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Thiol-disulfide homeostasis in ovarian cancer: comparative analysis with benign neoplasia and healthy women

Over kanserinde tiyol-disülfit homeostazı: benign neoplaziler ve sağlıklı kadınlarla karşılaştırmalı analiz

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Abstract

Objective: To evaluate thiol-disulfide (DS) homeostasis in women with ovarian cancer and to assess its ability to distinguish malignant ovarian tumors from benign ovarian neoplasia and healthy women.

Materials and Methods: This prospective comparative study included 39 women with histopathologically confirmed ovarian cancer, 30 with benign ovarian neoplasia, and 46 age- and body mass index-matched healthy women. Serum native thiol (NT), total thiol (TT), DS, and ischemia-modified albumin (IMA) levels were measured. Thiol-DS indices were calculated as DS/NT (DNT), DS/TT (DTT), and NT/TT (NTT). Data were analyzed statistically. The study was registered at ClinicalTrials.gov (NCT05011539).

Results: Compared with healthy women, the ovarian cancer group exhibited lower NT, TT, and NTT values, along with higher DS, DNT, and DTT values. When malignant and benign ovarian neoplasms were compared, NT and NTT values were lower, whereas DNT and DTT ratios were higher. IMA levels did not differ between groups. Serum CA-125 levels were positively correlated with DNT and DTT, and negatively correlated with NT, TT, and NTT.

Conclusion: Thiol-DS imbalance is more pronounced in ovarian cancer than in benign ovarian neoplasia and in healthy women, suggesting that these markers may be useful adjuncts in the preoperative evaluation of adnexal masses.

Keywords: Ovarian cancer, thiol, disulfide, oxidative stress, biomarker

Öz

Amaç: Over kanseri olan kadınlarda tiyol-disülfit (DS) homeostazını değerlendirmek ve bu dengenin malign over tümörlerini benign over neoplazileri ve sağlıklı kadınlardan ayırt etme potansiyelini araştırmaktır.

Gereç ve Yöntemler: Bu prospektif karşılaştırmalı çalışmaya histopatolojik olarak doğrulanmış over kanseri tanısı olan 39 kadın, benign over neoplazisi olan 30 kadın, yaş ve vücut kitle indeksi açısından eşleştirilmiş 46 sağlıklı kadın dahil edildi. Serum native tiyol (NT), total tiyol (TT), DS ve iskemi

PRECIS: In this prospective comparative study, women with ovarian cancer showed reduced thiol levels and increased disulfide indices compared with women with benign ovarian neoplasia and healthy women, reflecting a pronounced oxidative imbalance.

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modifiye albümin (IMA) düzeyleri ölçüldü. Tiyol-DS indeksleri; DS/NT (DNT), DS/TT (DTT) ve NT/TT (NTT) oranları olarak hesaplandı. Veriler istatistiksel olarak analiz edildi. Çalışma ClinicalTrials.gov'a kaydedilmiştir (NCT05011539).

Bulgular: Sağlıklı kadınlarla karşılaştırıldığında over kanseri grubunda NT, TT ve NTT değerleri daha düşük, DS, DNT ve DTT düzeyleri ise daha yüksek bulundu. Malign ve benign over neoplazilerinin karşılaştırılmasında NT ve NTT değerleri malign grupta daha düşükken, DNT ve DTT oranları daha yüksekti. Gruplar arasında IMA düzeyleri açısından anlamlı fark saptanmadı. Serum CA-125 düzeyleri DNT ve DTT ile pozitif, NT, TT ve NTT ile negatif korelasyon gösterdi.

Sonuç: Tiyol-DS dengesindeki bozulma, benign over neoplazileri ve sağlıklı kadınlara kıyasla over kanserinde daha belirgindir. Bu bulgular, tiyol-DS homeostazı belirteçlerinin adneksiyal kitlelerin preoperatif değerlendirilmesinde tamamlayıcı araçlar olarak kullanılabileceğini düşündürmektedir.

Anahtar Kelimeler: Over kanseri, tiyol, disülfit, oksidatif stres, biyobelirteç

Introduction

Ovarian cancer is the most lethal gynecologic malignancy, and survival outcomes have shown only limited improvement despite advances in treatment[1,2]. The absence of an effective population-based screening strategy contributes substantially to late-stage detection. Although transvaginal ultrasonography and serum CA-125 measurement are frequently used in clinical practice, CA-125 alone has restricted diagnostic accuracy due to its low specificity and variable sensitivity, particularly when distinguishing malignant from benign adnexal masses[3-5]. This limitation highlights the need for additional biochemical markers that may aid in evaluating ovarian tumors.

