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Factors Affecting Surgical Margin Positivity after Radical Prostatectomy in the Turkish Population: A Multicenter Study of the Urooncology Association

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Keywords
Prostate cancer · Radical prostatectomy · Surgical margin positivity · Predictive factors

Abstract
Background: The prediction of positive surgical margins (SM) after radical prostatectomy (RP) is important for planning the surgical modality and adjuvant therapy in patients with prostate cancer (PCa). ***Objectives:*** To investigate factors affecting SM positivity in patients diagnosed with PCa who underwent RP using the PCa database of the Urooncology Association (Turkey). ***Methods:*** Patients who underwent RP due to clinically T1c–T3 PCa and who had detailed SM data for the RP specimen were included in the study. Pathological data of 12 core transrectal ultrasound prostate biopsies and RP were evaluated. Patients were divided into 2 groups (SM positive and SM negative) according to SM status after RP. Data were compared between the groups. Factors affecting SM positivity, the number of positive SM sites, and the location of positive SM were separately evaluated with regression models. ***Results:*** A total of 2,643 patients from 6 different centers (median age: 63 years) with a prostate-specific antigen (PSA) level of 7.3 ng/mL were investigated in the study. BMI, PSA, biopsy Gleason score (GS), and perineural invasion (PNI) were found to be independent predictive factors for SM positivity and the number of positive SM locations, respectively ($p < 0.05$). According to the positive SM location, PSA was found to be associated with positive SM in apex, anterior prostate, and bladder neck locations. Also, according to posterolateral SM status, PNI and nerve-sparing RP (nsRP) rates were 21.3 and 44% for patients with negative posterolateral SM, and rates were 35.4 and 50.6% for patients with positive posterolateral SM, respectively ($p < 0.05$). In patients who underwent nsRP, positive SM was present in 22.2% of patients who did not have PNI on prostate biopsy, whereas positive SM was present in 40.6% of patients with PNI ($p < 0.001$). Similarly, 10.9% of patients without PNI had positive posterolateral SM, whereas 17.3% of patients with PNI had positive posterolateral SM ($p = 0.031$). ***Conclusions:***

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BMI, PSA, biopsy GS, and biopsy PNI positivity were found to be predictive factors affecting SM positivity. The most important factors affecting posterolateral positive SM were biopsy PNI and nsRP, indicating that the nsRP approach may cause positive SM in the posterolateral margin of the prostate (neurovascular bundle location) in patients with positive PNI on biopsy.

Introduction

Prostate cancer (PCa) is the most common cancer for men and cause of mortality and morbidity in patients around the world [1, 2]. A large proportion of all PCa patients suffer low-risk and intermediate-risk localized PCa, and these patients can be managed by radical prostatectomy (RP) as a curative approach. However, a few patients with PCa are diagnosed with high-risk localized and locally advanced PCa, and these patients with unfavorable pathological features and/or surgical margin (SM) positivity after RP must generally undergo adjuvant treatment [3, 4]. The prediction of positive SM is important for planning the surgical modality (such as nerve-sparing RP [nsRP] approach) and adjuvant therapy in patients with high-risk localized PCa. In these decision-making processes, unfavorable pathological features such as high Gleason score (GS) or high International Society of Urological Pathology (ISUP) grade (>7 GS or grade group >3), lymph node invasion, and seminal vesicle invasion, along with positive SM, are independent prognostic factors for PCa outcome after RP [5, 6]. All these prognostic factors also seem to be associated with each other. Because of the relationship between SM positivity and other unfavorable pathological features, defining factors to predict SM positivity will help in the management of PCa.

We aimed to investigate factors affecting SM positivity in patients diagnosed with PCa who underwent RP using the PCa database (PCD) of the Urooncology Association, Turkey (UOAT).

