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Original Article / Özgün Araştırma

Comparison of the Clinical Features and Prognostic Value of Inflammation-Based Markers in Uterine Leiomyosarcoma

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Abstract

Aim: Inflammation-related markers are the factors affecting prognosis in many types of cancer. In this study, we aimed to investigate the relationship between inflammation-related markers, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and prognostic nutritional index (PNI) with prognosis of patients with uterine leiomyosarcoma (uLMS).

Methods: Patients diagnosed with uLMS were reviewed retrospectively. NLR, PLR, SII, and PNI values were calculated at the diagnosis and before treatment. Totally 35 patients were included in the study.

Results: Median overall survival (OS) in the low-NLR (<2.10) group was not reached using Kaplan-Meier analysis, whereas in the high-NLR (≥2.10) group, median OS was 41.6 months (95% CI:25.7 – 57.4) (p=0.019). Median OS in the low-PLR (<145) group could not be reached using Kaplan-Meier analysis, whereas, in the high-PLR (≥145) group, the median OS was 43.0 months (95% CI:21.9 – 64.1) (p=0.046). The median OS was 107.7 months (confidence interval not reached using Kaplan-Meier analysis) in the low-SII (<806) group, while the median OS was 43.0 months (95% CI:23.7 – 62.3) in the high-SII (≥806) group (p=0.039). In the low-PNI, (<53.7) group, the median OS was 53.2 months (95% CI:20.8 – 90.9), while in the high-PNI (≥53.7) group, the median OS was 41.6 months (0 – 94.0) (p=0.652). In multivariate analysis, mitotic count and NLR were observed as independent factors affecting prognosis in OS (p=0.012 and p=0.035).

Conclusions: NLR≥2.10 is an independent marker showing a poor prognosis in uLMS patients.

Key words: Neutrophil-lymphocyte ratio, uterine leiomyosarcoma, survival, prognosis

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Uterin Leiomyosarkomda Klinik Özelliklerin ve İnflamasyon Bazlı Belirteçlerin Prognostik Değerinin Karşılaştırılması

Öz

Amaç: İnflamasyonla ilişkili belirteçler birçok kanser türünde prognozu etkileyen faktörlerdir. Bu çalışmada, inflamasyonla ilişkili belirteçler olan nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), sistemik immün-inflamasyon indeksi (SII) ve prognostik nutrisyonel indeks (PNI) ile uterin leiomyosarkomlu (uLMS) hastaların prognozu arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: ULMS tanısı alan hastalar retrospektif olarak incelendi. NLR, PLR, SII ve PNI değerleri tanı anında ve tedavi öncesinde hesaplandı. Toplam 35 hasta çalışmaya dahil edildi.

Bulgular: Kaplan-Meier analizi kullanılarak düşük NLR (<2.10) grubunda medyan genel sağkalım (OS) ulaşılamazken, yüksek NLR (≥2.10) grubunda medyan OS 41.6 ay (%95 GA:25.7 - 57.4) olarak bulundu (p=0.019). Kaplan-Meier analizi kullanılarak düşük PLR (<145) grubunda medyan OS'ye ulaşılamazken, yüksek PLR (≥145) grubunda medyan OS 43,0 ay (%95 GA:21,9 - 64,1) olarak saptanmıştır (p=0,046). Düşük-SII (<806) grubunda ortanca OS 107,7 ay (Kaplan-Meier analizi kullanılarak güven aralığına ulaşılamamıştır) iken, yüksek-SII (≥806) grubunda medyan OS 43,0 ay (%95 GA:23,7 - 62,3) olarak gözlenmiştir (p=0,039). Düşük-PNI (<53,7) grubunda medyan OS 53,2 ay (%95 GA: 20,8 - 90,9) iken, yüksek-PNI (≥53,7) grubunda medyan OS 41,6 ay (0 - 94,0) idi (p=0,652). Çok değişkenli analizde, mitotik sayı ve NLR, OS'de prognozu etkileyen bağımsız faktörler olarak gözlenmiştir (p=0.012 ve p=0.035).

Sonuçlar: NLR≥2.10 uLMS hastalarında kötü prognozu gösteren bağımsız bir belirteçtir.

