



Diagnostic and Prognostic Significance of Inflammatory Parameters in Diverticular Disease of the Colon

Kolonun Divertiküler Hastalığında İnflamatuvar Parametrelerin Tanısal ve Prognostik Önemi

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Abstract

Aim The aim of this study was to determine the presence of inflammation in asymptomatic diverticular disease using inflammatory parameters and to evaluate the relationship between inflammatory parameters and the degree of complication in symptomatic diverticular diseases.

Material and Method Clinical and dermographic findings of patients with acute diverticulitis, patients with diverticulosis and healthy volunteers were compared.

Results A healthy control group of 31 people, 40 patients with diverticulosis and 32 patients with acute diverticulitis were included in the study. Thirty-one (43.11%) patients were female and 41 (56.9%) male. RDW and MLR were significantly higher in patients with asymptomatic diverticulosis compared to the control group ($p=0.02$, $p=0.00$, respectively). NLR and SII were significantly different among Hinchey groups ($p<0.01$, $p<0.01$, respectively).

Conclusion We concluded that there may be a mild inflammation in asymptomatic diverticulosis patients, and NLR and SII can provide information about the degree of acute diverticulitis.

Keywords Diverticulosis, inflammation, acute diverticulitis

Özet

Amaç Bu çalışmanın amacı, inflammatuar parametreleri kullanarak asemptomatik divertiküler hastalıkta inflamasyon varlığını belirlemek ve semptomatik divertiküler hastalıklarda inflammatuar parametreler ile komplikasyon derecesi arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem Akut divertikülitli hastalar, divertikülozlu hastalar ve sağlıklı kontrol grubunun klinik ve dermografik bulguları karşılaştırıldı.

Bulgular 31 kişilik sağlıklı kontrol grubu, 40 divertikülozlu hasta, 32 akut divertikülitli hasta çalışmaya dahil edildi. Hastaların 31'i (%43,11) kadın, 41'i (%56,9) erkekti. Asemptomatik divertikülozlu hastalarda RDW ve MLR, kontrol grubuna göre anlamlı derecede yüksekti (sırayla $p=0.02$, $p=0.00$). Hinchey grupları arasında NLR ve SII anlamlı derecede farklıydı (sırayla $p<0.01$, $p<0.01$).

Sonuç Asemptomatik divertiküloz hastalarında ılımlı bir inflamasyon olabileceği, NLR ve SII' m akut divertikülitin derecesi hakkında bilgi verebileceği sonucuna varıldı.

Anahtar Kelimeler Divertiküloz, inflamasyon, akut divertikülit

INTRODUCTION

Diverticulum are structural changes that classically create pockets in the colon wall. Diverticulum occurs as a result of herniation of the mucosa and submucosa due to the defect in the circular muscle layers of the colon wall. Usually, diverticula form in areas where blood vessels penetrate the colon.¹ Diverticulum is the most common anomaly found in colonoscopy². Although most patients with diverticulum are asymptomatic, approximately 25% of cases are symptomatic and 5% of cases have an acute episode of diverticulitis³.

If complications such as inflammation, perforation, fistula, abscess formation, obstruction or bleeding associated with the diverticula occur, it is called a complicated diverticula. Individuals with uncomplicated diverticular disease may have left iliac fossa pain, bloating, changes in bowel habit, and mild left iliac fossa tenderness on examination. Persons with acute diverticulitis typically present with severe left iliac fossa pain, fever, tachycardia, malaise, and altered bowel habits.

The pathogenesis of diverticular disease is multifactorial, complex and still poorly understood⁴. It has been suggested that chronic low-grade inflammation plays a role in the pathogenesis and particularly in symptomatic diverticular disease^{5,6}. Few studies have been published with conflicting results regarding the coexistence of symptomatic diverticulosis, diverticulosis alone, and mucosal inflammation^{5,7,8}

Inflammatory parameters obtained from complete blood count are a useful index for differential diagnosis or prognostic prediction of diseases as they are easily calculated and known to provide information about inflammatory activity⁹⁻¹¹. Using inflammatory parameters, low-grade chronic inflammation characterized by a persistent increase in inflammatory cells and pro-inflammatory mediators can be detected.¹²

The aim of this study was to determine the presence of

inflammation in asymptomatic diverticular disease using inflammatory parameters and to evaluate the relationship between inflammatory parameters and the degree of complication in symptomatic diverticular diseases.

