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The Relationship between Preoperative CA 19-9 and CEA Levels and Histopathology of Tumors in Colorectal Cancer

Kolorektal Kanser Nedeniyle Opere olan Hastalarda Ameliyat Öncesi CA 19-9 ve CEA Düzeyleri ile Tümörün Histopatolojisi Arasındaki İlişki

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Abstract

Aim: Colorectal cancer (CRC) is a common and lethal disease. Since early diagnosis greatly increases the success rate of cancer treatment, the need to investigate cancer determinants in a multifaceted manner is ongoing. The tumor (T), node (N), and metastasis (M) classification of tumors is the most important prognostic indicator in colorectal cancers. In our study, the relationship between preoperative CEA and CA 19-9 values in patients with colorectal cancer and the TNM stage of cancer and its prognostic histopathological features, such as the depth of invasion of the tumor and lymphovascular and perineural invasion, was investigated.

Material and Method: A total of 153 patients diagnosed with colorectal cancer were included in the study. The histopathological data in the resection materials of the patients who were operated on by the General Surgery Department were collected from the pathology reports. Clinical data were collected through the retrospective scanning of patient files. Cases with a CEA value of 5 ng/ml and above and cases with a CA 19-9 value of 35 U/ml and above were considered positive.

Results: The median age of the patients was 64, and 51.6% of the patients were male and 48.4% female. CEA was found to be positive in 35.3% of the patients, while this rate was 20.9% for CA 19-9. In our study, CEA and CA 19-9 positivity were significantly correlated with the TNM stage of the tumor, depth of invasion, lymphovascular invasion, perineural invasion, lymph node metastasis, and distant metastasis. In addition, the mean age of the CA 19-9-positive cases was significantly higher than that of the negative ones. The mean tumor size of the CEA-positive cases was significantly higher than that of the negative ones.

Conclusion: CEA and CA 19-9 are valuable both in demonstrating advanced-stage tumors and in detecting malignancy in tumors at advanced ages. Since survival decreases with stage progression, positive CEA and CA 19-9 values are associated with a worse prognosis.

Keywords: CA 19-9; carcinoembryonic antigen; colorectal neoplasm

Öz

Amaç: Kolorektal kanser yaygın ve ölümcül bir hastalıktır. Erken tanı, kanser tedavisinin başarı yüzdesini büyük oranda arttırdığından kanser belirleyicilerinin çok yönlü olarak araştırılması gereksinimi sürmektedir. Kolorektal kanserlerde tümörün Tümör (T), Lenf Nodu (N), Metastaz (M) sınıflaması en önemli prognostik göstergedir. Çalışmamızda kolorektal kanserli hastalardaki preoperatif CEA ve CA 19-9 değerleri ile kanserin TNM evresi, tümörün invazyon derinliği, lenfovasküler ve perinöral invazyon gibi prognostik histopatolojik özellikleri arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: Çalışmaya kolorektal kanser tanısı alan 153 hasta dahil edildi. Genel Cerrahi Anabilim Dalı tarafından opere edilen hastaların rezeksiyon materyallerinde yer alan histopatolojik veriler patoloji raporlarından elde edildi. Klinik veriler, hasta dosyalarının geriye dönük taranmasıyla toplandı. CEA değeri 5 ng/ml ve üzerinde olan olgular ile CA 19-9 değeri 35 U/ml ve üzerinde olan olgular pozitif kabul edildi.

Bulgular: Hastaların yaş ortancası 64 olup, %51,6'sı erkek ve %48,4'ü kadındır. Hastaların %35,3 ünde CEA pozitif olarak saptanırken bu oran CA 19-9 için %20,9'dur. Çalışmamızda CEA ve CA 19-9 pozitifliği ile tümörün TNM Evresi, invazyon derinliği, lenfovasküler invazyon, perinöral invazyon, nodal tutulum, metastaz istatistiksel olarak anlamlı düzeyde ilişkilidir. Ayrıca CA 19-9 pozitif olguların yaş ortalaması, negatif olanlara kıyasla anlamlı derecede yüksektir. CEA pozitif olguların tümör boyutu ortalaması, negatif olanlara göre anlamlı derecede yüksektir.

