ORIGINAL ARTICLE

Diagnostic Utility of Beta 2 Microglobulin in Patients with Irritable Bowel Syndrome and Ulcerative Colitis

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ABSTRACT

Background: *Inflammatory bowel disease (IBD) is a chronically relapsing disease. It includes ulcerative colitis (UC) and crohn's disease (CD). Symptoms of IBD could be conflicting sometimes with irritable bowel syndrome (IBS) of diarrheal type. The ideal marker for IBD/IBS diagnosis has not yet been identified. B2 microglobulin (B2-M) is a low molecular weight protein released by activated T and B lymphocytes. It has been shown to increase in several chronic inflammatory conditions.* ***Objectives:*** *Assessment of the diagnostic role of (B2-M) in IBS cases presented with diarrhea (IBS-D type) and UC cases.* ***Methodology****: This case control study was conducted at Gastroenterology Unit in Tropical Medicine Department, Ain- Shams University Hospitals, Cairo, Egypt. Forty patients with UC, and twenty patients with IBS in addition to twenty healthy persons as control were included.* ***Results:*** *There was a higher mean of B2-M values among U.C group (1.93)(mean B2-M in Active UC was 2.26 and 1.61 in inactive disease) compared to the other two groups(1.51 in IBS and 1.43 in control group) and the difference was highly statistically significant(P=0.000).Using ROC curve analysis of different cut off values of (B2-M) for detection of UC cases among IBS cases, we found that at a cut off value of >1.5 , we got sensitivity, specificity, PPV, NPV and accuracy of 75 %, 70 %, 83.3%, 58.3 %, and 0.753% respectively and this was the best cut off value.* ***Conclusion:*** *B2-M level may have a diagnostic and differentiating utility between UC cases and IBS-D type as well as a potential indicator of disease activation in UC patients.*

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition characterized by repeated attacks of remissions and exacerbations throughout the course of the disease[1]. Diarrhea either bloody or not, abdominal pain and urgency of defecation are the most common symptoms of exacerbations[2].

The pathogenesis of ulcerative colitis (UC) and Crohn's disease (CD), the two main forms of IBD, is still unclear, but autoimmune and immune-mediated phenomena are both involved. Autoimmune phenomena involve the presence of mucosal and serum autoantibodies against intestinal epithelial cells in the two forms of IBD. Immune-mediated phenomena include multiple abnormalities of innate and adaptive immunity, with the most likely trigger being a dysregulated immune response to the commensal gut flora in a genetically predisposed individual [3,4].

CD is known to be mediated by Th-1 mediated immune response with high levels of IL-2 and IFN-γ while UC triggers Th-2 mediated response with high levels of IL-5 and IL-13 which contribute to intestinal inflammation. Also, an increased percentage of TH-17 cells have been observed in the mucosa of both UC and CD patients with increasing levels of IL-17 that exacerbate intestinal inflammation[5].

Irritable bowel syndrome is defined as abdominal discomfort or pain associated with altered bowel habits (include diarrhea-predominant, constipation-predominant, and mixed presentation with alternating diarrhea and constipation) for at least three days per month in the previous three months, with the absence of organic disease. IBD symptoms could be conflicting sometimes with IBS of diarrheal type[6].

IBD diagnosis has been based on a combination of clinical data, blood parameters, radiology, endoscopy and histopathological examination[7]. IBS diagnosis needs an exclusion of other organic causes as IBD. Laboratory markers have been investigated in IBD for diagnosis and differential diagnosis purposes, for assessment of degree of disease activity and risk of complications, for prediction of relapse, and for monitoring the effect of treatment[8]. The ideal marker for IBD/IBS diagnosis has not yet been identified. The marker should be

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easy, cheap, rapid to perform, disease specific, and having prognostic value for relapse or recurrence detection of the disease[8]. Gastrointestinal endoscopy is still the gold-standard diagnostic test for IBD diagnosis[9].C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count (WBC) and platelet count, albumin, fecal calprotectin and other laboratory markers have been investigated in IBD diagnosis and prognosis[10].