MATERIAL and METHODS

The Ethics Committee of the Sakarya University School of Medicine approved the study and data collection (Number: E-71522473-050.01.04-194704-338).

Patients admitted to the emergency department due to diverticulitis at Sakarya University Training and Research Hospital between January 2018 and July 2022 and who were found to have diverticulum during colonoscopy were retrospectively scanned. In addition, those who had no complaints, had a screening colonoscopy, and were not found to have any endoscopic pathological findings were retrospectively screened as a healthy control group. Demographic and laboratory characteristics of the patients were examined. Age, gender, hgb, white blood cell (WBC), total bilirubin (tbil), red blood cell (RBC), red cell distribution width (RDW), neutrophils, lymphocytes, monocytes, platelets, mean platelet volume (MPV), monocytes, mean erythrocyte volume (MCV), mean erythrocyte hemoglobin concentration (MCHC), mean corpuscular volume (MCH), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte ratio (NLR) and systemic inflammatory index (SII) values of the patients and control group were evaluated. Patients were classified as Hinchey 0 (H0), Hinchey 1 (H1), Hinchey 2 (H2), Hinchey 3 (H3) and Hinchey 4 (H4) in terms of the radiological Hinchey Classification. Data of the control group and asymptomatic patient group (H0) were compared. In addition, the data between Hinchey classes were compared.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analysis. Kolmogorov-Smirnov test was used to test the suitability of the data for normal distri-

bution. While performing descriptive statistics, the distribution of quantitative data was expressed as mean±standard deviation, and categorical data were expressed as percentages. One way Anova test was used for the analysis of parametric quantitative data, Krusgal Wallis H test was used for the analysis of non-parametric quantitative data, and Chi-Square test was used for the analysis of categorical data. The Mann-Whitney-U test was used for pairwise comparisons between the variables in which a significant difference was found in the Krusgal Wallis H test and evaluated by applying Bonforoni correction. The Tukey test was used to determine which groups had a statistically significant difference between the groups whose One Way Anowa test was significant. For statistical significance, the total type-1 error level was used as 5%.

RESULTS

When the control group was compared with the asymptomatic H0 patient group no statistically significant difference was found for gender (p=0.81), age (p=0.885), wbc

(p=0.394), tbil (p=0.949), NLR (p=0.954), PLR (p=0,430), SII (p=0,745), while statistically significant difference was found for RDW (p=0.02) and MLR (p=0.00) (Table 1).

Of the patients, 31 (43.11%) were female and 41 (56.9%) were male. When the patients were categorized in terms of the Hinchey classification, no statistically significant difference was found between the groups in terms of gender (p=0.21) (Table 2).

The mean age of the patients was 58.11±14.33. When the patients were categorized in terms of the Hinchey classification, there was a significant age difference between the groups. (F(4,71) = 3.480, p=0.012, r=0.41) (Table 3).

There was no significant difference between Hinchey classes in terms of platelet, MPV, MCV, MCH, lymphocyte values, and PLR, MLR (respectively H(4)=5.167, p=0.27, H(4)=8.56, p=0.07, H(4)=8.715, p=0.06, H(4)=7.118, p=0.13, H(4)=9.344, P=0.053, H(4)=7.288, p=0.121,

Table 1: Comparison of healthy control group and Hinchey 0 patient group

	Gender		Age	WBC	RDW	T.BİL	NLR	PLR	SII	MLR
	Female	Male								
Control	20 (%52,6)	11 (%33,3)	61.06± 12,7	6,83± 1,77	14,07± 1,59	0,64± 0,27	2,03± 0,75	129,61± 51,55	522,34± 237,59	0,19± 0,69
Hinchey 0	18(%47,4)	22(%66,7)	61,65± 11,7	7,35± 1,54	15,79± 3,23	0,62± 0,28	2,05± 0,86	125,72± 58,25	554,25± 348,16	0,26± 0,10
p value	0,810		0,885	0,394	0,02	0,949	0,954	0,430	0,745	0,00

