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Original Article

Validity of Systemic Inflammatory Markers as Predictors of Severity and Extent of Mucosal Inflammation in Ulcerative Colitis

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ABSTRACT

Background: The inflammatory process in the colonic mucosa among ulcerative colitis (UC) patients could be reflected as systemic inflammatory response with subsequent elevation of the various inflammatory biomarkers. We aimed at this research to evaluate the role of systemic inflammatory mediators; erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum albumin level, total leucocytic count, leucocyte/platelet ratio and mean platelet volume (MPV) as predictors of the severity of mucosal inflammation in patient with ulcerative colitis.

Methods: Our cross-sectional study included 30 cases diagnosed with ulcerative colitis in different stages of the disease. Estimation of serum ESR, CRP, TLC levels were done for all participants.

Results: After applying regression analysis, both WBCs count, and fecal calprotectin were significant predictors of disease activity. CRP and WBC/platelet ratio were significantly correlated to Mayo score of the patients ($p= 0.001, 0.007$ respectively). Sensitivity of CRP (>15) ESR (>19.5), WBCs count (>8500), WBCs/platelet ratio (>0.029), MPV (>8.75 f/L) serum albumin level (>4.15 gm) as a predictors of disease activity were 90.8%, 81.8%, 90.9%, 72.7%, 54.5% and 63.6%, respectively with the ability to exclude 81.3%, 73.5%, 85.2%, 78.9%, 53.1% and 57.3%, of negative cases respectively and accuracy of 86.7%, 76.7%, 86.7%, 76.7%, 53.3%, 60.0%, respectively.

Conclusions: The levels of CRP, white blood cell count, leucocyte/platelet ratio, and fecal calprotectin were significantly greater in individuals with active UC compared to those in remission. CRP, WBCs count, leucocyte/platelet ratio and fecal calprotectin may be utilized as useful indexes to assess the activity and severity of UC.

Keywords: Systemic Inflammatory Markers, Predictors, Mucosal Inflammation, Ulcerative Colitis.

INTRODUCTION

Ulcerative colitis (UC) represents a chronic illness that leads to inflammation of colonic mucosa [1].

Intestinal lesions are frequently revealed by the patient's symptoms (bloody diarrhea, abdominal pain, anemia as well as weight loss). Additional symptoms outside of the

digestive tract include arthritic pain, uveitis, and skin rashes [2]. Ulcerative colitis course is characterized by recurrent episodes of remission and exacerbation, that is why the main goal of treatment is to induce sustained remission for as long as possible [3].

It is crucial to do a colonoscopy examination to grade the inflammation of the mucosa. and by collecting multiple biopsies to reveal histological remission even if it is expensive, and invasive as mucosal inflammation may not always disappear when symptoms are clinically resolved [4]. There are now two endoscopic scoring systems in use in clinical practice, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Mayo Endoscopic Score (MES) [5].

Researchers have been looking for indicators that could take the place of colonoscopies and allow for close patient monitoring [6]. Alternative instruments have been reported, including fecal calprotectin, which is correlated with the endoscopic scores [7]. The ultimate target in Patients with ulcerative colitis receive therapy is to finally attain healing of the mucosa because the ongoing mucosal inflammation increases the risk of serious sequelae like carcinogenesis. [2]

Although endoscopy in conjunction with pathological biopsies is a dependable approach for assessing UC, its invasive and costly nature makes it challenging to employ for ongoing monitoring. Therefore, it is crucial to identify a practical, affordable, and precise way to assess UC activity [8]. With sensitivities and specificities ranging from 50 to 60, UC activity has been evaluated in various studies utilizing laboratory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein [9]. We aimed to evaluate the role of systemic inflammatory mediators(ESR, CRP, serum albumin level, total leucocytic count, leucocyte/platelet ratio and mean platelet volume) as predictors of the severity of mucosal inflammation among cases who had ulcerative colitis.

