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Dear Colleagues,

We are pleased to present the October 2026 issue of The New Journal of Urology (Volume 21, Issue 3). This issue features six original articles and two case reports, including spanning uro-oncology, endourology, functional urology, and the growing intersection of artificial intelligence with clinical decision-making.

Our original research stage opens with two studies centered on non-muscle invasive bladder cancer: one assessing quality of life outcomes in affected patients, and the another evaluating the prognostic value of oxidative stress markers, including ceruloplasmin, ADMA, MPO, XO, TAS, and TOS. Complementing this uro-oncologic focus, a cross-sectional methodological study examines the accuracy and adequacy of patient information generated by artificial intelligence chatbots regarding intravesical BCG therapy for bladder cancer.

In endourology, authors analyze the association between stone mucosal contact and the development of postoperative fever or systemic inflammatory response syndrome following retrograde intrarenal surgery. This current issue also features a clinical study on the relationship between postvoid residual urine volume and estimated glomerular filtration rate in men with benign prostatic obstruction, contributing to our understanding of the renal implications of lower urinary tract dysfunction.

Further extending the theme of artificial intelligence in clinical practice, a blinded audit evaluates GPT-5.2 as a guideline-decision support tool for penile squamous cell carcinoma, a rare malignancy, offering a cautionary yet informative perspective on the reliability of large language models in specialized oncologic decision-making process.

The case reports in this issue address rare and the instructive clinical presentations: a case of scrotal skin metastasis originating from lung adenocarcinoma, and a case of well differentiated liposarcoma presenting as a rare paratesticular tumor of the scrotum.

The New Journal of Urology has been indexed in the TÜBİTAK ULAKBİM TR Index since 2011. Our journal is also available across major databases, including DOAJ, Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, Scilit, Ideal Online Database, J-GATE, and EBSCO, utilizing the CrossRef DOI and ORCID systems for all publications. We are grateful to the authors for their valuable scientific contributions and to our reviewers for their thorough evaluation of these manuscripts. We invite you to read this new issue, submit your latest research to our journal, and contribute to the peerreview process.

Best regards

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CONTENTS

Original Research

Quality of Life in Patients with Non-Muscle Invasive Bladder Cancer 113–123
Jelena Ikadinović, Andrijana Ćorić, Vladimir Poznan, Mladen Popov

Prognostic Value of Oxidative Stress Markers in Bladder Cancer: A Study of Ceruloplasmin, ADMA, MPO, XO, TAS, and TOS 124–130
Murat Demir, Muhammed Fatih Keleş, Veli Duman, Halit Demir, Canan Demir, Recep Eryılmaz, Sıddık Keskin, Rahmi Aslan, Kerem Taken

Evaluation of Patient Information Provided by Artificial Intelligence Chatbots on Intravesical BCG Therapy for Bladder Cancer: A Cross-Sectional Methodological Study 131–137
Salim Zengin, Caglar Boyaci, Ahmet Olgun, Onur Kutluay, Abdullah Gul

Association Between Stone Mucosal Contact and Postoperative Fever or Systemic Inflammatory Response Syndrome After Retrograde Intrarenal Surgery 138–150
Ferhat Çoban, Bedreddin Kalyenci

Often Correct, Not Reliably Correct: A Blinded Audit of GPT-5.2 as Guideline-Decision Support for a Rare Cancer (Penile Squamous Cell Carcinoma) 151–161
Ahmet Şanlı, Serhat Göçer, Hasan Samet Güngör

Association Between Postvoid Residual Urine Volume and Estimated Glomerular Filtration Rate in Men with Benign Prostatic Obstruction 162–169
Ahmet Emin Dogan, Muhammed Yusuf Aydin

Case Report

Scrotal Skin Metastasis of Lung Adenocarcinoma: A Rare Case Report 170–174
Erdem Orman, Görkem Akça, Hakkı Uzun, Recep Bedir, Selim Yazar

Rare Paratesticular Tumor of the Scrotum: A Case of Well-Differentiated Liposarcoma 175–179
Caner Sönmez, Ahmet Turhan, Cemre Cin, Cuma Aytekin, Yasemin Yuyucu Karabulut, Mesut Tek

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RESEARCH ARTICLE

Quality of Life in Patients with Non-Muscle Invasive Bladder Cancer

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Abstract

Objective: Because non-muscle invasive bladder cancer (NMIBC) is characterized by frequent recurrence and intensive surveillance, patients may experience a substantial burden affecting their quality of life. Therefore, this study aimed to assess health-related quality of life and identify sociodemographic and clinical factors associated with quality of life in patients with NMIBC.

Methods: A cross-sectional observational study was conducted at the Urology Clinic of the University Clinical Center of Vojvodina. Health-related quality of life was assessed using the EORTC QLQ-C30 questionnaire. Sociodemographic variables (age and sex) and clinical characteristics (histopathological stage, BCG therapy, number of TUR procedures, number of cystoscopies, and follow-up duration) were analyzed to identify factors associated with quality of life.

Results: The mean general health status was 58.89/100, with the highest functioning observed in the physical and social domains, while role functioning was the lowest. The most common symptoms were fatigue, insomnia, and pain, whereas dyspnea, diarrhea, and nausea were the least reported. Women had better physical functioning than men ($p = 0.033$), while men more frequently reported insomnia ($p = 0.037$) and appetite loss ($p = 0.007$). Older patients had lower general health status and physical functioning ($p < 0.01$).

Conclusion: Patients demonstrated a moderate quality of life, with the highest scores in physical and social functioning, while the lowest scores were observed in role functioning. Older age and male sex were associated with poorer quality of life.

Keywords: quality of life, non-muscle invasive bladder cancer, urology

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INTRODUCTION

Quality of life (QoL) refers to the mental, physical, and spiritual well-being of an individual and a population, considering the positive and negative factors that affect an individual or population over a period of time. The World Health Organization (WHO) defines quality of life as an individual's perception of their position in life in the context of the culture and value system in which they live, in relation to their goals, expectations, standards, and concerns (1). Quality of life is an important aspect of medical decision-making, as it is a predictor of treatment success and has significant prognostic importance. It is also a significant predictor of survival, suggesting the need for routine assessment in clinical settings (2, 3).

In addition to the therapeutic effects of different treatment modalities, clinicians prioritize the overall quality of life of the oncology patient, regardless of the stage of the disease, the method of treatment, and the expected survival of the patient (4). Patients' quality of life is assessed using standardized questionnaires. Although the EORTC QLQ-C30 questionnaire is widely used to assess the quality of life of cancer patients, it is not tumor-specific (5).

Urothelial carcinoma is the most commonly diagnosed malignancy of the bladder in clinical and histopathological practice. On the epidemiological scale of malignant diseases of the male sex, it occupies the second place, while the first place is prostate adenocarcinoma. It is significantly more commonly diagnosed in men, which is associated with differences in exposure to carcinogens between the sexes. It occurs mainly in people over 70 years of age (6).

Given the unchanged mortality rates in recent years, the socio-medical impact of bladder cancer in the future will depend primarily on the number of newly diagnosed cases (7).

Bladder cancer is predominantly non-muscle invasive (about 75%), i.e., limited to the mucosa or submucosa (8). The most common clinical manifestation of bladder cancer is the appearance of painless hematuria. In patients with bladder tumors, dysuria problems may be present (9).

In the absence of non-invasive methods for predicting and monitoring the course of the disease, the gold standard for monitoring patients after treatment is repeated cystoscopy combined with urine cytological examination, which results in a serious financial burden and reduced adherence to the recommended follow-up regimen among patients (10). Side effects of intravesical immunotherapy and patient stress due to repeated invasive diagnostic procedures can cause negative emotions in patients. It is believed that 20–30% of cancer patients suffer from depression, sleep disorders, low self-esteem, and mental health problems, while 23% of patients in the advanced stages of the disease experience loss of consciousness and hallucinations. Ignoring these emotions can cause a range of physical and mental symptoms, which inevitably affect treatment outcomes and quality of life (11).

Despite significant progress in treatment, patients still face a high risk of recurrence of bladder cancer, which is approximately 60% over a 5-year period (12).

The impact of non-muscle-invasive bladder cancer on patients' quality of life throughout diagnosis, treatment, and surveillance remains insufficiently understood (13). Furthermore, data from the Serbian population are lacking. Therefore, this study aimed to evaluate health-related quality of life and identify sociodemographic and clinical factors associated with it in patients with NMIBC.

MATERIALS AND METHODS

The observational, analytical, cross-sectional study was conducted at the Clinic of Urology, University Clinical Center of Vojvodina, from December 1, 2024, to March 1, 2025. The research has been approved by the Ethics Committee of the University Clinical Center of Vojvodina (Ethics Approval Number: 6/00–90, Date: February 14, 2025). Patient consent to participate in the study was obtained in accordance with the Helsinki Declaration.

The study was conducted by surveying patients during regular urological check-ups in the specialist polyclinic of the University Clinical Center of Vojvodina. Patients completed the questionnaire after the examination in a separate room to ensure privacy. Socio-demographics (gender, age, place of residence) as well as clinical parameters (histopathological findings, number of cystoscopies, application of BCG

therapy, number of TUR bladder biopsies, and length of follow-up of the patient) were analyzed, which were available within the Clinical Information System of the University Clinical Center of Vojvodina.

Patients were selected using the convenience sample method, which included the inclusion of all patients who met the inclusion criteria below and gave their written consent to participate in the study.

Criteria for the inclusion of patients in the study:

- Patients with a diagnosis of non-invasive urothelial bladder cancer (stages Ta, T1, or CIS - carcinoma in situ)
- Regular check-up with a urologist within the estimated duration of the study (1.12.2024 to 1.3.2025)
- Adequate ability to read, that is, to understand the content of the questionnaire by the patient
- Giving written consent to voluntarily participate in the research

Criteria for excluding patients from the study:

- Inability of the patient to give written consent from the patient
- Refusal of the patient to participate in the study

Research Instrument

For the purposes of this study, the official Serbian version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3.0) was obtained from the EORTC Quality of Life Group and used with their permission. No bladder cancer-specific quality-of-life questionnaire was administered.

The EORTC QLQ-C30 is designed to assess the quality of life of cancer patients. Version 3.0 of the questionnaire is standard and is recommended for use in all recent surveys. The instrument consists of a total of 30 items arranged in scales, in addition to which individual questions are included to assess the severity of symptoms. It consists of 5 functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning, and social functioning), 3 symptom scales (fatigue, pain, nausea, and vomiting), general health/quality of life scales, and 6 individual questions. Scales contain different sets of questions, with each item appearing only within a single scale. The results of all scales and individual items are linearly converted to a range from 0 to 100. High scores on the global health status and functional scales indicate a high level of functionality, while low scores on the symptom scales mean a less intense experience of symptoms, which also indicates a better quality of life.

Items within the five domains are assessed on a 4-point Likert scale with the categories of not at all (1), little (2), quite a lot (3), and a lot (4). The Global Quality of Life Scale/QoL consists of two statements that are evaluated on a modified 7-point linear analogue scale (14,15).

The QLQ-C30 instrument demonstrates good reliability and validity in the assessment of health-related functional health, symptoms, and quality of life in patients with localized to advanced cancer (16).

The EORTC QLQ-C30 questionnaire requires official approval from the European Organization for Research and Treatment of Cancer. A completed form is available on the official website of EORTC, which includes all relevant information about the questionnaire, terms of use, and data protection.

Statistical Data Analysis

Statistical data processing was performed in IBM SPSS Statistics 29.0. Within descriptive statistics, absolute and relative frequencies for nominal and ordinal variables are calculated, as well as the arithmetic mean with standard deviation for continuous variables. The t-test and the $\chi 2$ test were used to calculate the differences, and the Pearson correlation was used to calculate the correlation. The p-value of < 0.05 was statistically significant.

RESULTS

Sociodemographic and Clinical Characteristics of Patients

The sample consisted of a total of 104 patients, i.e., 38 females and 66 males, aged 37 to 87 years. The mean age of all patients was 69.13 years, with a standard deviation of 9.39 years (male: 70.14, female: 67.37 years). There was no statistically significant difference in age between the sexes ($t = 1,456$, $p = 0.149$). There was no statistically significant difference in the place of residence of the patients ($\chi^2 = 2.46$, $p = 0.117$).