Beta 2 microglobulin (B2-M) is a 11.8 kD protein consisting of 100 amino acids encoded by a gene located in chromosome 15 in humans. It has been known that B2-M, associated with classical MHC Class I molecules on the surface of all nucleated cells, is crucial for antigen presentation, immunoglobulin transport and iron metabolism [11,12]. It has been also known that B2-M is continuously generated by all nucleated cells, and released by activated T and B lymphocytes[13]. B2-M has been shown to increase in multiple chronic inflammatory and hematologic disorders, such as systemic lupus erythematosus, acquired immunodeficiency syndrome, multiple myeloma, lymphoma and leukemia[14].

Few studies reported the possible diagnostic and prognostic value of serum B2-M level in IBD cases with conflicting results[15]. We aimed in this work to evaluate the diagnostic role of B2-M in UC patients in comparison to IBS patients.

METHODOLOGY

This case control study was conducted at Gastroenterology Unit in Tropical Medicine Department, Ain- Shams University Hospitals, Cairo, Egypt. Forty cases with (UC), and twenty cases with (IBS) in addition to twenty healthy persons as control were included. The studied groups were divided as the following: **Group I (cases) which included** 40 patients with diagnosed (UC) and they were divided into two subgroups: 20 patients with active UC and 20 patients with inactive UC (under treatment). **Group II (IBS):** 20 patients diagnosed as IBS (functional disorder). **Group III (control):** 20 healthy controls with matched age and sex.

For the diagnosis of IBS, Rome III criteria[16] were applied; the Rome III criteria require recurrent abdominal pain or discomfort ≥ 3 time /month in the last 3 months associated with ≥ 2 of the following: 1- improvement with defecation; 2- onset associated with a change in form (appearance) of the stool. 3- onset associated with a change in frequency of stool. There are no alarm symptoms as anemia or weight loss. They were normal stool analysis, abdominal ultrasound, normal endoscopic and histopathological workup.

The persons in the control group had no endoscopic workup. They were free of symptoms, had no chronic disease and have normal clinical examination, normal stool analysis and normal abdominal ultrasound. These people were not on any regular medication.

We excluded cases with infectious causes, incomplete ileocolonoscopic examination, cases with colorectal polyps or malignancies, except pseudo-polyps of UC, pregnant females, patients with liver cell failure, chronic renal failure and congestive heart failure.

All patients were subjected to full history taking and clinical examination with special emphasis on alarming symptoms and signs as abdominal pain, weight loss, rectal bleeding, diarrhea, constipation, tenesmus, abdominal distension, passage of mucous and vomiting. Laboratory investigations were obtained from each case Including CBC, PT, PTT and INR, serum creatinine, blood urea nitrogen, serum Na, serum K, total serum protein, serum albumin, AST, ALT, serum bilirubin, ESR, CRP titer and P-ANCA.

B2-M assay: Blood samples were collected from patients after an overnight fast and then centrifuged at the speed of 3000 rpm for 10 min at 4 ℃, to obtain serum. All serum samples were stored at -20 ℃ immediately after separation until analysis. B2-M assay (Siemens Healthcare Diagnostics Inc) was done using the ADVIA 2400 Chemistry device. A sample was diluted and reacted with a buffer that contains latex particles coated with an antibody specific for B2-M. The formation of the antibody-antigen complex during the reaction leads to increase in turbidity. The extent of turbidity was measured as the amount of light adsorbed at 545 nm. The concentration of B2-M in a sample is determined by setting up a standard curve from the absorbance of a reagent blank and a single-level calibrator[15].

