**Original Article**

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# Evaluation of Serum STARD3 Levels in Patients With Breast and Prostate Cancer: A Case-Control Study

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**ABSTRACT**

**Objective:** Cancer cells exhibit high metabolic demands and rely heavily on lipid metabolism for proliferation and membrane synthesis. Lipid transfer proteins, particularly the steroidogenic acute regulatory-related lipid transfer domain 3 (STARD3), play a significant role in intracellular cholesterol transport and may influence cancer progression. The aim of this study was to investigate serum STARD3 levels in patients with breast and prostate cancer and compare them with healthy controls, along with lipid parameters.

**Materials and Methods:** Patients with breast cancer (women) and prostate cancer (men) were recruited together with a control group matched by age-range and sex. Serum samples were collected, and STARD3 levels were measured using a commercial ELISA kit. Lipid parameters and tumor markers (carbohydrate antigen 15-3, prostate-specific antigen) were also evaluated.

**Results:** A total of 200 individuals were enrolled: 50 female breast cancer patients, 50 male prostate cancer patients, and 100 healthy controls. STARD3 levels were significantly lower in both breast cancer ($p$ = 0.045) and prostate cancer ($p$<0.001) groups compared to controls. However, no significant correlation was found between STARD3 levels and other biochemical parameters or tumor stage in either cancer group.

**Conclusion:** The results suggest that STARD3 may play a role in the pathogenesis of both hormone-related cancers, although the mechanism remains unclear. Given the limited studies evaluating STARD3 in both breast and prostate cancers simultaneously, our findings contribute novel data to the literature and may guide future research into the diagnostic or prognostic potential of STARD3 in oncology.

**Keywords:** Breast cancer; lipids; prostate cancer; STARD3

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**Key Points**

- Serum steroidogenic acute regulatory-related lipid transfer domain 3 (STARD3) levels were significantly lower in both breast and prostate cancer patients compared to healthy controls.
- No significant correlation was found between STARD3 levels and tumor markers or clinical parameters in either cancer group.
- This is the first study to evaluate serum STARD3 levels simultaneously in breast and prostate cancer.

## Introduction

Cancer is one of the leading causes of death in developed countries. Cancer cells exhibit an accelerated metabolic rate and require a continuous supply of cholesterol for cell division and membrane renewal (1). As tumors grow or metastasize, they trigger new lipid synthesis in order to adapt for future environmental conditions (2). Lipids play essential roles in metabolism, cellular homeostasis, and various biological activities. In normal tissue, lipogenesis is primarily limited to hepatocytes and adipocytes. However, cancer cells activate lipogenesis in response to their high metabolic demands or to the lack of serum-derived lipids in the tumor microenvironment, even in the presence of exogenous lipid sources (3). In addition to the metabolic and structural functions of lipids, they also act as intracellular and intercellular signaling molecules. Membrane phospholipids are hydrolyzed by phospholipases into lipid mediators (e.g., diacylglycerol, phosphatidic acid, lysophosphatidic acid, and arachidonic acid). Some of these, such as arachidonic acid, are further converted into prostaglandins and

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leukotrienes through the cyclooxygenase and lipoxygenase pathways, respectively. These bioactive lipids are secreted by cancer cells and function as autocrine or paracrine mediators, regulating various cellular processes involved in tumor development and metastasis, including proliferation, migration, invasion, and angiogenesis (4, 5).

Recent studies have shown characteristic changes in lipid parameters between patients with invasive breast cancer and those with benign breast tumors. These alterations are also observed in patients with different molecular subtypes of breast cancer (6). The metastatic potential of cancer cells is influenced by processes, such as fatty acid synthesis, oxidation, and intracellular lipid storage. These metabolic changes are important for metastasis of breast and prostate cancers (7, 8). High-density lipoprotein (HDL) exhibits functions including cholesterol efflux, and has antioxidant and anti-inflammatory properties. Through these effects, HDL may reduce oxidative stress, inflammation, and cholesterol content in tumor cells, thereby affecting their proliferation (9). Cancer cells may be capable of synthesizing cholesterol or acquiring it through low-density lipoproteins (LDL). Hormone-dependent tumors, such as prostate and breast cancers require cholesterol for proliferation (10).

