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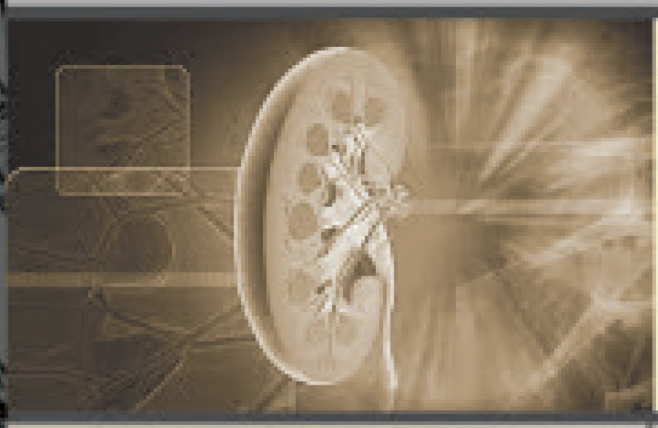
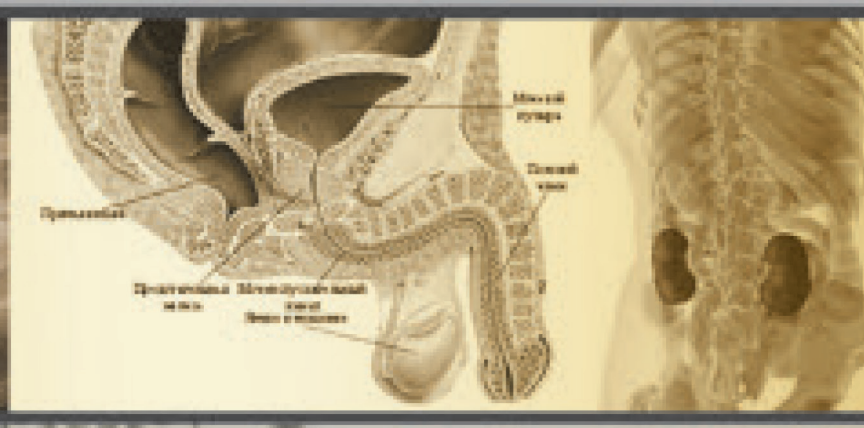
Society of Urological Surgery in Turkiye

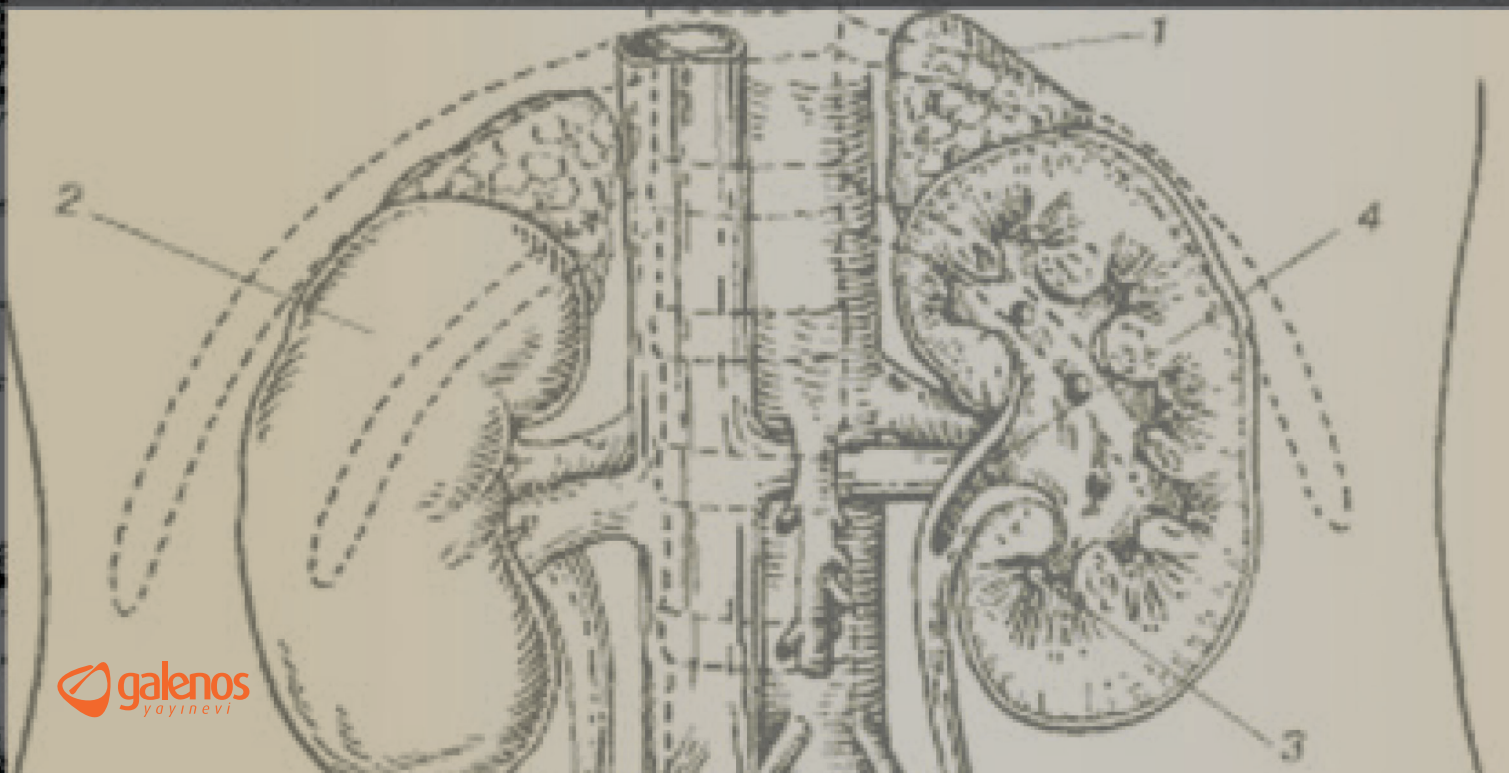
E-ISSN 2148-9580

# JOURNAL OF UROLOGICAL SURGERY

Volume 11 / Issue 2 / June 2024 www.jurolsurgery.org





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**Web:** www.galenos.com.tr
**Publisher Certificate Number:** 14521
**Publication Date:** June 2024
**E-ISSN:** 2148-9580
International scientific journal published quarterly.

*Reviewing the articles' conformity to the publishing standards of the Journal, typesetting, reviewing and editing the manuscripts and abstracts in English and publishing process are realized by Galenos.*

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# JOURNAL OF UROLOGICAL SURGERY

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ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2023.2023-6-17
J Urol Surg 2024;11(2):58-66

# Comparison of the Diagnostic Performance of Multiparametric Prostate Magnetic Resonance Imaging Results with Classical Parameters for Prostate Carcinoma in Gray Zone Patients

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**What's known on the subject? and What does the study add?**

Urology guidelines suggest that multiparametric prostate magnetic resonance imaging should be conducted for all patients before biopsy. However, not all centers can perform a targeted prostate biopsy. Nonetheless, it is beneficial for patients to undergo this imaging method even if a targeted biopsy cannot be performed. In patients with prostate-specific antigen levels between 4-10 ng/mL, classical parameters, such as prostate-specific antigen density and free total prostate-specific antigen ratio, remain crucial in making biopsy decisions.

## Abstract

**Objective:** To compare the diagnostic value of prostate imaging-reporting and data system (mpMRI) version 2.0 with classical parameters for prostate cancer detection in gray zone patients with ultrasonography-guided prostate biopsy as a reference point.

**Materials and Methods:** With the retrospective nature of the study, 438 biopsy-naïve patients in the gray zone with pre-biopsy mpMRI were reviewed. Ultrasonography-guided transrectal prostate biopsy was the reference point. Diagnostic performance of classical parameters compared with mpMRI results for prostate carcinoma and clinically significant prostate carcinoma.

**Results:** The overall cancer detection rate was 30%. Prostate-specific antigen density, free/total prostate-specific antigen ratio, prostate volume, suspicious digital rectal examination, and mpMRI score >3 were independent predictors of clinically significant prostate carcinoma. Prostate-specific antigen density followed by free/total prostate-specific antigen ratio had the largest area under the curve values compared with mpMRI score >3 for prostate carcinoma and clinically significant prostate carcinoma.

**Conclusion:** Classical parameters, prostate-specific antigen density, and f/t prostate-specific antigen ratio were still critical to deciding prostate biopsy in gray zone patients, in whom ultrasonography-guided transrectal prostate biopsy was used as a reference point. In centers where targeted fusion biopsies were unavailable, pre-biopsy mpMRI still had some benefits. However, biopsy decisions should be made according to each patient's individual characteristics.

**Keywords:** Prostate, biopsy, multiparametric prostate magnetic resonance imaging, prostate carcinoma

## Introduction

After skin cancer, prostate cancer (PCa) is the second most frequent malignancy in men (1). The decision to perform a systematic 10-12 core transrectal ultrasonography-guided prostate biopsy (TRUS-PB), which is typically performed in an outpatient clinic under local anesthesia and has an overall cancer detection rate of 30-40%, has long been based on elevated prostate-specific antigen (PSA) levels and abnormal digital rectal examination (DRE) results (2). Although the widespread use of TRUS-PB and PSA testing helped increase the early detection of PCa, this conventional pathway also resulted

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**Received:** 30.06.2023 **Accepted:** 07.10.2023

**Cite this article as:** Bostancı C, Demir DÖ. Comparison of the Diagnostic Performance of Multiparametric Prostate Magnetic Resonance Imaging Results with Classical Parameters for Prostate Carcinoma in Gray Zone Patients. J Urol Surg 2024;11(2):58-66.

in numerous unnecessary treatments for clinically insignificant prostate cancer (CISPCa) and missed up to 30% of clinically significant prostate carcinoma (CSPCa) (3-6).

A PSA level above 4 ng/mL is typically considered a threshold for biopsy indication. However, due to the low specificity of PSA in detecting PCa, no absolute cut-off value can entirely rule out the need for a biopsy (7). Additionally, when PSA is used to predict PCa likelihood in the 4-10 ng/mL range, known as the "gray zone", approximately 75% of biopsies yield negative results (8,9). To decrease these unnecessary biopsies, parameters such as PSA density (PSAD), the ratio of free PSA (f PSA) to total PSA (f/t PSA), PSA velocity, prostate volume (PV), and age-related PSA are also used to decide for biopsy in gray zone patients (10).

The traditional method of performing a prostate biopsy has changed with the increasing use of pre-biopsy prostate multiparametric magnetic resonance imaging (mpMRI). Research studies such as PRECISION and PROMIS have demonstrated that mpMRI can be used as a triage test, reducing unnecessary prostate biopsies by 25% and improving diagnostic accuracy for CSPCa (11,12). However, despite being a valuable tool for detecting CSPCa, mpMRI may not always provide accurate results because studies have shown that false negative outcomes can occur in 20-30% of patients with CSPCa (3-13).

According to the latest guidelines of the European Association of Urology (EAU) (14), mpMRI is now regarded as the initial imaging modality used before prostate biopsy in biopsy-naive and repeat biopsies. According to the EAU guidelines, we aim to obtain pre-biopsy mpMRI from almost all patients who are candidates for biopsy in the gray zone. However, the risk profile of patients who would benefit the most from mpMRI has yet to be clearly defined. Accordingly, the objective of this study was to assess the efficacy of classical diagnostic parameters such as age, PSA levels, f PSA, PSAD, DRE, and f/t PSA when compared with mpMRI prostate imaging-reporting and data system (PI-RADS) scores in predicting PCa and CSPCa in which systematic 12-core TRUS-PB was used as a reference point in grey zone patients. In addition, this study assessed the diagnostic accuracy of classical parameters and mpMRI PI-RADS scores in predicting PCa and CSPCa.

## Materials and Methods

Our hospital's electronic media was used to retrospectively collect data on 820 patients who underwent TRUS-PB between January 2018 and April 2023. PSA >4.0 ng/mL, PI-RADS score ≥3, suspicious DRE, prior suspicious biopsy results, and staging of patients with a history of PCa were the biopsy criteria. The study inclusion criteria included biopsy-naive patients who had undergone at least 12-core TRUS-PB with a PSA level ranging from 4 to10 ng/mL with pre-biopsy mpMRI. We eliminated 382 patients from the study without a pre-biopsy mpMRI, had PSA levels outside the gray zone, had a previous biopsy or diagnosis of PCa, had less than 12 core biopsies, or were using 5-alpha reductase inhibitors. As a result, the study included 438 patients.

Although the operator was aware of the PI-RADS score, no mpMRI ultrasound targeted fusion biopsies (MR/USTB) were performed because of a lack of equipment. In addition, cognitive fusion biopsies (CFB) were not conducted because of the lack of high-level MR reading and experience of the operator. However, all patients with PI-RADS scores ≥3 were referred to another hospital located 250 km away in the closest city where MR/USTB was available. Patients who accepted TRUS-PB in our institution were included in the study.

All systematic 12-core TRUS-PB operations were performed by the same urologist (CB) under local anesthesia in the left decubital position using an 18-gauge single-use biopsy needle and the same ultrasonography device. In all patients, 1 or 2 extra biopsy cores were taken from each suspicious lesion on transrectal ultrasonography in addition to systematic 12-core biopsies.

T2-weighted (T2W), diffusion-weighted, and dynamic contrast-enhanced imaging were used during mpMRI using a 1.5 Tesla MRI system (Magnetom Essenza, Siemens Healthcare Solutions). The radiology specialists contracted by our hospital described the mp-MRI findings using a PIRADS score of 2.0.

Within 4 h of blood collection, serum PSA and f PSA levels were measured in our hospital laboratory using chemiluminescent microparticle immunoassay. The ellipsoid formula was used to determine PV. Using MR images, three prostate dimensions were evaluated.

The core specimens were analyzed by pathologists from the same institution. According to the International Society of Urological Pathology, PCa with a Gleason score (GS) of 7 is classified as CSPCa, whereas those with a GS of 6 are classified as CISPCa (15).

The study was initiated with the approval of the Karabük University Non-invasive Clinical Research Ethics Committee (date: 07.11.2022, approval no: 2022/1150).

### Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested using the Shapiro-Wilk test. Factors affecting PCa and CSPCa were tested using univariate and multivariate binary logistic regression analysis. ROC curve analysis was used to calculate and compare the variables under

the curve. SPSS 22.0 Windows version package program and MedCalc 19.7.1 package program were used in the analysis. P<0.05 was considered significant.

## Results

Table 1 summarizes the patient's clinical information, including their median age of 66 years, PSA level of 5.9 ng/mL, f PSA level of 1.3 ng/mL, PV of 60.0 mL, PSAD of 0.09 ng/mL/mL, and f/t PSA of 0.23. The median number of biopsy cores was 12, and 31.6% of patients had a suspicious DRE. Of the 438 patients, 131 (29.9%) were diagnosed with PCa and 87 (19.8%) with CSPCa.

Age, PV, PSA level, PV, PSAD, f/t PSA, suspicious DRE, PI-RADS score 3, and PI-RADS score 4-5 were among the parameters identified by univariate logistic regression analysis as significant predictors of PCa. The multivariate analysis assessed the parameters that stood out in the univariate study. Age, PSAD, suspicious DRE, PI-RADS score 3, and PI-RADS score 4-5 were found to be independent predictors of PCa in multivariate analysis. Regarding CSPCa, it was found that age, PSA level, PV, PSAD, f/t PSA, suspicious DRE, PI-RADS 3, and PI-RADS score 4-5 were predictors in univariate analysis. However, upon further multivariate analysis, only age, f/t PSA, suspicious DRE, PI-RADS score 3, and PI-RADS score 4-5 were deemed independent predictors of CSPCa (Table 2).

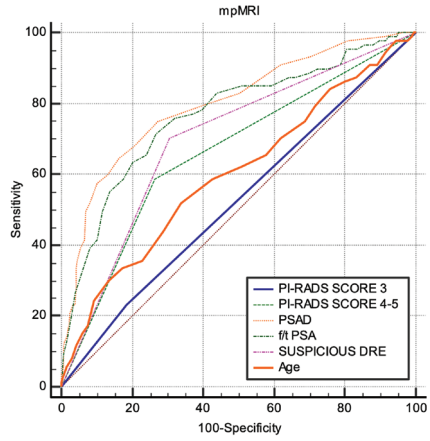
The diagnostic performance of the parameters for PCa and CSPCa was evaluated using ROC curve analysis. The ROC curve analysis for predicting PCa showed that the area under the curve (AUC) values of PSAD (0.771) were the highest, followed by f/t PSA (0.733) compared with other parameters. For CSPCa, PSAD had the highest AUC value (0.798) compared with the other parameters. The f/t PSA ratio had the second highest AUC value (0.768), followed by suspicious DRE (Figure 1).

ROC curve analysis revealed a cut-off value of PSAD of 0.11 ng/mL/mL in predicting PCa. With a cut-off value of 0.11 ng/mL/mL, the sensitivity and specificity were 61.8% and 83.7%, respectively. For CSPCa, the cut-off value of PSAD was calculated to be 0.12 ng/mL/mL with 64.3% sensitivity and 83.7% specificity.

For f/t PSA, using a cut-off value of 0.19 for PCa, the sensitivity and specificity of predicting PCa were 62.6% and 76.2%, respectively. The cut-off value of f/t PSA was the same for CSPCa, with 71.2% sensitivity and 73.5% specificity.

The PV, with a cut-off value of 49 mL, had 59.5% sensitivity and 81.4% specificity for PCa. For CSPCa, the cut-off value was calculated at 50 mL with 66.6% sensitivity and 75.5% specificity.

According to logistic regression analysis, a PI-RADS score of 3 and a PI-RADS score of 4-5 were independent predictors of PCa




| Variable | AUC | SE[a] | 95% CI[b] |
|---|---|---|---|
| PIRADS score 3 | 0.524 | 0.0249 | 0.476 to 0.571 |
| PIRADS score 4-5 | 0.662 | 0.0290 | 0.616 to 0.706 |
| PSAD | 0.798 | 0.0283 | 0.757 to 0.834 |
| f/t PSA | 0.768 | 0.0305 | 0.725 to 0.807 |
| Suspicious DRE | 0.698 | 0.0276 | 0.653 to 0.741 |
| Age | 0.600 | 0.0358 | 0.552 to 0.646 |

**Figure 1.** ROC curves of PI-RADS score 3, PI-RADS score 4-5, PSAD, f/t PSA, suspicious DRE, and age in clinically significant prostate cancer detect

PI-RADS: Prostate Imaging-Reporting and Data System, PSAD: Prostate specific antigen density, DRE: Digital rectal examination, f/t PSA: Free/total prostate specific antigen ratio, AUC: Area under the curve, ROC: Receiver operating characteristic, CI: Confidence interval

**Table 1. Main data of pre-biopsy mpMRI applied patients in grey zone with pathology results**

| Parameters | Pre-biopsy mpMRI applied patients in grey zone |
|---|---|
| No. of patients | 438 |
| Age, years median (IQR) | 66.0 (61.0-70.0) |
| PSA ng/mL median (IQR) | 5.9 (4.9-7.6) |
| Prostate volume mL median (IQR) | 60.0 (46.0-85.0) |
| Free PSA ng/mL median (IQR) | 1.3 (1.0-1.8) |
| PSAD ng/mL/mL median (IQR) | 0.09 (0.06-0.13) |
| f/t PSA % median (IQR) | 0.23 (0.16-0.29) |
| Suspicious DRE n, (%) | 145 (31.6) |
| No. of biopsy cores median (IQR) | 12.0 (12.0-12.0) |
| **Pathology results** | |
| PIN n, (%) | 22 (5) |
| ASAP n, (%) | 45 (10.2) |
| BPH n, (%) | 240 (54.7) |
| PCa n, (%) | 131 (29.9) |
| CISPCa n, (%) | 44 (10.0) |
| CSPCa n, (%) | 87 (19.8) |
| **PI-RADS scores** | |
| PI-RADS 1-2 n, (%) | 211 (48.2) |
| PI-RADS 3 n, (%) | 84 (19.2) |
| PI-RADS 4-5 n, (%) | 143 (32.6) |

PSA: Prostate specific antigen, PSAD: Prostate specific antigen density, f/t PSA: Free/total prostate specific antigen ratio, DRE: Digital rectal examination, PIN: Prostatic intraepithelial neoplasia, ASAP: Atypical small acinar cell proliferation, BPH: Benign prostatic hyperplasia, PCa: Prostate carcinoma, CISPCa: Clinically insignificant prostate carcinoma, CSPCa: Clinically significant prostate carcinoma, PI-RADS: Prostate imaging-reporting and data system, IQR: Interquartile range

**Table 2. Univariate and multivariate analysis of classical parameters and PI-RADS score for the prediction of prostate cancer and clinically significant prostate cancer**

| **PCa** | **Univariate a.** | **p** | **Multivariate a.** | **p** |
|---|---|---|---|---|
| Age | 1.04 (1.01-1.08) | 0.007* | 1.07 (1.02-1.12) | **0.003*** |
| PSA | 1.23 (1.097-1.38) | 0.001* | 0.93 (0.74-1.18) | 0.564 |
| Prostate volume | 0.96 (0.95-0.97) | 0.001* | 0.99 (0.98-1.01) | 0.376 |
| PSAD | 6.54 (4.16-10.26) | 0.001* | 3.91 (1.6-9.55) | **0.003*** |
| f/t PSA | 0.00 (0.00-0.00) | 0.001* | 0.04 (0-1.01) | 0.051 |
| Suspicious DRE | 4.52 (2.92-6.97) | 0.001* | 3.19 (1.86-5.5) | **0.001*** |
| No. of biopsy core | 1.09 (0.81-1.49) | 0.563 | 1.2 (0.79-1.82) | 0.404 |
| PI-RADS 3 | 2.84 (1.61-5.03) | 0.001* | 2.46 (1.23-4.95) | **0.011*** |
| PI-RADS 4-5 | 3.93 (2.42-6.41) | 0.001* | 2.53 (1.35-4.72) | **0.004*** |
| **CSPCa** | **Univariate a.** | **p** | **Multivariate a.** | **p** |
| Age | 1.06 (1.02-1.10) | 0.004* | 1.08 (1.02-1.13) | **0.003*** |
| PSA | 1.32 (1.17-1.51) | 0.001* | 1.09 (0.84-1.41) | 0.535 |
| Prostate volume | 0.96 (0.95-0.97) | 0.001* | 0.98 (0.96-1) | 0.088 |
| PSAD | 4.88 (3.26-7.32) | 0.001* | 1.84 (0.82-4.13) | 0.136 |
| f/t PSA | 0.00 (0.00-0.00) | 0.001* | 0 (0-0.31) | **0.013*** |
| Suspicious DRE | 5.35 (3.21-8.92) | 0.001* | 3.22 (1.71-6.06) | **0.001*** |
| No. of biopsy core | 0.94 (0.64-01.36) | 0.732 | 0.81 (0.5-1.34) | 0.415 |
| PI-RADS 3 | 3.81 (1.83-7.79) | 0.001* | 3.08 (1.31-7.21) | **0.010*** |
| PI-RADS 4-5 | 6.75 (3.66-12.48) | 0.001* | 4.85 (2.28-10.32) | **0.001*** |

PSA: Prostate specific antigen, PSAD: Prostate specific antigen density, f/t PSA: Free/total prostate specific antigen ratio, DRE: Digital rectal examination, PI-RADS: Prostate imaging-reporting and data system, a.: Analysis

or CSPCa. A PI-RADS score of 4-5 had a sensitivity of 48.8% and specificity of 74.2% for PCa, whereas it had a sensitivity of 58.6% and specificity of 73.9% for CSPCa. The cut-off values with the sensitivity and specificity results of the parameters for PCa and CSPCa are shown in Supplementary Table 1.

## Discussion

Our research aimed to evaluate the effectiveness of mpMRI in predicting PCa and CSPCa compared with classical parameters in gray zone patients. In our study, 29% of the patients were diagnosed with PCa, indicating that unnecessary biopsies were performed in 71% of the patients. Previously, elevated PSA levels were used as the primary indicator for prostate biopsy, but this resulted in overdiagnosis and unnecessary biopsies (16). Our study demonstrated that PSA was not an independent predictor of PCa and CSPCa in multivariate analysis. Nonetheless, PSA derivatives, such as f/t PSA and PSAD, remain widely used in deciding whether to perform a prostate biopsy. Multiple studies have suggested that a prostate biopsy should be recommended when f/t PSA <0.15 and PSAD >0.15 ng/mL (17-19). Our results showed that the cut-off values for PSAD were 0.11 for PCa and 0.12 for CSPCa, whereas for f/t PSA, these values were calculated as 0.19 for both PCa and CSPCa. We also observed that these two parameters had the highest AUC values in the ROC analysis for both PCa and CSPCa. However, we should note that f PSA has been reported to have a summary sensitivity of 70% in gray zone patients, and because of its instability in serum, it is not recommended to use it alone in determining whether to conduct a prostate biopsy or not (20).

Our study demonstrated that using mpMRI with a score of ≥3 had a lower AUC value for detecting PCa and CSPCa than PSAD, f/t PSA, and suspicious DRE. This may be due to the fact that we did not perform targeted biopsies on patients with a PI-RADS score ≥3. The introduction of mpMRI and PI-RADS scoring has changed the traditional PSA and its derivatives approach. According to the latest EAU guidelines, it is recommended to use pre-biopsy mpMRI to locate suspicious lesions or to avoid biopsy in low-risk patients and to perform both targeted and systematic biopsies on patients with suspicious lesions detected by mpMRI (14). The PROMIS study demonstrated that the use of pre-biopsy mpMRI can significantly reduce unnecessary biopsies by 27% while increasing the diagnosis of CSPCa by 18% and reducing the potential over-diagnosis and over-treatment of CISPCa by 5% (11). Similarly, the PRECISION study has shown that targeting biopsy alone is more effective than systematic biopsy for detecting CSPCa (12). However, the MR-FIRST study has indicated that combining systematic and targeted biopsy can yield better results than either method alone (21).

Moreover, large randomized controlled trials have supported the combination of targeted and systematic biopsy as the optimal approach for achieving the highest cancer detection rates in patients with suspicious mpMRI lesions (22,23). However, mpMRI fusion targeting biopsies, which are in-bore MRI-targeted and MR ultrasound-targeted fusion biopsies (MR/USTB), are not available in all hospitals. The alternative technique, CFB, requires no additional equipment but a high level of mpMRI reading knowledge. We opted not to use CFB because of its high reliance on mpMRI readings, despite its simplicity, speed, and lack of necessary equipment. To conduct a CFB, the operator must have a complete understanding of the location of the prostate lesion. This can only be achieved by carefully examining each MRI image, which requires a high level of mpMRI reading knowledge. Although the FUTURE study demonstrated that these three techniques did not have significantly different CSPCa detection rates (24), the success of CFB and MR/USTB heavily depends on the experience of the biopsy operators, making it imperative for skilled urologists proficient in mpMRI reading or a radiologist familiar with prostate MRI to perform cognitive biopsies (25,26).

Even if we did not perform fusion-targeted biopsies, pre-biopsy mpMRI provided two significant benefits. First, it helped us avoid unnecessary biopsies for patients in the gray zone who had no lesions on MRI by using other parameters. Second, patients with lesions in the anterior part of the prostate were referred directly to specialized hospitals for targeted biopsies. In addition, patients requiring repeat biopsies no longer have to wait eight weeks for mpMRI because they already had pre-biopsy mpMRI.

### Study Limitations

One of the study's main limitations was that it was conducted at a single-center and had a retrospective nature. This study did not involve targeted biopsies but used TRUS-PB as a reference point. However, TRUS-PB has been criticized for both underdetecting and overdiagnosing PCa.

## Conclusion

Classical parameters, PSAD, and f/t PSA are essential when deciding on prostate biopsy in gray zone patients. If targeted fusion biopsies are unavailable, pre-biopsy mpMRI can still provide some advantages. Nevertheless, it is essential to consider each patient's unique characteristics before deciding to proceed with a biopsy.

### Ethics

**Ethics Committee Approval:** The study was initiated with the approval of the Karabük University Non-invasive Clinical Research Ethics Committee (date: 07.11.2022, approval no: 2022/1150).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: C.B., D.Ö.D., Concept: C.B., D.Ö.D., Design: C.B., D.Ö.D., Data Collection or Processing: C.B., D.Ö.D., Analysis or Interpretation: C.B., D.Ö.D., Literature Search: C.B., D.Ö.D., Writing: C.B., D.Ö.D.

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

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

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## Supplementary Table 1a. The cut-off values of parameters with sensitivity and specificity for PCa

### 1. Age

#### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.592 |
| Standard error[a] | 0.0311 |
| 95% confidence interval[b] | 0.544 to 0.638 |
| z statistic | 2.949 |
| Significance level p (area=0.5) | 0.0032 |

| | |
|---|---|
| Youden index J | 0.1879 |
| Associated criterion | >67 |
| Sensitivity | 50.38 |
| Specificity | 68.40 |

#### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >67 | 50.38 | 41.5-59.2 | 68.40 | 62.9-73.6 |

### 2. PSA

#### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.612 |
| Standard error[a] | 0.0290 |
| 95% confidence interval[b] | 0.565 to 0.658 |
| Z statistic | 3.861 |
| Significance level p (area=0.5) | 0.0001 |

| | |
|---|---|
| Youden index J | 0.1926 |
| Associated criterion | >6.05 |
| Sensitivity | 60.31 |
| Specificity | 58.96 |

#### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >6.05 | 60.31 | 51.4-68.7 | 58.96 | 53.2-64.5 |

## 3. PSAD

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.771 |
| Standard error[a] | 0.0263 |
| 95% confidence interval[b] | 0.728 to 0.809 |
| z statistic | 10.312 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.4555 |
| Associated criterion | >0.11 |
| Sensitivity | 61.83 |
| Specificity | 83.71 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >0.11 | 61.83 | 52.9-70.2 | 83.71 | 79.1-87.7 |

## 4. f/t PSA

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.733 |
| Standard error[a] | 0.0280 |
| 95% confidence interval[b] | 0.689 to 0.774 |
| z statistic | 8.332 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.3882 |
| Associated criterion | ≤0.19 |
| Sensitivity | 62.60 |
| Specificity | 76.22 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| ≤0.19 | 62.60 | 53.7-70.9 | 76.22 | 71.1-80.9 |

## 5. PV

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.747 |
| Standard error[a] | 0.0268 |
| 95% confidence interval[b] | 0.704 to 0.788 |
| z statistic | 9.217 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.4098 |
| Associated criterion | ≤49 |
| Sensitivity | 59.54 |
| Specificity | 81.43 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| ≤49 | 59.54 | 50.6-68.0 | 81.43 | 76.6-85.6 |

## 6. PI-RADS 4-5

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.616 |
| Standard error[a] | 0.0252 |
| 95% confidence interval[b] | 0.568 to 0.661 |
| z statistic | 4.582 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.2312 |
| Associated criterion | >0 |
| Sensitivity | 48.85 |
| Specificity | 74.27 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >0 | 48.85 | 40.0-57.7 | 74.27 | 69.0-79.1 |

## 7. PI-RADS 3

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.532 |
| Standard error[a] | 0.0215 |
| 95% confidence interval[b] | 0.484 to 0.580 |
| z statistic | 1.485 |
| Significance level p (area=0.5) | 0.1374 |

| | |
|---|---|
| Youden index J | 0.06400 |
| Associated criterion | >0 |
| Sensitivity | 23.66 |
| Specificity | 82.74 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >0 | 23.66 | 16.7-31.9 | 82.74 | 78.0-86.8 |

## Supplementary Table 1b. The cut-off values of parameters with sensitivity and specificity for CSPCa

## 1. Age

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.600 |
| Standard error[a] | 0.0358 |
| 95% confidence interval[b] | 0.552 to 0.646 |
| z statistic | 2.784 |
| Significance level p (area=0.5) | 0.0054 |

| | |
|---|---|
| Youden index J | 0.1811 |
| Associated criterion | >67 |
| Sensitivity | 51.72 |
| Specificity | 66.38 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >67 | 51.72 | 40.8-62.6 | 66.38 | 61.2-71.3 |

## 2. PSA

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.645 |
| Standard error[a] | 0.0335 |
| 95% confidence interval[b] | 0.598 to 0.690 |
| z statistic | 4.319 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.2616 |
| Associated criterion | >6.3 |
| Sensitivity | 60.92 |
| Specificity | 65.24 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >6.3 | 60.92 | 49.9-71.2 | 65.24 | 60.0-70.2 |

## 3. PSAD

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.798 |
| Standard error[a] | 0.0283 |
| 95% confidence interval[b] | 0.757 to 0.834 |
| z statistic | 10.523 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.4813 |
| Associated criterion | >0.12 |
| Sensitivity | 64.37 |
| Specificity | 83.76 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >0.12 | 64.37 | 53.4-74.4 | 83.76 | 79.5-87.5 |

## 4. f/t PSA

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.768 |
| Standard error[a] | 0.0305 |
| 95% confidence interval[b] | 0.725 to 0.807 |
| z statistic | 8.792 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.4477 |
| Associated criterion | ≤0.19 |
| Sensitivity | 71.26 |
| Specificity | 73.50 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| ≤0.19 | 71.26 | 60.6-80.5 | 73.50 | 68.6-78.0 |

## 5. PV

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.757 |
| Standard error[a] | 0.0302 |
| 95% confidence interval[b] | 0.714 to 0.797 |
| z statistic | 8.525 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.4217 |
| Associated criterion | ≤50 |
| Sensitivity | 66.67 |
| Specificity | 75.50 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| ≤50 | 66.67 | 55.7-76.4 | 75.50 | 70.7-79.9 |

## 6. PI-RADS 4-5

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.662 |
| Standard error[a] | 0.0290 |
| 95% confidence interval[b] | 0.616 to 0.706 |
| z statistic | 5.580 |
| Significance level p (area=0.5) | <0.0001 |

| | |
|---|---|
| Youden index J | 0.3241 |
| Associated criterion | >0 |
| Sensitivity | 58.62 |
| Specificity | 73.79 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >0 | 58.62 | 47.6-69.1 | 73.79 | 68.9-78.3 |

## 7. PI-RADS 3

### Area under the ROC curve (AUC)

| | |
|---|---|
| Area under the ROC curve (AUC) | 0.524 |
| Standard error[a] | 0.0249 |
| 95% confidence interval[b] | 0.476 to 0.571 |
| z statistic | 0.954 |
| Significance level p (area=0.5) | 0.3401 |

| | |
|---|---|
| Youden index J | 0.04755 |
| Associated criterion | >0 |
| Sensitivity | 22.99 |
| Specificity | 81.77 |

### Criterion values and coordinates of the ROC curve [Show]

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI |
|---|---|---|---|---|
| >0 | 22.99 | 14.6-33.2 | 81.77 | 77.3-85.7 |

ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2023.2023-10-3
J Urol Surg 2024;11(2):67-71

# Robot-assisted Radical Cystectomy with Intracorporeal Urinary Diversion following Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer: An Initial Experience

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**What's known on the subject? and What does the study add?**

Robot-assisted techniques are frequently used in oncological surgeries. As these techniques achieve oncological and functional results comparable to open surgical approaches over time, the advantages of the laparoscopic approach can be provided to patients during recovery. The contribution of neoadjuvant chemotherapy to survival in the muscle-invasive bladder cancer patient group has been reported in the literature. In this study, we aimed to share our intracorporeal urinary diversion results, which may be technically challenging, in the patient group who received neoadjuvant chemotherapy.

