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Serum Biomarkers as Predictors of Disease Severity in Ulcerative Colitis

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Abstract

Ulcerative colitis (UC) represented as a chronic disease that causes inflammatory mucosal damage, which affects the patient's quality of life The purpose of the study is to evaluate the ability of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) to serve as biomarkers of disease severity in ulcerative colitis. This comparative cross-sectional study included 150 adult patients undergoing colonoscopy. Patients were divided into two groups: UC group (n=122) and control group (n=28) participant who scheduled for diagnostic colonoscopy for any other reason than UC. UC group subdivided into severe group (n=24) and non-severe group (n=98). To detect ulcerative colitis, ESR had 91.67% sensitivity and 66.33% specificity. CRP had 69.57% sensitivity and 98.99% specificity. WBC had 66.67% sensitivity, 70.41% specificity. NLR had 66.67% sensitivity, 73.47% specificity. PLR had 91.67% sensitivity, 82.65% specificity. ESR had 82.79 % sensitivity, 57.14 % specificity. CRP had 62.3% sensitivity, 67.86 % specificity. NLR had 86.07% sensitivity, 89.29% specificity. PLR had 97.54% sensitivity, 46.43% specificity. WBC cannot diagnose ulcerative colitis. ESR has good sensitivity, CRP has better specificity, and favorable sensitivity of PLR for detection of UC. For diagnosis of UC, NLR had best specificity, while PLR is most sensitive marker.

Keywords: Serum Biomarkers, Predictors, Ulcerative Colitis.

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1. Introduction

Ulcerative colitis (UC) represents a chronic disease that causes inflammatory mucosal damage, which affects the patient's quality of life both through the clinical manifestations of the disease and through invasive monitoring to assess the severity of the disease [1]. The most common manifestations that mirroring the intestinal lesions (abdominal pain, bloody diarrhoea, weight loss, and anaemia. Also, extra-digestive manifestations (arthritis, uveitis, skin lesions) may present [2]. Because the chronic course of the disease with recurrent episodes of exacerbation and remission, the main goal is to suppress the mucosal inflammation by inducing and sustaining the clinical remission [3]. Nowadays it is important to acquire mucosal healing objectified by ileo-colonoscopy even if it is expensive, invasive, and with risk for the patients because clinical resolution of symptoms does not mean the absence of mucosal inflammation [4]. Mucosal healing is established during the endoscopy and by multiple biopsies for the histopathology who can reveal histological remission. Currently, two endoscopic score systems are used in clinical practice, the Mayo Endoscopic Score (MES) and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [5]. MES consists of a 4-point scale, defining 4 grades of endoscopic disease activity: inactive (grade 0), mild (grade 1), moderate (grade 2), and severe disease (grade 3). These grades are based on endoscopic findings such as bleeding, ulceration, erosions, loss of vascular pattern, erythema, and friability [6]. Physicians have been interested in finding biomarkers that could replace the colonoscopy and monitor patients closely [7]. The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can be easily calculated from the complete blood count (CBC) and are simpler and less expensive biomarkers compared with fecal-calprotectin. NLR and PLR can serve as useful biomarkers for diagnosing and predicting mucosal inflammation in UC [8]. The purpose of the study is to evaluate the ability of NLR and PLR to serve as biomarkers of disease severity in ulcerative colitis.

2. Patients and Methods

This case control cross-sectional study enrolling 150 adult patients aged from 18–85 years old, undergoing colonoscopy. The study was done after approval from the committee of ethics of scientific research of Banha faculty of medicine approved the study protocol and written consented obtained from all patients.