Oxidative stress plays an important role in carcinogenesis by promoting DNA damage, altering cell survival pathways, enhancing chemoresistance, and increasing metastatic potential[6]. These biological effects emerge from an imbalance between reactive oxygen species (ROS) and endogenous antioxidant defenses, suggesting that redox alterations may reflect underlying tumor behavior.

Thiol-disulfide homeostasis (TDH) constitutes a key component of the antioxidant system. Native thiols (NTs) can reversibly oxidize to form disulfide (DS) bonds, and the dynamic equilibrium between these two forms provides a quantitative indicator of oxidative status[7,8]. Disruption of this balance has been reported in several malignant conditions. Ischemia-modified albumin (IMA), generated through oxidative modification of serum albumin, has likewise been studied as a marker of oxidative stress in ischemic and neoplastic disorders[9,10].

The present study aimed to evaluate TDH and IMA levels in women with ovarian cancer and to compare these findings with those in benign ovarian neoplasia and healthy women. Our objective was to determine whether these oxidative markers may assist in differentiating malignant ovarian tumors from benign adnexal masses.

Materials and Methods

This prospective comparative study was conducted at a tertiary obstetrics and gynecology department between April 2021 and January 2022. Ethical approval was obtained from the University of Health Sciences Türkiye, Tepecik Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021/04-10, date: 15.04.2021). All participants provided written and verbal informed consent prior to enrollment. The study was registered at ClinicalTrials.gov (NCT05011539) and conducted in accordance with the Declaration of Helsinki. All participants were evaluated and managed according to the same institutional protocols for adnexal masses.

Women presenting with a pelvic mass and scheduled for surgery were invited to participate. Only patients whose final histopathological diagnosis confirmed benign or malignant ovarian neoplasia were included. Patients with borderline ovarian tumors were excluded from the analysis. All malignant cases underwent primary surgery at our center. Patients referred after receiving neoadjuvant chemotherapy or who were previously treated elsewhere were excluded.

Similarly, women with extra-ovarian malignancies, acute inflammatory conditions, or chronic systemic diseases known to influence oxidative stress—such as diabetes mellitus, autoimmune disorders, thyroid dysfunction, or chronic inflammatory diseases—were not eligible.

Participants were also excluded if they smoked, consumed alcohol regularly, used antioxidant vitamin supplements (A, C, or E), or had cognitive limitations that could interfere with informed consent. Cognitive limitation refers to any documented neurological, psychiatric, or developmental condition impairing comprehension or decision-making.

The control group consisted of healthy women presenting for routine gynecologic check-ups during the study period. These women had no adnexal pathology, chronic systemic disease, or conditions affecting oxidative stress. They were prospectively matched to the patient groups based on two criteria: age within ±3 years and body mass index within ±2 kg/m².

Matching was performed sequentially during recruitment to ensure that participants in the ovarian neoplasia groups were comparable to those in the healthy control group.

Age, height, weight, gravida, parity, and medical history were recorded for all participants. Preoperative serum CA-125 levels for the patient groups were retrieved from the hospital information system.

For biochemical assays, 5 mL of pre-prandial venous blood was collected from surgical patients during hospitalization and from controls during outpatient visits. Samples were centrifuged, aliquoted, stored at -80 °C, and transported under appropriate conditions to an accredited, university-affiliated central laboratory.

Serum NT and total thiol (TT) levels were quantified using the automated spectrophotometric method developed by Erel and Neselioglu[8]. DS concentrations were calculated using the formula DS = (TT-NT)/2. Based on these measurements, thiol-DS indices were calculated as follows: the DS/NT ratio (DNT) was calculated as (DS/NT) x 100, the DS/TT ratio (DTT) was calculated as (DS/TT) x 100, and the native thiol/total thiol ratio (NTT) was calculated as (NT/TT) x 100.

IMA levels were measured using the albumin cobalt binding technique and expressed in absorbance units.

