ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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THE MODIFIED SYSTEMIC INFLAMMATION SCORE CAN BE USED TO PREDICT THE PRESENCE OF INVASIVE CARCINOMA IN COLORECTAL POLYPS WITH HIGH-GRADE DYSPLASIA

MODİFİYE SİSTEMİK İNFLAMASYON SKORU YÜKSEK DERECE DİSPLAZİLİ KOLOREKTAL POLİPLERDE İNVAZİV KARSİNOM VARLIĞINI ÖNGÖRMEDE KULLANILABİLİR

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Öz

Amaç

Son yıllarda sistemik inflamasyon skor (SIS) ve modifiye sistemik inflamasyon skor (mSIS) gibi skorların kolorektal kanserlerde prognostik ve prediktif değerleri araştırılmıştır. Bu çalışmada, basit labaratuvar testleri ile hesaplanan modifiye sistemik inflamatuar skorun (mSIS) high grade displazili (HGD) kolon poliplerinde invaziv karsinom varlığını öngörmedeki etkinliği araştırıldı.

Gereç ve Yöntem

Ocak 2019 -Ekim 2021 tarihleri arasında preoperatif HGD tanısıyla opere edilen 44 kolorektal polipli hastanın postoperatif verileri retrospektif olarak incelendi. Hastalar postoperatif histopatolojik inceleme sonuçlarına göre HGD, Tis veya adenomatöz polip ve invaziv karsinom olarak iki gruba ayrıldı. mSIS hesaplaması; mSIS 0 [albümin (ALB) ≥ 4.0 g/dL ve lenfosit/monosit oranı (LMR) ≥ 3.4], mSIS 1 (ALB <4.0 g / dL veya LMR <3.4) ve mSIS 2 (ALB <4.0 g / dL ve LMR <3.4) şeklinde yapıldı.

Bulgular

Postoperatif patoloji sonuçları HGD, Tis veya adenomatöz polip olan 17 hastanın 14'ünde (%82,4) mSIS skoru 0 ve 3'ünde ise (%17,6) mSIS skoru 1 veya 2 olarak saptandı. Patoloji sonuçları invaziv karsinom olan 27 hastanın 7'sinin (%25,9) mSIS skoru 0 ve 20'sinin (%75,1) mSIS skoru 1 veya 2 olarak bulundu. Hastaların mSIS skorları ile patoloji sonuçları invaziv karsinom olan hastalar arasında anlamlı ilişki bulundu (p<0,05).

Sonuç

HGD'li hastalarda preoperatif dönemde mSIS skoru hesaplanarak mSIS 1 veya 2 olan hastalarda postoperatif patoloji sonuçlarının invaziv karsinom olabileceği öngörülebilir ve tedavi planını belirlemeye katkısı olabileceği sonucuna varıldı.

Anahtar Kelimeler: Kolorektal konser, Modifiye sistemik inflamtuar skor, inflamatuar belirteçler, high-grade displazi

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Abstract

Objective
In recent years, the prognostic and predictive values of scoring systems such as systemic inflammation score (SIS) and modified systemic inflammation score (mSIS) have been investigated in colorectal cancers. To investigate the efficacy of the modified systemic inflammatory score (mSIS) calculated by simple laboratory tests in predicting the presence of invasive carcinoma in colon polyps with high-grade dysplasia (HGD).

Materials and Methods
The postoperative data of 44 patients with colorectal polyps who underwent surgery with the diagnosis of preoperative HGD between January 2019 and October 2021 were retrospectively analyzed. According to the results of the postoperative histopathological examination, the patients were divided into two groups as HGD/intramucosal carsinom (Tis)/adenomatous polyp and invasive carcinoma. mSIS calculation was made as follows: mSIS 0 [albumin (ALB)≥4.0 g/dL and lymphocyte/monocyte ratio (LMR)≥3.4], mSIS 1 (ALB<4.0 g/dL or LMR<3.4) and mSIS 2 (ALB<4.0 g/dL and LMR< 3.4).

Results
According to the postoperative pathology results, the mSIS score was 0 in 14 (82.4%) of 17 patients with Tis/adenomatous polyps, and 1 or 2 in three patients in this group (17.6%). Among the 27 patients with invasive carcinoma, mSIS was 0 in seven (25.9%) and 1 or 2 in 20 (75.1%). A significant correlation was found between mSIS and the pathology results of the patients with invasive carcinoma ($p<0.05$).

Conclusion
In patients with HGD, by calculating mSIS in the preoperative period, the postoperative pathology results in patients with mSIS 1 or 2 can be predicted to be invasive carcinoma, which can contribute to the determination of the appropriate treatment plan.