## Abstract

**Objective:** To investigate the outcomes of robot-assisted radical cystectomy, intracorporeal urinary diversion, and extended lymph node dissection in patients with muscle-invasive bladder cancer who underwent neoadjuvant chemotherapy.

**Materials and Methods:** A total of 14 patients underwent neoadjuvant chemotherapy for invasive bladder tumors, followed by robot-assisted radical cystectomy, extended lymph node dissection, and intracorporeal urinary diversion. Demographic, operative, and postoperative information of the patients was retrospectively evaluated. Gemcitabine plus cisplatin and cisplatin plus etoposide regimens were used as neoadjuvant treatments. Early and late-term complications were recorded.

**Results:** In the early postoperative period (0-30 days), Clavien-Dindo grade 2 complications occurred in 6 patients and grade 3 complications in 2 patients. In the late postoperative period (31-90 days), Clavien-Dindo grade 2 complications occurred in 1 patient and grade 3 complications in 1 patient. The mean follow-up period was 15.5±5.7 months.

**Conclusion:** Although the intracorporeal technique is more demanding in terms of learning and use, preoperative chemotherapy application should not be seen as a limitation in the application of this technique.

**Keywords:** Bladder cancer, neoadjuvant chemotherapy, radical cystectomy, robot-assisted surgery, urinary diversion

## Introduction

Bladder cancer diagnosis ranks second among urological cancers (1). A quarter of these cancers are detected in the muscle-invasive stage (2). The gold standard treatment for muscle-invasive bladder cancer is radical cystectomy and lymph node dissection, with neoadjuvant chemotherapy also applied in suitable patients (3).

Radical cystectomy can be performed classically as open, laparoscopic, or robot-assisted. The increasing approval of robotic surgery in recent years, and its comparable success

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**Received:** 16.10.2023 **Accepted:** 26.12.2023

**Cite this article as:** Doğanca T, Argun ÖB, Tuna MB, Tüfek İ, Öbek C, Kural AR. Robot-assisted Radical Cystectomy with Intracorporeal Urinary Diversion following Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer: An Initial Experience. J Urol Surg 2024;11(2):67-71.

with open surgery in oncological and functional outcomes, particularly in kidney and prostate cancer, brings the applicability of this approach to radical cystectomy as well (4,5). In recent years, radical cystectomy has been performed mostly with robot assistance, especially in clinics that perform high-volume surgery (6). With the minimally invasive approach provided by robotic surgery, it is intended to reduce perioperative fluid loss, blood loss, pain, normalization of bowel movements in a shorter time, and hospital stay. In addition, executing the urinary diversion intracorporeally, which is an important step of the surgery, will exploit these advantages (7,8). Evidently, the oncological and functional results of the robot-assisted approach should not be inferior to those of open surgery. Series on this topic demonstrate the efficacy and feasibility of this treatment approach (4,5).

Studies have shown the survival advantage of neoadjuvant chemotherapy before radical cystectomys (9-12). Therefore, neoadjuvant chemotherapy is being applied more frequently in patients who are suitable for chemotherapy. Although there is an outlook that neoadjuvant chemotherapy will cause additional perioperative complications for a morbid operation such as radical cystectomy, there are important studies contrary to this template (7,13). Furthermore, the manner in which urinary diversion is performed after radical cystectomy is another issue.

In this study, we aimed to share the outcomes of robot-assisted radical cystectomy, intracorporeal urinary diversion, and extended lymph node dissection in 14 patients with muscle-invasive bladder cancer who underwent neoadjuvant chemotherapy.

## Materials and Methods

Between February 2018 and June 2022, 14 patients underwent neoadjuvant chemotherapy for invasive bladder tumors followed by robot-assisted radical cystectomy, extended lymph node dissection, and intracorporeal urinary diversion using the DaVinci Surgical System Xi (Intuitive Surgical Inc., Sunnyvale, CA, USA). Demographic, operative, and postoperative information of the patients were evaluated (Table 1). The chemotherapy regimen was gemcitabine plus cisplatin combination for 13 patients and cisplatin plus etoposide combination for 1 patient. All patients were evaluated after the second cycle to determine the response to chemotherapy. For all 14 patients, after 2 cycles, evaluation consisted of radiologically stable or remission disease. At this point, it is decided to complete four cycles of chemotherapy for all patients. During the chemotherapy, there were no major complications that may indicate discontinuation of treatment or that prevented surgery.

**Surgical technique:** The surgical technique of robotic radical cystectomy and lymph node dissection has been described in detail in many previous studies (14-16). The steps for intracorporeal urinary diversion continue as follows: Preparation of the left ureter and its route to the right in a retromesenteric opening, followed by 25 mg of indocyanine green mixed with

**Table 1. Peroperative data**

| | | | |
|---|---|---|---|
| **Age (year ± SD)** | **66±7.6** | | |
| **ASA** | 2: 14 (100%) | | |
| **BMI** | 30.3±3.7 | | |
| **Sex** | M: 11 (78.5%)<br>F: 3 (21.5%) | | |
| **Preoperative T stage (n, %)** | T1: 2 (14%)<br>T2: 10 (71%)<br>T3: 1 (7%)<br>T4: 1 (7%) | | |
| **Concomitant CIS** | Yes: 6 (43%)<br>No: 8 (57%) | | |
| **Operation time (min ± SD)** | 295±137 | 278±140 (IC) | 311±110 (ON) |
| **Estimated blood loss (mL ± SD)** | 280±86 | 260±92 (IC) | 288±77 (ON) |
| **Length of stay (days ± SD)** | 6.7±1.6 | 6.5±1.5 (IC) | 6.9±1.7 (ON) |
| **Ileal orthotopic neobladder (n, %)**<br>**Ileal conduit (n, %)** | 7 (50%)<br>7 (50%) | | |
| **Postoperative pathologic t stage (n, %)** | 8 (57%) pT0<br>1 (7%) pT1 | 1 (7%) pT2 | 4 (28%) pT3 |
| **Lymph**<br>**Nodes dissected (n ± SD)** | 22.6±12.6 | 21±13 (IC) | 23±11 (ON) |
| **Postive lymph node (n, %)** | 2 (14%) | 1 (7%) (IC) | 1 (7%) (ON) |

IC: Ileal conduit, ON: Orthotopic neobladder, SD: Standard deviation, BMI: Body mass index

10 mL of distilled water, and 2 mL of this solution was injected intravenously just before spatulation and construction of the ureteroenteric anastomosis, following isolation and preparation of the ileal conduit or neobladder. For the intracorporeal neobladder, the steps defined by Wiklund and Poulakis (17) were performed. We verified the vascularity of the ureters with the intraoperative near-infrared fluorescence imaging system at the pre-anastomotic stage. Furthermore, the vascularity of the intestinal anastomosis and neobladder itself was controlled. Subsequently, healthy vascularized distal ureters were spatulate, and tension-free modified Wallace anastomoses were made over 6F single J stents using Stratafix 4/0 sutures. In patients in whom an ileal conduit was planned, the left ureter was passed to the right from the posterior of the sigmoid mesentery. A segment from the terminal ileum was isolated along with its mesentery, and ileo-ileal anastomosis was performed. Ureteroileal anastomosis was performed in the Wallace style. We also performed frozen section examinations of both distal ureters. Single J stents are maintained for 10 days for both the ileal conduit and neobladder.

### Statistical Analysis

Data about the patients were collected and evaluated retrospectively. These included demographic information, clinical stage, perioperative information, and postoperative pathology. The complication rates were analyzed for the early (30 days) and late (30-90 days) periods, according to the Clavien-Dindo classification system (18). Ethics committee approval was obtained for the study (approval number: 2022-19/02, date: 09.12.2022 - Acıbadem University Ethics Committee).

## Results

The mean patient age was 66±7.6 years. Mean operative time, intraoperative blood loss, and hospital stay were 295±137 mins, 280±86 mls and 6.7±1.6 days, respectively. Urinary diversion was performed as an orthotopic neobladder in 7 (50%) patients and as an ileal loop in 7 (50%) patients. The postoperative pathological stage was reported as pT0 in 8 (57%) patients, pT1 in 1 (7%) patient, pT2 in 1 (7%) patient, and pT3 in 54 (28%) patients. The mean number of lymph nodes removed in lymph node dissection was 22.6±12. Lymph node positivity was reported in the final pathology in 2 (14%) patients.

In the early postoperative period (0-30 days), Clavien-Dindo Grade 2 complications occurred in 6 (42%) and Grade 3 complications in 2 (14%) patients. In the late postoperative period (31-90 days), Clavien-Dindo Grade 2 complications occurred in 1 (0.7%) and Grade 3 complications in 1 (0.7%) patient (Table 2). The mean follow-up period was 15.5±5.7 months. In patients who underwent neobladder urinary diversion, no voiding problems requiring catheterization were observed during the postoperative follow-up period, and no incontinence was detected.

## Discussion

There are several studies in the literature that consider the effects of chemotherapy on the results of surgery. Predictions that chemotherapy may impact the results of surgery, including delayed wound healing and liability for infections. In addition, it is thought that hematological side effects such as neutropenia and thrombocytopenia due to chemotherapy may be effective in the early postoperative period. Radical cystectomy is one of the most morbid surgeries in urology and typically needs to be performed when the patient is in the fittest condition. However, because of the aggressive nature of the disease, sometimes there may not be an opportunity to wait for the fittest condition of the patients. These patients, who often have additional morbidities such as chronic obstructive pulmonary disease due to advanced age and smoking, can be operated on after chemotherapy to obtain the possible survival advantage of neoadjuvant chemotherapy, as mentioned in the literature (10). It is important that tissue healing is adequate for ureteral and intestinal anastomoses, which is an important step of urinary diversion.

**Table 2. Postoperative complications (Clavien-Dindo classification)**

| | **Postoperative period (0-30 days)** | **Postoperative period (31-90 days)** |
|---|---|---|
| Clavien-Dindo grade 2 (n) | Urinary tract infection (5) (35%) (2 IC, 1 ON)<br>Ileus (1) (0.7%) (1 ON) | Urinary tract infection (1) (0.7%) (ON) |
| Clavien-Dindo grade 3a (n) | Repositioning of neobladder catheter under local anasthesia (1) (0.7%) (ON) | - |
| Clavien-Dindo grade 3b (n) | Removing of an intraabdominal part of the draining catheter under general anesthesia (1) (0.7%) (IC) | Parastomal hernia repair (1) (0.7%) (IC) |
| **Follow-up (months)** | 15.5±5.7 | |

IC: Ileal conduit, ON: Orthotopic neobladder

The second main subheading in our study regarding the treatment of this patient group is the step of performing urinary diversion intracorporeally. There are significant expected benefits of performing this morbid surgery laparoscopically: less pain, therefore less use of painkillers, earlier onset of bowel movements and earlier oral nourishment, shortening of the duration of hospitalization, and therefore less risk of hospitalization-related complications with an expectation of earlier return to daily life.

Of course, performing the even more subtle urinary anastomosis phase of this delicate surgery intracorporeally may take a long learning curve. Consequently, we recommend a selective approach, focusing on surgeons' experience and cautiously assessing patient-based factors.

Studies in the literature report early-term complication rates for radical cystectomy between 20% and 40% and late-term complication rates between 11% and 20% (19-21).

In the study by Nguyen et al. (13), published in 2018, in which they presented data on 40 patients, the early and late complication rates after radical cystectomy in patients receiving neoadjuvant chemotherapy were 35% and 12.5%, respectively. Reported early complications include urinary tract infection, hemorrhage, urine leakage, acute renal failure, lymphocele, and pulmonary embolism. Late complications include urinary tract infection, ileus, and acute renal failure. Two of the patients died due to intestinal obstruction and sepsis (13). These rates are comparable with the complication rates in radical cystectomy series that did not receive neoadjuvant chemotherapy.

The early-term complication rate for our patient group seems high at 57% (8/14), but these complications generally present as infections that are controlled with appropriate antibiotic therapy. In the higher Clavien-Dindo group, complications included one patient requiring intervention under general anesthesia because of a retained drain fragment in the abdomen and another patient necessitating reinsertion of the 22 F Foley catheter under local anesthesia (lidocaine 2% gel) due to its dislodgement.

### Study Limitations

Noticeably, the small number of patients in our study is a limitation in the generalizability of the results. Additionally, there is a high possibility of patient selection bias in terms of the interpretation of retrospectively presented information. Nevertheless, we believe that our findings are encouraging in terms of the feasibility of robotic radical cystectomy, intracorporeal diversion, and extended lymph node dissection in patients receiving neoadjuvant chemotherapy.

It is quite possible to achieve a balance between the benefits of chemotherapy and its effects on surgery for the benefit of the patient. Of course, at this stage, a multidisciplinary approach is required, in which the evaluation of anesthesiologists as well as oncologists and urologists is at the forefront.

## Conclusion

There are benefits and drawbacks to intracorporeal or extracorporeal urinary diversion during robot-assisted radical cystectomy. When determining the technique, the surgeons' experience and patient factors should be considered. Although the intracorporeal technique is more demanding in terms of learning and application, it may provide the benefits of the laparoscopic approach. Preoperative chemotherapy application should not be seen as a limitation in the application of these techniques.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was obtained for the study (approval number: 2022-19/02, date: 09.12.2022 – Acıbadem University Ethics Committee).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: T.D., Ö.B.A., M.B.T., İ.T., C.Ö., A.R.K., Concept: T.D., Ö.B.A., Design: T.D., Ö.B.A., Data Collection or Processing: T.D., Ö.B.A., Analysis or Interpretation: T.D., Ö.B.A., M.B.T., İ.T., C.Ö., A.R.K., Literature Search: T.D., Writing: T.D., Ö.B.A.

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

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

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2024.2023-12-6
J Urol Surg 2024;11(2):72-79

# Lower Urinary Tract Symptoms in Patients with COVID-19: Results of a Cross-sectional Study

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**What's known on the subject? and What does the study add?**

The most prevalent Coronavirus disease-2019 (COVID-19) symptoms are those of the respiratory, however, lower urinary tract as well as the gastrointestinal, cardiovascular, central nervous, and urinary systems are also affected. To date, there are published articles regarding Lower urinary tract symptoms (LUTS) in COVID-19-infected patients. Some studies reported any association between the severity of symptoms, and LUTS, while the others did not find this link. Among 709 patients, 42.2% of women and 45.6% of men with COVID-19 had nocturia. The frequency of urination per day was higher than normal in 23% of women and 40.4% of men. 15% of women complained of a sense of urinary urgency while urinating, and 13.7% and 20% of men complained of straining and hesitancy in urinating, respectively. People with COVID-19 may acquire or experience de novo LUTS, particularly storage symptoms.

## Abstract

**Objective:** We aimed to investigate the effect of severe acute respiratory syndrome-coronavirus-2 infection on lower urinary tract function using validated questionnaires in patients with patients.

**Materials and Methods:** This descriptive cross-sectional study was conducted according to the inclusion and exclusion criteria on 709 patients with Coronavirus disease-2019 (COVID-19) on an outpatient basis from September 2020 to May 2021 in Kerman's health centers. After signing the consent form and completing the demographic information, the International Consultation on Incontinence Questionnaire male Lower Urinary Tract Symptoms Modules and International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms questionnaires were completed. Finally, the data were analyzed using the SPSS version 26 software.

**Results:** Patients with COVID-19 (n=709) (365 questionnaires related to women and 344 questionnaires related to men) were examined on an outpatient basis. In general, 42.2% of women and 45.6% of men with COVID-19 had nocturia. The frequency of urination per day was higher than normal in 23% of women and 40.4% of men. In addition, 15% of women complained of a sense of urinary urgency while urinating, and 13.7% and 20% of men complained of straining and hesitancy in urinating, respectively. Similar to the males, the common symptoms in women were nocturia and increased daily frequency. In addition, with increasing age, lower urinary tract symptoms (LUTS) became common in COVID-19 patients.

**Conclusion:** The results of our investigation imply that people with COVID-19 may acquire or experience *de novo* LUTS, particularly storage symptoms. All symptoms were more in people over 50 years old than in those younger. COVID-19 infection should be investigated in any patient presenting with LUTS during the current pandemic. Further research is needed to clarify the exact pathophysiology of this correlation.

**Keywords:** COVID-19, lower urinary tract symptoms, LUTS

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**Received:** 25.12.2023 **Accepted:** 04.03.2024

**Cite this article as:** Daneshpajooh A, Shamsi R, Mirzaei M, Salehi-Pourmehr H. Lower Urinary Tract Symptoms in Patients with COVID-19: Results of a Cross-sectional Study. J Urol Surg 2024;11(2):72-79.

## Introduction

The new severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-caused Coronavirus disease-2019 (COVID-19) was discovered in Wuhan, China. Millions of people have been infected, thousands have died, and the disease became a pandemic in 2020 (1). The severity of a disease's symptoms can range from none to serious (2). The most prevalent COVID-19 symptoms are those of the respiratory system, including coughing, rhinorrhea, and shortness of breath. Many reports indicate that symptoms of the lower urinary tract as well as the gastrointestinal, cardiovascular, central nervous, and urinary systems are also affected (3). A study found that patients with COVID-19 had pyuria and hematuria for unknown reasons. There are some tentative hypotheses concerning urinary tract infections and acute kidney injury (4,5). Lower urinary tract symptoms (LUTS), particularly in elderly people, are one of the early symptoms of COVID-19 (6). The International Continence Society defines LUTS as an all-encompassing term that is used to describe a wide range of symptoms that fall into three categories: voiding, storage, and postmicturition (7). According to a study, both male and female COVID-19 patients frequently report storage and voiding LUTS as their main presenting symptoms (8). Importantly, COVID-19 infection is only occasionally found in the urine of individuals who have the disease; as a result, it is unlikely that COVID-19 can be spread by urine (9). Patients with COVID-19 may experience a new onset or an aggravation of baseline urinary symptoms, most notably overactive bladder (OAB), which is less common but increasingly described (10,11). The term "COVID-19-associated cystitis" has been used to describe this condition (12,13). Although the underlying pathophysiology of urine symptoms in COVID-19 patients is unclear, theories have started to form as a result of smaller, single-center investigations that are currently shedding light on the effects of effects on the genitourinary system. Furthermore, it has not been adequately explored whether patients with post-acute COVID-19 syndrome or extended COVID experience urine symptoms and any related discomfort. To date, there are published articles regarding LUTS in COVID-19-infected patients (5,8,14,15), and some of them reported any association between the severity of symptoms and LUTS, whereas others did not find this link. Herein, we aimed to investigate the effect of SARS-CoV-2 infection on lower urinary tract function using validated questionnaires in patients admitted with patients referred to Kerman healthcenters in southeastern of Iran.

## Materials and Methods

This study was conducted in accordance with all the guidelines and directives on medical research in Kerman. All participants in this experiment provided written informed consent. The regional ethics committee gave its consent to this work, which followed the ethical code of (approval number: IR.KMU.AH.REC.1400.130, date: 25.09.2021 - Afzalipour Hospital-Kerman University of Medical Sciences Research Ethics Committees).

### Inclusion and Exclusion Criteria

Between September 2020 and May 2021, all patients over 18 years of age who were referred to the health centers of Kerman because of symptoms of COVID-19, such as fever and respiratory symptoms, and who tested positive for SARS-CoV-2 by real-time polymerase chain reaction and/or COVID-19 fast antigen were enrolled in our study. Informed consent was obtained from each patient before participation. Patients with pre-existing LUTS were excluded from the study. Additionally, women who had significant pelvic organ prolapse and consequently may experience certain degrees of LUTS were excluded from the study. Moreover, patients with urological malignancies, those who had undergone urological surgery in the past, and those who were taking drugs that changed urine patterns were excluded. The other exclusion criteria were neurogenic bladder, history of untreated BPH and prostatitis, history of recurrent urinary tract infection, diabetes, pregnancy, and Foley catheter use.

These patients did not present with LUTS symptoms that warranted evaluation using sonography, urodynamic testing, or other imaging studies. Instead, they sought medical attention for common COVID-19 symptoms. Our aim was to investigate LUTS symptoms in these patients, and diagnostic methods for evaluating LUTS were not considered in our study. To determine the prevalence of LUTS in COVID-19-confirmed outpatients in Kerman, Iran, a cross-sectional research approach was used in this investigation.

The three main categories of lower urinary tract disorders are storage, voiding, and post-micturition. LUTS in males and females were assessed using the International Consultation on Incontinence Questionnaire male Lower Urinary Tract Symptoms Modules and International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms, respectively.

These questionnaires evaluate the day urinary frequency, nocturia, urgency, urgency urinary incontinence (UUI), bladder pain, stress urinary incontinence (SUI), unexplained urinary incontinence, amount of urinary leakage, hesitancy, straining, intermittency, nocturnal enuresis, strength of urine stream, urinary retention, dysuria, and incomplete emptying. A score of 1 or more (grade 1: low, grade 2: moderate, grade 3: severe, grade 4: very severe) was considered as a sign of severe disease. This questionnaire has been translated and validated in Persian and has high validity and reliability (16).

### Statistical Analysis

To determine the effect of COVID-19 infection severity on the incidence of LUTS, a comparison statistical test was performed between the two variables. P-value less than 0.05, was considered statistically significant.

## Results

The current study included 709 confirmed confirmed patients, comprising 344 (48.5%) men and 365 (51.5%) women. The participants' average (standard deviation) age was 43.30 (16.30) years. For men, it was 37.95 (12.93) years and for women, 48.22 (17.50) years, respectively. Of the participants who were included, 241 (34.8%) and 452 (65.2%) were under the age of 50 years. The youngest patient was 18 years old, and the oldest was 85 years old. Tables 1 and 2 show LUTS in the studied patients. The common LUTS was nocturia, which was reported in 44.2% of cases. The second was day frequency, which was reported in 220 cases (31.7%), and the next was straining in 12.7%.

According to the results, the most prevalent symptom in males was nocturia (one episode) in 32.8%, occasionally incomplete emptying in 16.3%, and occasionally straining to continue urination in 14.2%. The common symptoms of the lower urinary tract in females were nocturia (one episode) in 29.3%, urgency in 12.9%, and UUI in 8.8%.

We compared the symptoms based on the gender of the participants. The results are summarized in Table 3. According to the results, the incidence of UUI, SUI, urgency, and unexplained UI was increased in female patients than in male patients ($p<0.001$). In contrast, the incidence of daytime frequency, straining, and hesitancy was high in male patients ($p<0.05$) (Table 3).

**Table 1. The frequency of LUTS in males according to the results of the ICIQ-MLUTS questionnaire**

| Symptoms | n (%) | Symptoms | n (%) |
|---|---|---|---|
| **Hesitancy** | | **Straining to continue urination** | |
| Never | 297 (86.3) | Never | 275 (79.9) |
| Occasionally | 43 (12.5) | Occasionally | 49 (14.2) |
| Sometimes | 3 (0.9) | Sometimes | 20 (5.8) |
| Most of the time | 1 (0.3) | Most of the time | |
| **Strength of urine stream** | | **Intermittency** | |
| Normal | 319 (92.7) | Never | 295 (85.8) |
| Occasionally reduced | 21 (6.1) | Occasionally | 42 (12.2) |
| Sometimes reduced | 3 (0.9) | Sometimes | 7 (2.0) |
| Reduced most of the time | 1 (0.3) | Most of the time | |
| **Incomplete emptying** | | **Stress urinary incontinence** | |
| Never | 284 (82.6) | Never | 341 (99.1) |
| Occasionally | 56 (16.3) | Occasionally | 3 (0.9) |
| Sometimes | 3 (0.9) | **Frequency** | |
| Most of the time | 1 (0.3) | 1 to 6 times | 205 (59.6) |
| **Urgency** | | 7 to 8 times | 108 (31.4) |
| Never | 327 (95.1) | 9 to 10 times | 29 (8.4) |
| Occasionally | 15 (4.4) | 11 to 12 times | 1 (0.3) |
| Sometimes | 2 (0.6) | 13 or more times | 1 (0.3) |
| **Urge urinary incontinence** | | **Nocturia** | |
| Never | 341 (99.1) | None | 187 (54.4) |
| Occasionally | 3 (0.9) | One | 113 (32.8) |
| **Unexplained urinary incontinence** | | Two | 39 (11.3) |
| Never | 344 (100.0) | Three | 4 (1.2) |
| | | Four or more | 1 (0.3) |
| **Nocturnal enuresis** | | **Post micturition dribble** | |
| Never | 342 (99.4) | Never | 342 (99.4) |
| Occasionally | 2 (0.6) | Occasionally | 2 (0.6) |

LUTS: Lower urinary tract symptoms, ICIQ-MLUTS: International Consultation on Incontinence Questionnaire male Lower Urinary Tract Symptoms Modules

| Table 2. The frequency of LUTS in females according to the results of the ICIQ-FLUTS questionnaire | | | |
|---|---|---|---|
| **Symptoms** | **n (%)** | **Symptoms** | **n (%)** |
| **Hesitancy** | | **Straining** | |
| Never | 3321 (91.0) | Never | 345 (94.5) |
| Occasionally | 29 (7.9) | Occasionally | 16 (4.4) |
| Sometimes | 2 (0.5) | Sometimes | 3 (0.8) |
| Most of the time | 1 (0.3) | All of the time | 1 (0.3) |
| All of the time | 1 (0.3) | **Intermittency** | |
| **Bladder pain** | | Never | 328 (89.9) |
| Never | 340 (93.2) | Occasionally | 33 (9.0) |
| Occasionally | 17 (4.7) | Sometimes | 3 (0.8) |
| Sometimes | 5 (1.4) | All of the time | 1 (0.3) |
| Most of the time | 3 (0.8) | **Frequency** | |
| **Urgency** | | 1 to 6 times | 281 (77.0) |
| Never | 310 (84.9) | 7 to 8 times | 66 (18.1) |
| Occasionally | 47 (12.9) | 9 to 10 times | 12 (3.3) |
| Sometimes | 6 (1.6) | 11 to 12 times | 2 (0.5) |
| All of the time | 2 (0.5) | 13 or more times | 4 (1.1) |
| **Urge urinary incontinence** | | **Nocturia** | |
| Never | 328 (89.9) | None | 211 (57.8) |
| Occasionally | 32 (8.8) | One | 107 (29.3) |
| Sometimes | 4 (1.1) | Two | 36 (9.9) |
| All of the time | 1 (0.3) | Three | 3 (0.8) |
| **Urine leakage** | | Four or more | 8 (2.2) |
| Never | 328 (89.9) | **Nocturnal enuresis** | |
| Once or less per week | 23 (6.3) | Never | 362 (99.2) |
| Two to three times per week | 8 (2.2) | Occasionally | 3 (0.8) |
| Once per day | 1 (0.3) | **Stress urinary incontinence** | |
| Several times per day | 5 (1.4) | Never | 321 (87.9) |
| **Unexplained urinary incontinence** | | Occasionally | 27 (7.4) |
| Never | 350 (95.9) | Sometimes | 12 (3.3) |
| Occasionally | 14 (3.8) | Most of the time | 2 (0.5) |
| All of the time | 1 (0.3) | All of the time | 3 (0.8) |

LUTS: Lower urinary tract symptoms, ICIQ-FLUTS: International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms

| Table 3. Association between LUTS and gender of COVID-19 patients | | | |
|---|---|---|---|
| | **Female (n=365)** | **Male (n=344)** | **P-value*** |
| **Nocturia** | | | 0.198 |
| No | 211 (57.8) | 187 (54.4) | |
| Yes | 154 (42.2) | 157 (45.6) | |
| **Urgency** | | | **<0.001** |
| No | 310 (84.9) | 325 (95.0) | |
| Yes | 55 (15.1) | 17 (5.0) | |
| **Frequency** | | | **<0.001** |
| No | 281 (77.0) | 205 (59.6) | |
| Yes | 84 (23.0) | 139 (40.4) | |

| Table 3. Continued | | | |
|---|---|---|---|
| | **Female (n=365)** | **Male (n=344)** | **P-value*** |
| **Hesitancy** | | | **0.034** |
| No | 332 (91.0) | 297 (86.3) | |
| Yes | 33 (9.0) | 47 (13.7) | |
| **Straining** | | | **<0.001** |
| No | 345 (94.5) | 275 (79.9) | |
| Yes | 20 (5.5) | 69 (20.1) | |
| **Intermittency** | | | 0.059 |
| No | 328 (89.9) | 295 (85.8) | |
| Yes | 37 (10.1) | 49 (14.2) | |
| **UUI** | | | **<0.001** |
| No | 328 (89.9) | 286 (99.0) | |
| Yes | 37 (10.1) | 3 (1.0) | |
| **SUI** | | | **<0.001** |
| No | 321 (87.9) | 341 (99.1) | |
| Yes | 44 (12.1) | 3 (0.9) | |
| **Unexplained UI** | | | **<0.001** |
| No | 350 (95.9) | 344 (100.0) | |
| Yes | 15 (4.1) | 0 | |
| **Enuresis** | | | >0.999 |
| No | 362 (99.2) | 342 (99.4) | |
| Yes | 3 (0.8) | 2 (0.6) | |

*: Chi-square; data are presented as n (%), LUTS: Lower urinary tract symptoms, COVID-19: Coronavirus disease-2019

In terms of the LUTS in different age groups, the results showed that with increasing age, the prevalence of symptoms increased except for those aged >70 years (p<0.001). The results are summarized in Table 4 and Figure 1.

In terms of filling, voiding, and incontinence scores, Table 5 shows the details of different domains of questionnaire scores.

Regarding the age groups (<50 years or ≥50 years old), Figure 2 illustrates the different LUTS in this age category.

