BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Anti-Outer-Membrane Porin C Antibody as Probable Biomarker for Ulcerative Colitis (UC)

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Received: 29 January 2022

Accepted: 14 April 2022

Abstract

Background: Ulcerative colitis (UC) is the commonest type of inflammatory bowel diseases (IBD) all over the world .**Aim of the work**: Compare the level of serum anti-outer membrane protein C (anti-Omp C) in UC patients and non-ulcerative colitis patients and correlate its level with the disease activity. **Patients and methods:** This study included 45 patients with UC and 45 non-ulcerative colitis patients. All cases were submitted to history taking, clinical examination and laboratory analysis (including assessment of anti-ompc antibodies). The cases in the UC group underwent colonic biopsy followed by microscopic histological examination of the obtained samples. **Results:** Endoscopic Activity Index for UC shows that 71.2% had active UC while 28.8% had inactive UC. The level of anti-ompc antibodies showed a statistically significant increase in the UC-group as compared with the non-UC group (31.11 ± 21.67 and 16.41 ± 15.06 respectively) ($p < 0.001$). The active UC group had statistically significantly higher level of anti-ompc antibodies as compared with the inactive cases (38.15 ± 18.02 and 26.61± 15.89 respectively) ($p=0.005$). ROC curve shows that,the best cut off point of anti-ompc level to identify cases with UC from non-ulcerative group was >13.8 with 63.4% sensitivity and 77.6% specificity ($p < 0.001$).**Conclusion:** Anti-OMPC may be a useful marker not only for diagnosis of UC but also in determination of the disease activity among UC patients.

Key words: Ulcerative colitis, Inflammatory bowel diseases, anti-ompc antibodies.

Introduction

Ulcerative colitis (UC) is a chronic relapsing form of inflammatory bowel disease (IBD) marked by mucosal inflammation in the colon and rectum's innermost layers. **[1]**.

Ulcerative colitis usually manifests itself over time, with abdominal pain and bloody diarrhea. Diarrhea is severe and frequent in more serious cases. There is a fever, as well as a loss of appetite and weight. The extent to which the colon is affected determines the severity of the disease **[2]**.

Clinical manifestations, as well as radiological investigations, endoscopic, and histopathological examinations, are used to diagnose ulcerative colitis. Endoscopy is the confirmatory technique that is required for ulcerative colitis **[3]**.

Unfortunately, due to potential complications in active ulcerative colitis or a lack of availability, colonoscopy may not always be appropriate. The first goal is to look for other options for evaluating these patients and to follow treatment effect in achieving endoscopic and clinical remission **[4]**.

In the last few decades, laboratory markers have been extensively studied in UC for two reasons: first, to obtain an objective measurement of disease activity because symptoms are often subjective; and second, to avoid invasive (endoscopic) procedures, which are often burdensome to patients **[5, 6]**.

Many laboratory markers have been used for diagnosis, monitoring of treatment and assessment of disease relapse including C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count (WBC) and platelet count. Yet, there are wide variations in these agents with different sensitivity and specificity **[7]**. As a result, more reliable biological markers are needed to confirm the presence of UC disease activity.

Porins, proteins embedded in the outer membrane of Escherichia coli, are targeted by anti-OmpC antibodies **[8]**. Anti-OmpC antibody positivity in Crohn’s disease (CD) patients has been reported in a few recent studies **[9-11]**. Positive anti-OmpC antibodies in 24% of CD, 11% of UC and 5% false positive rate were detected **[12]**, and in 55% of previously studied adult CD **[13]**.

The current study aims to compare the level of anti-OmpC in ulcerative colitis patients and non-ulcerative colitis group. Also, we investigated the role of anti-OmpC in the assessment of UC diagnosis and activity.

Patients and methods

This is **a cross sectional study that was** conducted at IBD Outpatient Clinics of Department of Hepatology, Gastroenterology and Infectious diseases Department, Mahalla Hepatology Teaching Hospital during the period between October, 2020 and April, 2021.

This study included a total of 90 subjects who were divided into two groups; group 1 (including 45 UC cases) and group 2 (45 non-ulcerative colitis (non-UC group).

