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Comparison of the Effects of Clinical Outcomes on the Number of Attacks in the Course of Ulcerative Colitis: A Single Center Study

Klinik Parametrelerin Ülseratif Kolit Seyrinde Atak Sayılarına Etkisinin Karşılaştırılması: Tek Merkezli Çalışma

Hakan Sivgin[1], Abdurrahman Şahin[2], Şirin Çetin[3]

[1]Department of Internal Medicine, Faculty of Medicine, Tokat Gaziosmanpasa University, Turkey
[2]Department of Gastroenterology, Faculty of Medicine, Tokat Gaziosmanpasa University, Turkey
[3]Department of Biostatistics, Faculty of Medicine, Amasya University, Turkey

Abstract

Aim: The aim of this study was to find the factors affecting the frequency of attacks of patients diagnosed with ulcerative colitis (UC).

Material and Method: In our single-center retrospective descriptive study, 40 UC patients who admitted to our hospital for follow-up from January 2021 to December 2022. The baseline demographic and clinical characteristics, laboratory values and, treatments during the disease course were compared among patients with number of attacks < 2 per year (Group1) and number of attacks ≥2 per year (Group 2).

Results: There were 25 (male/female:11/14) patients in Group 1 and 15 (male/female:7/8) patients in Group 2. No statistically significant difference was found between the mean age, sex, age of diagnosis, duration of disease, co-morbidities and extraintestinal involvement of both groups. The median CRP values were significantly higher in the Group 2, compared to the group 1 (P=0.04). There was statistically significant differences between groups in terms of endoscopic severe activity (12% vs, 40%; p<0.001), left-sided involvement(60% vs, 40%; p=0.02), pancolonic involvement (8% vs, 33%; p<0.001), the presence of blood in stool at the time of diagnosis (80% vs 100%; p=0.03), use of biologic agents (16% vs 40%; p< 0.001) and steroids (16% vs 33%; p=0.02).

Conclusion: In UC patients who have ≥ 2 attacks per year presented with more advanced clinical features at onset and more severe outcomes than the number attacks <2 per year. Symptoms and clinical parameters at the time of diagnosis are important criteria to be considered in determining the number of attacks in follow-up.

Keywords: Ulcerative colitis, Attack, Clinical feature, Outcomes

Öz

Amaç: Bu çalışmanın amacı, ülseratif kolit (UC) tanısı alan hastaların atak sıklığını etkileyen faktörleri bulmaktır.

Gereç ve Yöntem: Tek merkezli retrospektif tanımlayıcı çalışmamızda, Ocak 2021-Aralık 2022 tarihleri arasında takip için hastanemize başvuran 40 UC hastası dahil edildi. Demografik ve klinik özellikler, laboratuvar değerleri ve hastalık seyri sırasındaki tedaviler, atak sayısı yılda < 2 (Grup 1) ve atak sayısı ≥ yılda 2 (Grup 2) olan hastalar arasında karşılaştırıldı.

Bulgular: Grup 1'de 25 (erkek/kadın:11/14) hasta ve Grup 2'de 15 (erkek/kadın:7/8) hasta vardı. Her iki grubun yaş ortalaması, cinsiyeti, tanı yaşı, hastalık süresi, yandaş hastalıkları ve ekstraintestinal tutulumu arasında istatistiksel olarak anlamlı fark saptanmadı. Median CRP değerleri Grup 2'de grup 1'e göre anlamlı derecede yüksekti (P=0,04). Endoskopik şiddet aktivitesi (%12'ye karşı %40; p<0,001), sol taraflı tutulum (%60'a karşı %40; p=0,02), pankolonik tutulum (%8'e karşı %33; p<0,001), tanı anında dışkıda kan varlığı (%80'e karşı %100; p=0,03), biyolojik ajan kullanımı (%16'ya karşı %40; p<0,001) ve steroidler (%16'ya karşı %33; p=0,02) açısından gruplar arasında istatistiksel olarak anlamlı farklılıklar vardı.

Sonuç: Ülseratif kolit seyrinde yılda ≥ 2 atak olanlarda; yılda < 2 atak olanlara göre; tanı anında daha şiddetli semptomlar ve klinik parametreler ön plandadır. İlk tanı anındaki semptomlardan bilhassa dışkıda kan ve klinik parametrelerden şiddet indexi, ülseratif kolitin takip sürecinde atak sayısının belirlenmesinde ve öngörülmesinde göz önünde bulundurulması gereken önemli kriterlerdir.