METHODS

We did this cross-sectional study in Tropical Medicine and pathology departments in Faculty of Medicine, Zagazig University Hospitals during the period from August 2022 to February 2023. Assuming the $CRP \geq 0.23$ in active inflammation within splenic flexure was 26% compared to 83% beyond the splenic flexure at 80% power and 95 % CI, the estimated sample was 30 cases. Patients were included who aged more than 18 years old, and were diagnosed with ulcerative colitis in different stages of the disease. While patients were excluded who aged less than 18 years old, with any condition that can lead to systemic inflammatory response, and patients who refused to give informed consent to participate in the study. All participants provided informed and written consent. The study was approved by The Institutional Review Board (IRB) in zagazig university faculty of medicine with number (#9940) in 23-10-2022.

Every included patient was subjected to full history taking (the duration of illness, the frequency of relapses, the symptoms of their illness as well as the drugs they receive), and general and local examination was done on all participants. Imaging: All patients who were considered had diagnostic tools such abdominal ultrasound and triphasic abdominal and pelvic CT scans to rule out other possible reasons of abdominal pain. Following proper patient preparation, a colonoscopy was performed. Following this, sterile biopsy forceps were used to extract numerous biopsies from the afflicted areas .After that, the samples were gathered in a sterile container containing 10% formalin and sent for histopathological examination. A board-certified gastroenterologist conducted the endoscopic evaluation. Grading of the disease according to Mayo clinic grading system was done [10]. Multiple biopsies from the colon were taken with evaluation of the biopsy according to Nancy scoring system. There are

neutrophils and/or epithelial cells in lamina propria, with three grades [11].

Laboratory investigations: included complete blood count with attention to leucocytic count, leucocyte/platelet ratio, mean platelet volume, liver and kidney function tests with attention to serum albumin, C-reactive protein, Erythrocytic Sedimentation Rate. Patients' UC activity status was evaluated by measuring their serum C-reactive protein levels. The CRP Nephelometric quantitative assay was performed using the serum from Roche Cobas C311 (Roche Diagnostics, Mannheim, Germany). Additionally fecal calprotectin level was performed: The Phi-Cal Calprotectin ELISA Kit (Immunodiagnostic AG, Bensheim, Germany) was used to prepare a single stool sample from each patient following histological diagnosis [12].

Statistical Analysis

Data collection, tabulation, and analysis were carried out using SPSS 20 for Windows and Microsoft Office Excel 2010 for Windows (Microsoft Cor., Redmond, WA, USA) (IBM Inc., Chicago, IL, USA). Prior to commencing the study, the data was initially examined to ensure normality using the Kolmogorov-Smirnov test and to confirm homogeneity variances. Continuous variables with a symmetric distribution are shown by means and standard deviations (mean, SD). However, the categorical variables were shown as numbers (NO) and percentages, while the skewed variables were shown as median and range (IQR) (percent). For quantitative data, we utilised the Mann-Whitney U-test; for non-normally distributed and non-homogeneous variables, the Kruskal-Wallis test was employed; and for homogeneous normally distributed variables, the independent student-t-test was employed. The calculated P-value was the result of a two-tailed test.

RESULTS

the mean age of studied cases was 35.1 ± 11.2 , 46.7% were males, 53.3% were females, mean of duration of illness was 25.6 ± 10.3 and 63.3% were in clinical remission. Also