All women in the malignant neoplasia group underwent primary cytoreductive surgery. Staging was performed according to the International Federation of Gynaecology and Obstetrics (FIGO) ovarian cancer classification system. Benign lesions were managed surgically according to standard gynecologic practice. All pathological assessments were based on the final histopathological examination rather than on frozen-section results.

Statistical Analysis

Statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test together with Q-Q plots, while homogeneity of variances was examined using Levene's test. Comparisons between two groups were performed using the independent samples t-test when variables were normally distributed and the Mann-Whitney U test when they were not. Comparisons among three groups were analyzed using one-way ANOVA, with post-hoc testing by Tukey HSD or Tamhane, as appropriate, when the data were normally distributed, or with the Kruskal-Wallis test for non-normally distributed variables. Results were presented as mean ± standard deviation for normally distributed data and as median with interquartile range for non-normally distributed variables. A p-value below 0.05 was considered statistically significant.

Results

A total of 115 women were included in the study: 39 with malignant ovarian neoplasia, 30 with benign ovarian neoplasia, and 46 healthy controls. Among the benign lesions, the most frequent diagnoses were fibroma (23%), mature cystic teratoma (23%), endometrioma (20%), serous cystadenoma (17%), and mucinous cystadenoma (17%). In the malignant group, high-grade serous carcinoma was the predominant subtype (59%), followed by endometrioid carcinoma (13%), mucinous carcinoma (8%), granulosa cell carcinoma (8%), low-grade serous carcinoma (5%), clear cell carcinoma (5%), and dysgerminoma (2%). FIGO staging for malignant ovarian neoplasms was as follows: 14 patients were classified as stage I, 3 as stage II, 18 as stage III, and 4 as stage IV.

When demographic characteristics were compared across the three groups (malignant, benign, and control), no statistically significant differences were observed in age, body mass index, gravidity, or parity (all p>0.05) (Table 1).

Compared with healthy controls, women with malignant ovarian neoplasia had significantly higher serum DS levels and DNT and DTT ratios (p=0.009, p<0.001, and p<0.001, respectively). Conversely, NT, TT, and NTT values were significantly lower in the malignant group (all p<0.001). IMA levels did not differ significantly between the two groups (p=0.672) (Table 2).

When compared with all participants without malignancy (benign + control), the malignant group again showed significantly increased DS, DNT, and DTT values (all p<0.001) and significantly reduced NT, TT, and NTT levels (all p<0.001). IMA levels remained similar between groups (p=0.768) (Table 3).

A direct comparison of malignant and benign ovarian neoplasia revealed no significant differences in DS, TT, or IMA levels (p=0.081, p=0.057, and p=0.235, respectively). However, NT levels and NTT values were significantly lower in the malignant group (p=0.046 and p=0.012, respectively), while DNT and DTT ratios were significantly higher (both p=0.012). As expected, CA-125 levels were markedly elevated in the malignant group compared with the benign group (p<0.001) (Table 4).

Table 1. Comparison of three groups (malignant, benign, and control) according to demographic and clinical characteristics

Variables	Malignant ovarian neoplasia (n=39)	Benign ovarian neoplasia (n=30)	Control group (n=46)	p-value[a]
Age (years; mean ± SD)	53.41±7.57	49.60±7.10	52.13±5.51	0.065[b]
BMI (kg/m^2; mean ± SD)	29.46±6.12	27.29±3.15	29.27±4.94	0.155[b]
Gravidity (median, 25-75%)	2 (1-3)	3 (1-3)	2 (1-4)	0.988[c]
Parity (median, 25-75%)	2 (1-3)	2 (1-3)	2 (1-3)	0.872[c]

[a]: Significant at 0.05 level, [b]: One-way analysis of variance (ANOVA), [c]: Kruskal-Wallis test, BMI: Body mass index, SD: Standard deviation

Correlation analysis performed in women with ovarian neoplasia (benign and malignant) demonstrated a positive correlation of CA-125 with both DNT and DTT (r=0.38, p=0.001 for each). Significant negative correlations were observed between CA-125 and NT, TT, and NTT (r=-0.36, p=0.002; r=-0.34, p=0.004; and r=-0.38, p=0.001, respectively). When the analyses were repeated including only epithelial ovarian cancers from the malignant group, the results were consistent with those obtained in the overall malignant cohort.