Anahtar Kelimeler: Ülseratif Kolit, Atak, Klinik Parametreler

Corresponding *(İletişim)*: Hakan SIVGIN, Assistant Professor, M.D., Gazıosmanpasa University School of Medicine Department of İnternal Medicine, Tokat, Turkey
E-mail *(E-posta)*: sivginhakan@gmail.com
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INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease of unknown cause that primarily affects the mucous membranes of colon that often forming erosions and ulcers. [1] The mucosal inflammation, extend from the rectum to proximal segments of the colon in an interrupted pattern. Symptoms of UC include rectal bleeding, bloody diarrhea and abdominal pain. The diagnosis of ulcerative colitis is based on a combination of clinical symptoms, endoscopic findings, histopathologic findings, and with the exclusion of alternative diagnoses. At diagnosis, most patients have mild to moderate symptoms, and less than 10% have severe disease.[2]

Ulcerative colitis is characterised by remission and exacerbations in most of the patients. On the other hand, some patients have chronic continuous activity. A subgroup of patients with UC has also been described to have lifelong remission after the induction treatment. A first flare after the diagnosis which less than 2 years, the presence of symptoms at diagnosis like fever or weight loss, and active disease in the previous year increase the risk of subsequent relapse.[3]

At diagnosis, 30-50% of patients have distal colitis that confined to rectum or sigmoid colon, 20-30% have left-sided colitis, and about 20% have pancolitis. Extension of colonic disease can occur over time. Ulcerative colitis can progress proximally in 10-19% of patients after 5 years, and in up to 28% of patients at 10 years.[4] Disease flares associated with progression of anatomic extent usually follow a severe course and require more intensive therapy like immunosuppressants, biological agents or surgery. [2] Risk factors for progressive or complicated disease include a diagnosis of the disease less than 40 years, pancolitis, lack of endoscopic healing while in clinical remission, deep ulcerations, concomitant primary sclerosing colangitis and perinuclear antineutrophil cytoplasmic antibody positivity.[5]

Determining the severity and extent of ulcerative colitis is important for selecting the most appropriate treatment. In clinical practice, disease activity is assessed by the combination of clinical symptoms, endoscopic findings, histopathology, biomarkers and quality of life. Currently, complex indices that include clinical symptoms, endoscopic findings, patient's self assessment of quality of life and the physician's global assessment have been used in the assessment of disease activity such as the Mayo score, Lichtiger score, and Simple Clinical Colitis Activity Index.[6] Considering the complexity of these indexes, it is aimed in the current study to determine simple clinical and endoscopic findings at the time of diagnosis for predicting attack frequeny. The efficiacy of treatments were also investigated to prevent subsequent attacks. Thus, we aimed to determine which patients should be followed closely and treated more intensively according to the current study findings.

MATERIAL AND METHOD

The study was carried out with the permission of Tokat Gaziosmanpaşa University Clinical Non-interventional Clinical Researches Ethics Committee (Date: 08.09.2022, Decision No: 21-KAEK-079). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This retrospective study was carried out among UC patients who followed in the Gastroenterology Clinic of Tokat Gaziosmanpaşa University, Faculty of Medicine between January 2021 and December 2022. Patients were diagnosed as UC according to clinical, radiological, and endoscopic examinations, as well as histolopatological findings. A total of 63 patients aged 18 years and older UC patients were recruited. After the assessment of hospital records and database, it was determined that 6 of the 63 patients had psoriasis, 4 had chronic alcohol use, 3 had malignancies (2 patients lung cancer, 1 patient breast cancer), 2 had the diagnosis of autoimmune hepatitis, and 8 had missing the data required for the study. Thus, twenty-tree patients were excluded from the study.

A total of forty patients were included in the study and their data were retrospectively analyzed. Clinical symptoms and endoscopic findings including location and activity at diagnosis were recorded. All patients were classified according to the Montreal Classification of UC to determine disease extent as proctitis, left-sided colitis and pancolitis. Truelove- Witts (TW) Severity index was used to evaluate clinical activation as mild, moderate and severe ulcerative colitis. The treatments other than mesalazine, corticosteroids, immunomodulators, biological agents including anti-tumor necrosis factor (TNF)-α antibody and anti-integrins were recorded. Laboratory parameters at diagnosis which including hemogram, full biochemisty, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), were also recorded.

