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Original Article / Özgün Araştırma

Analysis of Prognostic Factors Affecting Postoperative Survival in Stage III Gastric Cancer Patients

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Abstract

Objective: In stage III gastric cancer patients who underwent resection, prognostic factors related to patient, tumor and treatment and their survival effects were investigated.

Method: One-hundred sixty three patients were included in the study and data was obtained retrospectively from hospital records. Investigated parameters; patient-related factors (age,gender,blood group,preoperative hemoglobin,albumin and serum tumor marker (carcinoembryonic antigen(CEA), cancer antigen 19-9(CA 19-9) levels), tumor related factors (tumor localization, tumor size , T and N stage, total lymph node count, metastatic/total lymph node ratio, surgical margin of tumor, pathology, differentiation, lymphovascular and perineural invasion status) and treatment-related factors (adjuvant treatment, nutritional support, and blood transfusion).

Results: Fifty-one out of the 163 patients were female, and the median age was 60. In univariate analysis, serum Ca19-9 level (p=0,03), serum CEA level(p=0.01) and the lymph node ratio(p=0.002) were found to be an independent factors associated with overall survival whereas only lymph node ratio was an effective parameter in multivariate analysis[(p = 0.004, relative risk =0.50, 95% confidence interval (0.32-0.80)]. When the study was finalized, patients were followed for a median of 16 months, 87 patients (53.4%) died due to the disease.

Conclusion: The metastatic tumor load in the lymph nodes around the stomach was negatively effective on survival. This result demonstrates the importance of lymphatic dissection.

Keywords:Gastric cancer,prognostic factors,survival

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Evre III Gastrik Kanserli Hastalarda Postoperatif Sağkalımı Etkileyen Prognostik Faktörlerin Analizi

Öz

Amaç: Evre III mide kanserli hastalarda hastaya, tümöre ve tedaviye ilişkin prognostik faktörler ve bunların sağkalıma etkileri araştırıldı.

Yöntemler: Yüz altmış üç hasta çalışmaya dahil edildi ve veriler geriye dönük olarak hastane kayıtlarından elde edildi. İncelenen parametreler; hastaya bağlı faktörler (yaş, cinsiyet, kan grubu, preoperatif hemoglobin, albumin ve serum tümör marker (karsinoembriyonik antijen (CEA), kanser antijeni 19-9 (CA 19-9) seviyeleri), tümör ilişkili faktörler (tümör lokalizasyonu, tümör boyutu) , T ve N evresi, total lenf nodu sayısı, metastatik / total lenf nodu oranı, tümörün cerrahi sınırı, patoloji, farklılaşma, lenfovasküler ve perinöral invazyon durumu) ve tedaviye bağlı faktörler (adjuvan tedavi, beslenme desteği ve kan transfüzyonu).

Bulgular: 163 hastanın 52'si kadın, ortanca yaş 60 idi. Tek değişkenli analizlerde serum Ca 19-9 düzeyi (p = 0,03), serum CEA düzeyi (p = 0.01) ve lenf nodu oranı (p = 0.002) genel sağkalım ile ilişkili bağımsız bir faktör olarak bulunurken, sadece lenf nodu oranı çok değişkenli analizde etkili bir parametre idi [(p = 0.004, göreceli risk = 0.50,% 95 güven aralığı (0.32-0.80)]. Çalışma sonlandırıldığında, hastalar ortanca 16 ay boyunca takip edildi, 87 hasta (%53,4) hastalık nedeniyle öldü.

Sonuç: Mide etrafındaki lenf nodlarındaki metastatik tümör yükü sağkalım üzerinde olumsuz yönde etkili olmuştur. Bu sonuç lenfatik diseksiyonun önemini göstermektedir.

Anahtar kelimeler: Mide kanseri, mide kanserinde prognoz, prognostik faktörler.

INTRODUCTION

Gastric cancer remains one of the most common forms of cancer worldwide. Similarly in Turkey, it occupies the third order in women, the second in men, and the third in cancer-related causes of death[1,2]. According to the World Health Organization (WHO), about 1 million new stomach carcinomas are diagnosed per year and 70% of these new cases are reported from developing countries[3]. The treatment of non-metastatic gastric cancers is curative surgery, yet prognosis is still poor. Today, "curative surgery" is recommended by radical gastrectomy with negative surgical margins, D2 rather than a D1 lymphadenectomy and by gastrectomy with a minimum of 16 regional nodes be assessed pathologically but that removal/evalution of more nodes(30 or more) is desirable[4].