Keywords: High-grade Dysplasia, Modified Systemic Inflammation Score, Inflammatory Markers, Colorectal Cancer

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and ranks second in cancer-related deaths [1]. The majority of CRC develops from precancerous polyps [2]. The histology of the polyp, the degree of dysplasia, and the size of the polyp are important in determining its malignant potential [3]. Over time, some polyps increase in size and low or high grade dysplasia (HGD) may occur, eventually leading to the development of invasive cancer [2]. The presence of advanced adenoma (AA) (polyp ≥ 10mm, tubulovillous or villous histology, or presence of HGD) is associated with an increased risk of CRC [4]. It has been reported that in the presence of preoperative HGD or carcinoma in-situ, there is a 35% risk of invasive carcinoma being found in the postoperative histopathological examination [5]. Although the exact duration of the transformation of polyps into cancer has not been fully elucidated, it has been reported that the time from a polyp that starts with an aberrant crypt to the development of invasive cancer is approximately 10-15 years, although this process can be faster in certain cases, such as Lynch syndrome [6-8].

The relationship between cancer and inflammation, first suggested by Rudolf Virchow in 1863, has recently become the focus of attention again, and although its mechanism has not yet been fully understood, it is known that systemic inflammation plays a critical role in cancer pathogenesis and progression [9, 10]. Systemic inflammatory markers have been reported to be clinically useful to distinguish patients at high risk for tumor progression in some common tumor types, including CRC [11]. Scoring systems, such as the modified Glasgow Prognostic Index and Systemic Inflammatory Score (SIS) have been used to predict the prognosis of CRC based on the levels of systemic inflammation markers, including lymphocyte-monocyte (LMR), C-reactive protein (CRP), and albumin (ALB) [10, 12]. Later, the predictive value of SIS modified by Lin et al. (mSIS) in different cancer types has also been investigated [13, 14].

A review of the literature shows no study evaluating the presence of invasive carcinoma in colon polyps with HGD in the preoperative period. In this study, we aimed to investigate the efficacy of mSIS calculated by simple laboratory tests in predicting the presence of invasive cancer in colon polyps with HGD.

Materials and Methods

Patient Data

After obtaining the ethics committee approval for the study (Ankara city hospital, clinical research ethics committee -1 , date: 09.12.2020; number: E1-20-1384), the patients with colorectal polyps diagnosed as HGD based on a histopathological examination between January 2019 and October 2021 in Ankara City Hospital were retrospectively screened and their data were obtained from the electronic records. The demographic, laboratory and clinicopathological data of 44 patients with preoperative HGD, whose complete electronic records were accessed, were analyzed.

The study included patients who underwent resection according to the oncological surgical principles were those with colorectal polyps that were not found suitable for endoscopic resection in the colonoscopic evaluation performed by specialist endoscopists and whose endoscopic biopsy results were HGD according to the histopathological evaluation. Resection materials were examined by expert pathologists. The depth of the invasion of the polyp in the intestinal wall was determined using the American Joint Committee on Cancer (AJCC) staging system version 8. According to the pathological diagnosis based on the postoperative histopathological examination of the excision material, the patients were divided into two groups as Group 1 comprising HGD, carcinoma in situ (Tis), and adenomatous polyps and Group 2 consisting of patients with submucosal (T1) or further invasion. The preoperative hemogram and biochemical parameters of the patients were examined, and mSIS was calculated using the ALB and LMR values. mSIS scoring was performed as follows: mSIS 0 if ALB ≥ 4.0 g/dL and LMR ≥ 3.4, mSIS 1 if ALB < 4.0 g/dL or LMR < 3.4, and mSIS 2 if ALB < 4.0 g/dL [15]. Due to the small sample size in our study, patients with mSIS 1 and mSIS 2 scores were evaluated together. Accordingly, the patients were divided into two groups as mSIS 0 and mSIS 1-2. The statistical relationship between mSIS and postoperative pathological diagnoses was investigated.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences version 26 (IBM SPSS Corp.; Armonk, NY, USA). Numerical data were given as a percentages (%). Mean ± standard deviation values were used to define normally distributed continuous variables, while non-normally distributed data were expressed as median (min-max). The area under the curve (AUC) analysis was performed for mSIS. $P < 0.05$ was considered statistically significant.

Results

Of the 44 patients included in the study, 32 (72.7%) were male and 12 (27.3%) were female. The mean age of the patients was 63 ± 14 years for Group 1 and 63 ± 9 years for Group 2. When the postoperative specimen pathologies of the 44 patients who underwent surgery due to preoperative HGD were examined, it was found that 17 (38.6%) patients were in Group 1 and 27 (61.4%) were in Group 2. According to the results of the histopathological examination, seven (41.2%) patients in Group 1 had Tis and HGD and 10 (58.8%) had adenomatous polyps, while 22 (81.5%) patients in Group 2 had invasive adenocarcinoma and five (18.5%) had mucinous adenocarcinoma. The demographic and clinicopathological characteristics of the patients are summarized in Table 1.