Patients were divided into 2 groups according to their annual attack counts per year; less than two attacs per year (Group 1) and, two or more attacks per year (Group 2). A comparison was performed between the two groups using clinical, endoscopicand laboratory findings at diagnosis and tratments.

Statistical Analysis

All statistical analyses were carried out using SPSS version 25.0 (IBM Corp. Released 2017. Armonk, NY). The normality of variables was tested by the Shapiro Wilk test. Categorical measurements were summarized as numbers and percentages, and numerical measurements with a normal distribution were represented as mean±SD; those with a non-normal distribution and ordinal variables were described as median (25%-75%). The differences were compared using either the Chi-squared test or Fisher's exact test for categorical variables. Parametric tests (t test) were used for numerical measurements with normal distribution, and nonparametric tests (Mann-Whitney U Test) were used for numerical measurements with normal distribution.

Univariate logistic regression modeling was used to measure the effect of independent variables on the dependent variable. In statistical tests, results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$.

RESULTS

Among 40 patients with UC, 24 (60%) of the patients were female and 16 (40%) were female. The mean age of ulcerative colitis patients was 48.3±17.1 years. The mean age of diagnosis was 42.1±16.8 years. The median disease duration was 7.2 (4.2-10.8) years. The most common presenting symptom was diarrhea in 36 patients (%90), blood in the stool in 35 patients (%87.5), and fever in 10 patients (%25) at the time of diagnosis. Accoding to the extent,12 patients (30%) had proctitis, 21 (52.5%) had left colitis and, 7 patients (17.5%) had pancolitis. Activity at the time of diagnosis were as follows; 10 patients (25%) mild, 21 patients (52.5%) moderate and 9 patients (22.5%) severe. All of the patients (% 100) were receiving mesalazine. Thirty-one patients (77.5%) were on immunomodulatory treatment and, 10 patients (%25) on biologic agent treatment. Nine (22.5%) patients received corticosteroids during the follow-up period. No one of our ulcerative colitis patients needed surgical treatment. Demographic and clinical features of patients and treatments were given in **Table 1**.

Table 1. Demographic characteristics and clinical data of patients

	n (%)
Gender, Male/Female	16 (40) /24 (60)
Age, year,mean±SS	48.3±17.1
Age of diagnosis,year, mean±SS	42.1±16.8
Duration of illness, years, median (%25-%75)	7.2 (4.2 -10.8)
Activity, active/remission	9 (22.5)/31 (77.5)
Disease activity at diagnosis, n(%)	
Mild, n (%)	10 (25)
Moderate, n (%)	21 (52.5)
Severe, n (%)	9 (22.5)
Montreal classification extent of UC, n(%)	
Proctitis	12 (30)
Left Side Colitis	21 (52.5)
Pancolitis	7 (17.5)
Comorbidities	
Diabetes	10 (25)
Hypertension	6 (15)
Hyperlipidemia	4 (10)
No Additional Diseases	20 (50)
Extraintestinal organ involvement	
Musculoskeletal system	6 (15)
Mucocutanöz	5 (12.5)
Ocular	2 (5)
Hepatobiliary	2 (5)
Treatment	
Mesalazine	40 (100)
Corticosteroid	9 (22.5)
Immunomodulator	31 (77.5)
Biologic agent	10 (25)

In the comparison of groups, the mean number of attacks was 2.11±0.79 per year in females and, 2.07±0.82 per year in males. There were 25 patients (M/F:11/14) in Group 1 and 15 patients (M/F:7/8) in Group 2. The clinical and laboratory features of the groups were given in **Table 2**. The mean age of the patients in the Group 1 was 50.1±7.5 years, and 56 percent of the patients were female. The mean age of the Group 2 was 49.4±7.7 years, and 53% of the patients were female. No statistically significant difference was found between the mean age, sex, age of diagnosis, duration of disease, co-morbidities and extraintestinal involvement of both groups (for all, p>0.05) (**Table 2**). Laboratory parameters of the groups was presented in **Table 3**. he median CRP values were significantly higher in the Group 2, compared to the Group 1 (p= 0.04). Other laboratory parameters did not significantly differ between the groups (for all, p>0.05).