Materials and Methods

In this study, we retrospectively reviewed data from 3,300 patients in the PCD of UOAT. Reviewed data were completely anonymized by their centers before being entered into the PCD in compliance with local regulations. The PCD covers clinical and pathological data associated with PCa from 10 nationwide tertiary centers since 2005. The clinical staging method of the PCD includes rectal examination prior to biopsy and radiological evaluations after diagnosis, i.e., CT, bone scan, MRI, and ^{68}Ga-PSMA PET/CT imaging methods according to recommendations of yearly published guidelines. Patients who underwent RP (open RP, laparoscopic RP [LRP], or robot-assisted laparoscopic RP [RALRP]) due to clinically T1c–T3 PCa with detailed information about SM status at RP specimens were included in the study. Patients with missing pathological data for transrectal ultrasound prostate biopsy and RP were excluded. A total of 2,643 patients from 6 different centers were evaluated in the study. Patients' characteristics (age, body mass index [BMI]), clinical data (prostate-specific antigen [PSA] and clinical T stage), pathological data from 12 core transrectal ultrasound prostate biopsies (Gleason score [GS], ISUP grade, number of positive cores, percent tumor in positive core, presence of far-lateral tumor, perineural invasion [PNI], lymphovascular invasion and high-grade prostatic intraepithelial neoplasia [HGPIN]), surgical data (operation type [open, LRP, or RALRP] and nsRP approach), and pathological data for RP (GS, ISUP grade, PNI, lymphovascular invasion, extraprostatic extension [EPE], seminal vesicle invasion, SM, tumor volume, tumor density, and lymph node positivity) were evaluated. For pathological processing, the surgical specimen was fixed with buffered formaldehyde for 24–48 h. After the apical and bladder base slices had been removed, the prostate was sliced at 3-mm intervals, and all of the material was processed for microscopical analysis [7]. Patients were divided into 2 groups: SM-positive and SM-negative groups according to SM status after RP. Data were compared between the groups. Then, the factors affecting SM positivity were also evaluated by a regression model. Also, the factors affecting the number of positive SM sites, and the factors affecting the positive SM location (apex, anterior, and posterolateral prostate, bladder neck, and circumference of seminal vesicles) were separately evaluated using regression models.

Statistical Analysis

The *t* test, Mann-Whitney U test, and the χ^2 test were used to analyze the relationship between categorical and continuous variables in the groups. To detect predictive factors for positive SM, variables significant in univariate analysis were evaluated using a linear regression predictive model and logistic regression analysis. In addition, these factors were also evaluated to predict the number and location of positive SM using separate regression models. The statistical package for the social sciences (SPSS; version 22.0) was used for all statistical analyses. p values <0.05 were considered statistically significant.

Results

A total of 2,643 patients with a median age of 63 years and PSA level of 7.3 ng/mL were investigated in this study. Open RP, LRP, and RALRP procedures were performed in 60.3, 25.4, and 14.2% of patients, respectively. Also, the nsRP approach was performed in 921 (45.1%) patients. SM positivity was seen in 893 (33.8%) patients. Accordingly, 1,750 patients were in the SM-negative group, whereas 893 patients were in the SM-positive group. When we examined the location of SM positivity, 291 patients had positive SM at the apex of the prostate

Table 1. Comparison of clinical and pathological data of SM-negative and -positive patients after RP

