Original Article

DOI: 10.4274/uob.galenos.2022.2021.12.1

Bull Urooncol 2022;21(4):124-129

The Effects of Metabolic Syndrome on the Prediction of Prostate Cancer in Patients with a PSA Value of 2.5-4 ng/mL

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Abstract

Objective: In this study, the aim was to evaluate the effect of metabolic syndrome (MetS) and criteria on the diagnosis of prostate cancer (PCa) in patients with a prostate-specific antigen (PSA) value of 2.5-4 ng/mL.
Materials and Methods: A total of 116 patients who underwent transrectal ultrasound-guided prostate biopsy between January 2016- June 2018 with a PSA value of 2.5-4 ng/mL were included in the study. Patient height, body weight, waist circumference (WC) and blood pressure were measured and body mass indexes were calculated. Blood samples were also collected and tested for fasting and postprandial blood glucose, along with lipid profiles. Patients were divided into two groups as those with and without PCa. The presence of MetS was evaluated according to the measurements and laboratory results.
Results: Patients were divided into two groups as those without PCa (n=101) and those with PCa (n=15). A significant difference was found between the groups in terms of the frequency of hypertension (p=0.024). There were no significant differences between the groups in terms of other demographic characteristics. There was a significant difference between the groups in terms of hypertension, a criterion for MetS. The presence of MetS and other MetS criteria (WC >102 cm, triglyceride ≥150 mg/dL, high density lipoprotein <40 mg/dL, fasting blood glucose ≥110 mg/dL or type 2 diabetes mellitus) was not associated with PCa in patients with PSA levels of 2.5-4 ng/mL.
Conclusions: Among the MetS criteria, there was only a positive relationship between hypertension and PCa in patients with PSA 2.5-4 ng/mL.
Keywords: Prostate biopsy, prostate cancer, prostate-specific antigen, metabolic syndrome

Introduction

Prostate cancer (PCa) is the fourth most common cancer in the world and the second most common cancer in men. Globally, nearly 1.4 million PCa diagnoses were made in 2020 and it comprises 14.1% of all cancers in men (1).

Men with prostate-specific antigen (PSA) values below 4 mg/mL are identified to have cancer at a rate of 15.2% (2). Another study found the cancer detection rate was 27.48% in the group with PSA value from 2.5-4.0 ng/mL, while it was 30.08% for the group with PSA value 4.0-10.0 ng/mL (3). According to the study results, it is necessary to lower the PSA threshold value to 2.5 ng/mL as an indication for prostate biopsy.

Metabolic syndrome (MetS) was first defined by Reaven in 1988 and is a systemic endocrinopathy that causes a group of diseases like glucose intolerance, type 2 diabetes mellitus (DM), abdominal obesity, dyslipidemia, hypertension and coronary artery diseases (4,5). A meta-analysis showed that the presence of MetS in men was associated with the liver, colorectal and bladder cancer, whereas it was associated with endometrial, pancreas, postmenopausal breast, rectal and colorectal cancer in women (6).

There are different results in the literature related to PCa development in the presence of MetS (7-9). In this study, the aim was to assess the effect of MetS and criteria and PSA on the prediction of PCa in patients with PSA value from 2.5-4.0 ng/mL with prostate biopsy performed accompanied by transrectal ultrasonography (TRUS-Bx).

Materials and Methods

After obtaining approval from the Ethics Committee of University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (decision no: 3, date: 26/01/2015), the study was planned prospectively and included 116 patients with prostate biopsy performed from January 2016-June 2018 with/without

Cite this article as: Aydın ME, Bolat D, Kozacıoğlu Z, Deyirmenci Ö. The Effects of Metabolic Syndrome on the Prediction of Prostate Cancer in Patients with a PSA Value of 2.5-4 ng/mL. Bull Urooncol 2022;21(4):124-129

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Received: 20.12.2021 **Accepted:** 14.03.2022

lower urinary tract complaints, PSA value 2.5-4 ng/mL and age above 55 years. The patients did not have a history of urinary tract surgery, had no previous prostate biopsy history, had no PCa diagnosis, were not using 5-ARI, had no history of prostate abscess and acute prostatitis, no history of hypogonadism, no history of PCa in the family and no type 1 DM. All patients were given information with an informed consent form and signed consent was obtained from each patient.