Exclusion criteria were incomplete colonoscopy, Crohn's disease, indeterminate colitis, history of colorectal surgery, primary immunodeficiency, colorectal cancer, pregnancy, neoplastic and hematologic disorders, hepatosplenic disease and renal insufficiency, having infectious colitis and underlying chronic disease at the time of the study. Patients were divided into two groups: UC group (n=122): patients with established diagnosis of UC and control group (n=28): Participant who scheduled for diagnostic colonoscopy for any other reason than UC. UC group was subdivided into 2 groups according to severity of disease activity to: severe group (n=24) and non-severe group (n=98). All patients were subjected to:

- History taking.
- Usual investigations CBC, NLR and PLR, inflammatory markers as C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were measured in all patients, colonoscopy and mayo score.
- Colonoscopy: the diagnosis of UC was based on clinical, radiological, and pathological criteria. The definition of Anti-Saccharomyces cerevisiae (ASC) was made using Truelove & Witt's criteria, defined as six or more bloody stools per day with one or more additional criteria (pulse > 90 bpm; temperature > 37.8 °C; hemoglobin < 105 g/L; ESR > 30 mm/h; or CRP > 30 mg/dL). The extent of colon involvement was determined by abdominal CT scan.

Disease activity based on Mayo score: clinical remission (Mayo score 0-2), mild activity (Mayo score 3-5), moderate activity (Mayo score 6-10) and severe activity (Mayo score 11-12). The range in the ulcerative colitis endoscopic index (UCEIS) scores is 0 to 8, which was stratified into four grades: clinical remission (UCEIS score 0-1), mild score (UCEIS score 2–4), moderate score (UCEIS score 5–6) and severe score (UCEIS score 7-8).

2.1. Sample Size Calculation

Using prevalence 11% Resulted in sample size of at least 150 subjects. Sample size was calculated according to the following formula, n= (z2×P(1-p))/ (sd2), where: n= minimal calculated sample size n= 150, z= standard normal variate at 5% type [I error] = 1.96. P= prevalence of UC (11%) and sd= 0.05

2.2. Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. Evaluation of diagnostic performance sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Receiver Operating Characteristic curve (ROC-curve) analysis: the overall diagnostic performance of each test was assessed by ROC curve analysis. The level of significance was adopted at $p<0.05$.

3. Results

Patient demographic futures, comorbidities and operation history were insignificantly different between both groups (Table 1). Medication use at NLR, PLR and FC measurement was 5-ASA in 82 (67.21%) patients, 5-ASA+AZA in 13 (10.66%) patients, 5-ASA+steroid in 9 (7.38%) patients, 5-ASA+steroid+AZA in 6 (4.92%) patients, 5-ASA+AZA+anti-TNF in 6 (4.92%) patients and 5-ASA+anti-TNF in 6 (4.92%) patients. 5 (35.7%) diabetic patients and 9 (69.2%) hypertensive patients had drug history, disease extension at diagnosis was E1 (proctitis) in 46 (37.7%) patients, E2 (left-sided colitis) in 26 (21.31%) patients and E3 (pan-colitis) in 50 (40.98%) patients. 24 (19.67%) patients had clinical remission (mayo score 0-2), 49 (40.16%) patients had mild activity (mayo score 3-5), 37 (30.33%) patients had moderate activity (mayo score 6-10) and 12 (9.84%) patients had severe activity (mayo score 11-12) (Table 2). 24 (19.67%) patients had clinical remission (UCEIS score 0-1), 49 (40.16%) patients had mild score (UCEIS score 2–4), 37 (30.33%) patients had moderate score activity (UCEIS score 5–6) and 12 (9.84%) patients had severe score (UCEIS score 7-8). 98(80.3%) cases were with simple clinical colitis activity index, 49 (40.16%) cases were with mild activity, 37 (30.33%) cases were with moderate activity and 12 (9.84%) cases were with severe activity (Table 3). CBC (platelets, Hb, lymphocyte, and neutrophil) were significantly lower in UC group than control group ($P<0.05$) while WBC, PLR and CRP were insignificantly different between both groups. NLR and ESR were significantly higher in UC group than control group ($P<0.05$). CBC (WBC, lymphocyte, platelets, neutrophil NLR, PLR ESR and CRP were significantly higher ($P<0.05$) while Hb was significantly lower in severe group than non-severe group ($P<0.025$) (Table 4). ESR can significantly detect UC (P value <0.001) with 0.827 AUC, 91.67% sensitivity, 66.33% specificity, 40% PPV and 97.01% NPV. CRP can significantly detect UC (P value <0.001) with 0.847 AUC, 69.57% sensitivity, 98.99% specificity, 94.1% PPV and 93.3% NPV. WBC can significantly detect (P value <0.001) with 0.746 AUC, 66.67% sensitivity, 70.41% specificity, 35.56% PPV and 89.61% NPV. NLR can significantly detect UC (P value <0.001) with 0.789 AUC, 66.67% sensitivity, 73.47% specificity, 38.10% PPV and 90.00% NPV. PLR can significantly diagnose UC (P value 0.022) with 0.666 AUC, 97.54% sensitivity, 46.43% specificity, 88.8% PPV and 81.2% NPV. ESR can significantly diagnose UC (P value <0.001) with 0.751AUC, 82.79 % sensitivity, 57.14 % specificity, 88.6 % PPV and 41.7 % NPV. CRP can significantly diagnose UC (P value <0.001) with 0.757 AUC, 62.3% sensitivity, 67.86 % specificity, 89.4 % PPV and 29.2 % NPV. NLR can significantly diagnose UC (P value <0.001) with 0.891 AUC, 63.11% sensitivity, 100.00% specificity, 100.00% PPV and 73.05% NPV. PLR can significantly diagnose UC (P value 0.022) with 0.666 AUC, 97.54% sensitivity, 46.43% specificity, 88.8% PPV and 81.2% NPV. WBC cannot diagnose UC (Figure 1).