	SM negative (*n* = 1,750)	SM positive (*n* = 893)	*p* value
Age, years	62.4±6.7 (41–87)	63.2±6.5 (41–83)	0.005
Body mass index, kg/m^2	26.7±3.6 (14.3–49.6)	27.7±4.1 (19.5–57.7)	0.004
Prostate-specific antigen, ng/mL	8.8±9.5 (1–196)	13±18.9 (1–118.4)	<0.001
Clinical T stage, *n* (*n* = 2,496)			
T1c	641 (38.7%)	213 (25.4%)	<0.001
T2a	311 (18.8%)	134 (16%)	
T2b	54 (3.3%)	23 (2.7%)	
T2c–T3	653 (39.2%)	469 (55.9%)	
Prostate biopsy total GS (*n* = 2,423)	6.3±0.9 (2–10)	6.8±1.1 (3–10)	<0.001
Prostate biopsy ISUP grade, *n* (*n* = 2,423)			
1	1,023 (58.5%)	321 (40.7%)	<0.001
2	414 (25.3%)	218 (27.6%)	
3	112 (6.9%)	98 (12.4%)	
4	55 (3.4%)	72 (9.1%)	
5	30 (1.8%)	80 (10.1%)	
Prostate biopsy			
Number of positive cores (*n* = 1,237)	2.8±2.2 (1–12)	3.9±3 (1–12)	<0.001
Percent tumor in positive core (*n* = 1,236))	42.8±31.1 (1–100)	56.7±34.4 (1–100)	<0.001
Presence of far-lateral tumor, *n* (*n* = 2,372)	454 (28.3%)	270 (35.1%)	0.001
PNI positivity, *n* (*n* = 2,058)	262 (18.8%)	232 (34.9%)	<0.001
LVI presence, *n* (*n* = 2,043)	54 (3.9%)	79 (11.9%)	<0.001
HGPIN presence, *n* (*n* = 1,997)	352 (25.8%)	144 (22.8%)	0.005
D'Amico risk classification for clinical T1c–T2c patients, *n* (*n* = 1,798)			
Low risk	476 (36.5%)	119 (24.1%)	<0.001
Intermediate risk	391 (30%)	152 (30.9%)	
High risk	438 (33.6%)	222 (45%)	
Operation type, *n* (*n* = 2,276)			
Open RP	930 (62.4%)	443 (56.4%)	0.001
Laparoscopic RP	375 (25.2%)	204 (26%)	
Robot-assisted RP	185 (12.4%)	139 (17.7%)	
Nerve-sparing RP, *n* (*n* = 2,044)	664 (47.7%)	257 (39.4%)	<0.001
Laterality, *n* (*n* = 906)			
Bilateral (*n* = 814)	593 (90.7%)	221 (87.7%)	0.184
Unilateral (*n* = 92)	61 (9.3%)	31 (12.3%)	
Right	29 (47.5%)	13 (41.9%)	0.610
Left	32 (52.5%)	18 (58.1%)	
RP pathological T stage, *n* (%)			
pT2	1,337 (76.4%)	427 (47.8%)	<0.001
pT3a	310 (17.7%)	229 (25.6%)	
pT3b	102 (5.8%)	227 (25.4%)	
pT4	1 (0.1%)	10 (1.1%)	
RP total GS (*n* = 2,618)	6.54±0.93 (3–10)	7.15±1 (3–10)	<0.001
Tertiary Gleason pattern (*n* = 306)	3.86±1.29 (1–5)	4.45±1 (1–5)	<0.001
RP ISUP grade, *n* (*n* = 2,618)			
1	787 (45%)	179 (20%)	<0.001
2	642 (37%)	349 (39.5%)	
3	173 (10%)	151 (17.1%)	
4	75 (4.3%)	75 (8.5%)	
5	58 (3.3%)	129 (14.6%)	
Clinical significance of PCa after RP, *n* (*n* = 2,627)			
Insignificant (GS <6, T2)	731 (42.1%)	151 (17%)	<0.001
Significant (GS >6, >T2)	1,006 (57.9%)	739 (83%)	
RP PNI positivity, *n* (*n* = 2,588)	747 (43.8%)	546 (61.9%)	<0.001
RP LVI presence, *n* (*n* = 2,586)	85 (5%)	157 (17.8%)	<0.001
RP EPE, *n*	413 (23.6%)	466 (52.2%)	<0.001
RP SVI, *n*	103 (5.9%)	237 (26.5%)	<0.001
RP tumor volume (*n* = 1,107)	3.8±5.3 (0.01–55)	11.1±17.2 (0.02–95)	<0.001
RP tumor density (*n* = 1,043)	13.8±15.5 (0.1–90)	24.2±22.2 (0.1–95)	<0.001
Patients with LND, *n* (*n* = 2,641)	812 (46.5%)	537 (60.1%)	<0.001
LN in patients with LND, (*n* = 1,349)	10±8.8 (1–57)	11.7±9.2 (1–68)	0.001
LN positivity, *n* (*n* = 1,036)	53 (6.5%)	101 (22.5%)	<0.001
Positive LN in patients with LN metastasis (*n* = 154)	2.1±2.6 (1–15)	2.7±2.5 (1–14)	0.196

Means ± SD (interquartile ranges) and n (%) are shown. *t* test, Mann-Whitney U test, and χ^2 test analyses were used. SM, surgical margin; GS, Gleason score; ISUP, International Society of Urological Pathology; PNI, perineural invasion; LVI, lymphovascular invasion; HGPIN, high-grade prostatic intraepithelial neoplasia; RP, radical prostatectomy; PCa, prostate cancer; EPE, extraprostatic extension; SVI, seminal vesicle invasion; LND, lymph node dissection; LN, lymph node.

