severe	2 (5.9%)
Harvey Bradshaw index	Median(IQR)	9 (4 – 11)
	Range	4 – 11
Severity of Harvey Bradshaw index	Mild	2 (33.3%)
	Moderate	4 (66.7%)
MES	Mild	18 (52.9%)
	Moderate	14 (41.2%)
	Severe	2 (5.9%)

Table 5: Colonoscopy results among cases (n=40).

Colonoscopy	No.	%
U.C	34	85%
C.D	6	15%

Table 6: Laboratory findings of cases (n=40).

Variants		Cases
WBCs Thousands/cmm	M±SD	6425.00 ± 2330.04
	Range	4000 – 11900
HB g/dL	M±SD	9.94 ± 0.81
	Range	8.5 – 11
Platelets Thousands/cmm		305825.00 ± 58097.13
	Range	210000 – 436000
ALT U/L	M±SD	20.20 ± 7.73
	Range	8 – 35
AST U/L	M±SD	20.18 ± 5.46
	Range	12 – 33
ALP mg/dl	M±SD	52.73 ± 7.95
	Range	35 – 65
Serum Albumin g/dl	M±SD	3.64 ± 0.23
	Range	3.2 – 3.9
Total bilirubin mg/dl	M±SD	0.76 ± 0.26
	Range	0.5 – 1.2
Direct bilirubin mg/dl	M±SD	0.31 ± 0.14
	Range	0.2 – 0.6
Urea mg/dl	M±SD	39.55 ± 9.42
	Range	25 – 60
CR mg/dl	M±SD	0.77 ± 0.27
	Range	0.4 – 1.2
CRP mg/l	Median(IQR)	4 (2.45 – 7.15)
	Range	0.8 – 9.1
ESR (1st hour) mm/hr	M±SD	26.45 ± 8.78
	Range	12 – 42

Table 7: Comparison between cases and controls regarding demographic data.

Variants		Controls (n=40)	Cases (n=40)	Test value	P-value	Sig.
Age	M±SD	35.55 ± 9.01	35.68 ± 7.69	-0.067	0.947	NS
	Range	22 – 51	18 – 45			
Sex	Female	25 (62.5%)	30 (75%)	1.455	0.228	NS
	Male	15 (37.5%)	10 (25%)			

Table 8: Comparison between cases and controls as regard LL-37.

		Controls (n=40)	Cases (n=40)	Test value	P-value	Sig.
LL-37	M±SD	34.91 ±13.28	57.27 ± 19.71	-5.949•	0.000	HS
	Range	22.4 –81	5.93 – 95.1			
CRP	Median(IQR)	1.95 (1 – 3)	4 (2.45 – 7.15)	-4.466‡	0.000	HS
	Range	0.8 – 4	0.8 – 9.1			

P >0.05: Non significant (NS); P <0.05: Significant (S); P < 0.01: highly significant (HS),

Table 9: Correlation between LL-37 & others parameters in 40 IBD patients.

Variants	r	p-value
Age	-0.120	0.462
WBCs	-0.028	0.864
HB	0.100	0.539
Platelets	0.292	0.067
ALT	0.230	0.153
AST	0.419**	0.007
ALP	-0.097	0.552
CRP	-0.369*	0.019
Serum Albumin	0.356*	0.024
Total bilirubin	-0.038	0.815
Direct bilirubin	0.017	0.917
Urea	-0.013	0.937
CR	-0.167	0.304
ESR	0.176	0.277
Partial Mayo score	-0.719**	0.000
Stool frequency	-0.515**	0.001
Rectal bleeding	-0.505**	0.001
Harvey Bradshaw index	-0.970**	0.001

P >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)

Table 10: Comparison between cases and controls regarding laboratory data.