4. Discussion

The colonic and rectal mucosa are affected by the chronic idiopathic inflammatory bowel disease known as UC. 5-aminosalicylic acid topical and/or systemic dosing is the initial therapy for active mild or moderate UC.

Patients with moderate to severe disease activity may benefit from the administration of systemic corticosteroids. For active moderate UC and active severe UC, the beginning dosages of prednisolone (PSL), a typical systemic corticosteroid treatment, are 40 mg/day and 60 mg/day, respectively [9]. Regarding our results, lymphocyte, and neutrophil were significantly lower in UC group than control group (P <0.05) while WBC was insignificantly different between both groups. These findings match to study of Okba et al., (2019) who explained that absolute lymphocytic count was significantly lower in UC group than control group [10]. On the other side, Zhang et al., (2023) had different observations as he noted increase in neutrophils in UC patients [11]. Also, Feng et al., (2022) stated that neutrophil count was elevated in UC group as compared with patients in remission [12]. This difference may be attributed to different study design and large sample size. Regarding our study, NLR was significantly higher in UC group than control group (P <0.001) while PLR was insignificantly different between both groups. Benvenuti et al., (2020) agreed to our results as he found high NLR in UC patients as NLR is inflammatory marker increasing with colitis [13]. Also, Al-Rshaidat et al., (2023) was in the same line as they stated that PLR was insignificant difference between UC patients and normal [14]. However, Jeong et al., (2021) who stated that UC patients have high PLR related to inflammation [8]. Regarding our results, ESR was significantly higher in UC group than control group (P 0.003) while CRP was insignificantly different between both groups. Okba et al., (2019) was in accordance with our results as they noted that ESR was significantly higher in active UC group compared to control [10]. On the other hand, Masoodi et al., (2011) who revealed high CRP in UC patients related to inflammation severity [15]. Our results state that 98 (80.33%) patients were with non-severe disease activity (Mayo score 0-10) while 24 (19.67%) patients were with severe disease activity (Mayo score 11-12). Regarding Kirchberger-Tolstik et al., (2020) Mayo score composed of four parts: rectal bleeding, stool frequency, physician assessment, and endoscopy appearance [16]. Each part is rated from 0 to 3, giving a total score of 0 to 12. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severely active disease. Our results display that CBC was significantly higher in severe group than non-severe group (P<0.05) while Hb was significantly lower in severe group than non-severe group (P <0.025). Mack et al., (2020) supported our results as they noted high TLC and thrombocytosis in severe UC compared to non-severe types [17]. Okba et al., (2019) agreed to our findings as they explained that Hb was significantly lower in UC group than control group [10]. On the other hand, Mizuta et al., (2003) disagreed with our finding as he noted thrombocytopenia in severe UC compared to non-severe [18]. Regarding our results, NLR and PLR were significantly higher in sever group than non-severe group (P<0.001). The study of Feng et al., (2022) matched with these results as it concluded that NLR and PLR were higher in severe UC compared to non-severe [12]. Zahmatkesh et al., (2023) explained high of NLR and PLR in severe UC due to severity of inflammation which caused increase of inflammatory markers as platelets and neutrophils relative to lymphocytes [19]. Our results state that ESR and CRP were significantly higher in sever group than non-severe group (P<0.001). Cioffe et al., (2015) supported the results as he assured that ESR and CRP are acute phase reactants of inflammation and were higher in sever UC compared to non-severe group [20]. Regarding our results, ESR can significantly detect UC (P value <0.001) with 0.827 AUC, 91.67% sensitivity, 66.33% specificity, 40% PPV and 97.01% NPV. Also, ESR can significantly diagnose UC (P value <0.001) with 0.751AUC, 82.79 % sensitivity, 57.14 % specificity, 88.6 % PPV and 41.7 % NPV. These results are in accordance with of Feng et al., (2022) who noted that ESR had had sensitivity of 58.3% and specificity of 75%. for differentiating active from inactive UC [12].