Table 2. Factors affecting surgical margin (SM) positivity and predictive results of these factors on SM positivity

Model $p < 0.001$	Pearson correlation with positive SM (R)		p value[1]	HR	95% CI
	R	p value			
Age	0.053	0.007	0.227	–	–
Body mass index	0.129	0.004	0.004	0.017	0.005–0.028
Clinical T stage	0.2	<0.001	0.250	–	–
Prostate-specific antigen	0.160	<0.001	0.001	0.001	0.002–0.007
Prostate biopsy					
Gleason score	0.229	<0.001	<0.001	0.104	0.07–0.032
Number of positive cores	0.207	<0.001	0.16	–	–
Percent tumor in positive core	0.201	<0.001	0.989	–	–
Presence of far-lateral tumor	0.068	0.001	0.124	–	–
Presence of perineural invasion	0.177	<0.001	<0.001	0.154	0.079–0.229
Presence of lymphovascular invasion	0.151	<0.001	0.749	–	–
HGPIN presence	–0.032	0.157	0.318	–	–
Nerve-sparing radical prostatectomy	0.079	<0.001	0.1	–	–
Operation type	0.074	<0.001	0.571	–	–

HR, hazard ratio; CI, confidence interval; HGPIN, high-grade prostatic ıntraepithelial neoplasia.
[1] Linear regression analysis was used for prediction.

(12%), 162 at the anterior prostate (6.7%), 342 at the posterolateral prostate (14.1%), 65 at the bladder neck (2.7%), and 39 patients had positive SM in the circumference of seminal vesicles (1.6%). In terms of the number of positive SM, only 1 positive SM site was present in 500 (56.1%) patients, while 1 patient had 5 different positive SM sites (2, 3, and 4 positive SM sites were present in 132, 32, and 8 patients, respectively). Clinical data including 12 core prostate biopsies, surgical details, and RP pathological data for the SM status and corresponding univariate analysis results are given in Table 1. In multivariate analysis, BMI ($p = 0.004$, HR 0.017 [95% CI 0.005–0.028]), PSA ($p = 0.001$, HR 0.001 [95% CI 0.002–0.007]), biopsy GS ($p < 0.001$, HR 0.104 [95% CI 0.07–0.032]), and biopsy PNI ($p < 0.001$, HR 0.154 [95% CI 0.079–0.229]) were found to be independent predictive factors for SM positivity (factors were also found to be correlated with positive SM: $R = 0.129$, $p = 0.004$; $R = 0.160$, $p < 0.001$; $R = 0.229$, $p < 0.001$, and $R = 0.177$, $p < 0.001$; respectively; Table 2). In addition, the same factors were also found to be independent predictive factors for number of positive SM sites after multivariate analysis (for BMI $p = 0.005$, HR 0.020 [95% CI 0.006–0.035]; for PSA $p < 0.001$, HR 0.011 [95% CI 0.006–0.016]; for GS $p = 0.015$, HR 0.08 [95% CI 0.016–0.144], and for PNI $p = 0.005$, HR 0.161 [95% CI 0.048–0.274]; Table 3). When patients were examined according to locations of positive SM, it was observed that PSA was associated with positive SM in apex and anterior prostate and bladder neck locations (Table 3). Posterolateral SM positivity was associated with prostate biopsy PNI positivity ($p = 0.032$, HR 0.074 [95% CI 0.006–0.141]) and nsRP approach ($p = 0.044$, HR 0.057 [95% CI 0.002–0.112]; Table 3). When we examined PNI and nsRP rates according to the posterolateral SM status, PNI and nsRP rates were 21.3 and 44% for patients with negative posterolateral SM, and rates were 35.4 and 50.6% for patients with positive posterolateral SM, respectively ($p < 0.001$ and $p = 0.031$, respectively). In the patients who underwent nsRP, positive SM was present in 130 (22.2%) of 585 patients who did not have PNI on prostate biopsy, whereas positive SM was present in 76 (40.6%) of 187 patients with PNI ($p < 0.001$, OR 2.4 [95% CI 1.7–3.4]). Similarly, 62 (10.9%) of 564 patients without PNI had positive posterolateral SM, whereas 29 (17.3%) of 168 patients with PNI had positive posterolateral SM ($p = 0.031$, OR 1.69 [95% CI 1.05–2.73]).