When the TNM stages of the patients in Group 2 were examined, eight (29.6%) were in Stage 1, 13 (48.2%) were in Stage 2, five (18.5%) were in Stage 3, and one was in Stage 4 (3.7%). The mean number of lymph nodes obtained from the resection materials of the patients with HGD that could not be excised by endoscopic methods and required oncological resection was 26 (13-74). As a result of the histopathological examination of patients who underwent surgical resection for HGD, six (22.2%) of the 27 patients in Group 2 were determined to have lymph node involvement. The depth of invasion of the tumor was T_3 in most of the patients with lymph node involvement (Table 3).

According to the pathological results, in Group 1, the preoperative mSIS was 0 in 14 (82.3%) of the 17 patients and 1 or 2 in three (17.8%). In Group 2, seven (25.9%) of the 27 patients had an mSIS of 0 and 20 (74.1%) had an mSIS of 1 or 2. A significant correlation was found between the mSIS of the patients and their pathology results ($p < 0.05$) (Table 2). The sensitivity and specificity of mSIS in predicting the presence of invasive carcinoma in patients with mSIS 1 or 2 were found to be 74% and 82%, respectively. In addition, the probability of invasive carcinoma was increased by 4.2 times among the cases with an mSIS of 1 or 2 (Table 4). In the receiver operating characteristic analysis, AUC was found to be 0.782 (95% confidence interval: 0.628-0.926, $p < 0.05$) (Figure 1).

Table 1 Demographic and clinicopathological characteristics of the patients

Variables	Group 1 (n = 17) (%)	Group 2 (n = 27) (%)
Age (Mean ± SD)	**63 ± 14**	**63 ± 9**
Gender		
Male	13 (76.5)	19 (70.4)
Female	4 (23.5)	8 (29,6)
Preoperative Pathology		
High Grade Dysplasia	17 (38.6)	27 (61,4)
Postoperative Pathology		
Invasive Adenocarcinoma		22 (81.5)
Mucinous Adenocarcinoma		5 (18.5)
Intramucosal Adenocarcinoma (Tis)	1 (5.9)	
High-Grade Dysplasia	6 (35.3)	
Tubular Adenoma	2 (11.8)	
Tubulovillous Adenoma	7 (41.2)	
Villous Adenoma	1 (5.9)	
mSIS		
0	14 (82.4)	7 (25.9)
1 or 2	3 (17.6)	20 (74.1)

Abbreviations: SD, standard deviation; mSIS, modified systemic inflammation score

Table 2 Association between mSIS and final pathology

Characteristics		mSIS 0 (n=21)	mSIS 1 or 2 (n=23)	p
Final Pathology	**Group 1**	14	3	
	Group 2	7	20	<0.05

Abbreviation: mSIS, modified systemic inflammation score

Table 3 TNM stage and LN ivolvement distribution of patients in group 2

Stage	n (27), (%)	LN (+), (%)
Stage 1	8 (29.6)	-
Stage 2	13 (48.2)	-
Stage 3	5 (18.5)	5 (83.3)
Stage 4	1 (3.7)	1(16.7)

Table 4 Efficacy of mSIS in the prediction of invasive carcinoma

mSIS	Sensitivity	Specificity	+LR (%95 CI)	-LR (%95 CI)
>1 or 2	74%	82%	4.2 (1.47-12.01)	0.31 (0.16-0.62)

Abbreviations: LR, likelihood ratio; CI, confidence interval; mSIS, modified systemic inflammation score

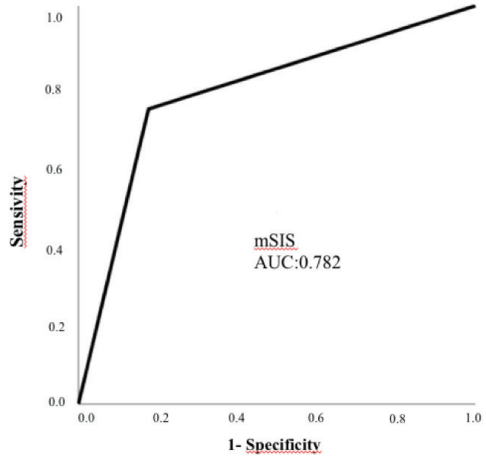

Figure 1
ROC Curve Analysis of mSIS

Variables	AUC	95% CI	p
mSIS 1 or 2	0.782	0.638-0.926	**<0.05**

Abbreviations: AUC, Area Under the Curve;
CI, Confidence Interval"

Discussion

Although there are many studies on the prognostic and predictive values of inflammatory markers, our literature review reveals that the efficacy of mSIS in predicting malignancy in premalignant colon neoplasms has not been investigated to date. In this study, we attempted to predict the presence of invasive carcinoma in the postoperative histopathological examination of patients with colorectal polyps with HGD using a score that can be calculated based on a combination of simple inflammatory markers, namely serum ALB concentration and whole blood measurement, which is both inexpensive and routinely used in clinical practice.