Anahtar kelimeler: Nötrofil-lenfosit oranı, uterin leiomyosarkom, sağkalım, prognoz.

INTRODUCTION

Uterine leiomyosarcoma (uLMS) is a highly aggressive malignancy with a poor prognosis that originates from uterine smooth muscle cells. Uterine sarcomas make up 3-7% of all uterine malignancies and constitute approximately 1% of malignancies within the female genital tract[1]. uLMS accounts for more than 50% of uterine sarcomas[1,2]. Although its incidence is low, it constitutes a significant portion of deaths due to uterine malignancies[3]. Surgery constitutes the essential form of treatment in treating uLMS. The unclear nature of adjuvant therapy stems from the limited number of patients with uLMS. Although chemotherapy options, radiotherapy, immunotherapy, and targeted therapies are still being investigated, the effect of adjuvant therapy is limited, and the prognosis is poor[4]. Despite surgical and adjuvant therapy, disease recurrence is quite common[5]. For this reason, overall survival (OS) and progression-free survival (PFS) times are not yet at the desired levels.

In patients with cancer, immune cells like neutrophils, lymphocytes and platelets have been shown to play a role in tumor development, prognosis and resistance to treatment[6]. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), which have been used to indicate inflammation, have been shown to be associated with prognosis in a variety of malignancies[7,8]. Furthermore, the prognostic significance of the systemic immune inflammation index (SII), a marker related to platelet and lymphocyte levels, has been established in cancers such as colorectal and hepatocellular cancer[9]. The prognostic nutritional index (PNI), a marker related to immunity and nutrition and calculated with albumin and lymphocyte values, has also been shown to be effective in the prognosis of many cancers such as colorectal, hepatocellular, and esophageal cancer[8,10].

Therefore, our study aimed to investigate the association between inflammation-based markers and the prognosis of uLMS, a topic that, to our knowledge, has not been addressed in the literature.

METHOD

Cases with histopathologic evidence of uLMS and follow-up in our medical oncology clinic between March 2004 and August 2022 were retrospectively reviewed. Patients over 18 years of age with histopathological diagnosis of uterine leiomyosarcoma and regular follow-up were included in the study. Patients under 18 years of age, uterine pathologies other than leiomyosarcoma, and extrauterine leiomyosarcomas were excluded from the study. 35 patients were enrolled for the study, provided the following parameters could be achieved. The clinicopathological characteristics, laboratory data and treatment details of the patients were collected from the hospital's automation and documentation system. Patients were staged using the FIGO 2009 staging system. Neutrophil, lymphocyte, platelet and albumin levels were recorded on admission to our clinic before any treatment was initiated.

PFS was defined as the time from surgery until relapse or death from any cause occurred. OS was defined as the time from the date of initial diagnosis to the date of death from any cause.

The neutrophil count divided by the lymphocyte count was used to calculate the NLR. The PLR value was obtained by dividing the platelet count by the lymphocyte count. SII was the product of platelet count multiplied by NLR. The PNI value was the addition of 0.005 x the lymphocyte value (in mm3) to the patients' albumin values (mg/dl).

Patients were categorized into two groups for each marker based on their NLR, PLR, SII, and PNI values. Cut-off values for these parameters were determined using the ROC curve with OS estimation. Based on these values, patients were stratified into two groups for each of the prognostic indexes. We used Pearson chi-square and Fisher's exact tests for the differences between these groups. We calculated OS and PFS times using the Kaplan-Meier method and compared results using the log-rank test. The Cox regression model was used for the analysis of the independent prognostic risk factors, with a p-value < 0.05 being considered significant. The Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. This study was approved by the institutional ethics committee. All procedures followed adhered to the ethical standards of the relevant committee and the most recent Declaration of Helsinki. Informed consent was not obtained due to the retrospective nature of the design. Our clinical research ethics committee decided that consent was unnecessary. (Date: 11.01.2023 / No: 3206).