Complete stool analysis and culture were done for each case to exclude the presence of infection**.**

Ileocolonoscopic examination with biopsy was done to all UC and IBS cases**:** Multiple biopsy samples were taken from diseased and healthy mucosa to give idea about the histopathological criteria if present as well as giving confirmation to the diagnosis. According to endoscopic findings, UC cases were divided according to the site and extension of the disease into ulcerative proctitis, proctosigmoiditis, left side colitis, extensive colitis (> splenic flexure) and pancolitis[17].The endoscopic assessment of UC was categorized according to Mayo activity scoring index: Normal mucosa= inactive disease , mild (erythema, decrease vascular pattern, mild friability),moderate (marked erythema, erosions, marked friability),severe (spontaneous bleeding, ulcerations, pseudo-polyps)[18]**.** Histopathological examination of biopsy specimens was essential to confirm the diagnosis of IBD, to assess the disease activity and degree of inflammation. In IBS it was important to exclude microscopic colitis.

Mayo activity scoring index was used to assess the disease activity in cases with UC. The Mayo score ranges from 0 to 12, with higher scores indicating more

severe disease as the following: 0 to 1: Remission; 2 to 5: Mild disease; 6 to 9: Moderate disease;10 to 12: severe disease[18].

The study was approved by the Ethical committee of Faculty of Medicine, Ain Shams University. A written consent was obtained from each patient under study.

Statistical analysis:

Data were collected, revised, verified then edited on P.C. Data were then analyzed statistically using SPSS statistical package version (17).The following tests were done: Mean ($\bar{x}$), Standard deviation (SD), ANOVA (analysis of variance) ,Chi-square test (X^2) (qualitative analysis),Post hoc test to detect the least significant difference (LSD) and Pearson correlation coefficient (r).

Diagnostic validity test was done: **Sensitivity, Specificity**, **PPV (Positive predictive value)**, **NPV (Negative predictive value)**, **Accuracy**, **ROC curve** (Receiver operating characteristic curve) which is a plot to compare the sensitivity and specificity of a certain method at different decision levels as well as the sensitivity and specificity of a different method at various cut off values. **P value** was considered significant if < 0.05, and highly significant if < 0.01.

RESULTS

The mean age of UC patients were 35.05±10.33 years old while the mean age in IBS cases were 33.40 ± 8.60 years old and 30.05 ± 6.57 years old in control group. Most of UC patients were females (23 patients (57.5%)) and non-smokers (27 patients (67.5%)) while 55% of IBS cases and 30% of control were females.

Regarding the laboratory investigations of the studied groups , there are lower mean hemoglobin(12.61 ± 1.47 gm/dl versus 14.09 ± 1.01 gm/dl) and albumin(3.32 ± 0.24 mg/dl versus 4.08 ± 0.32 mg/dl) values and higher mean CRP (14.50 ± 16.19 versus 0.75 ± 1.45) and mean ESR(30.95 ± 19.39 versus 9.55 ± 4.64) values among cases with UC when compared to those of IBS and the difference is highly significant(P=0.00). However, comparing mean WBCs (7.00 ± 2.44 versus 6.32 ± 1.74) and mean platelets count (303.83 ± 72.07 versus 314.90 ± 68.50) between both groups did not show significant statistical difference. Most of active UC cases (16 cases) (80 %) have positive P-ANCA while only 15 % of the inactive cases (3 cases) have positive P-ANCA. All IBS and control cases had negative P-ANCA.

Most of UC cases (42.5 %) had left sided disease,35% had proctosigmoiditis and 20 % of the cases had extensive UC. About 30% of the active UC cases had moderate endoscopic pictures (marked erythema, erosions and friability) while 12.5 % of active UC patients had severe endoscopic pictures.

