The Predictive Value of Inflammatory Markers in the First Year of Diagnosis in Ulcerative Colitis

Ülseratif Kolit Hastalarında Tanıdan Sonraki İlk Bir Yılda İzlenen İnflamatuar Belirteçlerin Prediktif Değeri

Rezzan Eren Sadioğlu[1], Tarkan Karakan[2]

[1]Gazi University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey
[2]Gazi University Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey

ABSTRACT

Objective: The aim of this study was to determine if the changes in inflammatory markers which were observed during the routine follow-up of patients with ulcerative colitis could predict the disease progression.
Methods: Levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), white blood cell count (WBC), neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV) and albumin (alb), which were observed at the time of diagnosis as well as in the 3rd, 6th, 9th and 12th months, were recorded retrospectively. The area under the curve (AUC) of the variation of these values with respect to time was calculated.
Results: 118 patients were subjects of this study, with a mean follow-up time of 3.4 years. The calculated AUCs for CRP, ESR, WBC, and NLO were significantly higher ($p < 0.001$, $p < 0.01$, $p < 0.01$, $p < 0.01$); whereas the ones for Hb, alb, and MPV were significantly lower ($p < 0.01$, $p < 0.001$, $p < 0.05$) in patients who used an immunomodulator compared to those who did not. The calculated AUCs for CRP and ESR were significantly higher ($p < 0.001$, $p < 0.05$); whereas the AUCs for Hb, alb, and MPV were significantly lower ($p < 0.01$, $p < 0.05$, $p < 0.01$) in patients who used an anti-tumor necrosing factor-alpha inhibitor (anti-TNF) compared to those who did not. Additionally, in patients who used anti-TNF, the AUCs for CRP were significantly higher ($p < 0.05$), than in patients who only used immunomodulators.
Conclusion: The levels of inflammatory markers in the early course of the disease are helpful for predicting the disease progression and prognosis. We assume that, the higher the CRP, the worse the prognosis.

Key Words: Ulcerative colitis, predictive factors, inflammatory marker, C-reactive protein.

ÖZET

Amaç: Bu çalışmanın amacı ülseratif kolitli hastaların rutin takibi sırasında bakılan inflamatuar belirteçlerdeki değişikliklerin hastalığın ilerlemesini öngörmedeki etkisini belirlemektir.
Yöntem: Ülseratif Kolit hastalarının rutin takipleri sırasında bakılan eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), hemoglobin (hb), beyaz küre (bk), nötrofil lenfosit oranı (NLO), ortalama platelet volumu (MPV) ve albumin (alb) düzeyleri tanı anı 0.ay, 3.ay, 6.ay, 9.ay ve 12.ayda olmak üzere her hasta için retrospektif olarak kaydedildi. Bu değerlerin zamana göre çizilen grafiğinde eğri altında kalan alanı (AUC) hesaplandı.
Bulgular: Ortalama 3,4 yıl takip süresi olan 118 hasta çalışmaya alındı. İmmunmodülatör tedavi alan hastalarda CRP, ESR, WBC ve NLO için hesaplanan AUC değerleri, immunmodülatör almayanlara göre anlamlı olarak daha yüksek saptanırken (p <0.001, p <0.01, p <0.01, p <0.01); Hb, alb ve MPV için hesaplanan AUC değerleri anlamlı olarak düşüktü (p <0.01, p <0.001, p <0.05). Anti-tümör nekrozan faktör-alfa inhibitörü (anti-TNF) kullanan hastalarda CRP ve ESR için hesaplanan AUC değerleri, anti-TNF almayan hastalara göre anlamlı olarak yüksek iken (p <0.001, p <0.05), Hb, alb ve MPV için hesaplanan AUC değerleri ise anlamlı olarak daha düşüktü (p <0.01, p <0.05, p <0.01). Ek olarak, anti-TNF kullanan hastalarda, CRP için hesaplanan AUC değerleri, sadece immünomodülatör kullanan hastalara göre anlamlı derecede yüksekti (p <0.05).
Sonuç: Hastalığın erken döneminde izlenen inflamatuar belirteçler, hastalık progresyonu ve prognozunu tahmin etmek için yararlıdır. Hastalık başlangıcında CRP ne kadar yüksek ise prognozun o kadar kötü gideceğini varsaymak mümkün görünmektedir.