Variants		Controls (n=40)	Cases (n=40)	Test value	P-value	Sig.
WBCs	M±SD	7292.50 ± 2412.19	6425.00 ± 2330.04	1.636•	0.106	NS
	Range	3500 – 11500	4000 – 11900			
HB	M±SD	12.45 ± 1.86	9.94 ± 0.81	7.825•	0.000	HS
	Range	10 – 15.2	8.5 – 11			
Platelets	M±SD	264850.00 ± 75929.64	305825.00 ± 58097.13	-2.711•	0.008	HS
	Range	22000 – 380000	210000 – 436000			
ALT	M±SD	21.80 ± 7.83	20.20 ± 7.73	0.919•	0.361	NS
	Range	9 – 37	8 – 35			
AST	M±SD	23.38 ± 7.07	20.18 ± 5.46	2.265•	0.026	S
	Range	12 – 35	12 – 33			
ALP	M±SD	48.10 ± 8.37	52.73 ± 7.95	-2.535•	0.013	S
	Range	34 – 60	35 – 65			
Serum Albumin	M±SD	4.33 ± 0.37	3.64 ± 0.23	9.996•	0.000	HS
	Range	3.9 – 5	3.2 – 3.9			
Total bili-rubin	M±SD	0.69 ± 0.23	0.76 ± 0.26	-1.227•	0.224	NS
	Range	0.3 – 1.1	0.5 – 1.2			
Direct bilirubin	M±SD	0.31 ± 0.13	0.31 ± 0.14	-0.166•	0.869	NS
	Range	0.1 – 0.5	0.2 – 0.6			
Urea	M±SD	42.35 ± 7.59	39.55 ± 9.42	1.463•	0.147	NS
	Range	30 – 55	25 – 60			
CR	M±SD	0.72 ± 0.24	0.77 ± 0.27	-0.872•	0.386	NS
	Range	0.4 – 1.1	0.4 – 1.2			
CRP	Medan(IQR)	1.95 (1 – 3)	4 (2.45 – 7.15)	-4.466‡	0.000	HS
	Range	0.8 – 4	0.8 – 9.1			
ESR	M±SD	25.18 ± 13.29	26.45 ± 8.78	-0.506•	0.614	NS
	Range	8 – 55	12 – 42			

•: Independent t-test; ‡: Mann Whitney test

Table 11: Correlation between CRP with LL-37, PMS, albumin and Harvey Bradshaw index.

Variants	CRP	
	r	P-value
LL-37	-0.369*	0.019
Partial mayo score	0.406*	0.017
Albumin	-0.091	0.575
Harvey Bradshaw index	0.970**	0.000

Table 12: Correlation between LL-37& sex, colonoscopy result, PMS, MES and HBI.

Variants		LL-37		Test value	P- value	Sig.
		M±SD	Range			
Sex	Female	61.60 ± 14.870	33.9 – 95.1	2.576•	0.014	S
	Male	44.27 ± 26.84	5.93 – 73.5			
Colonoscopy	U.C	58.871 ± 19.957	5.93 – 95.1	28.571≠	0.000	HS
	C.D	48.2 ± 16.886	33.9 – 69.6			
Severity partial mayo score	Mild	65.585 ± 23.033	5.93 – 95.1	11.136≠	0.004	HS
	Moderate	53.75 ± 7.335	46.9 – 66.4			
	Severe	34.3 ± 32.244	11.5 – 57.1			
Severity heavy Bradshaw index	Mild	41.1 ± 0.00	41.1 – 41.1	0.000•	1.000	NS
	Moderate	51.75 ± 20.611	33.9 – 69.6			
MES	Mild	65.59 ± 23.03	5.93 – 95.1	11.136≠	0.004	HS
	Moderate	53.75 ± 7.34	46.9 – 66.4			
	Severe	34.3 ± 32.244	11.5 – 57.1			

•: Mann Whitney test; ≠: Kruskal Wallis test

Discussion

In the present study, among the 40 IBD patients; six were diagnosed as CD while 34 were diagnosed as UC with a marked predominance than CD with a ratio of 5.5:1. This agreed with the fact that ulcerative colitis was greater than that of Cohn's **(**Douketis *et al,* 2015**),** and Kalubowila *et al.* (2018). Mahmoud *et al.* (2019) in New York reported that in a retrospective analysis of data from 2 large independent surveillance cohorts, PIPs were associated with greater severity and extent of colon inflammation and higher rates of colectomy, but were not as-

sociated with development of any degree of CRN. Therefore, intervals for surveillance should not be shortened based solely on the presence of PIPs.

In the present study, mean age of patients was 35.7 years, with a peak in 4th decade of life. Tozun *et al.* (2009) in USA reported that most patients were diagnosed between ages of 20 to 40 years. Esmat *et al.* (2014) in Egypt reported that the mean age was 27.9, that is to say mean seven years older than stated by them. Kalubowila *et al.* (2018) in Sri Lanka found that the mean age at diagnosis of IBD in their study was most frequently in the 30–40-year-old. Carroll *et al.* (2019) in Canada reported that the Canadian populations had among the highest rates of childhood-onset IBD in the world. Over 7000 children and youth less than 18 years old living with IBD in Canada, and 600 to 650 children less than16 years old were diagnosed annually. While the peak age of onset of IBD was highest in the second and third decades of life, over the past two decades incidence was raised most rapidly in children <5years old. Reuter *et al.* (2020) in Australia suggested that ageing affected sensorimotor adaptation by impairing explicit strategy use, and that there was a fundamental decline in this aspect of sensorimotor brain function with age.

In the present study, female to male ratio was 3:1. This disagreed with Esmat *et al.* (2014) reported that female to male ratio was 1.15:1 and disagreed with Kalubowila *et al.* (2018) found equal sexual distributions.