Table 2. According to the number of attacks, the clinical features of the groups at the time of diagnosis

	N. of attacks < 2/ per year (Group 1)	N. of attacks ≥ 2/ per year (Group 2)	p
Gender, Male/Female, n (%)	11 (44)/14 (56)	7 (47)/8 (53)	0.26
Age, year, mean±Sd	50.1±7.5	49.4±7.7	0.29
Age of diagnosis, year,mean±Sd	43.9±9.2	42.9±10.5	0.22
Duration of illness, years, median (%25-%75)	7.2 (3.6 -10.8)	7.1 (4.8 -8.4)	0.39
Comorbidities, n(%)			
Diabetes	7 (28)	6 (40)	0.42
Hypertension	4 (16)	3 (20)	0.57
Hyperlipidemia	3 (7.5)	2 (13)	0.18
No additional diseases	11 (44)	4 (27)	0.46
Disease activity at diagnosis, n(%)			
Mild	7 (28)	3 (20)	0.96
Moderate	15 (60)	6 (40)	0.89
Severe	3(12)	6 (40)	<0.001*
Montreal classification of extent of UC, n (%)			
Proctitis	8 (32)	4 (26)	0.54
Left Side Colitis	15 (60)	6 (40)	0.02*
Pancolitis	2 (8)	5 (33)	<0.001*
Symptoms n(%)			
Diarrhea	21 (84)	15 (100)	0.16
Blood in the stool	20 (80)	15 (100)	0.03*
Weight Loss	9 (36)	6 (40)	0.13
Fever	6 (24)	4 (26)	0.31
Extraintestinal involvement, n(%)	9 (36)	6 (40)	0.47
Musculoskeletal system	4 (16)	2 (13)	0.56
Mucocutanos	3 (12)	2 (13)	0.77
Ocular	1 (4)	1 (6)	0.89
Hepatobiliary	1 (4)	1 (6)	0.89
Treatment , n(%)			
Mesalazine	25 (100)	15 (100)	1
Corticosteroid	4 (16)	5 (33)	0.02*
Immunomodulator	19 (76)	12 (80)	0.66
Biologic agent	4 (16)	6 (40)	<0.001*

*:p<0.05, OR: Odds ratio, CI: Confidence interval, 1: Reference value
Values are presented as mean±SD, median (%25-%75) or number (%). Patients with missing values were not included. Data are expressed as raw numbers with proportions

The comparison of symptoms and clinical charactaristics at disease onset between the groups was presented in **Table 3**. Patients who had severely active at the time of diagnosis were significantly higher rates in Group 2 (12% vs 40%; p<0.001). According to the extent, there was no difference between the two groups for the ration of proctitis (32% vs 26%; p=0.54). There left-sided colitis was more commo in Group 1 than in Group 2 (60% vs 40%; p=0.02). Likewise, pancolitis was more common in Group 2 than in Group 1 (8% vs 33%; p<0.001). There was no difference between the groups in terms of symptoms, diarrhea, weight loss and fever. Blood in stool was statistically significantly higher in Group 2 than in Group 1 (80% vs 100%; p=0.03). No statistically significant difference was found between the extraintestinal involvement of both groups (p > 0.05). When the treatment methods were compared, it was seen that the use of biologic agents and steroids was significantly higher in group 2 than in group 1 (16% vs 33%; p=0.02), (16% vs 40%; p< 0.001).

Table 3. According to the number of attacks, laboratory parametres of the groups at the time of diagnosis