Anahtar Sözcükler: Ülseratif kolit, prediktif faktör, inflamatuar belirteç, C-reaktif protein

INTRODUCTION

Ulcerative colitis (UC), together with Crohn's disease, belongs to a group of diseases referred to as Inflammatory Bowel Diseases (IBD) that affect the mucosa and submucosa of the large intestine. The amount of patients claiming to have experienced attacks ever since they were diagnosed reach as high as fifty percent (1, 2). Some of the parameters that are frequently used in the close follow-up and treatment of Ulcerative Colitis are the increase rate of C-reactive protein (CRP) that shows the disease attacks and mucosal inflammation, the increase in the erythrocyte sedimentation rate (ESR), decrease in hemoglobin (Hb), decrease in albumin, neutrophile-lymphocite ratio (NLR), etc (3, 4). The treatment modality, which usually begins with a 5-aminosalicylic acid (5-ASA) at the beginning of the disease, is progressed into more intensive treatments such as steroids, immunomodulators and immunological agents in the event that the disease control results in failure (5-7). While the disease initially affects the distal part of the colon, it may progress towards the proximal, causing severe attacks requiring hospitalization or even colectomy (8). Therefore, it is important to determine the predictive factors.

The aim of this study is to show that changes in CRP, ESR, hemogram parameters, and albumin levels within one year after diagnosis, can predict the course of the disease and the cumulative bowel damage.

METHODS

The data recorded during the routine diagnosis and treatment procedure of the newly diagnosed UC patients treated between January 2010 and December 2016, in Gazi University, Faculty of Medicine, Department of Gastroenterology, were retrospectively scanned from the patient records at the hospital.

For each patient, the C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobine (Hb), white blood cell count (WBC), albumin (alb), neutrophile-lymphocyte ratio (NLR), mean platelet volume (MPV) levels were recorded at the time of diagnosis as well as in the 3rd, 6th, 9th and 12th months. On the graph that shows these values as a function of time, the area under the curve (AUC) was calculated. The treatments that the patients received were recorded as 5-ASA, immunomodulators (methotrexate, cyclosporine, azathioprine), anti-tumor necrosis factor-alpha inhibitors (anti-TNF) (adalimumab, infliximab) and systemic steroids. The conditions that were scanned had to do with whether or not there was a development of proximal extension in the patients, whether colectomy was necessary or if there had been attacks that required hospitalization. For each of the markers, a separate AUC was calculated, and the relationship between the treatment modalities and the course of the disease, as well as the severity of the attacks, was closely studied.

Statistical Analysis

From intermittantly measured inflammatory marker values (collected at the moment of the diagnosis, and in the 3rd, 6th, 9th, and 12th months), the area under the curve (AUC) was calculated with the trapezoidal method for each patient. The AUC values between the groups were compared via the Mann–Whitney U-test and T-test. A threshold value of $p < 0.05$ was considered to be statistically significant. The calculations were made on the software SPSS 16.0 (SPSS Inc, Chicago, Illinois).

The study was approved by the Gazi University Ethics Committee (30/01/2017-E.15291)

RESULTS

The study included 118 UC patients whose characteristics are shown in Table 1.