All patients included in the study provided information about age, PSA, chronic diseases, medications used, smoking and alcohol use. Later, the patients' height, body mass (Wunder RA200), waist circumference (WC) and blood pressure values were measured. WC was measured on a horizontal plane at mid-level between the lowest level costa and iliac crest (10). Blood pressure measurements were taken on the right arm after 5 minute rest with a standard pressure device (Erka Perfect Aneroid) in the sitting position. Measurements were taken twice at 5 minute intervals and mean values were recorded. Body mass index (BMI) was calculated by dividing the body weight by the square of height and patients with values above 30 were assessed as obese. Blood samples were taken after 12 hour fasting with blood sugar, total cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL) and postprandial blood sugar tests (Beckman Coulter, Olympus AU 2700) examined 2 hour after eating.

All patients had prostate size measurements taken by digital rectal examination (DRE) and TRUS (BK Medical Flex Focus) before biopsy. Prostate sizes were calculated using the prolate ellipsoid formula: length x height x width x $\pi/6$ (11). The prostate biopsy procedure was performed after check-up urine culture showed no infection.

All patients with biopsy planned underwent 12 core systemic prostate biopsies via the transrectal route.

Patients were divided into two groups as those with and without PCa according to pathology results. Patients with benign prostate biopsy results but with repeat biopsy indications had re-biopsy performed and were added to the groups according to final pathology results. The presence of MetS was assessed with National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III) criteria (Table 1) (12). Patients with the presence of three or more criteria were diagnosed with MetS. In patients with PSA value from 2.5-4 ng/mL, the effect of MetS and components on PCa diagnosis was assessed.

Statistical Analysis

Analysis of data used the IBM SPSS Statistics 25.0 (Windows software) statistical program. Descriptive statistics for data used mean, standard deviation, minimum, maximum, frequency and percentage values. The normal distribution of numerical variables was assessed with the Kolmogorov-Smirnov ($n \geq 50$) or Shapiro-Wilk ($n < 59$) tests. Comparison of numerical variables in the two groups used the independent two-group t-test or the Mann-Whitney U test. Comparison of categoric variables used the chi-square or Fisher's Exact test. All tests of hypotheses were completed at $\alpha = 0.05$ significance level; in other words, $p < 0.05$ was accepted as statistically significant.

Table 1. NCEP: ATP III diagnostic criteria for metabolic syndrome

- The presence of three or more of these components:
- Abdominal obesity (waist circumference: >102 cm in men, >88 cm in women)
- Hypertriglyceridemia (≥150 mg/dL)
- Low HDL (<40 mg/dL in men, <50 mg/dL in women)
- Hypertension (blood pressure ≥130/85 mmHg)
- Hyperglycemia (fasting blood glucose ≥110 mg/dL)

NCEP: National Cholesterol Education Program, ATP: Adult Treatment Panel, HDL: High density lipoprotein

Results

The study included 116 patients with PSA value 2.5-4 ng/mL. Mean age of patients was 61.37±7.43 (44-79) years. Thirty-one patients (26.7%) had hypertension and 27 patients (23.3%) had type 2 DM. According to the BMI, 15 patients (12.9%) were assessed as obese. The mean WC of patients was 95.84±7.49 cm and fasting blood sugar was 92.81±15.03 mg/dL. The demographic characteristics, lipid and other laboratory values of patients are shown in Table 2.

According to the prostate biopsy results, 101 patients without PCa were included in group 1, while 15 patients with PCa were included in group 2. In group 2, 73.3% of the patients had a Gleason score of 3+3 (Table 3). In terms of demographic