Table 1. Distribution of patients according to clinical parameters

Clinical Parameter	n (%)
Histopathological findings	
T0	73 (70.2)
T1	31 (29.8)
BCG therapy	
Yes	44 (42.3)
No	60 (57.7)
TUR bladder biopsy	
1	61 (58.7)
>1	43 (41.3)
Length of follow-up (years)	
<1	46 (44.2)
>1	58 (55.8)
	x̄ (SD)
Number of cystoscopies	3.52 (2.94)

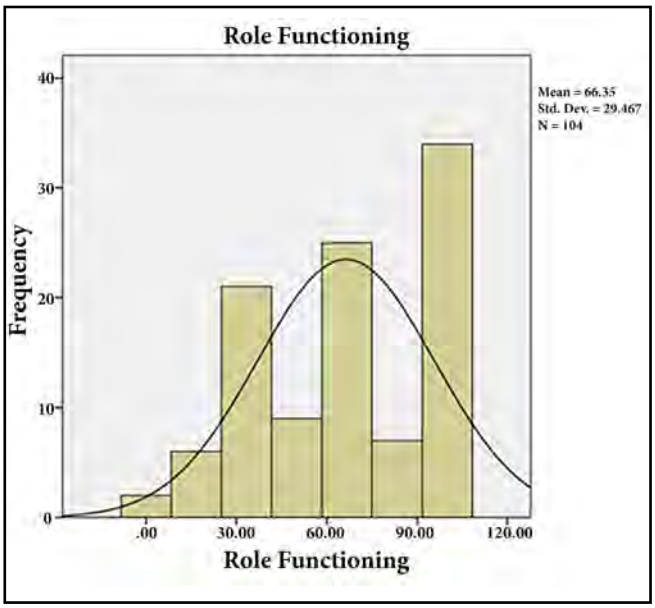

Figure 1. Distribution of the patient on the scale of functioning in life roles

Quality of Life for Patients with Non-Invasive Bladder Cancer

When it comes to the quality of life of patients with non-invasive bladder cancer, Table 2 shows the status of general health, and five scales of functioning (physical, role functioning, emotional, cognitive, and social). Analysis of the functioning scales revealed the highest levels of functioning in the physical and social domains, while role functioning demonstrated the lowest scores. This scale also showed the greatest variability among participants, with the distribution of responses suggesting the existence of several distinct response subgroups (Figure 1).

The histogram illustrates the distribution of scores for role functioning among participants (N = 104). The x-axis represents the role functioning scores, while the y-axis indicates the frequency of participants within each score range. A smooth curve representing the normal distribution is overlaid on the histogram. The mean score is 66.35 with a standard deviation of 29.47, indicating a moderate variability in role functioning across the sample.

Among the symptom scales, the highest mean scores were observed for fatigue (35.79 ± 24.08), insomnia (35.57 ± 31.25), and pain (30.44 ± 26.11), indicating that these were the most frequently reported and burdensome symptoms in the study population. Moderate symptom burden was observed for financial difficulties (21.15 ± 27.50), appetite loss (19.55 ± 26.11), and constipation (16.98 ± 29.00). In contrast, dyspnoea (8.01 ± 17.68), diarrhoea (11.85 ± 23.18), and nausea and vomiting (13.78 ± 23.27) had the lowest mean scores, suggesting that these symptoms were relatively uncommon among the participants.

The Relationship Between Sociodemographic Characteristics and the Quality of Life of Patients

Table 3 summarizes the associations between sex, age, and quality of life. Women had significantly better physical functioning than men, whereas men reported higher insomnia and appetite loss scores (all $p < 0.05$). Constipation was more pronounced in women ($p < 0.05$). Older age was associated with poorer global health status and physical functioning, as well as higher fatigue and appetite loss scores.

The Impact of Clinical Parameters on the Quality of Life of Patients

Differences between patients based on clinical parameters, such as histopathological findings, were examined by a series of t-tests for independent samples. A statistically significantly higher score on all examined scales was shown by patients with histopathological findings of Ta, compared with T1.

Significant differences were observed for all symptom scales except diarrhea and financial difficulties (Table 4).

A series of t-tests was also used to examine the differences between patients who underwent BCG therapy and those who did not in relation to their general health status, functioning, and symptoms. Detailed results are given in Table 5.

Determining the difference between patients who had one or more TUR bladder biopsies in relation to quality of life was examined by T tests for independent samples. The results presented in Table 6 show that there are no statistically significant differences between the examined groups on any dimension.

No statistically significant differences in quality of life were observed according to the duration of follow-up (all $p > 0.05$). Similarly, the number of cystoscopies was not associated with global health status or most functional and symptom scales. Weak positive correlations were found with physical functioning ($r = 0.215$, $p < 0.05$) and emotional functioning ($r = 0.205$, $p < 0.05$), whereas appetite loss was weakly negatively correlated with the number of cystoscopies ($r = -0.269$, $p < 0.05$).

Table 2. Descriptive statistics on the status of general health and the scale of functioning

	$\bar{x}$	SD	*Skewness* (SE)		*Kurtosis* (SE)	
Global Health Status/QoL	58.89	20.65096	0.140	(0.237)	-0.625	(0.469)
Functional scales						
Physical functioning	74.16	21.21	-0.682	(0.237)	-0.458	(0.469)
Role functioning	66.34	29.46	-0.303	(0.237)	-1,109	(0.469)
Emotional functioning	68.34	23.29	-0.843	(0.237)	0.750	(0.469)
Cognitive functioning	70.83	25.30	-0.604	(0.237)	-0.565	(0.469)
Social functioning	73.71	28.22	-0.825	(0.237)	-0.243	(0.469)

Table 3. Association of sex and age with quality of life in patients with non-muscle invasive bladder cancer

Scale	Men (n = 66) Mean ± SD	Women (n = 38) Mean ± SD	*p*	Age (r)
Global Health Status/QoL	57.07 ± 21.98	62.06 ± 17.93	0.237	-0.263**
Functional scales				
Physical functioning	70.80 ± 22.57	80.00 ± 17.39	0.033*	-0.287**
Role functioning	62.87 ± 29.35	72.36 ± 29.06	0.114	-0.167
Emotional functioning	65.27 ± 24.31	73.68 ± 20.64	0.076	-0.122
Cognitive functioning	68.93 ± 25.63	74.12 ± 24.71	0.317	-0.117
Social functioning	69.94 ± 30.97	80.26 ± 21.52	0.073	-0.028
Symptom scales/items				
Fatigue	38.38 ± 26.52	31.28 ± 18.60	0.149	0.198*
Nausea and vomiting	16.66 ± 26.14	8.77 ± 16.31	0.096	-0.021
Pain	31.56 ± 27.13	28.50 ± 24.47	0.568	0.155
Dyspnoea	9.09 ± 18.98	6.14 ± 15.21	0.415	0.101
Insomnia	40.40 ± 30.67	27.19 ± 30.85	0.037*	-0.012
Appetite loss	24.74 ± 28.23	10.52 ± 19.14	0.007*	0.245*
Constipation	12.12 ± 24.55	25.43 ± 34.16	0.023*	-0.123
Diarrhoea	12.62 ± 23.21	10.52 ± 23.38	0.659	-0.019
Financial difficulties	24.74 ± 29.99	14.91 ± 21.50	0.079	0.036

Notes: Data are presented as mean ± standard deviation (SD). Differences between sexes were analyzed using the independent samples t-test. Age was analyzed using Pearson's correlation coefficient (r). $p < 0.05$ was considered statistically significant. $p < 0.05$*, *$p < 0.01$.

Table 4. Differences between patients with Ta and T1 PH findings in relation to quality of life

	Histopathological findings	n	x̄	SD	t-test	p
Global Health Status/QoL	Ta	73	63.58	19.56	3,776	< 0.001*
	T1	31	47.84	19.12		
Functional scales						
Physical functioning	Ta	73	81.09	17.17	-4,549	< 0.001*
	T1	31	57.84	21.10		
Role functioning	Ta	73	73.74	26.77	-2,580	0.011
	T1	31	48.92	28.52		
Emotional functioning	Ta	73	76.02	17.67	-4,354	< 0.001*
	T1	31	50.26	25.13		
Cognitive functioning	Ta	73	78.53	19.53	-2,287	0.024*
	T1	31	52.68	28.25		
Social functioning	Ta	73	79.45	25.53	-4,163	< 0.001*
	T1	31	60.21	30.02		
Symptom scales/items						
Fatigue	Ta	73	29.37	20.56	-4,549	< 0.001*
	T1	31	50.89	25.30		
Nausea and vomiting	Ta	73	10.04	20.17	-2,580	0.011*
	T1	31	22.58	27.73		
Pain	Ta	73	23.74	22.20	-4,354	< 0.001*
	T1	31	46.23	28.12		
Dyspnoea	Ta	73	5.47	14.71	-2,287	0.024*
	T1	31	13.97	22.40		
Insomnia	Ta	73	27.85	28.87	-4,163	< 0.001*
	T1	31	53.76	29.41		
Appetite loss	Ta	73	11.87	19.53	-5,138	< 0.001*
	T1	31	37.63	30.72		
Constipation	Ta	73	11.87	23.15	-2,854	0.005*
	T1	31	29.03	37.25		
Diarrhoea	Ta	73	9.13	19.45	-1,862	0.065
	T1	31	18.27	29.61		
Financial difficulties	Ta	73	19.63	27.12	-0.863	0.390
	T1	31	24.73	28.50		

*Statistically significant difference.

Table 5. Differences between patients who received BCG therapy in relation to quality of life

	BCG therapy	n	x̄	SD	t-test	p
Global Health Status/QoL	Yes	44	61.55	22.74	1,126	0.263
	No	60	56.94	18.92		
Scale of operation						
Physical functioning	Yes	44	76.81	19.20	1,092	0.277
	No	60	72.22	22.53		

Table 5 Contuniued. Differences between patients who received BCG therapy in relation to quality of life

Role functioning	Yes	44	66.66	29.85	0.095	0.925
	No	60	66.11	29.42		
Emotional functioning	Yes	44	71.59	24.13	1,218	0.226
	No	60	65.97	22.56		
Cognitive functioning	Yes	44	73.86	24.48	1,046	0.298
	No	60	68.61	25.87		
Social functioning	Yes	44	75.00	23.97	0.395	0.694
	No	60	72.77	31.13		
Symptom scales/items						
Fatigue	Yes	44	31.81	21.10	-1,448	0.151
	No	60	38.70	25.83		
Nausea and vomiting	Yes	44	12.12	19.47	-0.621	0.536
	No	60	15.00	25.80		
Pain	Yes	44	28.78	25.25	-0.554	0.581
	No	60	31.66	26.87		
Dyspnoea	Yes	44	9.09	16.64	0.531	0.597
	No	60	7.22	18.50		
Insomnia	Yes	44	34.09	31.73	-0.414	0.680
	No	60	36.66	31.11		
Appetite loss	Yes	44	14.39	19.55	-1,742	0.085
	No	60	23.33	29.62		
Constipation	Yes	44	21.96	34.43	1,509	0.134
	No	60	13.33	23.92		
Diarrhoea	Yes	44	12.87	22.97	0.383	0.703
	No	60	11.11	23.50		
Financial difficulties	Yes	44	15.15	19.62	-1.931	0.056
	No	60	25.55	31.51		

Table 6. Differences between patients who have had one or more TUR biopsies in relation to quality of life

	TUR biopsy	**n**	**x̄**	**SD**	**t-test**	**p**
Global Health Status/QoL	1	61	59.69	20.53	0.472	0.638
	>1	43	57.75	21,001		
Functional scales						
Physical functioning	1	61	73.33	22.57	-0.475	0.636
	>1	43	75.34	19.32		
Role functioning	1	61	66.12	30.72	-0.093	0.926
	>1	43	66.66	27.93		
Emotional functioning	1	61	68.71	22.65	0.190	0.850
	>1	43	67.82	24.43		
Cognitive functioning	1	61	71.85	25.37	0.490	0.625
	>1	43	69.37	25.44		
Social functioning	1	61	76.22	27.63	1,082	0.282
	>1	43	70.15	28.99		