Discussion

SM positivity is defined only if cancer cells are detected on the surface of the RP specimen during microscopic evaluation [8]. SM positivity occurs with a range from 6 to 41% after RP for localized PCa [9–11]. In the current

Table 3. Factors affecting surgical margin (SM) positivity according to positive SM location and number, and their predictive values

SM positivity	Pearson correlation of SM positivity (*R*)		*p* value[1]	HR	95% CI
	R	*p* value			
According to the location of positive SM					
In the apex of the prostate (model $p = 0.001$)					
PSA	0.079	<0.001	0.018	0.03	0.001–0.006
In the anterior prostate (model $p = 0.003$)					
PSA	0.114	<0.001	0.002	0.003	0.001–0.005
In the posterolateral prostate (model $p = 0.001$)					
PSA	0.059	0.005	0.147	–	–
Prostate biopsy PNI positivity	0.092	<0.001	0.032	0.074	0.006–0.141
Nerve-sparing RP	0.053	0.02	0.044	0.057	0.002–0.112
In the bladder neck (model $p < 0.001$)					
PSA	0.124	<0.001	<0.001	0.002	0.002–0.003
Near the seminal vesicle (model $p = 0.697$)	–		–	–	–
According to the number of positive SM (Model $p < 0.001$)					
BMI	0.136	0.005	0.005	0.020	0.006–0.035
PSA	0.152	<0.001	<0.001	0.011	0.006–0.016
Prostate biopsy Gleason score	0.178	<0.001	0.015	0.08	0.016–0.144
Prostate biopsy PNI positivity	0.148	<0.001	0.005	0.161	0.048–0.274

HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; PNI, perineural ınvasion; RP, radical prostatectomy.
[1] Linear regression analysis was used for prediction.

study, SM positivity was seen in 33.8% of our population. Positive SM depends on many factors, including patient characteristics, surgical technique, and tumor features [12]. The location of positive SM is related to tumor volume and tumor location within the prostate and generally occurs in posterior, posterolateral, anterior, and apical prostate, and bladder neck locations on prostate [8]. Most studies reported that the location of positive SM does not affect PCa prognosis and biochemical recurrence. However, among locations, predictivity for posterolateral SM positivity is important for developing surgical techniques because of the association with the neurovascular bundle, and this also affects the equilibrium between protecting erectile function and performing adjuvant treatment due to SM status after RP [8]. Apical SM positivity is one of the most frequent sites for positive margins [8]. Although organ-confined disease can generally be defined for PCa, intra- or extraprostatic SM cannot be determined with apical SM positivity [8]. SM of the bladder neck is composed of bladder muscle bundles. SM positivity in this location is usually related to EPE of the tumor from the base of the prostate. However, the prognostic importance of positive SM of the bladder neck has not been determined [13, 14]. In previous reports, anterior SM positivity was possibly associated with large transitional zone tumors that are diagnosed as stage T1a/b PCa after transurethral prostatectomy [8]. In previous studies, there is a clear association between the linear extent of SM positivity and biochemical recurrence [15–18]. When we look at the current study results, SM positivity in posterolateral, apical, anterior, and bladder neck locations were 14.1, 12, 6.7, and 2.7%, respectively. In SM-positive patients, 56.1% of patients had only 1 positive SM site according to the number of positive SM locations. BMI, PSA, biopsy GS, and biopsy PNI ($p \leq 0.001$) were independent predictive factors for SM positivity according to our results. Similarly, these predictive factors were also associated with the number of positive SM locations ($p < 0.05$). Also, PSA was independently associated with SM positivity for the locations of the prostate apex, anterior prostate, and bladder neck. However, posterolateral SM positivity was associated with prostate biopsy PNI positivity and nsRP approach ($p < 0.05$).

In previous studies that included a comparison of the type of RP approach, possibility rates for positive SM were found to be equivalent between open RP, LRP, and

RALRP approaches [19, 20]. In our series, no type of RP approach affected SM positivity in accordance with the literature.

