



# Association of Pathological Tumor-to-kidney Volume Ratio with Adverse Pathological Features After Radical Nephrectomy: An Exploratory Retrospective Cohort Study

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## Abstract

**Objective:** To evaluate the association of the pathology-derived tumor-to-kidney volume ratio (T/K ratio) with adverse pathological features and assess whether it provides prognostic information for cancer-specific survival (CSS) beyond maximum tumor diameter in renal cell carcinoma (RCC) patients undergoing radical nephrectomy.

**Materials and Methods:** We retrospectively reviewed the records of 151 patients who underwent radical nephrectomy for non-metastatic RCC between 2005 and 2018. Tumor and kidney volumes were calculated from three orthogonal dimensions measured pathologically using the ellipsoid formula. An exploratory data-derived T/K ratio cut-off of 0.45 was used for group comparisons. Associations were evaluated using group comparisons, Spearman correlation, Kaplan-Meier analysis, and a parsimonious Cox model (T/K ratio and maximum tumor diameter), with CSS as the primary endpoint.

**Results:** The high T/K ratio group (n=28) had a greater tumor diameter than the low-ratio group (8.5 vs. 5.0 cm; p<0.001) and higher frequencies of renal vein involvement, microvascular invasion, tumor necrosis, collecting system invasion, and positive surgical margins (all p<0.05). The T/K ratio correlated strongly with tumor volume (p=0.789) and maximum diameter (p=0.747), but not with kidney volume (p=0.089). Median follow-up was 73 months [95% confidence interval (CI), 62-86]. Five-year CSS was 66.9% (95% CI, 42.2-82.9%) in the high-ratio group and 94.7% (95% CI, 87.6-97.8%) in the low-ratio group (p<0.001). In the parsimonious model, the T/K ratio was not independently associated with cancer-specific mortality after adjustment for diameter [hazard ratio (HR) per 0.10 increase, 1.14; 95% CI, 0.90-1.44; p=0.262], whereas diameter remained significant (HR per 1 cm, 1.21; 95% CI, 1.03-1.41; p=0.022).

**Conclusion:** A high T/K ratio was associated with adverse pathological findings and inferior unadjusted survival, but showed no independent association with cancer-specific mortality after adjustment for maximum tumor diameter. The ratio should be considered an exploratory morphometric index.

**Keywords:** Carcinoma, renal cell, nephrectomy, tumor burden, organ size, survival analysis

## Introduction

Renal cell carcinoma (RCC) accounts for approximately 2-3% of adult malignancies and 80-90% of malignant renal tumors (1-4). Tumor size remains central to the classification of localized RCC. In the eighth edition of the American Joint Committee on Cancer system, kidney-confined tumors are separated into T1 and T2 size categories according to maximum diameter (5). This approach does not describe the proportional tumor burden within the affected kidney.

Volumetric measurements may characterize tumor burden more comprehensively than a single linear diameter. Maximum diameter may not accurately represent true tumor volume,

particularly for larger or irregular tumors (6). Kidney volume has also been associated with tumor diameter and adverse histological findings (7). Three-dimensional tumor volume has shown prognostic associations with cancer-specific survival (CSS), overall survival (OS), recurrence, and metastasis in RCC cohorts (8-10). Kabay et al. (9) further reported that the ratio of tumor volume to kidney volume increased across RCC size categories.

Normalizing tumor volume to kidney volume is a practical morphometric approach, but it remains uncertain whether the resulting tumor-to-kidney volume ratio (T/K ratio) provides information beyond conventional tumor size. We therefore investigated the association of the pathology-derived T/K

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ratio with adverse pathological features and CSS—considered the primary survival endpoint given its direct relevance to RCC-specific outcomes—in patients undergoing radical nephrectomy. We also assessed its correlation with maximum tumor diameter and absolute tumor volume, examined whether it remained associated with CSS after adjustment for maximum tumor diameter, and described OS as a secondary, unadjusted outcome.

## Materials and Methods

### Study Design and Patients

This retrospective cohort study was conducted at a single tertiary referral center. The study was approved by the Local Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (decision no: 2018/08, date: 11.04.2018) and conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent was waived because of the retrospective design of the study. Medical records of 232 patients who underwent open or laparoscopic radical nephrectomy for a renal tumor between January 2005 and August 2018 were reviewed. Patients were excluded because of age <18 years (n=4), previous renal surgery (n=6), a known non-RCC malignancy (n=14), previous chemotherapy, radiotherapy, or immunotherapy (n=11), metastatic disease at diagnosis (n=5), chronic hepatitis or cirrhosis (n=4), benign or non-RCC histology (n=22), pathological stage pT3b or higher (n=2), or incomplete records (n=13). The final cohort comprised 151 patients.