Table 6 Contuniued. Differences between patients who have had one or more TUR biopsies in relation to quality of life

Symptom scales/items						
Fatigue	1	61	36.79	25.62	0.504	0.615
	>1	43	34.36	21.93		
Nausea and vomiting	1	61	14.20	26.32	0.221	0.825
	>1	43	13.17	18.38		
Pain	1	61	31.96	26.57	0.705	0.483
	>1	43	28.29	25.59		
Dyspnoea	1	61	7.10	18.37	-0.622	0.535
	>1	43	9.30	16.78		
Insomnia	1	61	36.61	30.85	0.401	0.689
	>1	43	34.10	32.11		
Appetite loss	1	61	22.40	27.02	1,332	0.186
	>1	43	15.50	24.50		
Constipation	1	61	15.84	24.80	-0.476	0.635
	>1	43	18.60	34.35		
Diarrhoea	1	61	11.47	21.84	-0.200	0.842
	>1	43	12.40	25.22		
Financial difficulties	1	61	21.31	29.20	0.069	0.945
	>1	43	20.93	25.22		

DISCUSSION

The treatment of many cancers has advanced significantly in recent years, allowing patients to have better therapeutic options, primarily hormonal treatments and advanced diagnostic methods, instead of the invasive surgical procedures that were previously considered the standard. Despite these advancements, bladder cancer has not received the attention it deserves in terms of treatment options and quality of care. The treatment of bladder cancer poses significant economic challenges due to the necessity for frequent therapies and ongoing monitoring. This situation creates a considerable burden not only for healthcare systems but also for patients. These patients often strive to maintain their daily activities without interruption while preserving a high quality of life (17).

Adequate treatment choices and continuous support throughout the treatment process are imperative to improving the quality of life of patients with bladder cancer. Due to the large number of patients that the urologist treats on a daily basis, the registered nurse in the urology cabinet further clarifies and explains the diagnostic procedures to patients on a daily basis and gives useful instructions to patients who have bladder cancer, which makes their everyday life easier during the implementation of periodic urethroscopic examinations and the administration of intravesical immunotherapy BCG.

A positive relationship between the registered nurse and the patient reduces the length of hospital treatment, improves the quality of health services provided, and has a very positive effect on the satisfaction of both parties (18).

The results of Jung et al.'s study (19) showed that the average general health status of patients with non-invasive bladder muscle cancer is 73.6/100, while the results of Catto et al. (20) are slightly lower at 71/100, and our results indicate that the average general health status is 58.89/100. Despite having a mean age of 69 years, patients in our study reported a lower global health status than patients in other studies, whose mean age was similar to or even higher than that of our study population.

In the context of the influence of sociodemographic factors (gender, age) on the quality of life, Beeren et al. (21) found that women have reduced physical functioning compared

with men, as shown by a study by Jung et al. (19). The results of these studies state that women reported problems such as constipation, diarrhea, fatigue, pain, and insomnia in a higher percentage. In our research, we also found the same results. In women, postmenopausal hormonal changes are associated with various physiological alterations, including urogenital symptoms, musculoskeletal changes, cardiovascular alterations, and psychological symptoms such as mood swings. These symptoms develop more rapidly in menopausal women who have undergone some surgical intervention compared with women in whom this process takes place over a long time and completely spontaneously (22). The reason for these results is most likely due to postmenopausal changes, the effects of which are primarily associated with estrogen deficiency (vasomotor symptoms, urogenital atrophy, osteoporosis, cardiovascular disease, decreased cognitive function, and sexual dysfunction).

Regarding the histopathological findings of tumors, Jung et al. (19) showed that patients with Ta findings have the best physical and social functioning with less frequent occurrence of fatigue and dyspnea, while patients with T1 have significantly worse results in the domain of physical and social functioning, with more frequent occurrence of fatigue, dyspnea, and financial difficulties. Furthermore, patients with histopathological findings of T1 who underwent intravesical therapy with BCG reported experiencing more significant issues compared with those with the same findings who did not receive this type of therapy.

In our study, we found results that support that patients with Ta had higher scores on the general health scale, as well as the functionality scale. When it comes to the symptom scale, there were differences within all symptoms, except diarrhea and financial difficulties. On all scales, patients with T1 score higher than those with Ta. The observed difference can be explained by the more intensive use of BCG therapy in cases of more extensive invasion of the malignant neoplasm, which is typical of T1 tumors. Additionally, these patients are more likely to come for follow-up cystoscopy, which further leads to irritation of the already damaged urothelium.

Regarding the length of follow-up, Catto et al. (20) found that there was a slight difference in scores for each questionnaire used, and Jung et al. (19) found that the only association observed was in the area of sexual functioning, which improved in the period since diagnosis. In our study, we found no statistically significant differences between the length of patient follow-up and their quality of life. Given that these parameters are observed continuously, this result can be explained by the limitation in terms of the duration of the research in a 3-month period.

It is significant to mention some other limitations of this research. Because the study was a cross-sectional study, baseline quality-of-life data before treatment were unavailable. Therefore, changes in quality of life over time or treatment-related trajectories could not be assessed. Our findings should be interpreted as a snapshot of health-related quality of life during routine follow-up.

There is a possibility that some patients, when self-assessing their quality of life, were biased, less precise, upset about the examination by the urologist that preceded the completion of the questionnaire, or gave socially desirable answers to certain questions. Furthermore, no bladder cancer-specific quality-of-life questionnaire was administered. Acute medical conditions or comorbidities not included in the study may affect patients' quality of life. It is necessary to conduct more thorough research, including the impact of an individualized approach to each patient with bladder cancer, as well as other urological diseases, on the quality of life. In clinical and outpatient settings, this approach should be continuously implemented, with a focus on age and gender differences between patients.

CONCLUSION

Our research indicated that,

- Patients with non-invasive bladder cancer have a moderate level of quality of life, with the best results within the domain of physical and social functioning.
- Male patients, as well as those of older age, have a lower level of quality of life.
- Histopathological findings significantly affect the quality of life, since patients with Ta findings had better results compared with those with T1 findings. In the context of other clinical parameters (BCG therapy, the number of TUR biopsies, and the number of cystoscopies), there is no significant impact on the patient's quality of life.
- The length of follow-up is not significantly related to

the level of quality of life, although patients who are followed for a longer period of time show slightly better results in emotional and cognitive functioning.

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Author Contribution: JI and AĆ contributed to the conception and idea of the research paper and also the study design and data acquisition. AĆ, VP and MP contributed to the data analysis and interpretation. All authors contributed to the preparation of the paper and gave their approval for the version that was submitted.

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RESEARCH ARTICLE

Prognostic Value of Oxidative Stress Markers in Bladder Cancer: A Study of Ceruloplasmin, ADMA, MPO, XO, TAS, and TOS

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Abstract

Objective: This study aimed to evaluate the oxidant and antioxidant balance in patients with bladder cancer and to investigate the association between oxidative stress markers ceruloplasmin, asymmetric dimethylarginine (ADMA), myeloperoxidase (MPO), xanthine oxidase (XO), total antioxidant status (TAS), and total oxidant status (TOS) with tumor grade and invasion.

Methods: This prospective study included 49 patients with histopathologically confirmed bladder cancer and 49 age- and sex-matched healthy controls. Serum levels of ceruloplasmin, ADMA, MPO, XO, TAS, and TOS were measured using standard biochemical methods.

Results: Compared with the control group, patients with bladder cancer had significantly higher levels of ceruloplasmin, ADMA, MPO, XO, and TOS ($p = 0.001$ for all), while TAS levels were significantly lower ($p = 0.001$). As tumor stage and grade increased, ceruloplasmin, ADMA, and MPO levels significantly increased ($p < 0.05$), whereas XO, TAS, and TOS levels showed no significant differences.

Conclusion: Our findings demonstrate that oxidative stress is markedly increased, while antioxidant defense is impaired in patients with bladder cancer. The disturbed oxidant-antioxidant equilibrium is prominently associated with tumor presence. Furthermore, progressive alterations in ceruloplasmin, ADMA, and MPO may reflect tumor progression and biological aggressiveness, suggesting their potential utility as supportive indicators alongside standard clinical parameters.

Keywords: ADMA, antioxidants, bladder neoplasms, ceruloplasmin, myeloperoxidase, oxidative stress

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INTRODUCTION

It can be stated that bladder cancer is one of the most common malignancies of the urinary system, accounting for about 3–4% of all cancer cases and 2–3% of cancer-related deaths. Tobacco use, exposure to aromatic amines, chronic inflammation, prior radiotherapy, and certain analgesic or chemotherapeutic agents are major aetiological factors (1). In recent years, strong evidence has shown that oxidative stress plays a decisive role in the development, progression, and biological behaviour of bladder cancer (2).

Oxidative stress results from an imbalance between reactive oxygen species (ROS) and antioxidant defence mechanisms, favouring oxidants. Free radicals damage DNA, lipids, and proteins, triggering mutation, oncogenic transformation, and apoptosis dysfunction (3). The body's antioxidant enzymes and molecules attempt to maintain cellular integrity by neutralising these radicals. Disruption of this oxidant-antioxidant balance is considered a key biochemical mechanism in cancer development and progression (2).

Previous studies have shown decreased antioxidant parameters (e.g., superoxide dismutase, glutathione reductase, paraoxonase, arylesterase, glutathione S-transferase) and increased oxidant markers (e.g., xanthine oxidase, protein carbonyl, malondialdehyde) in bladder cancer (4). Demir et al. (2022) reported elevated protein carbonyl levels and reduced activities of arylesterase, paraoxonase-1, and glutathione reductase, especially in high-grade and invasive tumours (2). These findings indicate that increased oxidative stress and weakened antioxidant defence are closely associated with tumour development and progression.

Ceruloplasmin, asymmetric dimethylarginine (ADMA), myeloperoxidase (MPO), and xanthine oxidase (XO) are oxidative stress markers that promote cellular oxidation through distinct biochemical pathways. Ceruloplasmin is a ferroxidase with physiological antioxidant properties that rises as a positive acute phase reactant under oxidative and inflammatory conditions (5), while ADMA inhibits endothelial nitric oxide synthase (eNOS), reducing nitric oxide production and causing endothelial dysfunction and hypoxia, which facilitate tumour proliferation and invasion (6). Furthermore, MPO released from neutrophils generates reactive chlorine compounds such as hypochlorous acid via hydrogen peroxide, promoting DNA and protein damage (7). Concurrently, XO produces superoxide and hydrogen peroxide during purine metabolism, and its increased activity serves as a strong indicator of intracellular ROS accumulation and oxidative damage (8). Together with these specific markers, total antioxidant status (TAS) represents the overall redox defence capacity, while total oxidant status (TOS) reflects the systemic oxidative load (9).

Based on this information, this study aimed to evaluate ceruloplasmin, ADMA, MPO, XO, TAS, and TOS levels in bladder cancer patients and to analyse their association with tumour presence, grade, and invasion level.

MATERIALS AND METHODS

This prospective study was conducted at the Urology Clinic of Van Yüzüncü Yıl University. Eighty patients with suspected bladder tumor were initially evaluated. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Van Yüzüncü Yıl University (Decision No. 04, Date: October 8, 2025). Written informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki principles.

Inclusion and Exclusion Criteria

The inclusion criteria for the patient group were age over 18 years, histopathologically confirmed primary bladder cancer, and voluntary provision of written informed consent.

The exclusion criteria for both the patient and control groups were strictly defined to eliminate confounding factors that directly alter systemic oxidative stress markers and antioxidant capacity, which could otherwise skew the biochemical analyses. Participants were excluded if they met any of the following criteria: current active smoking (defined as smoking at least one cigarette per day during the past year); habitual alcohol or substance use; a history or current diagnosis of other systemic malignancies; chronic systemic metabolic or vascular diseases (such as diabetes mellitus and hypertension); hepatic or renal failure; and acute or chronic active infectious or inflammatory diseases. After applying these exclusion criteria, 49 patients with bladder cancer were eligible for final evaluation.

