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RESEARCH ARTICLE

Corrected ESR/Albumin Ratio as a Simple, Practical Marker Predicts the Severity in Egyptian Ulcerative Colitis Patients

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Abstract:

Background:

Serum biomarkers are commonly used for diagnosing and monitoring the disease activity of Ulcerative Colitis (UC) patients. However, their role in predicting disease severity among Egyptian patients is unknown.

Objectives:

The aim of this study was to correlate these biomarkers with clinical, endoscopic and histologic severity.

Methods:

This is a cross-sectional survey where 55 patients with UC were included to measure corrected Erythrocyte Sedimentation Rate (ESR), hematocrit (Hct), corrected ESR/albumin ratio and albumin, as well as colonoscopy and biopsy. Sensitivity and specificity, positive and negative predictive values were correlated with clinical, endoscopic, histologic severity.

Results:

The mean age of patients was 33 ± 8.4 years. In total, 27 (49.1%) were males and 28 (50.9%) were females. Area Under the Curve (AUC) values for the diagnosis of severe clinical disease were 0.947, 0.932, 0.727 and 0.685 for corrected ESR/albumin ratio, corrected ESR, Het and albumin, respectively. Cut-off value to determine endoscopic severity for Het was 34 (sensitivity: 88.89%, specificity: 83.78%, PPV: 72.7%, NPV: 93.9%, AUC: 0.963, p<0.001).

Conclusion:

Corrected ESR/albumin ratio was the best predictor of severe clinical activity of UC disease. Hct may be a marker of endoscopic and histological severity due to its high sensitivity and specificity as a diagnostic test.

Keywords: Egypt, Ulcerative Colitis, Biomarkers, Prediction, Endoscopy, Disease activity.

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1. INTRODUCTION

Ulcerative Colitis (UC) is a chronic inflammatory intestinal disease (IBD) characterized by a disease relapse and period of remission [1]. Abdominal pain and blood-mixed diarrhea are the principal flags of active illness [2, 3].

UC specifically targets the superficial layers of the colonic

lining translated into endoscopic findings, including mucosal edema, erythema, granularity, friability and ulcers. Based on combined clinical and endoscopic evaluations, disease activity can be graded as mild, moderate, severe or fulminant [4, 5]. In addition, the endoscopic index of severity of ulcerative colitis (UCEIS) has been recently developed and validated as a method for accurately predicting the overall endoscopic severity assessment of UC [6, 7].

Mayo Endoscopic Score (MES) has been commonly used in research studies since 1987, and a grade between 0 and 1 is used as mucosal healing descriptor (MH) [8]. Nevertheless, the

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use of repeated endoscopy to check MH would be intrusive, painful and costly, and could be a risk of significant complications (*i.e.* colonic perforation). Consequently, non-invasive surrogate markers suggesting endoscopic healing were evaluated to replace repeated endoscopic procedures [9 - 13]. The main biomarkers in IBD are C-reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), White Blood Cells (WBC), acid glycoprotein, platelet count, fecal and serological marker albumin [14 - 16]. But, for predicting IBD activity, they have a little precision [17].

Albumin is an example of a negative acute phase reactant and may be found to have diminished levels during inflammatory conditions. A chronic inflammatory condition such as UC can affect albumin levels in the body in several ways [18].

The determination of the Erythrocyte Sedimentation Rate (ESR) represents the variations in the different acute-phase proteins. ESR varies with concentrations of plasma protein and hematocrit (Hct) value [19, 20]. Although the International Council for Standardization in Hematology (ICSH) recommends Westergren as a reference method for ESR, this method has limitations with regard to low rates of hematocrits and requires more time and large quantities of specimens to test [21, 22]. As the Westergren method overestimates ESR in low Hct specimens, Fabry's formula has been presumed to correct ESR calculation [21, 23].

In view of these considerations, the current research aimed to facilitate disease activity monitoring, predict the severity in UC by noninvasive markers (a combination of corrected ESR and albumin); as well as correlate these markers to clinical, endoscopic and histological scores and severity of the disease.

2. MATERIALS AND METHODS

2.1. Study Design and Setting

A prospective cross-sectional study was conducted among 55 Ulcerative colitis patients who had been attending the Department of Hepatology, Gastroenterology and Infectious Diseases, Kafr El-Sheikh University Hospital, Egypt, between January, 2018 and January, 2020. Informed consent was taken in writing by patients who agreed to participate before enrollment in this study.

2.2. Inclusion Criteria

The diagnosis of patients suffering from UC who agreed to participate and were included in this study was based on clinical data, pathological findings and endoscopic evaluation.

2.3. Exclusion Criteria

Patients who refused to participate in the study or to undergo colonoscopy; patients with other forms of IBD such as Cohn's disease, acute infectious colitis; patients with chronic diseases of the liver, malignancy, chronic diseases of the kidney, connective tissue disease, heart failure, vacuities, celiac disease, history of chronic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) intake or exposure to radiation were excluded from the study.

2.4. Method

Fifty-five ulcerative colitis patients were subjected to full history taking and thorough physical examination. All the patients were evaluated regarding albumin (NR, 3.5-5.5 g/dL; using the modified bromocresol green colorimetric method) [24], Hct levels (NR, 41–53%) and ESR (ESR; NR 0–15 mm/h; Westergren method). Corrected ESR for the actual Hct was calculated using Fabry's formula: Hct-Corrected ESR= ESR x 15/ 55-hematocrit [23]. Also, corrected ESR/ serum albumin ratio was calculated for all patients.

All patients had undergone a colonoscopy within 3 days of the aforementioned laboratory tests and multiple biopsies from inflamed areas were taken and put in tubes containing a predefined volume of 4% neutral buffered formalin. A paraffin block was made and a corresponding 5-µm haematoxylin-eosin stained slide was prepared for histopathological assessment.