## Discussion

The current study demonstrated that the common LUTS in outpatient COVID-19 males were nocturia, increased daily urinary frequency, and straining, followed by hesitancy, which was significantly higher in men than in females. On the contrary, urgency, SUI, and UUI were more common in females than in males. Similar to the males, the common symptoms in women were nocturia and increased daily frequency. In addition, with increasing age, LUTS became common in COVID-19 patients.

| Table 4. LUTS in different age groups of COVID-19 patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ***Age groups** | **Nocturia (n=693)** | **Urgency (n=691)** | **Frequency (n=693)** | **Hesitancy (n=693)** | **Straining (n=693)** | **Intermittency (n=693)** | **UUI (n=638)** | **SUI (n=693)** |
| **18-29** | 51 (34.0) | 7 (4.7) | 31 (20.7) | 2 (1.3) | 6 (4.0) | 2 (1.3) | 1 (0.8) | 2 (1.3) |
| **30-39** | 80 (37.4) | 9 (4.2) | 57 (26.6) | 13 (6.1) | 20 (9.3) | 14 (6.5) | 4 (2.1) | 4 (1.9) |
| **40-49** | 37 (42.5) | 8 (9.2) | 31 (35.6) | 11 (12.6) | 14 (16.1) | 9 (10.3) | 4 (4.7) | 6 (6.9) |
| **50-59** | 57 (61.3) | 17 (18.3) | 33 (35.5) | 19 (20.4) | 21 (22.6) | 28 (30.1) | 10 (10.9) | 12 (12.9) |
| **60-69** | 36 (43.4) | 18 (22.2) | 40 (48.2) | 20 (24.1) | 18 (21.7) | 17 (20.5) | 9 (12.7) | 10 (12.0) |
| **70<** | 45 (68.2) | 13 (19.7) | 28 (42.4) | 13 (19.7) | 9 (13.6) | 13 (19.7) | 12 (19.0) | 13 (19.7) |
| **Total** | 306 (44.2) | 72 (10.4) | 220 (31.7) | 78 (11.3) | 88 (12.7) | 83 (12.0) | 40 (6.3) | 47 (6.8) |

*: Chi-square; data are presented as n (%). P-value for all symptoms was <0.001, UUI: Urgency urinary incontinence, SUI: Stress urinary incontinence

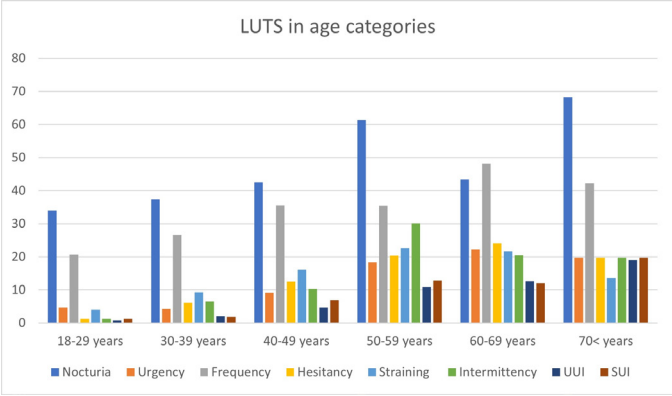


**Figure 1.** Lower urinary tract symptoms in different age groups of COVID-19 patients

COVID-19: Coronavirus disease-2019

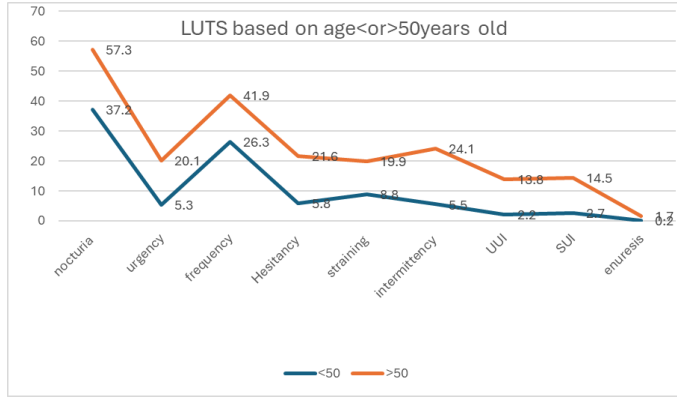


**Figure 2.** Lower urinary tract symptoms in COVID-19 patients older or younger than 50 years old

COVID-19: Coronavirus disease-2019

**Table 5. Filling, voiding and incontinence score of questionnaire**

| Questionnaires score | Females | Males |
|---|---|---|
| Filling score | 1.0 (0.0, 14.0) | - |
| Voiding score | 0.0 (0.0, 12.0) | 0.0 (0.0, 8.0) |
| Incontinence score | 0.0 (0.0, 16.0) | 0.0 (0.0, 2.0) |

One of the biggest global health issues currently facing the world is the COVID-19 outbreak, which has historically been the most significant disease worldwide. The strongest national health systems experienced a serious crisis because of this epidemic. Regardless of their specialties, almost all physicians have collaborated to deal with this issue. Most clinical researchers have concentrated on the consequences of the disease on these systems because of the nature of COVID-19 disease, which frequently affects the pulmonary and digestive systems. There is still a substantial gap in the thorough research of this clinical field, despite the studies that have been conducted in the field of urology and the impact of COVID-19 on it. In this context, it has been noted that certain COVID-19 patients experience uncomfortable urine symptoms and heartburn (6). Angiotensin-converting enzyme-2 (ACE2) receptors are highly affine to COVID-19. Therefore, COVID-19 infection is more likely to affect organs with high ACE2 receptor expression. Zou et al. (17) showed that there is a cut-off value for the ratio of ACE2 expression in organs. An expression level of more than 1% was considered to indicate a high risk of COVID-19. The bladder urothelium, which expresses ACE2 at a rate of 2.4%, is at high risk of viral invasion.

This study discovered that over 50% of the participants experienced nocturia. In addition, all symptoms were more common in people over 50 than in people under 50 years old. The results of this study were consistent with those of Daryanto et al. (18). According to their findings, the most common symptoms of the lower urinary tract were frequency, urgency, and nocturia. Complaints about the frequency of urination in the present study were much more than those in the study of Mumm and colleagues, where 7 out of 57 male patients (12%) had this symptom (10). In the study of Kaya et al. (8), on 46 out of 96 patients with COVID-19, all patients completed the LUTS-ICIQ questionnaire. The authors concluded that in male patients, there was no significant difference in the score of the questionnaire in the 3 periods (based on their condition pre-COVID-19, during hospitalization, and post-hospitalized time). In female patients, urinary incontinence and OAB scores were significantly different between the three periods. The presence of reports of intermittent urination in approximately one-eighth of the subjects in the current research is consistent with the study of Kaya et al. (8), who reported that male patients did not have significant voiding symptoms during the illness or after treatment, and these symptoms did not affect their quality of life. In addition, in Chen et al. (19), 5.5% of patients had intermittent urination. The data obtained from the sense of urgency were inconsistent with the results of Chen et al. (6), who stated that only 1.6% of the respondents had a sense of urgency. According to Can et al. (6), elderly patients' lutses dramatically increased with COVID-19 infection. The younger patients did not exhibit this increase. In addition, they stated that the distribution of ACE2 receptors and the various patient age groups are associated with these outcomes. This serves as a reminder of the importance of being aware of the various pathogenic strains of the COVID-19 virus, individual genetic variations, and potential triggers including drug use and urinary system function in patients. The individuals' average age was also lower in this study than in prior investigations. Urinary incontinence, nocturia, daytime urgency, and voiding issues are all common symptoms of LUTS. According to several studies, COVID-19 has been associated with an increased prevalence of LUTS in addition to reducing immunity in patients. Urinary

frequency (97.56%) and nocturia were the two most prevalent LUTSs among COVID-19 patients in Jain et al. (20). Similar conclusions were reached by Dhar et al. (12) in a case study conducted at a tertiary care COVID-19 unit, which found that the most common urological complaints were nocturia (87%) and a urine frequency of 13 episodes/24 hours (85%). They could establish a connection between cystitis and COVID-19 infection because of these findings. Another analysis (21) found a link between COVID-19 and the onset of acute renal damage, infection, and mortality (5.3%). This study discovered that patients' signs of renal dysfunction, such as a 59% rise in proteinuria, a 44% rise in haematuria a 14% rise in blood urea nitrogen, and a 10% rise in serum creatinine levels, increased considerably after contracting COVID-19. Along with a fever or cough, storage symptoms could be one of the first symptoms of COVID-19 because they might have developed after the patient became infected with the virus. The OAB symptoms that the female patients encountered at the outset of the disease and while they were in the hospital were similar to those that the male patients experienced, although these symptoms were managed while they were recovering at home.

A study of the patients' medical records revealed that no patients received either intravenous fluid supply or oral hydration therapy that could increase frequency. The results of our investigation, which excluded hospitalized cases, showed that in addition to nocturia, urine frequency was a typical complaint. According to Sakakibara et al. (22), psychogenic LUTS or an OAB were the other likely causes of storage symptoms. Patients with depression problems were hospitalized and infected with COVID-19, and their sad moods were all explained by a dread of dying once it was discovered that they would have voiding symptoms. Stress incontinence was more common during active infection than before and after, which is a first finding in the literature. The fact that cough is one of the main symptoms of COVID-19 may help explain this finding. An intensified cough may lead to incontinence. As COVID-19 recovers, the cough will lessen, decreasing the likelihood of detecting stress incontinence (8).

Our study's conclusions imply that people with COVID-19 may have or acquire de novo LUTS, particularly storage symptoms. However, only outpatient cases are included, which makes it difficult for us to find any links between LUTS and COVID-19 severity. Because patients were referred to health centers at various phases of COVID-19 disease, the primary study limitation was the inconsistent timing of questionnaire completion by patients. The lack of a control group against which the occurrence of symptoms could be compared was the second issue. We tried to use approved techniques to illustrate the urinary symptoms in large COVID-19 individuals. This research was conducted by referring patients with common COVID-19 symptoms (such as fever and respiratory symptoms) to the first referral level, the health center of Kerman University of Medical Sciences, at the city level. In these centers, a general practitioner was present and provided initial assessment and treatment for COVID-19, explaining COVID-19 warning signs (such as decreased oxygen saturation) to the patient. The patient would be referred to hospitals and higher specialized levels if these symptoms occurred. Therefore, diagnostic methods such as uroflowmetry, PVR measurement, and ultrasonography were not performed at this level, and if patients visited a urologist at higher levels, these tests would be conducted. Regarding the use of the MLUTS questionnaire, it is true that the use of the IPSS questionnaire for symptoms in male patients is more common, but the MLUTS questionnaire is also completely valid and usable. Because the patients were both male and female, a questionnaire was used that had more common aspects between them and could be compared. Our research indicates that storage symptoms, in particular, may be one of the first signs of signs and that physicians should evaluate storage symptoms together with other recognized viral symptoms if a patient is suspected of having the disease. Taken together, the study findings demonstrated that the effects of COVID-19 can impact organs other than the lungs and are not restricted to the lungs. Regardless of the severity of is, urinary symptoms can still develop. Therefore, when the cause of LUTS is unknown, individuals presenting with LUTS should also be assessed for COVID-19. To validate our findings, substantial prospective investigations are required. In particular, the detected mutations and various strains of COVID-19 have varying pathogenicities, and their effects on the operation of various bodily organs, including the urinary system, can vary.

## Conclusion

The findings of our study suggest that individuals with COVID-19 may develop or go through de novo LUTS, particularly storage symptoms. The common symptoms in outpatient COVID-19 males were nocturia, urinary frequency, and straining, followed by hesitancy, which were significantly higher than those in females. In contrast, urgency, SUI, and UUI were more common in females than in males. Similar to the males, the common symptoms in women were nocturia and frequency. In addition, with increasing age, LUTS became common in COVID-19 patients.

### Ethics

**Ethics Committee Approval:** The regional ethics committee gave its consent to this work, which followed the ethical code of (approval number: IR.KMU.AH.REC.1400.130, date: 25.09.2021 – Afzalipour Hospital-Kerman University of Medical Sciences Research Ethics Committees).

**Informed Consent:** All participants in this experiment provided written informed consent.

### Authorship Contributions

Concept: A.D., Design: A.D., R.S., M.M., Data Collection or Processing: A.D., R.S., M.M., H.S.-P., Analysis or Interpretation: H.S.-P., Literature Search: R.S., M.M., H.S.-P., Writing: R.S., M.M., H.S.-P.

**Conflict of Interest:** The authors declare no conflict of interest.

**Financial Disclosure:** No funding was received for this study.

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ORIGINAL RESEARCH
Endourology

Doi: 10.4274/jus.galenos.2023.2023-8-4
J Urol Surg 2024;11(2):80-86

# Assessing the Effects of Using a Ureteral Access Sheath on Kidney Injury in Retrograde Intrarenal Surgery with KIM-1 and NGAL Biomarkers in Urine: A Prospective Cohort Study

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**What's known on the subject? and What does the study add?**

The pressure effect of the irrigation fluid used during retrograde intrarenal surgery (RIRS) and mechanical occlusion of the f-URS may have a negative effect on the kidney by increasing intrapelvic pressure. Even though its use is not mandatory in routine practices, ureteral access sheath (UAS) is generally preferred to be used by urologists considering its advantages. The use of UAS ensures removal of stones, ease of access of f-URS and low intra-renal pressure. Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase associated lipocalin (NGAL) have been the leading tubule damage markers analysed in urine levels in recent years to show acute kidney injury. The use of UAS in RIRS applications was effective in preventing kidney damage and did not cause any complications. We demonstrated the development of kidney damage with KIM-1 and NGAL biomarkers measured in urine. It was revealed that more kidney damage developed in the group not using UAS compared to the group in which UAS was used, especially in the 24$^{th}$ postoperative hour.

## Abstract

**Objective:** This study aimed to investigate the effects of ureteral access sheath (UAS) use in patients undergoing retrograde intrarenal surgery (RIRS) due to kidney stones on postoperative early kidney injury development using urine kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) measurements.

**Materials and Methods:** Thirty patients using UAS (UAS group) and 30 not using UAS (non-UAS group), for whom RIRS was planned, and 30 healthy controls (control group) were included between January and June. Blood urea nitrogen and creatinine in the blood and KIM-1 and NGAL in the urine at the pre-operative and postoperative 24$^{th}$ hours and KIM-1 and NGAL at the postoperative 4$^{th}$ and 24$^{th}$ hours were studied. The same biomarkers were analyzed once in the control group. During follow-up, KIM-1 and NGAL were measured using the enzyme-linked immunosorbent assay method within 6 months.

**Results:** There was no significant difference between the pre-operative KIM-1 and NGAL values and the postoperative 24-h KIM-1 and NGAL values in the UAS group ($p>0.05$), whereas there was a significant difference in the non-UAS group ($p<0.05$). The postoperative 24-h KIM-1 and NGAL values were significantly higher in the UAS group than in the non-UAS group ($p<0.05$).

**Conclusion:** It was determined that more kidney injury developed in the non-UAS group UAS than in the UAS group, especially at the postoperative 24$^{th}$ hour. The use of UAS in RIRS is effective in preventing the development of potential kidney injury.

**Keywords:** Kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, retrograde intrarenal surgery, ureteral access sheath

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**Received:** 23.08.2023 **Accepted:** 14.10.2023

**Cite this article as:** Küçük E, Aydın M, Bitkin A, Yıldız H, Ordulu R, Görgün S, İrkılata L. Assessing the Effects of Using a Ureteral Access Sheath on Kidney Injury in Retrograde Intrarenal Surgery with KIM-1 and NGAL Biomarkers in Urine: A Prospective Cohort Study. J Urol Surg 2024;11(2):80-86.

## Introduction

Retrograde intrarenal surgery (RIRS) in kidney stone treatment is a minimally invasive surgical approach that is increasingly used with the development of laser technologies. Even though its use is not mandatory in routine practices, ureteral access sheath (UAS) is generally preferred by urologists because of its advantages.

Kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) are the leading biomarkers among tubular damage markers analyzed in urinary levels in recent years (1). These biomarkers are highly superior to blood urea nitrogen (BUN) and creatinine levels in revealing and detecting acute kidney injury early (2). KIM-1 and NGAL biomarkers have been shown to increase in proximal tubular cells in epithelial kidney injuries and after ischemia (3,4).

KIM-1 is a type-1 transmembrane glycoprotein that can adhere to the epithelium, has an immunoglobulin-like structure, and its ectodomain consists of mucin (3). It has been reported that most KIM-1-positive tubules (approximately 90%) are of proximal tubule origin in various renal diseases and were identified by double labeling with the proximal tubule marker aquaporin-1. In acute and chronic kidney injury, KIM-1 is located in the apical membrane of dilated tubules. In ischemic injury, *KIM-1* gene expression is most prominent in the S3 segment of the corticomedullary section, which is most sensitive to ischemia-induced damage. It has been reported that in acute kidney injury, the *KIM-1* gene and protein products are upregulated 3 h after experimental kidney injury, and the increase in urinary KIM-1 levels reaches a maximum at 24 h. The extracellular compartment of KIM-1 is widely used to measure urinary KIM-1 excretion. For this, 0.03 mL of urine sample is sufficient. Because the extracellular compartment of KIM-1 is stable at room temperature, KIM-1 can be measured in 24-h urine (5).

NGAL is a 25-kDa protein found in neutrophils and is easily detectable in urine. While NGAL was previously known to be found in neutrophil lysosomes, it has now been observed to be released at very low levels in tissues such as the renal tubular epithelium, colon, prostate, and breast. In addition to neutrophils, NGAL is released from epithelial cells in the thick ascending limb of the loop of Henle and collecting ducts (6). It may be affected by underlying kidney damage, systemic infection, or urinary tract infection. NGAL levels decrease when kidney damage improves. NGAL can be detected 24-48 h before the increase in serum creatinine values in acute renal failure. NGAL can identify low-level kidney damage to facilitate effective interventions. The *NGAL* gene is significantly upregulated in the kidney after ischemia (7).

Our objective in this study was to evaluate the effects of preferring UAS in patients undergoing RIRS on kidney injuries in the early postoperative period using KIM-1 and NGAL biomarkers.

## Materials and Methods

The present study protocol was reviewed and approved by the Institutional Review Board of Ondokuz Mayıs University College of Medicine (approval number: 2018/21, date: 20.03.2018). It was planned as a prospective cohort study, and informed consent was obtained from all subjects when they were enrolled.

Sixty patients with a planned RIRS operation due to kidney stones between January and June 2018 and a control group consisting of 30 healthy individuals were included in the study. The number of patients and the control group were specified according to power analysis. The 60-patient study group was randomly divided into two groups, namely group 1 consisting of 30 patients using UAS and group 2 consisting of 30 patients not using UAS. The BUN and creatinine levels at the pre-operative and postoperative 24$^{th}$ hour, KIM-1 and NGAL values in preoperative urine, and KIM-1 and NGAL values at the postoperative 4$^{th}$ and 24$^{th}$ hours were analyzed for each patient. After the urinary samples were collected from the patient groups, a urinary sample was obtained once from the control group consisting of healthy individuals without any urinary system stone disease, and the same biomarkers were then evaluated. By including the control group in the study, we confirmed that the kits used for KIM-1 and NGAL biomarkers were standardized within the normal range.

The inclusion criteria of the study were that the patients should be above 18 years of age, have an RIRS operation indication based on a kidney stone smaller than 15 mm, approve for anesthesia so that they could tolerate the operation, sign the informed consent form regarding the study, and for the 30-person control group, not have a history of any kidney stone and chronic disease. Patients with disorders that cause chronic kidney injuries, such as hypertension, diabetes mellitus, and ischemic heart disease, and with one kidney, urological surgery undergone, and congenital renal anomaly history were not included in the study.

RIRS was performed for all patients under general anesthesia with the standard flexible ureterorenoscopy (f-URS) steps. For the patients included in group 1, a UAS (9.5-11.5 Fr 45 cm hydrophilic coated UAS, Cook Medical Bloomington, IN) was posited on the ureter via a guidewire without any force, accompanied by fluoroscopy. For the patients in group 2, the collecting duct system of the kidney was accessed via a guidewire with f-URS (7.5 Fr Storz Flex-X2 Tuttlingen, Germany). After accessing the collecting duct system, the stone was fragmented with a holmium: YAG laser (Dornier Medilas H Solvo, Dornier MedTech, Germany) by sending a 270 µm laser probe (Singleflex holmium laser fiber, Dornier MedTech, Germany) via the f-URS

working channel. As the procedure of removing the stones was not implemented, the fragmentation process was continued until the stone was divided into fragments smaller than 2 mm. A JJ stent was then placed on the collecting duct system.

The urinary samples obtained from the sixty patients in the pre-operative period and postoperative 4th and 24th hours and from 30 healthy individuals from the control group were kept at -80°C until analysis. In the following six months, KIM-1 and NGAL measurements were performed using the enzyme-linked immunosorbent assay method.

For KIM-1, the standard at a concentration of 20.000 pg/mL included in the kit was diluted with standard dilution buffer. After dilution, the standards were adjusted to 5.000 pg/mL, 2.500 pg/mL, 1.250 pg/mL, 625 pg/mL, 312 pg/mL, 156 pg/mL, 78 pg/mL and 0 pg/mL concentration with the help of serial dilutions. Serum samples stored at -80°C were thawed at room temperature. KIM-1 Assay range: 78-5.000 pg/mL; sensitivity: 28 pg/mL. The measurement range is considered to be 78-5.000 pg/mL.

For NGAL, the standard included in the kit at a concentration of 20 ng/mL was diluted with standard dilution buffer. After dilution, the standards were adjusted to 10 ng/mL, 5 ng/mL, 2.5 ng/mL, 1.25 ng/mL, 0.625 ng/mL, 0.312 ng/mL, 0.156 ng/mL, and 0 ng/mL concentrations using serial dilutions. Serum samples stored at -80°C were thawed at room temperature. NGAL Assay range: 0.156-10 ng/mL; sensitivity: 0.065 ng/mL. The measurement range is considered to be 0.156-10 ng/mL.

These measurements were analyzed in accordance with the working procedures stated in the Cloud Clone Corp, Wuhan, China, SEB388Hu catalogs. The inner-test and intra-test variation coefficient values of the KIM-1 and NGAL kits were <10% and <12%, respectively.

### Statistical Analysis

The IBM Statistical Package for the Social Sciences version 21 software package was used for statistical analysis. The Shapiro-Wilk test, Kolmogorov-Smirnov test, Paired Sample t-test, Wilcoxon test, Student's t-test, and Mann-Whitney U test were used to evaluate the data. The mean standard deviation or median minimum-maximum values were used to reveal the distribution ranges based on normal distribution fitness. Any p-value 0.05 was regarded as statistically significant in all statistical analyses of the study.

## Results

The demographic data of all three groups are shown in detail in Table 1. A significant difference was observed between the pre-operative KIM-1 values and the postoperative 4th-hour KIM-1 values in both group 1 and group 2 (p<0.05). Preoperative

**Table 1. Demographic data according to the groups**

| | UAS (+) | UAS (-) | Control group | p |
|---|---|---|---|---|
| Number of patients | 30 | 30 | 30 | |
| **Sex (%)** | | | | |
| Male | 16 (53.3%) | 17 (56.7%) | 21 (70.0%) | 0.378 |
| Female | 14 (46.7%) | 13 (43.3%) | 9 (30.0%) | |
| Age (years) | 42.5±12 | 43±12.4 | 36.7±15.6 | 0.118 |
| BMI | 28.6±3.9 | 27±3.8 | 25.8±4.8 | **0.025** |
| **Operational side** | | | | |
| Right | 14 (46.7%) | 16 (53.3%) | | 0.606 |
| Left | 16 (53.3%) | 14 (46.7%) | | |
| **Localization** | | | | |
| Pelvis | 18 (60.0%) | 24 (80.0%) | | **0.040** |
| UP junction | 1 (3.3%) | 3 (10.0%) | | |
| Upper calyx | 1 (3.3%) | 1 (3.3%) | | |
| Middle calyx | 0 | 1 (3.3%) | | |
| Lower calyx | 10 (33.3%) | 1 (3.3%) | | |
| Stone volume ($mm^3$) | 14.4±1.7 | 11.1±2.8 | | **0.000** |
| HU | 1082±341 | 1030±314 | | 0.544 |
| **Hydronephrosis** | | | | |
| None | 0 | 1 (3.3%) | | **0.018** |
| G1 | 13 (43.3%) | 21 (70.0%) | | |
| G2-G4 | 17 (56.7%) | 8 (26.7%) | | |

UAS: Ureteral access sheath, BMI: Body mass index, HU: Hounsfield unit

KIM-1 values in both groups were higher. While there was no statistically significant difference between the pre-operative KIM-1 values and the postoperative 24th hour KIM-1 values in group 1 (p>0.05), the postoperative 24th hour KIM-1 values were found to be higher with a statistical significance than the pre-operative KIM-1 values in group 2 (p<0.05) (Table 2).

As for the NGAL values, while no significant difference was found between the pre-operative NGAL values and the postoperative 4th-hour NGAL values in group 1 (p>0.05), the pre-operative NGAL values were detected to be higher with a statistical significance than the postoperative 4th-hour NGAL values in group 2 (p<0.05). Upon comparing the pre-operative NGAL values and the postoperative 24th-hour NGAL values in both groups, no significant difference was seen in group 1 (p>0.05), whereas the postoperative 24th-hour NGAL values were observed to be higher with a statistical significance than the pre-operative NGAL values in group 2 (p<0.05) (Table 3).

In the between-group evaluation, there was no difference between group 1 and group 2 regarding both the pre-operative and postoperative 4th hour KIM-1 values (p>0.05). However, a statistically significant difference was found between group 1 and group 2 regarding the pre-operative and postoperative 24th hour KIM-1 values (p<0.05), with group 1 having a significantly lower median KIM-1 value (Table 4).

The intergroup NGAL values were similar to those of KIM-1, and no difference was observed between the pre-operative NGAL values (p>0.05). While there was no significant difference between group 1 and group 2 regarding the postoperative 4th-hour NGAL values (p>0.05), a statistically significant difference was found between their postoperative 24th-hour NGAL values (p<0.05), with group 1 having a significantly lower median value (Table 4).

**Table 2. The preoperative and postoperative KIM-1 values of both patient groups and the control group**

| Groups | Pre-op - control group KIM-1 | | p | Pre-op - Post-op 4th hour KIM-1 | | p | Pre-op - Post-op 24th hour KIM-1 | | p |
|---|---|---|---|---|---|---|---|---|---|
| UAS (+) | 0.75 (0.25-1.25) | 0.88 (0.36-5.00) | 0.068 | 0.75 (0.25-1.25) | 0.19 (0.09-0.85) | **0.000** | 0.75 (0.25-1.25) | 0.53 (0.16-2.25) | 0.910 |
| UAS (-) | 0.96 (0.15-5.00) | 0.88 (0.36-5.00) | 0.976 | 0.96 (0.15-5.00) | 0.21 (0.10-0.92) | **0.000** | 0.96 (0.15-5.00) | 1.05 (0.23-2.83) | **0.012** |

KIM-1: Kidney injury molecule-1, UAS: Ureteral access sheath, Pre-op: Pre-operative, Post-op: Post-operative

**Table 3. The preoperative and postoperative NGAL values of both patient groups and the control group NGAL values**

| Groups | Pre-op-control group NGAL | | p | Pre-op-Post-op 4th hour NGAL | | p | Pre-op-Post-op 24th hour NGAL | | p |
|---|---|---|---|---|---|---|---|---|---|
| UAS (+) | 4.16 (0.66-9.43) | 3.49 (0.25-8.05) | 0.236 | 4.16 (0.66-9.43) | 3.42 (1.89-6.05) | 0.210 | 4.16 (0.66-9.43) | 3.18 (1-10) | 0.773 |
| UAS (-) | 3.94 (0.27-8.17) | 3.49 (0.25-8.05) | 0.426 | 3.94 (0.27-8.17) | 3.04 (0.97-6.33) | **0.039** | 3.94 (0.27-8.17) | 5.31 (1.29-10) | **0.000** |

NGAL: Neutrophil gelatinase-associated lipocalin, UAS: Ureteral access sheath, Pre-op: Pre-operative, Post-op: Post-operative

**Table 4. Comparison of KIM-1 and NGAL values between the group that used UAS and the group that did not use UAS**

| | UAS (+) | UAS (-) | p |
|---|---|---|---|
| Preoperative KIM-1 (pg/mL) | 0.75 (0.25-1.25) | 0.96 (0.15-5.00) | 0.225 |
| Postoperative 4th hour KIM-1 (pg/mL) | 0.19 (0.09-0.85) | 0.21 (0.10-0.92) | 0.333 |
| Postoperative 24th hour KIM-1 (pg/mL) | 0.53 (0.16-2.25) | 1.05 (0.23-2.83) | **0.004** |
| Preoperative NGAL (ng/mL) | 4.16 (0.66-9.43) | 3.94 (0.27-8.17) | 0.709 |
| Post-operative 4th hour NGAL (ng/mL) | 3.42 (1.89-6.05) | 3.04 (0.97-6.33) | 0.123 |
| Post-operative 24th hour NGAL (ng/mL) | 3.18 (1-10) | 5.31 (1.29-10) | **0.039** |

UAS: Ureteral access sheath, KIM-1: Kidney injury molecule-1, NGAL: Neutrophil gelatinase-associated lipocalin

## Discussion

The general search and preference for minimally invasive approaches in surgical treatments are increasing with the development of technology. We can see the effects of these approaches in RIRS implementations increasing in kidney stone treatment (8). UAS can be frequently preferred to increase the chances of treatment success and surgical comfort in RIRS implementations. The use of UAS is generally up to the surgeon's choice, and objective criteria have yet to be defined regarding the issue. In our study, it was revealed that more kidney damage developed in the group not using UAS than in the group in which UAS was used, especially in the 24$^{th}$ postoperative hour. We demonstrated the development of kidney damage using KIM-1 and NGAL biomarkers measured in urine. Considering our findings, the use of UAS in RIRS is effective in preventing possible kidney damage.

In a prospective study consisting of 248 patients conducted to predict efficient UAS use, Mogilevkin et al. (9) concluded that sex, body mass index (BMI), and operation side on the body do not have any effect on the placement of UAS in probable predictions, but advanced age is an important determinant. Because patient selection was randomly conducted in our study, we could not evaluate the factors affecting UAS preference, and there were no statistically significant differences in sex, age, BMI, and operation side on the body between the patients who used UAS and those who did not use UAS. Although the stone weight was calculated to be statistically higher in the UAS-using group, no difference was observed between the two groups regarding the rate of stonelessness.

The use of UAS has been stated to decrease general costs and minimize operational duration in various studies (10,11). In our study, the surgical duration, anesthesia duration, laser duration, laser power, laser hit number, and the amount of irrigation solution used were higher in the UAS-using group. We believe that this resulted from the fact that the stonelessness rate of the UAS-using group was not different from that of the group not using UAS, although the stone weight was statistically higher in the UAS-using group, as mentioned above. In addition, stone size and grade 2-4 hydronephrosis were found to be significantly higher in the UAS-using group than in the group not using UAS. However, these data also show that the UAS-using patient group has all the factors that increase kidney injury risks. Even though the UAS-using group had all the factors increasing renal injury risks, their KIM-1 and NGAL levels were found to be lower than those of the group not using UAS. Considering these results, we can say that the use of UAS in RIRS practices protects the kidney from injuries.

In their prospective controlled study conducted to investigate the effects of RIRS on kidney injury, Dede et al. (12) compared a patient group consisting of 30 patients with kidney stones smaller than 2 cm and undergoing RIRS with a control group consisting of 47 individuals applying to a urology clinic and not having any specific symptoms. The patients' preoperative, postoperative 2$^{nd}$ hour, and postoperative 1$^{st}$-day urinary samples were obtained, and KIM-1, NGAL, N-acetyl-ß-D glucosaminidase (NAG), and liver-fatty acid binding protein (LFABP) molecules from these samples were analyzed. The postoperative 2$^{nd}$ hour KIM-1, NGAL, and serum creatinine levels increased significantly compared with the pre-operative levels, whereas they dropped in the postoperative 24$^{th}$ hour. No postoperative increases were observed in NAG and LFABP levels compared with pre-operative levels. The study concluded that RIRS is a safe method, and although the marker levels increased during the first 2 h, they dropped back to their initial levels within the postoperative 24 h (12). However, Dede et al. (12) excluded any information on whether they used UAS in their study. The harmful effects of high pressure, caused by the irrigation solution and laser energy used within the kidney in RIRS implementation, on the kidney with varying severity levels are known and expected. Even though Dede et al. (12) showed this kind of harm to be intentional and reversible, RIRS poses a risk for kidney health, and studies continue to be conducted to determine the conditions and methods to minimize these risks. As for our study, upon comparing the marker values of the two patient groups divided into those who used UAS and those who did not, the 24$^{th}$ hour KIM-1 and NGAL levels of the group that did not use UAS were detected to be higher than those of the group that used UAS. Besides, in the inner evaluations of both groups, while the 24$^{th}$-hour marker levels of the UAS-using group did not bear any difference to the pre-operative levels, the KIM-1 and NGAL levels of the group not using UAS were found to increase with a statistical significance, rendering UAS use to be effective in preventing renal injury.