16.7% had >3 stool frequency per day, 3.3% had bleeding per rectum, 13.3% had fever, 40% had weight loss, 6.6% had arthritis and 3.3% had Marfan syndrome. The mean of hemoglobin was 12.2 ± 1.65 , mean of WBCs was 7687.5 ± 2150.8 , mean of PLTs was 266 ± 98 , mean of ESR was 24.6 ± 14.9 and mean of leucocyte/ platelet ratio was 0.02 ± 0.008 . the mean of Albumin (g/dL) was 4.32 ± 0.61 , mean of Total bilirubin (mg/dL) was 0.81 ± 0.096 , mean of Direct bilirubin (mg/dL) was 0.54 ± 0.104 , mean of ALT (U/L) was 23.7 ± 31.8 , mean of AST (U/L) was 22.97 ± 31.1 , mean of Alkaline phosphatase (U/L) was 57.2 ± 30.4 and mean of CRP (mg/dL) was 9.94 ± 5.09 . according to endoscopy grade 66.7% had grade 1, 16.7% had grade 2, 3.3% had grade 3, according to Biopsy grade 36.7% had grade 1, 26.7% had grade 2, 36.7% had grade 3, according to Mayo grade 66.7% had grade 1, 16.7% had grade 2, 3.3% had grade 3, median of Fecal calprotectin was 747 (647.38-1332.5) and 93.3% were on biological therapy. Table 1 CRP, WBCs count, leucocyte/platelet ratio and fecal calprotectin are significantly higher among patients with active disease compared to patients in remission ($p=0.002$, <0.001 , 0.04, and 0.03 respectively) Table 2. The CRP and WBC/ platelet ratio were significantly correlated to Mayo score of the patients ($p= 0.001$, 0.007 respectively) Table3. After applying regression analysis for significant predictors of disease activity, both WBCs count, and fecal calprotectin were significant predictors of disease activity (Table 4). Sensitivity of CRP (>15) ESR (>19.5), WBCs count (>8500), WBCs/platelet ratio (>0.029), MPV (>8.75 f/L) serum albumin level (>4.15 gm) as a predictors of disease activity were 90.8%, 81.8%,90.9%, 72.7%, 54.5% and 63.6%, respectively with the ability to exclude 81.3%, 73.5%,85.2%,78.9%, 53.1% and 57.3%, of negative cases respectively and accuracy of 86.7%,76.7%,, 86.7%, 76.7%,53.3%,60.0%, respectively. Table 5 , figure(1,2,3,4,5,6).

Table (1): summery of patients all demographic, clinical, laboratory, and endoscopic data.

		mean ±SD
Age (years)		35.1 ± 11.2 18 – 59
Duration of illness (months)		25.6 ± 10.3 9 – 52
Gender	Male	14 (46.7%)
	Female	16 (53.3%)
Disease activity at time of evaluation	In clinical remission	19 (63.3%)
	Evidence of active disease	11 (36.7%)
Clinical data		N (%)
Stool frequency (per day)	0	4 (13.3%)
	2 – 3	21 (70%)
	>3	5 (16.7%)
Bleeding per rectum	No	29 (96.7%)
	Yes	1 (3.3%)
Fever		4 (13.3%)
Abdominal pain		0 (0.0%)
Weight loss		12 (40%)
Extraintestinal illness	Arthritis (Arthralgia)	2 (6.6%)
	Marfan syndrome	1 (3.3%)
Laboratory data		Mean ± SD
Hemoglobin (g/dL)		12.2 ± 1.65
WBC's (cells/μL)		7687.5 ± 2150.8
Platelet count (x10 ³ /μL)		266± 98
ESR (mm/h)		24.6 ± 14.9
leucocyte/ platelet ratio		0.02 ± 0.008
Albumin (g/dL)		4.32 ± 0.61
Total bilirubin (mg/dL)		0.81 ± 0.096
Direct bilirubin (mg/dL)		0.54 ± 0.104
AIT (U/L)		23.7 ± 31.8
AST (U/L)		22.97 ± 31.1
Alkaline phosphatase (U/L)		57.2 ± 30.4
CRP (mg/dL)		9.94 ± 5.09
Endoscopic data		N=30
Endoscopy grade	0	4 (13.3%)
	1	20 (66.7%)
	2	5 (16.7%)
	3	1 (3.3%)
Biopsy	0	0
	1	11 (36.7%)
	2	8 (26.7%)
	3	11 (36.7%)
Mayo grade	0	4 (13.3%)
	1	20 (66.7%)
	2	5 (16.7%)
	3	1 (3.3%)
Fecal calprotectin (μg/g)		747 (647.38-1332.5)
Treatment	5ASA	2 (6.75)
	corticosteroids	2 (6.7%)
	biological therapy	28 (93.3%)

Table (2): comparison between patients in remission and patients with active disease as regards the systemic inflammatory markers