With the most important prognostic factor in stomach carcinoma patients being the stage of the disease, location, number of lymph node involvement, lymphovascular invasion, perineural invasion, tumor burden, histopathologic type, patient's performance status, and co-morbid diseases are also affecting factors[5]. Although most of the studies consist of all stages of non-metastatic gastric cancer, we studied only stage III of the disease to determine factors affecting survival.

METHODS

Ethical Consideration

Ethics committee approval was received from Non-invasive Clinical Research Ethics Committee of University of Amasya(2019-8-42).Informed consent was obtained from the patients. Our work was done in accordance with Helsinki Declaration. Study Group

Information of 275 patients with histologically confirmed adenocarcinoma of the stomach who underwent any type of surgery was obtained retrospectively from hospital records. Patients who were applied paliative surgery, patients with insufficient file information, or no follow-up, and patients who died within the first six months after surgery were not included in the study. Patients were staged according to the National

Comprehensive Cancer Network (NCCN) 2017 guidelines. Most of the patients were stage III (78%). Since the factors affecting survival were investigated only 163 patients of stage III were included to the study. Medical records, operation detail, the tumor characteristics, and treatment were noted and survival rates were analyzed. Investigated parameters and classifications, These were; patient-related factors (age, gender, blood group, preoperative hemoglobin, albumin and serum tumor marker (carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9) levels), tumor related factors (tumor localization, tumor size , T and N stage, total lymph node count, metastatic/total lymph node ratio, surgical margin of tumor, surgical margin is negative, pathology, differentiation, lymphovascular, and perineural invasion status) and treatment-related factors (adjuvant treatment, nutritional support and blood transfusion). Patients were grouped according to age as 40 years and younger, between 40-70 years and over 70 years old, hemoglobin level as 9 g/dl and below and 9 and above, and albumin level as 2.5 and less, 2.5-3.5 g/dl, 3.5 and above. The normal limits of serum CEA were 0-10 ng / ml, the normal limits of CA 19-9 were 0-37 U / ml, and the values above these levels were evaluated as high. Tumor size was classified as 5 cm or less, 5-10 cm, 10 cm or more; the distance of the tumor to surgical margin after resection was classified as 10 mm and less, 10-20 mm, 20-40 mm, and 40 mm and over; total lymph node counts were classified as 15 and below, between 15-25 and 25 and above; and the metastatic/total excised lymph node ratio was also classified as 0.25 and below, 0.25-0.50, 0.50-0.75 and 0.75 and above.

Postoperative treatment

After surgery, only 34 patients were given chemotherapy and 117 patients were given radiotherapy and chemotherapy. Twelve patients did not receive adjuvant treatment. 115 patients received FUFA (5-fluorouracil and leucovorin), 25 patients received FAC (5-fluorouracil, doxorubicin, cisplatin) and 11 patients received TCF (dosetaksel, cisplatin, 5-fluorouracil). Patients receiving chemoradiotherapy received radiation at a dose of 45 Gy for 28 days. Chemotherapy with 5-fluorouracil and calcium folinate was administered for five days at the beginning and at the end of radiotherapy.

Follow-up procedure

Patients were followed up for every 3 months in the first two years, for six months between 2-5 years, and then yearly. During follow-up, physical examination, complete blood counts, liver function tests, carcinoembryonic antigen and carbohydrate antigen 19.9 were performed. All patients had ultrasonography and/or abdominopelvic tomography and at 6 month intervals and annually thereafter. Gastroscopy was tailored to the individual patient.

Statistical Analysis

The primary end point of the study was overall survival. Patients were followed up until either to death or to the last date the patient was known to be alive. Descriptive statistics were used to calculate frequencies and percentages for all variables involved. Univariate survival curves for overall survival and death were estimated by using the Kaplan-Meier method; group differences in survival time were tested by the log-rank test. All significant parameters in univariate analyses were entered into a multivariate Cox regression analyses and to calculate risk ratio. P values of <0.05 were considered statistically significant. All analyses were carried out using SPSS software (version 16.0; SPSS Inc, Chicago, IL).