Lipid transfer proteins (LTPs) are involved in the distribution of cholesterol between organelles. Among LTPs, certain members of the steroidogenic acute regulatory-related lipid transfer (START) protein family regulate cholesterol transport across organelles. Changes in their expression levels are involved in various diseases, including cancers. One membrane-targeted START protein, StAR-related lipid transfer domain-3 (STARD3), has been proposed as a regulator of cholesterol accumulation in endosomes and its inter-organelle distribution (1). The possible molecular mechanism by which STARD3 contributes to tumorigenesis is through the transport of cholesterol across mitochondrial membranes (11). Some researchers have hypothesized that STARD3 may be involved in the transfer of cholesterol from late endosomes to the endoplasmic reticulum and subsequently to mitochondria via mitochondria-associated membranes (12). Although the precise molecular mechanism remains unclear, current evidence suggests that high STARD3 expression affects membrane cholesterol accumulation, which may contribute to cancer aggressiveness. Amplification or overexpression of STARD3 in cancer may induce the movement of lysosomal cholesterol to mitochondria, potentially promoting the progression of hormone-driven cancers, such as breast and prostate cancers, by triggering independent steroidogenesis (1, 13). Most cells acquire cholesterol from plasma via LDL receptor-mediated endocytosis. STARD3, one of the cholesterol transporters in late endosomes/lysosomes, contributes to the transport of late endosomal/lysosomal cholesterol to other cellular compartments (14).

As STARD3 is a key protein in cholesterol trafficking in cancer cells, assessing its activity has recently gained interest. In the present study, serum STARD3 protein levels were measured in patients diagnosed with breast and prostate cancer, as well as in healthy controls, using ELISA analysis, and the lipid profiles of these three groups were compared with a focus on STARD3.

## Materials and Methods

### Study Population

This study included 50 female patients diagnosed with breast cancer and 50 male patients diagnosed with prostate cancer between August and December 2024. The control group consisted of healthy individuals (50 females and 50 males) within the same age range. Individuals with a history of cancer, systemic chronic diseases (chronic heart disease, chronic lung disease, chronic kidney failure, and liver disease), malabsorption disorders (celiac disease or radiation enteritis), thyroid and parathyroid diseases, those receiving hormone replacement therapy, individuals with psychiatric disorders, alcohol users, and pregnant women were excluded from the control group. The participants' total cholesterol, LDL, HDL, triglyceride levels, and preoperative tumor markers, specifically carbohydrate antigen 15-3 and prostate-specific antigen were evaluated. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Yozgat Bozok University Ethics Committee (protocol code: 2024-GOKAEK-247_2024.07.17_99, date: 17.07.2024). Informed consent was obtained from all subjects involved in the study.

### ELISA Analysis

Fasting venous blood samples were taken in the morning (7:00–8:00 a.m.). Blood samples were collected in a 5 mL serum-separating vacuum tube and centrifuged at 3000 rpm for 10 minutes to separate the serum. The obtained serum samples were stored at –20 °C until further analysis. Serum STARD3 levels were measured using a commercially available ELISA kit (Cat. No. E7700Hu, Bioassay Technology Laboratory, Zhejiang, China), with a measurement range of 0.63 ng/mL to 40 ng/mL. The optical density values of the samples and standards were measured at 450 nm using the Thermo Scientific (USA) Multiscan Go Microplate Reader. The results were expressed in ng/mL.

### Statistical Analysis

Statistical analyses were performed using SPSS, version 20 (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables between groups were analyzed using the chi-square test or Fisher's exact test. Comparisons between groups were conducted using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Correlation analysis was performed using Pearson's test for normally distributed data and Spearman's test for non-normally distributed data. A $p$-value of less than 0.05 was considered statistically significant.

## Results

The demographic characteristics, laboratory results, preoperative tumor markers, and ELISA findings of the study groups are presented in Table 1 and Table 2. When the groups were statistically compared, no significant differences were found in age and cholesterol levels between the breast cancer and control groups, nor in age and glucose levels between the prostate cancer and control groups ($p$>0.05). However, other parameters showed statistically significant differences between the groups ($p$<0.05).