Past history of any malignant condition, past history of major gastrointestinal surgical procedures, liver cell failure, chronic renal failure, congestive heart failure, and/or bleeding tendency, and patients taking non-steroidal anti-inflammatory drugs were all excluded from the study.

The study was conducted in accordance with Helsinki Standards as revised in 2013 **[14]**. The study was conducted after obtaining the approval from the local ethics committee, Faculty of Medicine , Benha University and after obtaining a written/oral informed consent from the included cases.

The presence of a diffuse mucosal disease of the colon with different proximal extensions from the rectum, superficial inflammation, crypt abscess, cryptitis, and rectal involvement without any evidence of small bowel involvement other than backwash ileitis was used to diagnose UC **[15]**.

The cases were subjected to the following; history taking (including the demographic data and history of present illness) and clinical examination to detect signs of inflammatory bowel disease including (diarrhea either nocturnal or postprandial, rectal bleeding**, t**enesmus, crampy abdominal pain, anorexia, nausea, vomiting, fever and weight loss) **[16].**

Laboratory investigations were done including CBC, C-reactive protein (CRP) liver functions (SGPT, SGOT, albumin and INR), renal functions (serum creatinine), and ESR. Serum anti-OmpC antibodies were investigated by means of ELISA (purchased from QUANTA Lite TM OMP Plus, INOVA Diagnostics, San Diego, USA).

Sample collection

A blood sample of 5 ml was obtained from each participant to be put into a plain

vacutainer. All samples were centrifuged and the sera were separated and kept frozen at -20 C for further analysis. According to the manufacturer's instructions, all sera samples were subjected to serological detection of Anti-outer membrane porin C using an enzyme linked immunosorbent assay (ELISA).

The Mayo UC score was used to determine the severity of the disease in cases of UC **[17]**.Rectal bleeding, stool frequency, physician assessment, and endoscopy appearance are the four components of the Mayo score. According to colonoscopy, they are classified as Mild (erythematous edematous rectal mucosa, absent or distorted vascular pattern), moderate (marked oedema, spontaneously bleeding mucosa, purulent exudates), and severe (frank ulcerations) endoscopic grades were assigned. Each component is scored on a scale of 0 to 3, for a total score of 0 to 12. Mildly active disease is indicated by a score of 3 to 5 points, moderately active disease by a score of 6 to 10 points, and severely active disease by a score of 11 to 12 points **[18, 19]**. Vascular congestion, crypt abscesses, mucin depletion, cellular infiltrate, cryptitis, and crypt branching were among the histopathological findings.[**20**].

The procedure: complete ileocolonoscopy was done to all patients in ulcerative colitis group and biopsies were taken for histopathology.

Histopathological examination

The biopsy was sent to a single expert pathologist, who performed the following procedures: Hematoxylin and eosin fixation, processing, embedding, sectioning, and staining.

Statistical analysis of data

The data collected were coded, processed and analyzed with SPSS version 26 for Windows® (Statistical Package for Social Sciences) (IBM, SPSS Inc, Chicago, IL, USA). Qualitative data as number (frequency) and percent was presented. The Chi-Square test (or Fisher's exact test) made the comparison between groups. The Kolmogorov-Smirnov test tested quantitative data for normality. Data was shown as median ± SD.

To compare two groups with categorical variables, Chi-Square test (or Fisher’s exact test) were used. To compare two groups with normally distributed quantitative variables, independent samples (student’s) t-test was used and Mann-Whitney U-test was used if the data were abnormally distributed.

Correlation of numeric data was done by Pearson's or Spearman correlation (r). The optimal cutoff value of anti-OmpC to differentiate between different groups was determined using **Youden index J** that is the farthest point on receiver operator characteristic (ROC) curve and expressed in terms of sensitivity and specificity. For all tests, P values <0.05 are considered significant.