RESULTS

Thirty-five patients, with a median age of 48 (range 34-73), were enrolled between March 2004 and August 2022 in this study. The relationship between the demographic characteristics, laboratory values, clinicopathological characteristics of the patients, and the groups formed using inflammatory markers is indicated in Table 1. There were significantly more stage II-IV patients in the higher NLR group (p=0.027) between the two groups formed by NLR. Patients with high LDH and those with tumor necrosis on pathology were statistically significantly more prevalent in the high PLR group (p=0.021, p=0.020) between the two groups created using the PLR value. The number of stage II-IV patients was more frequent in the higher SII arm (p=0.030) between the two groups based on SII scores. In the comparison of the two groups based on PNI, the number of patients who underwent lymphadenectomy was statistically significantly more in the low-PNI group (p=0.001).

Table I: Association between the NLR, PLR, SII, PNI, and clinicopathological features of uterine leiomyosarcoma patients.

Variables		NLR			PLR			SII			PNI		
	N	Low N (%)	High N (%)	p-value	Low N (%)	High N (%)	p-value	Low N (%)	High N (%)	p-value	Low N (%)	High N (%)	p-value
Total	35	12	23		13	22		16	19		19	16	
Age, years				0,193			0,826			0,600			0,229
<50	18	8 (67)	10 (44)		7 (54)	11 (50)		9 (56)	9 (47)		8 (42)	10 (63)	
≥50	17	4 (33)	13 (56)		6 (46)	11 (50)		7 (44)	10 (53)		11 (58)	6 (37)	
FIGO Stage				**0,027**			0,070			**0,030**			0,076
I	23	11(92)	12 (52)		11 (85)	12 (55)		14 (88)	9 (48)		10 (53)	13 (81)	
II-IV	12	1 (8)	11 (48)		2 (15)	10 (45)		2 (12)	10 (53)		9 (47)	3 (19)	
ECOG				0.903			0,826			0,877			0,130
0	17	6 (50)	11 (48)		6 (46)	11 (50)		8 (50)	9 (47)		7 (37)	10 (63)	
1-4	18	6 (50)	12 (52)		7 (54)	11 (50)		8 (50)	10 (53)		12 (63)	6 (37)	
LDH				0,099			**0,021**			0,285			0,744
<200	9	5 (63)	4 (25)		6 (75)	3 (19)		5 (50)	4 (29)		6 (40)	3 (33)	
≥200	15	3 (37)	12 (75)		2 (25)	13 (81)		5 (50)	10 (71)		9 (60)	6 (67)	
Unknown	11												
CA-125				0,548			0,193			0,079			0,193
<16,1	13	6 (67)	7 (54)		8 (73)	5 (45)		10 (77)	3 (33)		5 (45)	8 (73)	
≥16,1	9	3 (33)	6 (46)		3 (27)	6 (55)		3 (23)	6 (67)		6 (55)	3 (27)	
Unknown	13												
Tumor size				0,213			0,070			0,335			0,335
<10	19	8 (73)	11 (50)		10 (77)	9 (45)		10 (67)	9 (50)		9 (50)	10 (67)	
≥10	14	3 (27)	11 (50)		3 (23)	11 (55)		5 (33)	9 (50)		9 (50)	5 (33)	
Unknown	2												
Presence of Tumor Cell Necrosis				0,215			**0,020**			0,068			0,748
No	10	5 (42)	5 (22)		7 (54)	3 (14)		7 (44)	3 (16)		5 (26)	5 (31)	
Yes	25	7 (58)	18 (78)		6 (46)	19 (86)		9 (56)	16 (84)		14 (74)	11 (69)	
Ki-67				0,707			0,402			0,772			0,819
<40	8	2 (40)	6 (50)		2 (33)	6 (55)		3 (43)	5 (50)		4 (50)	4 (44)	
≥40	9	3 (60)	6 (50)		4 (67)	5 (45)		4 (57)	5 (50)		4 (50)	5 (56)	
Unknown	18												
Mitotic count (/10 HPF)				0,098			0,206			0,102			0,408
<20	12	7 (70)	5 (36)		6 (67)	6 (40)		4 (33)	8 (67)		4 (40)	8 (57)	
≥20	12	3 (30)	9 (64)		3 (33)	9 (60)		8 (67)	4 (33)		6 (60)	6 (43)	
Unknown	11												
Lymphadenectomy				0,832			0,601			0,154			**0,001**
No	19	7 (58)	12 (55)		8 (62)	11 (52)		11 (69)	8 (44)		5 (28)	14 (88)	
Yes	15	5 (42)	10 (45)		5 (38)	10 (48)		5 (31)	10 (56)		13 (72)	2 (12)	
Unknown	1												