Table 2. Comparison of malignant disease group and control group in terms of biochemical parameters

Variables	Malignant ovarian neoplasia (n=39)	Control group (n=46)	p-value[a]
Disulfide (µmol/L; median, 25-75%)	14.55 (11.25-18.95)	13.05 (11.26-14.18)	0.009[a,c]
NT (µmol/L; mean ± SD)	200.03±49.79	287.58±45.37	<0.001[a,b]
TT (µmol/L; median, 25-75%)	232.60 (204.30-260.20)	320.50 (281.20-342.70)	<0.001[a,c]
DNTx100 (median, 25-75%)	6.76 (5.37-12.75)	4.95 (3.63-5.24)	<0.001[a,c]
DTTx100 (median, 25-75%)	5.95 (4.85-10.16)	4.50 (3.39-4.74)	<0.001[a,c]
NTTx100 (median, 25-75%)	88.08 (79.68-90.28)	90.98 (90.51-93.21)	<0.001[a,c]
IMA (ABSU; median, 25-75%)	0.81 (0.73-0.94)	0.83 (0.65-0.99)	0.672[c]

[a]: Significant at 0.05 level, [b]: Independent samples t-test; [c]: Mann-Whitney U test, SD: Standard deviation, NT: Native thiol, TT: Total thiol, DNT: Disulfide/native thiol, DTT: Disulfide/total thiol, NTT: Native thiol/total thiol, IMA: Ischemia modified albumin, ABSU: Absorbance units

Table 3. Comparison of malignant disease group and others (benign + control) in terms of biochemical parameters

Variables	Malignant ovarian neoplasia (n=39)	Others (benign + control) (n=76)	p-value[a]
Disulfide (µmol/L; median, 25-75%)	14.55 (11.25-18.95)	12.60 (11.31-14.51)	0.010[a,c]
NT (µmol/L; mean ± SD)	200.03±49.79	264.29±61.78	<0.001[a,b]
TT (µmol/L; median, 25-75%)	232.60 (204.30-260.20)	304.40 (262.30-338.30)	<0.001[a,c]
DNTx100 (median, 25-75%)	6.76 (5.37-12.75)	5.19 (4.58-5.78)	<0.001[a,c]
DTTx100 (median, 25-75%)	5.95 (4.85-10.16)	4.70 (4.20-5.18)	<0.001[a,c]
NTTx100 (median, 25-75%)	88.08 (79.68-90.28)	90.58 (89.63-91.59)	<0.001[a,c]
IMA (ABSU; median, 25-75%)	0.81 (0.73-0.94)	0.82 (0.69-0.91)	0.768[c]

[a]: Significant at 0.05 level; [b]: Independent samples t-test; [c]: Mann-Whitney U test, SD: Standard deviation, NT: Native thiol, TT: Total thiol, DNT: Disulfide/native thiol, DTT: Disulfide/total thiol, NTT: Native thiol/total thiol, IMA: Ischemia modified albumin, ABSU: Absorbance units

Table 4. Comparison of malignant disease group and benign disease group in terms of biochemical parameters

Variables	Malignant ovarian neoplasia (n=39)	Benign ovarian neoplasia (n=30)	p-value[a]
Disulfide (µmol/L; median, 25-75%)	14.55 (11.25-18.95)	12.45 (11.25-15.40)	0.081[c]
NT (µmol/L; mean ± SD)	200.03±49.79	228.57±67.05	0.046[a,b]
TT (µmol/L; median, 25-75%)	232.60 (204.30-260.20)	263.10 (208.40-312.70)	0.057[c]
DNTx100 (median, 25-75%)	6.76 (5.37-12.75)	5.55 (5.22-6.69)	0.012[a,c]
DTTx100 (median, 25-75%)	5.95 (4.85-10.16)	5.00 (4.72-5.90)	0.012[a,c]
NTTx100 (median, 25-75%)	88.08 (79.68-90.28)	90.00 (88.18-90.54)	0.012[a,c]
IMA (ABSU; median, 25-75%)	0.81 (0.73-0.94)	0.77 (0.69-0.90)	0.235[c]
CA-125 (U/mL; median, 25-75%)	263.00 (57-535)	18.00 (14-42)	<0.001[a,c]

