ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Clinicopathologic Analysis of 43 Acral Melanomas and the Relevance of Predictors of Sentinel Lymph Node Positivity

Akral Melanom Tanılı 43 Hastanın Klinikopatolojik Bulgularının ve Sentinel Lenf Nodu Pozitifliğini Etkileyen Belirteçlerin Değerlendirilmesi

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ABSTRACT Objective: Acral melanoma is an uncommon subtype of melanoma that occurs on palmoplantar surfaces and the nail unit. The prognosis is usually poorer as compared to other subtypes of melanoma due to the delayed diagnosis. Breslow thickness, age at diagnosis, ulceration, and the sentinel lymph node status are the main prognostic factors. In this retrospective study, we aimed to analyze the clinicopathological features of 43 acral melanoma patients and to determine the predictors of sentinel lymph node positivity. **Material and Methods:** A total of 43 patients who were diagnosed with acral melanoma at our department or consulted to our department from January 2010 to January 2020 were enrolled in this study. Demographic features and histopathological data were collected from medical records. The statistical analysis was performed with the SPSS 21. **Results:** The mean age of the patients was 62.7±13 (28-82). Breslow thickness was 5.80±6.15 mm (0-29). Sentinel lymph node involvement was negative in 27 (62.7%) patients. Ulceration was detected in 30 (69.7%) patients. A statistically significant relation was detected between sentinel lymph node positivity and Breslow thickness and number of mitosis (p<0.001). There was a statistically significant relation between the ulceration and mitosis (p=0.033). Also, the relation between the ulceration and Breslow thickness was statistically significant (p=0.011). A significant difference was established between the patients with lymphovascular invasion and a moderate negative correlation was detected between tumor-infiltrating lymphocytes in terms of the sentinel lymph node positivity. **Conclusion:** In cases with acral melanoma alongside Breslow thickness, ulceration, mitosis rate, and lymphovascular invasion are major predictors of sentinel lymph node positivity. As taking into consideration of the delayed prognosis of acral melanoma, in every patient presence and intensity of these parameters should be carefully evaluated during patient follow-up.

Keywords: Acral melanoma; Breslow thickness; sentinel lymph node; ulceration

ÖZET Amaç: Akral melanom, palmoplantar bölge ve tırnak ünitesini etkileyen, melanomun nadir görülen bir alt tipidir. Prognozu, sıklıkla tanıda gecikme olması nedeniyle diğer melanom alt tiplerine göre daha kötüdür. Breslow kalınlığı, hastanın tanı yaşı, ülserasyon varlığı ve sentinel lenf nodu pozitifliği ana prognostik faktörlerdir. Bu retrospektif çalışmada, akral melanom tanısı alan 43 hastanın klinikopatolojik özelliklerinin ve sentinel lenf nodu pozitifliğini etkileyebilecek faktörlerin incelenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışmaya, Ocak 2010 ve Ocak 2020 tarihleri arasında hastanemizde akral melanom tanısı alan veya kliniğimize konsülte edilen akral melanom tanısı almış 43 hasta dâhil edilmiştir. Hastalara ait demografik özellikler ve histopatolojik veriler, hasta kayıtlarından taranmıştır. İstatistiksel analiz, SPSS 21 ile yapılmıştır. **Bulgular:** Hastaların ortalama yaşı 62,7±13 (28-82), Breslow kalınlığı 5,80±6,15 mm (0-29) idi. Yirmi yedi (%62,7) hastada, sentinel lenf nodu tutulumu negatifti. Ülserasyon varlığı, 30 (%69,7) hastada tespit edildi. Sentinel lenf nodu pozitifliği ile Breslow kalınlığı ve mitoz sayısı arasında istatistiksel olarak anlamlı ilişki tespit edildi (p<0,001). Ülserasyon ile mitoz arasında istatistiksel olarak anlamlı bir ilişki izlendi (p=0,033). Ülserasyon ile Breslow kalınlığı arasındaki ilişki istatistiksel olarak anlamlıydı (p=0,011). Sentinel lenf nodu pozitifliği ile lenfovasküler invazyon arasında istatistiksel olarak anlamlı ilişki gözlenirken, tümör infiltre eden lenfosit yoğunluğu ile sentinel lenf nodu pozitifliği arasında orta derecede negatif korelasyon izlenmiştir. **Sonuç:** Akral melanomlu olgularda Breslow kalınlığı, ülserasyon varlığı, mitoz oranı ve lenfovasküler invazyon varlığı, sentinel lenf nodu pozitifliğinin başlıca belirteçleridir. Akral melanomun kötü prognozu göz önünde bulundurulduğunda, bu hastaların takipleri sırasında bu parametrelerin varlığı ve yoğunluğu dikkatli değerlendirilmelidir.