	Activity N=11	Remission N=19	MW test t-test [#]	P value
CRP	34.8 ± 55.1	11.2 ± 6.59	2.81	0.002*
ESR	27.8 ± 10.2	22.7 ± 16.9	1.86	0.05
WBC count	20755 ± 36593.2	6863.2 ± 2412.3	3.45	<0.001**
leucocyte/platelet ratio	0.03 ± 0.01	0.022 ± 0.01	2.05	0.04*
MPV	9.2 ± 1.15	9.24 ± 1.31	0.078 [#]	0.939
albumin	4.31 ± 0.65	4.32 ± 0.59	0.051 [#]	0.959
fecal calprotectin	295.7 ± 232.5	118.1 ± 93.1	2.22	0.03*

Table (3): correlation of all systemic inflammatory mediators to the Mayo grade, biopsy grade and fecal calprotection

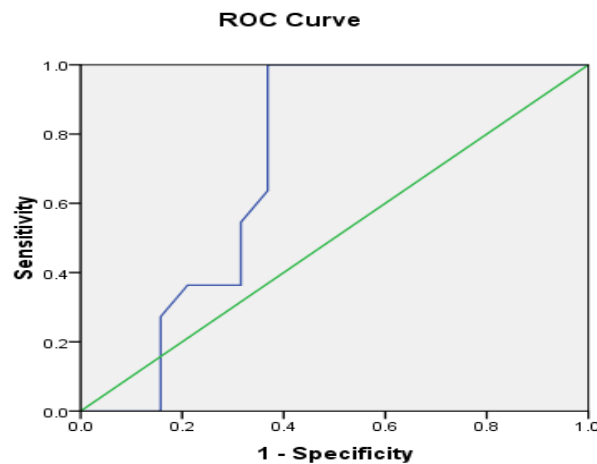
	Mayo grade		biopsy grade		fecal calprotectin	
	R	P	r	P	r	P
CRP	0.562	0.001*	-0.261	0.164	-0.01	0.945
ESR	0.096	0.615	-0.236	0.212	0.348	0.059
WBC count	0.297	0.111	-0.237	0.207	0.330	0.07
leucocyte/platelet ratio	0.485	0.007*	0.019	0.933	0.162	0.392
MPV	0.095	0.614	0.222	0.238	0.194	0.376
Albumin	0.004	0.954	-0.229	0.223	-0.09	0.635

Table (4): multivariate regression for significant predictors of disease activity

	B	S.E	Wald	P value
CRP	-0.144	0.105	1.88	0.170
WBC's count	0.001	0.00	4.08	0.04*
WBC/platelet ratio	12.55	76.8	0.027	0.811
fecal calprotectin	-0.006	0.007	7.93	0.002*

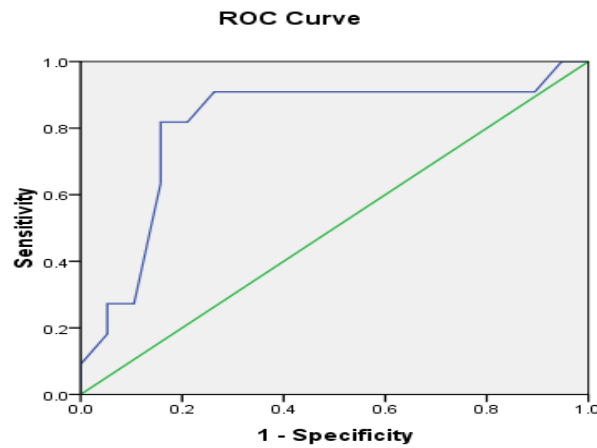
Table (5): clinical performance of different systemic inflammatory markers as predictors of inflammation

	Cut-off	AUC	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	P
CRP	>15	0.811	90.8	81.3	76.9	94.1	86.7	0.005
ESR	>19.5	0.718	81.8	73.5	64.3	87.5	76.7	0.05
WBC count	>8500	0.883	90.9	85.2	76.9	94.1	86.7	0.001
leucocyte/platelet ratio	>0.029	0.727	72.7%	78.9%	66.7%	83.3%	76.7%	0.04
MPV	>8.75	0.507	54.5%	53.1%	40.0%	66.7%	53.3%	0.959
albumin	>4.15	0.490	63.6%	57.3%	46.9%	73.3%	60.0%	0.935



Diagonal segments are produced by ties.