Table 2. Demographic characteristics and laboratory values of patients

		n=116
Age (m ± SD) (min-max)		61.37±7.43 (44-79)
Height (cm) (m ± SD) (min-max)		172.84±6.67 (155-185)
Weight (kg) (m ± SD) (min-max)		80.2±10.47 (52-107)
BMI (kg/cm^2) (m ± SD) (min-max)		26.83±3.17 (18.9-37.9)
Obesity (n, %)		15 (12.1%)
Diagnosed with hypertension (n, %)		31 (26.7%)
Diagnosed with type 2 DM (n, %)		27 (23.3%)
Use of insulin (n, %)		5 (4.3%)
Use of metformin (n, %)		34 (29.3%)
Use of statin (n, %)		24 (20.7%)
Smoking (n, %)		36 (31%)
Use of alcohol (n, %)		27 (23.3%)
Waist circumference (cm) (m ± SD) (min-max)		95.84±7.49 (71-118)
Blood pressure (mm Hg) (m ± SD) (min-max)	Systolic	124.09±13.95 (100-180)
	Diastolic	78.97±7.62 (55-100)
Fasting blood sugar (mg/dL) (m ± SD) (min-max)		92.81±15.03 (72-163)
Postprandial blood sugar (mg/dL) (m ± SD) (min-max)		118.2±37.41 (53-300)
Cholesterol (mg/dL) (m ± SD) (min-max)		213.65±40.41 (114-374)
Triglycerides (mg/dL) (m ± SD) (min-max)		147.86±77.69 (50-500)
LDL (mg/dL) (m ± SD) (min-max)		139.13±47.26 (23-453)
HDL (mg/dL) (m ± SD) (min-max)		47.97±47.26 (21-90)

m: Mean, SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, LDL: Low density lipoprotein, HDL: High density lipoprotein, min-max: Minimum-maximum

Table 3. Pathology results of patients diagnosed with prostate cancer		
	Gleason score	n=15
Pathological staging of prostate cancer diagnoses (n, %)	3+3	11 (73.3%)
	3+4	2 (13.3%)
	4+3	1 (6.7%)
	4+4	1 (6.7%)

data, both groups had no differences identified in terms of age, BMI, smoking and alcohol habits. PCa patients had higher hypertension diagnoses compared to those without PCa and this difference was at statistically significant levels (53.5% vs. 22.8%, p=0.024). The other demographic data in both groups were similar (Table 4).

When measurements were compared between the two groups, there were no statistical differences found (Table 5).

In the non-PCa group, the number of MetS patients was 12 (11.9%), while there were 2 in the PCa group (13.3%) (p=1.000). The number of patients diagnosed with hypertension or with high blood pressure (>130/85 mmHg) when blood pressure is measured, alone among the MetS criteria, was found to be significantly high in those with PCa compared with those without PCa (53.3% vs. 27.7%, p=0.048). MetS and other MetS criteria on their own had no correlation with PCa in patients with PSA value 2.5-4 ng/mL (Table 6).

Discussion

The threshold value of 4 ng/mL began to be accepted from the beginning of the 1990s and this value was also assessed as the threshold for prostate biopsy indications in males with normal DRE for the diagnosis of PCa (13). Though high PSA values are more associated with malignancy, malignancy may be observed even at low PSA values (2). the prostate cancer prevention trial published in 2004 included 2,950 patients with PSA values below 4 ng/mL with normal DRE and identified PCa in 449 patients (15.2%) (2). A study of 36,316 patients by Gilbert et al. (3) found that the PCa rate was 21.8% with the PSA value interval from 2-2.5 ng/mL. For the intervals from 2.5-4 ng/mL and 4-10 ng/mL cancer identification rates were 27.4% and 30.0%, respectively, and were assessed as similar (3). Due to these results, it was proposed that a PSA of 2.5 ng/mL should be used as the threshold value.

In our study of 116 patients with PSA value from 2.5-4 ng/mL and prostate biopsy performed, 15 patients (12.1%) had PCa identified and this rate is low compared to data in the

Table 4. Comparison of patients' demographic data			
	Group 1 (n=101)	Group 2 (n=15)	p-value
Age (m ± SD)	61.10±7.28	63.20±8.42	0.309*
Height (cm) (m ± SD)	172.94±6.83	172.20±5.57	0.586**
Weight (kg) (m ± SD)	80.18±10.68	80.33±9.28	0.627**
BMI (kg/cm^2) (m ± SD)	26.78±3.18	27.13±3.28	0.961**
Obesity (n, %)	12 (11.9%)	3 (20%)	0.460***
Diagnosed with hypertension (n, %)	23 (22.8%)	8 (53.3%)	0.024***
Diagnosed with type 2 DM (n, %)	26 (25.7%)	1 (6.7%)	0.187***
Use of insulin (n, %)	5 (5%)	0 (0%)	1.000***
Use of metformin (n, %)	30 (29.7%)	4 (26.6%)	1.000***
Use of statin (n, %)	21 (20.8%)	3 (20%)	1.000***
Smoking (n, %)	31 (30.7%)	5 (33.3%)	1.000***
Use of alcohol (n, %)	23 (22.8%)	4 (26.7%)	0.748***
m: Mean, SD: Standard deviation, BMI: Body mass index, DM: Diabetes mellitus, *Student t-test, **Mann-Whitney U, ***Fisher's Exact test			