Anahtar Kelimeler: Akral melanom; Breslow kalınlığı; sentinel lenf nodu; ülserasyon

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Melanoma is the malignant neoplasm deriving from the melanocytes within the skin and the mucosal tissues that has higher mortality compared to other types of skin cancers. Clinically, there are four main subtypes of melanoma including superficial malignant melanoma, nodular melanoma, acral melanoma, and lentigo malignant melanoma according to the histopathologic features, location, and growth pattern.[1] Acral melanoma is a rare subtype of melanoma that is deriving from the palmoplantar and the subungual region (Figure 1, Figure 2, Figure 3, Figure 4). It may develop from an existing mole or de novo in a normally-appearing skin and comprises approximately 2-3% of all melanoma cases. It is more common after 40 years of age, in Asians and Africans, and is rarely seen in Caucasians. Unlike other subtypes of melanomas, ultraviolet exposure is not related to acral melanoma.[2,3] The prognosis of acral melanoma is usually poor due to the advanced stage at the time of the diagnosis. The age at diagnosis, sex, Breslow thickness, the presence of ulceration, and sentinel lymph node status are among the main prognostic factors of acral melanoma.[4-6] In our study, we aimed to define the clinicopathological features of our patients who were diagnosed with acral melanoma and to determine the predictors of sentinel lymph node positivity.

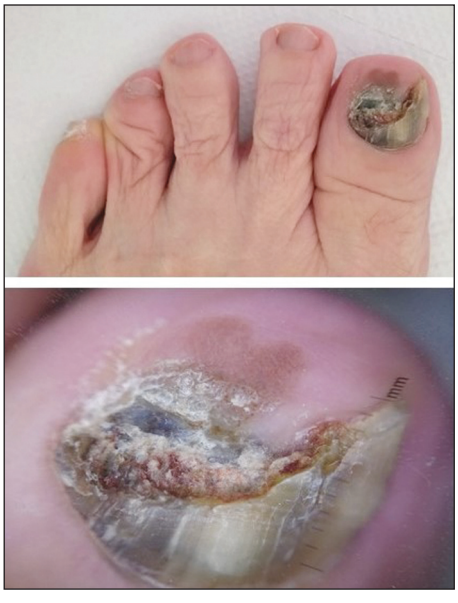

FIGURE 1: 63 year old female patient with subungal melanoma on left toenail, distal hyperpigmentation, yellow-grey discoloration, subungual hyperkeratosis and hemorhhage on dermoscopy.

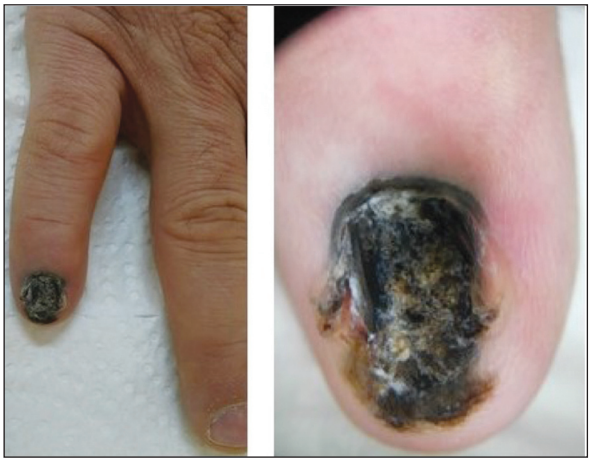

FIGURE 2: 32 year old male patient with subungal melanoma on fifth nail of right hand, diffuse black hyperpigmentation on nail apparatus with distal hyperpigmentation on dermoscopy.