### Clinical and Pathological Assessment

Demographic characteristics, surgical approach, and pathological findings were recorded. All specimens were re-evaluated by a single experienced pathologist. The histological subtype was classified according to the 2016 World Health Organization classification. The WHO/ISUP nucleolar grade was applied to clear cell and papillary RCC; chromophobe RCC was not graded and was therefore considered not applicable in grade-related analyses. Renal vein involvement, sarcomatoid differentiation, microvascular invasion, renal capsule invasion, tumor necrosis, collecting system invasion, perirenal fat invasion, and surgical margin status were recorded separately.

### Diameter-based Tumor Categorization

For descriptive morphometric analyses, tumors were categorized according to maximum tumor diameter, using the original unrounded measurements, as  $\leq 4$  cm, >4-7 cm, >7-10 cm, and >10 cm; dimensions displayed in the tables were rounded for reporting. Renal vein involvement, collecting system invasion, and perirenal fat invasion were analyzed as separate adverse pathological findings and were not incorporated into this diameter-based categorization.

### Volume Calculation and T/K Ratio

Kidney volume was defined as the total ellipsoid volume of the nephrectomy specimen, including the tumor mass, rather than the tumor-free parenchymal volume. Tumor and kidney

dimensions were abstracted from the contemporaneous gross pathology reports and reviewed for consistency by a single pathologist. Perinephric and hilar fat were excluded from measurements of kidney dimensions. Three orthogonal dimensions (length, width, and height) of the tumor and the kidney were used to calculate their volumes using the ellipsoid formula:  $V = \pi/6 \times \text{length} \times \text{width} \times \text{height}$ . Interobserver and intraobserver reproducibility of the gross measurements was not formally assessed. A kidney was operationally defined as atrophic when pathological volume was  $<130 \text{ cm}^3$  and/or the longest axis was  $<9 \text{ cm}$  (11,12). The T/K ratio was calculated by dividing tumor volume by kidney volume.

### Follow-up and Statistical Analysis

Patients were followed every 3-6 months during the first two years and annually thereafter. Vital status and cause of death were obtained from medical records and, when necessary, from telephone interviews with patients or relatives. CSS and OS were calculated from surgery to death from RCC and to death from any cause, respectively, or to the last known follow-up; CSS was considered the primary survival endpoint, and OS was examined descriptively. Median follow-up was estimated by the reverse Kaplan-Meier method. The T/K ratio cut-off of 0.45 was an exploratory data-derived threshold, selected in the original analysis using conventional receiver operating characteristic (ROC) methods with cancer-specific death status as the binary outcome. Because this approach did not account for censoring and the cut-off was derived and evaluated in the same cohort, it was used only for descriptive, hypothesis-generating comparisons and did not represent a validated clinical threshold. Analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA), and MedCalc Statistical Software Version 16 demo (MedCalc Software Ltd., Ostend, Belgium). Continuous variables are presented as median (range) and compared using the Mann-Whitney U test. Categorical variables were compared using Pearson's chi-square test, Yates-corrected chi-square test, or Fisher's exact test, as appropriate. Associations among continuous morphometric variables were assessed using Spearman rank correlation. Survival was estimated with Kaplan-Meier analysis and compared by the log-rank test. Given the limited number of cancer-specific deaths, a parsimonious Cox proportional hazards model was prespecified to examine whether the continuous T/K ratio provided information beyond maximum tumor diameter in predicting CSS. The T/K ratio was scaled per 0.10-unit increase, and tumor diameter was scaled per 1-cm increase. The proportional hazards assumption was assessed using Schoenfeld residuals. Analyses were complete-case; the WHO/ISUP grade was not applicable to chromophobe RCC. No adjustment was made for multiple comparisons, and all analyses were considered exploratory. A two-sided  $p < 0.05$  was considered statistically significant.