It has been reported that cancer-related inflammation is associated with tumor progression and proliferation in various cancer types [16]. Neutrophil-to-lymphocyte ratio, LMR, serum CRP, and serum ALB levels have been identified as systemic markers of inflammation with prognostic significance for CRC [12]. Low levels of ALB, whose synthesis is decreased in the liver due to systemic inflammation, are associated with continued inflammation and poor prognosis [17]. Low LMR is one of the poor prognostic markers due to the increase in the number of monocytes and the decrease in the number of lymphocytes that play an important role in anticancer immunity [17]. SIS based on LMR and serum ALB levels, which was previously indicated as a strong prognostic marker in clear-cell kidney cancers, was defined as a new prognostic factor by Suzuki et al. in patients with CRC [10]. Later, Lin et al. developed mSIS by modifying SIS with the newly defined LMR cut-off value of ≥3.4 and suggested that unlike SIS, mSIS was an independent prognostic factor in gastric cancer [14]. In a study investigating the predictive value of mSIS in thyroid nodules for which a malignant-benign differentiation could not be made, Ataş et al. reported that the malignancy rates were 100%, 64.7% and 34.3% in the mSIS 2, mSIS 1 and mSIS 0 groups, respectively [13]. In the same study, it was stated that the LMR and ALB values were statistically significantly lower in the malignancy group. In another study investigating the presence of malignancy in persistent thyroid nodules based on mSIS, the malignancy rates were reported as 100, 25.8 and 16.1% in cases with mSIS 2, mSIS 1 and

mSIS 0 scores, respectively [15]. In this study also demonstrated that the malignancy rate was higher at a statistically significant level in the mSIS 2 group compared to the mSIS 0 and mSIS 1 groups.

While the standard method in the treatment of CRC is surgical resection, the role of surgical treatment has decreased compared to the past due to advances in endoscopic excision methods in colorectal adenomas [18]. However, among the cases that cannot undergo colonoscopic polypectomy and are directed to referral centers, only 70% of polyps can be excised [19]. Although endoscopic submucosal dissection (ESD) is now easier to perform, it is still technically more difficult in lower gastrointestinal polyps compared to upper gastrointestinal polyps [20] . Furthermore, it is often difficult to distinguish between benign adenoma and carcinoma using colonoscopy alone [21]. Polyps and dysplastic polyps that cannot be excised by endoscopic methods, such as ESD and endoscopic mucosal resection should be referred to surgery for oncologic resection due to the risk of invasive cancer (32.4-41%) [5, 22, 23].

In CRC, as the depth of invasion of the tumor increases (from T_1 to T_4), the rate of lymph node involvement also increases. In the current study, when the depth of tumor invasion was investigated in the patients with lymph node involvement, all were determined to be in T_3 and T_4 stages. According to the postoperative pathology results of our patients with preoperative HGD, 22.2% that had invasive carcinoma also had lymph node involvement, which strongly support the necessity of performing oncological resection in patients with preoperative mSIS 1 or mSIS 2.

The accurate assessment of the depth of tissue invasion in CRC is crucial for selecting the appropriate management strategy[24]. Tis is defined as intramucosal disease or infiltration of the lamina propria [25]. Tis There is no muscularis mucosal involvement in Tis, intramucosal carcinoma, HGD, and intraepithelial neoplasia, and these lesions are considered not to metastasize [24]. T1 tumor is defined as the tumor's invasion of the submucosa, and the presence of lymphatic invasion in T1 stage has been reported as 10-12% in the literature [24, 26]. In the current study, considering the significance ($p < 0.05$) and efficacy (sensitivity 74% and specificity 82%) of mSIS in predicting cases with invasive carcinoma and the 4.2-fold increased risk of invasive carcinoma in the mSIS 1 or 2 group, we recommend that mSIS should be calculated in patients with polyps that are not suitable for removal by endoscopic methods and those with a diagnosis of HGD based on the biopsy from the polyp, and oncological surgical resection should be performed in cases with mSIS 1 or 2.

The major limitations of this study are its retrospective nature and the small study population. The small sample size also limited the statistical analysis power.

In conclusion, considering that some of the patients undergoing surgery with a preoperative diagnosis of HGD are reported to have invasive carcinoma in the postoperative pathological examination, the preoperative prediction of those with invasive carcinoma based on mSIS calculated with simple parameters can be useful in selecting the appropriate treatment strategy. We recommend performing resection with the oncological surgical principle as the first choice in the surgical treatment of patients with a preoperative mSIS value of 1 or 2.

Conflict of Interest

The authors have no conflicts of interest to declare

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