Table 2: Gender distribution by Hinchey classification

	Hichey 0	Hinchey 1	Hinchey 2	Hinchey 3	Hinchey 4	p value
Female	18 (%58.1)	10 (%32.3)	1 (%3.2)	0 (%)	2 (%6.5)	0.21*
Male	22 (%53.7)	14 (%34.1)	1 (%2.4)	4 ((%9.8)	0 (%)	
* Chi-square test						

Table 3: One Way Anova test between groups for age by Hinchey classification

	Sum of Squares	df	Mean Square	F	Sig
Between Groups	2509.428	4	627.357	3.480	0.012
Within Groups	12079.683	67	180.294		
Total	14589.111	72			

H(4)=8.522, p=0.07, H(4)=8.828, p=0.06) (Table 3).

H(4)=44.355, p<0.0, H(4)=13.302, p=0.01, H(4)=9.875, p= 0.04, H(4)=9.605, p=0.04, H(4)=35.356, p<0.01, H(4)=29.521, p<0.01) (Table 4).

WBC, RBC, neutrophil, MCHC, HGB, tbil levels, NLR and SII differ significantly between Hinchey classes (respectively H(4)=38.188, p<0.01, H(4)=16.731, p<0.01,

Table 4: Krusgal Wallis H analysis of variables by Hinchey classification						
	N	X	S.S	Mean Rank	X2	p value
RDW						
Hinchey 0	40	15.79	3.23	43.70	16.731	<0.01
Hinchey 1	24	13.74	1.55	25.73		
Hinchey 2	2	13.50	0.98	21.75		
Hinchey 3	4	13.60	1.60	23.50		
Hinchey 4	2	18.90	4.66	62.50		
MCHC						
Hinchey 0	40	32,50	1,20	30.55	13.302	0.01
Hinchey 1	24	33,21	0,63	44.33		
Hinchey 2	2	33,00	1,41	41.25		
Hinchey 3	4	33,90	0,84	58.00		
Hinchey 4	2	31,85	0,35	13.75		
MCH						
Hinchey 0	40	28,67	2,36320	32.91	9.344	0.053
Hinchey 1	24	29,62	1,63	42.83		
Hinchey 2	2	28,55	1,90	29.50		
Hinchey 3	4	30,40	3,46	51.88		
Hinchey 4	2	25,70	1,97	8.50		
NLR						
Hinchey 0	40	2,05	0.86	24.10	35.356	<0.01
Hinchey 1	24	4,27	2,73	48.83		
Hinchey 2	2	2,98	0,74	46.00		
Hinchey 3	4	9,49	4,55	64.75		
Hinchey 4	2	15,39	3,93	70.50		
SII						
Hinchey 0	40	554,25	348,16	25.68	29.521	<0.01
Hinchey 1	24	1068,31	712,28	47.75		
Hinchey 2	2	620,63	196,24	37.50		
Hinchey 3	4	2610,40	1223,87	65.00		
Hinchey 4	2	5064,53	1294,15	71.50		

In terms of SII value; there was a significant difference between H0 and H1, H3, H4, (respectively $p < 0.01$, $p < 0.01$, $p < 0.01$), between H1 and H0, H3, H4 (respectively $p < 0.01$, $p < 0.01$, $p < 0.01$), between H3 and H0, H1 (respectively $p < 0.01$, $p < 0.01$).

In terms of NLR value; A statistically significant difference between H0 and H1, H3, H4 (respectively $p < 0.01$, $p < 0.01$, $p < 0.01$), and between H1 and H0, H3, H4 ($p < 0.01$, $p = 0.01$, $p < 0.01$, respectively) detected.

DISCUSSION

Although the underlying pathological mechanisms in the formation of colonic diverticulum remain unclear, it is known that genetics, age, diet, constipation and microbiota have an effect¹.