[a]: Significant at 0.05 level, [b]: Independent samples t-test, [c]: Mann-Whitney U test, SD: Standard deviation, NT: Native thiol, TT: Total thiol, DNT: Disulfide/native thiol, DTT: Disulfide/total thiol, NTT: Native thiol/total thiol, IMA: Ischemia modified albumin, ABSU: Absorbance units

Discussion

The present study demonstrates that TDH, characterized by depleted NTs and increased disulfide-derived indices, is significantly impaired in women with ovarian cancer compared with both benign ovarian neoplasia and healthy women. The inclusion of a benign neoplasia group is clinically relevant because these lesions commonly mimic malignancy radiologically or by elevation of CA-125; however, our findings indicate that the oxidative shift in thiol-DS balance is more pronounced in malignant disease. These results suggest that TDH indices reflect biological processes that are more specific to malignant transformation than to non-specific inflammatory or cystic pathology, supporting their potential role as adjunctive biomarkers in the preoperative evaluation of adnexal masses.

A possible explanation for the more pronounced thiol-DS imbalance in ovarian cancer is the persistently increased oxidative stress associated with malignant transformation. ROS are known to promote tumor progression through effects on cell survival, proliferation, and invasion, while thiols represent a major component of antioxidant defense[6,7]. In this context, lower thiol levels and higher oxidation-related ratios in the malignant group may reflect increased thiol consumption in response to tumor-related oxidative burden. A more marked alteration observed in ovarian cancer compared with benign ovarian neoplasia may therefore indicate that thiol-DS homeostasis is influenced not only by the presence of an adnexal mass but also by its malignant biological behavior.

Oxidative stress is a fundamental driver of malignant transformation. ROS facilitate DNA mutations, epigenetic instability, angiogenesis, and remodeling of the tumor microenvironment, effectively promoting multiple hallmarks of cancer[6]. ROS also influence cell survival pathways such as MAPK, PI3K/Akt, and Nuclear factor kappa B signaling, promoting proliferation while inhibiting apoptosis[11]. Ovarian cancer has been shown to exhibit distinct oxidative signatures, including increased ROS generation and metabolic reprogramming that enhances oxidative phosphorylation activity[4]. Against this biological landscape, thiols—primarily cysteine residues on proteins and glutathione—function as key antioxidants buffering oxidative stress. As thiols neutralize ROS, they undergo reversible oxidation to generate DS bonds, which can subsequently be reduced back to thiols, making TDH an indicator of dynamic redox balance[7,8].

In the present study, decreased NT, TT, and NTT levels in ovarian cancer patients reflect diminished antioxidant capacity, while elevated DS, DNT, and DTT levels represent a compensatory increase in oxidized products. These findings align with the biochemical model proposed by Erel and Erdoğan[7], who emphasized that elevated DS formation signals consumption of NTs under oxidative challenge. Mechanistically, lower thiol levels may reflect increased cellular turnover, heightened mitochondrial ROS production, and metabolic stress associated with proliferating tumor tissue. Similar thiol-DS disturbances have been described in other malignancies, including breast, lung, endometrial, cervical, and prostate cancers, in which thiol-DS balance partially normalized following tumor resection, suggesting that TDH alterations may reflect tumor presence rather than patient predisposition. The consistency of TDH derangements across distinct tumor types supports the concept that redox disruption is a shared metabolic phenotype of malignancy[12-16].

When malignant ovarian tumors were compared with benign ovarian neoplasia, our findings demonstrated significantly reduced NT and NTT, and increased DNT and DTT in malignant disease. This observation is clinically relevant because benign lesions—including endometriomas, fibromas, and mature cystic teratomas—may mimic malignant disease radiologically or through elevation of CA-125. Earlier research in benign gynecologic conditions suggests that oxidative stress is present but quantitatively less pronounced than in malignancy. For example, Karatas et al.[17] reported altered TDH in uterine fibroids but with a magnitude lower than that observed in gynecologic cancers. This distinction may explain why thiol depletion and DS elevation are more pronounced in ovarian cancer than in benign tumors.