Table 1. Patient characteristics

|	n	%
Gender		
Female	53	44.9
Male	65	55.1
Disease type at diagnosis		
Proctitis	18	15.3
Distal	63	53.4
Pancolitis	37	31.4
Immunomodulator usage		
No	80	67.8
Yes	38	32.2
Anti-TNF usage		
No	109	92.4
Yes	9	7.6
Colectomy		
No	115	97.5
Yes	3	2.5
Systemic Steroid usage		
No	75	63.6
Yes	43	36.4
Proximal extension		
No	111	94.1
Yes	7	5.9

Anti-TNF: anti tumor necrosing factor-alpha

Amongst the patients, 38 of them used immunomodulators, nine of them used anti-TNF, and 43 of them had an attack requiring hospitalization. There were seven patients that had developed a proximal extension, and three that had undergone colectomy. The mean follow-up duration was 3.4 years.

In the patients that had used immunomodulators, the AUC values for CRP [$mean\ 99.33 \pm 11.32$ $vs.$ $324.36 \pm 281.63,\ p < 0.001$], ESR [$mean\ 282.28 \pm 169.30$ $vs.$ $392.76 \pm 205.94,\ p < 0.01$], WBC [$mean\ 96,559.37 \pm 27,180.6$ $vs.$ $108,178.07 \pm 26,408.69,\ p < 0.01$] and NLO [$mean\ 30.62 \pm 12.41$ $vs.$ $38.56 \pm 17.74,\ p < 0.01$] were observed to be significantly higher than in the patients that hadn't used immunomodulators; meanwhile, the AUC values calculated for Hb [mean 157.77 ± 18.97 $vs.$ $145.19 \pm 22.65,\ p < 0.01$], alb [$mean\ 51.18 \pm 4.89$ $vs.$ $46.54 \pm 7.38,\ p < 0.001$] and MPV [$mean\ 99.32 \pm 11.47$ $vs.$ $94.20 \pm 11.93,\ p < 0.05$] were observed to be significantly lower. (Table 2) (Figure 1).

Table 2. The Comparisons About Immunomodulatory Usage

	Immunomodulatory Usage				
	No		Yes		p
	Mean ± Sd	Median (min-max)	Mean ± Sd	Median (min-max)	
ESR AUC	282.28±169.30	234.7 (33-856)	392.76±205.94	339.7 (73.5-877)	0.003
CRP AUC	99.33±11.32	64.7 (15.1-769.5)	324.36±281.63	241.1 (29.3-1063.5)	0.000
Hb AUC	157.77±18.97	156 (110.9-209.2)	145.19±22.65	147.1 (91.8-183.9)	0.002
WBC AUC	96559.37±27180.6	88042.5 (59490-181410)	108178.07±26408.69	113520 (53970-175560)	0.007
NLO AUC	30.62±12.41	28.4 (13.3-79.1	38.56±17.74	36.1 (10.1-92.9)	0.009
MPV AUC	99.32±11.47	98 (74.9-137.5)	94.20±11.93	91.3 (75-127.2)	0.027
Alb AUC	51.18±4.89	52.2 (34.1-58.8)	46.54±7.38	49.03 (23.9-57)	0.000

CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, Hb; hemoglobine, WBC; white blood cell count, alb; albumin, NLR; neutrophile-lymphocyte ratio, MPV; mean platelet volüme, Sd; standart deviation, min; minimum, max; maximum
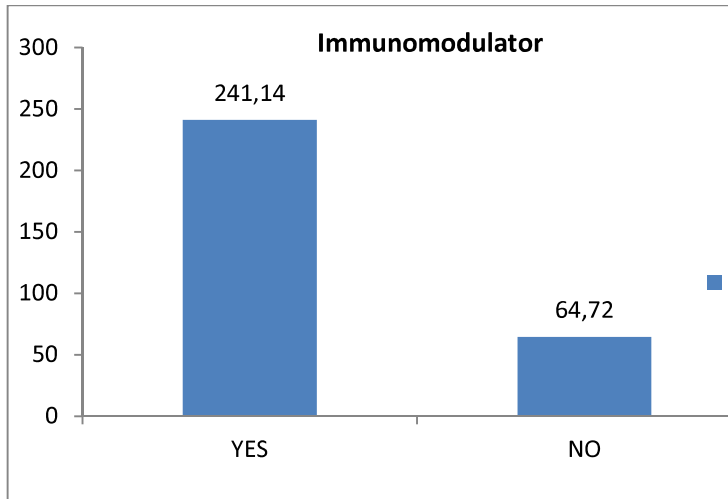
Figure 1. The median AUC values for CRP in immunomodulatory usage