The association of inflammation with colonic diverticulum formation has been investigated in studies. When Humes et al. compared symptomatic and asymptomatic uncomplicated diverticulosis patient groups, they showed higher TNF- α and IL-6 expression in the symptomatic patient group⁵. Tursi et al. investigated lymphocyte and neutrophil infiltration in the histopathological evaluation of the biopsy material taken from the colon of the healthy control group, the patient group with asymptomatic diverticulosis, the symptomatic uncomplicated patient group and the complicated patient groups. Even in the patient group with asymptomatic diverticulosis, increased lymphocytic infiltration was found compared to the healthy control group, while neutrophilic infiltration was reported to be higher in acute complicated diverticulitis compared to its grades¹³.

20-25% of patients with colonic diverticulosis become symptomatic and 25% of symptomatic patients develop diverticulitis^{14,15}. The pathogenetic mechanisms that cause the symptoms to occur are still debated as there is still no consensus on the definition of the disease. d¹⁶.

In a study by Peery et al. on 619 patients with diverticulosis and/or abdominal pain and irritable bowel syndrome (IBS) who underwent screening colonoscopy, tumor necrosis factor alpha (TNF- α), when CD4+ cells in biopsies from the sigmoid colon mucosa were compared with controls without diverticulosis. , mRNA measurements of CD8+ cells and CD57+ cells found no evidence of mucosal inflammation¹⁷.

NLR, PLR, SII, and LMR can be calculated using a complete blood count. In recent years, these biomarkers have seen significant clinical and scientific evaluation. It is used as an indicator of staging and prognosis in some types of cancer, as well as an indicator of inflammation¹⁸⁻²¹.

In studies on inflammatory indices and diverticulitis, Reynolds et al. found that NLR was a better guide than CRP, WBC, and neutrophil in determining the need for intervention²². Yaniv et al found that high NLR and PLR were associated with acute diverticulitis recurrence²³.

In our study, we wanted to investigate whether there would be mild inflammation in patients with diverticulosis, even if it was not symptomatic, with inflammatory indices obtained from complete blood count. We also investigated the relationship between the classification of diverticulitis and inflammatory indices. In our study, when we compared the healthy control group with asymptomatic diverticulosis patients, it was found that RDW and MLR were significantly higher in patients with asymptomatic diverticulosis. This result suggests that patients with diverticulosis may have mild inflammation, even if they are not symptomatic. Because monocyte is responsible for late inflammation after neutrophil. It has been reported in other studies that RDW is elevated in inflammatory bowel disease, celiac disease, pulmonary embolism and acute appendicitis^{24,25}. It was observed that WBC, RDW, neutrophil, MCHC, tbil, NLR and SII were significantly increased in terms of the grade of Hinchey classification. This shows us that NLR and SII can give information about the degree of severity

of diverticulitis. No significant difference was observed in MLR. We think that this is due to the fact that monocyte rises in the late phase after neutrophils in inflammation.

CONCLUSION

As a result, we demonstrated the relationship between asymptomatic diverticulosis patients and mild inflammation. In addition, NLR and SII may be decisive about the degree of acute diverticulitis. However, prospective studies with larger numbers of patients are needed.

Conflict of Interest

None declared by the authors.

Ethical Approval

This study was approved by Sakarya University Ethics Committee (05/12/ 2022: 71522473-050.01.04-194704-338)

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Informed Consent

Retrospective study

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Limitations of the Study

This study was conducted in a single center and with a small number of patients.