In their study in which they prospectively evaluated 30 patients undergoing f-URS for upper urinary system kidney disease treatment, Ertaş et al. (13) found that the NGAL and NGAL/creatinine ratio levels they analyzed in the spot urinary samples obtained from the UAS posited to the kidney undergoing an operation in the pre-operative period and the ureter catheter in the postoperative 1$^{st}$ and 24$^{th}$ hours increased 1 h after the operation and during the first postoperative day, but these differences were not seen to be significant. This study conducted by Ertaş et al. (13) has shown UAS-enhanced f-URS to be a safe procedure for treating kidney or upper ureter kidney disease with regard to renal injury and functional results. The postoperative urinary samples obtained in our study were mutual samples obtained from both healthy and operated kidneys. The superiority of the study conducted by Ertaş et al. (13) over our study stems from the fact that the obtained urinary samples exclusively came from the kidneys that were

operated on. Therefore, Ertaş et al. (13) preferred to use a ureter catheter in all postoperative patients and did not use a JJ stent in any of their patients. We preferred to use a JJ stent in our study to avoid possible risks stemming from not using a JJ stent (14,15).

Mishra et al. (4) observed higher NGAL expression in renal tubulointerstitial lesions in *in vitro* renal ischemia-reperfusion injury. They showed that NGAL concentration in urine began to increase 3 h after kidney injury and that NGAL concentration peaked at 24 h, supporting our findings. In our study, no significant difference was observed in KIM-1 and NGAL values between the groups at the pre-operative and postoperative 4$^{th}$ hour. However, contrary to expectations, when the intra-group marker levels were compared, it was found that NGAL was lower in the group not using UAS, and KIM-1 was lower in both groups at the 4$^{th}$ postoperative hour, which was statistically significantly lower than the pre-operative levels. We think that this may be due to the intense hydration applied peroperatively, increased diuresis in the early postoperative period, inability to collect separate urine, and the markers beginning to increase in the 2-3$^{nd}$ hour, reaching the maximum level in the 24$^{th}$ hour. The fact that KIM-1 and NGAL values were lower in the group in which UAS was used at the 24$^{th}$ postoperative hour than in the group in which UAS was not used shows that these biomarkers can be used to indicate early kidney damage and the importance of using UAS.

In addition to the contributions and benefits it provides, UAS use may also cause undesired results (16-19). In particular, the undesired results during the period when its procedures were first defined led Kourambas et al. (10) to introduce a new and more reliable generation of UASs in 2001, which again increased UAS use during RIRS X. In a study they conducted to investigate the long-term ureter stricture or short-term ureter injury potential of UAS use, Delvecchio et al. (20) used a 10, 12, 14 Fr UAS and determined in their regular 3-month patient follow-ups throughout the following year that only one patient developed ureteral stricture. Various studies suggest based on analyses that UAS should be routinely used during f-URS as it is predicted to decrease the duration and costs of operation and decrease morbidity rates (11,12,20). No complications were encountered during the positioning of the UAS in our study. We believe that the most important factor for this is that the operation was performed under fluoroscopy and suspended for a second session by placing a JJ ureteral stent if any resistance was encountered during UAS placement. In addition, as Lallas et al. (17) put forth in the conclusion of their study, the use of a UAS with low Fr levels is known to decrease negative effects on ureter bleeding. In our study, the thinnest 9.5/11.5 Fr UAS was used. In this way, damage to the ureter was minimized, enabling the secretion of proinflammatory cytokines to decrease. Therefore, we decreased the possibility of urinary KIM-1 and NGAL values, which we used to evaluate kidney damage, being affected by the ureter, minimizing the risk of possible negative effects due to UAS use.

Among 256 patients on whom they performed ureterorenoscopy, L'esperance et al. (21) reported the stonelessness rates of 173 who used UAS and 83 who did not use UAS to be 79% and 67%, respectively. Conclusively, UAS use was stated to significantly decrease the stonelessness rates (21). Conversely, in their study in which they retrospectively evaluated data from 280 patients, Berquet et al. (22) compared the stonelessness rates of patients who used UAS and those who did not use UAS and did not find any significant differences between the two groups. Our study supports the findings of Berquet et al. (22) as there was no statistically significant difference between our patient groups regarding their stonelessness rates.

### Study Limitations

If KIM-1 and NGAL could be measured in the urine at the postoperative 7$^{th}$ day and 1$^{st}$ month in our study, we might have obtained more valuable data and could have commented on late-stage kidney damage.

## Conclusion

Our study was conducted on patients whose kidney function tests were normal. Although early diagnosed kidney injury can be treated in a later period, it should be noted that a reversible process may not be obtained in patients with limited kidney function reserves. If the KIM-1 and NGAL values in the urine had been analyzed during the postoperative 7$^{th}$ day and 1$^{st}$ month, then we could have obtained more valuable data and could be commenting on the late-period kidney injury. That said, the fact that our study is a prospective randomized study and that all RIRS implementations were carried out in a single center by the same surgical team comprises the advantages of our study.

Based on our study, it has been concluded that the use of UAS in RIRS practices is effective in preventing kidney injury and does not cause any complications. Multi-centered, prospective, and randomized controlled studies, in which more comprehensive and long-term follow-ups can be performed, are needed to be conducted on the use of UAS during RIRS.

### Ethics

**Ethics Committee Approval:** The present study protocol was reviewed and approved by the Institutional Review Board of Ondokuz Mayıs University College of Medicine (approval number: 2018/21, date: 20.03.2018).

**Informed Consent:** Informed consent was obtained from all subjects when they were enrolled.

### Authorship Contributions

Surgical and Medical Practices: E.K., M.A., A.B., S.G., L.İ., Concept: A.B., R.O., Design: M.A., S.G., L.İ., Data Collection or Processing: E.K., H.Y., R.O., Analysis or Interpretation: E.K., M.A., H.Y., Literature Search: R.O., L.İ., Writing: E.K., L.İ.

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

**Financial Disclosure:** This study received financial support from the Samsun Training and Research Hospital Education Support Fund.

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2024.2023-6-4
J Urol Surg 2024;11(2):87-92

# Efficacy of Non-invasive Serum Markers in Predicting the Prognosis of Fournier Gangrene

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**What's known on the subject? and What does the study add?**

Fournier's gangrene is a life-threatening urological emergency. Prediction of mortality and morbidity is important to decide the intensity of treatment. Therefore, many non-invasive methods are being investigated. Biochemical non-invasive serum markers such as aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT), albumin/globulin, neutrophil/lymphocyte, and platelet/lymphocyte ratios are used to demonstrate general inflammatory conditions. Among these parameters AST/ALT and neutrophil/lymphocyte ratios appear to be useful in initial evaluation of the prognosis of patients with Fournier gangrene.

## Abstract

**Objective:** Fournier gangrene is a true urological emergency. This study aimed to evaluate the efficacy of biochemical diagnostic markers in predicting the prognosis of patients who presented to the hospital with Fournier gangrene.

**Materials and Methods:** Sixty-eight male patients who underwent aggressive debridement and drainage for Fournier gangrene were included in the study. The patients were divided into two groups: Group 1 comprised patients who died and group 2 comprised those who survived. Fournier Gangrene Severity index (FGSI), Uludağ FGSI (UFGSI), and age-adjusted Charlson Comorbidity index (ACCI) scores, and urea, creatinine, sodium, potassium, hemogram, aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT), total protein, albumin, globulin, alkaline phosphatase and lactate dehydrogenase values of all patients were recorded. The AST/ALT, albumin/globulin, neutrophil/lymphocyte, and platelet/lymphocyte ratios (PLR) were also noted.

**Results:** The mean age of all patients was 59.04±13.99 (25-89) years. The FGSI, UFGSI, and ACCI scores of the patients in group 1 were found to be significantly worse than those in group 2. When we evaluated systemic inflammation parameters, there was a statistically significant difference between the groups in terms of the AST/ALT and neutrophil/lymphocyte ratios (NLRs) (p=0.042 and 0.023, respectively), but no significant difference was found in relation to the albumin/globulin and PLRs.

**Conclusion:** Non-invasive serum markers, such as AST/ALT and NLR, appear to be useful in evaluating the prognosis of patients with Fournier gangrene. Therefore, we recommend the use of these ratios in the initial evaluation of this patient group.

**Keywords:** Fournier gangrene, serum markers, prognosis, mortality

## Introduction

Fournier's gangrene is a necrotizing fasciitis that rapidly progresses and affects the deep and superficial tissues of the perineum and ano-genital areas. This disease, which can lead to fatal results when diagnosed late, can sometimes be confused with benign processes (1,2).

Patients with Fournier's gangrene usually present with discomfort, swelling, and pain in the ano-genital region. In addition to being male, these patients may have a medical history of known risk factors for Fournier's gangrene, such as diabetes mellitus, cardiovascular disease, peripheral vascular disease, presence of malignancy, and/or alcohol overuse. Fournier's gangrene is a urological emergency that usually presents with

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**Received:** 20.06.2023 **Accepted:** 08.01.2024

**Cite this article as:** Güzel Ö, Asfuroğlu A, Aslan Y, Balcı M, Coşer Ş, Tuncel A. Efficacy of Non-Invasive Serum Markers in Predicting the Prognosis of Fournier Gangrene. J Urol Surg 2024;11(2):87-92.

sepsis when unmanaged with aggressive surgical intervention and intensive medical treatment (3). There are many factors that determine the prognosis of Fournier's gangrene. Laor et al. (4), in a study published in 1995, found that the Fournier Gangrene Severity Index (FGSI) was an extremely helpful tool in predicting disease-related prognosis. This index includes measurements of body temperature, heart and respiratory rate, serum electrolyte, creatinine and bicarbonate levels, hemoglobin/hematocrit, and white blood cell count. A study published in 2010 by Yilmazlar et al. (5) modified this index by including age score and an extent of disease score and obtained the Uludağ FGSI (UFGSI), which has been used in many studies to evaluate the prognosis of Fournier gangrene. Another widely used prognostic tool is the age-adjusted Charlson Comorbidity Index (ACCI), which was proposed by Charlson et al. (6). This index includes different scores for each comorbidity. The authors suggested that an ACCI score of >5 was associated with higher mortality rates.

The early systemic effects of Fournier's gangrene are the result of an excessive inflammatory reaction of the body against this progressive infectious course. Among these biochemical markers, a high aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT) (De Ritis) ratio is associated with liver diseases and many cancers and a poor prognosis in terms of systemic inflammation (7,8).

The albumin/globulin ratio is a frequently used marker in routine health examinations, with a low value of this ratio indicating greater severity of inflammation. In malnourished patients, inflammation can cause malnutrition, whereas malnutrition can cause an inflammatory response (9).

The neutrophil/lymphocyte ratio (NLR) is an important indicator of systemic inflammatory response and is found to be higher in inflammation. NLR is a simple tool to rapidly assess the inflammatory level of a patient (10,11).

Another useful parameter is the platelet/lymphocyte ratio (PLR). This ratio is a significant indicator of the systemic inflammatory response at increased levels (12,13).

In the current study, we aimed to evaluate the effectiveness of biochemical diagnostic markers in predicting the prognosis of patients admitted to the hospital with Fournier's gangrene.

## Materials and Methods

Of 82 patients, 68 fournier cases whose file information could be accessed were included in the study. In the current study, 68 male patients who underwent aggressive surgical debridement and drainage for Fournier gangrene between 2014 and 2021 were retrospectively evaluated. Since our study was retrospective and only laboratory data were evaluated, ethics committee approval was not obtained. The patients included in the study were divided into two groups, group 1 and group 2, in accordance with the presence or absence of mortality during the postoperative follow-up.

The body mass index (BMI), comorbidities, duration of symptoms and hospitalization, number of debridement procedures, revision date, need for total parenteral nutrition support, need for blood transfusion, infectious agents, skin percentage of Fournier gangrene, FGSI, UFGSI and ACCI scores, and urea, creatinine, sodium, potassium, hemogram, AST, ALT, globulin, albumin, total protein, alkaline phosphatase and lactate-dehydrogenase values of all patients were recorded. The AST/ALT ratio, albumin/globulin ratio, NLR, and PLR were also noted.

Aggressive resection including the area of necrosis was performed in all patients. Unilateral or bilateral orchiectomy was also performed in all patients due to necrosis. A surgical procedure was performed by the general surgery clinic in seven patients with perianal abscesses and one patient due to incarcerated hernia. The wound care of the postoperative patients was performed with vacuum-assisted closure and conventional rivanol dressing.

### Statistical Analysis

In the statistical analysis of the patient data, for descriptive statistics, categorical variables were expressed as absolute numbers and percentages, and continuous variables were expressed as mean ± standard deviation. The normal distribution of continuous variables was tested using histograms and the Kolmogorov-Smirnov test. The independent-samples t-test was used for independent variables and the paired t-test for dependent variables that were normally distributed. The chi-square test was used for the analysis of categorical variables. A p-value of $<0.05$ was considered statistically significant. Univariate analysis was performed on the appropriate parameters of the patients with $p<0.05$.

## Results

The results of all 68 patients were analyzed. There were 12 patients in group 1 and 56 patients in group 2. The mean age of all patients was 59.04±13.99 (25-89) years, and the mean duration of symptoms at the time of admission was 8.99±10.34 (1-72) hours. The mean duration of hospitalization was 16.62±8.84 (2-60) days, and 17.6% of the patients died during perioperative care.

The mean BMI was 26.49±3.75 (20-34) kg/m$^2$, and 25% of the patients had hypertension, 50% had diabetes mellitus, 16.2% had atherosclerotic heart disease, 22.1% had acute renal failure, 8.8% had chronic renal failure, 4.4% had pneumonia, 7.4% had

abnormal liver function test results, and 8.8% had a history of malignancy. The demographic data and comorbidities of the patients are shown in Table 1 by group. The FGSI, UFGSI, and ACCI scores of the patients in group 1 were found to be significantly worse than those in group 2. When evaluated in terms of systemic inflammation parameters, there was a statistically significant difference between the groups in terms of the AST/ALT ratio and NLR (p=0.042 and p=0.023, respectively), but no significant difference was observed in relation to the albumin/globulin ratio and PLR (Table 2).

The mean skin percentage of Fournier gangrene was 3.37±2.47% (1-10). In the pre-operative wound culture of the patients, *Escherichia coli* was isolated in 23.5% of the patients, *Enterococcus* species in 11.8%, *Streptococcus* species in 7.4%, *Acinetobacter baumannii* in 5.9%, *Klebsiella* species in 5.9%, *Pseudomonas* species in 5.9%, *Candida* in 5.9%, *Staphylococcus* species in 4.4%, and *Proteus* species in 1.5%. No methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococci* were detected. During perioperative care, 11.8% of the patients required total parenteral nutrition and 20.6% required blood transfusion. The number of debridement procedures following the initial surgery was 2.7 for group 1 and 2.5 for group 2.

**Table 1. Demographic data and comorbidities of the study groups**

| | **Group 1 (n=12)** | **Group 2 (n=56)** | **p** |
|---|---|---|---|
| Age (years) (mean ± SD) | 64.67±17.01 (min: 25, max: 89) | 58.3±13 (min: 29, max: 82) | 0.212 |
| Duration of symptoms (hours) (mean ± SD) | 6.42±3.15 (min: 2, max: 10) | 9.54±11.25 (min: 1, max: 72) | 0.081 |
| **Body mass index (kg/m²) (mean ± SD)** | 25.67±4.33 | 26.66±3.63 | 0.409 |
| Hypertension (n/%) | 4/33.3 | 13/30.2 | 0.340 |
| Diabetes mellitus (n/%) | 8/66.6 | 26/46.4 | 0.477 |
| Atherosclerotic heart disease (n/%) | 2/16.6 | 9/19.6 | 0.960 |
| Acute renal failure (n/%) | 4/33.3 | 11/24.4 | 0.422 |
| Chronic renal failure (n/%) | 2/16.6 | 4/7.1 | 0.285 |
| Abnormal liver function test results (n/%) | 0/0 | 5/8.9 | 0.577 |
| Malignancy (n/%) | 5/41.6 | 1/1.7 | 0.001* |
| Number of debridement procedures | 2.75±1.71 (min: 1, max: 7) | 2.52±1.51 (min: 1, max: 8) | 0.670 |

*: Statistically significant, chi-square test, SD: Standard deviation, Min: Minimum, Max: Maximum

**Table 2. Clinical scores and laboratory findings of the study groups**

| | **Group 1 (n=12) (mean ± SD)** | **Group 2 (n=56) (mean ± SD)** | **p** |
|---|---|---|---|
| FGSI score | 7.58±5.07 (min: 0, max: 15) | 2.64±2.59 (min: 0, max: 12) | 0.006* |
| ACCI score | 5.75±3.49 (min: 2, max: 15) | 3.07±1.74 (min: 0, max: 8) | 0.023* |
| UFGSI score | 10.00±5.77 (min: 2, max: 19) | 4.73±3.33 (min: 1, max: 19) | 0.009* |
| AST/ALT ratio (De Ritis ratio) | 1.58±0.57 (min: 1.07, max: 3.14) | 1.19±0.33 (min: 0.64, max: 2.40) | 0.042 |
| Albumin/globulin ratio | 1.08±0.69 (min: 0.59, max: 3.00) | 1.18±0.59 (min: 0.47, max: 4.20) | 0.646 |
| Neutrophil/lymphocyte ratio | 10.71±6.94 (min: 3.98, max: 22.82) | 5.80±5.60 (min: 0.40, max: 24.25) | 0.023* |
| Platelet/lymphocyte ratio | 171.79±144.56 (min: 3.00, max: 558.00) | 165.73±176.69 (min: 5.1, max: 871.70) | 0.901 |

*: Statistically significant, chi-square test, SD: Standard deviation, Min: Minimum, Max: Maximum, FGSI: Fournier Gangrene Severity index, ACCI: Age-adjusted Charlson Comorbidity index, UFGSI: Uludağ FGSI, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz

## Discussion

Fournier gangrene is a type I necrotizing fasciitis of the perineum and anogenital regions. Rapid progression of inflammation and infection causes thrombosis of small blood vessels, which leads to ischemia and necrosis of adjacent soft tissue and fascia planes. Fournier gangrene is a relatively rare urological emergency, representing only 0.02% of all hospitalizations, although its incidence is increasing with an aging population and a higher prevalence of diabetes (14). Necrotizing fasciitis often stems from infection of the anorectum (30-50%), urogenital tract (20-40%), anogenital skin, or perineal skin (20%). Sorensen et al. (15) reported an overall incidence rate of 1.6 cases per 100.000 men/year. He emphasized that this incidence peaks at 3.3 cases per 100.000 men per year in persons over 50 years of age (15,16).

The main aims of the management of Fournier gangrene are early patient resuscitation, broad-spectrum antibiotherapy, and aggressive debridement and drainage of necrotizing tissues. Treatment aims to prevent systemic toxicity, stop infective progression, and eliminate the causative multi-bacterial agents. The urgent and aggressive debridement of necrotic and devitalized tissues is the main step in preventing the spread of infection. Early aggressive debridement is crucial, and even a delay of a few hours is directly related to the risk of death (17,18). Frequent wound monitoring and repeated debridement are essential for the control of infection. It has been reported that an average of 3.5 debridements are required for sufficient infection control (19). In our study, we started broad-spectrum antibiotics in all patients, as recommended by the infectious diseases clinic, and we performed aggressive excision and drainage of necrotic tissue. The number of debridement procedures performed following initial surgery was 2.7 for group 1 and 2.5 for group 2.

The most important factor determining the prognosis of Fournier gangrene is the presence of comorbidities (20). Some prognostic tools, such as FGSI, UFGSI, and ACCI, are used for this purpose. The most widely used prognostic scoring system is FGSI, in which a score of greater than 9 has been associated with over 75% mortality, whereas a score of 9 has a 78% probability of survival (21). In UFGSI, a score >9 is associated with a 94% likelihood of death, whereas a score <9 is correlated with an 81% probability of survival. As stated for both FGSI and UFGSI, which are similar scoring systems, greater tissue and site involvement correlates with worse pronosis (4-6). Erol et al. (22) reported that the ACCI score was higher and the life expectancy was 10 years shorter among non-survivors than among survivors. Higher ACCI scores may be correlated with a worse outcome, which may also indicate mortality (22). ACCI can be useful in the evaluation of patients' outcomes with Fournier gangrene. In our study, the scores of the patients in group 1 were found to be significantly worse in all these scoring systems.

The systemic inflammatory response is an important part of disease progression in critical illness and is often associated with septicemia and increased mortality. ALT is considered a liver-specific enzyme, whereas AST is expressed in a variety of tissues (7). AST increased more than ALT in conditions of increased proliferation rate, tissue damage, and tumor cell turnover. Therefore, the De Ritis rate is considered to indicate systemic changes such as tumor proliferation and systemic inflammation (23). Serum albumin level is used to reflect nutritional status and serum globulin to evaluate chronic inflammation severity. Moreover, both albumin and globulin concentrations are influenced by many factors, e.g., the volume status of body fluid. Recently, the albumin-globulin ratio has begun to be accepted as a new prognostic marker (24-27). NLR is a marker that has proven its prognostic value in cardiovascular diseases, infections, inflammatory diseases, and various types of cancer (28,29). NLR is thought to reflect the balance between neutrophils and lymphocytes. Previous literature has shown that a high NLR is associated with an increased concentration of various proinflammatory cytokines that can cause cellular DNA damage (30-32).

Several studies have examined the relationship between PLR and disease-specific mortality. However, no study has explored the relationship between PLR and all-cause mortality in the general population. PLR has emerged as an informative marker revealing changes in platelet and lymphocyte counts due to acute inflammatory and prothrombotic conditions (33). In the current study, when evaluated in terms of systemic inflammation parameters, there was a statistically significant difference between the groups in terms of the AST/ALT ratio and NLR (p=0.042 and p=0.023, respectively), but no significant difference was detected in the albumin/globulin ratio and PLR. According to the findings of our study, we believe that the AST/ALT ratio and NLR are useful in predicting prognosis in the rapid evaluation of patients with Fournier gangrene.

### Study Limitations

There were a few limitations to our study, including the single-center and retrospective design. Multicenter studies with a larger number of patients may provide more information. Nevertheless, we believe that our study can shed light on future studies.

## Conclusion

Because Fournier gangrene is a urological emergency that can be fatal, prompt evaluation of patients and early and aggressive intervention are crucial. Non-invasive serum markers, such as AST/ALT and NLR, appear to be useful in initial evaluation of the prognosis of patients with Fournier gangrene. Therefore, we recommend the use of these ratios in the initial evaluation of this patient group.

### Ethics

**Ethics Committee Approval:** Since our study was retrospective and only laboratory data were evaluated, ethics committee approval was not obtained.

**Informed Consent:** Retrospective study.

### Authorship Contributions

Concept: A.T., Design: Ö.G., Data Collection or Processing: A.A., Analysis or Interpretation: Y.A., Ş.C., Literature Search: M.B., Writing: Ö.G.

**Conflict of Interest:** The authors declare no conflict of interest.

**Financial Disclosure:** No funding was received for this study.

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2024.2023-12-2
J Urol Surg 2024;11(2):93-98

# Association Between the Percentages of Lymphocytes, Monocytes, and Neutrophils and Brucella Epididymo-orchitis: A Multicentric Study

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**What's known on the subject? and What does the study add?**

Mononuclear leukocytes (monocyte cells and lymphocyte cells) play a crucial role in granulomatous infections, such as brucellosis. There is no sufficient data in the literature concerning whether cellular changes in tissue are reflected in blood circulation in brucellosis. In our study, the percentages of lymphocytes and monocytes were higher in patients with brucella epididymo-orchitis than in those with non-brucella epididymo-orchitis.

## Abstract

**Objective:** There are insufficient data in the literature concerning whether cellular changes in tissue are reflected in blood circulation in granulomatous infections, such as zoonotic brucellosis. In this study, we compared laboratory parameters between patients with brucella (BEO) and non-brucella epididymo-orchitis (NBEO).

**Materials and Methods:** This retrospective study included 84 patients with BEO and 92 with NBEO who presented to six medical centers between 2017 and 2021.

**Results:** The median age of the patients was 41 (interquartile range: 27-61) years. In the multivariate analysis, the presence of abdominal pain (p=0.003), the percentage of lymphocytes (p=0.012) and the percentage of monocytes (p=0.029) were significantly higher in the BEO group than in the NBEO group. In addition, the percentage of neutrophils (p=0.001) was significantly lower in the BEO group than in the NBEO group. In the receiver operating characteristic analysis, the percentage of lymphocytes had an area under the curve (AUC) value of 0.808 at a cut-off point of >22.1%, the percentage of monocytes had an AUC value of 0.745 at a cut-off point of >7.7%, and the percentage of neutrophils had an AUC value of 0.746 at a cut-off point of <66.8%.

**Conclusion:** To the best of our knowledge, there is no other study comparing the percentages of lymphocytes, monocytes, and neutrophils between patients with BEO and NBEO. The percentages of mononuclear leukocytes (monocytes and lymphocytes) and neutrophils may be useful for the pre-diagnosis of BEO in endemic areas.

**Keywords:** Brucella, orchitis, lymphocytes, monocytes, neutrophils

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**Received:** 05.12.2023 **Accepted:** 24.02.2024

**Cite this article as:** Bülbül E, Evlice O, İlki FY, Dindar EK, Üstün F, Sevinç AH, Alkan S, Fidan G, Bedir S. Association Between the Percentages of Lymphocytes, Monocytes, and Neutrophils and Brucella Epididymo-orchitis: A Multicentric Study. J Urol Surg 2024;11(2):93-98

## Introduction

Human brucellosis is the most common bacterial zoonosis (1), but its diagnosis can be delayed (2). Because it has a chronic and granulomatous nature (3,4), the timing of diagnosis and treatment is critical in terms of focal complications that may develop. If left untreated, brucellosis can lead to organ involvement, such as osteoarthritis, infective endocarditis, hepatitis, meningitis, and epididymo-orchitis (5).

It has been reported that 2.5-18.8% of men with brucellosis have testicular involvement (5-7). It is also difficult to diagnose brucella cases presenting with isolated orchitis (8,9). The local clinical findings of brucella (BEO) and non-brucella epididymo-orchitis (NBEO) are similar, and acute phase reactants may be elevated in all epididymo-orchitis cases (10,11). Mononuclear leukocytes (monocyte cells and lymphocyte cells, especially macrophages) play a crucial role in granulomatous infections, such as brucellosis. When monocytes in the bloodstream reach the tissue, they are called macrophages and are surrounded by lymphocytes. These reactions also represent lymphohistiocytic inflammation, which is a chronic inflammatory response (12). However, there is no sufficient data in the literature concerning whether cellular changes in tissue are reflected in blood circulation in brucellosis. A detailed evaluation of clinical parameters and the distribution of mononuclear leukocytes in the complete blood count may be useful for the differential diagnosis of epididymo-orchitis. In this study, we compared the clinical and laboratory parameters between the BEO and NBEO patients.

## Materials and Methods

### Study Design

The files of patients with NBEO and BEO who presented to six medical centers (urology and infectious diseases clinics) between 2017 and 2021 were retrospectively reviewed. The study included 84 patients with BEO and 92 with NBEO diagnosed with epididymo-orchitis based on physical examination and laboratory and/or ultrasonography findings. Patients with missing laboratory data, hematological disease, malignancy, or immunosuppressive disease, and those using immunosuppressive drugs were excluded from the study. The study was approved by the ethics committee (approval no: 2022/149, date: 22.11.2023 - University of Health Sciences Turkiye, Ankara Gülhane Training and Research Hospital Clinical Research Ethics Committee).

### Follow-up and Data Collection

The patient's demographic characteristics, physical examination findings, and laboratory parameters [complete blood count, C-reactive protein, and erythrocyte sedimentation rate (ESR)] were noted. The diagnosis of epididymo-orchitis was made according to the patients' scrotal complaints (pain, redness, tenderness, and/or swelling), acute phase reactants, and/or ultrasonography findings. When brucellosis was suspected clinically, patients with a Wright tube agglutination test result of ≥1/160) or a positive blood culture test were diagnosed with BEO. Additional focal involvements of patients with BEO were recorded.

### Statistical Analysis

The Kolmogorov-Smirnov test was used to evaluate the compliance of the data with the normal distribution. The Mann-Whitney U and chi-square tests were used in the statistical analysis of continuous and categorical variables, respectively. Multivariate logistic regression analysis was performed to determine statistically significant independent parameters. The optimal cut-off values of the percentage of lymphocytes, monocytes, and neutrophils for the differentiation of BEO and NBEO were calculated using receiver operating characteristic (ROC) analysis. A p-value of $<0.05$ was considered statistically significant.

## Result

The median age of all patients was 41 [interquartile range (IQR): 27-61] years. The median ages of the BEO and NBEO groups were 35 (IQR: 24-51) and 54 (IQR: 27-68) years, respectively ($p<0.0001$). Bilateral involvement was present in eight patients in each group (9.5% for BEO and 8.7% for NBEO) ($p=1$). The BEO and NBEO groups significantly differed in terms of ESR ($p=0.028$), presence of abdominal pain ($p<0.0001$), serum white blood cell count ($p<0.0001$), neutrophil count ($p<0.0001$) and percentage ($p<0.0001$), lymphocyte count ($p<0.0001$) and percentage ($p<0.0001$), monocyte count ($p=0.023$) and percentage ($p<0.0001$), neutrophil-to-lymphocyte ratio (NLR) ($p<0.0001$), and neutrophil-to-monocyte ratio (NMR) ($p<0.0001$). The clinical and laboratory data of the patients are detailed in Table 1.

In the multivariate analysis, the presence of abdominal pain ($p=0.003$), percentage of lymphocytes ($p=0.012$), and percentage of monocytes ($p=0.029$) were significantly higher in the BEO group than in the NBEO group. In addition, the percentage of neutrophils ($p=0.001$) was significantly lower in patients with BEO than in those with NBEO (Table 2).