MATERIAL AND METHODS

Forty-three patients, who were diagnosed with acral melanoma at our department or consulted to our department from January 2010 to January 2020 were included in this study. Demographic and pathological variables were recorded for every patient including, age, gender, disease onset, localization, Breslow thickness, mitosis rate, presence of ulceration and regression, the intensity of tumor infiltrating lymphocytes, and presence of lymphovascular invasion. All of the pathology specimens were reviewed by one specialist pathologists. Ulceration is the pathological term that includes the loss of all layers of the epidermis that is associated with the invasive part of the melanoma and can be measured by an ocular micrometer. The width of the tumor is evaluated linearly in millimeters between two edges. Lymphovascular infiltration is the term in which melanoma cells invade the vessels or lymphatics both in the peri□tumoral and tumoral areas. Perineural invasion can be evaluated according to the presence of tumoral cells nearby adjacent to the nerve sheath, usually representing a circumferential involvement. The rate of mitosis was noted according to the number of mitotic figures in a square millimetre.[7] Histologically, regression is defined as a decrease in the tumoral cells with an accompanying epidermal attenuation, melanophages, apoptosis of keratinocytes or

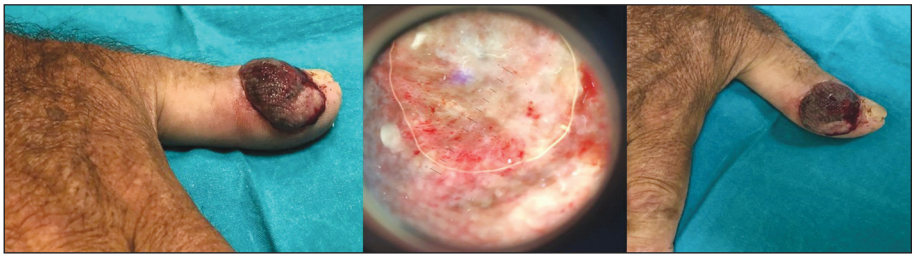

FIGURE 3: 57 year old male patient with 2 cm, vegetating, nodular acral lentiginous melanoma on right hand, clinical and serpiginous, dotted, globular and linear polymorphic vessels, white-grey pigmentation on dermoscopy.

melanocytes that is reflecting the host response, inflammatory infiltration in dermis, ectatic blood vessels and dermal fibrosis. The intensity of these features may change according to the stage of the regression.[8] Tumor-infiltrating lymphocytes (TILs) were scored and classified into three groups according to the intensity of the infiltration. In the first group, TILs were classified as the presence of a mild infiltration around the tumor in the vertical growth phase. This infiltration may represent a focal or multifocal involvement. In the second group, moderate infiltration of lymphocytes was detected but not affecting the base of the vertical growth phase entirely. In the last group, there was a continuous cumulation of lymphocytes at the base of the tumor or throughout the tumor at the vertical growth phase. The histopathological figures were received from the pathology department of the same public university hospital. This study was conducted according to the World Medical Association Declaration of Helsinki. It was approved by the local ethics committee (İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Clinical Research Ethics Committee, ethical approval date, and number: 8/10/2020, 132764). The informed consent form was taken from each patient before the surgical procedure.

STATISTICAL ANALYSIS

In the statistical analysis, the SPSS 21 program was used. The Shapiro-Wilk test was used in the evaluation of the distribution of the continuous data. The point-biserial correlation coefficient test was conducted in order to determine whether or not there was a statistically significant relationship between the presence of ulceration and the number of mitosis and Breslow thickness. Also, Fisher's exact test was applied in an attempt to find out whether there was a significant relationship between the presence of ulceration and the sentinel lymph node positivity. The p values of less than 0.05 were considered statistically significant.

RESULTS

The clinicopathological data of the patients involved in the study are demonstrated in Table 1. Of these 43 patients, 19 (44.2%) females and 24 (55.8%) males, diagnosed with acral melanoma were included in the study. The mean age of the patients was 62.7±13 (28-82). In 23 (53.4%) patients, the primary lesion was