As regarding B2-M, there was higher mean of B2-M values among IBD group (1.93) (mean B2-M in Active UC was 2.26 and 1.61 in inactive disease) compared to the other two groups (1.51 in IBS and 1.43 in control group) and the difference was highly statistically significant(P=0.000). But, between cases of IBS and controls, the mean (B2-M) values showed no significant difference(P=0.583). (Table 1)

Table 1: Comparison between cases of UC, IBS and control as regards the Beta 2 microglobulin

	Mean (B2-M)	SD	F	P	Post hoc analysis		
					IBD vs IBS	IBD vs control	IBS vs control
IBD N=40	**1.93**	0.54	11.828•	0.000 HS	0.001 HS	0.000 HS	0.583 NS
IBS N=20	1.51	0.32					
Control N=20	1.43	0.22					

•: One Way ANOVA

There was a higher mean B2-M among cases with extensive UC and pancolitis compared to cases with left sided colitis and the difference was highly significant statistically. Also, there was higher mean B2-M among cases with extensive UC and pancolitis compared to cases with proctosigmoiditis and the difference was statistically significant. But there was no significant difference in the mean B2-M among cases with left sided colitis compared to cases with proctosigmoiditis. We also compared different endoscopic extent with the control group as regard mean B2-M and the difference was statistically significant. (Table 2)

Table 2: Comparison between disease involvement by endoscopy in UC patients and the mean Beta 2 microglobulin

Disease involvement	B2 microglobin		F	P-value	LSD					
	Mean	SD			I vs II	I vs III	II vs III	I vs IV	II vs IV	III vs IV
Proctosigmoid N=14 I	1.91	0.52	15.033	0.000	0.157 NS	0.031 S	0.000 HS	0.000 HS	0.035 S	0.000 HS
Left side colon N=17 II	1.71	0.35								
Extensive N=9 III	2.38	0.63								
Control group N=40 IV	1.47	0.28								

•: One Way ANOVA
NB: one pancolitis patient has been added to group of extensive patients.

There was a higher mean of B2-M levels among moderate and severe cases compared to mild cases but the difference was not statistically significant. (Table 3)

Table 3: Comparison between severity of IBD (Mayo score for UC) in active cases as regards the mean Beta 2 microglobulin levels

IBD severity by scores	Beta 2 microglobulin (B2-M)	SD	t♦	P
Mild N=6	2.10	0.46	-0.818	0.424 NS
Moderate to severe N=14	2.32	0.59		

♦: Independent t-test
N=20 -Only one case was scored as severe IBD

When correlating cases with positive P-ANCA with B2-M level, we found that cases with positive P-ANCA had higher level of B2M(2.17 ± 0.54) and higher Mayo score(5.89 ± 2.81) than cases with negative P-ANCA(B2M was 1.72 ± 0.45 and Mayo score was 1.43 ± 0.99 with high statistical significance between the 2 groups (Table 4).After doing correlation between B2-M and other markers including ESR, CRP, hemoglobin level and WBCs in patients with IBD**,** there was a highly significant positive correlation between B2-M levels and CRP levels among IBD patients .(Table 5), (Figure 1)

Table 4: The relation between PANCA in ulcerative colitis patients and B2 microglobulin and Mayo score

		Negative PANCA No. = 21	Positive PANCA No. = 19	Test value*	P-value	Sig.
Mayo Score for A/UC	Mean±SD	1.43 ± 0.99	5.89 ± 2.81	5.850	0.000	HS
	Range	0 – 7	1 – 12			
B2 microglobulin	Mean±SD	1.72 ± 0.45	2.17 ± 0.54	2.867	0.002	HS
	Range	1.2 – 2.8	1.5 – 3.3			

*: Independent t-test

Table 5: Correlation coefficient between Beta 2 microglobulin and (ESR, CRP, hemoglobin level and WBCs) in patients with IBD

	B2 microglobin	
	r	P-value
Hb (g/dl)	-0.094	0.565
WBC (thousand/cmm)	0.189	0.243
Platelet (thousand/cmm)	-0.006	0.970
ESR mm/ hour	0.243	0.132
CRP (mg/dL)	0.526**	**0.000**
S.albumin (g/dl)	-0.340*	0.032

