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Research Article

Parameters of Complete Blood Count Might Predict the Prognosis of Patients with Advanced Gastric Cancer

Tam Kan Sayımı Parametreleri ile İleri Evre Mide Kanseri Olan Hastaların Prognozunu Tahmin Edilebilir Mi?

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Abstract

Aim: Metastatic gastric cancer is a common disease with poor prognosis. In this common disease, estimating the prognosis with a simple complete blood count has attracted the attention in many studies. However, the results of the studies are incompatible with each other. The aim of the study was to evaluate the relationship between parameters of the complete blood count and disease prognosis in patients with advanced gastric cancer(AGC).

Material and Methods: Blood counts of the patients were examined before receiving any treatment at the time of diagnosis of AGC. All parameters derived from complete blood count. These were; Neutrophil lymphocyte ratio(NLR), platelet lymphocyte ratio(PLR), monocyte lymphocyte ratio(MLR), systemic immune-inflammation index(SII). The patients were divided in two subgroups according to the median values of NLR, PLR, MLR and SII.

Results: A total of 105 patients with AGC were included in the study. The median survival in the patients with low NLR group was 14.6 months compared with high NLR group was 7.9 months(p=0.008). The median survival was 12.7 months in the low PLR group versus 8.2 months in the high PLR group (p=0.019). While the median survival time was 14.6 months in the high MLR group, it was 7.9 months in the low MLR group (p=0.06).

Conclusion: Through the parameters derived from complete blood count, NLR appears to be a promising prognostic marker in patients with AGC.

Keywords: gastric cancer, inflammation, neutrophil, overall survival, neutrophil-lymphocyte ratio, complete blood count

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Öz

Amaç: Metastatik mide kanseri sık görülen ve prognozu kötü olan bir hastalıktır. Bu yaygın hastalıkta prognozun basit bir tam kan sayımı ile tahmin edilmesi birçok çalışmada dikkatleri üzerine çekmiştir. Ancak çalışmaların sonuçları birbiriyle uyumlu değildir. Bu çalışmanın amacı, ilerlemiş mide kanserli (İMK) hastalarda tam kan sayımı parametreleri ile hastalık prognozu arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Hastaların İMK tanısı anında herhangi bir tedavi almadan önce kan sayımları incelendi. Tam kan sayımından elde edilen tüm parametreler kayıt edildi; Nötrofil lenfosit oranı (NLR), trombosit lenfosit oranı (PLR), monosit lenfosit oranı (MLR), sistemik immün-enflamasyon indeksi (SII). Hastalar medyan NLR, PLR, MLR ve SII değerlerine göre iki alt gruba ayrıldı.

Bulgular: Çalışmaya İMK'li toplam 105 hasta dahil edildi. Düşük NLR grubundaki hastalarda medyan sağkalım 14,6 ay iken, yüksek NLR grubunda 7,9 aydı (p=0,008). Ortanca sağkalım düşük PLR grubunda 12.7 aya karşı yüksek PLR grubunda 8.2 aydı (p=0.019). Ortanca sağkalım süresi yüksek MLR grubunda 14.6 ay iken, düşük MLR grubunda 7.9 aydı (p=0.06).

Sonuç: Tam kan sayımından elde edilen parametreler aracılığıyla NLR, İMK'li hastalarda umut verici bir prognostik belirteç gibi görünmektedir.

Anahtar Kelimeler: mide kanseri, inflamasyon, nötrofil, genel sağkalım, nötrofil-lenfosit oranı, tam kan sayımı

Introduction

Gastric cancer is one of the most common types of cancer and is usually diagnosed at an advanced stage and has a poor prognosis [1]. With the increase of cancer screening, more patients are diagnosed at an early stage and a contribution to survival is provided with the advances in treatments. Despite these developments, the median survival of patients with metastatic gastric cancer is poor. Although the Tumor Node Metastasis (TNM) stage is frequently used to predict the prognosis of patients, it is observed that patients with the same TNM stage progress differently. In addition to the TNM stage, many variables such as pathophysiological classification, tumor differentiation, serosa involvement, and lymphovascular invasion have been shown to affect the prognosis of the disease [2, 3]. Although these factors have been shown to affect gastric cancer prognosis, there is no single marker that can predict survival in patients with metastatic gastric cancer. Therefore, there is a need for a simple, easily accessible and cheap prognostic marker.