Table 5. Comparison of measurements and laboratory values between groups				
		Group 1 (n=101)	Group 2 (n=15)	p-value
Waist circumference (cm) (m ± SD)		95.78±7.61	96.20±6.88	0.990*
Blood pressure (mmHg) (m ± SD)	Systolic	123.96±14.38	125.00±11.02	0.440*
	Diastolic	78.91±7.83	79.33±6.23	0.587*
Fasting blood sugar (mg/dL) (m ± SD)		92.31±15.34	96.20±12.74	0.127*
Postprandial blood sugar (mg/dL) (m ± SD)		117.05±37.30	126.53±38.39	0.534*
Cholesterol (mg/dL) (m ± SD)		213.33±40.79	215.80±39.06	0.630*
Triglycerides (mg/dL) (m ± SD)		150.22±81.07	132.00±48.23	0.477*
LDL (mg/dL) (m ± SD)		138.34±49.04	144.47±33.76	0.226*
HDL (mg/dL) (m ± SD)		48.13±10.31	46.93±9.35	0.720*
m: Mean, SD: Standard deviation, LDL: Low density lipoprotein, HDL: High density lipoprotein, *Mann-Whitney U				

Table 6. Relationship of metabolic syndrome and criteria for prostate cancer				
		Group 1 (n=101)	Group 2 (n=15)	p-value
Abdominal obesity (waist circumference >102 cm) (n, %)		12 (11.9%)	3 (20%)	0.409*
Hypertriglyceridemia (≥150 mg/dL) (n, %)		31 (30.7%)	4 (26.7%)	1.000*
Low HDL (<40 mg/dL) (n, %)		16 (15.8%)	4 (26.7%)	0.289*
Hypertension (blood pressure ≥130/85 mmHg) or anti-hypertensive drug use (n, %)		28 (27.7%)	8 (53.3%)	0.048*
Hyperglycemia (fasting blood glucose ≥110 mg/dL) or presence of type 2 DM (n, %)		26 (25.2%)	2 (13.3%)	0.518*
Distribution of patients by MetS criteria (n, %)	0 1 2 3 4	36 (35.6%) 32 (31.7%) 21 (20.8%) 9 (8.9%) 3 (3%)	3 (20%) 6 (40%) 4 (26.7%) 1 (6.7%) 1 (6.7%)	0.730*
Number of MetS diagnostic criteria (m ± SD)		1.12±1.09	1.40±1.12	0.321**
Presence of MetS (n, %)		12 (11.9%)	2 (13.3%)	1.000*
m: Mean, SD: Standard deviation, HDL: High density lipoprotein, DM: Diabetes mellitus, MetS: Metabolic syndrome, *Fisher's Exact Test, **Mann-Whitney U				

international literature. The reason for this may be ethnic structure and differences in lifestyle. Additionally, the small number of patients in our study may have caused this difference.

MetS is a systemic endocrinopathy and according to one of the most comprehensive studies of the NCEP-ATP III, the MetS prevalence in the USA is 23.7% (14). A study in our country identified MetS in 28% of males (15). Another study in Turkey in 2010 determined the prevalence of MetS as 41.4% in men (16). In our study, 14 of the 116 patients included in the study (12.1%) had MetS diagnosis. When data from the world in general and from Turkey are examined in the literature, this rate is lower. The selection of the patient population may have caused this difference.