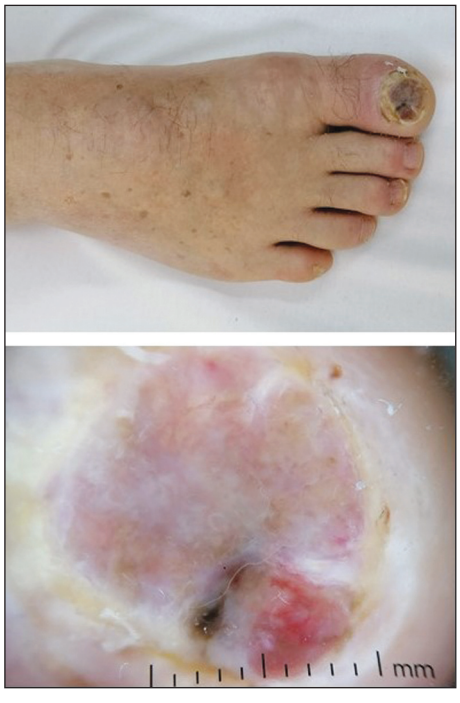

FIGURE 4: 62 year old female patient with subungal melanoma on right toenail, 1.5 cm, pinkish nodular lesion with a black-grey clod on inferior, serpiginous vessels and pinkish-grey structureless pattern on dermoscopy.

TABLE 1: Clinicopathological data of 43 patients.

Characteristic	No. (%)
Mean age at diagnosis, y	62.7±13
Sex	
Female	19 (44.2%)
Male	24 (55.8%)
Location of lesion	
Toe	12 (27.9%)
Plantar	23 (53.4%)
Finger	7 (16.2%)
Palmar	1 (2.3%)
Sentinel lymph node status	
Positive	16 (36.4%)
Negative	27 (61.4%)
Ulceration	
Yes	30 (69.7%)
No	13(30.3%)
Breslow thickness[a] (mm)	5.80 (0-29)
Mitotic rate[b]	8.58 (0-38)
Clark level	
5	17 (38.6%)
4	18 (40.9%)
3	2 (4.5%)
2	2 (4.5%)
1	3 (6.8%)
0	2 (4.5%)
Regression	
Yes	16 (37.2%)
No	27 (62.7%)
Lymphovascular invasion	
Yes	5 (11.7%)
No	38 (88.3%)
Perineural invasion	
Yes	8 (18.7%)
No	35 (81.3%)
Amputation	
Yes	16 (37.2%)
No	27 (62.7%)
Lymphocytic infiltration	
Severe	6 (13.9%)
Moderate	2 (4.6%)
Mild	32 (74.4%)
No	3 (6.9%)
Arising from existing mole	
Yes	8 (18.6%)
No	35 (81.3%)

[a]Data represents mean±standard deviation; [b]Data represents median value.

located on the plantar surface, in 12 (27.9%) on the toes, in 7 (16.2%) patients on the fingers, and in one patient (2.3%) found to be on the palmar surface. Clinical and dermoscopic images of some cases were demonstrated in Figure 1, Figure 2, Figure 3 and Figure 4. The median Breslow thickness was 5.80±6.15 mm (0-29 mm). In 27 (62.7%) patients, the sentinel lymph node involvement was negative while positive in 16 patients. Ulceration was detected in 30 (69.7%) patients whereas in 13 (30.3%) patients no ulceration was noted. A statistically significant difference was detected between sentinel lymph node positivity and Breslow thickness and number of mitosis (rpb=0.526 and rpb=0.588 with p<0.001 respectively) (Table 2). There was a statistically significant relation between the ulceration and mitosis (rp=0.326, p=0.033). Also, the relation between the ulceration and Breslow thickness was statistically significant (rp=0.381, p=0.011) (Table 3). Considering the relation between the ulceration and the sentinel lymph node positivity; of the patients with no ulceration only in 7.7% (n=1) there was a sentinel lymph node positivity while of the patients with ulceration in 50% (n=15) there existed a sentinel lymph node positivity. A significant difference was detected between the patients with and without ulceration in terms of the sentinel lymph node positivity (p=0.014, Fisher's exact test) (Table 4). There was no statistically significant difference between age, sex, and Breslow thickness (r=0.029, p=0.852 for age-Breslow correlation, r=0.0038, p=0.808 for sex and Breslow thickness correlation). Lymphovascular invasion was positive in 68.8% (n=11) of the patients with metastatic involvement but it was not detected in any of the patients without metastatic involvement (n=27). A significant relationship between the presence of metastatic involvement and lymphovascular invasion was detected (p=0.005, Fisher's exact test). Also, there was a moderately significant negative correlation between sen-

TABLE 2: The correlation between sentinel lymph node positivity and Breslow thickness and number of mitosis.