ROC analysis was performed to calculate the optimal cut-off values for the percentage of lymphocytes, monocytes, and neutrophils required to differentiate between the BEO and NBEO groups. The percentage of lymphocytes had an area under the curve (AUC) value of 0.808 (95% confidence interval: 0.745-0.870) at a cut-off point of >22.1%, and the

| Table 1. Comparison of the clinical and laboratory parameters between the BEO and NBEO groups | | | | |
|---|---|---|---|---|
| **(n)** | **Total (n=176)** | **BEO (n=84)** | **NBEO (n=92)** | **p** |
| **Age (years), median (IQR)** | **41 (27-61)** | **35 (24-51)** | **54 (27-68)** | **<0.0001[a]** |
| **Presence of abdominal pain n, (%)** | **85 (48.3)** | **59 (70.2)** | **26 (28.3)** | **<0.0001[b]** |
| **Involvement side n, (%)** | | | | |
| Unilateral | 160 (90.9) | 76 (90.5) | 84 (91.3) | 1[b] |
| Bilateral | 16 (9.1) | 8 (9.5) | 8 (8.7) | |
| CRP (mg/L), median (IQR) | 13 (0.1-49) | 12 (4-28) | 21 (0.1-170) | 0.351[a] |
| **ESR (mm/hour), median (IQR)** | **71 (3-103)** | **78 (3-118)** | **68 (32-99)** | **0.028[a]** |
| **WBC, median (IQR)** | **8.600 (3.200-13.110)** | **7.930 (3.200-11.813)** | **8.860 (5.350-14.930)** | **<0.0001[a]** |
| **Neutrophil count (cell/mL), median (IQR)** | **5.800 (2.320-9.815)** | **4.890 (2.330-8.592)** | **6.636 (2.800-10.936)** | **<0.0001[a]** |
| **Neutrophils (%), median (IQR)** | **66.8 (36.2-90.3)** | **60.3 (36.2-83.7)** | **74.9 (49-91.4)** | **<0.0001[a]** |
| **Lymphocyte count (cell/mL), median (IQR)** | **1.840 (100-2.780)** | **2.380 (900-3.680)** | **1.700 (100-2.350)** | **<0.0001[a]** |
| **Lymphocyte (%), median (IQR)** | **22.1 (2.2-39.8)** | **29.1 (6.8-39.3)** | **15.8 (2.2-29.5)** | **<0.0001[a]** |
| **Monocyte count (cell/mL), median (IQR)** | **720 (280-1320)** | **795 (280-1.925)** | **640 (300-1040)** | **0.023[a]** |
| **Monocyte (%), median (IQR)** | **7.7 (2.9-11.8)** | **9.1 (5.1-18.9)** | **7.1 (2.9-10.2)** | **<0.0001[a]** |
| Platelet count (cell/mL), median (IQR) | 240.000 (98.000-340.000) | 232.000 (98.000-312.000) | 245.000 (146.000-404.000) | 0.491[a] |
| MPV (fL), median (IQR) | 8.7 (5.8-9.7) | 8.7 (6.1-9.7) | 8.5 (5.8-10.9) | 0.698[a] |
| RDW (%), median (IQR) | 14 (8.1-17)<br>13.9 1.9 | 13.7 (8.1-16.5)<br>13.7 2.2 | 14.3 (11.2-17.4)<br>14.3 1.7 | 0.078[a] |
| **NMR, median (IQR)** | **8.7 (1.4-15.5)** | **6.2 (1.4-13.3)** | **10.2 (4.7-17.1)** | **<0.0001[a]** |
| **NLR, median (IQR)** | **3.13 (0.85-6.98)** | **2.16 (0.93-4.62)** | **4.61 (0.85-9.36)** | **<0.0001[a]** |

BEO: Brucella epididymo-orchitis, NBEO: Non-brucella epididymo-orchitis, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cells, MPV: Mean platelet volume, RDW: Red cell distribution width, NLR: Neutrophil-to-lymphocyte ratio, NMR: Neutrophil-to-monocyte ratio, MLR: Monocyte-to-lymphocyte ratio, IQR: Interquartile range, [a]: Mann-Whitney U test, [b]: Pearson chi-square test

| Table 2. Multivariate analysis of the clinical and laboratory parameters between the BEO and NBEO groups | | | | |
|---|---|---|---|---|
| | **Odds ratio** | **95% Confidence interval** | | |
| | | **Lower** | **Upper** | **p** |
| Age | 0.247 | 0.979 | 1.036 | 0.619[a] |
| ESR | 2.231 | 0.995 | 1.038 | 0.135[a] |
| **Presence of abdominal pain** | **8.706** | **0.055** | **0.558** | **0.003[a]** |
| WBC | 0.268 | 0.999 | 1.000 | 0.604[a] |
| Neutrophil count | 0.295 | 0.999 | 1.001 | 0.587[a] |
| **Neutrophil (%)** | **10.935** | **1.172** | **1.858** | **0.001[a]** |
| Lymphocyte count | 0.483 | 0.999 | 1.003 | 0.487[a] |
| **Lymphocyte (%)** | **6.366** | **1.089** | **1.974** | **0.012[a]** |
| Monocyte count | 0.006 | 0.992 | 1.009 | 0.936[a] |
| **Monocyte (%)** | **4.750** | **1.073** | **3.748** | **0.029[a]** |
| NLR | 0.009 | 0.423 | 2.187 | 0.926[a] |
| NMR | 0.155 | 0.794 | 1.415 | 0.693[a] |

BEO: Brucella epididymo-orchitis, NBEO: Non-brucella epididymo-orchitis, ESR: Erythrocyte sedimentation rate, WBC: White blood cells, NLR: Neutrophil-to-lymphocyte ratio, NMR: Neutrophil-to-monocyte ratio
[a]: Binary logistic regression analysis

percentage of monocytes had an AUC value of 0.745 (95% confidence interval: 0.670-0.820) at a cut-off point of >7.7%. Finally, the percentage of neutrophils had an AUC value of 0.746 (95% confidence interval: 0.699-0.836) at a cut-off point of <66.8%.

Isolated epididymo-orchitis was present in 27 (32%) patients with BEO, and other focal involvement was observed in 57 (68%). Fifty-six patients (66.7%) with BEO drank or ate unpasteurized dairy products. Occupational exposure was present in 32 patients (38.1%) with BEO. Other focal involvements, including osteoarticular involvement (39.2%), hepatosplenomegaly (29.8%), sacroiliitis (29.8%), spondylitis (16.7%), arthritis (6%), and endocarditis (4.7%) were observed (Table 3). Orchiectomy was performed in one BEO patient (1.2%) because there was no improvement with medical treatment.

**Table 3. Clinical presentations of the patients with BEO**

| | **n (%)** |
|---|---|
| Fever | 76 (90.5%) |
| Sweating | 68 (81%) |
| Scrotal pain and swelling | 84 (100%) |
| Lower urinary tract symptoms | 25 (29.8%) |
| Only epididymo-orchitis (no focal involvement) | 20 (23.8%) |
| **Other focal involvements** | |
| Hepatosplenomegaly | 25 (29.8%) |
| Osteoarticular involvement | 33 (39.2%) |
| Spondylitis | 14 (16.7%) |
| Arthritis | 5 (6%) |
| Sacroiliitis | 25 (29.8%) |
| Endocarditis | 4 (4.7%) |
| Positive blood culture | 16 (19%) |
| Positive Wright agglutination test (≥1/160) | 84 (100%) |

(Some patients had more than one involvement)
BEO: Brucella epididymo-orchitis

## Discussion

In this study, a significant difference was found between the BEO and NBEO groups in terms of the percentages of lymphocytes, monocytes, and neutrophils. The higher percentages of mononuclear cells (lymphocytes and monocytes) in patients with BEO may be due to the effects of chronic and granulomatous changes in tissues on blood circulation.

The signals developed in BEO increase the number of monocytes in the blood. An increase in the percentage of monocytes in the blood, which is one of the most important precursors of a granulomatous infection, may be an essential clue in the differential diagnosis. An increase in the percentage of lymphocytes is also one of the main parameters of chronic infections (12). The percentage of lymphocytes and monocytes in BEO were stronger parameters in differential diagnosis than NLR and NMR. This may be because neutrophils are inflammatory cells with less of a role in chronic infections.

The higher percentage of neutrophils in patients with NBEO may be due to NBEO being an acute infection. In the differential diagnosis of NBEO, neutrophil percentage was a stronger indicator than NLR and NMR. This may be because lymphocytes and monocytes are not essential inflammatory cells in acute infections.

The NLR is useful in the differential diagnosis of inflammatory diseases (13). Cift and Yucel (14) reported that NLR was lower in patients with BEO than in those with NBEO (14). In our study, there was a significant difference between the BEO and NBEO groups in terms of NLR in the univariate analysis, but no significant difference was detected in the multivariate analysis. This difference may be because the independent variables determined for differential diagnosis were not investigated in the previous study. Percentages of lymphocytes, monocytes, and neutrophils can provide a more comprehensive assessment. At the same time, because the number of patients with BEO in the study of Cift and Yucel (14) was lower than that in our study (n=22 vs. 84), the power of their statistical analysis may be lower.

It has been reported that the mean platelet volume (MPV) and red cell distribution width (RDW) are affected in many inflammatory diseases (15,16). Cift and Yucel (14) reported that MPV was lower in patients with BEO than in those with NBEO. They also noted that MPV was higher in pediatric patients with brucella arthritis than in the healthy control group (14). In Aydin et al. (17), RDW was similar between the BEO and NBEO groups. In our study, MPV and RDW were similar between patients with BEO and NBEO, which can be attributed to the presence of inflammation in both groups.

BEO may rarely require orchiectomy. In the literature, the rate of patients with BEO who underwent orchiectomy was reported to be 1.5-11.7% (18,19). In some studies, it has been stated that orchiectomy is not required in BEO (5,20). In our study, the rate of orchiectomy among patients with BEO was 1.2%. Performing the Wright tube agglutination test in patients with suspected BEO can prevent delayed treatment and unnecessary orchiectomy.

Brucellosis may present with isolated orchitis without systemic symptoms. Celen et al. (5) reported no other focal involvement in 22.2% of patients with BEO (5), whereas Gozdas and Bal (6) found this rate to be 12%. In our study, 23.8% of patients with BEO did not have any other focal involvement. Therefore, it should be noted that Brucella infections may present only with

epididymo-orchitis in suspected cases of brucellosis in endemic areas.

BEO is more common in young adults (21). One study noted that the mean age of patients with BEO was 25.5 years (22). Another study reported a median age of 34 years among patients with BEO (23). In our study, the median age of the BEO group was 35 years. These findings may be helpful in terms of identifying BEO in young adult patients from endemic areas.

Bilateral involvement is reported in 3.7-20.8% of patients with BEO (24,25). The rate of bilateral involvement among our patients with BEO (9.5%) is consistent with the literature. Baykan et al. (25) reported that bilateral involvement was higher in patients with BEO than in those with NBEO. However, bilateral involvement was similar between the BEO and NBEO groups in our study.

### Study Limitations

Our study was retrospective in nature. In addition, although patients with BEO were routinely evaluated in detail due to the difficulty of the disease treatment, some of the patients with NBEO did not have available laboratory data, which resulted in the inability to include consecutive NBEO cases in the study. Because BEO is a rare disease, the number of patients is limited. However, this study is important because it has the largest BEO cohort in the literature.

## Conclusion

To the best of our knowledge, there is no other study comparing the percentages of lymphocytes, monocytes, and neutrophils between patients with BEO and NBEO. According to our findings, the percentages of lymphocytes and monocytes were higher, and the percentage of neutrophils was lower in patients with BEO than in those with NBEO. In addition, abdominal pain may be an important sign in the differential diagnosis of BEO.

### Ethics

**Ethics Committee Approval:** The study was approved by the ethics committee (approval no: 2022/149, date: 22.11.2023 - University of Health Sciences Turkiye, Ankara Gülhane Training and Research Hospital Clinical Research Ethics Committee).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Concept: E.B., Design: E.B., Data Collection or Processing: O.E., F.Y.İ., E.K.D., F.Ü., A.H.S., S.A., G.F., Analysis or Interpretation: O.E., E.K.D., S.B., Literature Search: E.B., F.Ü., G.F., Writing: F.Y.İ., A.H.S., S.A., S.B.

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

**Financial Disclosure:** The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Andrology

Doi: 10.4274/jus.galenos.2023.2023-7-8
J Urol Surg 2024;11(2):99-104

# Cavernosal Smooth Muscle Function After Experimental Ischemic Priapism

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**What's known on the subject? and What does the study add?**

Ischemic priapism (IP) is a kind of compartment syndrome which develops in penis. The role of apoptosis is defined for the compartment syndrome however, the role of apoptosis during and after priapism are not known. Also, the possible treatment with apoptosis inhibitors for the consequences of priapism is not known. This experimental study has yielded important results such as apoptosis have an important role for the etiology of erectile dysfunction after IP and new treatment insights for IP treatment.

## Abstract

**Objective:** We aimed to investigate the role of apoptosis and its effects on cavernosal smoothmuscle (CSM) function after ischemic priapism (IP) in a rat model.

**Materials and Methods:** Twelve adult Sprague-Dawley rats were assigned into two groups: The priapism and control groups. In all rats, erections were obtained by the vacuum method; however, in the priapism group, erections were maintained with a rubber band for 4 h to mimic priapism. After 14 days following this procedure, penile excision was performed and cavernosal tissues were investigated pharmacologically and histopathologically. Isometric tension changes due to several contractile and relaxant pharmacological agents were investigated with/without nitric oxide synthase (NOS) and guanylate cyclase (GC) inhibition.

**Results:** Isometric contraction and relaxation responses due to the agents applied did not differ between the groups. However, with NOS and GC inhibition, the cavernosal tissues relaxed less in the priapism group than in the controls ($p<0.05$). Histopathological evaluation of the tissues revealed that the average apoptosis rates were greater in the priapism group than in the controls in both the CSM (60.3% vs. 31.8%) and cavernosal epithelia (40.2% vs. 7%).

**Conclusion:** IP induction caused fibrosis by the apoptotic process in rat CSM. After IP, apoptosis in endothelial tissue was more evident than that in smooth muscle tissue in the corpus cavernosum. IP is likely to affect the NO pathway, resulting in a decrease in the NO-dependent relaxation in the cavernosal tissue.

**Keywords:** Apoptosis, erectile function, ischemic priapism, priapism

## Introduction

Priapism is defined as complete or partial penile tumescence that continues for 4 h with or without sexual stimulation (1). Priapism is categorized as ischemic priapism (IP) (veno-occlusive, low-flow), stuttering priapism (intermittent), and non-IP (arterial, high-flow) (1). Sexual stimulation triggers the release of neurotransmitters from the cavernous nerve terminals, resulting in penile erection in men (2). Penile erection involves sinusoidal relaxation, arterial dilation, and venous compression (2). Detumescence involves the opposite: Cavernosal smooth muscle (CSM) contraction, decreased arterial flow, and increased venous

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**Received:** 31.07.2023 **Accepted:** 07.10.2023

**Cite this article as:** Hasırcı E, Kervancıoğlu E, Özer C, Erdem SR, Gören MR. Cavernosal Smooth Muscle Function After Experimental Ischemic Priapism. J Urol Surg 2024;11(2):99-104.

flow (3). Nitric oxide (NO) released from the noradrenergic/non-cholinergic nerves and endothelium is the principal neurotransmitter mediating penile erection (2). NO increases the production of cyclic guanylate monophosphate (cGMP), which in turn relaxes the CSM. Acetylcholine also contributes indirectly to penile erection (2).

Priapism may cause necrosis in the cavernosal tissue, which can lead to erectile dysfunction (4). IP can cause hypoxia, hypercarbia, and acidosis in the cavernosal tissue, which may lower adenosine triphosphate (ATP) levels and initiate the apoptotic process (5). This condition is analogous to muscle compartment syndrome, which has previously been well documented to cause histologic changes in the CSM within 12 h (1,6). The tone of the arterial and CSM cells is a key regulator of tumescence and detumescence and is determined by the balance between the relaxing and constricting factors (7). IP can cause necrosis in CSM, which may lead to resistance to $\alpha$-agonist treatment (5). However, the development of erectile dysfunction and CSM function after IP remains unclear.

This study aimed to evaluate the role of apoptosis and its consequences on CSM function after a single IP episode induction in a rat model.

## Materials and Methods

This study was approved by the Başkent University Institutional Review Board and Ethics Committee (project no: DA 06/39, date: 20.11.2006). The study was performed in 12 Sprague-Dawley adult (3 months and 10 days old) male rats (255.25±36.9 g), which were assigned into 2 groups (P: Priapism and C: Control). The number of rats calculated according to Festing and Altman's (8) guideline and assuming a significance level of 5%, a power of 90%, and a two-sided test revealed 5 animals per group. One more animal was added to the groups in case of animal loss due to surgical procedures. The rats were housed in standard rat cages under constant environmental conditions (20±2 °C room temperature, relative humidity 50±10%, light: dark cycle: 12-12 h) and were fed standard laboratory rat chow and tap water *ad libitum.* There was no blinding. Penile erection was induced by the vacuum method in both groups. In the control group, erection ended spontaneously within 5-10 min. To mimic priapism, erection was maintained for 4 h by constricting the base of the erected penis with a rubber band. Priapism was accomplished as previously described in the literature (9). En *bloc* penile excision was performed after 14 days of mimicked 4-h priapism. All surgical procedures were performed under anesthesia obtained by 10 mg/kg intraperitoneal (*ip*) xylazine (Rompun 2%, Bayer, Turkiye) and 60 mg/kg *ip* ketamine (Alfamine 10%, Ege Vet, Turkiye).

Penile cavernous tissues were placed in a dissection plate containing oxygenated, ice-cold Krebs-Henseleit solution and trimmed free of the surrounding connective tissue. The corpus cavernosum was divided and prepared for isolated organ bath (IOB) experiments. One of the parts was fixed in Bouine's solution for histopathological evaluation. The terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay was used to investigate apoptotic parameters in the smooth muscle and cavernosal endothelium. The tunical continuity of the second cavernosal portion was broken by three incisions (upper-middle-lower) before the strips were transferred into the IOBs.

### IOB Experiments

The IOB system is a useful tool for examining isometric responses (contraction-relaxation) of a muscle-containing organ to various bioactive agents under physiological circumstances. Each corpus cavernosum strip was mounted longitudinally in a double-jacket glass IOB containing 10 mL of Krebs-Henseleit solution. The solution was maintained at 37 °C, pH 7, and aerated with carbogen (95% $O_2$ + 5% $CO_2$). To obtain the optimum isometric response, an initial resting tension of 1 g was applied to the tissues, which were allowed to equilibrate for 60 min without adding any test agent into the baths, during which the baths were washed out with fresh Krebs-Henseleit solution every 15 min. The isometric responses were perceived by a transducer (FT03, BioPac, MAY, Turkiye) connected to a computerized physiological data collection and acquisition system (Bio Pac, MP100, MAY, Turkiye).

The composition of the Krebs-Henseleit solution was as follows (mmol): NaCl, 118.2; KCl, 4.7; $MgSO_4$, 12; $CaCl_2$, 2.5; $KH_2PO_4$, 1.2; $NaHCO_3$, 25; and glucose, 11.1.

### Drugs and Test Agents Used

Phenylephrine (PE; $\alpha_1$-adrenoreceptor agonist; Sigma, St. Louis, USA), acetylcholine (Ach; Sigma), L-arginine [L-Arg; NO synthase (NOS) substrate; Sigma], sodium nitroprusside (SNP; exogenous NO donor; Sigma), Nitro-L-arginine methyl ester hydrochloride (L-NAME; inhibitor; Sigma), 1H-[1, 2, 4] Oxadiazolo [4, 3-a] quinoxalin-1-one [ODQ; guanylate cyclase (GC) inhibitor; Sigma].

All drugs were dissolved in distilled water. The mentioned concentrations are the final concentrations in the IOBs. The drugs were added to the IOBs cumulatively. The inhibitors and/or antagonists were added to the IOB 15-30 min before any agonist administration. Before adding the subsequent test agent, the baths were washed three times with fresh Krebs-Henseleit solution at 5-min intervals.

Concentration-contraction curves were obtained from the responses of the cavernosal strips to increasing logarithmic concentrations of the test agents. Each response was normalized

to the submaximal concentration (10 mmol/mL) of PE to avoid interindividual variations among preparations.

### Experimental Protocols

Logarithmic PE concentration-contraction curves were obtained for the cavernosal strips. Then, concentration-relaxation curves for ACh, L-Arg, and SNP were obtained by applying these agents at increasing consecutive concentrations to PE (0.1 mmol/L)-pre-contracted cavernosal strips. These protocols were repeated after incubating the IOBs for 15 min with L-NAME (1 mmol/L) or ODQ (1 mmol/L).

### Histopathological Evaluation

The cavernosal strips, fixated in Bouine's solution, were evaluated under a light microscope with routine hematoxylin and eosin (H&E) staining. The strips were also evaluated using the TUNEL method for apoptosis. The results of TUNEL staining expressed the percentage of smooth muscle cells and cavernosal endothelium cells with TUNEL-positive nuclei.

### Statistical Analysis

The randomization scheme for the rats according to the experimental groups was generated using a computer-based program (http://www.randomization.com). The data are expressed as the mean and standard error of the mean (SEM). Two-Way analysis of variance preceding post-hoc Bonferroni's test was used for the statistical analysis of the effects of priapism induction and/or the drugs applied. A p-value of 0.05 was considered statistically significant. The data were calculated with Microsoft Excel 2003 (Microsoft, WA, USA), and statistical analyses were performed using Graphad Prism v4.0 (GraphPad, CA, USA).

## Results

PE caused concentration-dependent contractions, whereas ACh, L-Arg, and SNP caused concentration-dependent relaxation in the cavernosal strips in both groups. The inhibition of neither nitric oxide synthase (NOS) nor guanylyl cyclase (GC) did not alter the relaxation induced by ACh, L-Arg, and SNP in the control group, whereas the concentration-dependent relaxation in response to ACh and L-Arg were decreased by NOS or GC inhibition in the priapism group (for the $E_{max}$ levels of ACh and L-Arg; -8.8±2.63% for NOS inhibition and -9.0±5.54 for GC inhibition vs. -18.9±1.47% for basal control; and -15.0±3.29% for NOS inhibition vs. -28.1±3.84% for basal control; respectively $p<0.05$; Figure 1). However, NOS or GC inhibition did not significantly affect SNP relaxation and PE contraction. The half maximal effective concentration ($EC_{50}$) values indicating the potency of PE are summarized in Table 1.

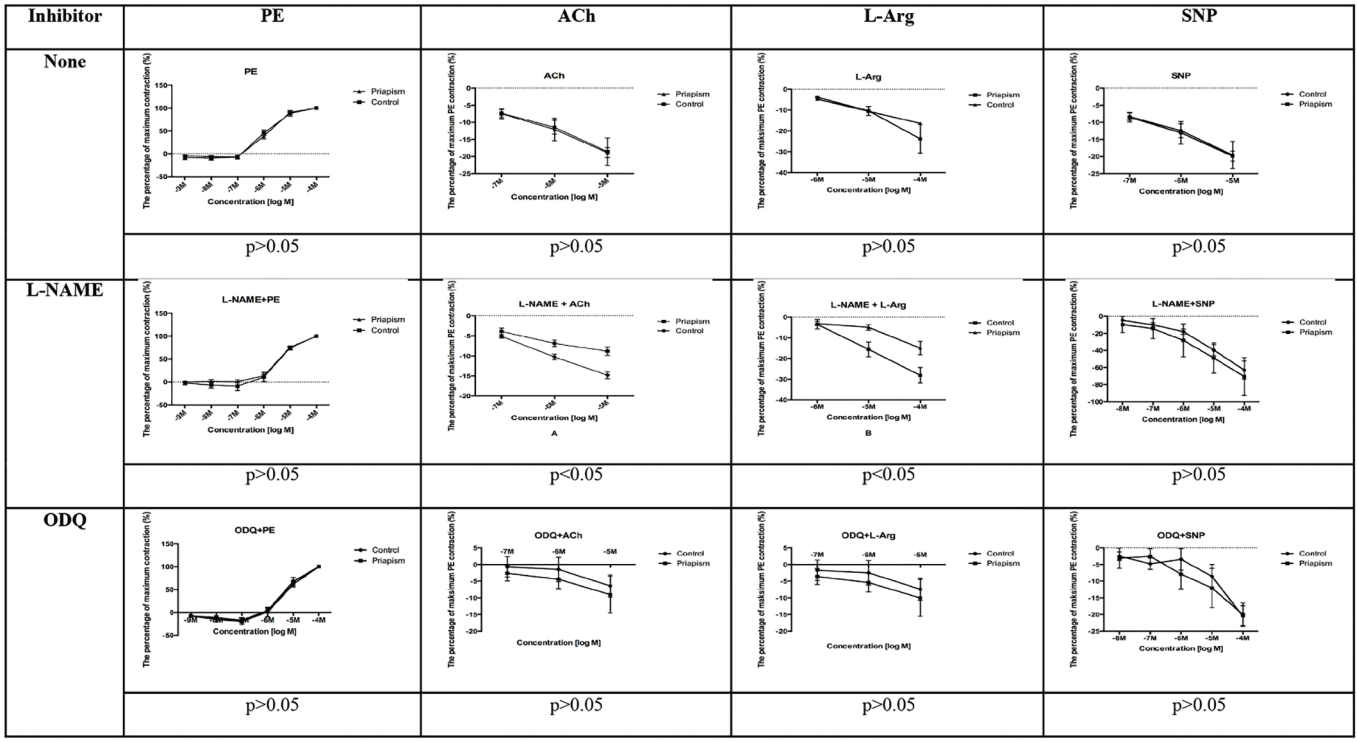


**Figure 1.** The contraction-relaxation responses due to test agents

PE: Phenylephrine, ACh: Acetylcholine, L-Arg: L-Arginine, SNP: Sodium nitroprusside, L-NAME: Nitro-L-arginine methyl ester (NOS inhibitor), ODQ: 1H-[1, 2, 4] Oxadiazolo [4, 3-a] quinoxalin-1-one (Guanylate Cyclase inhibitor)

| Table 1. Comparison of the half maximal effective concentration ($EC_{50}$) values of phenylephrine between the groups | | | | | | |
|---|---|---|---|---|---|---|
| | Basal | | L-NAME | | ODQ | |
| | $EC_{50}$ (mmol/mL) | log $EC_{50}$ | $EC_{50}$ (mmol/mL) | log $EC_{50}$ | $EC_{50}$ (mmol/mL) | log $EC_{50}$ |
| **Control** | 1.03 | -5.986 | 4.32 | -5.365 | 6.16 | -5.25 |
| **Priapism** | 1.4 | -5.855 | 4.64 | -5.334 | 5.21 | -5.283 |
| L-NAME: Nitro-L-arginine methyl ester hydrochloride (0.1 mmol/L), ODQ: 1H-[1, 2, 4] Oxadiazolo [4, 3-a] quinoxalin-1-one (0.1 mmol/L), $EC_{50}$: Half maximal effective concentration | | | | | | |

Histopathological examinations revealed that priapism induction increased the apoptotic parameters indicated by mean values of TUNEL-positive CSM and endothelial cells [60.3% vs. 31.8%, p=0.02 and 40.2% vs. 7%, p=0.02, respectively (see, Figure 2)].

## Discussion

IP is the most common form of priapism, accounting for >95% of all priapism episodes (1,10). According to our findings, the consequences of IP can be summarized in three headings.

### Cavernosal Fibrosis

IP causes CSM fibrosis, probably initiated by apoptosis. The apoptotic process is initiated with cavernosal ischemia and is followed by the reperfusion process as a typical compartment syndrome (4,11). If IP is not treated, it might cause penile necrosis (12). However, inappropriate or delayed treatment of IP can cause erectile dysfunction (1). The acting component of the cavernosal tissue during erection is the cavernosal and arterial smooth muscle (7). After priapism, the alteration of the erectile function depends on the degree of the affected CSM. Our data revealed that CSM fibrosis is encountered within 14 days of 4-h IP. The contraction and relaxation experiments showed that these functions of CSM were preserved in the priapism group compared with the controls. Thus, in our study, both functions of the CSM were preserved within a 4-h period of priapism. Muneer et al. (5) reported that CSM contractility was impaired within a 4-h period of hypoxia, acidosis, and glucopenia. They reported that there were no visible changes on CSM with H&E staining (5). Our data are in contrast with their report. This might be due to the *in vivo* nature of our experiment and/or the 14-day period of investigation after priapism induction, which might have provided enough time for the protective mechanism to maintain CSM function (13). Because of the *in vitro* study design of the study by Muneer et al. (5), it was not possible to show fibrosis. In addition, ischemia-reperfusion studies of cardiac muscle revealed that overall contractility of cardiac myocytes reduces in the early phases of reperfusion (14). After the reperfusion phase, myocytes develop hypertrophy in time to preserve cardiac contractility (15). Although cardiac muscle is not smooth muscle, this mechanism may explain how CSM contractility is preserved after 14 days of a 4-h period of priapism.

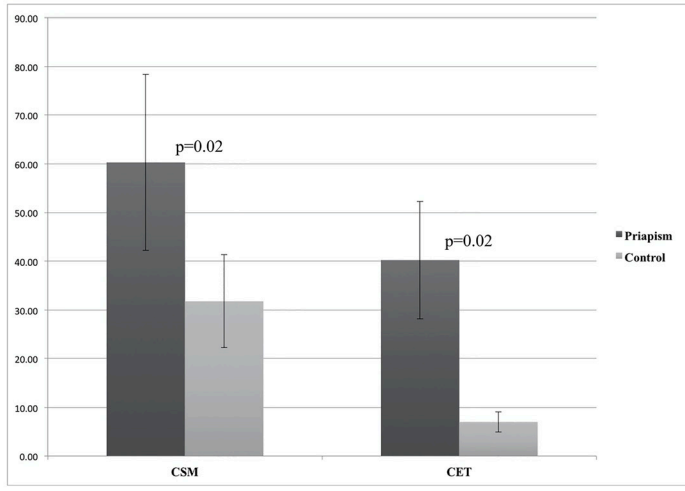


**Figure 2.** Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positive nuclei rates of the priapism and control groups.

CSM: Cavernosal smooth muscle, CET: Cavernosal endothelial tissue, SD: Standard deviation

### Apoptosis

The apoptotic process after IP has been shown in several studies that have mainly focused on CSM apoptosis causing erectile dysfunction after IP (5,16). The TUNEL staining findings revealed that the priapism group had almost two-fold more TUNEL staining than the controls. The TUNEL- positive cells were 60.8% in the priapism group and 31.8% in the control group. It is obvious that IP caused apoptosis in the CSM, but our data showed that both functions of the CSM, contraction and relaxation, were preserved after IP for 4 h. This is in concordance with the daily clinical practice in which most IP cases, which last more than 4 h, can be treated with aspiration and irrigation.

Apoptosis in the control group and in the CSM (31.8%) was unexpectedly higher than that in previously reported studies. Muneer et al. (5) reported 1% TUNEL-positive CSM under *in vitro* control conditions. However, our results were obtained from *in vivo* experiments. The differences *in vivo* and *in vitro* apoptotic processes due to IP require further research to explain these results.

In the present study, apoptosis in the cavernosal endothelium was higher in the priapism group than in the control group. The TUNEL-positive cavernosal endothelium was 40.2% in the priapism group and 7% in the controls. The penile erection is initiated by

the release of NO from the cavernosal endothelium (2). Our data also elicited that the CSM functions were preserved; thus, the main cause of the ED after IP might be the destructed cavernosal endothelium. To the best of our knowledge, this is the first report on apoptosis of the cavernosal endothelium.

### NOS Malfunction

In the present study, one of the most obvious results was NOS malfunction of the cavernosal strips in the priapism group. The L-Arg-NOS-NO pathway is crucial in the physiology of erectile function, and its impairment is associated with the pathophysiology of priapism. NO produced by neuronal NOS (nNOS) within the nitrergic nerves is responsible for the initiation and most of the smooth muscle relaxation, whereby NO from endothelial NOS (eNOS) contributes to the maintenance of erection (2). However, exaggerated erectile responses have been reported in mice lacking the gene encoding for eNOS (17,18). Thus, this pathway might be responsible for the development of priapism as well. Several researchers have investigated the therapeutic effects of phosphodiesterase type-5 inhibitors (PDE-5i) on priapism (19,20). Bivalacqua et al. (19) have shown that in the absence of eNOS, PDE-5i can restore eNOS and prevent priapism. In the present study, in comparison with the control group, NOS inhibition significantly decreased the relaxation of the cavernosal strips in response to ACh in the priapism group. It has been reported that L-NAME is not selective for any NOS subtype, but as mentioned above, eNOS is the major NOS subtype responsible for maintaining the relaxation of the CSM tissue (2,21). In the present study, basal relaxation in response to ACh were similar in both groups; however, inhibition of NOS diminished the dysfunctional relaxation of the cavernosal strips only in the priapism group. This finding was also consistent with cavernosal endothelium apoptosis. Nevertheless, further research is needed to evaluate the role of eNOS in both erectile function and IP, especially focusing on non-adrenergic non-cholinergic signaling and NO-dependent relaxation in the cavernosal tissue.

Contrary to our expectations, in both groups, L-NAME or ODQ incubations shifted the PE concentration-contraction curves rightward, indicating the inhibitory role of NOS or GC inhibition on the contractility of the corpus cavernosum. It might be speculated that this surprising finding is due to the effect of peroxynitrite, a non-enzymatic product of the NO and superoxide reactions. It has been reported that peroxynitrite can contract the vascular smooth muscle (22). However, because the $EC_{50}$ value of PE-induced contractions was not significantly changed by NOS or GC inhibition, it is early to propose a mechanistic explanation, and it remains to be established by further research.

### Study Limitations

Our study has three limitations. First, we did not evaluate the rate of fibrosis. Although histological changes after priapism have been reported, the exact rates of fibrosis both in the CSM and endothelium might be more explanatory. Second, the expression levels of NO-cGMP pathway enzymes were not evaluated. Third, we evaluated the CSM functions. Although CSM relaxation and sinusoidal relaxation are important steps of tumescence/erection, the whole process of erectile function cannot be interpreted just with CSM functions.

## Conclusion

IP induction caused fibrosis in the CSM of rats, which was probably initiated by the apoptotic process due to ischemia. After IP, apoptosis in endothelial tissue was more evident than that in smooth muscle tissue in the corpus cavernosum. IP is likely to affect the NO pathway, resulting in a decrease in the NO-dependent relaxation of the cavernosal tissue.

### Ethics

**Ethics Committee Approval:** This study was approved by the Başkent University Institutional Review Board and Ethics Committee (project no: DA 06/39, date: 20.11.2006).

**Informed Consent:** Not necessary.

### Authorship Contributions

Surgical and Medical Practices: C.Ö., M.R.G., Concept: E.K., S.R.E., M.R.G., Design: S.R.E., M.R.G., Data Collection or Processing: E.H., C.Ö., M.R.G., Analysis or Interpretation: E.H., C.Ö., S.R.E., Literature Search: E.H., E.K., Writing: E.H., E.K.