Results

The demographic, clinical and laboratory data of studied groups are shown in table (1). There was no significant difference between the UC group and non UC group regarding age. However, regarding the sex distribution there was a statistically significant difference between the two groups as there was predominance of females in the UC group (62.2%) vs 42.2% in the non-ulcerative group (p=0.015). The mean BMI was statistically significantly higher in the non-ulcerative group (28.72± 3.44kg/m2) versus 23.09 ± 2.11kg/m2 in ulcerative group (with p=0.042).

There was no statistically significant difference in the presence of chronic diseases including DM, HTN and CLD between the two study groups. The incidence of smoking was 26.7% and 33.3% in the UC group and non-UC group respectively with no statistically significant difference between the two groups (p=0.221).

The percentage of joint affection in the UC group was 31.1% which was statistically significantly higher as compared with the non-UC group (p=0.001).

Regarding the symptom, diarrhea, bleeding per rectum, Abdominal pain were significantly higher in U.C group than the non-UC group. However, weight loss and anemia were only detected in the U.C group.

The mean WBCs count ,CRP,ESR were statistically significant higher in the UC group as compared with the non UC group (The mean levels were 11.71 ± 1.25 VS 9.09 ± 1.49, 16.9 ± 3.7 VS 3.02 ± 0.87 and 29.66 ± 4.25 VS 10.14 ± 2.34, respectively).

On the other hand, the mean hemoglobin level and mean serum albumin level were statistically significantly lower in the UC group as compared with the non-ulcerative group,(the mean 8.3±1.39 and 11.33±2.63 ,respectively)

Table (3) shows that, the extension of disease in UC group, left side colon was affected in 40%, rectosigmoid was affected in 35.6% , extensive affection in 20% while

pancolitis was present only in (4.4%). According to the degree of UC disease activity, there were 13 cases (28.9%) with inactive disease state, 8 cases (17.8%) with mild activity, 13 cases (28.9%) with moderate activity and 11 cases (24.4%) with severe activity.

The microscopic histopathological examination in the UC group revealed ulceration in 88.9% of the cases, crypt abscess in 82.2%, mucosal neutrophil infiltration in 84.4% and dysplastic changes in 17.7% of the cases. According to Ulcerative Colitis Activity Index, there was 32 cases (71.2%) with active UC and 13 cases (28.8%) with inactive UC.

Table (4) shows colonoscopic findings in the non-UC group, anal fissure was detected in 17.8% of the subjects, colonic polyp in 15.6%, internal piles in 11.1%, nonspecific colitis in 22.2% and solitary rectal ulcer in 6.7%. However, in 12 subjects (26.7%) there was no abnormality detected. the endoscopic examination revealed mild nonspecific colitis in 22.2% of the subjects, Polypoid large pedunculated in 4.4% and Polypoid sessile in 11.1%. The microscopic findings showed Adenomatous changes in 13.3%, collagenous colitis in 8.9%, hyperplastic changes in 1 case only (2.2%) and lymphocytic colitis in 13.3%.

As shown in table (5), the mean WBCs count, mean CRP, and mean ESR were statistically significantly higher in the active UC group as compared with the inactive UC group.

On the other hand, the mean hemoglobin level was statistically significantly lower in the active UC group as compared with the inactive UC group

According to the ROC curve, the best cut off point of anti-ompc level to identify cases with UC from non-ulcerative group was >13.8 with 63.4% sensitivity and 77.6% specificity. This value was considered statistically significant ($p < 0.001$).

Table (1): Demographic data, risk factors, chronic diseases, symptoms and laboratory data in the two groups