RESULTS

One hundred sixty three patients were included in this study. Fifty-one of the patients were female, 112 were male and the median age was 60 (border: 19-79 years). 41% out of the 163 patients in stage IIIA, 53 patients in stage IIIB and 69 patients in stage IIIC. The histological subtypes were; adenocarcinoma in 128 patients (78.5%) and signet ring carcinoma in 35 patients (21.5%). The distribution of cancer's location reported was as follows; cardia in 21 patients (12.9%), fundus in 8 patients (4.9%), corpus in 58 patients (35.6%), antrum in 71 patients (43.6%), and whole stomach (3.1%). Gastric cancers consist mostly of poorly differentiated (55.2% patients), well-differentiated cancer was seen quite

(8% patients) and the remainder were moderately differentiated.

Patient-related factors affecting survival and outcomes were given Table I.

Table I: Patient-related factors affecting survival and outcomes

		No(%)	Median survival time (min-max months)	P values
Age	≤40 40-70 ≥70	11(6.7%) 131(80.4%) 21(12.9%)	19(8-53) 16(7-79) 14(8-46)	0,10
Sex	Female Male	51(31.3%) 112(68.7%)	15(7-79) 16(7-63)	0,83
Blood group	0 A B AB	54(33.1%) 78(47.9%) 27(16.6%) 4(2.5%)	16.5(7-63) 16(7-79) 19(8-62) 10.5(8-20)	0,25
Hgb level before operation	≤9 g/dl >9 g/dl	18(11%) 145(89%)	14(8-58) 16(7-79)	0,93
Alb level before operation	≤2.5 g/dl 2.5-3.5 g/dl ≥3.5 g/dl	15(9.2%) 95(58.3%) 53(32)	19(8-58) 18(7-79) 14(7-59)	0,14
Serum Ca19-9 level	Normal High Unknown	102(62.6%) 31(19%) 30(18.4%)	18.5(7-63) 14(7-79) 12(7-49)	**0,03**
Serum CEA level	Normal High Unknown	121(74.2%) 10(6.1%) 32(19.6%)	18(7-79) 13.5(7-44) 12(7-49)	**0,01**

Only serum tumor marker's CEA and CA 19-9 were predictors for survival in univariate analysis. Survival curves were given in Figure 1. and Figure 2.

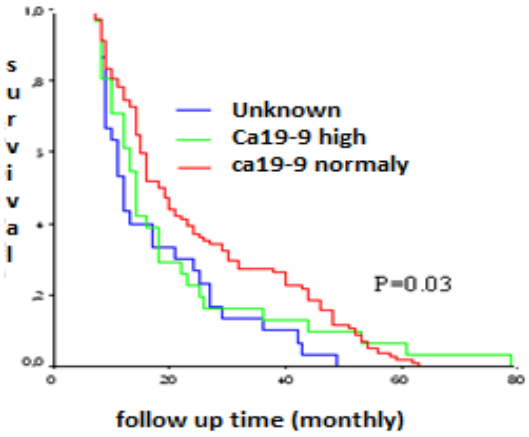


Figure 1: Survival analysis according to ca 19-9 level by Kaplan Meier curve

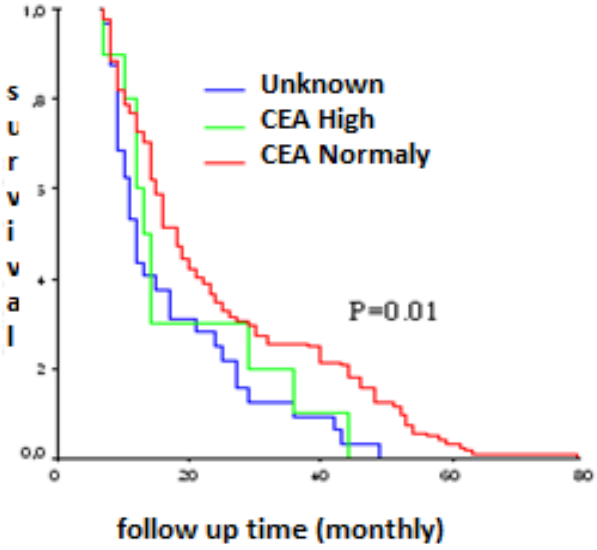


Figure 2: Survival analysis according to CEA size by Kaplan Meier curve

Tumor-related factors and survival outcomes were shown in Table 2.