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

**Financial Disclosure:** The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Andrology

Doi: 10.4274/jus.galenos.2024.2023-8-8
J Urol Surg 2024;11(2):105-110

# Assessment of the Relationship Between the Quality of YouTube Videos on Penile Enlargement Surgery and Scholarly Profiles of Surgeons

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**What's known on the subject? and What does the study add?**

There are no restrictions on uploading Medical YouTube videos. In our study, we found a relationship between the quality of YouTube videos on penile enlargement surgery and the scholarly profiles of surgeons.

## Abstract

**Objective:** To investigate the relationship between the quality of YouTube videos on penile enlargement surgery and the scholarly profiles of surgeons.

**Materials and Methods:** A YouTube search was conducted using the keyword "penile enlargement surgery". Of the first 200 videos from the search results, 66 that met the study criteria were included in the analyses. Two urologists scored each video using the DISCERN score, the Journal of the American Medical Association (JAMA) score, and the global quality scale (GQS) in a double-blind manner. After the video quality scores were determined, the number of publications and h-indexes of surgeons were obtained from Google Scholar.

**Results:** Of the videos, 31 (46.9%) were uploaded by plastic surgeons and 35 (53.1%) by urologists. The median duration of the videos was 4.1 min (interquartile range: 1-8.5) minutes. Eighteen (27.2%) videos had low quality, 9 (13.6%) had medium quality, and 39 (59.1%) had high quality. A statistically significant correlation was found between the h-index of surgeons and video quality scores (DISCERN, r=0.678; JAMA, r=0.646; GQS, r=0.689; p<0.0001). There was also a statistically significant correlation between the total publication counts of surgeons and the video quality scores (DISCERN, r=0.614; JAMA, r=0.569; GQS, r=0.607; p<0.0001). Lastly, a weak, statistically significant correlation was detected between the DISCERN scores of the videos and the number of likes (r=0.278, p=0.029).

**Conclusion:** This study revealed a significant correlation between the quality of YouTube videos on penile enlargement surgery and the h-indexes and total publication counts of surgeons. This study was the first to analyze the relationship between the quality of YouTube videos on penile enlargement surgery and the scholarly profiles of surgeons.

**Keywords:** Penile enlargement, andrology, publications, h-index, surgeon, quality score

## Introduction

The use of the internet and social media is becoming more prominent within the healthcare sector. Many medical doctors and patients seeking medical advice refer to these resources for information (1). YouTube, a widely used platform for the dissemination of information, offers free videos to more than 30 billion daily users (2).

Andrology holds significant interest among male patients within the context of urology, although this notion lacks scientific evidence (3). Men's interest in andrology usually stems from their pursuit of sexual self-confidence. Within the field of

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**Received:** 25.08.2023 **Accepted:** 08.01.2024

**Cite this article as:** Bülbül E, İlki FY. Assessment of the Relationship Between the Quality of YouTube Videos on Penile Enlargement Surgery and Scholarly Profiles of Surgeons. J Urol Surg 2024;11(2):105-110.

andrology, one of the popular areas of interest for men is penile enlargement techniques. There is no clear definition of a small penis (4). In the literature, a micropenis is described as having a flaccid length of less than 4 cm and a stretched or erect length of less than 7.5 cm (5). Some men may perceive their penis to be small, despite it falling within the range considered normal for penile dimensions. This psychological phenomenon is referred to as small penis anxiety (6). Another diagnosis that can be observed among these individuals is body dysmorphic disorder, a condition characterized by the presence of obsessive thoughts related to one's body image, which persist for at least one hour a day, continue during the follow-up process, and cause significant psychological problems (7). For these patients, it is essential to consult a psychiatrist before penile enlargement treatment because some cases may be suicidal.

The literature describes a variety of penile enlargement surgical materials, such as autologous grafts, biological or synthetic fillings used for injections, and synthetic implants (8-10). Autologous cartilage grafts or tissue-engineered biodegradable scaffolds can be implanted into the tunica albuginea (11,12). Filling materials injected into the penile subcutaneous tissue include acellular dermal matrix, free dermal fat grafts, free fat, hyaluronic acid, collagen, polymethylmethacrylate microspheres, polyacrylamide hydrogel, and silicone (13). A silicone implant designed to increase penile length can also be surgically inserted into the tunica albuginea (14).

Penile enlargement surgery is also often performed on patients who lack appropriate indications, such as those with body dysmorphic disorder who have a normal penis size but seek cosmetic enhancements rather than addressing a genuine micropenis condition (15). This can result in the development of mortal complications, such as fat embolism, although they are rare (16). Ensuring comprehensive coverage of significant complications related to penile enlargement surgery in online sources is crucial for patients seeking information about this treatment. However, the absence of peer-review in the uploading of YouTube videos on penile enlargement surgery raises questions concerning the educational value and reliability of such content. The scholarly profile of surgeons is another important factor that determines the quality of these videos. In this study, we hypothesized that the quality of YouTube videos on penile enlargement surgery correlates with the h-index of surgeons.

Despite the availability of research on the quality of medical YouTube videos over the past 15 years (17,18), no study has investigated the relationship between the quality of YouTube videos on penile enlargement surgery and the scholarly profiles of surgeons. The aim of this study was to fill this gap in the literature.

## Materials and Methods

Ethical approval was not obtained because animal and human subjects were not included in the study, and the videos examined within the scope of the study were publicly available. Previous studies on medical YouTube videos also did not seek ethical approval (19,20). This study was conducted in accordance with the principles outlined in the 2004 Declaration of Helsinki.

### YouTube Search

The YouTube search history was deleted to ensure that the results would not be affected. Two urologists accessed YouTube anonymously on separate computers. A YouTube search was conducted on September 8, 2022, using the keyword "penile enlargement surgery", and the first 200 videos from the search results were evaluated. The YouTube search engine ranked the videos according to length, number of views, likes, comments, and watch time.

Only videos in English uploaded by plastic, reconstructive, and esthetic surgeons and urologists were included in the study. Excluded from the analysis were videos that were duplicated, those that were not related to the topic, those that were presented in a language other than English, and those that had not been created by surgeons. As a result, 66 videos that met the study criteria were analyzed.

### Video and Surgical Analysis

The examined video features included video duration, number of views, number of comments, number of likes and dislikes, video content, time since upload, and presence of real case videos or animations. The surgeon's specialty is stated. The video power index (VPI) was calculated using the following formula: [(total likes/total likes + total dislikes) 100]. Two urologists scored each video using the DISCERN score, the Journal of the American Medical Association (JAMA) benchmark score, and the global quality scale (GQS) in a double-blind manner. The average of the scores provided by the reviewers was calculated.

The DISCERN tool is a standardized quality index of consumer health information regarding treatment options (21). This index uses 15 questions to measure the reliability of materials by assessing the currency and verifiability of sources, the presence of evident biases, and the inclusion of alternative options for consideration. Based on these questions, the videos are rated on a numerical scale ranging from 1 to 5. In the DISCERN scoring system, over 50 points are considered high quality, and 38 points are considered low quality. The GQS employs a scoring system ranging from 1 (lowest quality) to 5 (highest quality). In the GQS scoring system, 1-2 is considered low quality, 3 is intermediate quality, and 4-5 is high quality content. The JAMA rating system consists of a set of criteria to evaluate the

authorship, attribution, disclosure, and currency of videos. The JAMA scores were 0-1 low quality, 2-3 intermediate quality, and 4 for high quality content.

In the current study, after the determination of video quality scores, the number of publications and h-indexes of surgeons were recorded using Google Scholar. The h-index is a quantitative metric that measures the productivity level and citation effect of a researcher's publications based on specific criteria (22). All articles written by the authors were scanned into Google Scholar. The h-index was calculated according to the citation numbers of the articles. It was noted whether the surgeon had any publications on penile surgery.

### Statistical Analysis

All data were analyzed using SPSS version 25. The Kolmogorov-Smirnov test was used to test whether the data were normally distributed. Normally distributed parameters were specified using the mean and standard deviation values. Data that did not have a normal distribution were expressed as median and interquartile range (IQR) values. Correlation analysis was performed using Pearson's and Spearman's tests. The Mann-Whitney U test was employed to compare the variables between the two groups. Results were considered statistically significant if the p-value was <0.05.

## Results

### Video Features

Of the videos, 31 (46.9%) were uploaded by plastic surgeons and 35 (53.1%) by urologists. Sixty-one (92.4%) of the videos contained real case videos, and five (7.6%) were animated. The median duration of the videos was 4.1 (IQR: 1-8.5) minutes. The median numbers of views and likes were 11.719 (17-118.620) and 52 (2-469), respectively. The videos were grouped according to their scores. Detailed data on video features are shown in Table 1.

**Table 1. Features of videos**

| | Total | Low quality | Intermediate quality | High quality |
|---|---|---|---|---|
| Number of videos (%) | 66 (100) | 18 (27.2) | 9 (13.6) | 39 (59.1) |
| Video length (minutes), median (IQR) | 4.1 (1-8.5) | 4.1 (1-7.2) | 4.2 (1.1-12.1) | 4.1 (1-11.8) |
| View count (n), median (IQR) | 11719 (17-118620) | 17655 (396-140742) | 2887 (1009-8115) | 34750 (17-189368) |
| Comments (n), median (IQR) | 21 (0-83) | 25 (0-103) | 13 (0-39) | 21 (0-149) |
| Likes (n), median (IQR) | 52 (2-469) | 65 (2-502) | 14 (4-33) | 86 (2-757) |
| Dislikes (n), mean ± SD | 41.5±36.3 | 37.3±29.6 | 49.4±32.8 | 42.1±34.7 |
| Time since upload (months), median (IQR) | 22 (1-66) | 19.5 (5-83.5) | 29 (1-73) | 22 (1-66) |
| Video content, n (%) | | | | |
| Indication | 14 (21.2) | 3 (16.7) | 2 (22.2) | 9 (23.1) |
| Perioperative features and techniques | 59 (89.4) | 15 (83.3) | 7 (77.8) | 37 (94.9) |
| Postoperative follow-up | 37 (56.1) | 5 (27.7) | 5 (55.6) | 27 (69.2) |
| Complications | 8 (12.1) | 0 | 3 (33.3) | 5 (12.8) |
| VPI, median (IQR) | 117.5 (1-1220.5) | 178 (4-1408) | 28 (10-81) | 354 (1-1909) |
| Surgeon specialty, n (%) | | | | |
| Plastic | 31 (46.9) | 13 (72.2) | 6 (66.7) | 12 (30.8) |
| Urology | 35 (53.1) | 5 (27.8) | 3 (33.3) | 27 (69.2) |
| h-index of surgeon median (IQR) | 1 (0-4) | 0 (0-1) | 0 (0-1) | 2 (0-6) |
| Total publication count of surgeon (n), median (IQR) | 3 (0-9) | 0.5 (0-2) | 0 (0-3) | 5 (0-15) |
| Presence of related publications about penile surgery, n (%) | 15 (22.7) | 0 | 1 (11.1) | 14 (35.9) |
| GQS score, median (IQR) | 4 (1-4) | 2 (1-2) | 3 (3-3) | 5 (4-5) |
| DISCERN score, median (IQR) | 57.5 (19-68) | 27.5 (20-36) | 43 (40-47) | 66 (51-75) |
| JAMA score, median (IQR) | 3 (1-3) | 1 (1-2) | 2 (2-2) | 4 (3-4) |
| Real case videos, n (%)<br>Animation | 61 (92.4)<br>5 (7.6) | 17 (94.4)<br>1 (5.6) | 9 (100)<br>0 | 35 (89.7)<br>4 (10.3) |

VPI: Video power index (likes/dislikes + likes) x 100, JAMA: Journal of the American Medical Association, GQS: Global quality scale, h-index: A quantitative metric that measures the productivity level and citation effect of a researcher's publications based on certain criteria, SD: Standard deviation, IQR: Interquartile range

### Quality Assessment

The quality categories of the videos were the same according to the evaluation using DISCERN, GQS, and JAMA. Eighteen (27.2%) videos had low quality, 9 (13.6%) had intermediate quality, and 39 (59.1%) had high quality. When the scholarly profiles of surgeons in the high-quality video group were examined, the median h-index was 2 (0-6), and the number of publications was 5 (0-15). Fifteen (22.7%) surgeons had published on penile surgery (Table 1). The median DISCERN, GQS, and JAMA scores were 68 (41-75), 5 (3-5), and 4 (2-4), respectively, for the videos of surgeons who had publications about penile surgery and 49 (20-73), 3 (1-5), and 2 (1-3), respectively, for the remaining videos ($p<0.0001$ for all).

The results of the correlation analysis between the video features and the DISCERN, JAMA, and GQS scores are shown in Table 2. A statistically significant correlation was found between the h-index of the surgeons and the video quality scores (DISCERN, $r=0.678$; JAMA, $r=0.646$; and GQS, $r=0.689$; $p<0.0001$). There was less than a 10% difference between the reviews' scores. There was also a statistically significant correlation between the total publication count of the surgeons and the video quality scores (DISCERN, $r=0.614$; JAMA, $r=0.569$; and GQS, $r=0.607$, $p<0.0001$). Lastly, a weak, statistically significant correlation was found between the DISCERN scores of the videos and the number of likes ($r=0.278$, $p=0.029$) (Table 2).

A statistically significant correlation was found between the JAMA and DISCERN scores ($r=0.939$, $p<0.0001$). A statistically significant correlation was found between the JAMA and GQS scores ($r=0.963$, $p<0.0001$). A statistically significant correlation was found between the GQS and DISCERN scores ($r=0.951$, $p<0.0001$).

## Discussion

In this study, there was a significant correlation between the quality of videos on penile enlargement surgery and the h-index and total publication counts of surgeons. Balta et al. (23) reported a positive correlation between the number of likes of YouTube video-assisted thoracoscopic lobectomy videos and the h-index of surgeons. Chen et al. (24) found that the number of views of YouTube pulmonary lobectomy videos was lower among surgeons with an h-index of >10 than among those with an h-index of ≤10. It can be predicted that academics with a high h-index will publish more reliable and quality videos. However, surgeons with a low h-index can also upload a video to advertise. Additionally, these videos made for advertising purposes can be viewed moreoften. Although the exact relationship between the scholarly profiles of surgeons and the popularity of YouTube videos remains unclear, the scholarly profiles of surgeons seem to significantly affect the quality of surgical videos.

The topics covered by surgeons in their previous publications can also have a significant effect on the surgical videos they create for YouTube. Shires et al. (25) reported that the rate of thyroid-related publications by surgeons in YouTube thyroid surgery videos was 44.8%. In our study, in which we examined YouTube videos on penile enlargement surgery, the percentage of surgeons with publications on penile surgery was 22.7%, and the quality of videos was higher among these surgeons. This suggests that the surgeon's scholarly experience on this subject can improve the quality of the videos they produce.

Existing literature indicates that medical YouTube videos exhibit low quality, and those of high quality are generally produced by medical doctors (26). Production of medical videos by non-healthcare professionals can lead to information pollution. The current study only focused on evaluating YouTube videos on penile enlargement surgery created by surgeons, and the rate of high-quality videos was 59.1%. Toprak and Tokat (27) reported that 25.8% of YouTube videos on nocturnal enuresis were of high quality, but the authors also included videos from non-medical doctors. Tolu et al. (28) determined that 50% of YouTube videos on anti-tumor necrosis factor injections (including those uploaded by non-medical doctors) were of high quality. The results suggest that medical YouTube videos produced by medical doctors are more reliable in terms of content.

**Table 2. Correlations between the quality scale scores and video features**

| | DISCERN | | JAMA | | GQS | |
|---|---|---|---|---|---|---|
| | r | p | r | p | r | p |
| **H-index of surgeon** | **0.678** | **<0.0001** | **0.646** | **<0.0001** | **0.689** | **<0.0001*** |
| **Total publication count of surgeon** | **0.614** | **<0.0001** | **0.569** | **<0.0001** | **0.607** | **<0.0001*** |
| VPI values | 0.229 | 0.065 | 0.205 | 0.099 | 0.184 | 0.138* |
| Video length | 0.072 | 0.567 | 0.081 | 0.572 | 0.372 | 0.112* |
| View count | 0.225 | 0.070 | 0.201 | 0.106 | 0.181 | 0.146* |
| Number of comments | 0.064 | 0.651 | 0.019 | 0.895 | -0.010 | 0.945* |
| Number of likes | 0.278 | **0.029** | 0.248 | 0.052 | 0.231 | 0.071* |
| Number of dislikes | 0.204 | 0.64 | 0.184 | 0.113 | 0.197 | 0.091& |

VPI: Video power index, JAMA: Journal of the American Medical Association, GQS: Global quality scale, *: Spearman's test, &: Pearson's test

In the literature, there are conflicting findings concerning the relationship between the quality of medical YouTube videos and their popularity. Toprak and Tokat (27) reported no correlation between the quality of YouTube videos on nocturnal enuresis and VPI values, view rates, or the number of comments, views, likes, and dislikes. Arslan et al. (29) detected a weak correlation between the quality of YouTube videos on laparoscopic and robotic radical prostatectomy and the number of likes. In our study, there was a weak correlation between the number of likes and the quality of YouTube videos on penile enlargement surgery only according to the DISCERN score. However, there was no correlation between the quality of the videos and the view count or VPI values. Therefore, it may be misleading to evaluate the educational quality of medical YouTube videos by the number of likes.

Medical videos uploaded to YouTube do not undergo a review process; therefore, their evaluation can only be made based on their source and popularity. The number of views, VPI value, and viewer comments affect the popularity of a video, and popular videos and advertisements can influence treatment decisions regardless of the accuracy of the video content, especially for patients seeking penile enlargement surgery for cosmetic concerns. This can also lead to the dissemination of incomplete or inaccurate information among medical students and residents doing their research on similar websites.

### Study Limitations

The first limitation of our study is that we were unable to compare our findings on the relationship between the scholarly profiles of surgeons and YouTube videos on penile enlargement surgery with the literature because of the absence of previous research in this area. The second limitation concerns the dynamic nature of YouTube, to which videos are continually uploaded. Finally, the evaluation of only videos in English can be considered a limitation.

## Conclusion

This study revealed a significant correlation between the quality of YouTube videos on penile enlargement surgery and the h-index and total publication counts of surgeons. This study was the first to analyze the relationship between the quality of YouTube ideas on penile enlargement surgery and the scholarly profile of surgeons.

### Ethics

**Ethics Committee Approval:** Ethical approval was not obtained because animal and human subjects were not included in the study, and the videos examined within the scope of the study were publicly available. Previous studies on medical YouTube videos also did not seek ethical approval. This study was conducted in accordance with the principles outlined in the 2004 Declaration of Helsinki.

**Informed Consent:** Not necessary.

### Authorship Contributions

Surgical and Medical Practices: E.B., F.Y.İ., Concept: E.B., F.Y.İ., Design: E.B., F.Y.İ., Data Collection or Processing: E.B., F.Y.İ., Analysis or Interpretation: E.B., F.Y.İ., Literature Search: E.B., F.Y.İ., Writing: E.B., F.Y.İ.

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

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

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ORIGINAL RESEARCH
Pediatric Urology

Doi: 10.4274/jus.galenos.2024.2024-1-3
J Urol Surg 2024;11(2):111-115

# Efficacy of Parasacral Transcutaneous Electrical Nerve Stimulation in Children with Refractory Detrusor Overactivity

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**What's known on the subject? and What does the study add?**

There are limited studies on the application of transcutaneous tens stimulation (TENS) in the treatment of refractory lower urinary tract symptoms. Nine articles have been published in high-impact journals in the last three years related to parasacral TENS in voiding dysfunction in children. The content of these articles includes the recommended sequences and treatment responses. When evaluated from this point of view, there are still no precise results regarding parasacral TENS application, and clinical evaluations are still valuable. Although ICCS states that 10-25 Hz is effective in TENS application, treatment protocols at different frequencies and durations for refractory bladder overactivity and success rates for different durations have been published in the literature. We aimed to present the success rate of the protocol we created based on the lowest recommended Hz and the shortest treatment duration because continuity in the pediatric group and compliance with treatments planned at high Hz is difficult. In this study, p-TENS was applied in children diagnosed with detrusor overactivity. It was shown that the protocol positively affected symptoms and incontinence.

## Abstract

**Objective:** This study aimed to evaluate the effectiveness of parasacral transcutaneous electrical nerve stimulation (p-TENS) in children with detrusor overactivity (DO) who were subjected to standard medical treatment, urotherapy, and/or biofeedback.

**Materials and Methods:** Thirty-two children (female: 17, male: 15) underwent p-TENS because of refractory lower urinary tract dysfunction symptoms between 2017 and 2019. Children with neurogenic bladder (n=7) and dysfunctional voiding (n=13) were excluded. The data of 12 children diagnosed with DO after the urodynamic study (boys: 8, girls: 4), were evaluated for treatment response 6 months after the last session. p-TENS was performed using S2-3 dermatome 2 days a week for 3 months. Each session lasted 20 min with a frequency of 10 Hz and generated a pulse of 250 μs.

**Results:** The median age of 12 children was 11 years (interquartile range 25-75, range: 9.5-12.5). Incontinence is the main complaint. Significant improvement in uroflow parameters was detected in all children. Urgency, urge incontinence (p=0.016), and constipation (p=0.031) rates were significantly decreased. Voiding dynamics revealed improved voiding patterns (pre/post tower shaped pattern; n=7 *vs.* n=2), and incontinence was completely resolved in nine children (75%).

**Conclusion:** P-TENS has emerged as a therapeutic alternative in children with DO refractory to standard treatment protocol and medication.

**Keywords:** lower urinary tract dysfunction, refractory overactivity, TENS, urinary incontinence

## Introduction

Detrusor overactivity (DO) is a condition characterized by involuntary detrusor contractions during the bladder-filling phase that can result in urinary incontinence. DO is a common problem in pediatric urology practice that may lead to renal deterioration and affect children's quality of social life (1-3).

Behavioral changes, medication (anticholinergics), and animated biofeedback effectively treat lower urinary tract dysfunction (LUTD) symptoms in DO (2-6). However, a limited number of children are refractory to standard therapies.

Parasacral transcutaneous electrical nerve stimulation (p-TENS) has been used to treat LUTD refractory to standard treatment

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**Received:** 08.01.2024 **Accepted:** 17.03.2024

**Cite this article as:** Altınay Kırlı E, Selçuk B, Aferin U, Önal B. Efficacy of Parasacral Transcutaneous Electrical Nerve Stimulation in Children with Refractory Detrusor Overactivity. J Urol Surg 2024;11(2):111-115.

protocols in children. Nevertheless, previous studies have reported different treatment protocols and outcomes (7-11).

In the present study, we evaluated the efficacy of p-TENS for refractory LUTD symptoms related to DO in children. We hypothesized that p-TENS is a non-invasive and effective alternative treatment option for the restoration of voiding dynamics and for reducing incontinence.

## Materials and Methods

Regarding treatment response, medical records of children who underwent p-TENS for refractory LUTD symptoms were retrospectively evaluated (2017-2019). Children with neurological disease (n=7) and dysfunctional voiding (n=15) were excluded, and children diagnosed with refractory DO were included in the study.

Based on the protocols recommended by the International Children's Continence Society (ICCS) for LUTD, standard urotherapy training is provided to all children by the same urotherapy nurse in which behavioral regulations (fluid consumption and diet regulation) and recommendations for voiding and defecation (posture during voiding and defecation, timed voiding) are explained. Anticholinergic treatment (0.3-0.6 mg/kg/day in three doses) was the initial treatment protocol. The animated biofeedback protocol was added to anticholinergic refractory DO, and the combination treatment was continued for three months (6,12). The animated biofeedback sessions are performed once a week in the first month and once every two weeks in the second and third months. Before p-TENS, it was ensured that all children applied these routine protocols completely. Although the children completely applied these standardized treatment protocols, incomplete treatment responses in incontinence were accepted as resistant to treatment (4).

Dysfunctional voiding symptom scoring was used for LUTD symptom assessment, and urinary incontinence, frequency, urgency, urge incontinence, and holding maneuvers were noted (13). The urinary system was examined anatomically and functionally with uroflow electromyogram (UFM-EMG) (at least twice at different times), and post-void residual urine (PVR) was measured by ultrasound immediately after voiding before and after p-TENS. Voiding diaries were also checked before and after treatment to confirm the reliability of anamnesis. However, medical records kept by the physician and uroflow parameters were evaluated.

The protocols of the children who underwent urodynamic study before treatment were re-evaluated for misdiagnosis. Moreover, urodynamics was performed in children who were diagnosed using noninvasive evaluation. In all children, urodynamic evaluations were performed following the ICCS standard, and DO diagnosis was made by detection of detrusor contractions during filling cystometry (6).

In UFM-EMG, $Q_{max}$, voiding time, voiding volume, and voiding curve were evaluated (14). The bladder capacity was calculated using the formula (age+1) x 30 mL (15). A single PVR was considered significant when it was greater than 15% of the estimated bladder capacity for age or greater than 20 mL (6).

The frequency of urinary tract infections (UTI) was determined from the children's medical records based on urine cultures with bacterial growth. Antibiotics were initiated in children with UTI at a suppression dose appropriate for their weight (16).

Constipation was evaluated by clinical findings and the Bristol stool scale (17). Treatment was based on hold training, time habits, and dietary guidance for all children,and laxative treatment for children with constipation classified as Bristol 1 and 2.

P-TENS was performed using the S2-3 dermatome with the electrodes placed in the parasacral region while the children were in the prone position (Figure 1, BioBravo, dual channel MTRplus Vertriebs GmbH) (18). The sessions were held twice a week in the hospital. During the p-TENS sessions at the hospital, the family was informed about how to apply p-TENS. After ensuring that they applied p-TENS correctly, the device was loaned to the family for home use for the rest of the sessions. The total

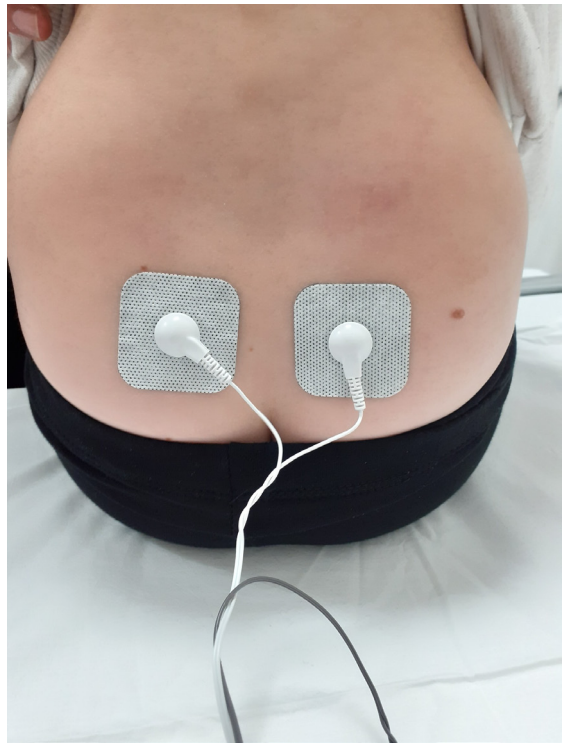

**Figure 1.** Electrode location in p-TENS therapy

p-TENS: Parasacral transcutaneous electrical nerve stimulation

duration of treatment was limited to 3 months. Each session lasted 20 min, with a frequency of 10 Hz and a generated pulse of 250 µs twice a week. The intensity was determined by the child's sensitivity threshold. Standard urotherapy was continued during p-TENS. Before p-TENS, anticholinergic treatment and biofeedback sessions of the children were terminated. Standard urotherapy was continued. Children were evaluated for treatment response six months after the last p-TENS session.

### Statistical Analysis

The statistical examination was performed using IBM SPSS v21.0 software. Descriptive statistics are presented as frequency (n) and percentage (%) for categorical variables and mean, standard deviation, and median (25.p-75.p) for numerical variables. The conformity of continuous variables to normal distribution was evaluated by the Shapiro-Wilk test. The chi-square test and Fisher's exact test were used to compare categorical variables; the categorical McNemar test was used for the dependent group comparison of variables. The independent groups' t-test and Mann-Whitney U test were used to compare the numeric variables of the two independent groups. Dependent groups t-test and Wilcoxon test were used to compare the two dependent groups. In addition, a generalized linear model was used to evaluate the pre-and post-treatment changes in continuous variables that met normal distribution conditions according to the diagnostic group. A p-value of <0.05 was considered significant.

## Results

Twelve children were evaluated for the study. There were 8 boys (67%) and 4 girls (33%). At the time of diagnosis, 7 (58%) children had non-monosymptomatic enuresis, 3 (25%) had daytime urinary incontinence, and 2 (17%) had monosymptomatic enuresis.

Improvement was detected in the holding maneuver (58 *vs.* 25%), frequency (58 *vs.* 25%), and urinary tract infection (33 *vs.* 17%). However, these treatment responses did not reach statistical significance. Urgency (p<0.001), urge incontinence (p=0.016), and constipation (p=0.031) complaints decreased significantly after treatment. Among the uroflow parameters, $Q_{max}$ decreased (p=0.012), voiding time prolonged (p=0.001), voided volume increased (p=0.001), and PVR decreased (p=0.012). The tower-shaped voiding pattern (n=7) was dominant at the beginning of treatment. After treatment, the tower-shaped pattern continued in 2 children, and the others were in a bell-shaped configuration. Urinary system symptoms and uroflow parameters in children with DO before and after p-TENS are summarized in Table 1.

After p-TENS, it was found that the incontinence completely resolved in nine children (75%). Complete response was detected in 50% of monosymptomatic enuresis (n=1), 86% of non-monosymptomatic enuresis (n=6), and 67% of daytime incontinence (n=2).

## Discussion

Recently, p-TENS has been used as an alternative treatment option in children with non-neurogenic LUTD symptoms who do not benefit from standard urotherapy, biofeedback, and/or medical treatment (7-11,19-21). However, there are few studies on transcutaneous administration in children with refractory symptoms. Because of the lack of a standard treatment protocol,

**Table 1. Urinary system symptoms and uroflow parameters in patients with detrusor overactivity (DO) before and after p-TENS treatment**

| | DO (n=12) | | |
|---|---|---|---|
| | Before | After | p |
| **Symptoms** | | | |
| Holding maneuver | 7 (58) | 3 (25) | 0.125[1] |
| Frequency | 7 (58) | 3 (25) | 0.125[1] |
| Urgency | 12 (100) | 3 (25) | <0.001[1*] |
| Urge incontinence | 10 (83) | 3 (25) | 0.016[1] |
| Urinary tract infection | 4 (33) | 2 (17) | 0.5[1] |
| Constipation | 7 (58) | 1 (8) | 0.031[1] |
| **Uroflow parameters** | | | |
| $Q_{max}$ mL/s[*] | 21.9 (20.2-24.75) | 19.9 (18.70-21.30) | 0.012[2] |
| Voiding time s[*] | 20 (16.5-22.5) | 26.50 (23.50-30) | 0.001[2] |
| Voiding volume (mL)[*] | 270 (170-312) | 370 (345-441) | 0.001[2] |
| Postvoid residue urine (mL)[*] | 5 (3.5-6) | 1 (0-4) | 0.012[3] |

[1]: McNemar test, 1* the p-value is less than one per thousand, [2]: Paired t-test, [3]: Wilcoxon test, [*]: median, IQR: Interquartile range (25-75), p-TENS: Parasacral transcutaneous electrical nerve stimulation

clinical results obtained with different treatment protocols have been reported in the literature (7-11,21). In this study, we determined that administering 20 min of TENS twice a week to the parasacral region at 10 Hz frequency and 250 µs generated pulse operation mode effectively treated refractory LUTD symptoms and urinary incontinence secondary to DO, after 6 months of follow-up.

In the literature, different treatment responses related to p-TENS applied at different times and frequencies have been reported (7-11). Finazzi Agrò et al. (22) evaluated the effect of this protocol difference on the treatment response and concluded that the important factor in the success of the treatment was not the duration of the treatment but the number of stimulations in a day. In this study, we observed treatment results similar to those of daily practices with applications of 2 days a week. In addition, the complaints of urge and urge incontinence symptom resolution rates have similar incidence compared with the third-month control rates obtained by Tugtepe et al. (7) with a protocol of 20 min at 10 Hz frequency and 350 generated pulse.

The regression of LUTD symptoms indicates that p-TENS affects voiding dynamics. The reflection of this effect on the uroflowmetry parameters of the children in this study was the positive change in $Q_{max}$ values after treatment. In addition, significant normalization was observed in the voiding patterns. The mechanism of action of p-TENS has not yet been fully elucidated; the stimulation may act on reflexogenic pathways involved in the control of the lower urinary tract and inhibit the parasympathetic excitatory neurons that come and go to the bladder or interneurons in the spinal cord (23,24). In addition, this result may be associated with the proximity of neural networks between the bladder and rectum and changes in innervation affecting both systems (25). TENS is effective for treating chronic constipation (26). Discontinuation of oxybutynin treatment during sessions and stimulation may also have affected the improvement of refractory constipation. The reduced effect of chronic constipation on the bladder may have decreased LUTD symptoms.