The control group comprised 49 age- and sex-matched healthy volunteers who admitted to our outpatient clinic for routine check-ups. These individuals had no history of malignant diseases or chronic systemic illnesses and met the same exclusion criteria as the patient group.

Statistical Analysis

Data distribution was evaluated using the Kolmogorov-Smirnov test. For comparisons between two independent groups (Patient vs. Control and Low-grade vs. High-grade), the Independent Student's t-test or Mann-Whitney U test was used where appropriate. For comparisons among three groups (Ta, T1, and T2 stages), 1-way ANOVA followed by Duncan's post-hoc test (or Kruskal-Wallis test for non-normal data) was applied. Pearson correlation analysis was performed to evaluate the relationships among the continuous variables. Statistical significance was set at $p < 0.05$.

RESULTS

Among the 49 bladder cancer patients and 49 controls, 35 were male, and 14 were female in each group. The mean age was 61.9 ± 7.0 years in patients and 62.6 ± 6.8 years in controls ($p = 0.61$). Ceruloplasmin, ADMA, MPO, XO, and TOS levels were significantly higher in the bladder cancer group, while TAS levels were higher in controls (all $p = 0.001$) (Table 1).

With increasing T stage, ceruloplasmin, ADMA, and MPO levels rose significantly ($p < 0.05$), whereas XO, TAS, and TOS showed no significant differences (Table 2).

Similarly, as tumour grade increased, ceruloplasmin, ADMA, and MPO levels were elevated, while XO, TAS, and TOS remained unchanged (Table 3).

DISCUSSION

This study indicates that the systemic oxidant-antioxidant balance is profoundly disrupted in bladder cancer patients, and this redox imbalance correlates closely with tumor presence, histological grade, and invasion depth. Our findings revealed that total antioxidant capacity (TAS) was significantly depleted in the bladder cancer group, whereas specific oxidative stress markers, including ceruloplasmin,

Table 1. Comparison of oxidant and antioxidant levels in the patient and control groups

		N	Mean	p
Ceruloplasmin (mg/dL)	Control	49	21.07 ± 0.04	0.001
	Patient	49	42.06 ± 0.03	
	Total	98	31.46 ± 10.54	
ADMA (µmol/L)	Control	49	2.49 ± 0.03	0.001
	Patient	49	4.59 ± 0.18	
	Total	98	3.53 ± 1.06	
MPO (ng/mL)	Control	49	126.82 ± 3.18	0.001
	Patient	49	261.53 ± 4.35	
	Total	98	193.49 ± 67.80	
XO (mU/mL)	Control	49	0.15 ± 0.22	0.001
	Patient	49	0.28 ± 0.27	
	Total	98	0.21 ± 0.07	
TAS (mmol/L)	Control	49	8.57 ± 0.11	0.001
	Patient	49	4.42 ± 0.09	
	Total	98	6.52 ± 2.08	
TOS (µmol/L)	Control	49	5.29 ± 0.07	0.001
	Patient	49	11.19 ± 0.38	
	Total	98	8.21 ± 2.97	

Table 2. Comparison of patient characteristics according to T stage

		N	Mean	p
Ceruloplasmin (mg/dL)	Ta	24	42.04 ± 0.02 b	0.001
	T1	17	42.06 ± 0.03 b	
	T2	8	42.10 ± 0.01 a	
ADMA (µmol/L)	Ta	24	4.51 ± 0.14 b	0.001
	T1	17	4.59 ± 0.18 b	
	T2	8	4.84 ± 0.05 a	
MPO (ng/mL)	Ta	24	260.02 ± 3.8 b	0.001
	T1	17	261.32 ± 4.33 b	
	T2	8	266.54 ± 1.46 a	
XO (mU/mL)	Ta	24	0.28 ± 0.26	0.759
	T1	17	0.29 ± 0.26	
	T2	8	0.28 ± 0.36	
TAS (mmol/L)	Ta	24	4.42 ± 0.10	0.623
	T1	17	4.44 ± 0.09	
	T2	8	4.41 ± 0.06	
TOS (µmol/L)	Ta	24	11.22 ± 0.40	0.751
	T1	17	11.14 ± 0.36	
	T2	8	11.23 ± 0.41	

a, b: The difference between stages with different letters is significant ($p < 0.05$)

Table 3. Comparison of patient characteristics according to grade

		N	Mean	p
Ceruloplasmin (mg/dL)	Low grade	32	42.05 ± 0.02	0.001
	High grade	17	42.08 ± 0.02	
ADMA (µmol/L)	Low grade	32	4.53 ± 0.17	0.001
	High grade	17	4.72 ± 0.16	
MPO (ng/mL)	Low grade	32	260.07 ± 4.13	0.001
	High grade	17	264.29 ± 3.38	
XO (mU/mL)	Low grade	32	0.290 ± 0.02	0.424
	High grade	17	0.28 ± 0.03	
TAS (mmol/L)	Low grade	32	4.42 ± 0.09	0.377
	High grade	17	4.44 ± 0.08	
TOS (µmol/L)	Low grade	32	11.19 ± 0.41	0.937
	High grade	17	11.20 ± 0.33	

Values are presented as Mean ± SD (Standard Deviation).

Abbreviations: ADMA, asymmetric dimethylarginine; MPO, myeloperoxidase; XO, xanthine oxidase; TAS, total antioxidant status; TOS, total oxidant status; N, number of subjects.

Units: mg/dL, milligrams per deciliter; µmol/L, micromoles per liter; ng/mL, nanograms per milliliter; mU/mL, milliunits per milliliter; mmol/L, millimoles per liter.

ADMA, MPO, XO, and total oxidant status (TOS), were prominently elevated compared to healthy controls. Notably, while XO, TOS, and TAS levels were primarily altered by the mere presence of the malignancy, advancements in tumor grade were characterized by further progressive elevations in ceruloplasmin, ADMA, and MPO levels. These results reinforce the understanding that oxidative stress is not merely a bystander effect of carcinogenesis but a driving biochemical mechanism fueling the progression and aggressive biological behavior of bladder cancer.

Our findings align with existing literature documenting a suppressed antioxidant defense system coupled with an escalated oxidative burden in bladder malignancies. For instance, Güneş et al. (4) observed heightened xanthine oxidase activity alongside a concomitant reduction in critical antioxidant enzymes such as glutathione reductase and superoxide dismutase. Similarly, Demir et al. (2) identified elevated protein carbonyl levels alongside depleted paraoxonase-1 and arylesterase activities, particularly within high-grade and invasive tumors. The systemic manifestation of these alterations in our study evidenced by high TOS and low TAS highlights a profound inadequacy in the organism's capability to neutralize reactive oxygen species (ROS) generated during tumor development. This pervasive oxidative load can be directly attributed to the complex interplay of localized hypoxia, accelerated cellular metabolism, chronic intratumoral inflammation, and active immune cell infiltration within the bladder tumor microenvironment.

The individual markers evaluated in this study represent distinct yet highly interconnected biochemical pathways that collectively reinforce this oxidative-nitrosative stress cycle. Xanthine oxidase (XO), a key enzyme in purine catabolism, serves as a primary intracellular source of superoxide anions and hydrogen peroxide, which induce genotoxic stress and DNA damage, thereby promoting oncogenic transformation (10,12). Concurrently, myeloperoxidase (MPO) released predominantly by activated neutrophils infiltrating the tumor stroma utilizes these hydrogen peroxide substrates to generate hypochlorous acid and other highly reactive chlorine derivatives (13). These MPO-derived oxidants exacerbate tissue destruction, lipid peroxidation, and genetic instability, directly facilitating basement membrane degradation and subsequent tumor invasion (14).

Crucially, the pathogenic footprint of MPO and XO is intricately linked to endothelial dysfunction and tissue hypoxia through their negative impact on nitric oxide (NO) bioavailability. This process is further compounded by the marked elevation of asymmetric dimethylarginine (ADMA) observed in our patient cohort. ADMA acts as an endogenous inhibitor of endothelial nitric oxide synthase (eNOS), effectively shutting down NO production (15). While ADMA suppresses NO synthesis, MPO actively scavenges and oxidizes the remaining available NO, leading to severe microcirculatory impairments and localized hypoxia within the tumor bed (13,14). This oxygen-deprived microenvironment serves as a potent biological stimulus for tumor proliferation, angiogenesis, and aggressive invasion, explaining why ADMA and MPO levels were significantly higher in our advanced and high-grade cases, consistent with observations in other solid tumors (16–19).

In response to this severe localized hypoxia and the overwhelming oxidative-inflammatory cascade, the organism undergoes systemic metabolic adaptations. This is reflected in the marked elevation of ceruloplasmin levels among our bladder cancer patients. Under physiological conditions, ceruloplasmin exerts antioxidant effects by oxidizing toxic free iron (Fe+2 to Fe+3), preventing harmful Fenton reactions (20). However, as a positive acute-phase reactant, its hepatic synthesis is dramatically upregulated by tumor-mediated inflammatory signaling and hypoxia. The parallel rise of ceruloplasmin with advancing tumor stage and grade indicates that it represents a systemic compensatory mechanism attempting to cushion the high oxidative load. Nevertheless, persistent copper ion accumulation associated with prolonged ceruloplasmin elevation may inadvertently transition from a protective response to a pro-oxidant stimulus, potentially fostering angiogenesis and tumor progression within the malignant niche (20,21). Taken together, the synchronized alterations of ceruloplasmin, ADMA, MPO, XO, TAS, and TOS present strong biochemical evidence of a self-sustaining cycle where inflammation, hypoxia, and redox failure converge to dictate the aggressiveness of bladder cancer.

Limitations

Despite its prospective nature and comprehensive evaluation of multiple novel oxidative biomarkers, several limitations of this study must be acknowledged. First, the sample size was

relatively modest and drawn from a single clinical center, which may restrict the immediate generalizability of the findings across broader demographic populations. Second, the single-point baseline measurement of serum biomarkers precludes the assessment of longitudinal variations; evaluating how these oxidant and antioxidant parameters fluctuate following transurethral resection (TUR-BT) or systemic chemotherapy would provide deeper insight into their dynamic monitoring utility. Lastly, because tissue-level expressions of these specific enzymes were not evaluated, the precise intra-tumoral cellular sources and local concentrations of these markers remain inferred through their systemic circulation profiles. Future large-scale, multi-center studies utilizing paired tissue and serum analyses are required to validate the definitive prognostic efficacy of these biomarkers.

CONCLUSION

In conclusion, this study suggests that the systemic oxidant-antioxidant balance is compromised in patients with bladder cancer. The alteration of specific parameters namely ceruloplasmin, ADMA, MPO, XO, and TOS, alongside decreased TAS reflects a disturbed redox equilibrium associated with the presence of the disease. Furthermore, the progressive elevation of ceruloplasmin, ADMA, and MPO in correlation with higher tumor grade and advanced invasion suggests that these biomarkers may reflect tumor biological aggressiveness and clinical progression. While further longitudinal tracking and survival data are required to establish their definitive prognostic value, these interconnected markers hold potential to serve as non-invasive, supportive indicators in the clinical evaluation of bladder cancer.

Conflict of Interest: The authors declare no conflicts of interest.

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Ethics Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Van Yüzüncü Yıl University (Decision No. 04, Date: October 8, 2025). Written informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki principles.

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RESEARCH ARTICLE

Evaluation of Patient Information Provided by Artificial Intelligence Chatbots on Intravesical BCG Therapy for Bladder Cancer: A Cross-Sectional Methodological Study

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Abstract

Objective: Artificial intelligence (AI) chatbots are increasingly used as accessible sources of medical information. However, concerns remain regarding the quality, reliability, readability, and clinical applicability of AI-generated health content. Intravesical Bacillus Calmette-Guérin (BCG) therapy is a standard adjuvant treatment for intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) and requires adequate patient understanding of treatment procedures and potential adverse effects. This study aimed to evaluate the quality, reliability, readability, and guideline adherence of information provided by commonly used AI chatbots regarding intravesical BCG therapy.