** P<0.01 highly significant

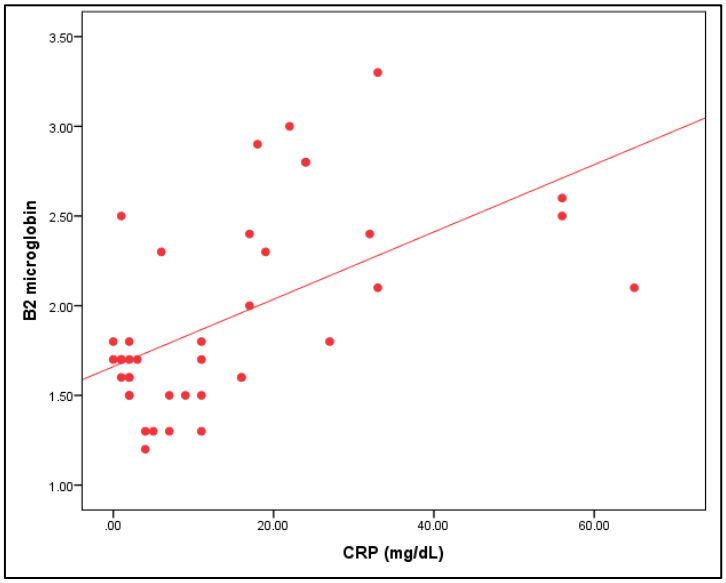
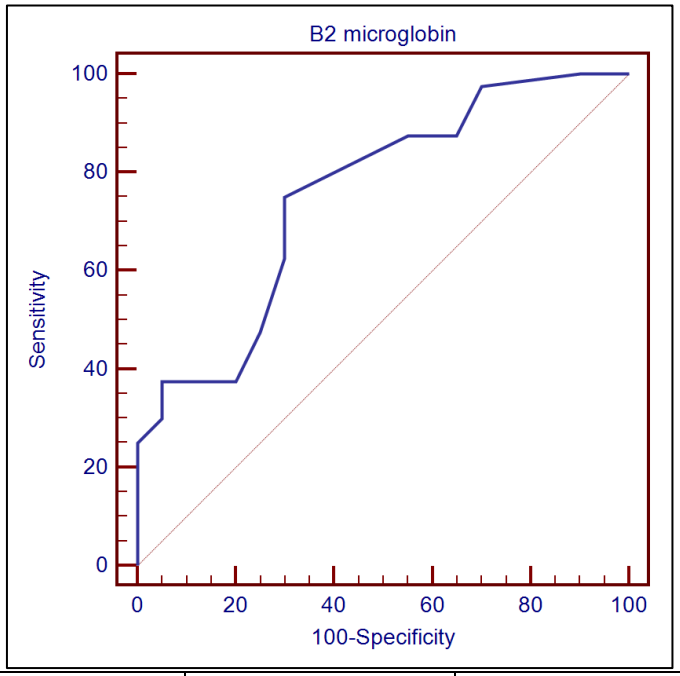


Fig. 1: Correlation coefficient between Beta 2 microglobulin and CRP

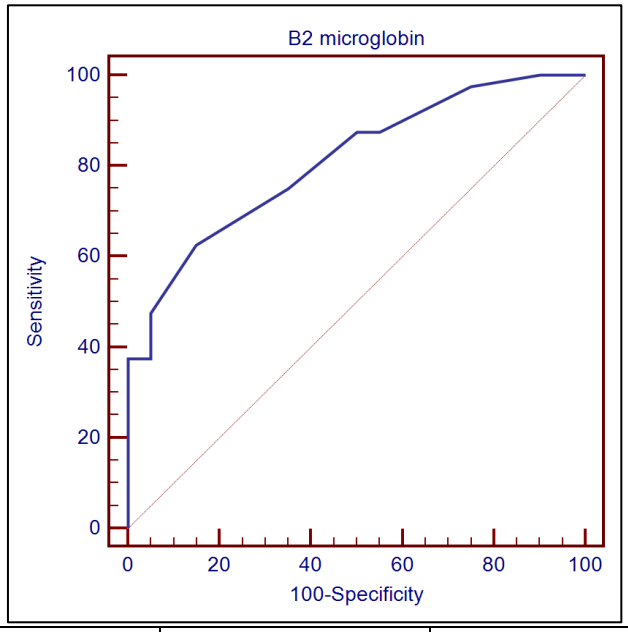
Using ROC curve analysis of different cut off values of B2-M for detection of UC cases among IBS cases, we found that at a cut off value of >1.5 , we got sensitivity, specificity, PPV, NPV and accuracy of 75 %, 70 %, 83.3%, 58.3 %, and 0.753% respectively and this was the best cut off value.(Figure 2)