References

1. Thompson, A. E. Diverticulosis and Diverticulitis. *JAMA* 316, 1124 (2016).
2. Everhart, J. E. & Ruhl, C. E. Burden of digestive diseases in the United States part II: lower gastrointestinal diseases. *Gastroenterology* 136, 741–754 (2009).
3. Tursi, A. Advances in the management of colonic diverticulitis. *CMAJ* 184, 1470–1476 (2012).
4. Walker, M. M. & Harris, A. K. Pathogenesis of diverticulosis and diverticular disease. *Minerva Gastroenterol. Dietol.* 63, 99–109 (2017).
5. Humes, D. J. et al. Visceral hypersensitivity in symptomatic diverticular disease and the role of neuropeptides and low grade inflammation. *Neurogastroenterol. Motil.* 24, 318–e163 (2012).
6. Spiller, R. How inflammation changes neuromuscular function and its relevance to symptoms in diverticular disease. *J. Clin. Gastroenterol.* 40 Suppl 3, S117–20 (2006).
7. Elli, L. et al. Absence of mucosal inflammation in uncomplicated diverticular disease. *Dig. Dis. Sci.* 56, 2098–2103 (2011).
8. Tursi, A. et al. Musosal tumour necrosis factor α in diverticular disease of the colon is overexpressed with disease severity. *Colorectal Dis.* 14, e258–63 (2012).
9. Kelly, M. E. et al. The Utility of Neutrophil-to-Lymphocyte Ratio as a Severity Predictor of Acute Appendicitis, Length of Hospital Stay and Postoperative Complication Rates. *Dig. Surg.* 32, 459–463 (2015).
10. Yamanaka, T. et al. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. *Oncology* 73, 215–220 (2007).
11. Gönüllü, E., Kucuk, F., Bayhan, Z., Harmantepe, A. T. & Capoglu, R. Akut Kolesistite Kolesistektomi veya Kolesistostomi Yapılması Gerekecek Hastaların Ayırt Edilmesinde Biyolojik İndeksler Kullanılabilir mi? *Sakarya Tıp Dergisi* 12, 489–495.
12. Nøst, T. H. et al. Systemic inflammation markers and cancer incidence in the UK Biobank. *Eur. J. Epidemiol.* 36, 841–848 (2021).
13. Tursi, A. et al. Assessment and grading of mucosal inflammation in colonic diverticular disease. *J. Clin. Gastroenterol.* 42, 699–703 (2008).
14. Tursi, A., Papa, A. & Danese, S. Review article: the pathophysiology and medical management of diverticulosis and diverticular disease of the colon. *Aliment. Pharmacol. Ther.* 42, 664–684 (2015).
15. Painter, N. S. & Burkitt, D. P. Diverticular disease of the colon, a 20th century problem. *Clin. Gastroenterol.* 4, 3–21 (1975).
16. Tursi, A. & Elisei, W. Role of Inflammation in the Pathogenesis of Diverticular Disease. *Mediators Inflamm.* 2019, 8328490 (2019).
17. Peery, A. F. et al. Colonic Diverticula Are Not Associated With Mucosal Inflammation or Chronic Gastrointestinal Symptoms. *Clin. Gastroenterol. Hepatol.* 16, 884–891.e1 (2018).
18. Gönüllü, E. et al. andisit Öngörme Başarısı Açısından Nötrofil/Lenfosit, Trombosit/Lenfosit Oranı ile Sistemik İmmün İnflamatuvar İndeksin Karşılaştırılması. *Tek Merkez Deneyimi. Kocaeli Tıp Dergisi* 11, 130–137 (2022).
19. Hajibandeh, S., Hajibandeh, S., Hobbs, N. & Mansour, M. Neutrophil-to-lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: A systematic review and meta-analysis. *Am. J. Surg.* 219, 154–163 (2020).
20. Lee, W. S. & Kim, T.-Y. Is mean platelet volume a new predictor in confirming a diagnosis of acute appendicitis? *Clinical and applied thrombosis/hemostasis: official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis* vol. 17 E125–6 (2011).
21. Absenger, G. et al. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. *Br. J. Cancer* 109, 395–400 (2013).
22. Reynolds, I. S. et al. The Utility of Neutrophil to Lymphocyte Ratio as a Predictor of Intervention in Acute Diverticulitis. *Dig. Surg.* 34, 227–232 (2017).
23. Zager, Y. et al. Associations of novel inflammatory markers with long-term outcomes and recurrence of diverticulitis. *ANZ J. Surg.* 90, 2041–2045 (2020).
24. Hagh, A. R., Pourmohammad, P. & Rabiee, M. A. S. Accuracy of Mean Platelet Volume (MPV) and Red Cell Distribution Width (RDW) for the Diagnosis of Acute Appendicitis: Evaluation of Possible New Biomarkers. *Adv J Emerg Med* 4, e20 (2020).
25. Anand, S. et al. Utility of Red Cell Distribution Width (RDW) as a Noninvasive Biomarker for the Diagnosis of Acute Appendicitis: A Systematic Review and Meta-Analysis of 5222 Cases. *Diagnostics (Basel)* 12, (2022).