Methods: This cross-sectional methodological study evaluated responses generated by four AI chatbots (ChatGPT, Copilot, Gemini, and Perplexity) to a standardized question regarding intravesical BCG therapy. Responses were independently assessed by five urologists using validated tools including DISCERN, PEMAT-P, WRR, and the Coleman-Liau Index (CLI). Compliance with European Association of Urology (EAU) guidelines was evaluated using a 5-point Likert scale.

Results: Responses ranged from 454 to 550 words and required a university-level reading ability (CLI range: 16.02–19.35). DISCERN scores indicated moderate information quality across all chatbots, with Gemini demonstrating the numerically highest median score (51 [47–59]). PEMAT-P actionability scores were generally low (median 40%). Guideline adherence was moderate, with all chatbots receiving a median Likert score of 3.

Conclusion: AI chatbots provide moderate-quality information regarding intravesical BCG therapy but require high reading-grade levels and offer limited actionable guidance. AI-generated information may support patient education but should not replace physician counseling.

Keywords: artificial intelligence, bladder cancer, chatbots, intravesical BCG, patient education, readability

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INTRODUCTION

With the increasing use of the internet and digital technologies, patients increasingly seek health-related information through online sources. In recent years, advances in artificial intelligence (AI) have led to the development of chatbot systems based on large language models, allowing users to obtain rapid and easily accessible medical information without direct interaction with healthcare professionals. Although these systems provide fast and convenient access to medical knowledge, concerns remain regarding the accuracy, reliability, readability, and clinical applicability of the information they generate. Previous studies evaluating AI chatbots in healthcare have demonstrated that the quality of AI-generated medical information is generally moderate, and responses may contain incomplete or non-referenced information, potentially leading to misunderstandings among patients (1,2). Furthermore, readability analyses have shown that many AI-generated texts require a high level of education, which may limit their usefulness for patient education (3).

Bladder cancer is one of the most common malignancies of the urinary tract, accounting for a significant proportion of cancer-related morbidity worldwide. Approximately 70–75% of newly diagnosed bladder cancer cases are classified as non–muscle invasive bladder cancer (NMIBC), which is characterized by a high risk of recurrence and progression despite local treatment (4). The standard initial management of NMIBC consists of transurethral resection of bladder tumor (TURBT) followed by risk-adapted intravesical therapy aimed at reducing recurrence and disease progression (5). Among available intravesical treatment options, Bacillus Calmette–Guérin (BCG) immunotherapy remains the gold standard adjuvant therapy for patients with intermediate- and high-risk disease (6).

Intravesical BCG therapy involves the administration of a live attenuated strain of *Mycobacterium bovis* into the bladder, stimulating a local immune response that reduces tumor recurrence and progression rates compared with TURBT alone (6,7). Current clinical guidelines recommend induction BCG therapy followed by maintenance treatment in selected patients in order to achieve optimal oncological outcomes (5). However, intravesical BCG therapy may cause local and systemic side effects, including dysuria, urinary frequency, hematuria, fever, and rarely, systemic BCG infection (7). In addition, the prolonged treatment schedule and potential adverse effects may lead to anxiety and uncertainty among patients undergoing therapy.

Recent studies evaluating AI chatbot performance in urological diseases have demonstrated that chatbot-generated responses generally provide moderate-quality information but often exhibit high reading-grade levels and limited actionable recommendations (8–10). Moreover, variability between chatbot responses and incomplete adherence to clinical guidelines have been reported as important limitations (9,10). These findings suggest that AI chatbots may serve as supportive tools for patient education; however, their reliability in providing accurate and guideline-consistent information remains uncertain.

Intravesical BCG therapy is a complex treatment requiring adequate patient understanding of treatment schedule, expected benefits, and possible side effects. Inadequate or misleading patient information may negatively affect treatment adherence and increase treatment-related anxiety. Therefore, evaluation of the quality and reliability of AI-generated patient information regarding intravesical BCG therapy is of particular importance.

The aim of this study was to evaluate the quality, reliability, readability, and guideline adherence of information provided by commonly used AI chatbots regarding intravesical BCG therapy for bladder cancer using validated assessment tools, including DISCERN, the Patient Education Materials Assessment Tool for Printable Materials (PEMAT-P), the Web Resource Rating (WRR), and the Coleman–Liau Index (CLI), together with an assessment of compliance with European Association of Urology (EAU) guidelines. Responses were independently evaluated by five urologists in order to determine the potential role and limitations of AI chatbots in patient education.

MATERIALS AND METHODS

This study was designed as a cross-sectional methodological investigation to evaluate the quality of patient education texts generated by artificial intelligence (AI) chatbots regarding intravesical Bacillus Calmette–Guérin (BCG) therapy for bladder cancer. As the study did not involve human

participants, animal subjects, or identifiable patient data, ethics committee approval was not required. The research was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Four commonly used AI chatbots were included in the study: ChatGPT (GPT-5.3 Instant; OpenAI, USA), Copilot (GPT-5.3 Instant, Quick response; Microsoft, USA), Gemini (Gemini 3 Flash; Google DeepMind, USA/UK), and Perplexity (standard/default response setting; Perplexity AI Inc., USA). All chatbots were asked the same standardized question:

"What is intravesical BCG therapy for bladder cancer, why is it used, how is it administered, what are the possible side effects, and is it safe?"

For each chatbot, a new chat session was initiated in order to prevent previous interactions from influencing the responses. All chatbot responses were obtained on April 4, 2026, and recorded for analysis. The generated texts were included in the evaluation process without any editing or modification.

The chatbot responses were independently evaluated by five urologists. During the assessment process, widely used and validated evaluation tools for patient education materials were employed.

The quality and reliability of the information were assessed using the DISCERN instrument (11). DISCERN consists of 15 scored quality criteria and a separate overall quality rating (Question 16). Questions 1–8 evaluate the reliability of the information, whereas questions 9–15 assess the quality of treatment-related information. Each of the first 15 questions is scored from 1 to 5, yielding a cumulative score ranging from 15 to 75, with higher scores indicating better quality. Question 16 provides a separate overall quality rating based on the preceding 15 items and was not included in the cumulative DISCERN score.

The understandability and actionability of the texts were evaluated using the Patient Education Materials Assessment Tool for Printable Materials (PEMAT-P) (12). PEMAT-P consists of two subdomains, understandability and actionability, and the results are reported as percentages.

The reliability and transparency of the information were evaluated using the Web Resource Rating (WRR) scale (13). WRR is a 13-item tool developed to assess the evidence base, transparency, and usability of online health information, and scores range from 0 to 100.

The readability level of the chatbot responses was assessed using the Coleman–Liau Index (CLI) (14). This index estimates the educational level required to understand a text. A CLI score above 11 indicates that a university-level reading ability is required for comprehension.

Compliance of the chatbot responses with the European Association of Urology (EAU) guidelines was evaluated using a 5-point Likert scale. In this assessment, a score of 1 indicated serious deficiencies, whereas a score of 5 indicated minimal deficiencies. Guideline compliance was assessed with reference to the main principles of intravesical BCG therapy, including indications, method of administration, expected therapeutic role, adverse effects, safety considerations, and general treatment course.

Scoring systems and guideline compatibility were reported as median (minimum-maximum) values, whereas word count and CLI scores were reported as mean values. Given the descriptive nature of the study and the evaluation of a single response from each chatbot, no inferential statistical comparisons were performed between chatbot platforms. Therefore, all findings were summarized using descriptive statistics. Statistical analyses were conducted using IBM SPSS Statistics (Version 25, IBM Corp., Armonk, NY, USA).

RESULTS

The standardized question regarding intravesical BCG therapy for bladder cancer was directed to four different artificial intelligence chatbots, and the generated responses were evaluated by five independent urologists.

The length of chatbot responses ranged from 454 to 550 words. The longest response was generated by Gemini (550 words), whereas the shortest response was provided by Copilot (454 words). Readability analysis using the Coleman–Liau Index (CLI) demonstrated that all chatbot responses required a university-level reading ability (CLI range: 16.02–19.35).

Evaluation of information quality using the DISCERN instrument showed variability among chatbot responses. Gemini demonstrated the numerically highest median DISCERN score of 51 (47–59), indicating moderate-to-good quality information. ChatGPT and Copilot demonstrated similar performance, with DISCERN scores of 42 (29–52) and 41 (32–44), respectively. Perplexity had the lowest DISCERN score, with a median value of 31 (23–41). Overall, these findings indicate that AI chatbots provide generally moderate-quality information regarding intravesical BCG therapy.

Assessment of understandability using PEMAT-P demonstrated that Gemini demonstrated the numerically highest understandability score at 75% (71–86.6), followed by ChatGPT at 71% (69–75). Copilot demonstrated moderate understandability at 64% (62–66.6), whereas Perplexity showed the lowest score at 60% (58–66.6).

Regarding actionability, PEMAT-P scores were generally low across all chatbots. Gemini demonstrated the numerically highest actionability score at 60% (0–100), while ChatGPT, Copilot, and Perplexity each demonstrated a median actionability score of 40%, indicating limited guidance for patients regarding practical decision-making or behavioral steps related to treatment.

The Web Resource Rating (WRR) scores indicated variability in reliability and transparency of information across chatbots. Gemini demonstrated the numerically highest WRR score (44.2), followed by ChatGPT (38.2) and Copilot (28.9). Perplexity demonstrated the numerically lowest WRR score (14.3), suggesting relatively lower transparency and evidence-based support compared to other chatbot responses.

Evaluation of guideline adherence using a 5-point Likert scale demonstrated moderate compatibility with European Association of Urology (EAU) guidelines across all chatbot responses. All chatbots received a median Likert score of 3 (range: 1–3), indicating moderate consistency with guideline recommendations but also the presence of clinically relevant deficiencies.

Overall, chatbot responses demonstrated moderate-quality information, high reading-grade levels, and limited actionable recommendations. Variability between chatbot responses was observed across multiple evaluation domains.

DISCUSSION

In this study, we evaluated the quality, readability, reliability, and guideline adherence of patient information provided by commonly used artificial intelligence (AI) chatbots regarding intravesical Bacillus Calmette–Guérin (BCG) therapy for bladder cancer. The results suggested that AI chatbot responses generally provided moderate-quality information, with considerable variability among different platforms. However, the texts required high reading-grade levels, and actionable recommendations were limited. In addition, adherence to European Association of Urology (EAU) guidelines was moderate across all chatbots. These findings suggest that AI chatbots may serve as supportive tools for patient education, but their outputs should be interpreted cautiously and should not replace physician counseling.

Table 1. Comparison of the quality, readability, and guideline adherence of information provided by artificial intelligence chatbots regarding intravesical BCG therapy for bladder Cancer

	ChatGPT	Copilot	Gemini	Perplexity
Total DISCERN score, median (min–max)	42 (29–52)	41 (32–44)	51 (47–59)	31 (23–41)
PEMAT-P Understandability	71 (69–75)	64 (62–66.6)	75 (71–86.6)	60 (58–66.6)
PEMAT-P Actionability	40 (40–80)	40 (20–80)	60 (0–100)	40 (20–80)
WRR	38.2	28.9	44.2	14.3
Word Count	476	454	550	496
Coleman Liau Index	16.65	16.02	19.35	17.74
Likert score (compatibility of the treatment options offered with the EAU guidelines 1–5)	3 (1–3)	3 (1–3)	3 (1–3)	3 (1–3)

The use of AI-based chatbots in healthcare has increased rapidly in recent years. Large language models are capable of generating fast and accessible medical information, which may facilitate patient education and improve access to healthcare knowledge (1,2). Studies evaluating AI chatbot performance in medical examinations and clinical knowledge have demonstrated that these systems can produce generally accurate information; however, concerns remain regarding incomplete responses, lack of referencing, and variability in the quality of medical content (2,15). The reliability of AI-generated medical information has therefore become an important topic of investigation, particularly in specialties such as urology where treatment decisions may be complex.