Sonuç: CEA ve CA 19-9, hem ileri evre tümörü göstermede hem de ileri yaşlarda saptanan tümörlerde malignite saptanmasında değerlidir. Evre ilerledikçe sağ kalım düştüğünden pozitif CEA ve CA 19-9 değerleri her ikisi birden daha kötü prognoz ile ilişkilidir.

Anahtar Kelimeler: CA 19-9; karsinoembriyonik antijen; kolorektal kanser

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INTRODUCTION

Colorectal cancer (CRC) is a serious disease that can result in death. It is the third most common cancer in Turkey. In 2020, CRC accounted for 21,191 (9%) of 233,834 cancer cases in Turkey. Moreover, it ranks second among deaths caused by cancer. CRC caused approximately 935,000 deaths in 2020, with 1.9 million newly diagnosed patients.[1] CRC can be prevented if detected in the precancerous stage and treated if diagnosed early. Early detection of cancer or adenoma development, i.e., in the asymptomatic period, using tumor markers and screening methods significantly reduces mortality and morbidity.[2,3]

Carcinomas are malignant tumors originating from epithelial tissue and are referred to as adenocarcinomas when they form a gland structure.[4] More than 95% of CRCs are of the adenocarcinoma type and are graded according to the appearance and differentiation of the glandular structures.[5] According to this distinction, there are 3 degrees of differentiation – well differentiated (Grade-I), moderately differentiated (Grade-II), and poorly differentiated (Grade-III).

CRC staging is important in determining both the prognosis and the method of treatment.[6] It is based on the depth of the tumor and whether there are lymph nodes or distant organ metastases. The Dukes classification and its modification by Astler–Coller have been replaced by the TNM staging system.[7] The processes of staging and prognosis for patients with CRCs are shown in **Figure 1**.[8]

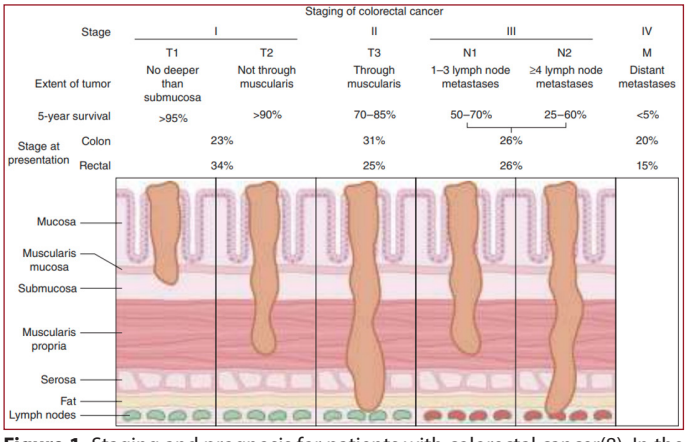

Figure 1. Staging and prognosis for patients with colorectal cancer(8). In the figure, non-metastasized lymph nodes are shown in green and metastatic lymph nodes are shown in red.

Additionally, tumor markers are substances produced by tumor tissue that can be used to distinguish a tumor from normal tissues. They can be measured by various methods to detect the presence of cancer.[9] Tumor markers, which generally represent the re-formation of substances, are produced by tissues that are embryologically closely related.[10] Markers can be used to determine the success of initial treatment (e.g., surgery, chemotherapy, or radiation) to monitor treatment, detect cancer recurrence, and determine the type of treatment. Although there have been significant advances in cancer treatment in recent years, approximately half of malignant diseases are at a stage where curative treatment is not possible when clinical symptoms appear. Therefore, tumor markers are becoming increasingly important as they help in early diagnosis.[11]

In some cases, tumor markers can provide very useful information at the diagnostic stage, in monitoring the efficacy of treatment after diagnosis, and in the post-op follow-up of patients. In our study on tumor markers, we aimed to investigate the predictive value of CEA and CA 19-9 tumor markers by comparing preoperative CEA and CA 19-9 values with histopathological prognostic features and the TNM stage of the tumor in patients operated on for colorectal cancer.