Table II. Tumor-related factors affecting survival and outcomes

		No(%)	Median survival time (min-max months)	P values
Tumor localization	Cardia	21(12.9%)	14(7-53)	0,32
	Fundus	8(4.9%)	12(9-51)	
	Corpus	58(35.6%)	18(7-61)	
	Antrum	71(43.6%)	17(7-79)	
	All stomach	5(3.1%)	16(9-54)	
Pathology	Adenocarcinoma	128(78.5%)	16(7-79)	0,12
	Signet ring cell carcinoma	35(21.5%)	15(7-54)	
Differentiation	Well	13(8%)	13(8-61)	0,58
	Moderate	60(36.8%)	18.5(7-62)	
	Poor	90(55.2%)	15(7-79)	
T stage	T1	0	-	0,06
	T2	5(3.1%)	36(9-48)	
	T3	11(6.7%)	9(7-59)	
	T4a	143(87.7%)	16(7-79)	
	T4b	4(2.5%)	10(8-23)	
N stage	N1	30(18.4%)	15(8-61)	0,63
	N2	55(33.7%)	18(7-54)	
	N3a	54(33.1%)	16(7-79)	
	N3b	24(14.7%)	14(7-62)	
Total removed lymph node count	≤15	50(30.7%)	14(7-63)	0,23
	15-25	58(35.6%)	16(7-79)	
	≥25	55(33.7%)	22(7-61)	
Metastatic/total excised lymph node ratio	≤0,25	65(39.9%)	19(7-61)	**0,002**
	0,25-0,5	38(23.3%)	15.5(7-62)	
	0,5-0,75	31(19%)	20(8-79)	
	≥0,75	29(17.8%)	13(7-36)	
Lymphovascular invasion	Yes	107(65.6%)	16(7-63)	0,86
	No	56(34.4%)	16(7-79)	
Perineural invasion	Yes	95(58.3%)	16(7-62)	0,30
	No	68(41.7%)	16,5(7-79)	
Surgical margin (millimeters)	≤10	32(19.6%)	15.5(8-48)	0,09
	10-20	44(27%)	19(7-53)	
	20-40	67(41.1%)	16(7-79)	
	≥40	20(12.3%)	12.5(7-32)	

There was no difference in survival between those with a tumor size of 5 cm or less, those between 5-10 cm and patients with a height of 10 cm or more (p = 0.80 and p = 0.47, respectively). In addition, patients with tumor size of 5-10 cm and patients with tumor size of 10 cm and above were similar (p = 0.42). Invasion depth was not an effective parameter for survival (p = 0.06). However, the distribution of patients among the groups was not homogeneous. Of the 163 patients in the study, 143 were T4a. In the subgroup analysis, only survival was different between the T4a patient group and the T4b patient group (p = 0.04). Survival curves were given in Figure 3.

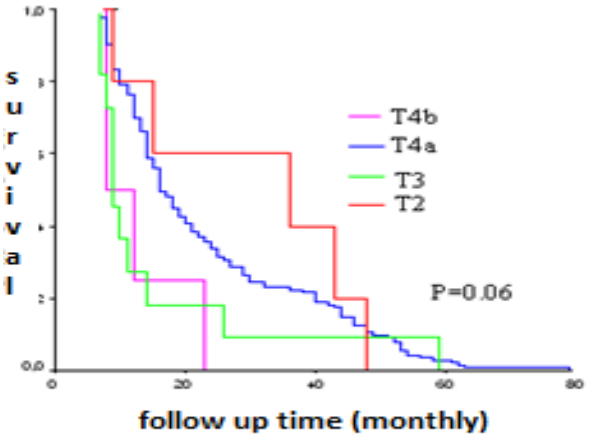


Figure 3: Survival analysis according to invasion depth by Kaplan Meier curve

Among the tumor-related factors, only only the lymph node ratio affected the survival and survival curves were given in Figure 4.

The factors related to the treatment and the survival time were shown in table 3.