		Ulcerative colitis (UC) group (N=45)	Non-ulcerative group (Non-UC group) (N=45)	P Value
Age (years)		32.09 ± 10.63	34.72± 8.57	0.220
Sex	**Males**	17 (37.8%)	26 (57.8%)	0.015*
	Females	28 (62.2%)	19 (42.2%)	
BMI (kg/m^2)		23.09 ± 2.11	28.72± 3.44	0.041*
Risk factors and chronic diseases				
DM		9 (20%)	7 (15.6%)	0.258
HTN		13 (28.8%)	10 (22.2%)	0.232
CLD		6 (13.3%)	9 (20%)	0.204
Smoking		12 (26.7%)	15 (33.3%)	0.221
Joint affection		14 (31.1%)	4 (11.1%)	0.001*
Symptoms				
Diarrhea		41(91.1 %)	28 (62.2%)	**< 0.001***
Bleeding per rectum		39 (86.7 %)	23 (51.1%)	**< 0.001***
Abdominal pain		31 (68.9 %)	17 (37.8%)	**< 0.001***
Laboratory analysis				
Hemoglobin (g/dl)		8.30 ± 1.39	11.33 ± ٢.63	**0.015***
PLTs(10^3/µl)		272.20 ± 52.39	259.60 ± 40.35	0.143
WBCs (10^3/ml)		11.71 ± 1.25	9.09 ± 1.49	**0.019***
Blood glucose level (mg/dl)		122.79 ± 15.51	127.87 ± 13.01	0.108
Albumin		2.98 ± 0.21	3.78 ± 0.38	**0.002***
SGPT (ALT)		21.08 ± 5.83	23.72 ± 5.22	0.215
SGOT (AST)		25.01 ± 6.41	24 .70 ± 5.20	0.378
INR		1.01 ± 0.06	1.02 ± 0.03	0.897
Creatinine (mg/dl)		0.92 ± 0.26	0.94 ± 0.27	0.980
CRP (mg/l)		16.9 ± 3.7	3.02 ± 0.87	**< 0.001***
ESR (mm/dl)		29.66 ± 4.25	10.14 ± 2.34	**< 0.001***

BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, CLD :chronic liver disease, PLTs :platelets, WBCs :white blood cells, ALT: alanine transaminase, AST :aspartate transaminase, SGPT: serum glutamic pyruvic transaminase, SGOT: serum glutamic oxaloacetic transaminase, INR: International normalized ratio, CRP: c reactive protein, ESR: erythrocyte sedimentation rate.

Table(2): Analysis of Anti-outer membrane porin c Antibody in the two study groups

Anti-outer-membrane Porin C Antibody (anti-ompc)	Ulcerative colitis (UC) group (N=45)	Non-ulcerative group (Non-UC group) (N=45)	P Value
Mean ± SD	31.11 ± 21.67	16.41 ± 15.06	**< 0.001***
IQR	(11.4 -28.6)	(9.3 – 13.5)	

SD: standard deviation, IQR: interquartile range, UC: Ulcerative Colitis.

Table (3): The site of involvement, microscopic findings and activity in the UC group

	UC group (N=45)	
	Number	percentage
Site of involvement		
Rectosigmoid	16	35.6 %
Left side colon	18	40 %
Extensive	9	20 %
Pancolitis	2	4.4 %
Severity of UC		
Normal/inactive	13	28.9 %
Mild	8	17.8 %
Moderate	13	28.9 %
Severe	11	24.4 %
Microscopic findings		
Ulceration	40	88.9 %
Crypt abscess	37	82.2 %
Mucosal neutrophil infiltration	38	84.4 %
Dysplastic changes	8	17.7 %
Disease activity grading according to Ulcerative Colitis Activity Index		
Active UC	32	71.2 %
Inactive UC	13	28.8 %

UC: Ulcerative colitis. ,N: number.

Table (4): Endoscopic and histologic findings in non-UC group

	Non-UC group (N=45)	
	Number	percentage
Aetiology		
Anal fissure	8	17.8%
Colonic polyp	7	15.6%
Internal piles	5	11.1%
NAD (no abnormality detected)	12	26.7%
Nonspecific colitis	10	22.2%
Solitary rectal ulcer	3	6.7%
Endoscopic findings (n=17)		
Mild nonspecific colitis	10	22.2
Polypoid large pedunculated	2	4.4
Polypoid sessile	5	11.1
Microscopic findings (n=17)		
Adenomatous	6	13.3
Collagenous colitis	4	8.9
Hyperplastic	1	2.2
Lymphocytic colitis	6	13.3

UC :ulcerative colitis, n: number.

Table (5): laboratory parameters that indicate disease activity in UC group compared to non UC group.