In the patients that had used anti-TNF, the AUC values calculated for CRP [$mean\ 142.36 \pm 166.34\ vs. 528.23 \pm 352.15,\ p < 0.001$] and ESR [$mean\ 305.15 \pm 177.66\ vs.\ 471.83 \pm 252.06,\ p < 0.05$] were found to be significantly higher than in the patients that hadn't used anti-TNF; meanwhile, the AUC values calculated for Hb [$mean\ 155.89 \pm 19.21\ vs.\ 127.43 \pm 24.81,\ p < 0.01$], alb [$mean\ 50.27 \pm 5.34\ vs.\ 42.56 \pm 10.53,\ p < 0.05$], and MPV [$mean\ 98.51 \pm 11.64\ vs.\ 87.4 \pm 9.26,\ p < 0.01$] were found to be significantly lower. No significant difference was spotted for the NLO and WBC values. (Table 3)

Table 3. The Comparisons About anti-TNF usage

| | Antı-Tnf Usage | | | | |
| | NO | | Yes | | |
	Mean±Sd	Median (Min-max)	Mean±Sd	Median (Min-max)	p*
ESR AUC	305.15±177.66	255 (33-867)	471.83±252.06	457.5 (73.5-877.5)	0.031
CRP AUC	142.36±166.34	82.98 (15.1-813.6)	528.23±352.15	398.2(147.3-1063.5)	0.000
HB AUC	155.89±19.21	155.8(110.9-209.2)	127.43±24.81	130 (91.8-160.3)	0.003
WBC AUC	100972.51±27420.9	95955 (53970-181410)	92168±26917.11	100602 (57024-126285)	0.444
NLO AUC	33.61±14.96	30.6 (13.3-92.9)	27.94±11.24	31.3 (10.1-43.1)	0.397
MPV AUC	98.51±11.64	97.8 (74.9-137.5)	87.4±9.26	86.7 (75-107.9)	0.005
Alb AUC	50.27±5.34	50.8 (29.7-58.8)	42.56±10.53	43.1 (23.9-55.9)	0.030

CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, Hb; hemoglobine, WBC; white blood cell count, alb; albumin, NLR; neutrophile-lymphocyte ratio, MPV; mean platelet volüme, Sd; standart deviation, min; minimum, max; maximum

In patients that had attacks requiring hospitalization, the AUC values calculated for ESR $[mean\ 259.58 \pm 148.75\ vs.\ 419.51 \pm 206.02,\ p < 0.001]$, CRP $[mean\ 96.03 \pm 99.93\ vs.\ 303.95 \pm 280.2,\ p < 0.001]$, WBC $[mean\ 95,548.48 \pm 24,942.21\ vs.\ 108,590.23 \pm 29,665.44,\ p < 0.05]$, NLR $[mean\ 29.81 \pm 10.20\ vs.\ 39.03 \pm 19.16,\ p < 0.01]$ were found to be significantly higher than the patients who didn't have attacks; meanwhile, the AUC values for Hb $[mean\ 160.18 \pm 18.91\ vs.\ 142.45 \pm 19.80,\ p < 0.001]$, alb $[mean\ 52.37 \pm 3.45\ vs.\ 45.01 \pm 7.06,\ p < 0.001]$, and MPV $[mean\ 100.23 \pm 11.01\ vs.\ 93.21 \pm 11.98,\ p < 0.01]$ were found to be lower. Additionally, in patients that had to use systemic steroids, the AUC values calculated for ESR, CRP, NLR, and WBC were found to be significantly higher than the patients who didn't; whereas the AUC values for Hb, alb, and MPV were found to be lower.