The clinical activity of the disease was classified according to Trulove and Witts' criteria for UC into mild, moderate or severe [25]. Qualified gastroenterology doctors evaluated the endoscopic activity using standardized colonoscopy definitions (EG-3890, Pentax, Tokyo, Japan). Endoscopic activity was assessed using MES. According to this index, patients with the normal appearance of the endoscopic mucosal have been described as Mayo: 0; those with the existence of mild friability, mucosal erythema and reduced vascular pattern have been described as Mayo: 1(mild activity); those with the existence of friability and erosions, marked erythema and the disappearance of the vascular pattern have been described as Mayo: 2 (moderate activity) and those with the existence of spontaneous bleeding and ulceration have been described as Mayo: 3 (severe endoscopic activity) [8]. The haematoxylin and eosin stain (H&E) stained specimens were histologically classified according to Geboes Score from 0-5 grade [26].

2.5. Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov, Shapiro and D'agstino tests were used to verify the normality of the distribution of variables. ANOVA was used for comparing the four studied groups. Kruskal Wallis test was used to compare different groups for abnormally distributed quantitative variables. The Receiver Operating Characteristic curve (ROC) was used to determine the diagnostic performance of the markers. Area more than 50% gives acceptable performance, and area about 100% is the best performance for the test. The correlation coefficient was determined by spearman's correlation. The significance of the obtained results was judged at the 5% level.

3. RESULTS

Fifty-five patients with ulcerative colitis were enrolled in our study, 27 (49.1%) patients were female and 28 (50.9%) were male. The mean age was 33 ± 8.4 years. According to the clinical activity index, 10.9% were in remission, 25.5% had mild disease, 36.4% had moderate disease and 27.3% had severe disease (Table 1).

Table 1. Demographic and clinical characteristics of the UC patients (n=55).
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Parameters	No. (%)
Sex	
Male	27(49.1%)
Female	28(50.9%)
Age (years)	
<30	15 (27.3%)
30 - <40	27 (49.1%)
≥40	13 (23.6%)
Median (Min. – Max.)	33 (15 –55)
Mean \pm SD.	33 ± 8.4
Smoking	
No smoker	44 (88%)
Smoker	11 (20%)
Serum albumin (g/dl)	
Median (Min. – Max.)	3.5 (2.9 - 5)
Mean \pm SD.	3.6 ± 0.5
Hematocrit%	
Median (Min. – Max.)	36 (27 – 48)
Mean \pm SD.	36.8 ± 5.5
Corrected ESR/albumin ratio	
Median (Min. – Max.)	6.3 (2.9 – 17.2)
Mean \pm SD.	7.3 ± 3
Corrected ESR, mm	
Median (Min. – Max.)	22.5 (12.5 - 50)
Mean \pm SD.	25.8 ± 8.9
Clinical activity	
Remission	6 (10.9%)
Mild	14 (25.5%)
Moderate	20 (36.4%)
Severe	15 (27.3%)
Median (Min. – Max.)	3 (1 - 4)
Mean \pm SD.	2.8 ± 1
Index of severity by colonoscopy (mayo score)	
Mild	17 (30.9%)
Moderate	20 (36.4%)
Severe	18 (32.7%)
Median (Min. – Max.)	2 (1 - 3)
Mean \pm SD.	2 ± 0.8
Geboes histologic score	
Median (Min. – Max.)	3 (1 – 5)
Mean ± SD.	3.1 ± 1.4

There was a statistically significant difference regarding corrected ESR, Hct, corrected ESR/albumin ratio and albumin levels (p<0.001). When patients were classified into categories according to their clinical activities, they were mild, moderate, severe and remission groups. As the clinical activity of the disease increased from remission to severe activity, corrected ESR and corrected ESR/albumin ratio increased significantly, while albumin values and Hct decreased significantly (p<0.001) (Table **2**).

When the laboratory findings were evaluated according to endoscopic disease severity (mild, moderate and severe), a significant difference was detected between the median of three groups. As MES increased, corrected ESR (p=0.010) and corrected ESR/albumin ratio (p<0.001) showed a significant increase, while albumin and Hct showed a significant decrease (p<0.001) (Table 3).

Patients with high Geboes histologic score were found to have significantly higher corrected ESR and corrected ESR/albumin ratio; significantly lower albumin and Hct levels than those with low Geboes histologic score (p<0.001). However, there was no significant difference in corrected ESR among the groups (p=0.056), so the combined tests (corrected ESR/albumin ratio) provided better detection of histological activity of UC than corrected ESR alone (Table 4).

Table 2. Comparison of laboratory parameters in different clinical activity of ulcerative colitis (n=55).

		Clinical Activity					
-	Remission (n=6)	Mild (n=14)	Moderate (n=20)	Severe (n=15)	Test of sig.	р	
Serum albumin (g/dl)							
Median (Min. – Max.)	4.1(3.7–4.3)	4.3(3.3-5)	3.3(3-4)	3.4(2.9-4)	F=	<0.001*	
Mean \pm SD.	4.1 ± 0.2	4.2 ± 0.5	3.3 ± 0.2	3.4 ± 0.4	26.171*	<0.001*	
Hematocrit%							
Median (Min. – Max.)	38.5(36-40)	44(32-48)	34(30-41)	32(27-46)	F=	<0.001*	
Mean \pm SD.	38.2 ± 2	42.1 ± 4.8	34.9 ± 3	33.9 ± 6.2	10.158*	<u>∼0.001</u> •	
Corrected ESR/ albumin ratio							
Median (Min. – Max.)	4.1(2.9–4.8)	5.2(3.6-6.2)	6.8(5.1-12.5)	11.1(6.5-17.2)	H=	<0.001*	
Mean \pm SD.	4 ± 0.6	5.2 ± 0.6	7.1 ± 1.7	10.8 ± 2.7	43.118*	<0.001	
Corrected ESR, mm							
Median (Min. – Max.)	16.2(12.5-19)	22.1(15-27.9)	21(19.1-37.5)	35.5(22.1-50)	H=	<0.001*	
Mean \pm SD.	16.3 ± 2.5	22 ± 3.6	23.3 ± 4.6	36.2 ± 9.1	31.773*	<0.001*	

F: F for ANOVA test H: H for Kruskal Wallis test

p: p-value for comparing between the three categories *: Statistically significant at $p \leq 0.05$

Table 3. Comparison of laboratory parameters in different endoscopic activity (mayo score) of ulcerative colitis (n=55).