MATERIAL AND METHOD

This is a retrospective cross-sectional study in which the relationship between preoperative tumor markers CEA and CA 19-9 levels and the clinical and histopathological data of patients operated on for CRC were examined. The population of the study was 153 patients, all of whom were diagnosed with colorectal carcinoma in the Training and Research Hospital Medical Pathology Laboratory between 1 January 2014 and 1 February 2018 and operated at the General Surgery clinic. Patients over 18 years of age with post-op pathology reports and preoperative tumor markers in their files were included, and those for whom the required data were not fully met were excluded. Histopathologic data of the resection material, such as histological grade, depth of invasion, lymphovascular invasion, and perineural invasion, were obtained from the pathology reports. In addition, clinical data were collected through a retrospective review of patient files. In terms of tumor location, the colon was categorized into three groups – the right colon, the left colon, and the rectum. The cecum, ascending colon, and right half of the transverse colon were grouped into the right colon, and the left half of the transverse colon, descending colon, and sigmoid colon were grouped into the left colon. The cases with CEA values of 5 ng/ml and above and CA 19-9 values of 35 U/ml and above were considered positive. The necessary ethical approval was obtained by the Clinical Research Ethics Committee (Date: 24 January 2018 / Decision number 130).

Statistical Analysis

The IBM SPSS Statistics 22 package program was used for the statistical analyses while evaluating the findings obtained in the study. While evaluating the study data, the Shapiro–Wilk test was used to check the normal distribution. In addition, descriptive statistical methods are shown as mean, standard deviation, and frequency. A P value < 0.05 was considered significant.

RESULTS

Our study was conducted on a total of 153 patients, 74 (48.4%) females and 79 (51.6%) males. The median age was 64 (range: 39–89). The tumor was located in the rectum in 34% of

the cases, on the right side in 22.9% cases, and on the left side in 43.1% cases.

In 84.3% cases, the tumor was Grade 2, in 10.5%, Grade 1, and in 5.2%, Grade 3. While the depth of tumor invasion was T1 in only 6.5% of cases, it was T2 in 15%, T3 in 39.2%, and T4 in 39.2%. There was lymphovascular invasion in 53.6% cases and perineural invasion in 26.1% cases. Lymph node invasion was N0 in 58.8% cases, N1 in 28.1% cases, and N2 in 13.1% cases. Moreover, 9.8% cases had metastases, 35.3% cases were CEA positive, and 20.9% cases were CA 19-9 positive.

The mean ages of CEA-positive and CA 19-9-positive cases were statistically significantly higher than those of the negative cases (**Table 1**). The mean tumor size of CEA-positive cases was statistically significantly higher than that of negative cases (p: 0.022; $p < 0.05$). There was no statistically significant difference between the mean tumor sizes of positive or negative CA 19-9 cases (**Table 2**).

Table 1. Age assessment according to CEA and CA 19-9 positivity

	Age Mean±SD	p
CEA		0.033*
Positive	66.65±10.60	
Negative	62.55±11.60	
CA 19-9		0.010*
Positive	68.56±10.60	
Negative	62.79±11.33	

Student t test; Data were presented as mean±SD.; CEA: Carcinoembriogenic antigen; CA 19-9: Carbohydrate antigen 19-9; SD: Standart Deviation. CEA value of 5ng/ml and above was considered positive. CA 19-9 value of 35U/ml and above was considered positive.

Table 2. Tumor size assessment according to CEA and CA 19-9 positivity

	Tumor Size Mean±SD	p
CEA		0.022*
Positive	5.47±2.56	
Negative	4.56±2.22	
CA-19-9		0.137
Positive	5.44±2.66	
Negative	4.73±2.29	

Student t test; Data were presented as mean±SD.; CEA: Carcinoembriogenic antigen; CA 19-9: Carbohydrate antigen 19-9; SD: Standart Deviation. CEA value of 5ng/ml and above was considered positive. CA 19-9 value of 35U/ml and above was considered positive.

There was no statistically significant difference between the rates of CEA positivity according to tumor location. CEA was positive in 40.4% of rectal patients, 4.3% of right-sided patients, and 31.8% of left-sided patients. CEA positivity was observed in 37.5% Grade 1 cases, 34.1% Grade 2 cases, and 50% Grade 3 cases. There was no statistically significant difference between them. However, there was a statistically significant difference between the rates of CEA positivity according to the depth of tumor invasion (p: 0.000; $p < 0.05$). The rate of CEA positivity in T4 patients (61.7%) was significantly higher than in T1 (0%), T2 (13%), and T3 (23.3%) patients.