Figure (1): shows that sensitivity of ESR (>19.5) as a predictor of disease activity is 81.8% with the ability to exclude 73.5% of negative cases and 76.7% accuracy.



Diagonal segments are produced by ties.

Figure (2): shows that sensitivity of CRP (>15) as a predictor of disease activity is 90.8% with the ability to exclude 81.3% of negative cases and 86.7% accuracy,

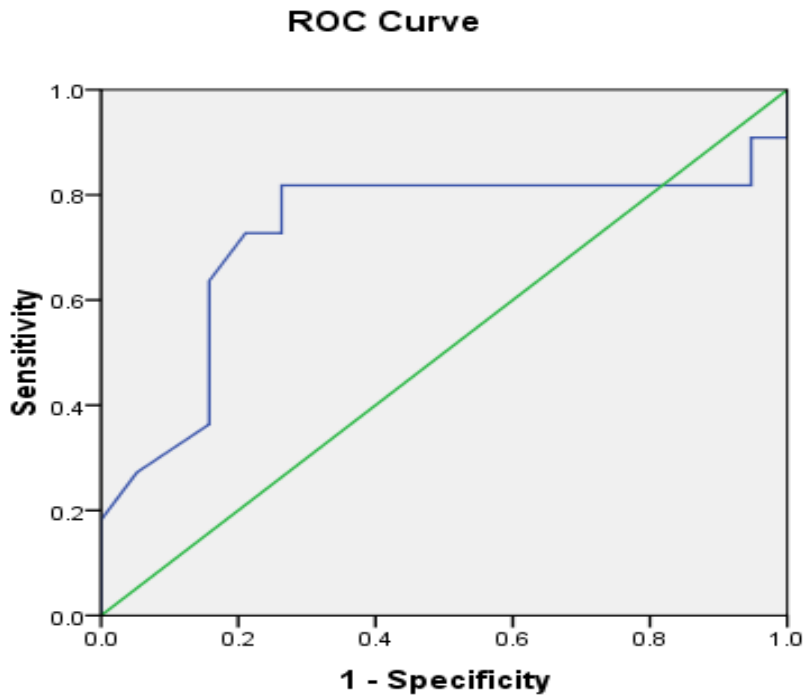


Figure (3): shows that sensitivity of WBCs count (>8500) as a predictor of disease activity is 90.9% with the ability to exclude 85.2% of negative cases and 86.7% accuracy, it was a statistically significant predictor