]	Endoscopic Mayo score	•			
	Mild (n=17)	Moderate (n=20)	Severe (n=18)	Test of sig.	р	
Serum albumin (g/dl)						
Median (Min. – Max.)	4.3 (3.7–5)	3.4(3-4)	3.2(2.9–3.5)	F=	<0.001*	
Mean \pm SD.	4.3 ± 0.3	3.4 ± 0.3	3.3 ± 0.2	59.873*	<0.001*	
Hematocrit%						
Median (Min. – Max.)	43(36–48)	36.5(30-46)	32(27-36)	F=	-0.001*	
Mean \pm SD.	42.1 ± 3.8	36.7 ± 4.5	31.9 ± 2.5	32.513*	<0.001*	
Corrected ESR/albumin ratio						
Median (Min. – Max.)	4.9(2.9-6.2)	6.6(4.7–12.5)	7.9(6.3–17.2)	H=	-0.001*	
Mean \pm SD.	4.8 ± 0.9	7.8 ± 2.6	9.1 ± 3.1	31.019*	< 0.001*	
Corrected ESR, mm						
Median (Min. – Max.)	21(12.5–27.9)	22.6(18.3-50)	25.4(20-50)	H=	0.010*	
Mean \pm SD.	20.6 ± 4.5	26.6 ± 8.9	29.7 ± 9.8	9.277*	0.010*	

F: F for ANOVA test H: H for Kruskal Wallis test

p: p-value for comparing between the three categories *: Statistically significant at $p \le 0.05$.

Table 4. Relation between histological activity (Geboes score) and different parameters (n=55).

-	1 2 (n=9) (n=13)		3 (n= 9)	Severe (n=24)	Test of sig.	р
Serum albumin (g/dl)						
Median (Min. – Max.)	4.3 (3.7 – 5.0)	4.0 (3.3 – 4.5)	3.4 (3.0 – 4.3)	3.3 (2.9 – 4.0)	F=	< 0.001*
Mean \pm SD.	4.3 ± 0.4	3.9 ± 0.4	3.6 ± 0.5	3.3 ± 0.3	18.359*	<0.001
Hematocrit%						
Median (Min. – Max.)	40.0 (40.0 - 48.0)	43.0 (38.0 - 46.0)	36.0 (33.0 - 37.0)	32.0 (27.0 - 37.0)	F=	< 0.001*
Mean \pm SD.	42.8 ± 3.4	42.3 ± 3.1	35.4 ± 1.4	32.1 ± 2.6	56.599*	<0.001
Corrected ESR/albumin ratio						
Median (Min. – Max.)	5.0 (3.6 - 6.2)	5.9 (4.8 - 12.5)	5.9 (2.9 – 11.1)	7.5 (4.7 – 17.2)	H=	0.001*
Mean \pm SD.	4.9 ± 0.8	7.0 ± 2.3	6.2 ± 2.5	8.7 ± 3.3	16.514*	0.001*
Corrected ESR, mm						

(Table 4) contd.....

-	1 (n= 9)	2 (n= 13)	3 (n= 9)	Severe (n=24)	Test of sig.	р
Median (Min. – Max.)	20.0 (15.0 - 27.9)	24.0 (19.1 - 50.0)	19.7 (12.5 - 35.5)	24.5 (18.3 - 50.0)	H=	0.056
Mean ± SD.	21.5 ± 4.9	26.9 ± 8.9	21.2 ± 6.9	28.4 ± 9.7	7.570	0.030

F: F for ANOVA test H: H for Kruskal Wallis test

p: p-value for comparing between the three categories

*: Statistically significant at $p \le 0.05$

As indicated in Table 5, the corrected ESR/albumin ratio exhibited a significant positive correlation with clinical activity, Mayo endoscopic score and Geboes histologic score (P<0.001), while albumin and Hct exhibited significant negative correlations correlation with previous scores (P<0.001). On the other hand, corrected ESR showed a significant positive correlation with clinical activity, MES (P<0.001, P=0.002 respectively). So, corrected ESR exhibited weaker correlations with the MES, as compared to Hct, albumin and corrected ESR/albumin ratio. Moreover, there was no correlation between corrected ESR and Geboes histologic score (P= 0.062).

In order to identify the best cut-off values that could indicate severe clinical, histological and endoscopic disease episodes, ROC analysis was conducted for the corrected ESR, Hct, albumin values and corrected ESR/albumin ratio.

Regarding the severe clinical activity of UC disease; the area under the ROC curve (AUC) for corrected ESR/albumin ratio was found to be 0.947 at cut-off point 8.2. Moreover, this cut-off point showed sensitivity (88.9%), specificity (90.3%), positive predictive value (85.1%) and negative predictive value (92.8%) (Table 6 and Fig. 1A). It is, therefore, the best predictor of severe clinical activity.

Table 5. Correlation of laboratory paran	eters with different index of severity in ulcerative colitis (n=55).