In recent studies, the relationship between immunity and tumor microenvironment has been investigated, and the effects of systemic immune response on tumor development and progression have been revealed [4-6]. Therefore, it is thought that analyzing the data of the host immune system may give clues about the prognosis of cancer. There are various markers that can give information about the immune system. For example, with advances in the field of immunotherapy, immune markers related to treatment response, such as tumor mutation burden, PD-L1 level, have been identified [7]. Besides, the relationship between more easily accessible acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate and cancer prognosis has been studied many times [8-10]. In addition to these markers, the Neutrophil / lymphocyte ratio (NLR), which can be detected by complete blood count, is known as a good marker of host immunity and has shown its power to predict prognosis in many types of cancer [11-13]. In addition to NLR, the platelet / lymphocyte ratio (PLR) and monocyte / lymphocyte ratio (MLR) and systemic inflammation index (SII), which can be calculated with parameters of complete blood count, in predicting the prognosis of gastric cancer have been demonstrated by various studies [14-16]. These ratios could not be used in routine practice because the results were inconsistent.

In this study, we aimed to evaluate the relationship between NLR, PLR, MLR and SII and the median overall survival (mOS) of patients with de novo metastatic gastric cancer. The secondary aim of this study is to evaluate the combined clinical use of NLR and other blood count parameters and the effect of these rates on progression-free survival.

Materials and Methods

Study design and population

After the approval of the Gazi University Faculty of Medicine

Ethics Committee, the data of the patients who applied to the medical oncology department and whose diagnosis of metastatic gastric cancer was confirmed at the time of diagnosis were retrospectively analyzed. The data of the patients were collected through oncology files and the hospital operating system.

All patients had pathologically diagnosed gastric adenocarcinoma. Patients who were followed up in the medical oncology department, received at least 1 course of chemotherapy, ≥18 years old and had complete blood count at the time of diagnosis were included in the study. The exclusion criteria of the study were defined as the presence of bone marrow involvement, active infection at the time of diagnosis, relapsed gastric cancer and additional hematological disease (eg. myelodysplatic syndrome, polistemia vera, essential thrombocytosis). Patients with insufficient file data and lost to follow up were not included in the study. 44 of these patients were not included in the study for various reasons (12 patients insufficient file data, 24 patients lost to follow up, 4 patients active infection at diagnosis, 2 patients with bone marrow involvement and 2 patients additional hematological diseases). Overall survival (OS) was determined as the time from diagnosis to the patient's final visit. Progression free survival (PFS) was calculated as the time from diagnosis to progression, death or final visit.

Data collection

Patients' demographic data, clinical characteristics, Eastern Clinical Oncology Group performance status (ECOG), pathological data, Her-2 status and data on the chemotherapy regimens they received were collected. Data of complete blood count (hemoglobin, platelet, leukocyte, neutrophil, monocyte, lymphocyte) and serum biochemistry measurements at the time of diagnosis were analyzed. Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) data were collected before starting oncological treatment. Absolute neutrophil, platelet and monocyte counts were divided by absolute lymphocyte counts to calculate NLR, PLR and MLR, respectively. The systemic inflammation index was calculated by dividing the multiplication value of absolute platelet and neutrophil measurements by the absolute lymphocyte measurement (SII= Neutrophil x Platelet / Lymphocyte).

Statistical analysis

Statistical analyses were performed using SPSS software version 23. Mean (standard deviation) was used for normally distributed data and median ± min / max values were used for non-normally distributed data. Categorical data are expressed as percentages (%). Distribution analyzes were performed for NLR, PLR, MLR and SII values and cut-off values were determined according to their medians. The patients were divided into two groups according to these cut-off values. We used 2 different models for survival analysis. For univariate analysis, Kaplan-Meier analysis was performed and log-rank analysis was performed and Hazard Ratios (HR) was calculated using Cox proportional hazard regression models. Possible factors determined by univariate analyzes were evaluated by Cox regression analysis with backward selection to determine independent predictors of overall survival rate of gastric cancer. HR values determined by multivariate analysis are presented with the 95% confidence interval (95% CI). In the interpretation of all analyzes, $p < .05$ value was considered statistically significant.