The significant correlations observed between CA-125 and thiol-DS indices further strengthen the argument that TDH reflects tumor activity. The positive association between CA-125 and DNT/DTT and the negative association with NT/NTT suggest that as tumor burden increases, the oxidative conversion of thiols to disulfides intensifies. These relationships persisted when analyses were restricted to epithelial ovarian cancers, supporting applicability across the most clinically relevant subtypes. Similar correlations between tumor markers and oxidative parameters were observed in endometrial, cervical, and prostate cancer, suggesting potential prognostic or monitoring value[14-16]. While no conclusions about causality can be inferred due to the cross-sectional nature of our study, these findings highlight the potential of TDH parameters as dynamic biomarkers warranting longitudinal evaluation.

Unlike TDH parameters, IMA levels did not differ significantly between malignant and non-malignant groups in our cohort. This outcome is consistent with the biochemical nature of IMA formation, which is primarily driven by abrupt ischemia-reperfusion injury causing structural modification of the amino-terminal region of albumin[9]. Huang et al.[10] reported inconsistent performance of IMA in chronic gastric malignancy and suggested that IMA is more reflective of acute hypoxia than sustained oxidative stress. The chronic non-ischemic oxidative environment in ovarian cancer likely does not produce the rapid albumin modifications required to increase IMA which explains its limited diagnostic value in this context.

Beyond diagnosis, several studies have proposed prognostic implications of TDH. The partial restoration of thiol levels following radical prostatectomy and the association between TDH and disease stage in other cancers suggest that TDH may serve as a surrogate marker of tumor burden[16]. ROS-associated alterations are implicated in treatment resistance; redox-sensitive signaling influences chemotherapy response, platinum sensitivity, and ferroptosis susceptibility—critical pathways in ovarian cancer management. Therefore, future studies measuring TDH before and after cytoreduction, chemotherapy, or maintenance therapy could clarify its potential role in monitoring treatment response or predicting recurrence.

The heterogeneity of ovarian cancer presents a challenge in interpreting serum biomarkers. Distinct histopathologic subtypes exhibit characteristic metabolic and oxidative profiles: clear-cell carcinoma is characterized by glutathione-driven chemoresistance, whereas high-grade serous carcinoma displays significant genomic instability and mitochondrial dysfunction. In our study, epithelial tumors accounted for the majority of cases, and subgroup analysis yielded results consistent with those of the overall cohort. However, subtype-specific TDH signatures cannot be excluded. Future work incorporating genomic data—such as BRCA mutation status, homologous recombination deficiency, or metabolic phenotype—could identify redox-based biomarker clusters for precision stratification.

The strengths of our study include a prospective design, the inclusion of both benign and healthy control groups, and the measurement of an integrated panel of redox markers. By demonstrating TDH alterations in ovarian cancer relative to both comparison groups and identifying associations with CA-125, our findings contribute to the growing evidence that TDH may serve as an accessible adjunctive biomarker in the evaluation of adnexal masses. As healthcare systems seek cost-effective biomarkers, the simplicity, reproducibility, and low cost of thiol-DS measurement enhance its translational appeal.

Study Limitations

This study has limitations. The sample size was modest and derived from a single center. The absence of serial postoperative or treatment-associated measurements restricts insight into the temporal behavior of TDH. Furthermore, the focus on serum concentrations does not address local oxidative changes within tumor tissue. Tissue-level analysis, including markers of oxidative DNA damage and enzymatic antioxidant activity, could clarify mechanistic pathways.

Conclusion

This study demonstrated that women with ovarian cancer exhibit a distinct thiol-DS profile characterized by reduced thiol levels and increased oxidation-derived indices compared with both healthy women and those with benign ovarian neoplasia. These findings suggest that TDH reflects the heightened oxidative environment associated with malignant disease and may serve as an adjunctive biomarker in the preoperative evaluation of adnexal masses. While these results are promising, larger homogeneous cohorts and longitudinal assessments are required to establish their diagnostic, prognostic, and monitoring utility.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Tepecik Training and Research Hospital Clinical Research Ethics Committee (approval number: 2021/04-10, date: 15.04.2021).
Informed Consent: All participants provided written and verbal informed consent prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., M.S., V.K., S.K., Concept: A.K., M.S., V.K., Design: A.K., M.S., V.K., Ö.E., Data Collection or Processing: A.K., A.A.U., Ö.E., S.N., Analysis or Interpretation: A.K., S.K., A.A.U., Ö.E., S.N., A.İ., Literature Search: A.K., S.K., A.A.U., A.İ., Writing: A.K., Ö.E., S.N., A.İ.
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