The rate of CEA positivity in patients with lymphovascular invasion (47.6%) was statistically significantly higher than in patients without lymphovascular invasion (21.1%) (p: 0.001; $p < 0.05$). Additionally, the rate of CEA positivity in cases with perineural invasion (52.5%) was statistically significantly higher than in cases without perineural invasion (29.2%) (p: 0.014; $p < 0.05$).

There was also a statistically significant difference between the rates of CEA positivity according to lymph node invasion (p: 0.000; $p < 0.05$). The rate of CEA positivity was 21.1% in N0 patients, 48.8% in N1 patients, and 70% in N2 patients, and it was observed that CEA positivity increased with every level.

The CEA positivity rate in patients with metastases (100%) was statistically significantly higher than that in patients without metastases (28.5%) (p: 0.000; $p < 0.05$). CEA positivity was observed in 39.2% of the women and 31.6% of the men, and there was no statistically significant difference between them (**Table 3**).

Table 3. CEA assessments by research parameters

		CEA Positive n (%)	CEA Negative n (%)	p
Tumor Location	Rectum	21 (40.4%)	31 (59.6%)	[1]0.620
	Right	12 (34.3%)	23 (65.7%)	
	Left	21 (31.8%)	45 (68.2%)	
Histological grade				[1]0.647
	Grade 1	6 (37.5%)	10 (62.5%)	
	Grade 2	44 (34.1%)	85 (65.9%)	
	Grade 3	4 (50%)	4 (50%)	
Depth of invasion				[1]0.000*
	T1	0 (0%)	10 (100%)	
	T2	3 (13%)	20 (87%)	
	T3	14 (23.3%)	46 (76.7%)	
	T4	37 (61.7%)	23 (38.3%)	
TNM stage				[1]0.000*
	Stage I	2(8%)	23(92%)	
	Stage II	14(27%)	47(73%)	
	Stage III	22(47%)	25(53%)	
	Stage IV	16(84%)	3(16%)	
Lymphovascular invasion				[2]0.001*
	Negative	15 (21.1%)	56 (78.9%)	
	Positive	39 (47.6%)	43 (52.4%)	
Perineural invasion				[2]0.014*
	Negative	33 (29.2%)	80 (70.8%)	
	Positive	21 (52.5%)	19 (47.5%)	
Lymph nodes				[1]0.000*
	N0	19 (21.1%)	71 (78.9%)	
	N1 (1-3 LN +)	21 (48.8%)	22 (51.2%)	
	N2 (4 and above +)	14 (70%)	6 (30%)	
Metastases				[2]0.000*
	Negative	39 (28.5%)	98 (71.5%)	
	Positive	15 (100%)	0 (0%)	
Gender				
	Female	29 (39.2%)	45 (60.8%)	[1]0.329
	Male	25 (31.6%)	54 (68.4%)	

1Chi-Squared Test, 2Continuity (yates) correction; T: Tumor; TNM: Tumor-LymphNode-Metastasis; CEA: Carcinoembriogenic antigen; CEA value of 5ng/ml and above was considered positive.

However, there was a statistically significant difference between the rates of CA 19-9 positivity according to tumor location (p: 0.037; p < 0.05). CA 19-9 was positive in 11.5% rectal patients, 17.1% right-sided patients, and 30.3% left-sided patients. The rate of CA 19-9 positivity was significantly higher on the left side.

CA 19-9 positivity was observed in 18.8% of Grade 1 cases, 20.2% of Grade 2 cases, and 37.5% of Grade 3 cases, and there was no statistically significant difference between them. However, there was a statistically significant difference between the rates of CA 19-9 positivity according to the depth of tumor invasion (p: 0.002; p < 0.05). The rate of CA 19-9 positivity in T4 patients (36.7%) was significantly higher than in T1 (10%), T2 (4.3%), and T3 (13.3%) patients.

The rate of CA 19-9 positivity in patients with lymphovascular invasion (32.9%) was statistically significantly higher than in patients without lymphovascular invasion (7%) (p: 0.000; p < 0.05), and the rate of CA 19-9 positivity in cases with perineural invasion (40%) was statistically significantly higher than in cases without perineural invasion (14.2%) (p: 0.001; p < 0.05).