Results

Between January 2009 and January 2019, a total of 149 patients with de novo metastatic gastric cancer were detected. After these patients were excluded, a total of 105 patients were included in the study. The characteristic features of the patient population are given in Table 1. he median age of the patients was 61 years (range 31-85), and the majority of the cases involved men (70%). The ECOG performance status of 70 patients was found to be 0 or 1.

When the histopathological features of the tumors were examined, it was found that the majority (59%) had poorly differentiated tumors. Tumor subtypes were analyzed and it was seen that 67 (64%) patients were diagnosed with adenocarcinoma and 37 (35%) patients with ring cell cancer. HER-2 positivity was detected in only 15% of patients. The most common site of metastasis was the peritoneum (34%). It was also found that almost half of the patients (47%) received a combination of taxane, platinum and 5-fluorouracil chemotherapy.

The median overall survival of 105 patients included in the study was calculated as 9.03 months. When the variables affecting overall survival were examined with univariate analysis, no relationship was found between age, gender, ECOG performance status and overall survival. There was no association between median overall survival and anemia (Hgb <12gr/dl) ($p = 0.29$). Similarly, no statistically significant relationship was found between thrombocytopenia (100,000/µL) and mOS ($p = 0.49$). While the median survival was 11.2 months in patients with high CEA levels, this rate is 9 months in the low group ($p= 0.46$). Patients were divided into groups according to the medians of NLR, PLR, and MLR values, and survival in these groups was evaluated. The median overall

survival was 14.5 months in the patient group with a low NLR levels and this period was calculated as 7.9 months in the group with a high NLR levels (p= 0.008). In addition to this information, in the patient group with low PLR and MLR levels, mOS was measured 12.7 months and 8.2 months, respectively. In the patient group with high PLR and MLR levels, these durations were found to be 8.2 months and 7.8 months (p = 0.019 and p = 0.006, respectively). Although there was a 3.6-month difference between low-SII and high-SII patients, it could not reach a statistically significant value (p = 0.375). Survival charts created according to these ratios are presented in Figure I. The data of univariate and multivariate analyses of factors for the prediction of mOS are presented in Table 2.

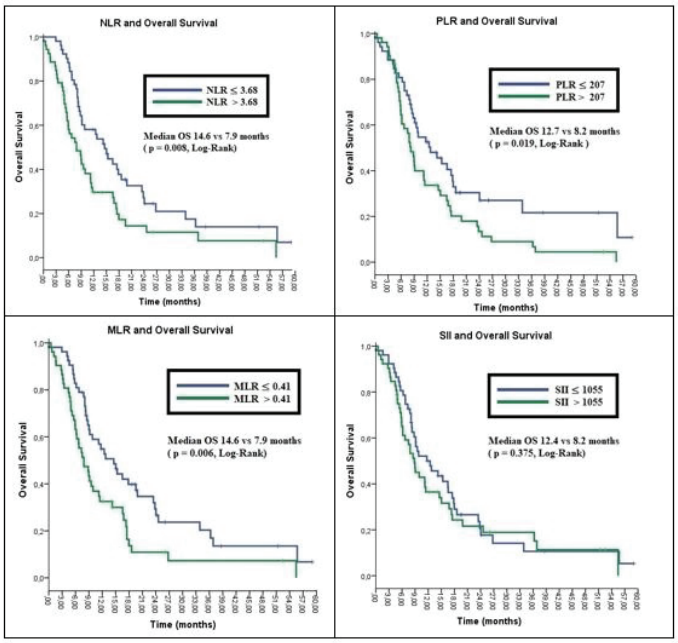

Figure I. NLR, PLR, MLR and Overall Survival

The factors affecting PFS were evaluated and it was found that age, gender and ECOG performance status at the time of diagnosis had no effect on PFS. The median PFS of patients with liver metastasis was 6.3 months, this time was measured as 5.9 months in patients without liver metastatic disease (p = 0.95). There was no effect of PLR and SII values on PFS (p = 0.83 and p = 0.75). The median progression free survival in the patients with low NLR group was 7.5 months compared with high NLR group was 5.2 months. (p = 0.0012). In low MLR group the PFS was 8.5 months compared with high MLR was 4.9 months respectively (p = 0.009). When multivariate analysis was done, it was seen that the only factor affecting PFS was MLR (p = 0.003). The data of univariate and multivariate analysis of factors affecting progression-free survival are presented in Table 3.