In the present study, there was highly significant decrease in Hb level in patients compared to controls with a mean of 9.94 g/dl, This agreed with Esmat *et al.* (2014), who found the mean Hb level was 11.2g/dl, and agreed with Bengi *et al*. (2018) in Turkey who reported significant decrease in Hb level among 465 IBD anemic patients. But, the Hb result disagreed with Brahmania and Bernstein (2004) in Canada who reported mean Hb level of 13.9 g/dl.

In the present study, there was significant increase in platelets level among patients with mean of 305.6, which was considered as marker of inflammation. This agreed with Esmat *et al.* (2014), who reported increase in PLT in cases with mean of 335.6. Also, Salamah *et al.* (2018) in the United Kingdom reported the impact of LL-37 in modulation of platelet reactivity; and added that LL37 significantly increased thrombus formation. When compared to vehicle-treated samples, maximum dose of LL37 (50mM) enhanced thrombus intensity by 70%. Vehicle-treated patients had a mean bleeding duration of 370.8 seconds, but, LL37 infusion reduced bleeding time to a mean of 225.2 seconds. LL37 was found in many types of cells, including neutrophils that were mostly housed in granules. The results agreed with Mihai *et al.* (2018) in USA who reported that platelets were inflammatory biomarker and IBD associated with thrombocytosis.

In the present study, there was highly significant reduction of serum albumin among IBD patients with mean 3.64g/dl compared to control with mean 4.3. This agreed with Pircher *et al.* (2018) in Germany found that mean of albumin was 3.7g/dl, and with Jha *et al.* (2018) in India found that mean albumin level was 3.67g/dl. Inflammation and malnutrition reduce albumin concentration by decreasing its synthesis rate, and inflammation alone was associated with a greater fractional catabolic rate, and when extreme, increased transfer of albumin out of the vascular compartment (Don and Kaysen, 2004).

In the present study, there was significant increase in serum LL-37 levels in patients compared to controls due to the anti-inflammatory and antimicrobial effects. This agreed with Tran *et al.* (2017) who reported significant increase in serum LL-37 levels in patients compared to controls. Also, LL-37 had anti-inflammatory activity against intestinal inflammation that agreed with Yoo *et al.* (2015)**,** who in vivo found intracolonic mCRAMP peptide or cathelicidin gene exp-

ressing lentiviruses with induced colitis and led to its improvement.

In the present study, LL-37 levels variation in IBD patients were protective factor against bacterial invasion by levels elevated in mild and moderate patients and dropped at severe UC ones. So, LL-37 negatively correlated with disease activity in patients, as serum cathelicidin levels were inversely proportional with significance to PMS of UC; but, without significant increase in LL-37 correlated between LL-37 and HBI in mild to moderate cases of CD patients. This agreed with Schauber *et al.* (2006) and Cheng *et al.* (2013) who found that cathelicidin level was inversely proportional to IBD activity. Also, the present study agreed with Hing *et al.* (2013), who reported that cathelicidin have anti-inflammatory effects as a potential agent in prevention and management of infectious, toxin-associated inflammatory diarrhea, and inflammatory bowel disease caused by *C difficile*, as intracolonic mCRAMP given to *C. difficile*-infected mice showed significantly reduced colonic damage, apoptosis and TNFα levels.

Tai *et al.* (2007) showed that cathelicidin influenced in inflammation and wound healing indicated by effects of mCRAMP on colitis, the synthetic peptide was administered intrarectally to mice daily during colitis induction. Same peptide doses injected to normal colitis free mice didn't show symptom, but colitis, and without mCRAMP treated showed severe symptoms as diarrhea; sever bleeding, and administration of mCRAMP at a dose of 5.0mg/kg/day significantly ameliorated disease severity.

Also, the role of cathelicidin disagree with the present result as to its anti-inflammatory effect agreed with Duan *et al.* (2018), who reported that LL-37 have a protection dual role against colitis due to its antimicrobial action. But, LL-37 had a role in the pathogenesis of UC as up-regulation of LL-37 in UC, especially those suffered from continuous chronic inflammatory activation contributed to UC pathogenesis, by forming complex with bac-DNA, LL-37bacDNAcomplex induced secretion of IFN-α & TNF-α. The LL-37-bacDNA complex was also involved in neutrophils activation and secretion of IL-6, IL-8, TNF-α, and MCP-1. Consequently, the released cytokines and chemokines induced amplification of inflammatory cascades. The increased amount of LL-37-bacDNA complex in patients with UC was due to LL-37-mediated lysis of bacteria led to bacDNA releasing and more forming complex with LL-37.

However, the present point disagreed with Ganguly *et al.* (2009) who proved that LL37 was continuously overexpressed in colitis ulcerous led to sustained formation of nucleic acid complexes. Self-RNA-LL37 and self-DN-LL37 complexes also sustained the pathogenic inflammatory responses via TLR-mediated activation of dendritic cells inducing high levels of selfantigen-specific T cells with development of overt autoimmunity and strategies to inhibit expression of LL37 or formation of LL37-nucleic acid complexes explored for treating such diseases.