The breast cancer group had significantly lower levels of serum STARD3 compared to the control group ($p$ = 0.045) (Table 1, Figure 1). Moreover, the prostate cancer group also had significantly lower levels of serum STARD3 compared to the control group ($p$<0.001) (Table 2, Figure 2).

**Table 1. Demographic, laboratory, tumor marker, and STARD3 results and comparisons between breast cancer patients and healthy individuals**

| | Groups | | |
|---|---|---|---|
| | **Control (*n* = 50)** | **Breast cancer (*n* = 50)** | ***p*** |
| **Age (year)** | 56.34±6.76 (57.0) | 55.67±14.75 (55.0) | 0.863 |
| **STARD3 (ng/mL)** | 15.20±7.89 (12.65) | 13.04±8.23 (11.65) | **0.045** |
| **HDL (mg/dL)** | 54.02±17.47 (48.3) | 32.69±11.97 (33.0) | **<0.001** |
| **LDL (mg/dL)** | 136.24±38.18 (129.22) | 169.13±49.86 (174.5) | **0.002** |
| **Cholesterol (mg/dL)** | 217.35±42.62 (217.1) | 217.10±56.97 (215.0) | 0.921 |
| **TG (mg/dL)** | 143.70±62.52 (138.4) | 238.77±67.09 (229.0) | **<0.001** |
| **Glucose (mg/dL)** | 110.69±49.90 (97.7) | 127.98±31.47 (130.0) | **<0.001** |
| **HbA1C (%)** | 6.22±1.13 (6.11) | 6.35±0.53 (6.4) | **0.006** |
| **CA15-3 (U/mL)** | | 58.87±65.45 (38.8) | |
| **Stage of cancer, n (%)** | | | |
| **Stage 1** | | 11 (22) | |
| **Stage 2** | | 15 (30) | |
| **Stage 3** | | 12 (24) | |
| **Stage 4** | | 12 (24) | |

STARD3: StAR-related lipid transfer domain-3; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; HbA1c: Hemoglobin A1c; CA15-3: Carbohydrate antigen 15-3. The results are expressed as frequency (%), mean±standard deviation and median (interquartile range). Significant *p* (<0.05) values are in bold

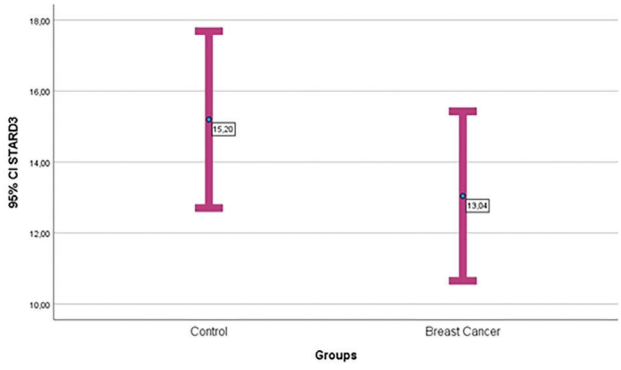


**Figure 1.** Distribution of serum STARD3 levels between the breast cancer group and the control group

*STARD3: StAR-related lipid transfer domain-3*

Correlation analysis of STARD3 serum levels in the breast and prostate cancer patient groups found no significant correlations between STARD3 and other parameters, age, lipid profile components, glucose, hemoglobin A1c or tumor markers, in either group (Tables 3, 4). The relationship between cancer stage and STARD3 was also analyzed. In the breast cancer group, since the variances were homogeneously distributed ($p$ = 0.203), a one-way ANOVA test was performed, but no significant difference was found in STARD3 levels between cancer stage groups ($p$ = 0.851). In the prostate cancer group, the variances were not homogeneously distributed ($p$<0.001), and thus the non-parametric Kruskal-Wallis test was used, which also showed no significant difference ($p$ = 0.103).

## Discussion and Conclusion

The present study is the first to evaluate serum STARD3 levels in breast and prostate cancer patients in relation to lipid parameters. We found that STARD3 levels were significantly lower in both the breast and prostate cancer groups compared to healthy controls. However, no significant association was found between lipid levels and STARD3.