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>1.5	0.753	75.00	70.00	83.3	58.3

Fig. 2: ROC curve analysis of Beta 2 microglobulin in UC versus IBS cases
(Area under the curve 0.975 95% CI 0.943-1.007)

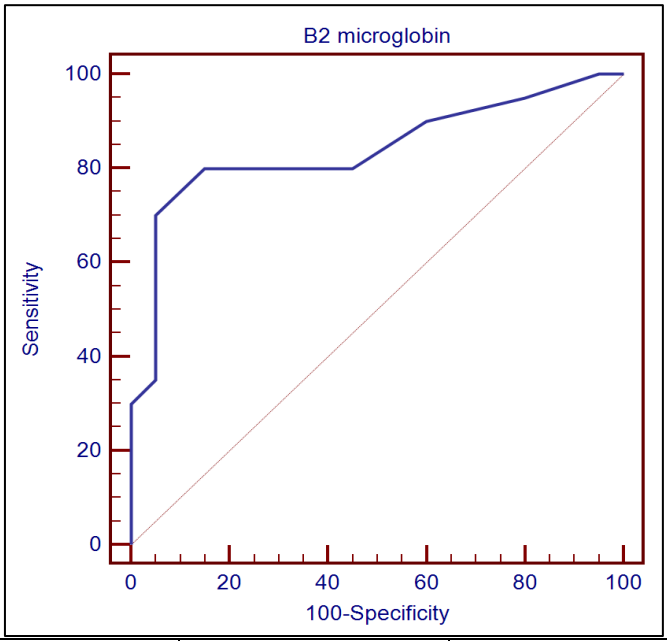
Similarly, on using different cut off values of B2-M for detection of UC among normal controls, we found that at a cut off value of >1.6 , we got sensitivity, specificity, PPV, NPV and accuracy of 62.5 %, 85 %, 89.3 %, 53.1 %, and 0.810% respectively and this was the best cut off value.(Figure 3)



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>1.6	0.810	62.50	85.00	89.3	53.1

Fig. 3: ROC Curve analysis of Beta 2 microglobulin in IBD cases versus normal controls
(Area under the curve 0.995 95% CI 0.982-1.007)

Finally, by analysis of B2-M different levels for detection of active cases of UC versus inactive cases, we found that the best cut off value was >1.7 at which the sensitivity, specificity, PPV, NPV and accuracy were 80%, 85%, 84.2%, 81%, and 0.840% respectively. (Figure 4)



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>1.7	0.840	80.00	85.00	84.2	81.0

Fig. 4: ROC curve analysis of Beta 2 microglobulin (B2-M) in active versus Inactive cases with UC
(Area under the curve 1.0 95% CI 1.0-1.0)

DISCUSSION

Ulcerative colitis [UC] is a chronic inflammatory disease characterized by exacerbation and remission course[19]. Laboratory markers have been investigated in inflammatory bowel disease (IBD) for diagnostic purposes, assessment activity, relapse prediction and monitoring the effect of treatment. CRP, ESR, WBC, platelet count and fecal calprotectin were heavily investigated in IBD for diagnosis, monitoring of activity and assessment of response to therapy[20]**.** Also, studies have tried to clarify any correlations of multiple cytokines and disease severity in IBD[21]. The ideal marker should be easy, rapid to perform, cheap, able to monitor disease activity and the effect of treatment[9].