Table 1: Patient demographic futures, comorbidities, Previous operation history of studied groups.

		UC group (n=122)	Control group (n=28)	P value
Age (years)		37.6 ± 12.17	39.5 ± 15.25	0.479
Sex	**Male**	67 (54.92%)	16 (57.14%)	0.831
	Female	55 (45.08%)	12 (42.86%)	
Family history of UC		13 (10.66%)	3 (10.71%)	0.993
Smoking		84 (68.85%)	19 (67.86%)	0.918
DM		14 (11.48%)	5 (17.86%)	0.976
HTN		13 (10.66%)	4 (14.29%)	
Previous operation history		13 (10.66%)	6 (21.43%)	0.122
Appendectomy **Perianal operation** **Others**		3(23.08%) 6 (46.15%) 4 (30.77%)	3(50%) 1(16.67%) 2(33.33%)	0.298

Data are presented as mean ± SD, UC: ulcerative colitis.

Table 2: Medication use, drug history of comorbidities, disease extension and disease activity of UC group.

	UC group (n=122)
Medication	
5-ASA	82 (67.21%)
5-ASA+AZA	13 (10.66%)
5-ASA+steroid	9 (7.38%)
5-ASA+steroid+AZA	6 (4.92%)
5-ASA+AZA+anti-TNF	6 (4.92%)
5-ASA+anti-TNF	6 (4.92%)
Drug history of comorbidities	
DM (n=14)	5 (35.7%)
HTN (n=13)	9 (69.2%)
Disease extension	
E1 (proctitis)	46 (37.7%)
E2 (left-sided colitis)	26 (21.31%)
E3 (pan-colitis)	50 (40.98%)
Disease activity	
Clinical remission (Mayo score 0-2)	24 (19.67%)
Mild activity (Mayo score 3-5)	49 (40.16%)
Moderate activity (Mayo score 6-10)	37 (30.33%)
Severe activity (Mayo score 11-12)	12 (9.84%)

Data are presented as UC: ulcerative colitis.

Table 3: UCEIS score and simple clinical colitis activity index of the UC group.

	UC group (n=122)
UCEIS score	
Clinical remission	24 (19.67%)
Mild score	49 (40.16%)
Moderate score	37 (30.33%)
Severe score	12 (9.84%)
Simple clinical colitis activity index	
Simple clinical colitis activity index	98(80.3%)
Mild activity	49 (40.16%
Moderate activity	37 (30.33%)
Severe activity	12 (9.84%)

Data are presented as UC: ulcerative colitis.

Table 4: CBC, comparisons of NLR, PLR, ESR and CRP between UC and control groups and severe and Non-severe UC group.