Hypertension and Prostate Cancer

In our study, the MetS criterion of hypertension on its own was found to be significantly high in those with PCa compared with those without PCa (p=0.048). When the literature is examined, a meta-analysis by Esposito et al. (17) showed that hypertension increased the PCa risk by 15%. A meta-analysis by Gacci et al. (7) in 2017 investigated 7 studies and showed that hypertension was the only MetS component significantly associated with PCa, causing a 10% increase in PCa risk.

In the literature, there are studies with contrary findings to our study. In Sweden, 336,159 men were monitored and 10,002 patients received PCa diagnosis with an inverse correlation was observed between high blood pressure and PCa risk (18). Again, a study in Sweden followed 289,866 patients for mean 12 years and there was no correlation found between high blood pressure and PCa incidence (9). Worldwide studies are needed to explain the correlation and physiopathology between hypertension and PCa, as these studies both reflect the Swedish population.

Waist Circumference and Prostate Cancer

One of the MetS criteria of WC is used as a marker of abdominal obesity. WC is a marker of visceral fat mass and this situation is considered to have occurred because of different visceral fat mass among those with similar BMI (19). Esposito et al. (17) investigated MetS and PCa in a meta-analysis and found that WC above 102 cm increased the risk of PCa by 56%. Research in Canada in 2015 assessed WC above and below 102 cm and observed no difference between the groups with and without PCa in terms of WC (20).

Boehm et al. (19) assessed subgroups according to BMI in 2015, and WC above 102 cm was shown to increase PCa risk by 23%. In our study, there was no significant correlation found between WC and PCa. In our study, the mean age of patients was higher compared to studies, which found a significant correlation and this may have caused this situation.

Obesity and Prostate Cancer

Obesity is defined as BMI >30 kg/m^2 and is among the MetS diagnostic criteria of the World Health Organization (21). A study with the ProtecT study group found no correlation between BMI and PCa. As the natural progression of PCa is long term, it is thought that obesity at early ages may increase the risk of PCa (22).

A systematic review investigating 56 studies and 68,753 patients by MacInnis et al. (23) found that every 5 kg/m^2 increase in BMI increased PCa risk by 5% and increased risk of advanced-stage PCa by 12%. However, the patient measurements assessed in this review were variable in terms of being performed before, during and after diagnosis.

The REDUCE study showed that obesity did not increase PCa risk; simultaneously, there were associations with reduced risk of low-grade PCa and increased risk of high-grade PCa. Obesity is stated to be a risk factor for high-grade disease independent of PSA levels (24). A 2015 study in Canada observed that those with PCa had significantly lower BMI (20). Again, a study in 2015 by Boehm et al. (19) showed that obese patients had significantly lower prostate risk. The different results obtained in studies were linked to differences in the study groups. Though people have similar BMI, the body fat distribution may be different between populations (19).

A 2017 study of the prostate, lung, colorectal and ovarian cohort compared those with BMI >30 kg/m^2 from 20 to 50 years of age with those with BMI from 18.5-25 kg/m^2 and observed a significant degree of reduction in PCa risk. This inverse correlation was explained by PSA hemodilution in obese cases reducing the diagnosis of PCa (25).

In our study, there was no difference between obese and non-obese patients in terms of PCa. The small total patient numbers and incidence of obesity may have affected our results.

Serum Lipids and Prostate Cancer

The role of serum lipids in PCa risk is unclear. The meta-analysis by Esposito et al. (17) investigated 7 studies, including 3,866 cases and found that high triglyceride levels increased PCa risk by 11% and low HDL levels (<40 mg/dL) increased PCa risk by 7%. However, these correlations were weak and not statistically significant. In 2015, a meta-analysis investigating 14 prospective studies in different populations did not find a correlation between total cholesterol, HDL and LDL with PCa risk (26). A meta-analysis study of MetS and PCa in 2017 investigated 8 studies on triglyceride and HDL and found no significant correlation with PCa risk. They explained this situation as due to the heterogeneity of the investigated studies (7).

In our study, there were no differences in terms of serum lipid levels between patients without PCa and those with PCa. Our study, being cross-sectional and including small patient numbers, may have prevented the investigation of this situation.