	Clinical activity		Mayo	score	Original Geboes Score		
-	r	р	r	р	r	р	
Serum albumin (g/dl)	-0.616*	<0.001*	-0.751*	<0.001*	-0.673*	<0.001*	
Hematocrit	-0.513*	< 0.001*	-0.752*	<0.001*	-0.885*	<0.001*	
Corrected ESR/albumin ratio	0.892*	<0.001*	0.727*	<0.001*	0.536*	<0.001*	
Corrected ESR	0.715*	<0.001*	0.413*	0.002*	0.254	0.062	

Table 6. ROC analysis of Hct, albumin, corrected ESR and corrected ESR/s albumin ratio in the diagnosis of severe ulcerative colitis disease.

AUC	JC p value	95% C.I		C+ - 66	G	S: 6 -: 4	DDV	NDV
AUC		L.L	U.L	Cut on	Sensitivity	specificity	PPV	NPV
0.685	0.016*	0.546	0.804	≤4	100.0	35.0	36.6	100.0
0.812	< 0.001*	0.683	0.904	≤3.5	100.0	62.16	56.2	100.0
0.856	< 0.001*	0.735	0.936	≤3.5	91.67	67.74	68.7	91.3
0.727	0.016*	0.590	0.838	≤30	46.67	97.50	87.5	83.0
0.898	< 0.001*	0.786	0.963	≤34	88.89	83.78	72.7	93.9
0.961	< 0.001*	0.871	0.995	≤35	91.67	93.55	91.7	93.5
0.947	< 0.001*	0.850	0.989	>8.2	86.67	95.0	86.7	95.0
0.820	< 0.001*	0.693	0.910	>6.2	100.0	72.97	64.3	100.0
0.765	< 0.001*	0.632	0.869	>5.9	87.50	64.52	65.6	87.0
0.932	< 0.001*	0.830	0.982	>26.7	86.67	90.0	76.5	94.7
0.707	0.003*	0.569	0.822	>19.9	100.0	35.14	42.9	100.0
0.633	0.083	0.492	0.759	>28.1	41.67	87.10	71.4	65.9
	0.685 0.812 0.856 0.727 0.898 0.961 0.947 0.820 0.765 0.932 0.707	0.685 0.016* 0.812 <0.001* 0.856 <0.001* 0.727 0.016* 0.898 <0.001* 0.961 <0.001* 0.947 <0.001* 0.947 <0.001* 0.942 <0.001* 0.943 <0.001* 0.944 <0.001* 0.945 <0.001* 0.947 <0.001* 0.947 <0.001* 0.947 <0.001* 0.947 <0.001* 0.947 <0.001* 0.705 <0.001* 0.705 <0.001*	AUC p value L.L 0.685 0.016* 0.546 0.812 <0.001* 0.683 0.856 <0.001* 0.735 0.727 0.016* 0.590 0.727 0.016* 0.590 0.898 <0.001* 0.871 0.961 <0.001* 0.871 0.947 <0.001* 0.850 0.725 <0.001* 0.632 0.947 <0.001* 0.632 0.942 <0.001* 0.632 0.765 <0.001* 0.632 0.735 <0.001* 0.632 0.735 <0.001* 0.632	AUC p value $I.L$ U.L 0.685 0.016* 0.546 0.804 0.812 <0.001* 0.683 0.904 0.856 <0.001* 0.735 0.936 0.727 0.016* 0.590 0.838 0.898 <0.001* 0.786 0.963 0.961 <0.001* 0.850 0.9995 0.820 <0.001* 0.850 0.989 0.765 <0.001* 0.632 0.869 0.932 <0.001* 0.830 0.982 0.775 <0.001* 0.830 0.982	AUC p value L.L U.L Cut off 0.685 0.016* 0.546 0.804 ≤ 4 0.812 $< 0.001*$ 0.683 0.904 ≤ 3.5 0.856 $< 0.001*$ 0.735 0.936 ≤ 3.5 0.856 $< 0.001*$ 0.735 0.936 ≤ 3.5 0.727 0.016* 0.590 0.838 ≤ 30 0.727 0.016* 0.590 0.838 ≤ 30 0.898 $< 0.001*$ 0.786 0.963 ≤ 34 0.961 $< 0.001*$ 0.871 0.995 ≤ 35 0.947 $< 0.001*$ 0.850 0.989 > 8.2 0.820 $< 0.001*$ 0.633 0.910 > 6.2 0.765 $< 0.001*$ 0.633 0.989 > 5.9 0.932 $< 0.001*$ 0.830 0.982 > 26.7 0.707 0.003* 0.569 0.822 > 19.9	AUC p value L.L U.L Cut off Sensitivity 0.685 0.016* 0.546 0.804 ≤ 4 100.0 0.812 $<0.001*$ 0.683 0.904 ≤ 3.5 100.0 0.856 $<0.001*$ 0.735 0.936 ≤ 3.5 91.67 0.727 0.016* 0.590 0.838 ≤ 30 46.67 0.898 $<0.001*$ 0.786 0.963 ≤ 34 88.89 0.961 $<0.001*$ 0.871 0.995 ≤ 35 91.67 0.947 $<0.001*$ 0.870 0.989 ≤ 34 88.69 0.941 $<0.001*$ 0.870 0.995 ≤ 35 91.67 0.947 $<0.001*$ 0.870 0.995 ≤ 35 91.67 0.947 $<0.001*$ 0.850 0.989 > 8.2 86.67 0.820 $<0.001*$ 0.632 0.869 > 5.9 87.50 0.932 $<0.001*$ 0.830 0.982 <th>AUC p value I_{LL} U.L Cut off Sensitivity Specificity 0.685 0.016* 0.546 0.804 \leq4 100.0 35.0 0.812 <0.001* 0.683 0.904 \leq3.5 100.0 62.16 0.856 <0.001* 0.735 0.936 \leq3.5 91.67 67.74 0.856 <0.001* 0.735 0.936 \leq3.5 91.67 67.74 0.727 0.016* 0.590 0.838 \leq30 46.67 97.50 0.898 <0.001* 0.786 0.963 \leq34 88.89 83.78 0.961 <0.001* 0.871 0.995 \leq35 91.67 93.55 0.947 <0.001* 0.850 0.989 >8.2 86.67 95.0 0.820 <0.001* 0.632 0.869 >5.9 87.50 64.52 0.932 <0.001* 0.830 0.982 >26.7 86.67 90.0 0.932</th> <th>AUC p value L.L U.L Cut off Sensitivity Specificity PPV 0.685 0.016* 0.546 0.804 \leq4 100.0 35.0 36.6 0.812 <0.01* 0.683 0.904 \leq3.5 100.0 62.16 56.2 0.856 <0.001* 0.735 0.936 \leq3.5 91.67 67.74 68.7 0.727 0.016* 0.590 0.838 \leq30 46.67 97.50 87.5 0.898 <0.001* 0.786 0.963 \leq34 88.89 83.78 72.7 0.961 <0.001* 0.871 0.995 \leq35 91.67 93.55 91.7 0.947 <0.001* 0.871 0.995 \leq35 91.67 93.55 91.7 0.947 <0.001* 0.850 0.989 \leq35 91.67 95.0 86.7 0.820 <0.001* 0.693 0.910 $<$6.2 100.0 72.97 64.3</th>	AUC p value I_{LL} U.L Cut off Sensitivity Specificity 0.685 0.016* 0.546 0.804 \leq 4 100.0 35.0 0.812 <0.001* 0.683 0.904 \leq 3.5 100.0 62.16 0.856 <0.001* 0.735 0.936 \leq 3.5 91.67 67.74 0.856 <0.001* 0.735 0.936 \leq 3.5 91.67 67.74 0.727 0.016* 0.590 0.838 \leq 30 46.67 97.50 0.898 <0.001* 0.786 0.963 \leq 34 88.89 83.78 0.961 <0.001* 0.871 0.995 \leq 35 91.67 93.55 0.947 <0.001* 0.850 0.989 >8.2 86.67 95.0 0.820 <0.001* 0.632 0.869 >5.9 87.50 64.52 0.932 <0.001* 0.830 0.982 >26.7 86.67 90.0 0.932	AUC p value L.L U.L Cut off Sensitivity Specificity PPV 0.685 0.016* 0.546 0.804 \leq 4 100.0 35.0 36.6 0.812 <0.01* 0.683 0.904 \leq 3.5 100.0 62.16 56.2 0.856 <0.001* 0.735 0.936 \leq 3.5 91.67 67.74 68.7 0.727 0.016* 0.590 0.838 \leq 30 46.67 97.50 87.5 0.898 <0.001* 0.786 0.963 \leq 34 88.89 83.78 72.7 0.961 <0.001* 0.871 0.995 \leq 35 91.67 93.55 91.7 0.947 <0.001* 0.871 0.995 \leq 35 91.67 93.55 91.7 0.947 <0.001* 0.850 0.989 \leq 35 91.67 95.0 86.7 0.820 <0.001* 0.693 0.910 $<$ 6.2 100.0 72.97 64.3