	Active UC (N=32)	**Non UC (N=13)**	**P value**
Hemoglobin (g/dl)	8.81 ± 1.2	11.9 ± 0.96	0.008*
WBCs (10^3/ml)	**10.54 ± 2.06**	**8.49 ± 1.41**	0.046*
CRP (mg/l)	18.42 ± 2.48	12.51 ± 1.69	0.015*
ESR (mm/h)	23.06 ± 3.18	17.57 ± 2.2	0.001*

WBCs: white blood cells, CRP: c reactive protein, ESR: erythrocytes sedimentation rate, , UC: Ulcerative colitis.

Table (6): Anti outer membrane porin c level in the subgroups of ulcerative colitis(UC)according to disease activity.

Anti-ompc	**Active UC (N=32)**	**Inactive UC (N=13)**	**P value**
	38.15 ± 18.02	26.61± 15.89	0.005*

OMPC :outer membrane porin C

Table (7): Diagnostic ability of Anti-outer-membrane Porin C Antibody (anti-ompc) differentiate UC group from non-ulcerative group

Diagnostic criteria	Anti-ompc
AUC	0.724
Cut off point	>13.8
Sensitivity	63.4%
Specificity	77.6%
PPV	70.2%
NPV	76.4%
Accuracy	86.8%
P	< 0.001*

AUC: area under the curve.
PPV: Positive predictive value. NPV: Negative predictive value.

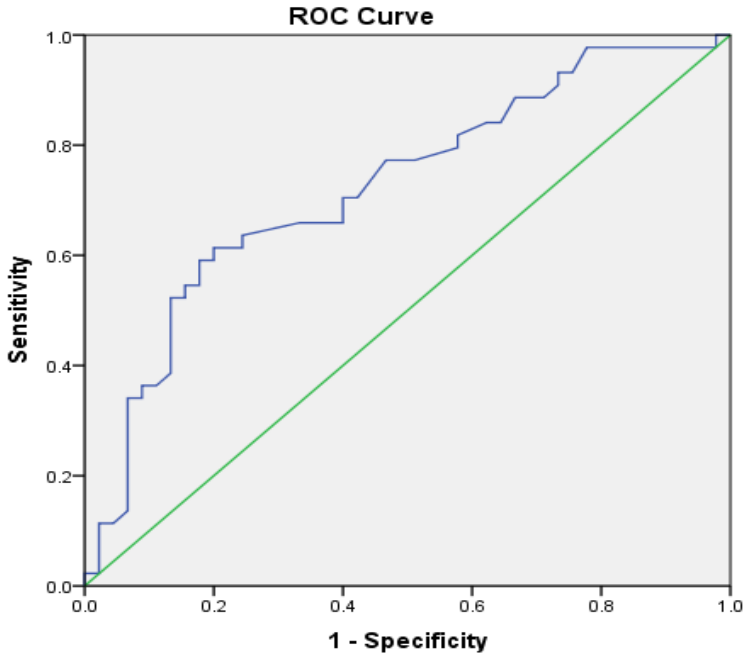

Figure (1): ROC curve for diagnostic ability of Anti-outer-membrane Porin C Antibody (anti-ompc) differentiate UC group from non-UC group

Discussion

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that can involve any aspect of the colon starting with mucosal inflammation in the rectum and extending proximally in a continuous fashion. A diagnosis of UC is made on the basis of presenting symptoms, endoscopic evidence and biopsies of the colon documenting chronic inflammation **[21]**. Anti-OmpC is a heritable immunophenotype

which its expression was found to be elevated in 31-55% of CD patients and 24% of UC patients **[22].**

As regards disease extension of UC in the current study; rectosigmoid area was the commonest affected in 35.6% of the cases followed by left side colon was affected in 40%, extensive affection in 20% while pancolitis was present only in 2 cases (4.4%). In agreement to our study with Okba et al. (2019) showed that among 80 patients with UC included in their study, proctosigmoid was affected in 35 % of the cases, left side colon was affected in 42.5%, extensive affection in 20% and pancolitis in 2.5% of the cases **[23]**.