The median OS in the low NLR (<2.10) group could not be reached using Kaplan-Meier analysis, whereas in the high NLR (≥2.10) group, the median OS was 41.6 months (95% CI: 25.7 – 57.4). The statistical significance of the difference between the two groups was confirmed (p=0.019). The median OS in the low PLR (<145) group could not be reached by Kaplan-Meier analysis, whereas the median OS in the high PLR (≥145) group was 43.0 months (95% CI: 21.9 - 64.1). A statistically significant difference between the two groups was observed (p=0.046). While the median OS was 107.7 months (confidence interval not reached using Kaplan-

Meier analysis) in the low-SII (<806) group, the median OS was 43.0 months (95% CI: 23.7 – 62.3) in the high-SII (≥806) group, statistically significant (p=0.039). In the low PNI group (<53.7), the median OS was 53.2 months (95% CI: 20.8-90.9), while in the high PNI group (≥53.7), it was 41.6 months (0-94, 0). No difference was observed between both groups (p=0.652) (Figure 1-3).

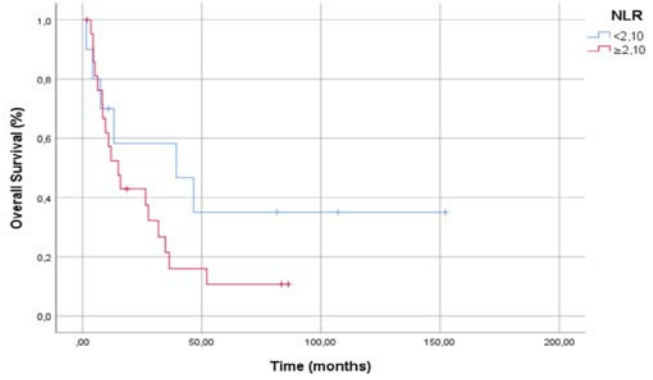

Figure 1. Kaplan-Meier Survival Curves for Overall Survival of All Patients with NLR Groups

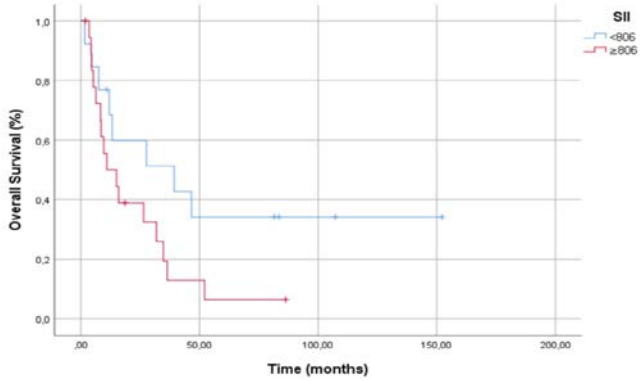

Figure 2. Kaplan-Meier Survival Curves for Overall Survival of All Patients with SII Groups

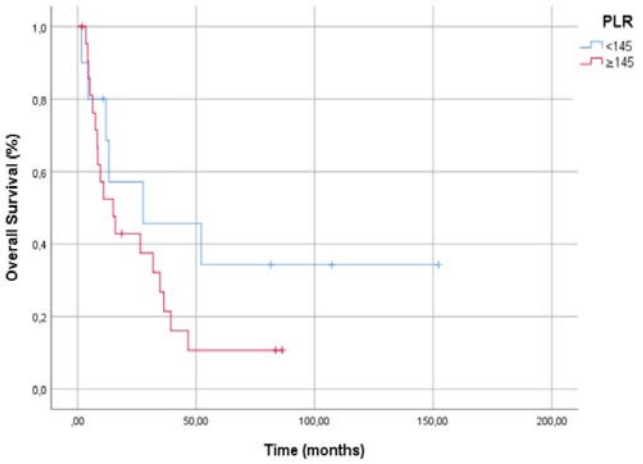

Figure 3. Kaplan-Meier Survival Curves for Overall Survival of All Patients with PLR Groups