In a recent study, higher levels of total cholesterol, LDL-C, and triglycerides (TG) were statistically associated with negative expression of estrogen receptor (ER) and progesterone receptor, positive human epidermal growth factor receptor 2 (HER2) status, non-luminal subtypes, and solitary lesions. Low HDL-C levels were linked specifically to negative ER expression. Tumors from patients with high LDL-C and low HDL-C levels exhibited a higher nuclear grade. Furthermore, patients with elevated TG and reduced HDL-C levels presented with more advanced disease stages, whereas total cholesterol and LDL-C levels showed no significant association with cancer stage (15). Johnson et al. (16) demonstrated through locus-specific Mendelian randomization analyses targeting HDL- and LDL-related genes that increased HDL and LDL levels may have a direct effect on breast cancer risk. Ossoli et al. (9) reported that HDL may inhibit LDL-induced cell proliferation by reducing intracellular cholesterol content in prostate cancer cell lines, suggesting that cholesterol plays a key role in prostate cancer progression. These findings highlight the therapeutic potential of targeting cellular cholesterol homeostasis as a strategy to suppress tumor growth. Another study found that high total serum cholesterol was associated with an increased risk of high-grade prostate cancer, while no association was observed between cholesterol levels and the risk of overall or low-grade prostate cancer. Interestingly, elevated serum HDL was linked to a higher risk of both

**Table 2. Demographic, laboratory, tumor marker, and STARD3 results and comparisons between prostate cancer patients and healthy individuals**

| | Groups | | |
|---|---|---|---|
| | **Control (*n* = 50)** | **Prostate cancer (*n* = 50)** | ***p*** |
| **Age (year)** | 57.95±6.49 (58.0) | 58.08±7.27 (58.0) | 0.776 |
| **STARD3 (ng/mL)** | 16.95±8.85 (13.22) | 10.79±8.65 (8.98) | **<0.001** |
| **HDL (mg/dL)** | 42.02±10.05 (39.6) | 34.92±12.14 (35.0) | **0.021** |
| **LDL (mg/dL)** | 115.35±35.17 (110.88) | 150.64±50.98 (134.0) | **0.002** |
| **Cholesterol (mg/dL)** | 191.86±39.97 (188.6) | 215.18±55.56 (220.0) | **0.025** |
| **TG (mg/dL)** | 179.06±92.02 (161.0) | 254.58±68.51 (262.5) | **<0.001** |
| **Glucose (mg/dL)** | 125.69±65.17 (104.0) | 119.92±36.06 (107.0) | 0.621 |
| **HbA1C (%)** | 5.85±0.58 (5.8) | 6.31±0.62 (6.3) | **<0.001** |
| **PSA (ng/mL)** | - | 66.29±161.35 (16.8) | - |
| **Stage of cancer, n (%)** | | | |
| **Stage 1** | | 28 (52) | |
| **Stage 2** | | 4 (8) | |
| **Stage 3** | | 6 (12) | |
| **Stage 4** | | 5 (10) | |
| **Stage 5** | | 7 (14) | |

STARD3: StAR-related lipid transfer domain-3; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; HbA1c: Hemoglobin A1c; PSA: Prostate-specific antigen. The results are expressed as frequency (%), mean ± standard deviation and median (interquartile range). Significant *p* (<0.05) values are in bold

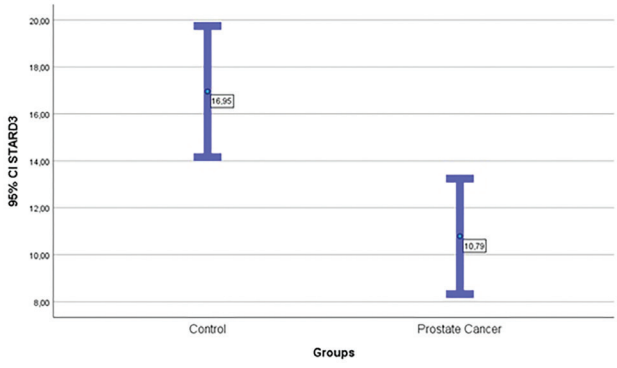


**Figure 2.** Distribution of serum STARD3 levels between the prostate cancer group and the control group

*STARD3: StAR-related lipid transfer domain-3*

overall and high-grade prostate cancer, while serum LDL levels showed no significant correlation with prostate cancer risk (17). In both breast and prostate cancer patients, LDL and TG levels were significantly higher and HDL levels significantly lower compared to healthy controls. Moreover, total cholesterol levels were notably elevated in the prostate cancer group. The significantly decreased levels of STARD3 observed in our cohort suggest that this protein may play a role in lipid metabolism and that its expression could be suppressed during tumor development.