For the purpose of this study, twenty-nine patients who only received immunomodulators (without anti-TNF) and nine patients who received anti-TNF were considered to have the poorest prognosis. The patients who received anti-TNF had already received immunomodulators as anti-TNF treatment is an option for resistant diseases. When these two groups were compared, the AUCs related to CRP $[mean\ 261.09 \pm 227.75\ vs.\ 528.23 \pm 352.15,\ p < 0.05]$ were found to be significantly higher in patients that received anti-TNF;meanwhile, the AUCs related to Hb $[mean\ 150.70 \pm 19.22\ vs.\ 127.43 \pm 24.81,\ p < 0.05]$ were found to be significantly lower. There was no difference between the two groups concerning the ESR, WBC, MPV, and alb values. Calculations for the NLR turned out to be the opposite of our previous results. (Table 4) (Figure 2).

Table 4. The Comparisons about usage of anti-TNF and immunomodulatory

| | Only Immunomodulatory (N=29) | | Antı-Tnf (N=9) | | |
	Mean ± Sd	Median (Min-max)	Mean ± Sd	Median (Min-max)	P
ESR AUC	368.22±187.77	295.5 (100.5-867)	471.83±252.06	457.5 (73.5-877.5)	0.152
CRP AUC	261.09±227.75	178.2 (29.3-813.6)	528.23±352.15	398.2 (147.3-1063.5)	0.021
HB AUC	150.70±19.22	148.1 (115.4-183.9)	127.43±24.81	130 (91.8-160.4)	0.016
WBC AUC	113146.71±24629.70	115530 (53970-175560)	92168.0±26917.11	100602 (57024-126285)	0.053
NLO AUC	41.87±18.21	36.6 (18.1-92.8)	27.89±11.24	31.3 (10.1-43.1)	0.049
MPV AUC	96.31±12.01	94.3 (79.3-127.2)	87.43±9.26	86.7 (75 -107.9)	0.053
Alb AUC	47.77±5.81	49.4 (29.7-57)	42.57±10.53	43 (23.9-55.9)	0.248

CRP; C-reactive protein, ESR; erythrocyte sedimentation rate, Hb; hemoglobine, WBC; white blood cell count, alb; albumin, NLR; neutrophile-lymphocyte ratio, MPV; mean platelet volüme, Sd; standart deviation, min; minimum, max; maximum
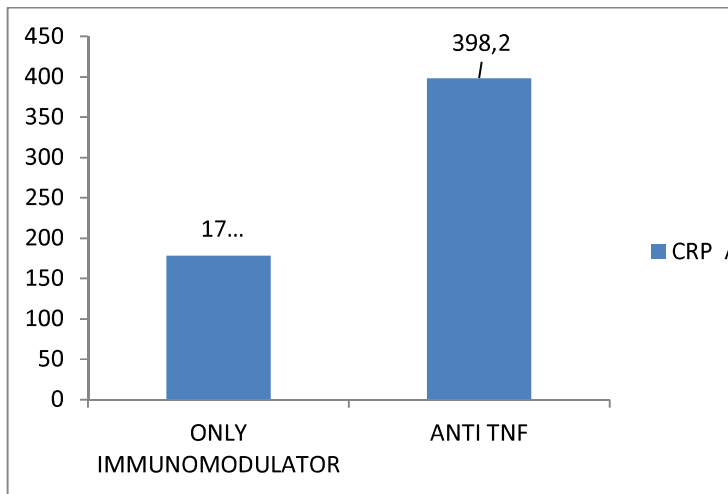
Figure 2. The median AUC values for CRP in immunomodulatory vs. anti-TNF usage

DISCUSSION

In this study, it was concluded that hospitalization and requirement for an intensive treatment were more frequent in patients with constantly high inflammatory markers or those who showed changes in the direction of inflammation. It was also observed that the patients, for whom the CRP value was calculated to be high in the first year, were more likely to require an anti-TNF treatment.