Intravesical BCG immunotherapy remains the gold standard adjuvant treatment for intermediate- and high-risk non–muscle invasive bladder cancer (NMIBC) and plays a crucial role in reducing tumor recurrence and progression rates (5,16). The mechanism of BCG therapy involves stimulation of the local immune response through activation of both innate and adaptive immune pathways, resulting in anti-tumor activity within the bladder mucosa (17). Despite its established efficacy, intravesical BCG therapy is associated with local and systemic side effects such as dysuria, urinary frequency, hematuria, and fever, which may lead to treatment-related anxiety among patients (16,17). Adequate patient education is therefore essential in order to improve treatment adherence and reduce uncertainty related to potential complications.

Previous studies evaluating AI chatbot performance in urological conditions have demonstrated similar findings to those observed in the present study. Investigations assessing AI-generated information regarding urological cancers have shown that, although responses to general patient questions may be of relatively high quality, performance can be lower when addressing guideline-based clinical questions (10). Similarly, studies evaluating chatbot performance in benign urological conditions have demonstrated moderate DISCERN scores, high reading-grade levels, and low actionability scores (8,9). These findings are consistent with the results of the present study, in which DISCERN scores indicated moderate information quality, while PEMAT-P results demonstrated limited actionable guidance for patients.

One of the most important findings of the present study was the consistently high reading-grade level of chatbot-generated texts. Coleman–Liau Index scores indicated that all responses required a university-level education for comprehension. Previous studies have shown that patient education materials should ideally be written at a reading level corresponding to the 6th–8th grade in order to ensure accessibility for the general population (18). High reading-grade levels may reduce patient comprehension and negatively affect treatment adherence, particularly in complex therapies such as intravesical BCG immunotherapy.

Another important finding of this study was the limited actionability of chatbot responses. Although AI-generated texts generally provided descriptive information about BCG therapy, they often lacked clear practical guidance regarding treatment expectations, management of side effects, and indications for seeking medical attention. Previous studies have similarly reported that AI chatbot responses frequently provide general medical explanations but insufficient practical recommendations for patients (10,15). This limitation may reduce the clinical usefulness of AI-generated information in real-world patient decision-making.

Evaluation of guideline adherence demonstrated moderate compatibility with EAU recommendations across all chatbot responses. Although chatbot outputs generally included basic information regarding treatment purpose and administration, important clinical details such as patient selection criteria, maintenance therapy protocols, and contraindications were not consistently addressed. Previous studies have similarly demonstrated variability in chatbot performance and reduced quality when addressing guideline-based clinical questions (9,10). This finding highlights the importance of physician supervision when patients use AI-generated medical information.

Intravesical BCG therapy represents a relatively complex treatment requiring patient understanding of treatment schedule, expected benefits, and possible adverse effects. Insufficient or inaccurate patient information may lead to increased anxiety and reduced treatment adherence. AI chatbots may provide easily accessible preliminary information for patients prior to clinical consultation; however, variability in response quality suggests that these

systems should be considered complementary rather than primary sources of medical information.

This study has several limitations. First, AI chatbot responses may change over time as models are continuously updated. Second, the evaluation was performed using a single standardized prompt, and different question formulations may produce different responses. Third, although responses were evaluated by five independent urologists, subjective scoring systems may introduce interobserver variability. Furthermore, although understandability and actionability were assessed using validated instruments, actual patient comprehension and real-world usability of the chatbot-generated information were not directly evaluated. In addition, the study was designed as a descriptive methodological evaluation and was not intended to determine statistically significant differences between chatbot platforms. Therefore, the findings should be interpreted as descriptive observations rather than evidence of superiority of any specific chatbot. Finally, AI chatbot responses may vary depending on the language of the prompt and the specific version of the chatbot used.

CONCLUSION

To conclude, AI chatbots provide moderate-quality and generally guideline-consistent information regarding intravesical BCG therapy; however, high reading-grade levels and limited actionable guidance remain important limitations. AI-generated information may serve as a supportive educational tool for patients but should not be considered a substitute for professional medical consultation. Future studies should focus on improving readability, enhancing guideline adherence, and increasing the clinical applicability of AI-generated patient education materials.

Conflict of Interest: The authors declare that they have no competing financial or non-financial interests that could have influenced the preparation or publication of this manuscript.

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Data analysis and interpretation: SZ, AG
Drafting the manuscript: SZ, AO,OK
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RESEARCH ARTICLE

Association Between Stone Mucosal Contact and Postoperative Fever or Systemic Inflammatory Response Syndrome After Retrograde Intrarenal Surgery

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Abstract

Objective: To evaluate the association between the Mucosal Contact Index (MCI), a novel imaging-based parameter reflecting stone-mucosa interaction, and postoperative fever/SIRS after retrograde intrarenal surgery, and to compare its predictive performance with systemic inflammatory markers.

Methods: This retrospective study included 666 patients undergoing RIRS for upper urinary tract stones. Patients with preoperative infection, malignancy, or missing CT data were excluded. Mucosal Contact Index was calculated on non-contrast CT using a 2-dimensional planimetric method on the axial slice with the largest stone cross-section, defined as the ratio of mucosal contact length to total stone circumference. The primary outcome was postoperative fever/SIRS. Logistic regression analyses were performed, and predictive performance was evaluated using ROC analysis. Internal validation was conducted with bootstrap resampling.

Results: Postoperative fever/SIRS occurred in 53 patients (8.0%). MCI was significantly higher in patients who developed postoperative fever/SIRS ($p < 0.001$). In univariate analysis, age, multiple stones, stone volume, preoperative double-J stent, and MCI were associated with postoperative fever/SIRS. MCI demonstrated the highest discriminative performance, with an area under the curve (AUC)=0.811, outperforming inflammatory markers (NLR, PLR, LMR). The optimal cutoff was 0.157. In multivariable analysis, age (adjusted OR=1.06, $p < 0.001$), multiple stones (OR=3.95, $p = 0.001$), stone volume (OR=1.04 per 100 mm^3, $p = 0.029$), preoperative DJ stent (OR=2.64, $p = 0.026$), and MCI as a continuous variable (OR=1.087 per 0.01-unit increase, $p < 0.001$) remained independent predictors. The model showed good discrimination (AUC=0.874), with an optimism-corrected AUC of 0.863 on internal validation.

Conclusion: MCI is a strong and independent predictor of postoperative fever/SIRS in patients with negative preoperative urine cultures undergoing RIRS, outperforming systemic inflammatory markers. As a preoperative imaging-based parameter, it may improve risk stratification in this selected population. External validation in broader patient cohorts is warranted.

Keywords: retrograde intrarenal surgery, mucosal contact index, urolithiasis, postoperative fever, systemic inflammatory response syndrome, risk prediction

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INTRODUCTION

Retrograde intrarenal surgery (RIRS) has been widely adopted in recent years as a minimally invasive treatment modality with high success rates for upper urinary tract stones (1,2). Advances in flexible ureteroscope technology, improvements in laser systems, and the increasing use of ureteral access sheaths have enabled the safe management of larger and more complex stones (3,4). Despite these technical advancements, postoperative infectious complications remain one of the most significant causes of morbidity following RIRS (5,6). The incidence of postoperative fever, systemic inflammatory response syndrome (SIRS), and sepsis after RIRS has been reported to range between 5% and 15% in the literature. These complications prolong hospital stay, increase healthcare costs, and may rarely result in life-threatening clinical conditions (5,7,8). Therefore, accurate preoperative prediction of postoperative fever/SIRS risk is of critical importance for clinical decision making.

Previous studies have identified several risk factors, including advanced age, higher comorbidity burden, positive urine culture, larger stone volume, prolonged operative time, and the presence of a preoperative double-J (DJ) stent. In addition, certain systemic inflammatory markers derived from complete blood count have been reported to predict postoperative infectious complications (9). However, these parameters primarily reflect systemic inflammatory status and do not directly provide information regarding the local anatomical characteristics of the stone or its interaction with the urothelial mucosa.

The extent of stone contact with the urothelial mucosa may be clinically relevant in terms of local inflammation, increased intrarenal pressure, and potential bacterial biofilm formation. Stones with a larger mucosal contact surface area may theoretically cause greater mucosal irritation and facilitate bacterial translocation during surgery. Nevertheless, no standardized parameter has been defined in the literature to objectively and quantitatively assess stone–mucosa interaction.

The primary aim of this study was to evaluate the association between stone mucosal contact and the development of postoperative fever/SIRS in patients undergoing RIRS. As a secondary objective, we sought to compare the predictive performance of mucosal contact with systemic inflammatory markers and to determine its independent contribution within a multivariable model.

MATERIALS AND METHODS

Study Design and Patient Population

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for observational studies.

For this retrospective study, consecutive patients who underwent RIRS for upper urinary tract stones between January 2020 and April 2025 were screened. A total of 782 patients were assessed for eligibility. Inclusion criteria were availability of complete clinical and laboratory data, negative preoperative urinalysis and urine culture, and availability of preoperative CT imaging suitable for MCI assessment. Patients with evidence of preoperative infection, urinary tract malignancy, unavailable CT imaging for MCI assessment, or incomplete clinical or laboratory data were excluded.

Of the 782 patients screened, 116 were excluded: 27 because of evidence of preoperative infection, 34 because preoperative CT images obtained at external institutions were not accessible in a format suitable for MCI measurement, and 55 because of incomplete clinical or laboratory data. Among the 27 patients excluded because of preoperative infection, 21 had a positive preoperative urine culture and 6 additional patients had preoperative fever despite a negative urine culture; 5 of the 21 patients with a positive urine culture also had fever. No patients were excluded because of urinary tract malignancy. Consequently, 666 patients fulfilled the eligibility criteria and were included in the final analysis (Figure 1).

The primary endpoint was postoperative fever or systemic inflammatory response syndrome (SIRS), analyzed as a composite binary outcome (0 = no event, 1 = event). This endpoint was intended to capture clinically relevant postoperative inflammatory events. Microbiological confirmation was not required; therefore, fever/SIRS was not considered synonymous with microbiologically confirmed postoperative infection.

This study was approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (Decision No: 2025/10–10; Date: December 16, 2025).

Data Collection and Variables

Demographic characteristics, stone-related variables, preoperative laboratory parameters, and perioperative data were obtained from patient records.

The Mucosal Contact Index was calculated using a 2-dimensional (2D) analysis method based on non-contrast CT images. The axial slice demonstrating the largest cross-sectional area of the stone was selected. This slice was chosen because it best reflects stone morphology, allows measurement of the maximum circumference, and represents the plane where mucosal contact is most prominent. Additionally, this approach was adopted to reduce partial volume effects, improve measurement standardization, and minimize interobserver variability. For assessment of interobserver reliability, two urology residents independently evaluated the preoperative CT images of all 666 patients and calculated MCI at separate time points, without access to each other's measurements. Interobserver agreement was assessed using the intraclass correlation coefficient (ICC) based exclusively on these independent measurements. After completion of the independent assessments, discrepant measurements were jointly reviewed and resolved by consensus for use in the final analyses. Consensus measurements were not used for the calculation of the ICC.

On the selected slice, the total stone circumference (perimeter) was determined using manual planimetric measurement. The length of the stone surface directly contacting the urothelial mucosa was measured on the same section. The MCI was defined as the ratio of the mucosa-contacting length to the total stone circumference (Figure 2).

In patients with multiple stones, MCI was calculated separately for each stone, and the values were summed to obtain a patient-based total MCI. MCI measurements were independently performed by two observers for interobserver agreement analysis. Discrepant cases were subsequently reviewed jointly to obtain the final consensus measurement used in the analyses.

Stone localization was categorized based on preoperative CT findings as ureter (0), renal pelvis (1), lower calyx (2), middle calyx (3), and upper calyx (4).

Maximum stone diameter was defined as the largest measured stone dimension on preoperative non-contrast CT. Stone volume was calculated using the ellipsoid formula: volume = $(\pi/6) \times$ length $\times$ width $\times$ depth, with all dimensions measured in millimeters.

A negative urine culture obtained within 14 days before RIRS was required before surgery. If the most recent negative urine culture had been obtained more than 14 days before the scheduled procedure, urine culture was repeated, and only patients with a negative repeat culture proceeded to RIRS.