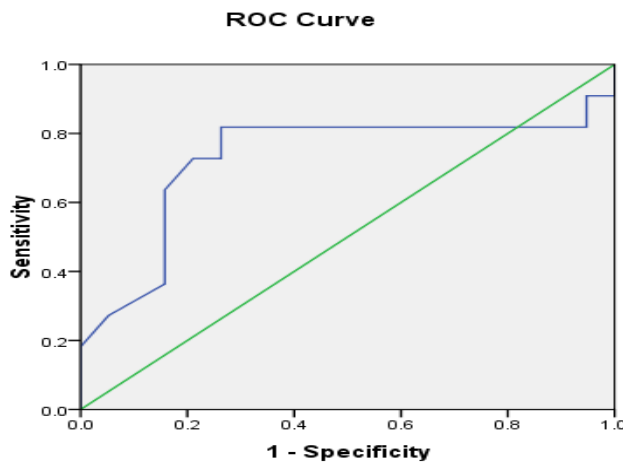
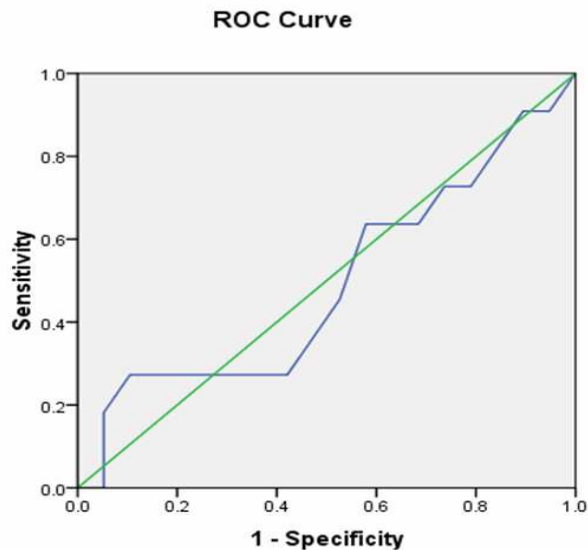
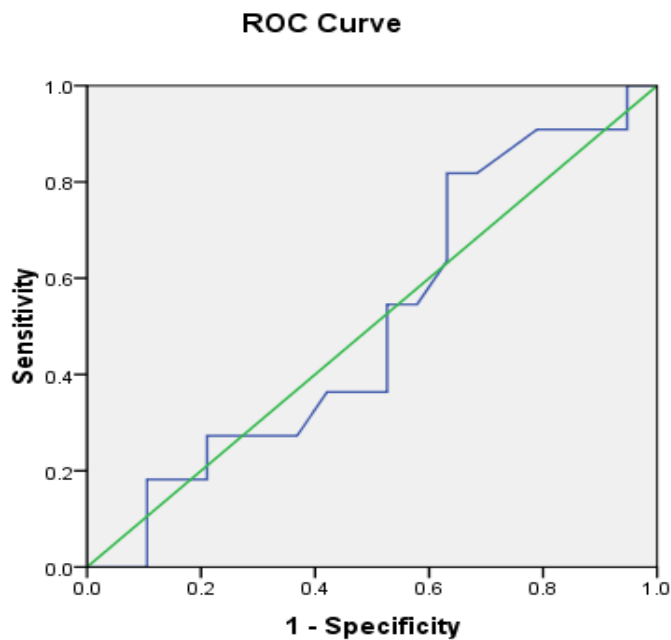


Figure (4): shows that sensitivity of WBCs/ platelet ratio (>0.029) as a predictor of disease activity is 72.7% with the ability to exclude 78.9% of negative cases and 76.7% accuracy,



Diagonal segments are produced by ties.

Figure (5): shows that sensitivity of serum albumin level (>4.15 gm) as a predictor of disease activity is 63.6% with the ability to exclude 57.3% of negative cases and 60.0% accuracy.



Diagonal segments are produced by ties.

Figure (6): shows that sensitivity of MPV (>8.75 f/L) as a predictor of disease activity is 54.5% with the ability to exclude 53.1% of negative cases and 66.7% accuracy

DISCUSSION

In this study we found that CRP, WBCs count, leukocyte/platelet ratio and fecal calprotectin are significantly higher among active group compared to remission group ($p < 0.05$). This agrees with Sayar et al. 2020 who found that when patients were categorized as being in remission, mild, moderate, or severe according to their clinical activities, a statistically significant difference was observed ($p < 0.001$) in the leukocyte/platelet ratio, CRP, albumin, and ESR values among the groups. CRP and ESR considerably increased whereas albumin level dramatically decreased as disease activity increased from remission to severe activity ($p = 0.001$; $p < 0.05$). [8]

This also aligns with Feng et al. 2022 who stated that the platelet and neutrophil counts of patients with clinically active UC were higher than those in remission. Compared to individuals in remission, those with active UC had significantly greater FC, ESR, and CRP [13]. Hassan et al. 2017 also demonstrated that patients with clinical remission had significantly lower levels of both CRP and FC than those without; only FC, however, was significantly lower in patients with endoscopic remission than in those without [14]. The observation that FC seems to be a more accurate measure of mucosal inflammation than blood indicators, such as CRP, helps to explain this finding. Moreover, El Sharawy et al. 2021 stated that individuals with remission, mild, moderate, and severe clinical activity had statistically significant changes in albumin ($p < 0.001$) [15]. Another study by Okba et al. 2019 revealed that the active UC group had significantly greater WBC, absolute neutrophilic count, absolute monocytic count, CRP, and ESR than the controls and inactive UC patients. However, when compared to controls and patients with

In this study we found that ESR was not significantly correlated to Mayo score of patients. Moreover, it shows no statistically significant correlation to the grade of biopsy or fecal calprotectin level. This is in contrast to El Sharawy et al. 2021 [15], who discovered

inactive UC, it showed a significant drop in the absolute lymphocyte count in active UC patients [16].