Patient-related predictive factors for SM positivity were determined in previous reports. BMI was found to be one of the most important patient-related predictive factors for SM positivity after RP [21, 22]. When we look at the current study results, BMI was found to be an independent predictive factor for SM positivity after RP in accordance with the literature. Also, BMI was not found to be associated with any positive SM location, whereas it was related with the number of positive SM sites. These results show us that high BMI and presence of obesity causes higher SM positivity in patients with PCa who underwent RP.

The nsRP approach may be performed to protect erectile function after surgery in eligible patients. However, the risk of SM positivity may be increased in some patients after nsRP according to previous reports [23]. In one of the previous studies, Sofer et al. [24] reported that nsRP was not found to be associated with SM status or biochemical recurrence after RP. In their series, the nsRP approach was performed for 33% of patients, and they found that presence of EPE was a risk factor for SM positivity [24]. However, the EPE site is not only related to the region of the neurovascular bundle [25]. Therefore, nsRP is not contraindicated in patients who have a risk of EPE after RP [23, 26]. However, SM positivity is an independent prognostic factor for biochemical recurrence after RP [27]. Accordingly, in the prediction of the relationship between EPE risk of the neurovascular bundle region and nsRP, site-specific assessment was recommended [28]. Tumor volume, number of site-specific positive cores, GS, and tumor of the prostate base were predictors of site-specific EPE [28]. PSA, clinical stage, percentage of positive cores, percentage of tumor in positive cores, and PNI were also found to be predictors for EPE after RP in other previous studies [29–31]. In one of the previous studies, an algorithm was developed for use before the surgery, including GS, tumor volume, and PNI, to predict SM positivity in patients who were undergoing nsRP [23, 31]. In our series, the nsRP approach was performed in 45.1% of all patients, and the nsRP procedure was lower (39.4%) in patients with positive SM. However, the nsRP approach was found to be higher in posterolateral SM-positive patients compared to posterolateral SM-negative patients (50.6 vs. 44%, $p = 0.031$). When we look at the patients who underwent the nsRP approach, positive SM was present in 22.2% of 585 patients who did not have PNI on biopsy, whereas positive SM was present in 40.6% of 187 patients with PNI ($p < 0.001$). Similarly, 10.9% of 564 patients without PNI had positive posterolateral SM, whereas 17.3% of 168 patients with PNI had positive posterolateral SM ($p = 0.031$). According to these results, although the nsRP approach cannot cause positive SM in index patients, in patients with high risk of positive SM in the posterolateral prostate, such as EPE presence in the location of the neurovascular bundle on the radiological images and high BMI, the nsRP approach may cause positive posterolateral SM after RP. In addition, according to our retrospective data, it may be said that PNI positivity in prostate biopsy may cause posterolateral SM positivity after RP. However, there was not any clear relationship between PNI-positive biopsy core and positive SM location because of unknown PNI status for each biopsy core. Therefore, in order to clarify these possible findings, studies need to be planned to analyze the relationship between the number and location of PNI in biopsy cores, nsRP procedure, and location of positive SM in detail.

The major limitations of our study are its retrospective nature and analysis. Another important limitation is that there were changes proposed in the Gleason grading system over time. However, these proposed changes could not affect the results of the study because the obtained and compared pathological data for biopsy and RP were from the same time interval. Also, capsular incision, which is usually performed with posterolateral SM location in the range from 1.3 to 71% [7], was not assessed in the study. Although there was no centralized pathological examination, multicentric pathological examinations by uropathologists at respective centers and long-term data acquisition may reflect the real-life nationwide picture.

Conclusions

In conclusion, BMI, PSA, biopsy GS, and biopsy PNI positivity were found to be predictive factors affecting SM positivity. These factors were also found to be related to the number of positive SM sites. The most important factors affecting posterolateral positive SM were biopsy PNI and nsRP. Based on our findings, the nsRP approach may increase the risk of positive SM at the posterolateral region of the prostate (neurovascular bundle location) in patients with positive PNI on biopsy and should be further investigated.

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Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.Ç.: project development, data collection, data analysis, and manuscript writing; G.A.: project development, data collection, and manuscript editing; S.S., H.Ö., B.A., S.B., V.İ., Z.T., and L.T.: data collection and manuscript editing.

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