Inflammatory biomarkers provide information regarding the activity of the disease and are widely accepted as they are non-invasive; therefor, there is an increasing interest for detection of new biomarkers which can differentiate the subtypes of IBD, predict the disease course and the therapeutic response (Xavier and Podolsky, 2007). In IBD there was no single best marker of disease activity. The commonest used markers are the acute phase reactants: CRP, ESR, fibrinogen, ferritin, platelets and albumin. These are accessible, cheap, non-invasive, but have a reduced sensitivity and specificity (Gearry and Day, 2011).

In the present study, sensitivity of CRP was (52.50%) and specificity was (92.50%), and CRP level was significantly high in patients compared to controls. The high CRP levels indicated moderate and severe disease, and low ones indicated mild disease activity. Thus, serum CRP levels were directly proportional to PMS of UC and HBI of CD,

thus LL-37 was negatively correlated with CRP. C-reactive protein (CRP) is an acute inflammatory protein increased up to 1,000-fold at sites of infection or inflammation. CRP is produced as a homopentameric protein, termed native CRP (nCRP), which can irreversibly dissociate at sites of inflammation and infection into five separate monomers, termed monomeric CRP. CRP is synthesized primarily in liver hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, & adipocytes (Sproston and Ashworth, 2018). The present CRP point agreed with Kaplan *et al.* (2006), and Lewis (2011), they reported that CRP increased in serum of IBD patients compared to control as one of many acute phase proteins. Dave and Loftus (2006) reported that CRP elevations were significantly associated with severe clinical activity and active disease at ileocolonoscopy. Also, Sharifi *et al.* (2016) reported that CRP was the commonly used marker of systemic inflammation in IBD and patients with higher levels of CRP was more susceptible to relapse, and high correlation with clinical and endoscopic in both CD and UC. But, Vermeire *et al.* (2006) disagreed with the present CRP point as they found that CRP was not a specific IBD marker and only an objective marker of inflammation and correlated with disease activity in CD but rare with UC. Also, Mihai *et al.* (2018) Romania reported that despite CRP was considered a powerful serum marker co-or-dinated with inflammatory activity, there were patients with a normal CRP and increased disease activity, as well as with a raised CRP and inactive disease in 196 (48 with CD &148 with UC) IBD patients at the Institute of Gastroenterology and Hepatology. The disease severity of flare in CD was determined by the CDAI score and UC by using Mayo (UCDAI) scoring system. Tible *et al.* (2000) reported that CRP did not correlate with disease severity as there were third patients with a normal CRP and increased disease activity, and another third with a raised CRP and inactive disease. Jones *et al.* (2018) did not find any relationship between CDAI and CRP.

In the present study, there was a negative correlation between LL-37 & CRP of patients by comparing diagnostic accuracies of LL-37 alone, CRP alone, and combined LL-37 and CRP for indicating various clinical and mucosal disease activities. LL-37 was more accurate than CRP with sensitivity of (82.50 %), specificity (87.5%) PPV (86.8) and AUC (84.1%) but sensitivity of CRP was (52.50%), specificity (92.50) PPV (87.5%) & AUC was (78.9%). A combination of both LL-37 & CRP (AUC=93.7%), sensitivity (92.5%) and specificity (87.5 proved that combined CRP and LL-37 were more accurate than LL-37 alone or CRP alone. LL-37 test may be a promising alternative to the CRP test.

The present results agreed with Tran *et al*. (2017) they reported a negative correlation between LL-37, CRP, and LL-37 was more accurate than CRP and for combined LL-37 and CRP as sensitivity and specificity of LL-37 and CRP combined test were (71% & 80% respectively), AUC for LL-37+CRP was (84%), AUC of LL-37 was (76%), and AUC for CRP was (71%). Moreover, Kusaka *et al.* (2018) in Japan showed that the LL-37 negatively correlated with CRP.

Conclusion

Serum cathelicidin showed significant increase in IBD active patients, but cathelicidin with significant reverse correlation with Partial Mayo Scores of severity in UC patients. Serum cathelicidin levels didn't show significant correlation with Harvey Bradshaw severity indices in CD patients.

Co-evaluation of LL-37 & CRP levels was more accurate than CRP alone or LL-37 alone in correlation with Mayo Endoscopic Score of UC patients.

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Explanation of figures

Fig. 1: Receiver operating characteristic curve (ROC) for prediction of IBD cases.
Fig. 2: Receiver operating characteristic curve (ROC) for prediction of IBD cases according to CRP.
Fig. 3: Receiver operating characteristic curve (ROC) for prediction of IBD cases according to LL-37.