There was also a statistically significant difference between the rates of CA 19-9 positivity according to lymph node invasion (p: 0.000; p < 0.05). The rate of CA 19-9 positivity was 13.3% in those with N0, 20.9% in those with N1, and 55% in those with N2. It was observed that CA 19-9 positivity increased as the level increased.

The rate of CA 19-9 positivity in patients with metastases (80%) was statistically significantly higher than in patients without metastases (14.6%) (p: 0.000; p < 0.05). CA 19-9 positivity was observed in 21.5% of the women and 20.3% of the men, and there was no statistically significant difference between them (**Table 4**).

Table 4. CA 19-9 assessments by research parameters

	CA 19-9 Positive	CA 19-9 Negative	p
	n (%)	n (%)	
Location			[1]0.037*
Rectum	6 (11.5%)	46 (88.5%)	
Right	6 (17.1%)	29 (82.9%)	
Left	20 (30.3%)	46 (69.7%)	
Histological grade			[2]0.528
Grade 1	3 (18.8%)	13 (81.3%)	
Grade 2	26 (20.2%)	103 (79.8%)	
Grade 3	3 (37.5%)	5 (62.5%)	
Depth of invasion			[2]0.002*
T1	1 (10%)	9 (90%)	
T2	1 (4.3%)	22 (95.7%)	
T3	8 (13.3%)	52 (86.7%)	
T4	22 (36.7%)	38 (63.3%)	
TNM stage			[2]0.000*
Stage I	2(8%)	23(92%)	
Stage II	8(13%)	54(87%)	
Stage III	10(21.3%)	37(78.7%)	
Stage IV	32(63.2%)	7(36.8%)	
Lymphovascularinvasion			[3]0.000*
Negative	5 (7%)	66 (93%)	
Positive	27 (32.9%)	55 (67.1%)	
Perineural invasion			[3]0.001*
Negative	16 (14.2%)	97 (85.8%)	
Positive	16 (40%)	24 (60%)	
Lymph nodes			[1]0.000*
N0	12 (13.3%)	78 (86.7%)	
N1 (1-3 LN +)	9 (20.9%)	34 (79.1%)	
N2 (4 and above +)	11 (55%)	9 (45%)	
Metastases			[3]0.000*
Negative	20 (14.6%)	117 (85.4%)	
Positive	12 (80%)	3 (20%)	
Gender			[3]1.000
Female	15 (20.3%)	59 (79.7%)	
Male	17 (21.5%)	62 (78.5%)	

1Chi-Squared Test, 2 Fisher Freeman Halton Test, 3Continuity (yates) correction; T: Tumor; TNM: Tumor-LymphNode-Metastasis; CEA: Carcinoembriogenic antigen; CA 19-9: Carbohydrate antigen 19-9. CA 19-9 value of 35U/ml and above was considered positive.

DISCUSSION

Tumor markers are used to estimate prognosis, diagnoses and stage, classify the cancer, select an appropriate treatment, detect cancer residual disease, and assess the treatment process. Since tumor markers can be used to predict the response of a tumor to treatment and for prognosis, researchers believe that they might also be useful in screening tests that aim to detect cancer early before there are any symptoms. However, studies to determine whether circulating tumor markers can be used to screen for cancer have generally found that these markers are neither sensitive nor specific enough. When a test has low specificity, people must undergo further testing to determine whether cancer is present. Some screening tests based on tumor markers have been shown to lead to overdiagnosis, which happens when people are diagnosed with cancers that would never have affected them during their lifetimes.[12]

The median age of the 153 patients included in the present study was 64 years. The average age of diagnosis for CRC is 67 years, and it has been observed that patients are diagnosed and operated on at an earlier age in our country.

In a prospective study conducted with 333 patients by Yu et al., CEA positivity was found to be 33.6% and CA 19-9 positivity 18.3% in patients with CRC, and this rate was 35.3% for CEA and 20.9% for CA 19-9 in our study, which is compatible with the literature.[13]

In 1999, the American College of Pathologists' consensus statement reported preoperative CEA elevation as a Category 1 prognostic factor. For Category 1 factors, it has been stated that "It has been conclusively proven to have prognostic significance based on statistically robust evidence from multiple publications and is generally used in patient

management.".[14] However, at the time, preoperative CEA was the only Category 1 factor not included in the current American Joint Committee on Cancer (AJCC) staging system.[15] Later, according to the European Group on Tumor Markers (EGTM) guidelines, preoperative CEA was accepted as an independent prognostic indicator.[16] Other reports have suggested that advanced tumors are significantly associated with higher preoperative and postoperative CEA levels.