According to the 2022 GLOBOCAN report, breast cancer is the second leading cause of cancer-related death among women in the United States (18). A significant proportion of breast cancer patients experience recurrence and frequently develop metastases. HER2 overexpression is present in approximately 15% to 20% of breast cancers and is generally associated with an increased risk of developing systemic metastases and poor survival outcomes (19). The *STARD3* gene has been reported to be co-amplified with HER2 in breast carcinoma. STARD3 is essential for cholesterol transport and metabolism in tumor cells. It has been demonstrated that STARD3 expression is significantly associated with HER2+ breast cancer tumors and breast cancer cell lines, while low levels of STARD3 mRNA and protein expression have been observed in ER-positive (ER+) and triple-negative breast cancer patients (20). Lodi et al. (21) found that STARD3 expression was strongly associated with pathological complete response in a cohort of 112 patients with HER2+ breast cancer. They suggested that identifying STARD3 overexpression in baseline biopsies of HER2+ tumors may provide additional value in managing a subgroup of patients who are less likely to achieve a pathological response. Vassilev et al. (22) reported that STARD3-overexpressing cells exhibited non-adherent morphological characteristics and altered cholesterol homeostasis. In a study conducted in Finland, approximately 10% of breast cancer cases displayed high STARD3 protein levels that were strongly associated with HER2 amplification. Furthermore, the results provided evidence that STARD3 overexpression leads to increased cholesterol biosynthesis in breast cancer cells. This suggests that high STARD3 expression may contribute to the aggressiveness of breast cancer by increasing membrane cholesterol and enhancing oncogenic signaling. Analysis of a total of 136 samples obtained from 85 female breast cancer patients showed that STARD3 overexpression enhanced the prognostic power of HER2 overexpression in predicting disease-free survival (23).

**Table 3. Correlation coefficient values in the breast cancer patient group**

| | STARD3 | Age | HDL | LDL | Cholesterol | TG | Glucose | HbA1C | CA15-3 |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | 0.102 | 1.000 | | | | | | | |
| **HDL** | -0.184 | -0.130 | 1.000 | | | | | | |
| **LDL** | 0.155 | 0.172 | 0.074 | 1.000 | | | | | |
| **Cholesterol** | 0.149 | 0.069 | -0.204 | -0.137 | 1.000 | | | | |
| **TG** | 0.026 | -0.246 | 0.215 | -0.178 | -0.046 | 1.000 | | | |
| **Glucose** | 0.036 | -0.142 | 0.087 | 0.021 | 0.065 | 0.101 | 1.000 | | |
| **HbA1C** | 0.128 | 0.063 | -0.117 | 0.187 | -0.017 | -0.131 | **0.492**** | 1.000 | |
| **CA15-3** | -0.231 | 0.050 | -0.093 | -0.122 | -0.260 | -0.145 | -0.138 | **0.295*** | 1.000 |
| **Stage** | 0.172 | -0.153 | -0.055 | -0.087 | 0.017 | 0.046 | -0.026 | -0.013 | 0.063 |

**: Correlation was significant at the 0.01 level (2-tailed); *: Correlation was significant at the 0.05 level (2-tailed); STARD3: StAR-related lipid transfer domain-3; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; HbA1c: Hemoglobin A1c; CA15-3: Carbohydrate antigen 15-3