In this study we demonstrated that CRP was significantly correlated to Mayo score of patients. On the other hand, it shows no statistically significant correlation to the grade of biopsy or fecal calprotectin level. Our findings were in agreement with that of D'Haens et al. [17] who revealed that C-reactive protein levels were significantly correlated with endoscopic disease scores (Mayo subscores) in predicting endoscopic remission [17]. In line with our findings, Solem et al. [18] found that in UC patients, high CRP levels were linked to severe clinical activity symptoms, an increase in ESR levels, and active disease, but not to inflammation in the histology of the disease. [18] Also in this study we found that leukocyte/platelet ratio was significantly correlated to Mayo score of patients. On the other hand, it shows no statistically significant correlation to the grade of biopsy or fecal calprotectin level. Similarly, Zhang et al. 2021 and Osada et al. 2015 also found that the Mayo scores showed a moderate correlation with leukocyte/platelet ratio [19, 20]. But in this study we illustrated that WBCs count was not significantly correlated to Mayo score of patients. Moreover, it shows no statistically significant correlation to the grade of biopsy or fecal calprotectin level. Zhang et al. 2021 found that the Mayo scores showed a moderate correlation with WBCs [19]. This comes in disagreement with a study by Langhorst et al. 2008 who had demonstrated that endoscopic inflammation scores were significantly correlated with WBCs ($p < 0.001$) [21]. Osada et al. 2015 also reported that WBC counts and the total of endoscopic and histological scores were correlated [20].

that ESR showed a significant positive correlation with clinical activity, the Mayo endoscopic score ($P < 0.001$), and Hanafy et al. 2018 [22], who discovered a correlation between ESR and the higher endoscopic severity in moderate and severe cases, as well

as with biopsy-verified histological activity. In this study we demonstrated that MPV was also not significantly correlated to Mayo score of patients. It also shows no statistically significant correlation to the grade of biopsy or fecal calprotectin level. This disagrees with Zhang et al. 2021[19] who stated that the Mayo scores showed a moderate correlation with MPV and Kapsoritakis et al. 2001[23] who discovered a significant correlation between MPV and histological activity ($p = 0.01$) and endoscopic severity (mild and severe) ($p = 0.03$). In this study we found that Albumin was not significantly correlated to Mayo score of patients, the grade of biopsy or fecal calprotectin level. This disagreed with El Sharawy et al. 2021[15] who found albumin shown a significant negative correlation with clinical activity, Mayo endoscopic score ($P < 0.001$). This disagreement between our study and the previous studies regarding most of the studied inflammatory markers may be due to the fact that all patients in our studies were on therapy and most of them were in remission, the thing that may have manipulated the levels of various inflammatory markers in their serum. In this study we found that after applying regression analysis for significant predictors of disease activity, both WBCs count and fecal calprotectin were proved to be independent predictors of activity. This finding corresponds with Nakarai et al. 2018 and Hassan et al. 2017 who found that WBC's and When compared to serum indicators, FC exhibited the highest AUC for predicting both endoscopic and clinical remission. [24, 14]. In this study we found that sensitivity of ESR (>19.5) as a predictor of disease activity is 81.8% with the ability to exclude 73.5% of negative cases and 76.7% accuracy. The previous studies came out with similar results. The cut off value ranging between 8.2 to 36 mm/h gave sensitivity ranging between 71% and 88.9% and specificity between 84.6% and 90.3% [8, 16, and 22] figure (1). On the other hand we demonstrated that sensitivity of CRP (>15) as a predictor of disease activity is 90.8% with the ability to exclude 81.3% of negative cases and 86.7% accuracy, it was a