		Breslow thickness	Number of mitosis
Sentinel lymph node positivity	Pearson correlation	0.526**	0.588**
	Sig. (2-tailed)	0.000	0.000
	N	43	43

Note: The point-biserial correlation coefficient test; ** istatiksel yorumu içeriyor
p value: <0.05, statistically significant.

TABLE 3: The correlation between ulceration and Breslow thickness and number of mitosis.

	Breslow thickness	Number of mitosis
Ulceration	0.381	0.326
Total	43	43

Note: r, Pearson correlation test; p value: <0.05, statistically significant.

TABLE 4: The correlation between ulceration and sentinel lymph node positivity.

			Sentinel lymph node positivity		
			No	Yes	Total
Ulceration	No	Count	12	1	13
		% within ulceration	92.3%	7.7%	100.0%
	Yes	Count	15	15	30
		% within ulceration	50.0%	50.0%	100.0%
Total		Count	27	16	43
		% within ulceration	62.8%	37.2%	100.0%

Note: Fisher's exact test; p value: <0.05, statistically significant.

TABLE 5: The negative correlation between sentinel lymph node positivity and tumor infiltrating lymphocytes.

Correlations			
		SLNB_positivity	TILs
SLNB_positivity	Pearson correlation	1	-0.403**
	Sig. (2-tailed)		0.007
	N	43	43
TILs	Pearson correlation	-0.403**	1
	Sig. (2-tailed)	0.007	
	N	43	43

**Correlation is significant at the 0.01 level (2-tailed); SLNB: Sentinel lymph node biopsy; TILs: Tumor-infiltrating lymphocytes.

tinel lymph node biopsy (SLNB) positivity and TILs [rpb=-0.403 (point biserial correlation coefficient) p<0.007] (Table 5).

DISCUSSION

In this study, the clinicopathological data of the patients diagnosed with acral melanoma have been retrospectively evaluated. Acral melanoma was more common in males, though the ratio of female patients was higher in the literature varying from 50.8% to 59.5%.[9-11]

The mean age for diagnosis in our study was 62.7±13 which was similar to the literature.[12-16] As we compare the localization of primary melanoma lesions, out of 43 patients, the primary lesion was localized on the feet in 35 (81.3%) patients while in the remaining 8 (18.6%) patients, the primary lesion was localized on the hands. In the literature, Borkowska et al. reported that 84.6% of the acral melanoma cases were localized in the feet.[16] In another study, the ratio of the foot to hand melanoma was reported to be higher on feet with a ratio of 9:1.[13]

The Breslow thickness is one of the most important prognostic factors in melanoma. It is measured by the depth from the granular layer of the epidermis or from the base of the ulceration to the deepest point where the tumor invasion was observed. The studies have indicated that the Breslow thickness values of more than 4 mm, in particular, have been associated with poor prognosis.[7,14] In our study, the mean Breslow thickness was found to be 5.80 mm (0-29 mm). In 14 (32.6%) of the patients, the Breslow thickness was above 4 mm while in 29 (67.4%) patients it was found to be less than 4 mm. In different epidemiological studies, similar tumor thickness was reported.[7,15] The sentinel lymph node positivity in our study was detected in 16 (37.2%) patients, while it ranged between 22.2% and 28.3% in the other studies in the literature.[8,12] In our study, there was no statistically significant difference between age, sex, and Breslow thickness.

As stated in the previous studies, the presence of ulceration in melanoma is associated with a poorer prognosis.[16-18] In this respect, whereas the presence of ulceration in the patients in our study was 69.7%, the ulceration rate in the literature was in the range 25.5%-62.4%.[7-9,12,19,20] Our study yielded relatively higher median Breslow thickness values, sentinel lymph node positivities, and ulceration rates as compared to the previous studies. While there was metastatic involvement in 7.7% (n=1) of patients without ulceration, metastatic involvement was observed in 50% of patients with ulceration (n=15). A significant difference was found between patients without ulceration and patients with ulceration in terms of metastatic involvement (p=0.014, Fisher's exact test).