**Table 4. Correlation coefficient values in the prostate cancer patient group**

| | STARD3 | Age | HDL | LDL | Cholesterol | TG | Glucose | HbA1C | PSA |
|---|---|---|---|---|---|---|---|---|---|
| **Age** | -0.068 | 1.000 | | | | | | | |
| **HDL** | -0.104 | -0.027 | 1.000 | | | | | | |
| **LDL** | -0.081 | 0.169 | 0.193 | 1.000 | | | | | |
| **Cholesterol** | -0.147 | -0.240 | 0.114 | 0.140 | 1.000 | | | | |
| **TG** | 0.054 | 0.039 | -0.103 | 0.067 | -0.194 | 1.000 | | | |
| **Glucose** | -0.034 | 0.133 | **0.329*** | 0.083 | 0.075 | -0.151 | 1.000 | | |
| **HbA1C** | 0.006 | 0.100 | **0.437**** | **0.336*** | 0.038 | -0.045 | **0.786**** | 1.000 | |
| **PSA** | 0.170 | 0.241 | -0.014 | 0.044 | 0.059 | 0.046 | 0.077 | 0.111 | 1.000 |
| **Stage** | 0.275 | 0.149 | 0.158 | -0.127 | -0.004 | **-0.385**** | 0.100 | 0.020 | 0.263 |

**: Correlation was significant at the 0.01 level (2-tailed); *: Correlation was significant at the 0.05 level (2-tailed); STARD3: StAR-related lipid transfer domain-3; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; HbA1c: Hemoglobin A1c; PSA: Prostate-specific antigen

Malignant breast cancer tissues were found to have higher levels of STARD3 immuno-expression compared to normal tissues. STARD3 is strongly correlated with HER2+ breast cancer, suggesting that it may serve as a potential biomarker for this cancer subtype (24).

The prostate is an organ regulated by androgens. Androgens exert three main effects on prostate cells: they promote proliferation; support differentiation; and inhibit programmed cell death or apoptosis (25). When reviewing the limited number of published studies concerning prostate cancer and STARD3, a linear correlation has been identified between STARD3 expression and the expression of CYP17, an enzyme involved in the steroid biosynthesis pathway. In prostate cancer, the expression of STARD3 and CYP17 may lead to steroidogenesis through continuous cholesterol transfer to the mitochondria and increase androgen biosynthesis through the catalytic activity of cytochrome CYP17. Therefore, dysregulated expression of STARD3 and CYP17 is associated with poor prognosis in prostate cancer patients (26). Another study showed that high mitochondrial cholesterol levels could inhibit apoptotic cell death in various cancer types, thereby potentially driving tumor progression (22). STARD3 overexpression in cancer may support the development of hormone-dependent cancers, such as prostate cancer, by promoting independent steroidogenesis. High STARD3 levels in prostate cancer patients are associated with metastasis, local recurrence, and shorter overall survival. For these reasons, *STARD3* is considered a potential oncogene for which the first inhibitor has already been reported (1).

**Study Limitations**

This study has certain limitations. First, it was conducted at a single center with a limited sample size, which may restrict the generalizability of the results. Second, STARD3 levels were assessed only in serum via ELISA, providing no information regarding tissue-level expression or cellular localization. Lastly, although the study evaluated the correlation between STARD3 levels and the lipid profile, other potential metabolic pathways and molecular mechanisms were not investigated.

In conclusion, the current literature on STARD3 remains limited. Although recent studies have explored the relationship between STARD3 and cancer, there are no studies that have simultaneously evaluated STARD3 in both breast and prostate cancer cases. In this context, our research provides unique data and may serve as an important resource for future investigations. Future studies with larger patient cohorts, inclusion of tissue-based analyses, and long-term follow-up data will help to better elucidate the role of STARD3 in cancer biology.

## Ethics

**Ethics Committee Approval:** The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Yozgat Bozok University Ethics Committee (protocol code: 2024-GOKAEK-247_2024.07.17_99, date: 17.07.2024).

**Informed Consent:** Informed consent was obtained from all subjects involved in the study.

## Footnotes

### Authorship Contributions

Concept: A.N.K., D.Ş.A., N.İ.; Design: A.N.K., D.Ş.A., N.İ.; Data Collection or Processing: A.N.K., M.B.B., D.Ş.A., A.N.K., Ş.B., A.Ö., N.İ.; Analysis or Interpretation: A.N.K., M.B.B., D.Ş.A., A.Ö., N.İ.; Literature Search: A.N.K., D.Ş.A., N.İ.; Writing: A.N.K., M.B.B., D.Ş.A., A.N.K., Ş.B., A.Ö., N.İ.

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

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