The complete response rates in daytime incontinence differ between studies. Tugtepe et al. (7) reported a complete response in daytime incontinence of 70% in 3$^{rd}$ month of treatment. Hoebeke et al. (11) used TENS for 2 h/day to treat 41 children and reported a success rate of 68% at one month and 51% at one year. Our complete response rate in daytime incontinence was 67% 6 months after treatment. These response rate differences can be associated with differences in the protocols applied or are related to the time at which the outcome is evaluated. The complete response rates were also high in non-monosymptomatic patients (86%). An advantage of p-TENS is that no side effects were detected in our study and other studies in the literature (18). However, its effectiveness on LUTD and incontinence is unclear in the long-term follow-up.

### Study Limitations

The most important limitation of this study is that it was retrospectively designed with a small sample size. Despite these limitations, it helps to evaluate the functional effects of p-TENS. Better treatment responses can be obtained using the protocols to be defined for specific voiding problems in the future.

## Conclusion

The response to p-TENS was significant in the symptoms of children with refractory DO. It is also effective in preventing constipation. P-TENS can be considered an alternative treatment method for refractory DO symptoms in children because it is independent of children and family-dependent factors that will decrease the effectiveness of standard treatments.

### Ethics

**Ethics Committee Approval:** Approved by Istanbul University-Cerrahpaşa Ethic Committee (number: 431.10-2777, date: 18.08.2023).

**Informed Consent:** Retrospective study.

### Authorship Contributions

Concept: E.A.K., B.Ö., Design: E.A.K., B.Ö., Data Collection or Processing: B.S., U.A., Literature Search: B.S., U.A., Writing: E.A.K., B.Ö.

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

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

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ORIGINAL RESEARCH
Basic Science

Doi: 10.4274/jus.galenos.2023.2023-9-1
J Urol Surg 2024;11(2):116-121

# Hydrogen Sulfide ($H_2S$) and Reactive Oxygen Species (ROS) Scavengers Have a Protective Effect on Carbachol-induced Contractions That are Impaired by High Glucose in Detrusor Smooth Muscle

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**What's known on the subject? and What does the study add?**

One of the most frequent diabetic complications is urinary bladder dysfunction, which is associated with increased bladder capacity and impaired smooth muscle contractions. Smooth muscle tissues isolated from diabetic rats have altered contractile responses. However, the mechanisms responsible for altered smooth muscle contractility remain poorly understood. Increased production of reactive oxygen species (ROS) plays a role in bladder disorders, and $H_2S$ has a cytoprotective effect that might have a scavenging effect on ROS. It is important to determine the effect of $H_2S$ on impaired detrusor contractility caused by ROS in order to develop new treatment principles.

## Abstract

**Objective:** Urinary bladder dysfunction, that is one of the most common diabetic complications, is associated with bladder overactivity, increased bladder capacity and also impaired bladder smooth muscle contractions. The involvement of hydrogen sulfide ($H_2S$) in pathological disorders such as diabetes mellitus has been suggested. NaHS-treatment can distinctly reduce high glucose-induce cytotoxicity and oxidative stress. Reactive oxygen species are produced in increased concentrations in diabetes and may cause tissue damage, thus impaired smooth muscle function. The aim of the study was to investigate the role of $H_2S$ and reactive oxygen scavenger (ROS) on carbachol-induced detrusor smooth muscle contractions under high glucose conditions.

**Materials and Methods:** Cumulative (10 nM-30 µM) carbachol contraction responses were obtained in bladder detrusor smooth muscle strips isolated from male New Zealand albino rabbits bladder in control group and in high glucose conditions (30 min incubation in Krebs' Henseleit solution with high glucose). Responses were repeated in the presence of sodium hydrosulfide (NaHS), catalase, superoxide dismutase (SOD) and their combinations. Contractions were expressed as a percentage of 80 mM K+ response and $p<0.05$ was accepted as statistically significant.

**Results:** Cumulative contractile responses were elicited with carbachol in control group and these responses were significantly increased in the presence of high glucose. Increased carbachol contractile responses in high glucose were significantly reduced in the presence of catalase, SOD and NaHS.

**Conclusion:** Depending on these results we may propose that $H_2S$ donors and ROS scavengers have probable benefits in treating diabetic complications such as urinary bladder dysfunction.

**Keywords:** Basic science, bladder, carbachol, high glucose, hydrogen sulfide, reactive oxygen scavenger

## Introduction

Urinary bladder dysfunction, which is one of the most common diabetic complications, is associated with bladder overactivity, increased bladder capacity, and impaired bladder smooth muscle contraction. The prevalence of dysfunction is between 43% and 87%. It is not life threatening but considerably affects life quality (1). Evaluation of bladder smooth muscle

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**Received:** 01.09.2023 **Accepted:** 08.09.2023

**Cite this article as:** Denizalti M, Durlu-Kandilci NT. Hydrogen Sulfide ($H_2S$) and Reactive Oxygen Species (ROS) Scavengers Have a Protective Effect on Carbachol-induced Contractions Impaired by High Glucose in Detrusor Smooth Muscle. J Urol Surg 2024;11(2):116-121.

contractility is important for understanding the mechanisms underlying diabetic dysfunction. Alterations in contractile responses have been reported in smooth muscle tissues isolated from diabetic models. Increased carbachol-induced contraction was observed in bladder smooth muscle in streptozotocin (STZ)-induced diabetic rats (2). Pretreatment of bladders under high glucose (HG) conditions enhanced carbachol-induced contraction in control animals (3). Nobe et al. (4) showed that glucose-dependent enhancement of contraction in the diabetic bladder is involved in the activation of the Rho kinase and calcium-independent PKC pathways. The increased vascular smooth muscle contraction, which was enhanced under HG conditions, was also reported in a type II diabetic mouse model (5,6). However, the mechanisms responsible for altered smooth muscle contractility remain poorly understood.

The involvement of hydrogen sulfide ($H_2S$) in pathological disorders such as diabetes mellitus has been suggested although its physiological role is still not known. Increased formation of $H_2S$ and expression of endogenous $H_2S$-synthesizing enzymes, cystathionine γ-lyase (CSE) and cystathionine b-synthase (CBS), have been demonstrated in the liver and pancreas of STZ-induced diabetic rats (7). Inhibition of CSE, a synthase of endogenous $H_2S$, promotes endothelial cell dysfunction induced by hyperglycemia (8) and reduces $H_2S$ levels in STZ-induced diabetic rats (9). In diabetic mice, treatment with $H_2S$ can restore nitric oxide efficacy and decrease oxidative stress in the mouse aorta (10). However, possible accompanying changes in the functional effects of $H_2S$ have not been elucidated.

The cytoprotective effect of $H_2S$ may also be attributed to its scavenging effect on reactive oxygen species (ROS). ROS are produced in increased concentrations in pathological conditions such as cardiac ischemia, reperfusion, or sepsis and cause tissue damage. ROS can alter smooth and striated muscle contraction by affecting many intracellular pathways associated with excitation-contraction coupling. It has been shown that carbachol- and potassium-induced contractions are reduced in the presence of hydrogen peroxide in the rat urinary bladder detrusor muscle (11). In our previous study, $H_2S$ reduced carbachol-induced contraction in the permeabilized guinea pig taenia cecum and that intracellular hydrogen peroxide formation and calcium storage mitochondria are responsible for this response (12). It is also known that superoxide anions reduce the release of calcium by preventing the opening of the calcium channels of the sarcoplastic reticulum in the myocardium (13).

The aim of this study was to investigate the role of $H_2S$ and ROS scavengers in alterations of carbachol-induced detrusor smooth muscle contraction under HG conditions.

## Materials and Methods

The study was approved by the Hacettepe University Animal Ethics Committee (no: 2023/06-06). Male New Zealand albino rabbits (4-6 months old) were used in this study.

### Tissue Preparation

Rabbits were euthanized under high-dose anesthesia (Ketamine/Xylazine, 50/5 mg/kg, i.p.) and their urinary bladders were isolated. Bladder strips were isolated and mounted in 5 mL organ baths containing Krebs' Henseleit solution under a resting tension of 800 mg. Tissues were equilibrated for 1 h and washed with Krebs' Henseleit solution every 15 min before each experimental procedure. Isometric changes in tension were recorded using an isometric force transducer (MP 150-Transducer Data Acquisition System; BIOPAC Systems).

### Experimental Protocol

Sodium hydrogen sulfide (NaHS) is used as an $H_2S$ donor, and its aqueous solution is introduced directly into the organ bath by an automated pipette. NaHS dissociates to $Na^+$ and $HS^-$ in aqueous solution and then $HS^-$ associates with $H^+$ to form $H_2S$ (Hosoki et al., 1997).

At the beginning of each experiment, KCl (80 mM)-induced contractions were elicited in bladder strips. After a 30-min washout period, cumulative (10 nM-30 μM) carbachol-induced contraction responses were obtained in bladder strips in the control group and under HG conditions. The HG condition means 30 min incubation of bladder strips in Krebs' Henseleit solution with 4.7; $MgSO_4$, 1.2; $CaCl_2$, 2.5; $KH_2PO_4$, 1.2; $NaHCO_3$, 25.0; glucose, 11.6 and this was gassed with 95% $O_2$-5% $CO_2$ at 37 °C and pH 7.4. Krebs' Henseleit solution with HG content contains 44 mM glucose. Cumulative carbachol-induced contraction responses were elicited in the presence of ROS scavengers catalase (1.000 U/mL), superoxide dismutase (SOD; 150 U/mL), $H_2S$ donor sodium hydrosulfide (NaHS, 300 μM), $H_2S$-synthesizing enzyme inhibitors propargylglycine (PAG; 300 mM) and aminooxyacetic acid (AOAA; 1 mM) in control and HG conditions.

### Drugs and Solutions

The drugs used were carbamylcholine chloride (carbachol), catalase, SOD, NaHS, PAG, and AOAA from Sigma (St. Louis, Missouri). All drugs and solutions were prepared by using distilled water.

### Statistical Analysis

Contractions are expressed as a percentage of KCl (80 mM)-induced contraction. Data are represented as mean ± standard error of the mean. Statistical analysis was performed by ANOVA/Newman-Keuls and Student's t-test using GraphPad Prism9 software. $P<0.05$ was accepted as statistically significant.

## Results

### Effect of High Glucose in Bladder Cumulative Carbachol Contraction

Cumulative contractile responses were elicited with carbachol (10 nM-30 μM) in the control group. Bladder strips were incubated with HG (Krebs' Henseleit solution with 44 mM glucose). The contraction responses were significantly increased under HG conditions compared with the control group (Figure 1).

### Effects of ROS Scavengers Catalase and SOD on Cumulative Carbachol Contraction

Increased carbachol contractile responses under HG conditions were significantly reduced in the presence of hydrogen peroxide ($H_2O_2$) scavenger catalase (1000 U/mL) and superoxide ($O_2^-$) scavenger SOD (150 U/mL) (Figure 2). There was no difference in the control group between the absence and presence of catalase or SOD (Table 1).

### Effects of $H_2S$ donor NaHS on Cumulative Carbachol Contraction

Cumulative carbachol (10 nM-30 μM) contractile responses were obtained in the presence of $H_2S$ donor NaHS (300 mM) in control and under HG conditions. Increased carbachol contractile responses under HG conditions were significantly reduced in the presence of NaHS. Contractile responses were also significantly decreased in the presence of NaHS in the control group (Figure 3).

### Effects of Combination of $H_2S$ donor NaHS and ROS Scavenger Catalase or SOD on Cumulative Carbachol Contraction

To investigate the interaction between $H_2S$ and ROS, bladder strips were incubated with NaHS and catalase or with NaHS and SOD. There was no further inbibition in cumulative carbachol (10 nM-30 μM) contractile responses incubated with the combination of NaHS and catalase or NaHS and SOD compared with incubation with NaHS alone in the control group. In contrast, further inhibition was observed in carbachol contraction responses under HG conditions when bladder strips were incubated with the combination of NaHS and catalase or NaHS and SOD compared with incubation with NaHS alone (Table 1).

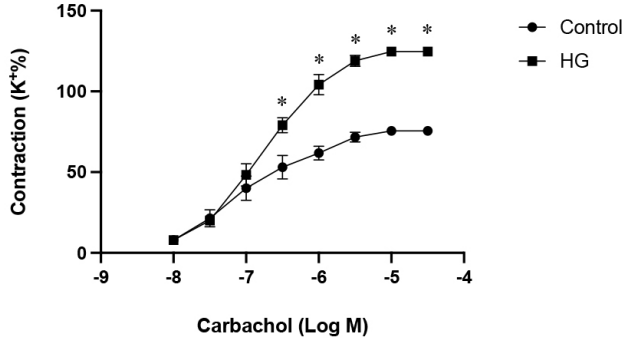


**Figure 1.** The cumulative contractile response elicited with carbachol (10 nM-30 μM) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 significant compared to control; n=6)

HG: High glucose

### Effects of $H_2S$-synthesizing Enzyme Inhibitors PAG and AOAA on Cumulative Carbachol Contraction

Increased carbachol contractile responses under HG conditions did not change in the presence of CSE enzyme inhibitör PAG (300 μM) and CBS enzyme inhibitor AOAA (1 mM) (Figure 4).

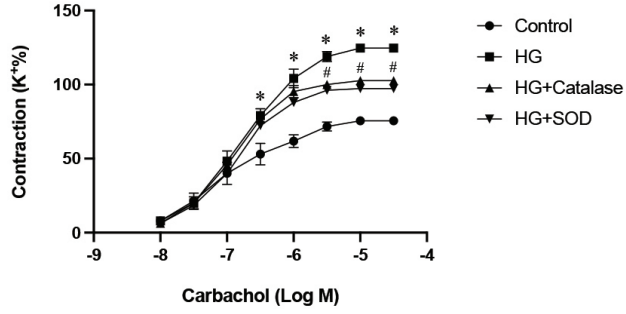


**Figure 2.** The cumulative contractile response elicited with carbachol (10 nM- 30 μM) in the absence and presence of catalase (1000 U/mL) and SOD (150 U/mL) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 significant compared to control, #p<0.05 significant compared to HG; n=5-6).

HG: High glucose, SOD: Superoxide dismutase

**Table 1. Maximum contraction values ($E_{max}$) obtained with carbachol in the presence of catalase, SOD, NaHS and their combinations in the control and HG-incubated bladder detrusor smooth muscle**

| Group | | $E_{max}$ | n |
|---|---|---|---|
| Control | | 75.53±2.58 | 6 |
| HG | | 124.65±2.36* | 6 |
| Catalase | Control | 70.88±3.84 | 5 |
| | HG | 102.71±2.71# | 5 |
| SOD | Control | 72.59±0.80 | 5 |
| | HG | 97.28±0.84# | 6 |
| NaHS | Control | 64.03±1.72* | 5 |
| | HG | 94.57±0.97# | 5 |
| NaHS + catalase | Control | 66.10±1.18 | 6 |
| | HG | 84.57±0.97# | 5 |
| NaHS + SOD | Control | 65.47±1.75 | 5 |
| | HG | 85.51±1.26# | 5 |

*: p<0.05 compared to control, #: p<0.05 significant compared to HG, HG: High glucose, NaHS: Sodium hydrogen sulfide, SOD: Superoxide dismutase, max: Maximum

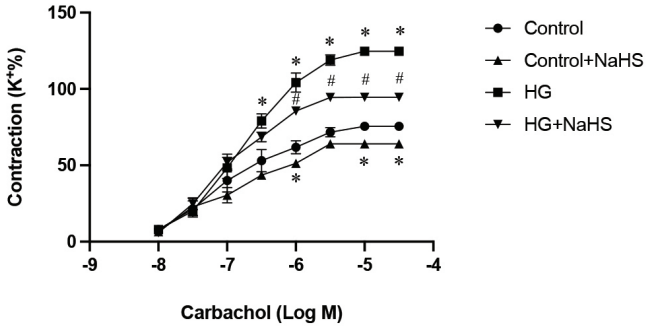


**Figure 3.** The cumulative contractile response elicited with carbachol (10 nM-30 µM) in the absence and presence of NaHS (300 µM) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 compared to control, #p<0.05 significant compared to HG; n=5-6)

HG: High glucose, NaHS: Sodium hydrogen sulfide

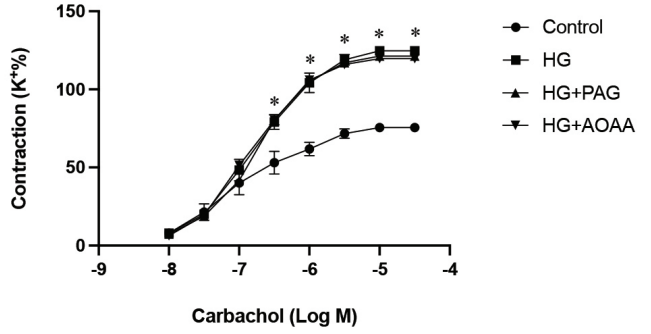


**Figure 4.** The cumulative contractile response elicited with carbachol (10 nM-30 µM) in the absence and presence of PAG (300 mM) and AOAA (1 mM) in control and HG-incubated bladder detrusor smooth muscle of rabbits (*p<0.05 compared to control; n=5-6)

PAG: Propargylglycine, HG: High glucose, AOAA: Aminooxyacetic acid

## Discussion

Many neurological, cardiovascular, urological, gastrointestinal, and biochemical complications develop in patients with diabetes due to increased glucose. Bladder dysfunction is one of the most common diabetic complications associated with bladder overactivity, increased bladder capacity, and impaired smooth muscle contractile function. Investigating the mechanism of impaired bladder smooth muscle contractility is important for understanding the underlying mechanisms of diabetes complications. Moreover, bladder dysfunction problems, especially those more common in women, lead to social problems as well. Our aim in this study was to elucidate the effect of ROS scavengers and $H_2S$ on impaired contractile functions under HG conditions.

Changes in contractile responses in bladder smooth muscle experimentally induced or incubated with HG have been reported (2-4). In our study, cumulative carbachol contractile responses were significantly increased in the HG group compared with the control group. An increase in carbachol-induced contractile responses was demonstrated in bladder strips isolated from STZ-induced diabetic rats and in tissues pre-treated with HG (2,3). Many mechanisms are believed to be responsible for the impaired contractile response due to HG. The consequence of hyperglycemic stimulation is the increase of ROS, thus initiating oxidative stress, which causes bladder smooth muscle damage, resulting in impaired bladder function (14-16). Growing evidence has shown that high-glucose-relatedoxidative stress has an essential role in the remodeling of smooth muscle function that eventually results in the decompensation of the detrusor muscle (17-19). The complications of diabetes are thought to be the result of oxidative stress associated with HG in several tissues (20) including the detrusor smooth muscle (21). It has been reported that repeated stimulation of rabbit bladder strips leads to increased lipid peroxidation and impaired smooth muscle contractility in the ischemic and hypoxic media as well as in the normal physiological media (22).

Samples from rats with STZ-induced type 1 diabetes showed that genes involved in the production or enhancement of ROS and oxidative pathways are upregulated in the bladder of these rats, whereas antioxidative enzymes are downregulated (17-20). Xue et al. (23) 2021 showed that the viability of bladder smooth muscle cells significantly decreased and apoptotic cells increased after HG treatment; at the same time, the SOD level decreased and MDA increased. SOD is an important antioxidant enzyme, and its level decreases, suggesting a decline in antioxidant capacity. MDA is a lipid oxidative damage marker, and its increased level indicates a higher level of oxidative stress (23). In this study, we investigated the effects of ROS scavengers, $O^{2-}$ radical scavenger SOD and $H_2O_2$ scavenger catalase, on increased carbachol contractile responses under HG. In the present study, we observed that contractile response under HG conditions was decreased in the presence of catalase and SOD. There was no difference in the control group in the presence of catalase and SOD. Consistent with previous studies, our results indicate that HG causes impaired contractile responses in the detrusor smooth muscle through oxidative stress.

Exogenous $H_2S$ significantly prevented cell death, decreased the generation of apoptotic markers, and suppressed mitochondrial ROS production in rat aortic endothelial cells under HG conditions (24). NaHS treatment can distinctly reduce HG-induced cytotoxicity, apoptosis, oxidative stress, and inflammation in HUVECs (25). In diabetic mice, treatment with $H_2S$ can restore nitric oxide efficacy and decrease oxidative stress in the mouse aorta (10). $H_2S$ may act as a cytoprotective

hormone in mouse islets and in MIN6 cells exposed to HG, fatty acids, or a mixture of cytotoxic cytokines (26,27). The effects of $H_2S$ on increased carbachol contractile responses under HG conditions were also investigated. According to our results, increased carbachol contractile responses were significantly reduced under HG conditions in the presence of NaHS. Contractile responses were also significantly decreased in the control group in the presence of NaHS. Inhibition was seen in 14% (the control group) and 24% (HG group) ratios. In parallel with previous studies, our results suggest that $H_2S$ reduces the oxidative stress caused by HG and, as a result, improves the impaired contractile responses. Moreover, when the combined effects of $H_2S$ and ROS scavengers were examined under HG conditions, after incubation of NaHS and catalase or NaHS and SOD together, a further reduction 32% and 31% in carbachol contractile responses were obtained, respectively. According to studies examining the possible interaction of $H_2S$ and ROS, Muzaffar et al. (28) showed that $H_2S$ suppressed $O^{2-}$ production in pulmonary artery endothelial cells. In another study, NaHS infusion decreased $O^{2-}$ production in hypertensive rats (29).

$H_2S$-synthesizing enzyme inhibitors PAG and AOAA were examined to support the regulating effect of $H_2S$ on deteriorated contractile responses in bladder smooth muscle under HG conditions. Increased carbachol contractile responses under HG were not changed in the presence of CSE enzyme inhibitör PAG and the CBS enzyme inhibitor AOAA.

### Study Limitations

The fact that our study is an animal study is an important limitation. It is difficult to mimic hyperglycemia in animal tissues. Studies on the effects of $H_2S$ and ROS on humans should be conducted to strengthen these findings.

## Conclusion

The study identified alterations in contractile responses in bladder smooth muscle under HG conditions. Cumulative carbachol-induced contractile responses were significantly increased in HG-incubated bladder detrusor muscle. These increased contractile responses decreased in the presence of catalase, SOD, and NaHS. Therefore, we can suggest that agonist-induced contractile functions in diabetes are related to $H_2S$ and ROS such as $H_2O_2$ and $O_2^-$. In conclusion, these results may become a valuable source for assessing the probable benefits of $H_2S$ donors and ROS scavengers in treating diabetic complications such as urinary bladder dysfunction.

### Ethics

**Ethics Committee Approval:** The study was approved by the Hacettepe University Animal Ethics Committee (no: 2023/06-06).

**Informed Consent:** Not necessary.

### Authorship Contributions

Concept: M.D., N.T.D.K., Design: M.D., N.T.D.K., Data Collection or Processing: M.D., Analysis or Interpretation: M.D., N.T.D.K., Literature Search: M.D., Writing: M.D., N.T.D.K.

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

**Financial Disclosure:** The authors declare that they have no relevant financial.

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VIDEO ARTICLE
Video

Doi: 10.4274/jus.galenos.2024.2023-12-4
J Urol Surg 2024;11(2):122-123

# Pyeloplasty in the Pelvic Kidney: A Step-by-step Video

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## Abstract

Ectopic kidneys, with a prevalence of 1/1000-4000, often manifest in the pelvic region, can be complicated with problems such as ureteropelvic junction (UPJ) obstruction. This video article presents a case of open pyeloplasty in a 15-month-old infant with a pelvic kidney, emphasizing technical details for educational purposes. The patient was prenatally diagnosed with pelvic kidney hydronephrosis at 22 weeks of gestation, progressing to grade 4 postnatally. MAG-3 scintigraphy confirmed UPJ obstruction, warranting open pyeloplasty. A Pfannenstiel incision provided access to the Retzius space. The ureter was dissected, revealing the adhered renal pelvis. Stay sutures facilitated dissection, and 5/0 polyglactin sutures were strategically placed due to anatomical anomalies. Ureteropelvic anastomosis was performed using 6/0 PDS sutures. A 3-Fr Double J catheter preceded the closure of the renal pelvis. The procedure was concluded with meticulous layer closure. The operation lasted for 50 min, with minimal blood loss (10 mL). Drain was removed on postoperative day 2, and the patient was discharged. Ureteral stent was removed at 4 weeks. A 3-month follow-up ultrasound revealed a notable reduction in hydronephrosis, with an anteroposterior diameter of 6 mm. This video article elucidates the nuances of open pyeloplasty in pelvic kidneys and serves as a valuable resource for residents and fellows. The concise procedure, with a brief operative time and minimal blood loss, indicates the efficacy of the surgery.

**Keywords:** Pediatric, pelvic kidney, pyeloplasty, renal anomalies, surgery, ureteropelvic junction obstruction

## Introduction

The incidence of ectopic kidney is approximately 1/1000-4000, and the most common location of renal ectopia is the pelvis (1,2). Ureteropelvic junction obstruction in the pelvic kidney may be observed as high as 37% (3). Here we report a case of open pyeloplasty in a pelvic kidney in a 15-month-old infant with technical details.

### Patients

The patient was antenatally diagnosed with hydronephrosis in the left pelvic kidney at 22$^{nd}$ week of gestation. His initial postnatal renal ultrasonography revealed grade 4 hydronephrosis, and MAG-3 scintigraphy revealed an obstructed ureteropelvic junction. The patient was indicated for open pyeloplasty.

A Pfannenstiel incision was used, anatomical folds were opened, and the Retzius space was entered. An 8 Fr feeding tube was inserted to empty the bladder and then taken out. The distal segment of the left ureter was superior-lateral to the bladder. The ureter was then dissected proximally, and the renal pelvis of the ectopic kidney was found where the renal pelvis wall was adhered to the peritoneum. A stay suture was placed at the ureteropelvic junction to facilitate dissection. Furthermore, 5/0 polyglactin stay sutures were placed on the anteromedial side of the ureter (due to the rotation anomaly) as well as the most dependent and upper part of the renal pelvis. Then, the ureter was cut within the limits of the stay sutures, and the ureteropelvic junction was excised. Moreover, the ureter was spatulated to a few centimeters below the healthy segment. Three 6/0 PDS sutures were placed on the corner of the ureteropelvic anastomosis. Afterwards, the posterior wall was closed with continuous 6/0 PDS sutures over a 5-Fr feeding tube followed by the anterior wall, which was closed in the same fashion. Before closing the renal pelvis, a 3 Fr 12 cm Double J catheter was placed. Anastomosis was completed. After bleeding control, a minivac drain was placed. The operation was concluded after the anatomical layers were properly closed.

## Results

The total operative time was 50 min, and blood loss was 10 mL. The drain was removed on postoperative day 2, and the patient

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**Received:** 17.12.2023 **Accepted:** 09.01.2024

**Cite this article as:** Ergül RB, Selvi İ, Gürcan M, Kart M, Dönmez Mİ, Ziylan O, Oktar T. Pyeloplasty in the Pelvic Kidney: A Step-by-step Video. J Urol Surg 2024;11(2):122-123.

was discharged on the same day. Ureteral stent was removed after 4 weeks. Follow-up renal ultrasonography at 3 months postoperatively demonstrated regression of hydronephrosis with an AP diameter of 6 mm.

## Conclusion

In this video article, we attempted to highlight the technical details of open pyeloplasty for pelvic kidneys that could be a source for all residents and fellows.

### Ethics

**Informed Consent:** Informed consent was obtained from the patient.

### Authorship Contributions

Surgical and Medical Practices: R.B.E., İ.S., M.G., M.K., M.İ.D., Concept: R.B.E., M.K., Design: R.B.E., O.Z., T.O., Data Collection or Processing: R.B.E., M.K., Literature Search: O.Z., T.O., Writing: R.B.E., M.G.

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

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

**Video 1.**

### Ethics

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CASE REPORT
Case

Doi: 10.4274/jus.galenos.2023.2023-6-1
J Urol Surg 2024;11(2):124-128

# Use of Yang-Monti Procedures for Ureteral Defect Repair in Different Clinical Cases: A Case Series

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## Abstract

The repair of long-segment ureteral defects poses a challenge for urologists. Surgical techniques such as ureteroureterostomy, a psoas hitch, a Boari flap, or autotransplantation can be used as alternative treatment techniques depending on the length and location of the ureteral injury. Due to the difficulties and limitations of all these techniques, ileal substitution methods may be required in some cases. The Yang-Monti procedure, a well-known ileal substitution technique, allocates a retubularized ileal segment after detubularization at the antimesenteric axis to create an isoperistaltic conduit. This case series features the Yang-Monti procedure for various acquired and iatrogenic ureteral defects.

**Keywords:** Ileal substitution, reconstruction, ureteral defect, Yang-Monti

## Introduction

Several intestinal interposition techniques have been described in the literature for treating congenital or acquired ureteral defects (1). Although less invasive procedures, such as ureteroureterostomy, a Boari flap, and a Psoas Hitch, are widely used for ureteral reconstruction, intestinal interposition techniques can be considered the last resort in selected patients (2). Ileal interposition techniques that can overcome this impediment by providing isoperistaltic motion are the Yang-Monti, Ghoneim, and Abol-Enien procedures (3). In this case series, we present the Yang-Monti procedure in four patients with different clinical manifestations to demonstrate that this technique can be conveniently used with good clinical outcomes even in the most complicated cases.

## Materials and Methods

The archival data of patients with long segment ureteral injuries of different etiologies who underwent the Yang-Monti procedure in our clinic were retrospectively analyzed. The medical history, preoperative examination, and postoperative follow-up data of the patients were compiled after obtaining the consent of each patient.

## Case Presentation

The first patient was a 26-year-old man with a history of multiple operations after falling from a height three years ago. After bilateral hydronephrosis was detected on computed tomography (CT), bilateral nephrostomy tube insertion was performed. No contrast transition was observed between the ureteric segments 4 cm distal to the right ureteropelvic junction (UPJ) and 3 cm proximal to the right ureterovesical junction.

The second patient was a 50-year-old woman with right flank pain and hydronephrosis after an emergent right hemicolectomy due to perforation secondary to ulcerative colitis. CT-urography demonstrated contrast transition below the level of UPJ. Diagnostic ureterorenoscopy (URS) and retrograde pyelography revealed that the ureter was occluded at the iliac crossing level (Figure 1).

The third patient was a 39-year-old man referred to our clinic with bilateral nephrostomy tubes due to obstructive calculus located in the bilateral UPJ. Multiple surgical interventions, including a Boari flap, were performed for the left distal ureteral stenosis that developed after stone treatment was completed. However, the obstructive pathology in the left upper urinary tract recurred after these interventions. No contrast transition

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**Received:** 04.06.2023 **Accepted:** 12.08.2023

**Cite this article as:** Önal B, Gültekin MH, Kalender G, Şahin KC, Özden SB, Özkaya M, Özkara H. Use of Yang-Monti Procedures for Ureteral Defect Repair in Different Clinical Cases: A Case Series. J Urol Surg 2024;11(2):124-128.

was noted distal to the UPJ, and the left neo-orifice could not be accessed on URS.

The last case was a 53-year-old woman with a previous diagnosis of retroperitoneal fibrosis. In the first operation, laparoscopic ureterolysis was performed with no remarkable adverse events. In the second operation, the robot-assisted laparoscopic technique was used. While retroperitoneal attachments were liberated, complete avulsion occurred. Primary repair with robotic arms was performed, and the ureter was wrapped in omentum. After discharge from the hospital, the patient could not tolerate stent removal, and the Yang-Monti procedure was recommended.

### Surgical Technique

Midline incision and transperitoneal approach were used to reach the collecting systems of all patients. Depending on the length of the defected ureter, an approximately 2-9 cm-long ileal segment was harvested, preserving the mesencteric vasculature. Ileorrhaphy was performed by anastomosing the dissected ends of the ileum in a side-to-side fashion using two 80-mm linear staplers. Then, one to three separate ileal segments of 2-3 cm length were formed. The segments were detubularized from the anti-mesenteric border and retubularized over a Foley catheter to form the neuroter. The harvested and tubularized ileal segments were sewn together end-to-end fashion using 4.0 polyglactin suture material (Figures 2-5).

As the first step of reconstruction, the obtained neo ureters were anastomosed to the proximal ureteral stump in an end-to-end fashion over a 6-Fr ureteral catheter using 4.0 polyglactin suture material. In two patients with ureteral stenosis at the UPJ level ureterocalicostomies were performed. Finally, we anastomosed the neoureteric segment to the distal ureteric stump with 4.0 polyglactin sutures and administered methylene blue to the bladder and nephrostomy tube separately to identify any possible anastomosis leakage. In one patient, we anastomosed the distal part of the neuroter to the bladder using the split-cuff nipple technique. After assessment of water tightness with bladder filling test, the surgeries were completed with the insertion of a drain into the operation site and abdominal wall closure.