## Results

### Patient Characteristics

A total of 151 patients were included: 107 men (70.9%) and 44 women (29.1%); the median age was 62 years (range, 34-89). Radical nephrectomy was performed through an open

approach in 144 patients (95.4%) and laparoscopically in 7 patients (4.6%). The median maximum tumor diameter was 5.5 cm (1.8-18.0); the median tumor volume was 45.04 cm<sup>3</sup> (1.24-1647.36); the median kidney volume was 293.02 cm<sup>3</sup> (13-2808); and the median T/K ratio was 0.18 (<0.01-0.91). The diameter categories were ≤4 cm in 41 patients (27.2%), >4-7 cm in 71 (47.0%), >7-10 cm in 21 (13.9%), and >10 cm in 18 (11.9%). Twenty-one patients (13.9%) had an atrophic kidney. Histological subtype was clear cell in 123 patients (81.5%), papillary in 13 (8.6%), and chromophobe in 15 (9.9%). WHO/ISUP grade was evaluable in 136 clear cell or papillary tumors (Table 1).

### Exploratory T/K Ratio Groups

In the original exploratory analysis, ROC analysis, using cancer-specific death as the binary outcome, yielded an area under the curve (AUC) of 0.698 [95% confidence interval (CI), 0.612-0.744;  $p=0.005$ ] for the T/K ratio; the Youden index identified 0.45 as the value that maximized the sum of sensitivity (50.0%) and specificity (86.6%) in this cohort. This value should not be interpreted as a clinically validated optimal threshold. As noted in the Methods, this approach did not account for censoring, and the cut-off was derived and evaluated in the same cohort; therefore, it was used only as an exploratory, data-derived cut-off for descriptive and hypothesis-generating comparisons.

**Table 1. Demographic, clinical, and pathological characteristics and comparison of the exploratory T/K ratio groups**

| Variable                                        | All (n=151)            | Low T/K (n=123)        | High T/K (n=28)        | p-value |
|-------------------------------------------------|------------------------|------------------------|------------------------|---------|
| Age, years, median (range)                      | 62 (34-89)             | 62 (34-89)             | 62 (40-82)             | 0.538   |
| Sex, male, n (%)                                | 107 (70.9)             | 82 (66.7)              | 25 (89.3)              | 0.032   |
| Body weight, kg, median (range)                 | 78 (45-118)            | 79 (49-118)            | 75.5 (45-115)          | 0.850   |
| Tumor volume, cm <sup>3</sup> , median (range)  | 45.04 (1.24-1647.36)   | 37.44 (1.24-946.40)    | 207.02 (6.86-1647.36)  | <0.001  |
| Kidney volume, cm <sup>3</sup> , median (range) | 293.02 (13.00-2808.00) | 283.92 (23.40-2808.00) | 360.62 (13.00-2242.24) | 0.276   |
| Maximum tumor diameter, cm, median (range)      | 5.5 (1.8-18.0)         | 5.0 (1.8-14.0)         | 8.5 (2.5-18.0)         | <0.001  |
| T/K ratio, median (range)                       | 0.18 (<0.01-0.91)      | 0.14 (<0.01-0.44)      | 0.54 (0.45-0.91)       | <0.001  |
| Diameter category, n (%)                        |                        |                        |                        | <0.001  |
| ≤4 cm                                           | 41 (27.2)              | 40 (32.5)              | 1 (3.6)                |         |
| >4-7 cm                                         | 71 (47.0)              | 65 (52.8)              | 6 (21.4)               |         |
| >7-10 cm                                        | 21 (13.9)              | 10 (8.1)               | 11 (39.3)              |         |
| >10 cm                                          | 18 (11.9)              | 8 (6.5)                | 10 (35.7)              |         |
| Atrophic kidney, n (%)                          | 21 (13.9)              | 19 (15.4)              | 2 (7.1)                | 0.368   |
| Histological subtype, n (%)                     |                        |                        |                        | 0.399   |
| Clear cell                                      | 123 (81.5)             | 100 (81.3)             | 23 (82.1)              |         |
| Papillary                                       | 13 (8.6)               | 12 (9.8)               | 1 (3.6)                |         |
| Chromophobe                                     | 15 (9.9)               | 11 (8.9)               | 4 (14.3)               |         |
| WHO/ISUP grade, n (%)                           |                        |                        |                        | 0.061   |
| Grade 1                                         | 14/136 (10.3)          | 13/112 (11.6)          | 1/24 (4.2)             |         |
| Grade 2                                         | 83/136 (61.0)          | 67/112 (59.8)          | 16/24 (66.7)           |         |
| Grade 3                                         | 31/136 (22.8)          | 28/112 (25.0)          | 3/24 (12.5)            |         |
| Grade 4                                         | 8/136 (5.9)            | 4/112 (3.6)            | 4/24 (16.7)            |         |
| Renal vein involvement, n (%)                   | 10 (6.6)               | 5 (4.1)                | 5 (17.9)               | 0.020   |
| Sarcomatoid differentiation, n (%)              | 5 (3.3)                | 3 (2.4)                | 2 (7.1)                | 0.231   |
| Microvascular invasion, n (%)                   | 15 (9.9)               | 7 (5.7)                | 8 (28.6)               | 0.001   |
| Renal capsule invasion, n (%)                   | 42 (27.8)              | 31 (25.2)              | 11 (39.3)              | 0.162   |
| Tumor necrosis, n (%)                           | 26 (17.2)              | 16 (13.0)              | 10 (35.7)              | 0.010   |
| Collecting system invasion, n (%)               | 13 (8.6)               | 6 (4.9)                | 7 (25.0)               | 0.003   |
| Perirenal fat invasion, n (%)                   | 14 (9.3)               | 10 (8.1)               | 4 (14.3)               | 0.295   |
| Positive surgical margin, n (%)                 | 4 (2.6)                | 1 (0.8)                | 3 (10.7)               | 0.020   |