The studies indicating that laboratory values as a function of time, quite frequently used in patient follow-ups, could give an idea regarding the clinical course and treatment, have led us believe that this hypothesis could very well be utilized in UC.

Arsik et al. reported in their study that the percent change of alanine transferase (ALT) from baseline was a significant predictor of progression could be used in the follow-up of non-alcoholic steatohepatitis seemed to yield a better correlation in terms of a response to treatment in liver fibrosis compared to individual ALT values that were studied on a one-on-one basis (9). So we thought that the changes in inflammatory markers might very well help predict the disease progression in Ulcerative Colitis, as well.

Solem et al. found out that the CRP elevation was associated with disease activation, elevation of ESR, anemia, and hypoalbuminemia in UC patients (3). Furthermore, Iwasa et al.'s study concluded that CRP was useful when it came to predicting the response to the anti-TNF treatment two weeks beforehand. The higher the CRP values of the patients were, the lower was the response to infliximab. Additionally, in patients who responded well to infliximab, the CRP values seemed to have decreased by the second week of the therapy (10). Cacheux et al. discovered three predictive factors for colectomy in their study with steroid refractory 134 UK patients: body temperature >37.5, heart rate >90 beats/min and CRP>45 mg/l (11).

In our study, comparisons were made between the patients who received and who did not receive immunomodulatory, anti-TNF and systemic steroids. We found out that the AUC values calculated from the CRP and ESR measured in the first year of the disease were significantly higher in the immunomodulatory group, anti-TNF group and systemic steroid group. Additionally, the AUC values for ESR in patients who had experienced disease attacks requiring hospitalization were higher than those who had not been hospitalized. The values were found to be significant for the CRP values in comparison with the immunomodulating therapy; whereas the anti-TNF therapy was not significant for ESR. This may be related to the fact that CRP is a more sensitive marker than ESR, as supported by Turner et al (12). In 68 UC patients with a 1-year follow-up study, the prior oral corticosteroid treatment duration and the Hb reduction seemed to predict the response to intravenous steroid treatment in the second week. The response rate is lower in these patients (13).

In the light of the evidence that low Hb levels are associated with disease activity and poor prognosis, and are useful for predicting the patients in need of an intensive treatment, it was found, in our study, that the AUC values for Hb were low in the patients with poor prognosis.

In a study from Turkey, NLR was higher with a target value of 2.16 in a group with active UC, compared to a group with inactive UC and a control group. It was found that the value calculated as 2.16 indicated a disease activity with an 81.8% sensitivity and an 80.5% specificity. NLR also showed correlation with WBC and ESR (14). MPV levels were significantly higher in active UC patients, compared to the inactive ones and the control group. A negative correlation was found between endoscopic activity index and MPV (15).

In our study the values calculated for the NLO were found to be significantly higher and those for the MPV to be significanty lower in patients with poor prognostic groups (immunomodulatory group, anti-TNF group, systemic steroid group, attacks requiring hospitalization) as can be found in the literature. Unfortunately, this relation couldn't be shown between the group that received anti-TNF and the group that did not. This finding was considered to be a first in the literature, showing that MPV could be used as a predictive factor.

In conclusion, it was thought that the AUC values calculated for the CRP were predictors of the worst prognostic group, the one that received anti-TNF.

Despite the limitations of our study, combined with the small sample size of the poor prognostic group and the retrospective design, the idea of using inflammatory markers at the onset of the disease as a predictor may be considered as a novelty and a valuable contribution. In order to support and strengthen this new information and to facilitate its use in clinical practice with a threshold value, there is still room for further studies that need to be conducted on a higher amount of patients.

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