	UC group (n=122)	Control group (n=28)	P value
Platelets (*103/µL)	191 ± 120.84	335.52 ± 68.57	**0.004***
Hb (mg/dL)	12.61 ± 1.43	14.05 ± 1.15	**<0.001***
WBC (*10^9/L)	6.61 ± 1.91	6.08 ± 1.76	0.182
Lymphocyte (*10^3/µL)	1.5 ± 0.6	2.43 ± 0.65	**<0.001***
Neutrophil (*103/µL)	1.5 ± 3.19	2.68 ± 0.94	**<0.001***
NLR	2.99 ± 1.47	1.18 ± 0.5	**<0.001***
PLR	164.94 ± 33.84	150.22 ± 60.13	0.081
ESR (mm/h)	38.2 ± 17.93	19.59 ± 14.23	<0.001*
CRP (mg/dL)	1.04 ± 1.19	0.34 ± 0.18	0.003*
	Severe UC group (n=24)	**Non-severe UC group (n=98)**	**P value**
WBC (*10^6/µL)	7.93 ± 2.2	6.29 ± 1.7	**<0.001***
Hb (mg/dL)	12.03 ± 1.8	12.75 ± 1.29	**0.025***
Lymphocyte (*10^3/µL)	1.87 ± 0.63	1.53 ± 0.58	**0.014***
Platelets (*10^3/µL)	398.13 ± 133.31	232.99 ± 92.64	**<0.001***
Neutrophil (*10^3/µL)	8.04 ± 4.69	3.99 ± 2.06	**<0.001***
NLR	4.52 ± 2.17	2.62 ± 0.94	**<0.001***
PLR	216.55 ± 35.57	152.31 ± 17.56	**<0.001***
ESR (mm/h)	57.75 ± 17.91	33.42 ± 14.4	**<0.001***

Data are presented as mean ± SD, *: significantly P value≤ 0.05. UC: ulcerative colitis; WBC, white blood cell; NLR: neutrophil to lymphocyte ratio, Hb: hemoglobin, PLR: platelet to lymphocyte ratio; ESR: erythrocyte sedimentation rate, CRP:C-reactive protein.