WHO/ISUP grade was applicable to clear cell and papillary RCC and was not assigned to chromophobe RCC; grade was evaluable in 136 patients overall, 112 in the low-ratio group, and 24 in the high-ratio group. The T/K ratio cut-off (0.45) used to define the low and high groups was an exploratory, data-derived threshold (see Methods) and has not been externally validated  
Data are median (range) or n (%), T/K: Tumor-to-kidney volume ratio, RCC: renal cell carcinoma

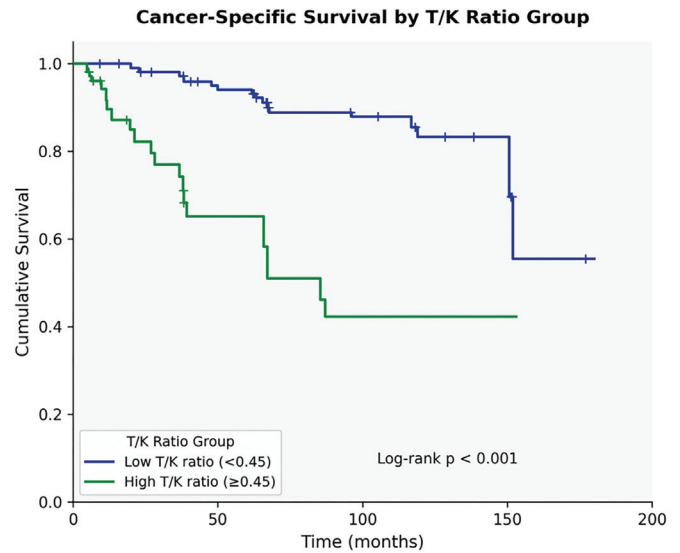
Using this cut-off, 123 patients (81.5%) were classified as having a low T/K ratio, and 28 (18.5%) were classified as having a high ratio. Median maximum tumor diameter was significantly greater in the high-ratio group than in the low-ratio group (8.5 vs. 5.0 cm;  $p < 0.001$ ), as was median tumor volume (207.02 vs. 37.44 cm<sup>3</sup>;  $p < 0.001$ ). Kidney volume did not differ significantly between groups ( $p = 0.276$ ). The high-ratio group had a higher proportion of men (89.3% vs. 66.7%;  $p = 0.032$ ). The high-ratio group had larger diameter categories ( $p < 0.001$ ) and higher frequencies of renal vein involvement (17.9% vs. 4.1%;  $p = 0.020$ ), microvascular invasion (28.6% vs. 5.7%;  $p = 0.001$ ), tumor necrosis (35.7% vs. 13.0%;  $p = 0.010$ ), collecting system invasion (25.0% vs. 4.9%;  $p = 0.003$ ), and positive surgical margins (10.7% vs. 0.8%;  $p = 0.020$ ) (Table 1). As a continuous variable, the median T/K ratio increased across the  $\leq 4$  cm,  $>4$ -7 cm,  $>7$ -10 cm, and  $>10$  cm diameter categories (0.06, 0.18, 0.45, and 0.47, respectively;  $p < 0.001$ ).

