I

Colorectal cancer is the second most common type of cancer in women and the third one in men. In terms of worldwide prevalence, it ranks third [1].   e prognosis of colorectal cancer is dependent on the stages in the TNM system.   e development of tumors and metastases depend on a delicate balance between endogenous angiogenic factors, which cause the formation of new blood vessels, and anti-angiogenic factors [2].   e process of angiogenesis consists of a multitude of sequential and interconnected steps including positive and negative regulators [3]. Today, it is known that angiogenesis is not only essential for tumor growth but also is responsible for the cancerous transformation of a premalignant tumor, circulation of cancer cells, and the transformation of micro-metastases into typical metastatic lesions [4]. Without doubt, the vascular endothelial growth factor (VEGF) is the most important molecule that plays a role in the angiogenetic process [5,6]. VEGF does not only induce the proliferation of endothelial cells but also increases the vascular permeability and causes the formation of a   brin matrix that enables stromal cell invasion by increasing the extravasation of proteins through tumor vessels [7].   e data provided by preclinical and clinical studies indicate that VEGF is the predominant angiogenic factor in colorectal cancer [8]. A positive correlation was detected between increased VEGF levels and lymph node involvement, and distant organ metastasis [9].

beginning (basal). Body composition [total body water (TBW), fat-free mass (FFM), fat mass (FM), percent body fat] was measured by bioelectrical impedance analysis using TANITA BC-420MA scale. One nurse performed the measurements for all patients.

A   EGF

Two tubes of ethylenediamine tetra-acetic acid (EDTA) venous blood were extracted from the patients a er 8-12 hours of fasting, in the morning (08:00-09:00 AM), before chemotherapy [15]. A er half an hours rest, the blood samples were centrifuged at 2000 g for a period of 10 minutes. Separated serum samples were portioned into closed Eppendorf tubes and saved at -20°C throughout the study of tests. Serum VEGF and Endocan levels were determined with enzyme-linked immunosorbent assay (ELISA) kits used for scienti c research purposes.

A er the serums were solved at room temperature, the deposits of protein molecules were mixed with a vortex and the sample was homogenized [16].   e patient serums were studied following the procedures speci ed in ELISA kits. A er the study procedures, the microplate was checked at 450nm wave-length at the ELISA reader to calculate concentrations.

e SPSS 21.0 Inc (IL, USA) was used for the statistical analyses of the research ndings. Descriptive analyses were presented using mean and standard error (S.E.M.) for variables. Due to the non-normal distribution of variables, non-parametric tests were conducted to compare those parameters.   e Mann-Whitney U-test was used to compare the parameters between control and patient groups. In independent groups, distribution and variance analyses were performed when it included more than two groups. We used the one-way ANOVA test for groups with normal distribution and variance and used Kruskal-Wallis test for groups without normal distribution.

e correlation of Endocan, VEGF and overall survival rates with other variables was analyzed with Pearson's correlation test. A p-value o less than 0.05 were taken to indicate statistical signi cance.

Twenty-six of the patients had rectal cancer, and 41 of them were diagnosed with colon cancer. Regarding the stage at diagnosis, 1 patient was Stage-1, 12 were Stage-II, and 25 were Stage-III.   e patient group's mean age was 60.6, which was 52.8 for the control group.   e mean weight of the former was 69.2 kg and BMI was 25.4, which were 76.1 kg and 26.1 for the latter.   e patients' demographic characteristics are given in Table 1.

In the follow-up period, 43 patients presented metastasis at the onset or during the follow-up, while 24 patients presented no metastasis or progression (tumor-free patient group). Endocan and VEGF levels of metastatic patients were 10.43 ± 2.59pg/mL and 304.2 ± 314.07pg/ml respectively. No signi cant di erence was nd between the patient and control groups in terms of height, weight, age or BMI levels.   e examinations showed no signi cant di erence between the groups except the VEGF level. A comparison of two groups with respect to VEGF levels revealed a signi cant di erence (p: 0.040). No signi cant di erence was observed between the groups in terms of Endocan levels. Table 2 presents the serum VEGF, Endocan levels, body composition and anthropometric measurements of patients and the control group.

e correlations of VEGF, Endocan and overall survival rates were observed in the patient group.   e correlation analysis presented no