AUC: Area under a curve

CI: Confidence Intervals

PPV: Positive predictive value

NPV: Negative predictive value

*: Statistically significant at $p \le 0.05$.



Fig (1). ROC curve for laboratory parameters for the prognosis of severe cases (A: clinical activity, B: index of severity by colonoscopy, C: Geboes histologic score)

Concerning severe endoscopic activity of the disease; (AUC) for Hct was found to be 0.963 at cut-off value 34 with specificity (83.78%), sensitivity (88.89%), positive predictive value (72.7) and negative predictive value (93.9). However, (AUC) for the corrected ESR/albumin ratio was found to be 0.820 at cut-off point 6.2. In addition, sensitivity (100.0%), specificity (72.97%), positive predictive value (64.3%) and negative predictive value (100.0%) for this cut-off point were noticed at this cut-off point (Table 6 and Fig. 1B).

Severe histological activity-related (AUC) was found to be 0.961 for Hct at cut-off value 35, including sensitivity (91.67%) and specificity (93.55%). However, (AUC) for the corrected ESR/albumin ratio was found to be 0.765 at cut-off point 5.9, including sensitivity (87.50%) and specificity (64.52%) (Table 6 and Fig. 1C).

The Hct yielded the best accuracy for the determination of

the severe endoscopic and histological activity of the disease at cut-off values of 34 and 35, respectively.

4. DISCUSSION

UC non-intrusive markers may have the significant advantage of avoiding invasive diagnostic tests and their complications [27]. In the diagnosis of inflammatory conditions, ESR is important [28]. ESR is an attractive alternative to new methods due to its simplicity of performance and low cost [29]. Current research findings indicate that the ESR remains high once it increases, until the primary inflammatory process is resolved [30]. The ESR procedure cannot be calibrated and is therefore vulnerable to different sources of error. There is no way to ensure multiple variables, such as hematocrit, not influencing ESR measurement [31]. In inflammatory hypoalbuminemic conditions, the ESR could also be higher than if the serum albumin was normal [32]. So in our study, we corrected ESR to overcome the hematocrit factor and correlate it with albumin. To our knowledge, this is the first study to directly compare the correlation coefficients of corrected ESR/albumin ratio with clinical activity, endoscopic severity and histological activity in comparison with corrected ESR, Hct, and albumin levels.