Median PFS in the low NLR (<2.10) group was 39.3 months (95% CI: 0 - 85.9), while it was 15.0 months (7.6 - 22.5) in the high NLR (≥2.10) group (p=0.186). The median PFS was 26.4 months (95% CI: 3.0 – 49.9) in the low PLR (<145) group, while the median PFS was 15.0 months (95% CI: 4.7 – 25,4) in the high PLR (≥145) group (p= 0.571). While the median PFS was 21.8 months (95% CI 0 – 82.1) in the low-SII (<806) group, the median PFS was 10.9 months (95% CI: 0 – 22.2) in the high-SII (≥806) group (p=0.083). In the low PNI (<53.7) group, the median PFS was 15.9 months (95% CI: 5.8 – 20.6), while in the high PNI (≥53.7) group, the median PFS was 10.9 months (95% CI: 0 – 50.8) (p=0.394). The difference between groups in terms of PFS was not significant (Table 2).

Table II: Predictive ability of NLR, PLR, SII and PNI for OS and PFS in uterine leiomyosarcoma patients

Variables	AUC	Median OS (%95 CI)	p	Median PFS (%95 CI)	p
NLR	0,677				0,186
<2,10		NA	0,019	39,294 (0,001 – 85,867)	
≥2,10		41,626 (25,762 – 57,491)		15,047 (7,580 – 22,514)	
PLR	0,727		0,046		0,571
<145		NA		26,448 (2,988 – 49,907)	
≥145		43,039 (21,962 – 64,116)		15,047 (4,666 – 25,429)	
SII	0,700		0,039		0,083
<806		107,729 (NA)		21,849 (0,001 – 82,119)	
≥806		43,039 (23,761 – 62,317)		10,908 (0,001 – 22, 177)	
PNI	0,570		0,652		0,394
<53,7		53,224 (20,804 – 90,972)		15,901 (0,001 – 50,803)	
≥53,7		41,626 (0,001 – 93,999)		13,175 (5,759 – 20,590)	

**p < 0.05; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; OS, overall survival;PFS: progression-free survival; CI, confidence interval; AUC, area under curve*

For OS analysis in this study, in addition to inflammation-based markers; age (p=0.090), FIGO staging (p=0.008), ECOG performance level (p=0.821), tumor size (p=0.494), tumor necrosis in pathology (p=0.162) Ki-67 proliferation rate in pathology (p=0.784), mitotic count in pathology (p=0.002), level of CA-125 (p=0.057), LDH level (p=0.083), lymphadenectomy (p=0.618), adjuvant chemotherapy type (p=0.677) and radiotherapy (p=0.666) were evaluated in the univariate analysis. In multivariate analysis for OS, FIGO staging (p=0.079), mitotic count in pathology (p=0.012), level of NLR (p=0.035), PLR (p=0.067), and SII (p=0.078) were evaluated. As a result of multivariate analysis, independent factors with prognostic significance for OS were NLR level (p=0.035) and mitotic count on pathology (p=0.012) (Table 3).

Table III: Univariable and multivariable analysis of overall survival in uterine leiomyosarcoma

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p	HR (95%CI)	p
FIGO Stage IV vs stage I-III	3,358 (1,306 – 8, 635)	0,008	3,315 (0,799 – 13,754)	0,99
NLR ≥2,10 vs <2,10	4,189 (1,166 – 15,045)	0,019	6,285 (1,100 – 35,902)	0,039
PLR ≥145 vs <145	2,999 (1.002 – 9,248	0,046	2,563 (0,345 – 19,047)	0,358
SII ≥806 vs <806	2,887 (1,013 – 8,233)	0,039	NA**	
Mitotic count ≥20 vs <20	6,105 (1,753 – 21,260)	0,002	5,127 (1,291 – 20,359)	0,020

**HR, hazard ratio; NLR, neutrophil-lymphocyte ratio; PLR, platelet lymphocyte ratio; SII, systemic immune-inflammation index*