### Correlation Analysis

The T/K ratio was strongly correlated with tumor volume (Spearman  $\rho = 0.789$ ;  $p < 0.001$ ) and maximum tumor diameter ( $\rho = 0.747$ ;  $p < 0.001$ ), but not with kidney volume ( $\rho = 0.089$ ;  $p = 0.280$ ). Tumor volume was strongly correlated with maximum diameter ( $\rho = 0.968$ ;  $p < 0.001$ ). Full correlations among morphometric variables are presented in Supplementary Table 1.

### Survival Outcomes

The median follow-up calculated using the reverse Kaplan-Meier method was 73 months (95% CI, 62-86). Thirty-nine patients (25.8%) died, including 20 (13.2%) from RCC. Five-year CSS was 94.7% (95% CI, 87.6%-97.8%) in the low-ratio group and 66.9% (95% CI, 42.2%-82.9%) in the high-ratio group (log-rank  $p < 0.001$ ; Figure 1). OS also differed significantly between the low- and high-ratio groups (log-rank  $p = 0.008$ ). Because OS was examined descriptively only, consistent with CSS being the primary endpoint, group-specific OS estimates are not reported in further detail. In univariate Cox analysis, the exploratory high-ratio group was associated with cancer-specific mortality [hazard ratio (HR), 6.05; 95% CI, 2.51-14.56;  $p < 0.001$ ]. In the parsimonious model containing the two continuous morphometric variables, the T/K ratio was not independently associated with cancer-specific mortality after adjustment for maximum tumor diameter (HR per 0.10-unit increase, 1.14; 95% CI, 0.90-1.44;  $p = 0.262$ ), whereas maximum tumor diameter remained significant (HR per 1-cm increase, 1.21; 95% CI, 1.03-1.41;  $p = 0.022$ ) (Table 2). The proportional hazards assumption was not violated.



**Figure 1.** Kaplan-Meier cancer-specific survival curves according to the exploratory T/K ratio cut-off of 0.45. Vertical marks indicate censored observations

T/K: Tumor-to-kidney volume ratio

### Discussion

This exploratory study assessed a pathology-derived T/K volume ratio in patients undergoing radical nephrectomy for non-metastatic RCC. A high ratio was associated with larger tumors, higher tumor- diameter categories, several adverse pathological findings, and inferior unadjusted CSS and OS. However, the T/K ratio was strongly correlated with maximum tumor diameter and absolute tumor volume, not correlated with kidney volume, and not independently associated with cancer-specific mortality after adjustment for maximum diameter. These findings indicate that, in this cohort, the ratio predominantly reflects tumor burden and that there was no independent association with cancer-specific mortality after accounting for maximum diameter.

Prior studies support the prognostic relevance of RCC volumetry. Jorns et al. (8) reported a stronger association of three-dimensional tumor volume than diameter with CSS in pT1 clear cell RCC, and Chen et al. (10) found tumor volume to predict CSS, OS, metastasis, and local recurrence in localized clear cell RCC. Kabay et al. (9) showed that the T/K ratio increased across RCC stages. We observed a similar gradient across diameter categories. Nevertheless, tumor volume and diameter were almost collinear in our cohort ( $\rho = 0.968$ ), and the T/K ratio itself correlated strongly with both measures. Secil et al. (13) similarly

**Table 2.** Cox proportional hazards analysis for cancer-specific survival

| Variable                                                                                                              | Univariate HR (95% CI) | p-value | Parsimonious adjusted HR (95% CI) | p-value |
|-----------------------------------------------------------------------------------------------------------------------|------------------------|---------|-----------------------------------|---------|
| T/K ratio, per 0.10-unit increase                                                                                     | 1.36 (1.15-1.61)       | <0.001  | 1.14 (0.90-1.44)                  | 0.262   |
| Maximum tumor diameter, per 1-cm increase                                                                             | 1.28 (1.13-1.44)       | <0.001  | 1.21 (1.03-1.41)                  | 0.022   |
| High T/K ratio group ( $\geq 0.45$ )                                                                                  | 6.05 (2.51-14.56)      | <0.001  | -                                 | -       |
| The high T/K ratio group ( $\geq 0.45$ ) reflects the same exploratory, data-derived cut-off described in the Methods |                        |         |                                   |         |
| CI: Confidence interval, HR: Hazard ratio, T/K: Tumor-to-kidney volume ratio                                          |                        |         |                                   |         |

found that tumor volume stratified survival in unadjusted analyses but did not remain independently prognostic after multivariable adjustment.