In the present study, the corrected ESR/s albumin ratio was the best predictor of severe clinical activity of UC disease and superior to the other laboratory parameters with a positive prediction value (r=0.892; P<0.001). Also, it was a good predictor for both endoscopic and histologic activity. However, in the current study, corrected ESR was a good predictor of severe disease episode with sensitivity and specificity 86.67% and 90.0%, respectively, which is consistent with that of Sayer et al., who reported that ESR is accurate in determining disease activity with sensitivity (88.4%) and specificity (84.6%) [33]. In our study, the corrected ESR was significantly higher in the UC patients with moderate and severe endoscopic changes, which came in accordance with the study by Hanafy et al., who reported higher ESR among these patients' group [34]. Conversely, Minderhoud et al., found that the changes in ESR are not necessarily associated with mucosal inflammation and may not represent reliably the severity and extent of mucosal inflammation [35]. Also, Mabrouk et al., found that ESR did not adequately reflect disease activity because of low sensitivity and specificity for intestinal inflammation [36]. We found no significant correlation between corrected ESR and histological activity of the disease (p=0.062). However, Hanafy et al., found a significantly positive correlation between ESR and clinical severity (p = 0.006, 0.71 endoscopic severity (p=0.000, 0.56) pathological activity (p=0.03, 0.32) [35].

We found statistically significant differences concerning albumin among patients with remission, low, moderate, and severe clinical activity (p<0.001). These results were in agreement with those of Sayar et al., who found the effectiveness of albumin in assessing disease severity according to clinical activity score (p= 0.001) [34]. In our study, the cut-off point for albumin in the presence of severe disease episode was 4. The sensitivity, specificity, positive predictive value, and negative predictive value for this cut-off point were 100.0%, 35.0%, 36.6%, and 100.0%, respectively. Similar results were reported by Sayar et al., who found albumin at a cut-off value of 3.6. The sensitivity, specificity, positive predictive value, and negative predictive value for this cut-off point were 91.1%, 70.8%, 66.1%, and 92.7%, respectively [34]. This negative correlation between albumin and UC disease activity could be explained by loss of protein from the intestine and malnutrition may affect serum albumin level [37]. In contrast, Ripoli et al., observed no significant difference in the levels of albumin in patients during the disease activity period compared to that of remission as they enrolled outpatient who did not require hospitalization [38]. In line with the study by Xie et al., we found a significant difference in albumin among different MES (p<0.001) [39].

In the current study, we showed that the Hct value was the best predictor of endoscopically active disease with a negative correlation (r=-0.752; P<0.001). In accordance with these

results, Akpinar et al., found that Hct level had a negative correlation with the endoscopic activity of UC disease. (r=-0.318; P<0.001) [40]. Indeed, we reported that Hct was the best predictor of histologic activity of disease with a negative correlation (r=-0.885; P<0.001). These results were in agreement with those of Rodríguez et al., who found that hemoglobin (Hgb) and Hct were negative predictive values and correlated with the degree of activity in the biopsy. Within sixty patients suffering from UC, the specificity and sensitivity were (100%, 51%) for Hgb and (100%, 51%) for Hct, respectively [41]. Moreover, Reinisch et al., reported that a low level of Hgb predicted a more aggressive disease course [42]. Hgb also is useful in the early prediction of treatment response among patients with severe acute UC [43]. This can be explained by more inflammatory activity, which possibly contributes to more blood loss, increased hepcidin release and decreased iron absorption from the intestine [44]. Thus, assessing Hgb and Hct in patients in IBD is simple, fast to perform, cheap and is part of the standard of care tests [45]. However, Ripoli et al., observed no significant difference in the levels of hematocrit in patients during the disease activity period compared to that of remission [37]. Also, LOK et al., demonstrated that commonly used serum biomarkers in Chinese UC patients were positive in only a small proportion of cases with endoscopically and histologically confirmed active colonic inflammation. However, several limitations were noted in their study [46].

CONCLUSION

The current research observed that the association between corrected ESR/albumin ratio and disease clinical, endoscopic and histologic activity was significant. Hct demonstrated greater positive predictive value and specificity than either corrected ESR/albumin ratio and albumin in predicting severe endoscopic and histologic activity in ulcerative colitis. Therefore, the current study recommends that corrected ESR/albumin and Hct; cheap, simple and easily calculated parameters, could be good indicators of UC severity.

ETHICS APPROVAL AND CONSENT TO PARTI-CIPATE

The research steps were explained and the permission for conducting the research was obtained from the approving authority, Faculty of Medicine, Kafr El-Sheikh University, Egypt.

HUMAN AND ANIMAL RIGHTS

No animals were used as the basis of this study. This research was conducted according to the Declaration of Helsinki principles.

CONSENT FOR PUBLICATION

Informed consent was taken in writing by patients who agreed to participate before enrollment in this study.

AVAILABILITY OF DATA AND MATERIALS

The data sets used during the current study can be provided from the corresponding author [I.A.], upon reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

- Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: Analysis of changes in disease activity over years. Gastroenterology 1994; 107(1): 3-11.
 [http://dx.doi.org/10.1016/0016-5085(94)90054-X] [PMID: 8020674]
- [2] IIa T, IuI T. Klin Med (Mosk) 2013; 91: 27-33. [Ulcerative colitis and Crohn's disease. Part 1. Definition, terminology, prevalence, etiology
- and patogenesis, clinical features, complications, classification].
 Sacco R, Tanaka T, Yamamoto T, Bresci G, Saniabadi AR. Adacolumn leucocytapheresis for ulcerative colitis: Clinical and endoscopic features of responders and unresponders. Expert Rev Gastroenterol Hepatol 2015; 9(3): 327-33.
- [http://dx.doi.org/10.1586/17474124.2014.953060] [PMID: 25160857]
 [4] Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009; 361(21): 2066-78.
- [http://dx.doi.org/10.1056/NEJMra0804647] [PMID: 19923578]
 [5] Baumgart DC, Sandborn WJ. Inflammatory bowel disease: Clinical aspects and established and evolving therapies. Lancet 2007; 369(9573): 1641-57.
 [http://dx.doi.org/10.1016/S0140-6736(07)60751-X] [PMID: 17499606]
- [6] Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: The Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Gut 2012; 61(4): 535-42.
- [http://dx.doi.org/10.1136/gutjnl-2011-300486] [PMID: 21997563]
 [7] Travis SP, Schnell D, Krzeski P, *et al.* Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology 2013; 145(5): 987-95.
- [http://dx.doi.org/10.1053/j.gastro.2013.07.024] [PMID: 23891974]
 [8] Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317(26): 1625-9.
 [http://dx.doi.org/10.1056/NEJM198712243172603] [PMID: 3317057]
- [9] D'Haens G, Ferrante M, Vermeire S, *et al.* Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. Inflamm Bowel Dis 2012; 18(12): 2218-24. [http://dx.doi.org/10.1002/ibd.22917] [PMID: 22344983]
- [10] Ricanek P, Brackmann S, Perminow G, et al. Evaluation of disease activity in IBD at the time of diagnosis by the use of clinical, biochemical, and fecal markers. Scand J Gastroenterol 2011; 46(9): 1081-91.
- [http://dx.doi.org/10.3109/00365521.2011.584897] [PMID: 21619483]
 [11] Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin more accurately reflects endoscopic activity of ulcerative colitis than the Lichtiger Index, C-reactive protein, platelets, hemoglobin, and blood leukocytes. Inflamm Bowel Dis 2013; 19(2): 332-41.
 [http://dx.doi.org/10.1097/MIB.0b013e3182810066] [PMID: 23328771]
- [12] Schoepfer AM, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, Creactive protein, and blood leukocytes. Inflamm Bowel Dis 2009; 15(12): 1851-8.

[http://dx.doi.org/10.1002/ibd.20986] [PMID: 19462421]

[13] Theede K, Holck S, Ibsen P, Ladelund S, Nordgaard-Lassen I, Nielsen AM. Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing in ulcerative colitis. Clin Gastroenterol Hepatol 2015; 13(11): 1929-36. e1921 [http://dx.doi.org/10.1016/j.cgh.2015.05.038]

[14] Mack DR, Langton C, Markowitz J, et al. Laboratory values for children with newly diagnosed inflammatory bowel disease. Pediatrics 2007; 119(6): 1113-9.

[http://dx.doi.org/10.1542/peds.2006-1865] [PMID: 17545378]

- [15] Xiang JY, Ouyang Q, Li GD, Xiao NP. Clinical value of fecal calprotectin in determining disease activity of ulcerative colitis. World J Gastroenterol 2008; 7;14(1): 53-7. [http://dx.doi.org/10.3748/wjg.14.53]
- [16] Yüksel O, Helvaci K, Başar O, et al. An overlooked indicator of disease activity in ulcerative colitis: Mean platelet volume. Platelets 2009; 20(4): 277-81.
 - [http://dx.doi.org/10.1080/09537100902856781] [PMID: 19459134]
- [17] Cakal B, Akoz AG, Ustundag Y, Yalinkilic M, Ulker A, Ankarali H. Red cell distribution width for assessment of activity of inflammatory bowel disease. Dig Dis Sci 2009; 54(4): 842-7. [http://dx.doi.org/10.1007/s10620-008-0436-2] [PMID: 18716874]
- [18] Don BR, Kaysen G. Poor nutritional status and inflammation: Serum albumin: relationship to inflammation and nutrition. Proceedings of

the Seminars in dialysis. 432-7. [http://dx.doi.org/10.1111/j.0894-0959.2004.17603.x]

- [19] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340(6): 448-54.
 [http://dx.doi.org/10.1056/NEJM199902113400607] [PMID: 9971870]
- Mendoza JL, Abreu MT. Biological markers in inflammatory bowel disease: practical consideration for clinicians. Gastroenterol Clin Biol 2009; 33(3)(Suppl. 3): S158-73.
 [http://dx.doi.org/10.1016/S0399-8320(09)73151-3]
 [PMID: 20117339]
- [21] Romero A, Muñoz M, Ramírez G. Length of sedimentation reaction in blood: a comparison of the test 1 ESR system with the ICSH reference method and the sedisystem 15. Clin Chem Lab Med 2003; 41(2): 232-7.

[http://dx.doi.org/10.1515/CCLM.2003.037] [PMID: 12667012]

- [22] Arikan S, Akalin N. Comparison of the erythrocyte sedimentation rate measured by the Micro Test 1 sedimentation analyzer and the conventional Westergren method. Ann Saudi Med 2007; 27(5): 362-5. [http://dx.doi.org/10.5144/0256-4947.2007.362] [PMID: 17921682]
- [23] Fabry TL. Mechanism of erythrocyte aggregation and sedimentation. Blood 1987; 70(5): 1572-6. [http://dx.doi.org/10.1182/blood.V70.5.1572.1572] [PMID: 3663946]
- [24] Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromcresol green. Clin Chim Acta 1971; 31(1): 87-96.
- [http://dx.doi.org/10.1016/0009-8981(71)90365-2] [PMID: 5544065]
 [25] Truelove SC, Witts LJ. Cortisone in ulcerative colitis; Final report on a therapeutic trial. BMJ 1955; 2(4947): 1041-8.
- [http://dx.doi.org/10.1136/bmj.2.4947.1041] [PMID: 13260656]
 [26] Geboes K, Riddell R, Ost A, Jensfelt B, Persson T, Löfberg R. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. Gut 2000; 47(3): 404-9.
 [http://dx.doi.org/10.1136/gut.47.3.404] [PMID: 10940279]
- [27] Dubinsky MC, Ofman JJ, Urman M, Targan SR, Seidman EG. Clinical utility of serodiagnostic testing in suspected pediatric inflammatory bowel disease. Am J Gastroenterol 2001; 96(3): 758-65.
 [http://dx.doi.org/10.1111/j.1572-0241.2001.03618.x] [PMID: 11280547]
- [28] van den Hoogen HMM, Koes BW, van Eijk JTM, Bouter LM. On the accuracy of history, physical examination, and erythrocyte sedimentation rate in diagnosing low back pain in general practice. A criteria-based review of the literature. Spine 1995; 20(3): 318-27. [http://dx.doi.org/10.1097/00007632-199502000-00010] [PMID: 7732468]
- [29] Ng T. Erythrocyte sedimentation rate, plasma viscosity and C-reactive protein in clinical practice. Br J Hosp Med 1997; 58(10): 521-3. [PMID: 10193457]
- [30] Selker RG, Wilder BL. The erythrocyte sedimentation rate: an interface between science and the law. Surg Neurol 1995; 43(3): 290-3.