statistically significant predictor. The cut off value was higher than what was found by previous similar studies. Sayar et al. 2020 discovered that in bouts of severe illness, the AUC for CRP was 0.931 (standard error 0.025). The CRP cut-off point was determined to be 2 in cases of severe illness episodes. This cut-off point's sensitivity, specificity, positive predictive value, and negative predictive value were, in order, 91.1%, 86.1%, 80.4%, and 93.9%, respectively. Hanafy et al. 2018[22] discovered that CRP has a 71.7% specificity and an 88% sensitivity at a threshold of 6.85 mg/L for predicting UC activity (AUC 0.890, $p = 0.001$, 95% CI 0.82–1). In this study we found that sensitivity of WBCs count (>8500) as a predictor of disease activity is 90.9% with the ability to exclude 85.2% of negative cases and 86.7% accuracy, it was a statistically significant predictor. This is in line with findings from Hanafy et al. (2018), who discovered that WBCs at a threshold of 9 cells/HPF have an 80% sensitivity and an 85.7% specificity in predicting UC activity (AUC 0.93, $p = 0.001$, 95% CI 0.86–1)[22]. In this study we found that sensitivity of serum albumin level (>4.15 gm) as a predictor of disease activity is 63.6% with the ability to exclude 57.3% of negative cases and 60.0% accuracy. AUC for albumin in a severe illness episode was found by Sayar et al. 2020 to be 0.883 (standard error 0.03). When a severe illness episode was present, the albumin cut-off value was 3.6. For this cut-off point, Positive predictive value, negative predictive value, sensitivity, and specificity matching values were 91.1%, 70.8%, 66.1%, and 92.7% [8]. In this study we demonstrated that sensitivity of MPV (>8.75 f/L) as a predictor of disease activity is 54.5% with the ability to exclude 53.1% of negative cases and 66.7% accuracy. This clinical performance is lower than what Hanafy et al. 2018[22] found. The latter stated that When it comes to predicting activity in UC, MPV at a cutoff of 8.8 fL offers an 86% specificity and 71% sensitivity (AUC 0.837, $p = 0.005$, 95% CI 0.69–0.97). This distinction maybe because of the tiny sample size we used. In this research we

illustrated that sensitivity of leukocyte/platelet ratio (>0.029) as a predictor of disease activity is 72.7% with the ability to exclude 78.9% of negative cases and 76.7% accuracy, it was a statistically significant predictor. The receiver-operating characteristic (ROC) curve analysis was carried out by Feng et al. in 2022 in order to identify the precise biomarker cut-off values for activity prediction in UC. The Platelet-to-lymphocyte ratio (PLR) had an area under the curve (AUC) of 0.673 (95% CI 0.613 to 0.733), a cut-off value of 147.96, a sensitivity of 58.3%, and a specificity of 75% [13]. According to Fidan et al. (2017), ROC analysis revealed that the cut-off value for PLR to identify active UC was ≥ 133.87 (sensitivity: 63%; specificity: 68%; AUC: 0.700 (0.574-0.825)). [25]. According to the ROC curves, Hassan et al. (2017) discovered that Hb, WBCs, ESR, CRP, and FC had good prognostic accuracy for the prediction of clinical remission. FC produced the highest AUC (0.826) and 95% confidence interval (CI) (0.682–0.923, $P < 0.001$), along with 87.5% sensitivity, 89% specificity, 86.9% PPV, 89.5% NPV, and 8 +LR at cut-off of $<100 \mu\text{g/g}$ [14].

CONCLUSIONS

The levels of fecal calprotectin, ESR, CRP, MPV, white blood cell count and leukocyte/platelet ratio were significantly greater in individuals with active UC compared to those in remission. CRP, WBCs count, leukocyte/platelet ratio and fecal calprotectin may be utilized as useful indexes to assess the activity and severity of UC. After further validation, its qualities and ease of acquisition should make it a viable option for clinical practice, where it can help in the UC diagnosis with relative simplicity and reliability.

LIMITATIONS

There are some limitations in our research. Firstly, the sample size might be relatively small, with a total of 30 cases included. Secondly, since the research was conducted in a single hospital, there is a potential for selection bias. So, furthermore multi-center

study with greater sample size is essential to establish our results.

-Conflict of interest: None

-Financial disclosure: None

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