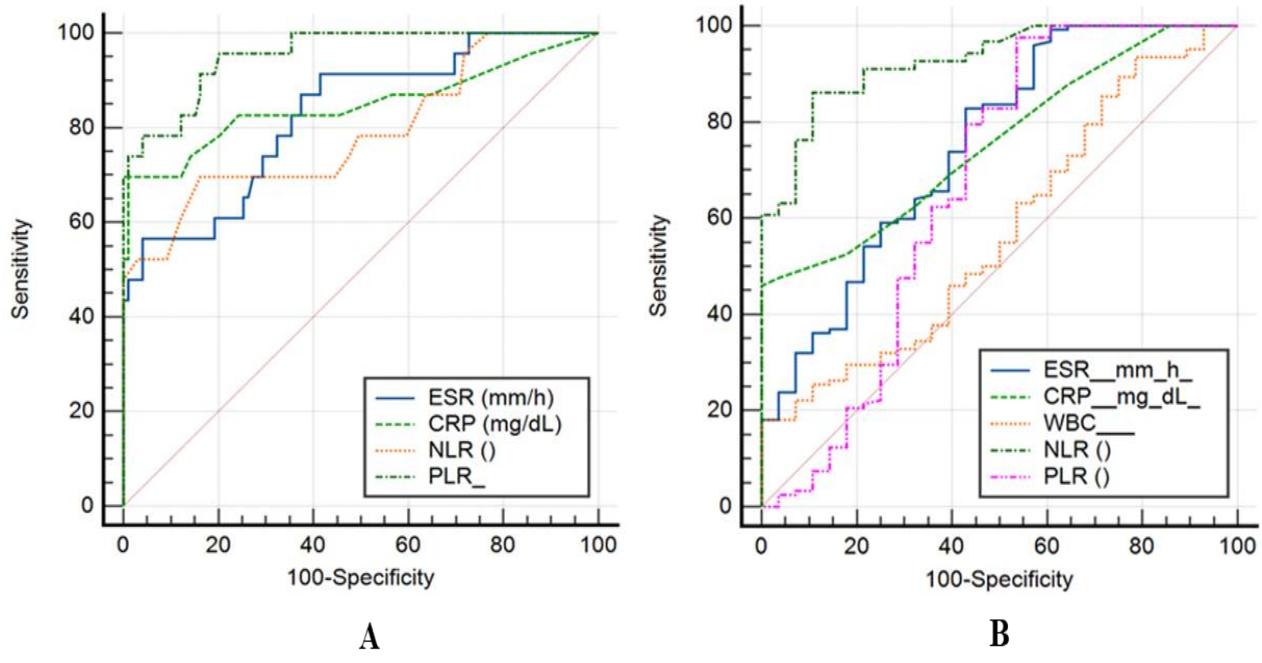

Figure 1: ROC curve showing diagnostic performance of serum biomarkers for (A) diagnosing severity of UC and (B) diagnosing UC.

Regarding the results, CRP can significantly detect UC (P value <0.001) with 0.847 AUC, 69.57% sensitivity, 98.99% specificity, 94.1% PPV and 93.3% NPV. Also, CRP can significantly diagnose UC (P value <0.001) with 0.757 AUC, 62.3% sensitivity, 67.86 % specificity, 89.4 % PPV and 29.2 % NPV. These results are in accordance with of Feng et al., (2022) who noted that CRP had had sensitivity of 58.3% and specificity of 75%. for differentiating active from inactive UC [12]. Regarding our results, WBC can significantly detect UC (P value <0.001) with 0.746 AUC, 66.67% sensitivity, 70.41% specificity, 35.56% PPV and 89.61% NPV. Also, WBC cannot diagnose ulcerative colitis. These results are in agreement with Nakari et al., (2014) who found that WBC had good sensitivity 85%-95% and less specificity 76%-87% for detection of UC [21]. Torun et al., was in accordance with our results as he concluded that WBC can't diagnosis of ulcerative colitis [22]. Regarding the results, NLR can significantly detect UC (P value <0.001) with 0.789 AUC, 66.67% sensitivity, 73.47% specificity, 38.10% PPV and 90.00% NPV. Also, NLR can significantly diagnose UC (P value <0.001) with 0.891 AUC, 63.11% sensitivity, 100.00% specificity, 100.00% PPV and 73.05% NPV. Our results are in agreement with Torun et al., (2012) who noted that NLR was good predicator (specificity 100%) for diagnosis of ulcerative colitis [22]. On the other Hand, Zahmatkesh et al., (2023) disagreed with our results as he concluded that NLR had sensitivity 82.1%; specificity 82.9 % [19]. Regarding our work, PLR can significantly detect UC (P value <0.001) with 0.955 AUC, 91.67% sensitivity, 82.65% specificity, 56.41% PPV and 97.59% NPV. Also, PLR can significantly diagnose UC (P value 0.022) with 0.666 AUC, 97.54% sensitivity, 46.43% specificity, 88.8% PPV and 81.2% NPV. Endo et al., (2021) had the same results as ne noted that PLR had specificity of 85.7% for diagnosis of ulcerative colitis [23]. Also, Akpinar et al., (2018) agreed to our results as he noted that PLR had good sensitivity of diagnosis of ulcerative colitis [24]. On the other side, Feng et al., (2022) disagreed with our findings as they stated that PLR had sensitivity of 58.3% and specificity of 75% [12].

5. Limitations

Single center study may result in different findings than elsewhere. Small sample size that may produce insignificant results.

6. Conclusions

UC patients are anemic, size platelets count, neutrophils, lymphocytes, high ESR and neutrophil to lymphocytes ratio, while severe cases are more anemic, with high TLC, neutrophils and lymphocytes, ESR and CRP, and high NLR and PLR in contrast to non-severe types. ESR has good sensitivity, CRP has better specificity, and favorable sensitivity of PLR for detection of UC. For diagnosis of UC, NLR had the best specificity, while PLR is the most sensitive marker.

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Conflict of Interest
Nil

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