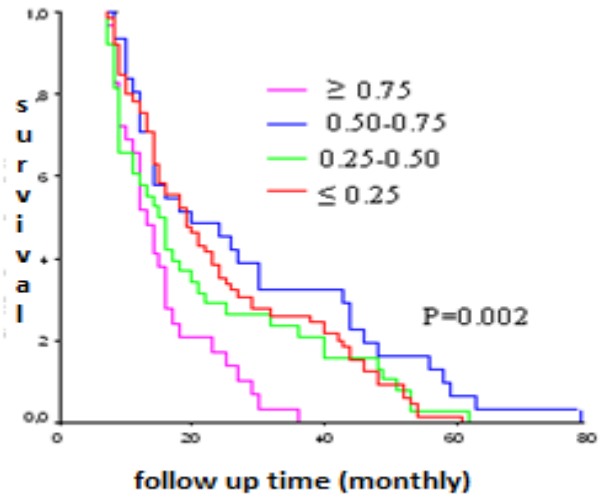


Figure 4: Survival analysis according to lymph node rate by Kaplan Meier curve

Table III: Treatment characteristics and median survival effects

		No(%)	Median survival time (min-max months)	P
Adjuvant treatment	CT CT+RT No treatment	34(20.9%) 117(71.8%) 12(7.4%)	14(8-62) 18(7-63) 11,5(7-79)	0,15
Blood transfusion	Yes No	63(38.7%) 100(61.3%)	15(7-62) 16(7-79)	0,22
Nutritional support	Yes No	115(70.6%) 48(29.4%)	16(7-63) 16,5(8-79)	0,36

CT: ChemotherapyRT: Radiotherapy

The chemotherapy (CT) group lived for 14 months while the chemoradiotherapy (CRT) group lived for 18 months. The overall survival in the CRT group was better but not statistically significant (p = 0.06). Survival curves were given in Figure 5.

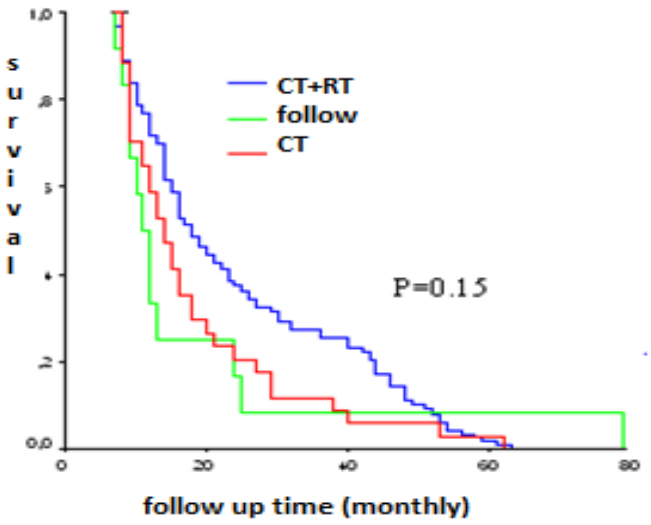


Figure 5: Survival analysis according to adjuvant treatment by Kaplan Meier curve

In univariate analysis, serum Ca 19-9 level (p=0,03), serum CEA level (p=0.01) and the lymph node ratio (p=0.002) were found to be an independent factors associated with overall survival whereas only lymph node ratio was an effective parameter in multivariate analysis [(p = 0.004, relative risk = 0.50, 95% confidence interval (0.32-0.80)]. When the study was finalized, patients were followed for a median of 16 months (range: 7-79 months). 87 patients (53.4%) died due to the disease.

DISCUSSION

Gastric cancer is still an important cause of cancer-related deaths. In a study consist of 10,092 patients undergoing gastrectomy by Song et al argued that young patients suffer a higher survival rate after surgery compared to elderly patients, and survival becomes worse with increasing age[6]. Sex steroid hormones in gastric carcinoma and their clinicopathological significance is unclear and divergent[7]. Age and sex did not affect survival in our study.

However, the number of patients over the age of 70 was very low in our series and was limited to only 12 patients. So the effect of survival of old age was not revealed in this study. The incidence of gastric cancer is higher in people with A blood group than in those with 0 blood group[8]. In addition, it is argued that survival is better in patients with A blood group than the ones in 0 blood group. In our study, 70.6% of gastric cancer patients were in the A blood group while 33.1% of the patients were in the 0 blood group. There was no relationship between blood groups and survival.