The following inflammatory indices were derived from preoperative complete blood count parameters: Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR).

Statistical Analysis

All statistical analyses were performed using Python version 3.12 (Python Software Foundation, Wilmington, DE, USA). Statistical computations and data analysis were conducted using the pandas, NumPy, SciPy, statsmodels, and scikit-learn libraries. Receiver operating characteristic analyses and bootstrap validation procedures were performed using scikit-learn–based implementations. Continuous variables were presented as mean ± standard deviation or median (interquartile range), depending on distribution. Normality was assessed using the Kolmogorov–Smirnov test. Given the relatively large sample size, the Kolmogorov–Smirnov test was preferred because the Shapiro–Wilk test may detect trivial departures from normality in large datasets. Visual inspection of distributional characteristics was also considered during data evaluation. Univariate logistic regression analysis was performed to identify factors associated with postoperative fever/SIRS. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Because the Mucosal Contact Index, when analyzed as a continuous variable, resulted in quasi-complete separation in conventional logistic regression, Firth's penalized logistic regression method was applied to obtain bias-reduced estimates. For clinical interpretability, the OR for MCI was reported per 0.01-unit increase. The relationship between maximum stone diameter and MCI was assessed using Spearman's rank correlation coefficient.

The discriminative performance of MCI and inflammatory indices was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) and corresponding 95% confidence intervals (CIs) were calculated using a bootstrap method with 1.000 resamples. Pairwise comparisons of correlated ROC curves were performed using the DeLong test, and *p*-values were calculated to assess differences in AUC values between predictors.

Optimal cutoff values were determined using the Youden index. Variables were then dichotomized according to ROC-derived optimal cutoff values, and univariate logistic regression analyses were repeated.

The final multivariable logistic regression model included age, multiple stones, stone volume, preoperative DJ stent placement, continuous MCI, and operation time. These variables were selected a priori based on their clinical relevance and potential association with postoperative fever/SIRS. Operation time was modeled per 10-minute increase to facilitate clinical interpretation. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), and calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF), with VIF <5 considered acceptable.

Internal validation of the final multivariable model was performed using a Harrell-type bootstrap optimism-correction procedure with 1.000 resamples. In each bootstrap replicate, the entire modelling strategy was repeated and model performance was evaluated in both the bootstrap and original samples. The optimism-corrected AUC and calibration slope were calculated to assess model stability and potential overfitting.

RESULTS

A total of 666 patients were included in the analysis, of whom 53 (8.0%) developed postoperative fever or SIRS. Among these 53 patients, 35 (66.0%) developed postoperative fever and 18 (34.0%) met the criteria for SIRS. Of the 18 patients with SIRS, 8 (44.4%) required admission to the intensive care unit (ICU), and one of these patients died due to urosepsis. Patients who developed postoperative fever/SIRS were older and more frequently had multiple stones, a larger stone burden, and preoperative DJ stent placement. Hospital stay was statistically longer in patients with postoperative fever/SIRS, although the absolute difference between groups was modest. In addition, MCI was significantly higher in patients who developed postoperative fever/SIRS (Table 1).

In univariate analysis, age was significantly associated with postoperative fever or SIRS (OR=1.05 per year; 95% CI: 1.03–1.07; $p < 0.001$). Multiple stones were also associated with a higher odds of postoperative fever/SIRS (OR=5.17; 95% CI: 2.83–9.47; $p < 0.001$), as were greater stone length, stone width, stone perimeter, contact length, stone surface area, and stone volume. Preoperative DJ stent placement was another significant predictor (OR=3.01; 95% CI: 1.46–6.23; $p = 0.003$). Operation time was comparable between patients without and with postoperative fever/SIRS (45 [38–55] vs. 45 [40–60] min, respectively; $p = 0.405$). In univariable logistic regression, operation time was not significantly associated with postoperative fever/SIRS (OR=1.010 per 1-minute increase; 95% CI: 0.987–1.033; $p = 0.405$). MCI remained strongly associated with postoperative fever/SIRS in univariate analysis (OR=1.07 per 0.01-unit increase; 95% CI: 1.04–1.10; $p < 0.001$) (Table 1).

Maximum stone diameter was significantly greater in patients who developed postoperative fever/SIRS than in those who did not (17 [13–19] mm vs. 11 [8–15] mm, $p < 0.001$). In univariable logistic regression, each 1-mm increase in maximum stone diameter was associated with higher odds of postoperative fever/SIRS (OR=1.223; 95% CI: 1.147–1.303; $p < 0.001$). Maximum stone diameter showed only a very weak correlation with MCI (Spearman's $\rho=0.089$, $p = 0.022$), indicating limited correlation between the two measures (Table 1).

Interobserver agreement for MCI was excellent (ICC=0.993; 95% CI: 0.988–0.997; n = 666).

When preoperative hematologic and inflammatory markers were evaluated, patients who developed postoperative fever or SIRS had significantly higher neutrophil and monocyte counts, as well as higher NLR and PLR values, whereas lymphocyte count and LMR were significantly lower.

Table 1. Comparison of demographic, clinical, and stone-related characteristics between patients with and without postoperative fever/SIRS

Variable	Group A (No fever/SIRS)	Group B (Fever/SIRS)	OR	95% CI	p value
Age (year)	42 (33–54)	60 (49–69)	1.053	1.034–1.072	<0.001
Male sex, n (%)	372 (60.7%)	31 (58.5%)	0.91	0.52–1.59	0.742
BMI (kg/m^2)	24.97 (23.51–27.41)	24.97 (24.00–27.68)	1.038	0.954–1.130	0.382
Maximum stone diameter (mm)	11 (8–15)	17 (13–19)	1.223	1.147–1.303	<0.001
Stone volume (per 100 mm^3)	900 (554–1.542)	1.524 (849–2.139)	1.10	1.06–1.14	<0.001
Hounsfield unit	857 (625–1.150)	945 (635–1.238)	1.000	0.999–1.001	0.447
Stone localization, n (%)			-	-	0.266
Ureter	21 (3.4%)	5 (9.4%)			
Pelvis	324 (52.9%)	27 (50.9%)			
Lower Pole	80 (13.1%)	5 (9.4%)			
Middle Pole	161 (26.3%)	13 (24.5%)			
Upper Pole	27 (4.4%)	2 (3.8%)			
Multiple stones, n (%)	132 (21.5%)	29 (54.7%)	5.174	2.826–9.472	<0.001
Preop hydronephrosis	2 (1–3)	2 (2–3)	1.215	0.883–1.672	0.231
Preoperative double-J stent	49 (8%)	11 (20.8%)	3.015	1.460–6.226	0.003
Access sheath use	528	46	1.058	0.462–2.420	0.894
FANS use	293	21	0.717	0.404–1.271	0.254
Intraoperative double-J stent	554	46	0.700	0.302–1.620	0.405
Hospital stay (hours)	24 (21–26)	28 (24–49)	1.030	1.019–1.041	<0.001
Operation time	45 (38–55)	45 (40–60)	1.010	0.987–1.033	0.404
Mucosal Contact Index (per 0.01)	0.11 (0.08–0.14)	0.20 (0.15–0.24)	1.069	1.044–1.096	<0.001

Statistical Notes: Continuous variables are presented as median (Q1–Q3), and categorical variables as number (n, %). Between-group comparisons were performed using the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were obtained from univariate logistic regression analyses. A 2-sided *p*-value <0.05 was considered statistically significant.

Hemoglobin, total leukocyte count, and platelet count were not significantly associated with postoperative fever/SIRS (Table 2).

ROC analysis showed that MCI had the highest discriminative performance among the evaluated inflammatory and composite markers, with an AUC of 0.811. The optimal cutoff value for MCI was 0.157, corresponding to a sensitivity of 73.6% and a specificity of 81.6%. Among the inflammatory indices, LMR demonstrated an AUC of 0.731, followed by NLR (0.717) and PLR (0.711) (Table 3). The ROC-derived cutoff value was subsequently used in secondary exploratory analyses and was not incorporated into the primary multivariable model.

As a secondary exploratory analysis, ROC-derived cutoff values were applied to evaluate the association between dichotomized inflammatory markers and postoperative fever or SIRS. All evaluated markers remained significantly associated with postoperative fever/SIRS. The strongest association was observed for MCI. Patients with MCI >0.157 had an approximately 11-fold higher risk of postoperative fever/SIRS (OR=11.21; 95% CI: 5.96–21.08; $p < 0.001$). NLR, PLR, and LMR were also significantly associated with postoperative fever/SIRS, although their discriminative performance was lower than that of MCI (Table 4). Because the cutoff value was derived and evaluated within the same cohort, these results should be interpreted as exploratory and may overestimate the true effect size.

Table 2. Preoperative Hematologic and Inflammatory Markers Associated with Postoperative Fever or SIRS

Variable	Group A (No fever/SIRS)	Group B (Fever/SIRS)	OR	95% CI	p value
Hemoglobin	14.3 (12.8–15.4)	13.6 (12.1–15.2)	0.866	0.744–1.008	0.064
Leukocyte	8.6 (7.5–9.6)	8.2 (7.3–9.2)	0.924	0.779–1.095	0.361
Neutrophil	4.5 (3.8–5.4)	4.7 (4.3–6.0)	1.224	1.013–1.479	0.036
Lymphocyte	2.57 (2.10–3.00)	2.00 (1.60–2.72)	0.358	0.220–0.583	<0.001
Monocyte	0.75 (0.68–0.82)	0.82 (0.74–0.86)	1.042	1.017–1.068	<0.001
Platelet	253 (210–301)	264 (213–315)	1.001	0.997–1.005	0.627
NLR	1.80 (1.46–2.21)	2.71 (1.61–3.41)	5,181	3,308–8,115	<0.001
PLR	102 (82–123)	128 (107–152)	1.029	1.018–1.039	<0.001
LMR	3.42 (2.76–4.20)	2.52 (2.08–3.28)	0.404	0.282–0.578	<0.001

Statistical Notes: Continuous variables are presented as median (Q1–Q3). Univariate logistic regression analysis was performed to evaluate the association between each variable and postoperative fever/SIRS. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A 2-sided *p*-value <0.05 was considered statistically significant.

Table 3. ROC Analysis of Inflammatory Markers and MCI for Predicting Postoperative Fever/SIRS

Marker	AUC	95% CI	Optimal Cut-off	Sensitivity	Specificity
NLR	0.717	0.625–0.803	2,783	0.491	0.945
PLR	0.711	0.628–0.791	122,500	0.604	0.749
LMR	0.731	0.651–0.803	2,798	0.642	0.741
MCI	0.811	0.747–0.863	0.157	0.736	0.816

In the multivariable logistic regression model, age (aOR=1.059; 95% CI: 1.037–1.081; $p < 0.001$), multiple stones (aOR=3,865; 95% CI: 1.661–8,996; $p = 0.002$), stone volume (aOR=1.038 per 100 mm^3; 95% CI: 1.004–1.074; $p = 0.030$), preoperative DJ stent placement (aOR=2,609; 95% CI: 1.108–6,146; $p = 0.028$), and MCI (aOR=1.087 per 0.01 increase; 95% CI: 1.056–1.120; $p < 0.001$) remained independently associated with postoperative fever/SIRS. Operation time was not independently associated with the outcome (aOR=1.062 per 10-minute increase; 95% CI: 0.793–1.422; $p = 0.687$) (Table 5).

The multivariable model demonstrated good discriminative ability, with an apparent AUC of 0.874. Calibration analysis showed no evidence of poor fit (Hosmer-Lemeshow $p = 0.242$). Internal validation using a Harrell-type bootstrap optimism-correction procedure yielded an optimism-corrected AUC of 0.862 and a calibration slope of 0.926, indicating limited overfitting. Overall, model performance remained stable after the inclusion of operation time as a clinically relevant perioperative covariate.