Variables	Group 1	Group 2	p
Leukocyte (10^3/mm³), median (%25- %75)	9410 (6670-10610)	9720 (6030-11520)	0.22[b]
Neutrophil (10^3/mm³), median (%25- %75)	5230 (4015-6610)	5160 (4060-6020)	0.25[b]
Lymphocyte (10^3/mm³), median (%25- %75)	2015 (1580-2660)	2080(1600-2670)	0.13[b]
Hemoglobin, median (%25- %75)	12.5 (10.8-13.9)	13.7 (11.9-14.8)	0.12[b]
Platellet,median (%25- %75) (10^3/mm³)	305 (242-395)	306 (259-347)	0.9[b]
ESR, median (%25- %75)	23 (10-41)	21.5 (8-30)	0.19[b]
CRP(mg/dl), median (%25- %75)	22 (3-17.5)	28.7 (1.5-15)	0.04[b]
BUN(mg/dl), mean±Sd	12.4±4.8	12.8±4.7	0.23[a]
Creatinine, mean±Sd	0.80±0.28	0.80±0.22	0.83[a]
Sodium,mean±Sd	139.0±2.8	139.3±3.1	0.67[a]
Potassium,mean±Sd	4.34±0.23	4.45±0.43	0.16[a]
Calcium,mean±Sd	9.18±0.45	9.19±0.39	0.95[a]
ALT(IU/L), median (%25- %75)	13 (10-19)	14 (11-21)	0.55[b]
AST(IU/L), median (%25- %75)	16 (13-20)	17 (14-21)	0.52[b]
GGT(IU/L), median (%25- %75)	17 (12-28)	19 (13-27)	0.51[b]
ALP(IU/L), median (%25- %75)	79.4 (23-114)	80.3 (43- 128)	0.44[b]
T. Protein (mg/dl), mean±Sd	7.1±0.9	7.14±0.8	0.31[a]
Albumin (mg/dl), mean±Sd	4.1±0.8	4.2±0.6	0.29[a]

*p<0.05, a:Student's t- Test , b:Mann-Whitney U test, Sd:Standard deviation

Univariate analysis for the identification of the annual attack frequency demonstrated that the presence of blood in stool and endoscopic severe activity at diagnosis were statistically significant independent predictive factors. The results of univariate logistic regresiion were given in **Table 4**. Endoscopic severe activity at diagnosis had 6 times higher risk for two or more attacks per year (OR:6.01, CI:1.66-23.56, p=0.007). Similarly, the presence of blood in the stool at onset was related with 5.71 times higher risk in more frequent attack (OR: 5.71, CI: 1.06-30.66, p=0.034).

Table 4. Factors related to ≥ 2 attacks per year of ulcerative colitis (univariate logistic regression analysis results)

Variables	n	(%)	OR	95%CI	P
Severe UC activity (severe/non severe)	9	22.5	6,01	1.66-23.56	0.007*
Blood in Stool (Yes/No)	35	87.5	5.71	1.06-30.66	0.034*
Use of Biologic agent (Yes/No)	10	25	0.99	0.64-1.57	0.91
Use of Steroid (Yes/No)	9	22.5	1.14	0.74-1.76	0.547
Pancolitis (Yes/No)	7	17.5	1.07	0.66-6.33	0.58
Left Side Colitis (Yes/No)	21	52.5	1.09	1.66-19.33	0.56

*:p<0.05, Multiple Logistic regression, Method=Enter, OR: Odd Ratio, CI: Confidence Interval, R2 (Nagelkerke)=0.10, Model χ2=52.78, p<0.001, Dependent variable: number of attacks per year ≥2 (1=yes, 0=no), Correct classification probability of the model:78%, 1: Reference value

DISCUSSION

Ulcerative colitis is a chronic inflammatory bowel disease that involves the mucosa and submucosa of the colon diagnosed and treated with clinical presentation, endoscopic appearance and laboratory values, and may also present with extraintestinal findings with attacks and remissions.[7,8] Since UC is a chronic and lifelong disease, to predict the course of the disease at the time of diagnosis or in the early stages is very important because it will change the approach to the patient and the treatment. In the literature, many predictor factors have been identified for UC based on both clinical (age, gender, involvement status, etc.) and laboratory values. These prognostic predictors were: diffuse disease, proximal extension of lesions during the course of the disease, extraintestinal findings, young age of disease onset, severity of inflammation, and poor response to treatment.[9-15] Ulcerative colitis is a lifelong disease that is generally diagnosed in young adulthood, often at the age of 30-40 years. Although the female-to-male ratio has different results in different studies, it is generally accepted as equal. In accordance with the literature, the median age of diagnosis was 42 years in our study and the female patient rate was 60%. In the comparison of the two groups, there was no difference in terms of age and gender. Most clinicians have been using the partial Mayo score or the Truelove and Witts severity index for deciding treatments. This index is primarily based on the symptom category to assess the disease activity of UC at diagnosis and subsequent follow-up. Those in remission were categorized by less than 3 defecations per day, while those in severe ones were categorized by more than 6 bloody defecations per day and the presence of systemic symptoms. In our study in accordance with the literature, it was found that there was a positive significant relationship between the presence of bloody defecation and the frequency of attacks during diagnosis. The frequency of attacks was 5.7 times higher in patients with bloody defecation than in other patients.