The stage of the disease, the state of the lymph nodes (N stage) and the tumor tissue's invasion grade (T stage) in the stomach wall are the most important factors determining the prognosis 5-year overall survival rates were as follows: 5-year survival is stage IA (94.7%), stage IB (89.9%), stage IIA (80.7%), stage IIB (72.5%), stage IIIA (58.4%), stage IIIB (40.8%), stage IIIC (20.2%), and stage IV (8.8%)[9]. For this reason, we studied only stage III diseases. Jun and colleagues argue that tumor size isn't only effect, but tumor invasion depth and metastatic lymph node involvement are the effective factors for survival, as well[10]. Adachi and his colleagues divided the patients into three groups; those with a tumor diameter less than 4 cm, those with a diameter of 4-10 cm and those with a diameter of 10 cm. They showed that, as the size increased, survival of patients with gastric cancer was adversely affected and this was a prognostic parameter[11]. Saito et al. also found that the appropriate tumor size threshold to affect survival was 8 cm and that tumor size was an independent factor that would affect survival[12]. In our study we did not detect any effect of tumor size on survival. There are a large number of researchers who argue that the depth of tumor invasion affects survival[13]. However, there are also some who argue that the depth of tumor invasion and stage does not affect the prognosis[14]. The depth of tumor invasion was not found as an effective parameter for survival in our study. However, the distribution of patients among the groups was not homogeneous. In the sub-group analysis, only survival was different between the T4a patient group and the T4b patient group. Survival is increasing in direct proportion to the number of lymph nodes removed. To mention a good lymph node dissection, over[15] lymph nodes should be dissected in the D2 dissection[15]. In our series, the median number was[20]. Patients were found to be more alive when the number of removed lymph nodes was increased, but this effect was not statistically significant. Lymph node metastasis is the another important prognostic factor in gastric cancer[16]. As the number of metastatic lymph nodes increases, survival decreases, which is the increase of the disease stage. In studies conducted by Oh Cheong et al. with 3979 patients, and Roberto Persiani et al. with 219 patients, survival decreased as the number of metastatic lymph nodes increased[17]. In our series, the survival differences was not seen, it may be all the patients in the same stage. Like our study, Chen et al have found that metastatic lymph node ratio was also important prognostic and predictive value in stage III gastric cancer[18]. The effect of lymphovascular invasion and perineural invasion on survival is controversial. Ersan Y et al. have argued that lymphovascular invasion and perineural invasion are not the sole cause but are more significant with factors such as tumor size, surgical margin, lymph node ratio, etc.[19], while Bilici et al.'s research with 238 patients have shown that the presence of perineural invasion in the disease series is a prognostic factor[20]. In our study, lymphovascular invasion and perineural invasion did not affect survival. Whether prognostic significance of proximal surgical margin especially advanced carcinoma is not clear. Ohe et al. study results considered that a sufficient resection margin is not the absolute factor associated with the rate of

survival and recurrence[21]. In this study, the surgical margin had no effect on survival.

While surgical treatment is the strongest predictor of long-term survival, poor results with surgery alone, especially in patients with stage III disease. In nowadays, adjuvant and neoadjuvant approaches using chemotherapy, radiation therapy, or a combination of the two are recommended[22,23]. However, perioperative chemotherapy versus postoperative chemoradiotherapy in patients with resectable gastric is controversial[24,25]. In our study, chemoradiotherapy receiving patients had a better life expectancy than patients receiving only chemotherapy but this difference was not significant.

In a conclusion, the metastatic tumor load in the lymph nodes around the stomach was negatively affect on survival.Manuscript wasn't presented as part at a meeting, the organization, place, and exact date on

Author meet the ICMJE authorship criteria

My work was done in accordance with helsinki declationa. Patients included in the study were informed about the patient before and after the study.

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There is no conflict of interest.

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Patient Recognition: Informed consent was obtained from the patients

Ethics Committee Approval: Ethics committee approval was received from Non-invasive Clinical Research Ethics Committee of University of Amasya (2019-8-42).

Interest was declared by the authors

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