The effects of NLR, PLR, and MLR on overall survival were statistically significant, and the predictive value of these rates was thought to increase when they were combined. Since NLR was found to be the only variable affecting median OS in multivariate analysis, we examined the effect of combining MLR and PLR with NLR on prognosis. Survival charts are presented in Figure II.

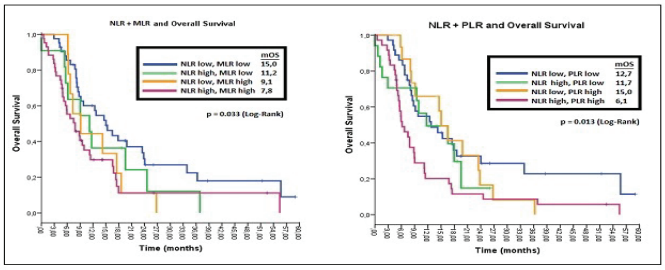

Figure II. NLR, PLR, MLR combinations and Overall Survival

Discussion

Gastric cancer is an aggressive disease with a poor prognosis, and markers are needed to predict prognosis. In this study, we showed the relationship between complete blood count parameters and the prognosis of metastatic gastric cancer. Increased NLR, PLR and MLR values were associated with shorter overall survival. On the other hand, combining scores into NLR-PLR and NLR-MLR rather than using them alone increases the predictive value of the ratios.

Studies conducted with inflammation-related scores are quite diverse and it has been found that an increase in scores such as NLR and PLR is associated with poor survival in diseases such as breast cancer, lung cancer, and colon cancer [13, 17, 18]. Additionally, studies focusing on gastric cancer revealed the effect of these immune scores on overall survival [14, 19]. In a meta-analysis conducted by Zhang et al., data of 2952 gastric cancer patients were analyzed and it was found that a lower NLR rate was associated with longer OS (HR1.83 ([95% CI], 1.62–2.07)) [20]. Unlike supporting data, the NLR score does not appear in routine practice. The most important reason for this situation may be the differences in the NLR cut-off values used in the studies. In our study, the median value for NLR was determined as 3.68 and 3.68 was used as the cut-off value. In some studies, a NLR level above 2, 2.5 or 3 was determined as the cut-off value, while there are studies that determine the cut-off value based on the ROC analysis or as we also use, the median value [21-24]. Different cut-off values make standardization difficult and limit its international use.

Infiltrated neutrophils and lymphocytes may be the underlying cause of the prognostic power of NLR and PLR. The progression of

Table I. Characteristics of the study population			
Group		Number	(%)
Age			
	< 65 years	66	(62%)
	≥ 65 years	39	(38%)
Gender			
	Female	31	(30%)
	Male	74	(70%)
ECOG performance status			
	0-1	70	(67%)
	≥ 2	35	(33%)
Differentiation status			
	Poor	61	(59%)
	Moderately	33	(31%)
	Well	11	(10%)
Her-2 Status			
	Negative	89	(85%)
	Positive	16	(15%)
Metastasis site			
	Peritoneum	36	(34%)
	Liver	29	(28%)
	Lymph Node	18	(17%)
	Bone	15	(14%)
	Others	7	(7%)
	Multiple	26	(25%)
Chemotherapy			
	5-Fluorouracil monotherapy	9	(8%)
	Platinum based doublet regimens	26	(25%)
	Combinations with anti HER-2 agents	10	(9%)
	Taxane and Platinum based triplet regimens	48	(47%)
	Others	12	(11%)
		Median	(min- max))
CEA (ng/mL)		6.7	(0.6-2100)
CA 19-9 (U/mL)		22	(0.5-10.800)
Hemoglobin (g/dL)		11.9	(5.8-17.0)
Platelet (/µL)		322000	(32000-978000)
Absolute neutrophil count (/µL)		5500	(1900-39000)
Absolute lymphocyte count (/µL)		1500	(500-3600)
Absolute monocyte count (/µL)		660	(90-2300)