Distribution of the included UC patient according to their disease activity showed that 28.9% had inactive disease state, followed by moderate activity (28.9%), sever activity (24.4%) and 17.8% with mild activity. In comparison to a study conducted by Okba et al. (2019) which revealed that according to endoscopic picture, normal findings were detected in 50 % of the cases, mild affection in 7.5%, moderate in 30% and severe affection in 12.5% **[23]**.

In the current study, the mean WBCs count was statistically significantly higher in the active UC group as compared with the inactive UC group. Our findings agreed with Okba et al. (2019), who found that active UC patients had significantly higher WBC than both inactive UC patients. When compared to inactive UC patients and controls, it showed a statistically significant decrease in haemoglobin concentration in active UC patients **[23]**

The current study revealed that elevated CRP and ESR were significantly higher in UC group than non UC group. This agrees with Okba et al. and Erbayrak et al. who showed that the mean serum ESR and CRP were significantly higher in the cases with UC as compared with the non UC **[23, 24]**.

Both CRP and ESR were observed to be significantly elevated among active UC than non-active UC group. The same was reported by Okba et al. and Solem et al. who showed that the serum CRP and ESR were statistically significantly higher in the active UC cases as compared with the inactive cases **[23] [25]**. In aggreement with Fagan et al. study which found that both CRP and ESR correlated well with disease activity **[26]**. Also, CRP values varied widely, with overlap between mild to moderate (10–50 mg/l), moderate to severe (50–80 mg/l), and severe disease (>80 mg/l) **[27]**.

As regards our marker; serum level of Anti OmpC was significantly elevated in UC compared to non- UC group. This goes in run with Kohoutova et al. (2014) who showed that anti-OmpC IgA was a statistically significant higher in UC group than non-UC group **[28]**. Similarly, **Davis et al. (2007)** detected elevated anti-OmpC in 29.6% of patients with UC **[29]**. Moreover, Mei et al. (2006) found a significantly increased prevalence of anti-OmpC was observed in UC patients from mixed families (24.2%, $P < .0001$), and to a lesser degree in UC-only families (12.8%, $P = .01$), as compared with healthy controls (6.0%) **[30]**. In the same line; Petersen and colleagues also reported a statistically significant elevation of Anti-Omp C among patients with IBD compared to control group with p-value <0.05 **[31]**.

Anti Omp C was found to be significantly associated also with UC disease activity in our study with p-value <0.001. In contrast to Pterson et al. study which found no statistically significant associateion between IBD activity and Anti OmpC **[31]**.

The best cut off point of anti-ompc level to identify cases with UC from non-ulcerative group was >13.8 with 63.4% sensitivity and 77.6% specificity. This value was considered statistically significant (p < 0.001). Compared to what was reported by Yulan Ye et al. which found Anti Omp C ad 26.7% sensitivity, 95% specificity, 88.9%PPV and 46.4%NPV for diagnosis of UC **[32]**. Our results agreed with Davis et al. (2007) who reported a high titer of OmpC IgA was shown to have a positive predictive value of 85% for IBD **[29]**. However, in another study, anti-OmpC has poor sensitivity as an isolated marker, detecting only 24% of patients with CD and 11% of patients with UC **[13]**.

Conclusion

Based on our findings, Association of anti outer membrane porin c with ulcerative colitis was confirmed ,Anti-ompc may be a serologic marker distinguishing UC fron non UC patients .Also significantly associated with increased disease activity

Limitations

Despite the obtained results; the present study had several limitations. The study was performed at a single center and involved a limited number of patients. So further studies still needed for better evaluation of the role of serum Anti Omp C in UC and other types of inflammatory bowel diseases.

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To cite this article: Samar M. Darwish, Yehia S. Younis , Yousry E. Abo-Amer , Radwa M. Elsharaby, Hatem S. Alegaily. Anti-Outer-Membrane Porin C Antibody as Probable Biomarker for Ulcerative Colitis (UC). BMFJ 2022;39(2): 357-371, DOI: 10.21608/bmfj.2022.118947.1537