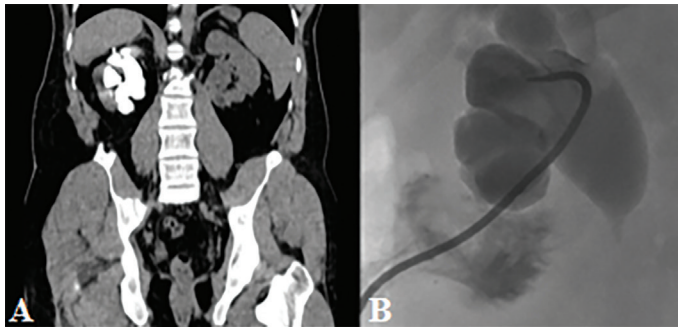


**Figure 1.** Preoperative computed tomography-nephrostography images of Case 1, revealing the complete obstruction of the ureteropelvic junction. A. Coronal CT image, B. Antegrade pyelography image

CT: Computed tomography

## Results

All four patients were discharged from the hospital after a median of 7 (4-12) days of inpatient clinic follow-up without complications. Antegrade pyelography was performed on the patients at postoperative follow-up. After contrast transition to the bladder was observed (Figure 6A), the nephrostomy tubes were removed in the second to fourth postoperative week. Each patient was checked by cross-sectional imaging at the 3rd postoperative month. The ureteral catheters of all patients were removed three to six months postoperatively. After removal of the catheter, each patient underwent a control dynamic renal scintigraphy or cross-sectional scan (Figure 6B, C). No metabolic or obstructive pathology was observed during the 1-year follow-up. All patients were followed up in a catheter-free state for over a year, and the operations were deemed successful. Pre-operative and post-operative 1st year creatinine and creatinine clearance values of the patients are given in Table 1.

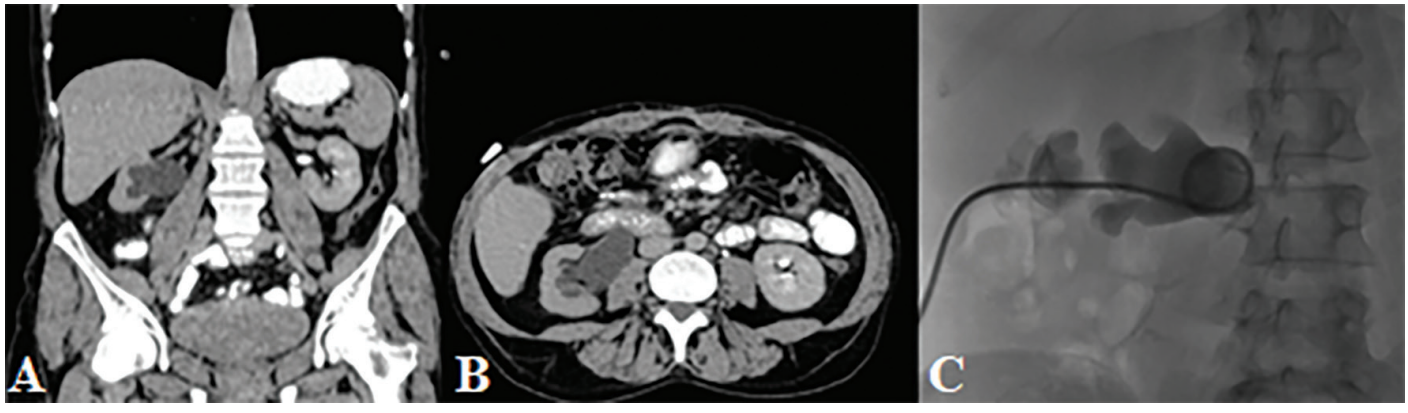


**Figure 2.** Computed tomography (CT)-urography and antegrade pyelography images of Case 2 in the preoperative period. A. Coronal CT image B. Axial CT image C. After the placement of a right nephrostomy tube, antegrade pyelography image reveals complete proximal ureteric obstruction

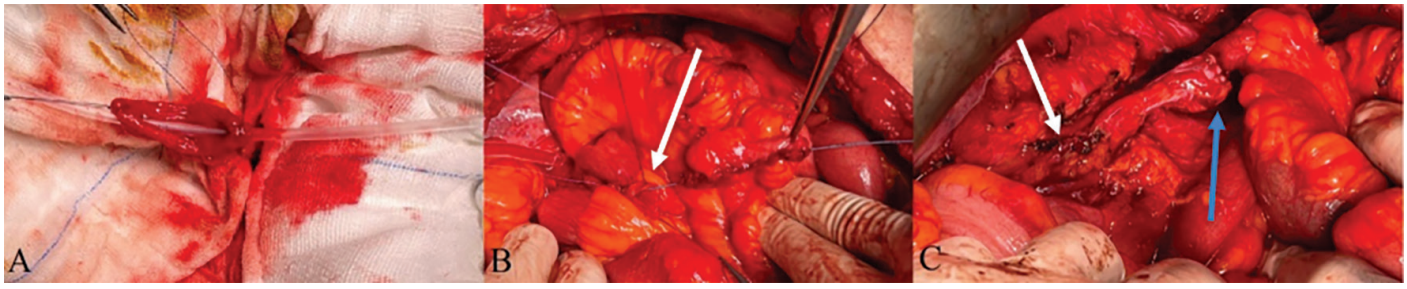


**Figure 3.** Perioperative images from the single Yang-Monti procedure of Case 1. A. Retubularization of the neoureter. B. Anastomosis of the neoureter to the proximal part of the ureter defect (white arrow). C. Complete anastomosis of the neoureter (white arrow: proximal part, blue arrow: distal part)

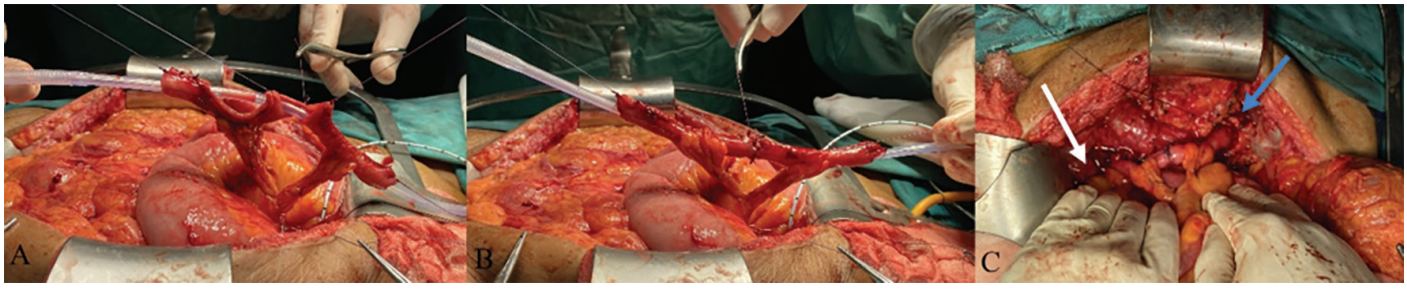


**Figure 4.** Peri-operative images from the double Yang-Monti procedure of Case 2. A. Retubularization of the neo-ureter. B. Completion of retubularization with a 16-Fr Foley catheter. C. Anastomosis of the whole neoureter (white arrow: proximal part, blue arrow: distal part)


**Figure 5.** Peri-operative images from the triple Yang-Monti procedure of Case 3. A. Retubularization of the triple Yang-Monti neoureter. B. Completion of retubularization with a 16-Fr Foley catheter. C. Ureteroneocystostomy of the distal part of the neoureter (white arrow)

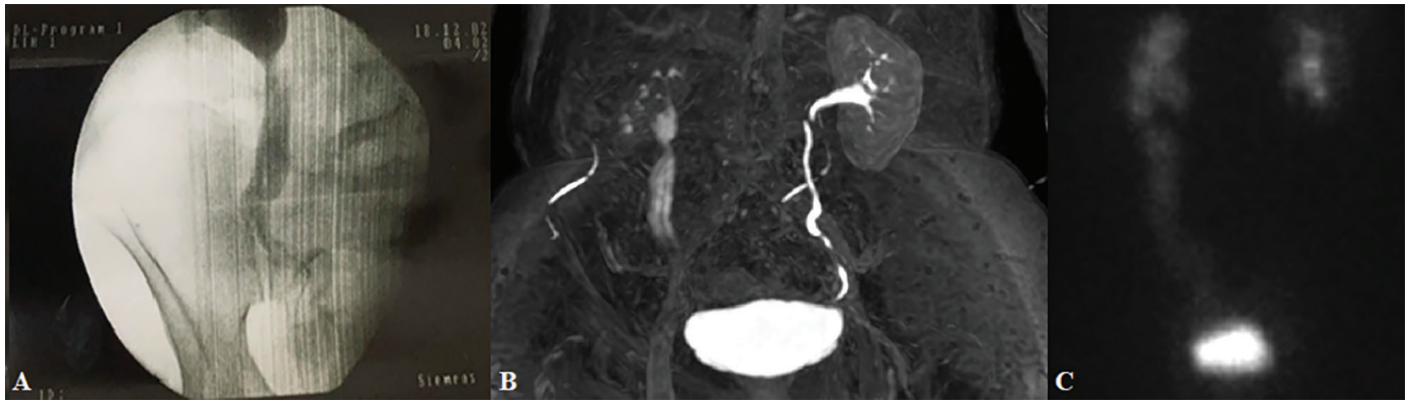


**Figure 6.** Images from the postoperative follow-up of the patients. A. Antegrade pyelography image of Case 2, in the first postoperative month. B. MR-urography image of Case 2, six months after the surgery. C. Dynamic renal scintigraphy image of Case 3, six months after the surgery

MR: Magnetic resonance

**Table 1. Pre-operative and post-operative 1st year creatinine and creatinine clearance values of the patients**

| | Pre-operative | | Post-operative 1st year | |
|---|---|---|---|---|
| | Creatinine value (mg/dL) | Creatinine clearence (mL/min) | Creatinine value (mg/dL) | Creatinine clearence (mL/min) |
| Case 1 | 1.28 | 94 | 0.94 | 128 |
| Case 2 | 0.68 | 115 | 0.65 | 120 |
| Case 3 | 1.53 | 73 | 1.1 | 101 |
| Case 4 | 0.76 | 126 | 0.8 | 121 |

**Note:** Creatinine clearance was calculated using Cockgroft-Gault equation

## Discussion

Most forms of ureteral replacement procedures have been frequently used since Shoemaker (4) first described the methodology of using gut segments for ureteric reconstruction in 1906. Interposition techniques have mainly been indicated for treating iatrogenic injuries in the past few decades (1). Yang (5) was the first to retubularize ileal segments in a respective antimesenteric axis to provide continence in cystectomy patients. Monti et al. (6) conducted a study on dogs in 1997 and reported that this procedure not only reduced the size of the harvested gut segment but also provided an anti-reflux mechanism propelled by the isoperistaltic motion of the segment.

The Yang-Monti procedure has certain advantages over other conduit harvesting techniques by allowing the surgeon to reconstruct longer defects while maintaining physiological peristaltic movement (6). Because smaller segments are used, metabolic disturbances are rare (1). However, some metabolic disadvantages have also been noted, such as hyperchloremic metabolic acidosis, renal insufficiency, and hepatic dysfunction (7).

Retrograde transmission of intravesical pressure constitutes another important problem that mostly depends on the defect site, anastomosis technique, and intravesical pressure (8). It should also be noted that the isoperistaltic capacity of neoureteric segments can prevent urinary reflux through the affected collecting system (5,6,8).

Reconstructive techniques for luminal organs are evolving. In the past decade, advancements in three-dimensional bioprinting-guided organ regeneration have allowed reconstruction of the urinary bladder and intestines (9). However, these protocols are still experimental; therefore, it seems that surgical techniques requiring ileal substitution will remain relevant soon.

## Conclusion

The Yang-Monti technique provides certain advantages because it offers the possibility of long-segment ureter reconstruction with a short ileal segment. The physiological peristaltic movement of the ileal wall used in this procedure mimics the peristalsis of the ureter. Our case series is important, considering the lack of studies reporting the use of the Yang-Monti procedure in various clinical cases. In this study, we demonstrated the Yang-Monti procedure as a feasible option for treating both iatrogenic and acquired ureteral defects.

### Ethics

**Informed Consent:** The medical history, preoperative examination, and postoperative follow-up data of the patients were compiled after obtaining the consent of each patient.

### Authorship Contributions

Surgical and Medical Practices: B.Ö., M.H.G., H.Ö., Concept: M.H.G., Design: M.H.G., Data Collection or Processing: G.K., K.C.Ş., S.B.Ö., Analysis or Interpretation: G.K., K.C.Ş., Literature Search: G.K., K.C.Ş., Writing: M.H.G., M.Ö.

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

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

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CASE REPORT
Case

Doi: 10.4274/jus.galenos.2023.2023-7-5
J Urol Surg 2024;11(2):129-133

# Treatment of Recurrent Giant Angiomyolipoma After Nephrectomy with Selective Arterial Embolization: A Case Report

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## Abstract

Angiomyolipomas (AMLs) are mesenchymal tumors that typically originate from the kidneys and contain smooth muscle cells, fat cells, and blood vessels. They are usually benign in nature but can be fatal due to complications. AMLs almost always involve the kidneys, and only a few studies have reported the possibility of extrarenal involvement as a rare entity. In this study, we examined a patient who presented to our clinic with left-sided pain and was found to have a large AML measuring approximately 15 cm in size in the left kidney. The patient underwent a simple left nephrectomy, and AML was diagnosed after histopathological examination, with intact surgical margins. During the patient's routine 6-month follow-up visits, approximately four years after nephrectomy, a mass of approximately 13 cm was observed in the nephrectomy bed and radiologically interpreted as a recurrent AML. A tru-cut biopsy of the mass confirmed AML diagnosis. The patient was treated with selective arterial embolization, which was successful without any complications. We believe that our rare case of recurrent large AML will contribute to the diagnosis and treatment choices for patients with recurrent renal and extrarenal AML in the future and will add to the existing literature.

**Keywords:** Angiomyolipoma, nephrectomy, selective angioembolization

## Introduction

Renal angiomyolipomas (AMLs) are benign mesenchymal tumors containing fat cells, smooth muscle cells, and blood vessels. AMLs constitute approximately 0.3-3% of all kidney tumors (1,2). Approximately 80% of AMLs are sporadic, while the remaining 20% are associated with tuberous sclerosis complex (3).

Although AMLs commonly exhibit renal localization, they can rarely present with extrarenal localization. Studies on extrarenal AMLs have shown their occurrence in various regions such as the liver, retroperitoneum, adrenal glands, colon, bladder, hilar lymph nodes, lungs, abdominal wall, fallopian tubes, hard palate, head, penis, spermatic cord, vagina, and uterus. The retroperitoneal space is the second most commonly observed site for extrarenal AMLs. Because of their ability to mimic other retroperitoneal tumors and the lower fat density of these lesions compared with renal AMLs, the diagnostic process through imaging can be more challenging for clinicians. Similar to renal AMLs, extrarenal retroperitoneal AMLs are more frequently observed in females (4).

AMLs were previously symptomatic (presenting with flank pain, palpable mass, hematuria, etc.) in approximately 64% of cases before the advent of radiological imaging, but nowadays they are mostly detected incidentally and asymptomatic (5,6).

Diagnosis of renal AMLs through radiological examinations such as computed tomography (CT), ultrasonography (USG), and magnetic resonance imaging is almost 100% sensitive. Lesions with negative attenuation values of 10 Hounsfield units or lower detected by CT, the presence of fat in the lesion, and the presence of a hyperechoic signal and acoustic shadowing on USG are diagnostic for AMLs (7).

The most important complication of AML is life-threatening retroperitoneal or collecting system bleeding, particularly in patients with large lesions (8). In a recent series, approximately 58% of patients required total or partial nephrectomy and

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**Received:** 22.07.2023 **Accepted:** 19.10.2023

**Cite this article as:** Nebioğlu A, Doruk HE, Gökalp Satıcı FE, Yuyucu Karabulut Y, Özer C. Treatment of Recurrent Giant Angiomyolipoma After Nephrectomy with Selective Arterial Embolization: A Case ReportJ Urol Surg 2024;11(2):129-133.

42% required embolization to control bleeding symptoms (2). One of the most significant complications of renal AMLs is the occurrence of massive retroperitoneal hemorrhage, often seen in pregnant individuals, following the rupture of an AML, a condition known as Wunderlich syndrome (9).

A wide range of treatment options are available for AML, ranging from active surveillance to total nephrectomy. Among these, the most commonly preferred treatments in recent years are selective arterial embolization and nephron-sparing surgical procedures (10-12). Although prophylactic treatments to prevent bleeding and interventions to treat active bleeding are effective and safe, preserving kidney function remains an important goal for new therapeutic approaches (13).

We present a rare case of AML that recurred in the nephrectomy bed after simple nephrectomy and was subsequently treated with selective arterial embolization.

## Case Presentation

A 47-year-old female patient presented to our clinic with severe left flank pain. According to her medical history, four years ago, a large AML was detected in her left kidney, and a left simple nephrectomy was performed by our team. Pathological examination after surgery revealed AML, and the tumor was completely removed with intact surgical margins. The patient was invited to routine outpatient clinic follow-ups every 6 months because of having a solitary kidney in the postoperative period. During each visit, the patient underwent physical examination, renal function tests, and complete urinalysis. In addition, the aim was to detect any pathology in the solitary kidney, such as stones, masses, or pyelonephritis, to prevent renal failure due to preventable causes through early diagnosis. In routine follow-ups, the recurrent mass was detected by ultrasound in the second year of follow-up, with its size initially measured at 4 cm. Therefore, we decided to monitor the recurrent mass at regular intervals. Because of the absence of complications during the follow-up period and the patient's lack of request for intervention, despite an increase in the size of the mass, the patient was continued to be followed up for an additional 2 years. During the final physical examination conducted in the fourth year of follow-up, before embolization, the mass was palpable in the left costovertebral area, and imaging studies revealed that it had reached a length of 13 cm. Laboratory tests showed normal serum creatinine and hemogram values, but 26 erythrocytes were found in the complete urinalysis. Multiphasic renal CT was requested for the patient. In multiphasic renal CT, the left kidney was observed in an operated appearance, and a mass of 131x99x137 mm in size, macroscopic fat and soft tissue density, with prominent vascularity and compatible with AML was observed in the left renal fossa (Figure 1).

A true-cut biopsy was performed for definitive diagnosis of this recurrent lesion, and histopathological examination revealed a tumor lesion compatible with AML, containing a rich lipomatous component and thick-walled hyalinized vascular structures. The case was evaluated as recurrent AML (Figure 2a,b).

After the patient was diagnosed, the interventional radiology department was consulted for treatment purposes, and the patient underwent selective arterial embolization (Figure 3a,b). There were no complications during or after the procedure. The patient was discharged in a healthy condition on the first postoperative day after undergoing AML embolization. For follow-up purposes, the patient was invited to the urology

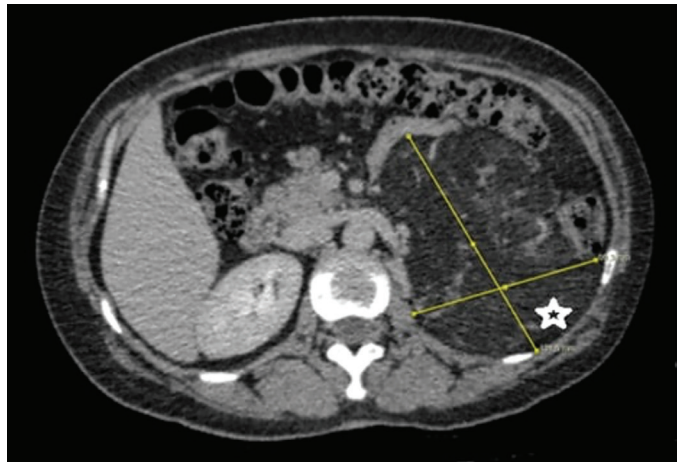

**Figure 1.** Late-phase images of multiphase renal computed tomography examination; a mass consistent with angiomyolipoma with heterogeneous density, located in the left retroperitoneal area, measuring 131x99x137 mm, well-defined, lobulated contours, and containing dense fatty content (indicated with a star)

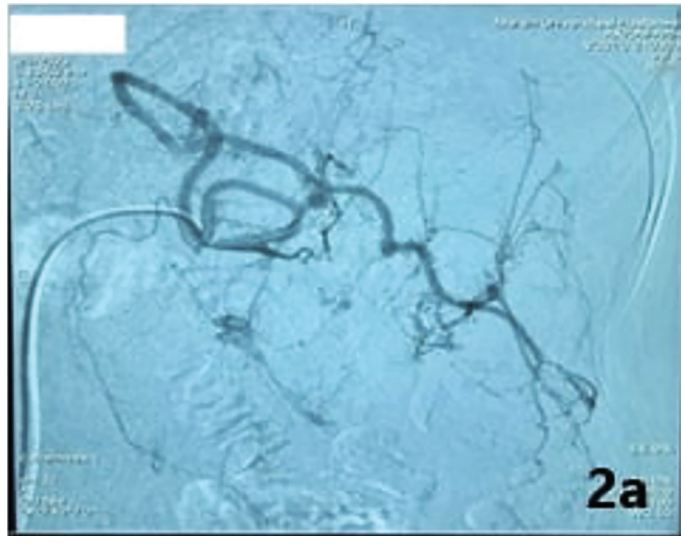


**Figure 2a**. Pre-embolization digital subtraction angiography image showing hypertrophic, tortuous, arterial structures supplying the angiomyolipoma consistent mass located in retroperitoneal localization on the left, and aneurysm formations within the mass

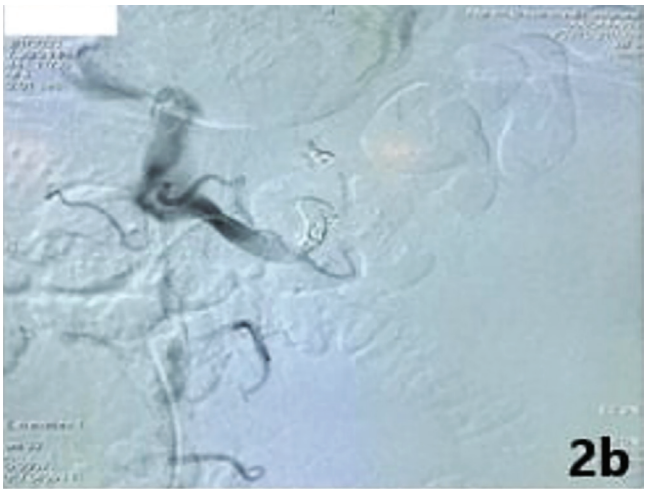


**Figure 2b**. Post-embolization angiographic examination shows complete devascularization of the mass after embolization of arterial structures supplying the mass with embolic particles and coils

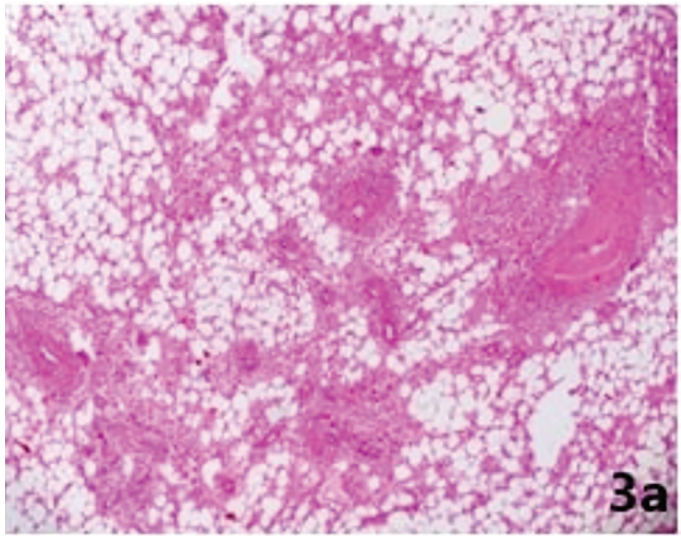


**Figure 3a**. Thick-walled vascular structures are observed in a background rich in adipocytes (H&E x40)

clinic at the 1-month and 6-month postoperative periods. At the first and sixth month follow-ups after the embolization procedure, serum creatinine levels, complete blood counts, and full urine analyses were within normal ranges. At the 6-month follow-up ultrasound imaging after the embolization procedure, it was observed that the recurrent mass had regressed to dimensions of 96x92x90 mm, and Doppler examination revealed no vascular coding within the mass. Verbal and written informed consent was obtained from the patient for the study.

## Discussion

Renal AMLs are benign mesenchymal tumors composed of blood vessels, smooth muscle cells, and adipose tissue in the kidney.

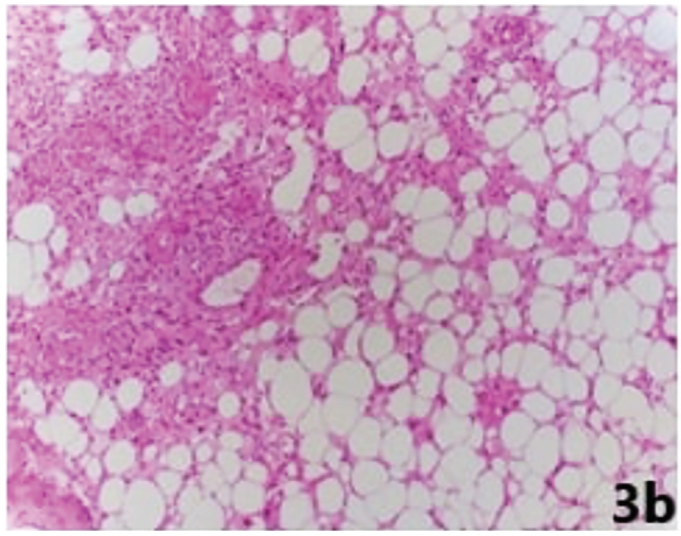


**Figure 3b**. Thick-walled vascular structures are observed in a background rich in adipocytes (H&E x100)

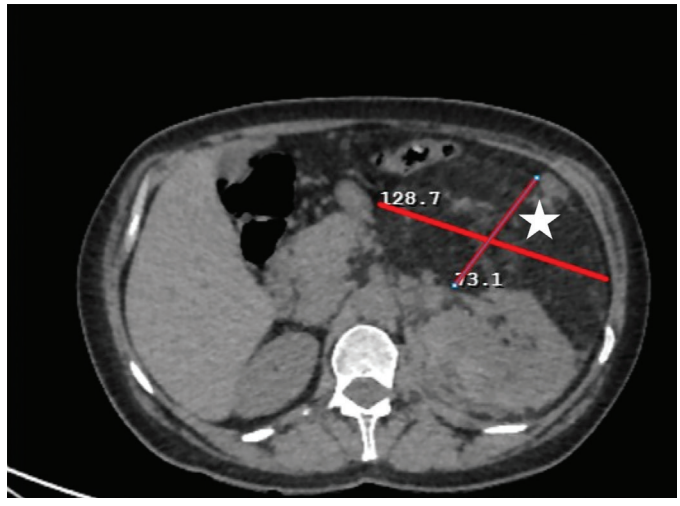


**Figure 4.** In the non-contrast abdominopelvic computed tomography examination; it demonstrates a mass consistent with angiomyolipoma, originating from the left kidney, with approximate dimensions of 15 cm in length, well-defined, lobulated contours, and containing dense fatty content (indicated with a star)

AMLs commonly exhibit renal localization, but they can rarely also present with extrarenal localization. AMLs with extrarenal localization are often incidentally found, and the retroperitoneal space is the second most common site of occurrence. Although most these extrarenal AMLs have a benign nature, excluding malignancy is challenging because of similarities in imaging techniques. Differential diagnosis includes lipoma, liposarcoma, papillary RCC, and adrenal myolipoma. Since the first case report by Friis and Hjortrup in 1982, sixty cases of extrarenal AML have been reported. Among them, only 16 have been reported as retroperitoneal extrarenal AML (RERAML) (4).

RERAMLs are usually larger than 10 cm in size and often have an asymptomatic course because of their retroperitoneal location.

However, they can manifest with non-specific symptoms such as abdominal pain, hematuria, epigastric fullness, and constipation. Imaging techniques play a crucial role in the diagnosis of RERAML, particularly in determining tumor size and localization, as well as guiding surgical planning. Additionally, they provide valuable guidance to clinicians in the follow-up of patients who have undergone nephrectomy due to AML (14).

In the follow-up and treatment selection of AML, bleeding risk should always be considered because of the unique structure of the mass. Generally, most symptomatic AMLs are relatively large, and most studies in the literature emphasize a cut-off value of 4 cm (3). In a comprehensive literature review, it was reported that 82% of patients with AMLs larger than 4 cm were symptomatic, with 9% experiencing hemorrhagic shock at admission, whereas only 23% of patients with small tumors were symptomatic (5). During the follow-up process of our case, the patient was called in for check-ups at the first and sixth months after the embolization procedure. Routine biochemical tests, complete blood count, full urinalysis, and abdominopelvic Doppler ultrasound examinations were performed during follow-up. It was observed that the mass had decreased in size and there was no vascularization.

In the treatment approach for these tumors, the most important goal is to avoid renal parenchymal damage as much as possible, especially in patients with hereditary AML or renal dysfunction, through nephron-sparing surgery or selective embolization. Preventive embolization can be applied in large asymptomatic tumors, in women of childbearing age, or in patients who may have limited access to follow-up or emergency care. Although some patients may experience post-embolization complications, selective transarterial embolization has been found to be effective in reducing tumor size in most renal AML cases with acceptable complication and recurrence rates. In our case, approximately 4 years ago, when we detected a large-sized AML in the left kidney (Figure 4), the reasons for choosing left simple nephrectomy as the treatment were as follows: At that time, our interventional radiology clinic did not have adequate physical equipment, and the tumor was quite large, significantly increasing the likelihood of spontaneous rupture.

In patients with sporadic AML, selective transarterial embolization can prevent recurrence for many years. However, patients with tuberous sclerosis and multiple AMLs continue to pose a therapeutic challenge with high recurrence rates of up to 60% for clinicians. Selective transarterial AML embolization has shown significant success in preventing recurrences and is considered safe (13). The question of whether selective transarterial AML embolization preserves normal renal parenchyma to the maximum extent compared with new percutaneous and laparoscopic ablative techniques such as cryoablation, radiofrequency ablation, and partial nephrectomy remains relevant.

In patients with acute or potentially life-threatening bleeding or those at risk of bleeding, total nephrectomy has been used as a treatment option. However, in cases such as the one presented here with recurrent AML after nephrectomy and a high risk of bleeding due to its size, selective transarterial AML embolization is a reliable treatment method that is much less invasive than surgery and can be applied with lower morbidity and mortality rates in experienced clinics to prevent recurrence and avoid the possibility of a high-risk, fatal bleeding.

Based on the literature search, in a case presentation published by Jawahar and Kazan-Tannus (14) in 2017, a recurrent mass, approximately 9 cm in size, consistent with renal AML, was identified in the nephrectomy site 8 years later. However, despite the clinical similarities with our case, a different treatment approach was chosen, which involved the administration of an mTOR inhibitor called everolimus, resulting in a minimal reduction in the size of the mass (13).

## Conclusion

There are many treatment options for AML ranging from surveillance to nephrectomy. However, there are limited studies comparing nephron-sparing surgical procedures with total nephrectomy or selective arterial embolization among treatment options. As in our study, the application of selective arterial AML embolization, which is a minimally invasive treatment method, in the presence of extrarenal retroperitoneal AML with a high risk of bleeding and recurrence is both promising in terms of outcomes and more reliable in terms of complications when used in conjunction with surgical treatments. However, in post-embolization follow-ups, there may be a reduction in tumor size or AML revascularization, unchanged or increased tumor size, or unplanned re-embolization or re-operation due to acute retroperitoneal bleeding. Therefore, patient follow-up after AML embolization is also of great importance.

### Ethics

**Informed Consent:** Verbal and written informed consent was obtained from the patient for the study.

### Authorship Contributions

Surgical and Medical Practices: H.E.D., Concept: Y.Y.K., Design: H.E.D., C.Ö., Data Collection or Processing: F.E.G.S., Analysis or Interpretation: Y.Y.K., Literature Search: A.N., F.E.G.S., Writing: A.N.

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

**Financial Disclosure:** The authors declare that they have no relevant financial.

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