In our study, when the stages were compared with patients with positive CA 19-9 and CEA levels, it was observed that an increase in CA 19-9 was correlated with advanced stages, and this was statistically significant. In a study by Zheng et al.[17] investigating the prognostic value of CEA, CA 19-9, and CA 72-4 in patients with CRC, the Dukes stages of the patients and tumor marker values were examined, and it was found that the values of all three tumor markers increased statistically significantly in advanced stages. Yang et al.[18] also compared preoperative CEA and CA 19-9 values with tumor stages in a case–control study with CRC patients and found that tumor marker values increased when correlated with stage. Moreover, in Zheng et al.[17] case–control study, a significant correlation was found between CEA and CA 19-9 levels, depth of invasion, and number of positive lymph nodes. In our study, the rate of CA 19-9 positivity in T4 patients (36.7%) was significantly higher than in T1, T2, and T3 patients. The rate of CEA positivity according to the depth of tumor invasion was significantly higher in T4 patients (61.7%) than in T1, T2, and T3 patients. In addition, a significant association was found with lymphovascular and perineural invasion. In the same study, no statistically significant correlation was found between histologic grade, age, and gender. In a study by Tumay et al.[19] in which 315 CRC patients were followed up for 13 years after treatment, elevated CEA levels were found to be associated with advanced stage, depth of invasion, lymph node involvement, and tumor size, similar to our study.

Some studies have reported that CEA is informative in determining the prognosis of the disease independent of the cancer stage.[20-22] However, it has been reported that it can be used to determine the prognosis in Stage 2. Some studies have reported that CEA should be evaluated together with histopathologic parameters in newly diagnosed cases in order to determine which patients should receive adjuvant chemotherapy.[16,23,24] In our current study, we compared CEA and CA 19-9 levels with histopathologic features of the tumor and obtained similar results with depth of invasion, liver metastasis, and histologic type, similar to Sato et al.[25]

The presence of metastases is classified as Stage 4 in the TNM staging of CRC. In our study, the rate of CA 19-9 positivity in patients with metastasis (80%) was statistically significantly higher than that in patients without metastasis (14.6%), and the rate of CEA positivity in patients with metastasis (100%) was statistically significantly higher than that in patients without metastasis (28.5%), which is consistent with the literature.[13,25]

CONCLUSION

The following points summarize our findings and conclusions:

- The median age at diagnosis for CRC was 64 years. In Turkey, it is important to start screening programs from the age of 50 for those who do not have a first-degree relative with CRC in terms of early diagnosis of the disease.
- CEA and CA19-9 positivity is not statistically significant with gender and the histological grade of the tumor.
- CEA and CA 19-9 positivity rates increase as the depth of tumor invasion increases.
- In tumors with metastasis, lymphovascular and perineural invasion, and progression of lymph node involvement, the levels and positivity rates of the markers increase.
- Elevated CA 19-9 may be a predictor, especially for left-sided tumors.
- Tumor markers are significantly higher in older patients, suggesting that older patients are more important for screening than younger patients.

In light of this information, CEA and CA 19-9 are still valuable biomarkers in predicting advanced-stage tumors in our country. CRC is a deadly disease that must be screened in line with the recommendations of our Ministry of Health due to the financial and labor losses it causes. Our physicians should also refer patients with symptoms suggestive of CRC, such as rectal bleeding, changes in bowel habits, unexplained anemia, and a positive fecal occult blood test, especially those over the age of 50, to the relevant specialist for endoscopic imaging of the gastrointestinal tract. The retrospective nature of our study poses a problem in terms of sample size. We believe that multicenter, prospective, and larger patient-based studies regarding the prognostic importance of tumor markers in colorectal cancer are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpasa Taksim Training and Research Hospital Clinical Researches Ethics Committee (Date: 24.01.2018, Decision No: 130).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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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