Characteristics	Patient Group (n:67) n%
Œ*^ÁÇ{^æ}ÅʉÙÖD	Î€ĖÍ ÏÁʉÁFHĖFI
P^à*@cÁÇ{^æ}ÅʉÙÖDÁ&{	FÎ ÍĖHFÁʉÁF€ĖÏ
Y^à*@cÁÇ{^æ}ÅʉÙÖDÁ*	Î JĖGFÁʉÁFIĖJ
ÓTQ	
Ù^¢	
Tæ|^	I ÍÁÇÎ Ï ÃD
Ø^{æ|^	GGÁÇHH ÃD
Ü^&c˘{ÐÔ[I[}	
Ü^&c˘{	GÎÁÇHJ ÃD
Ô[I[}	IFÁÇÎ F ÃD
Üæ•ÅT˘cæcä[}ÁÇHGÁ]æcä^}c•D	
Úæ}¡æ•ÅYä|å	GÁÇÎ ÃD
Yä|å	FÍÁÇI Ï ÃD
T˘cæ}c	FÍÁÇI Ï ÃD
Ùcæ*^ÅæcÁÖäæ*}[•ä•ÁÇÙŒVD	
Q	FÁÇF ÃD
QQ	FGÁÇF Ì ÃD
QQQ	GÍÁÇHÌ ÃD
QX	GJÁÇI H ÃD
Þ^[ÉŒäb˘çæ}cÔV	FIÁÇFJ ÃD
Œäb˘çæ}cÔV	HÏÁÇÍ Í ÃD
F•ùÅŠä}^ÔV	I€ÁÇÎ€ ÃD
GàùÅŠä}^ÔV	FÎÁÇGH ÃD
Ü^&^}cÁÔ[}äácä[}	
Œ|äç^	I€ÁÇI€ ÃD
Ò¢äc˘•	GÏÁÇI€ ÃD

Table 1: ÁÖ^{[*¦æ]@ä&Å&@æ¦æ&c^¦ä•cä&•Å[¬Å]æcä^}c•Á¸äc@Å&[|[¦^&cæ|Å&æ}&^¦È

signi cant di erence. Although a negative correlation was detected between VEGF levels and overall survival, it was not signi cant (Table 3).

Table 4 presents a comparison of parameters between groups in order to examine intergroup di erences of VEGF levels. No signi cant di erence was found between the control group and tumor-free colorectal cancer group in terms of VEGF levels. However, VEGF levels in metastatic colorectal cancer cases were signi cantly higher than that of the tumor-free colorectal cancer cases (p: 0.005, p:0.038, respectively).

D

In this study, we found no signi cant di erence in terms of Endocan levels between the groups. Moreover, there was no correlation between Endocan levels and VEGF levels.

Endocan is a proteoglycan that plays a role in many pathophysiological processes such as in ammatory diseases, adhesion,

angiogenesis and tumor progression. However, Endocan is reported to be expressed at lower rates in colorectal cancers [12,13,17].

A study conducted by vant Weer et al. on 78 patients with breast cancers shows that Endocan expression is associated with reduced 5 years survival and increased risk of metastasis [18]. Likewise, previous studies demonstrated that increased tissue-level expression of Endocan levels was associated with poor prognosis and metastasis in breast cancer, renal-cell carcinoma and lung cancer [18,19].

Zou et al. showed that Endocan expression was higher in healthy subjects and well- and moderately-di erentiated colorectal cancer cells, whereas it was low in poor-di erentiated colorectal cancer [20]. In another study by Jiang et al., Endocan expression was detected signi cantly higher in patients with colorectal cancer than healthy subjects. e same study also demonstrated a correlation between increased tumor stage, lymph node positivity, increased histological tumor grade, and Endocan levels [21].

Although high Endocan levels are associated with poor prognosis in many other types of cancer, it was examined at the tissue level and no positive correlation was observed with stage, unlike other cancers [22].

VEGF is a lymphangiogenic marker that is typically expressed by cancer cells to a high degree than normal cells. In a study conducted on 121 patients, Cascinu et al. showed that VEGF expression was higher in metastatic patients than non-metastatic patients. e tissue-level VEGF expression was evaluated in patients with Stage-II colorectal cancer; 5 years disease-free survival was 90% in patients without VEGF expression than those with VEGF expression, which remained at 50% for the latter group. erefore, it is suggested that high VEGF levels may be associated with advanced stage and worse prognosis [22]. In a meta-analysis by Des Guets et al. that included 27 studies examining the relationship between VEGF and colorectal cancer, high VEGF expression was observed to have a marked correlation with reduced overall survival [23]. If one generally considers the ndings reported by other studies, colorectal cancer cells seem to be directly or indirectly related to the high expression of neovascularization-associated molecules.

C

In this study we found pre-treatment serum VEGF levels in the

metastatic patient group signi cantly higher than both the tumor-free patient group and the control group. A comparison of tumor-free colorectal cancer cases with the control group showed no signi cant di erence in terms of VEGF levels. ese ndings support the idea that high VEGF levels could be associated with poor prognosis. An assessment for a cut-o value to indicate poor prognosis revealed no threshold VEGF level to anticipate prognosis. In the present study, although a negative correlation was observed between VEGF levels and overall survival, the di erence was not signi cant.

 e limitations of the present study include a small sample size and short follow-up period. Only 27 patients passed away throughout the period of study, which could account for the non-signi cance of overall survival ndings. ere is a limited number of studies on Endocan levels in colorectal cancer, and the ndings are contradictory when compared with the ndings reported by previous studies investigating other types of cancer. is study is the most current study on Endocan levels in colorectal cancer. In conclusion, this study showed that there was no signi cant relationship between pretreatment Endocan levels with prognosis and VEGF levels. Further studies with larger samples are required to clarify this issue.

References

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