Hyperglycemia and Prostate Cancer

A meta-analysis by Esposito et al. (17) investigated 9 studies including 4,211 patients and did not show a correlation between hyperglycemia and DM with PCa. A meta-analysis by Gacci et al. (7) investigating 10 studies showed high fasting blood glucose (≥110 mg/dL) or DM diagnosis did not increase PCa. They explained this situation as due to not knowing the duration of DM disease and the efficacy of glycemic control of the treatment given (7).

A study by Dankner et al. (27) followed 1 million men for mean 11 years and showed that PCa risk increased in the first year following diagnosis in patients developing DM and reduced in later years. A study of the ProtecT patient group showed that the presence of DM reduced PCa risk by 22% (28).

When DM worsens, testosterone levels fall and this may result in low PSA (27). The low PCa incidence in men with DM may be explained by low PSA level and fewer biopsies being performed (27). Additionally, because of damage to pancreatic beta cells in long-term DM, insulin levels may fall below those of men without DM. This hypoinsulinemia may directly suppress prostate carcinogenesis or indirectly by reducing the levels or activity of insulin-like growth factor 1 (IGF-1), a risk factor for PCa (29).

In our study, there was no correlation between DM and PCa. The lack of knowledge about the duration of DM and the low number of patients with DM may be insufficient to explain this correlation.

Metabolic Syndromes and Prostate Cancer

When MetS and PCa risk is assessed, there are different outcomes have in the literature. A study including 6,429 people with 385 PCa patients reported 23% fewer patients with MetS developed PCa. This situation was associated with low androgen levels in MetS (30). Blanc-Lapierre et al. (20) found that patients with MetS had PCa risk reduced significantly by 30%. The cause was predicted to be low insulin, IGF-1 and testosterone levels (20).

Bhindi et al. (31) found that the components of MetS on their own did not increase PCa risk, while the PCa risk significantly increased as the number of components increased and those with 3 or more components had 54% greater PCa risk compared with those without any component. The reason for this increase was thought to be the greater number of biopsies and increased diagnostic frequency (31).

However, another study including 1,880 patients with mean 13-year follow-up found that PCa development was 1.9 times greater in MetS patients and associated this with IGF-1 metabolism, sex hormones and SHBG disorder. This was the first study in the literature showing that MetS increased the PCa risk (32).

Esposito et al. (17) found that patients with MetS had 12% increase in PCa risk. They stated that correlations between MetS and PCa may be different between races and PCa detection rates may display differences between countries (17). Gacci et al. (7) reported MetS increased PCa risk by 17%. Simultaneously, high-grade PCa (GS ≥8) risk was significantly increased. MetS criteria alone are not effective, but the combination of these criteria was correlated with PCa (7).

Another meta-analysis by Hammarsten et al. (8) revealed a reduction in low-grade PCa risk and an increase in high-grade PCa risk. They explained that the diagnostic frequency of low-grade PCa reduced due to reasons such as low PSA levels due to low testosterone levels leading to small numbers of patients with biopsy, and reduced sensitivity of biopsy due to large prostate volume in MetS patients. Because of PSA-focused diagnostic procedures, diagnosis was made at high-grade due to progression of PCa in MetS (8).

In our study, only the MetS component of hypertension was found to have a significant correlation with PCa. The other criteria on their own or the presence of MetS diagnosis were not correlated with PCa.

Study Limitations

The most important limitation of this study was the limited number of patients. Additionally, the low diagnostic frequency of MetS may have prevented the determination of a significant correlation between PCa and MetS.

Conclusions

MetS and PCa are two common situations related to the aging population around the world. In our study, only the MetS component of hypertension was found to correlate positively with PCa. Though some factors associated with MetS appear to be related to PCa, the definite relationship between these two will remain uncertain until all these factors are researched in detail.

Acknowledgements

Publication: Abstract of this manuscript was presented as an oral presentation at the 14th Urooncology Congress in Antalya, Turkey on 6-10 November 2019.

Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Ethics Committee Approval: After obtaining approval from the Ethics Committee of University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (decision no: 3, date: 26/01/2015).

Informed Consent: All patients were given information with an informed consent form and signed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.E.A., Design: M.E.A., Supervision: D.B., Z.K., Data Collection or Processing: Ö.D., Analysis-Interpretation: D.B., Z.K., Literature Review: M.E.A., Writing: M.E.A., D.B., Critical Review: Z.K.

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