Ulcerative colitis presents approximately 45% proctitis, 35% left side colitis and 20% pancolitis, and colectomy rates and proximal extension rates vary between 10-30% throughout the course.[16,17] In our study, 12 patients (30%) with ulcerative colitis had proctitis, 21 patients (52.5%) had left colitis and 7 patients (17.5%) had pancolitis. In the comparison of the two groups, the rate of pancolitis at the time of diagnosis was statistically higher in the group with a high number of attacks. Interestingly, those who had left-sided colitis at the time of diagnosis were found to be more in the group with a low number of attacks. According to the disease activity at the time of diagnosis, it was seen that the severe ones between the two groups were statistically higher in the group with the highest number of attacks. The frequency of attacks was 6.1 times higher in severe cases than in other patients. In the studies carried out, values such as ESR, CRP, Hb, leukocytes, albumin, which are called inflammatory markers, are used. In particular, there are studies showing that CRP is associated with UC disease activity and severity of activity.[11,12,18-20] In our study, CRP values were found to be significantly higher at the time of initial diagnosis of those with a high number of attacks between the two groups. In other inflammatory and biochemical parameters, there was no difference between the two groups.

Studies have reported cumulative colectomy rates of 20% at 5 years and 25% at 10 years.[21] The rate of UC-related operation are lower in Asian patients than they are in Western patients, with a rate of 5.9% at 5 years and 10% of 10 years.[22] One Western study showed that the age of onset was younger in patients who had undergone previous operation.[23] In our study, there was no colectomy. This finding may reflect the fact that a top-down strategy including biologic agents was more frequently used in patients because of their more severe disease state upon diagnosis. The administration of immunosuppressants and/or biologic therapy early in the course of the disease has been shown to be superior to conventional treatment in terms of better mucosal recovery, induction of steroid-free remission, and prevention of hospitalization in patients with recent IBD.[24-26] In cases with steroid dependence or steroid refractory, azathioprine (2.5 mg/kg/day) or 6-mercaptopurine (1.5 mg/kg/day) should be added to the treatment to achieve and maintain remission.[24-26] In steroid-refractory cases, in cases that are dependent on steroids even though they have taken enough tiopurine, or in cases that cannot tolerate tiopurine treatment, infliximab is an effective treatment option as a tumor necrosis factor alpha (TNF-α) blocker. A meta-analysis of 9 randomized controlled trials involving a total of 1226 patients with moderate to severe ulcerative colitis showed better short-term response, short-term improvement, long-term response, and long-term improvement in patients receiving biologic agents. In our study, it was seen that all patients in two groups used mesalazine. In the group with a high number of attacks, the use of biological agents and steroids was found to be statistically significantly higher. This study has several limitations. There were only 40 UC patients because data were collected from medical records had to include the number of attacks. Despite the small number of patients; however, there were significant differences in the severity of clinical features and outcomes between the two groups in the present study. In addition, the results of outcomes analysis using patient history including UC-related admission and steroid or biologic agents use during follow-up after diagnosis of UC were limited because of inconsistent reference points. Further study is needed to confirm the associations and trends observed here.

CONCLUSION

Consequently, UC is a relapsing and remitting disease, currently with no cure. The purpose of treatment UC is to maintain remission and prevent complications. Long-standing mucosal inflammation can lead to complications and colorectal carcinoma. It is possible that severe outcomes including symptoms such as blood in stool, disease severity, using steroid or biologic agents may be higher in more attacks patients compared to in less attacks patients with prolonged follow-up. Intensive care and uninterrupted follow-up are especially important for patients with more attacks per year..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University, Noninvasive Clinical Researches Ethics Committee (Date: 18.03.2021, Decision No: 21-KAEK-079)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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