Table 2. Univariate and multivariate analyses of factors for the prediction of overall survival

Characteristics		n, %	mOS (months)	Univariate analyses HR (95% CI)	p value	Multivariate analyses HR (95% CI)	p value
Age							
	<65y	66 (62%)	11.1	1.00			
	≥65y	39 (38%)	8.9	1.30 (0.83-2.02)	0.24	-	-
Gender							
	Female	31 (30%)	9.0	1.00			
	Male	74 (70%)	9.8	1.08 (0.66-1.77)	0.73	-	-
ECOG							
	0-1	70 (67%)	11.2	1.00			
	≥ 2	35 (23%)	8.9	1.18 (0.75-1.87)	0.45	-	-
Differentiation status							
	Well	11 (10%)	9.0	1.00		-	-
	Moderately	33 (31%)	12.7	1.00			
	Poor	61 (59%)	9.5	0.78 (0.55-1.12)	0.17		
Liver metastasis							
	No	76 (72%)	8.8	1.00			
	Yes	29 (28%)	12.3	0.62 (0.37-1.03)	0.06	-	-
CEA (ng/mL)							
	Low CEA	45 (43%)	9.0	1.00			
	High CEA	60 (57%)	11.2	0.83 (0.52-1.33)	0.46	-	-
CA 19-9 (U/mL)							
	Low CA 19-9	62 (59%)	9.1	1.00			
	High CA 19-9	43 (41%)	9.5	1.25 (0.73-2.00)	0.34	-	-
NLR							
	Low NLR	52 (%50)	14.6	1.00			
	High NLR	53 (%50)	7.9	1.77 (1.15-2.74)	0.008	2.14 (1.30-3.50)	0.002
PLR							
	Low PLR	53 (%50)	12.7	1.00			
	High PLR	52 (%50)	8.2	1.68 (1.08-2.61)	0.019	1.15 (0.66-1.99)	0.61
MLR							
	Low MLR	53 (%50)	14.6	1.00			
	High MLR	52 (%50)	7.9	1.81 (1.18-2.83)	0.006	1.45 (0.80-2.62)	0.21
SII							
	Low SII	53 (%50)	12.4	1.00			
	High SII	52(%50)	8.2	0.82 (0.53-1.26)	0.375	-	-

Table 3. Univariate and multivariate analyses of factors for the prediction of progression free survival

Characteristics		n, %	mOS (months)	Univariate analyses HR (95% CI)	p value	Multivariate analyses HR (95% CI)	p value
Age							
	<65y	66 (62%)	6.5	1.00			
	≥65y	39 (38%)	5.8	1.31 (0.86-1.98)	0.20	-	-
Gender							
	Female	31 (30%)	5.4	1.00			
	Male	74 (70%)	6.5	0.83 (0.54-1.28)	0.40	-	-
ECOG							
	0-1	70 (67%)	6.5	1.00			
	≥ 2	35 (23%)	5.8	1.24 (0.81-1.91)	0.30	-	-
Differentiation status							
	Well	11 (10%)	6.1	1.00		-	-
	Moderately	33 (31%)	7.9	1.00			
	Poor	61 (59%)	5.7	1.26 (0.72 -1.62)	0.51		
Liver metastasis							
	No	76 (72%)	5.9	1.00			
	Yes	29 (28%)	6.3	1.01 (0.65-1.57)	0.95	-	-
CEA (ng/mL)							
	Low CEA	45 (43%)	5.2	1.00			
	High CEA	60 (57%)	6.1	1.00 (0.65-1.53)	0.99	-	-
CA 19-9 (U/mL)							
	Low CA 19-9	62 (59%)	5.3	1.00			
	High CA 19-9	43 (41%)	5.9	1.09 (0.71-1.69)	0.67	-	-
NLR							
	Low NLR	52 (%50)	7.5	1.00			
	High NLR	53 (%50)	5.2	1.67 (1.11-2.51)	0.012	1.30 (0.80-2.11)	0.28
PLR							
	Low PLR	53 (%50)	6.7	1.00			
	High PLR	52 (%50)	5.8	1.04 (0.69-2-1.55)	0.83	-	-
MLR							
	Low MLR	53 (%50)	8.5	1.00			
	High MLR	52 (%50)	4.9	1.85 (1.22-2.78)	0.009	1.85 (1.22-2.78)	0.003
SII							
	Low SII	53 (%50)	6.7	1.00			
	High SII	52(%50)	5.9	1.06 (0.74-1.59)	0.752	-	-