The examination of the sentinel lymph node is one of the leading factors in the treatment of melanoma. The sampling of the sentinel lymph node has been carried out routinely in many centers in cases where the Breslow thickness is higher than 1mm and where there exists ulceration. No doubt enabling the foreseeing of the sentinel lymph node positivity will constitute an important step in the treatment of the patients. Most of the previous studies have demonstrated that as the Breslow thickness increases, the sentinel lymph node positivity increases, too.[21-30]

Some authors also recommend performing SLNB in cases that have thin melanoma with evidence of extensive regression.[24,27] Our study also showed that the likelihood of sentinel lymph node positivity increases with an increase in Breslow thickness, ulceration, and mitosis rate. On the other hand, the results of the studies as to whether there is a correlation between the sentinel lymph node positivity and ulceration have been controversial. Whereas in some studies no relation could be established between the sentinel lymph node positivity and ulceration.[21-26] Nguyen et al. have shown that in addition to the Breslow thickness there existed a significant relationship between ulceration and mitosis and sentinel lymph node positivity.[27] In our study, we found a statistically significant correlation between the presence of ulceration with sentinel lymph node positivity (p=0.008). A moderate positive correlation was found between SLNB positivity and mitosis rate [rpb=0.588 (point biserial correlation coefficient, positive direction medium relationship)] (p<0.001). Taking into consideration the relationship between the ulceration and the sentinel lymph node positivity, our study also showed that there was a statistically significant difference in terms of the sentinel lymph node positivity between the patients with higher mitosis rate.

The relation between the ulceration and the number of mitoses and the Breslow thickness was also evaluated in our study. There was a statistically significant correlation between the ulceration and the number of mitoses (p=0.033). Also, a significant correlation between ulceration and Breslow thickness was detected (p=0.011). All these findings support that presence of ulceration is a good predictor not only for sentinel lymph node status but also for Breslow thickness and number of mitosis.

As the role of the immune response in melanoma has been better understood, it was shown that melanoma may induce the T lymphocytes that can recognize the tumor-specific antigens. These TILs are passed for reflecting the host response and were thought to have a critical role in melanoma progression. Although the role of TILs in cutaneous melanoma is not clear yet, in some studies they were reported to be associated with a good prognosis in terms of survival. Also in some studies, TILs were reported to be a predictor of lymph node metastases while in other studies no association between TILs and lymph node status was found.[31-33] In our study, there is a moderately significant negative correlation between SLNB positivity and lymphocytic infiltration [rpb=-0.403 (point biserial correlation coefficient) p<0.007].

LIMITATION

The main limitation of our study is being a retrospective study that was conducted in a single center. Also, no data were available regarding the survival rates of consulted cases.

CONCLUSION

Acral melanoma, as an aggressive subtype of melanoma, usually represents a higher tumoral thickness at the time of diagnosis as shown in this study. Alongside Breslow thickness, ulceration, mitosis rate, lymphovascular invasion, and presence of TILs are major predictors of sentinel lymph node positivity. As taking into consideration of the delayed prognosis of acral melanoma, in every patient presence and intensity of these parameters should be carefully evaluated during patient follow-up. Although we found no statistically significant difference between Breslow thickness with age and sex, in every age group, especially in the elderly, the clinical and dermoscopic examination of acral surfaces and the nail unit may provide early diagnosis and treatment of acral melanoma.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tuğba Kevser Uzunçakmak, Sera Nur Yücesoy;* ***Design:*** *Tuğba Kevser Uzunçakmak, Sera Nur Yücesoy, Özge Aşkın;* ***Control/Supervision:*** *Özge Aşkın, Server Serdaroğlu; Tuğba Kevser Uzunçakmak;* ***Data Collection and/or Processing:*** *Tuğba Kevser Uzunçakmak, Sera Yücesoy, Övgü Aydın;* ***Analysis and/or Interpretation:*** *Tuğba Kevser Uzunçakmak, Sera Nur Yücesoy, Ayşenur Özdil, Server Serdaroğlu;* ***Literature Review:*** *Tuğba Kevser Uzunçakmak, Sera Nur Yücesoy, Övgü Aydın;* ***Writing the Article:*** *Tuğba Kevser Uzunçakmak, Sera Nur Yücesoy, Övgü Aydın, Ayşenur Özdil;* ***Critical Review:*** *Özge Aşkın, Server Serdaroğlu;* ***References and Fundings:*** *Tuğba Kevser Uzunçakmak, Server Serdaroğlu; Sera Nur Yücesoy;* ***Materials:*** *Tuğba Kevser Uzunçakmak, Sera Nur Yücesoy, Övgü Aydın.*

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