The high-ratio group also exhibited higher frequencies of renal vein involvement, microvascular invasion, collecting-system invasion, tumor necrosis, and positive surgical margins. These findings are clinically relevant because venous and microvascular invasion, collecting system invasion, necrosis, and margin status have been associated with adverse RCC outcomes (14-18). However, these associations should not be interpreted as evidence of a distinct biological mechanism. Because tumor volume forms the numerator of the ratio, larger and more locally extensive tumors are expected to yield higher T/K values. The significant sex imbalance between the ratio groups and the lack of normalization of pathological kidney measurements to body size or sex may also contribute to residual confounding.

The survival separation produced by the exploratory data-derived cut-off of 0.45 was substantial, but the threshold was derived and tested in the same cohort and did not account for censoring when originally selected; it should therefore continue to be regarded as descriptive and hypothesis-generating rather than a validated clinical threshold. The limited model was deliberately restricted to the T/K ratio and maximum diameter because only 20 cancer-specific deaths occurred; more extensive regression would produce unstable estimates in this sample (19). In this model, maximum diameter remained significant while the T/K ratio was not independently associated with cancer-specific mortality after adjustment for maximum diameter. Thus, the present data do not provide evidence of incremental prognostic value over conventional tumor size in this cohort, and the ratio should not currently be used to determine treatment or surveillance.

### Study Limitations

Several limitations should be acknowledged. The study was retrospective and single-center, spanning 2005-2018, during which surgical practice, pathological reporting, and follow-up may have changed. The cohort included only patients selected for radical nephrectomy and, therefore, did not represent all localized renal masses, particularly patients treated with partial nephrectomy or active surveillance. The number of cancer-specific deaths was limited, and the exploratory data-derived cut-off lacked internal resampling and external validation. OS was examined only descriptively, given the decision to restrict the adjusted model to CSS in order to limit overfitting risk; conclusions regarding OS are therefore limited to unadjusted comparisons. The diameter categories used for descriptive analysis do not represent complete pathological TNM stages, as invasion-related findings were recorded and analyzed separately. Tumor and kidney dimensions were abstracted from gross pathology reports, using an ellipsoid approximation rather than from manual segmentation or from cross-sectional imaging-based volumetry; irregular shapes may be misrepresented, and interobserver and intraobserver reproducibility were not assessed. Preoperative imaging-based volumetry was not included; therefore, the preoperative applicability of the index cannot be inferred. Cause of death was occasionally determined

through interviews with relatives, which may introduce misclassification. Finally, multiple exploratory comparisons were performed without multiplicity adjustment.

### Conclusion

The pathology-derived T/K ratio was associated with larger tumors, adverse pathological findings, and poorer unadjusted survival. However, in this cohort, no independent association with cancer-specific mortality was detected after adjustment for maximum tumor diameter. The T/K ratio should therefore be regarded as an exploratory morphometric index rather than a validated prognostic tool.

### Ethics

**Ethics Committee Approval:** The study was approved by the Local Clinical Research Ethics Committee of Zonguldak Bülent Ecevit University (decision no: 2018/08, date: 11.04.2018).

**Informed Consent:** Retrospective study.

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**Publication:** The results of the study were not published in full or in part in form of abstracts.

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

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: E.D.D., R.G., Ö.Ç., B.A., N.A.M., Concept: E.D.D., N.A.M., Design: E.D.D., Data Collection or Processing: E.D.D., Ö.Ç., Analysis or Interpretation: E.D.D., R.G., Literature Search: E.D.D., Writing: E.D.D., Ö.Ç., N.A.M.

**Conflict of Interest:** Necmettin Aydın Mungan is a member of the journal's Editorial Board. However, they were not involved in the editorial evaluation, peer-review process, or decision-making regarding this manuscript. The other authors declared no conflict of interest.

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**Supplementary Table Link:** <https://d2v96fxpocvxx.cloudfront.net/68ab204c-182b-49da-b227-bc7efe058632/content-images/29609ea3-cc08-47e5-a992-c06799bb2ada.pdf>

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