cancer cells increases neutrophil flow to that area and increased neutrophils cause the release of many proinflammatory cytokines (Interleukin-6, Interleukin-10, Vascular endothelial growth factor, Tumor necrosis factor alpha) [25]. Vascular endothelial growth factor, one of these cytokines, contributes to tumor progression by increasing tumor angiogenesis and studies have also revealed the relationship of increased vascular endothelial growth factor levels with cancer cachexia [26]. In addition, increased interleukin-10 and tumor necrosis factor-alpha levels leads to a decrease in lymphocyte function and number, and suppresses T-lymphocyte-related antitumor response [27]. These pathophysiological results, resulting from changes in the levels of peripheral blood cells, explain the rationale of our idea to predict the mOS of metastatic gastric cancer through complete blood count measurements. In point of fact, in our study, a decrease in mOS was found in patients with gastric cancer with increased NLR, PLR and MLR. These scores can be thought to be a reflection of the underlying immune response and various released cytokines.

Although there are studies arguing that increased monocyte count negatively affects cancer prognosis, the underlying mechanism was not fully explained [28, 29]. However, there was evidence that the monocyte / lymphocyte ratio was more closely related to the malignant process rather than the absolute monocyte count effect alone [30]. In a retrospective study by Chen et al., it has been proven that increased MLR rate was associated with shorter survival times in gastric cancer patients receiving neoadjuvant therapy [31]. In addition, in a study investigating the factors affecting PFS duration in patients with metastatic gastric cancer, it has been revealed that MLR is sensitive in predicting PFS duration [32]. In our study, it was found that the only factor affecting PFS value independent from the other factors was MLR and these results support the results of the study conducted by Zhou et al.

In our study, unlike rates such as NLR, PLR and MLR, no relationship was found between SII and metastatic gastric cancer survival times. When the literature was reviewed, it was found that lower SII values were associated with better postoperative outcomes and longer survival in patients with gastric cancer [33]. In our study, the systemic inflammatory index not being correlated with gastric cancer survival may be associated with the cut-off value determination method or the low number of patients. It is necessary to determine a certain cut-off value for SII and to conduct additional studies with more patients.

This study has some limitations. Its retrospective design and including patients from a single center can be stated as the biggest limitation of the study. Detection of changes in neutrophil, thrombocyte and monocyte levels with control blood counts after oncological treatments may guide the evaluation of treatment response. In addition, poor differentiation, high CEA levels and liver metastasis are known to be poor prognostic factors for gastric cancer. In our study, when the survival of patients with these poor prognostic features and those who did not were examined, no statistically significant difference in survival was found. Although there was no statistically significant difference, patients with poor characteristics had numerically better survival times. The small number of patients in the groups, differences such as the patients' ECOG status and age may explain these surprising results. Therefore, prospective, multicenter studies including more patients with metastatic gastric cancer are needed.

Conclusion

In conclusion, increases in NLR, PLR and MLR levels were found to be associated with poor gastric cancer survival. The association of NLR with poor gastric cancer survival has been demonstrated, independent of other factors. Regardless of other factors and ratios, the increase in NLR level is associated with shorter gastric cancer survival. These rates are an in-direct reflection of the patient's immune system and we think that after standardization with clinical studies, oncology physicians will benefit more from these parameters in their daily practice.

Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Osman Sütcüoğlu], [Abdülkadir Fincan], [Bediz Kurt İnci] [Fatih Gürler] and [Ozan Yazıcı]. The first draft of the manuscript was written by [Osman Sütcüoğlu], [Ozan Yazıcı] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declerations

Part or all of the article has not been published elsewhere. It is not in the process of being evaluated in another journal at the same time.

Etthical approval

Ethical approval was waived by the local Ethics Committee of Gazi University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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Conflict of interest

The authors declare that they have no conflict of interest.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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