B2-M is a low-molecular-weight protein released by activated T and B lymphocytes[15]. Serum and plasma B2-M values reflect the activation of the cellular immune system. B2-M has been shown to increase in several inflammatory conditions as well as a tumor marker in certain hematologic malignancies[14]. B2-M levels also rise during infection with some viruses, including cytomegalovirus and human immunodeficiency virus[22]. Also, a cerebrospinal fluid B2-M level may be used to assess some central nervous system diseases[23]. Abnormality of urinary B2-M values indicates renal filtration or reabsorption disorders[24].

ESR and CRP are considered the most common activity markers in IBD cases. However, CRP response may differ between CD and UC. Whereas CD may be correlated with CRP significantly, but UC may not[25]. In the present study, CRP and ESR values were higher in active than inactive ulcerative colitis. Also, they were higher in IBD cases than IBS cases and control which are compatible with many other studies[20-23,25,26]**.**

B2-M has been shown to increase in some hematologic and inflammatory conditions[15]. A number of studies investigated the role of B2-M in IBD with conflicting results[27-30].

A study by *Zissis et al* [27] previously reported that B2-M levels could be a marker of CD activity and severity. They studied the role of B2-M serum levels in 3 groups of patients (87 UC patients ,74 CD patients and 68 healthy control persons. They found that B2-M levels were significantly higher in CD group of patients, but they could not prove such correlation in U.C patients. In the current study, we studied a group of UC patients only in comparison to IBS group and control group with significant higher B2-M serum values among UC group in comparison to the other 2 groups. Also, the active UC group should significantly higher serum B2M values in comparison to inactive group. This is compatible with the study conducted by *Yılmaz et al.* [15] where serum level B2-M was higher in active U.C group than inactive group. Also, in their study, there was no significant difference between B2-M and UC extension (P = 0.694). However, in the present study, there was a higher mean of B2-M serum level among cases with extensive UC and pancolitis compared to cases with left sided colitis and proctosigmoiditis. Further studies are needed on larger sample of patient to prove the correlation between extent of the disease and B2-M level.

Researchers tried to define a sensitive and reliable biochemical marker for differentiating IBD from IBS-D and active from inactive diseases. Many inflammatory markers like ESR, CRP and fecal calprotectin were studied with variable results. In the present study, there was a highly significant positive correlation between B2-M levels and CRP levels among IBD patients. In recent years, fecal calprotectin and lactoferrin are the most extensively studied biomarkers. There is a lack of agreement on the best cut-off levels of fecal calprotectin for differentiating IBD from IBS, and for predicting disease activity, remission, and relapse. Also, the fecal calprotectin cut-off levels vary from country to country[31].

One of the interesting results of the present study by using ROC curve analysis of different cut off values of B2-M for detection of UC cases among IBS cases, a cut off value of >1.5 got sensitivity, specificity, PPV, NPV and accuracy of 75%, 70%, 83.3%, 58.3%, and 0.753% respectively and this was the best cut off value. Also, we found that the best cut off value of B2-M was >1.7 at which the sensitivity, specificity, PPV, NPV and accuracy were 80%, 85%, 84.2%, 81%, and 0.840% respectively for differentiating active from inactive disease. The results were compared with *Yılmaz B et al.* [15] where analysis of the ROC curve of their study revealed that the optimum B2-M cut-off value for active UC was 2.02 mg/L, with a sensitivity, specificity, PPV, and NPV of 79%, 78%, 88%, and 64% respectively.

CONCLUSION

We concluded that B2-M level may have a diagnostic and differentiating utility between UC cases and IBS-D type as well as a potential indicator of disease activation in UC patients.

- The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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