[http://dx.doi.org/10.1016/0090-3019(95)80018-C] [PMID: 7792696]

- [31] Clinical and Laboratory Standards Institute. Procedures for erythrocyte sedimentation rate test; approved standard. 5th ed. CLSI document H02-A5. Wayne: The Clinical and Laboratory Standards Institute 2011; pp. 1-14.
- [32] Reinhart WH, Nagy C. Albumin affects erythrocyte aggregation and sedimentation. Eur J Clin Invest 1995; 25(7): 523-8.

[http://dx.doi.org/10.1111/j.1365-2362.1995.tb01739.x] [PMID: 7556371]

- [33] Sayar S, Kurbuz K, Kahraman R, et al. A practical marker to determining acute severe ulcerative colitis: CRP/albumin ratio. North Clin Istanb 2019; 7(1): 49-55. [PMID: 32232203]
- [34] Hanafy AS, Monir MH, Abdel Malak H, Desoky Aiad M. A simple noninvasive score predicts disease activity and deep remission in ulcerative colitis. Inflamm Intest Dis 2018; 3(1): 16-24. [http://dx.doi.org/10.1159/000490795] [PMID: 30505838]
- [35] Minderhoud IM, Samsom M, Oldenburg B. What predicts mucosal inflammation in Crohn's disease patients? Inflamm Bowel Dis 2007; 13(12): 1567-72.
- [http://dx.doi.org/10.1002/ibd.20233] [PMID: 17663422]
 [36] Mabrouk El-Shafae A, Ali Abd El-Aziz S, Mohamed Abu Mohamed N, Mostafa M. Evaluation of serum adenosine deaminase level in correlation to the activity of ulcerative colitis. Azhar Med J 2019; 48(3): 301-12.
- [37] Bendixen G, Goltermann N, Jarnum S, Jensen KB, Weeke B, Westergaard H. Immunoglobulin and albumin turnover in ulcerative colitis. Scand J Gastroenterol 1970; 5(5): 433-41. [http://dx.doi.org/10.1080/00365521.1970.12096616] [PMID: 5455831]
- [38] Ripoli J, Miszputen SJ, Ambrogini O Jr, Carvalho Ld. Nutritional follow-up of patients with ulcerative colitis during periods of intestinal inflammatory activity and remission. Arq Gastroenterol 2010; 47(1): 49-55. [http://dx.doi.org/10.1590/S0004-28032010000100009] [PMID:

[http://dx.doi.org/10.1590/S0004-28032010000100009] [PMIE 20520975]

[39] Xie T, Zhang T, Ding C, et al. Ulcerative Colitis Endoscopic Index of Severity (UCEIS) versus Mayo Endoscopic Score (MES) in guiding the need for colectomy in patients with acute severe colitis. Gastroenterol Rep (Oxf) 2018; 6(1): 38-44.

- [http://dx.doi.org/10.1093/gastro/gox016] [PMID: 29479441]
- [40] Akpinar MY, Ozin YO, Kaplan M, et al. Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio predict mucosal disease severity in ulcerative colitis. J Med Biochem 2018; 1;37(2): 155-62. [http://dx.doi.org/10.1515/jomb-2017-0050]
- [41] Ibarra-Rodríguez JJ, Santiago-Luna E, Velázquez-Ramírez GA, et al. Sensitivity, specificity, and predictive values of the level of hemoglobin, hematocrit and platelet count as an activity index in ulcerative colitis. Cir Cir 2005; 73(5): 355-62. [PMID: 16336799]
- [42] Reinisch W, Reinink AR, Higgins PD, Peter DR. Factors associated with poor outcomes in adults with newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol 2015; 13(4): 635-42. [http://dx.doi.org/10.1016/j.cgh.2014.03.037] [PMID: 24887059]
- [43] Ghoshal U C, Rai S, Kulkarni A, Gupta A. Prediction of outcome of treatment of acute severe ulcerative colitis using principal component analysis and artificial intelligence J Gastro Hepatol 2020; 4(5): 889-97.
- [44] Høivik ML, Reinisch W, Cvancarova M, Moum B. Anaemia in inflammatory bowel disease: a population-based 10-year follow-up. Aliment Pharmacol Ther 2014; 39(1): 69-76. [http://dx.doi.org/10.1111/apt.12541] [PMID: 24172277]
- Kulnigg S, Gasche C. Systematic review: Managing anaemia in Crohn's disease. Aliment Pharmacol Ther 2006; 24(11-12): 1507-23.
 [http://dx.doi.org/10.1111/j.1365-2036.2006.03146.x] [PMID: 17206940]
- [46] Lok KH, Ng CH, Hung HG, Li KF, Li KK, Szeto ML. Correlation of serum biomarkers with clinical severity and mucosal inflammation in Chinese ulcerative colitis patients. J Dig Dis 2008; 9(4): 219-24. [http://dx.doi.org/10.1111/j.1751-2980.2008.00350.x] [PMID: 18959594]

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