***Due to colinearity SII was removed from the multivariate model*

For PFS analysis, in addition to inflammation-based markers; age (p=0.807), FIGO staging (p<0.001), ECOG performance level (p=0.124), tumor necrosis in pathology (p=0.623), Ki-67 proliferation rate in pathology (p=0.302), mitotic count in pathology (p=0.016), tumor size (p=0.512), CA-125 level (p=0.057), LDH level (p=0.041), lymphadenectomy (p=0.396), type of adjuvant chemotherapy (p=0.281) and radiotherapy (p=0.295) were evaluated in univariate analysis. In multivariate analysis for PFS, FIGO staging (p=0.066), mitotic count in pathology (p=0.304), and LDH level (p=0.207) were evaluated. As a result of multivariate analysis, no parameter affecting PFS was found.

DISCUSSION

Our study is the first in the literature to examine the effects of inflammation-based markers on the prognosis of OS and PFS in uLMS patients. Our study observed high NLR, high PLR, and high SII levels as factors affecting OS negatively in uLMS patients. When the multivariate analysis was performed, it was observed that high NLR level was an independent poor prognostic marker affecting OS in uLMS patients.

In our study, other factors affecting OS were observed as FIGO staging and the mitotic count in pathology. When multivariate analysis was performed, the mitotic count in pathology was observed as an important prognostic factor for OS.

The relationship between inflammation-based markers and prognosis in many cancer types has been investigated previously. In many cancers, high levels of NLR are related to worse prognosis[11,12]. High PLR levels are a bad prognostic risk factor in many tumors, including pancreatic, ovarian, and colorectal[13,14]. Elevated SII levels have been observed to correlate with a poorer prognosis in various cancers, including hepatocellular cancer, glioblastoma, and small-cell lung cancer[15,16]. High PNI levels are a good prognostic factor in many carcinomas, including ampulla of Vater, non-small cell lung and pancreatic cancer[17,18]. In our study, median OS was lower at high NLR levels in uLMS patients than at low NLR levels. The difference was

statistically significant in both univariate and multivariate analyses. In higher PLR and SII levels, the median OS was shorter than in low PLR and SII levels. While the difference showed statistical significance in univariate analysis, no significant difference was identified in multivariate analysis. PNI level was found to be a factor that did not affect the prognosis of OS in uLMS patients. Although median PFS was found to be less at high NLR, PLR, and SII levels, no statistically significant difference was observed. It was observed that PNI level was a factor that did not affect the prognosis for the PFS of the patients.

Upon reviewing studies on factors influencing the prognosis of uLMS, Takehara et al. conducted a retrospective study revealing that advanced stage, high LDH level, and menopausal status were identified as poor prognostic factors[19]. In a retrospective study by Ayhan et al., it was observed that lymphovascular invasion, nuclear atypia, not performing lymphadenectomy, and not performing omentectomy were poor prognostic factors affecting disease-free survival[19]. The same study observed that lymphovascular invasion, high mitotic count, nuclear atypia, advanced stage, and residual disease were poor prognostic factors affecting OS. In a study by Seagle et al., adjuvant chemotherapy treatment was shown to increase the patient's OS[20]. In our study, although the advanced stage was seen as affecting both OS and PFS, no significant difference was found in the multivariate analysis. Although high LDH levels were observed to affect PFS, it was not regarded as statistically significant in multivariate analysis. Our study also observed high mitotic count as a poor prognostic factor affecting OS. It is thought that the results of our study came out in this way since the efficacy of adjuvant treatments in sarcomas is limited, and these tumors have a very aggressive course[4].

CONCLUSION

In our study, it was observed that NLR level is a prognostic factor affecting OS. Although PLR and SII levels are thought to be among the factors affecting the prognosis, a statistically significant result could not be obtained. The lack of a significant difference is attributed to the small number of patients in our study. The effect of PLR and SII levels on the prognosis can be revealed with more comprehensive studies to be conducted in this area.

Ethics Committee Approval: This study was approved by the institutional ethics committee. All procedures followed adhered to the ethical standards of the relevant committee and the most recent Declaration of Helsinki. Informed consent was not obtained due to the retrospective nature of the design. Our clinical research ethics committee decided that consent was unnecessary. (Date: 11.01.2023 / No: 3206).

Conflict of Interest: The authors declared no conflicts of interest.

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