Receiver operating characteristic (ROC) curve analysis was also performed to evaluate the discriminative performance of individual predictors. Among these, MCI showed the highest discriminative ability (AUC=0.811). Pairwise comparison of ROC curves using the DeLong test demonstrated that the AUC of MCI was significantly higher than that of PLR ($p = 0.045$), whereas the differences between MCI and NLR ($p = 0.080$) and between MCI and LMR ($p = 0.074$) did not reach statistical significance (Figure 3).

DISCUSSION

In this study, we demonstrated that MCI, which quantitatively reflects the extent of stone–mucosa interaction, is a significant and independent predictor of postoperative fever/SIRS

Table 4. Univariate Analysis According to ROC-Derived Cut-off Values

Marker	Cut-off Definition	Group A (n above cutoff)	Group B (n above cutoff)	OR	95% CI	p value
NLR	>2,783	34	25	15,205	8,012–28,856	<0.001
PLR	>122,500	154	31	4,200	2,361–7,472	<0.001
LMR	≤2,798	159	34	5,110	2,833–9,215	<0.001
MCI	>0.157	113	39	11.209	5,961–21.080	<0.001

Statistical Notes: Variables were dichotomized according to optimal cutoff values derived from receiver operating characteristic (ROC) analysis. Univariate logistic regression analysis was performed to assess the association between each variable and postoperative fever/SIRS, and results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Since lymphocyte-to-monocyte ratio (LMR) is inversely associated with infection risk, values below the cutoff were considered indicative of high risk. A 2-sided p value <0.05 was considered statistically significant.

Table 5. Multivariable Logistic Regression Analysis and Model Performance

Variable	Adjusted OR	95% CI	p	VIF
Age	1.059	1.037–1.081	<0.001	1.01
Multiple stones	3.865	1.661–8.996	0.002	1.24
Stone volume (per 100 mm^3)	1.038	1.004–1.074	0.030	1.24
Preop DJ stent	2.609	1.108–6.146	0.028	1.01
MCI (per 0.01 increase)	1.087	1.056–1.120	<0.001	1.02
Operation time per 10 min	1.062	0.793–1.422	0.687	1.02

Statistical Notes: Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from the multivariable logistic regression model. MCI was analyzed as a continuous variable and reported per 0.01-unit increase. The model demonstrated good discrimination (AUC=0.874) and adequate calibration (Hosmer-Lemeshow $p = 0.242$). Internal validation yielded an optimism-corrected AUC of 0.862 and a calibration slope of 0.926. No significant multicollinearity was observed (all VIFs <1.3).

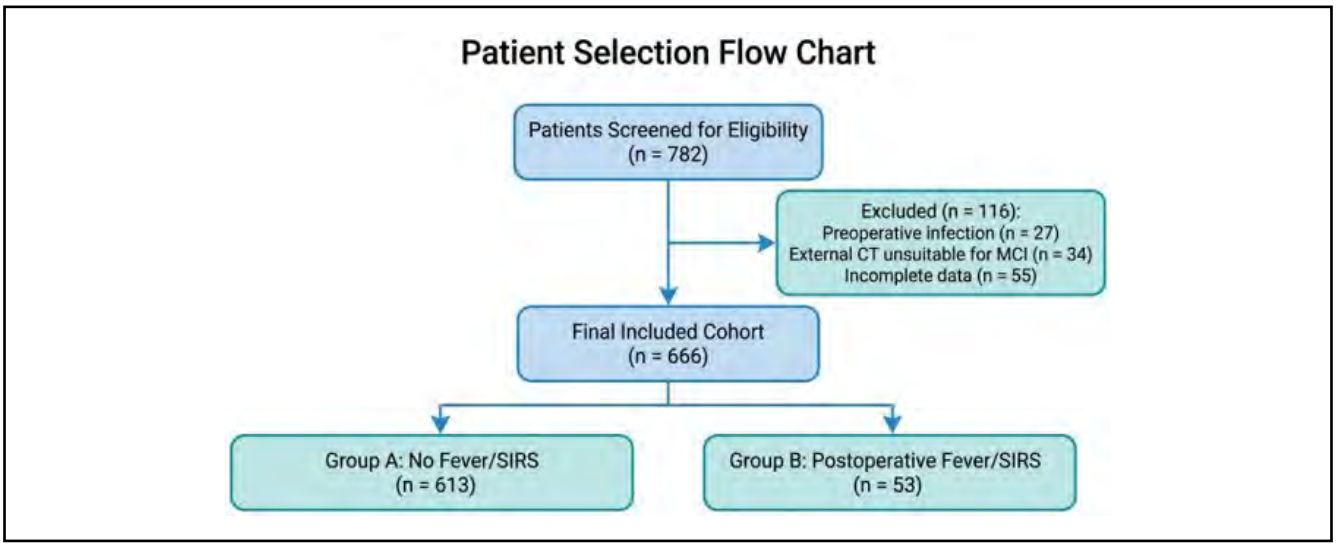

Figure 1. STROBE-compliant flowchart of patient selection and study enrollment process.

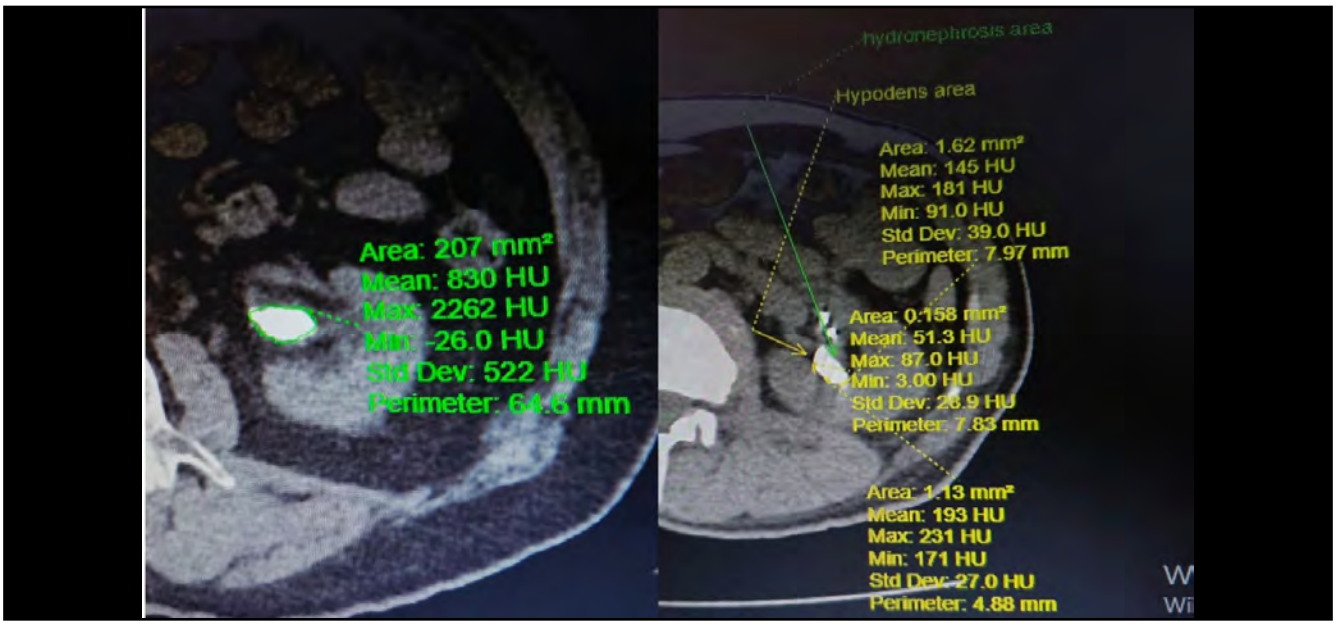

Figure 2. Measurement method of the Mucosal Contact Index.

(Panel 1) Measurement of the total stone circumference on the widest axial section using a 2D planimetric method. (Panel 2) Measurement of the segments of the stone directly contacting the renal pelvis or calyceal mucosa. Areas of hydronephrosis indicated by the green were excluded from the mucosal contact surface. Hypodense regions surrounding the stone, indicated by the yellow arrow, were considered non-contact areas and were excluded from measurement.

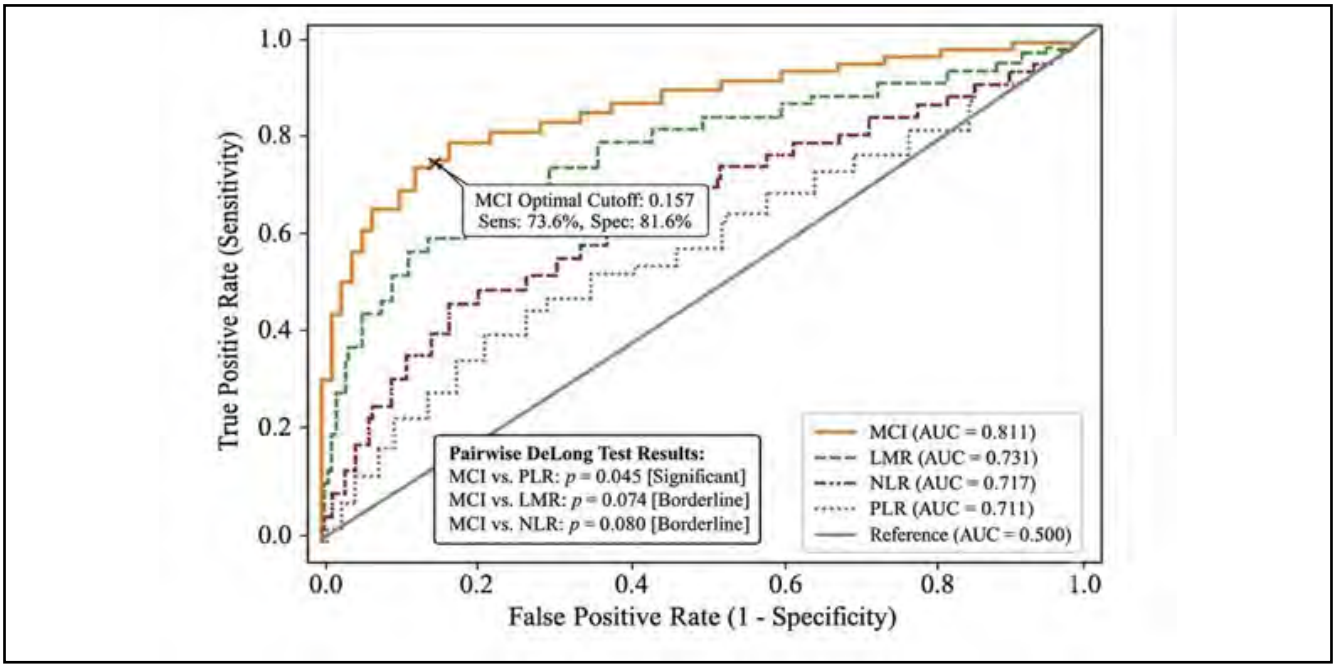

Figure 3. ROC curves of MCI and inflammatory markers for predicting postoperative fever or SIRS after RIRS. MCI demonstrated the highest discriminative performance (AUC=0.811), followed by LMR (AUC=0.731), NLR (AUC=0.717), and PLR (AUC=0.711). Pairwise comparisons of correlated ROC curves were performed using the DeLong test. The AUC of MCI was significantly higher than that of PLR ($p = 0.045$), whereas the differences between MCI and NLR ($p = 0.080$) and between MCI and LMR ($p = 0.074$) did not reach statistical significance. The optimal cutoff value for MCI was 0.157, corresponding to a sensitivity of 73.6% and a specificity of 81.6%.

following RIRS. Our findings indicate that MCI showed higher discriminative performance compared with systemic inflammatory markers and remained independently associated with postoperative fever/SIRS in multivariable analysis.

The incidence of postoperative infectious complications after RIRS has been reported to range between 5% and 15% in previous studies (5,10). In our cohort, postoperative fever/SIRS was 8.0%, which is consistent with the existing literature. Several clinical risk factors have been identified, including advanced age, larger stone burden, multiple stones, and preoperative DJ stent placement (7,11,12). In line with these findings, age, multiple stones, stone volume, and preoperative DJ stent placement were significantly associated with postoperative fever/SIRS in both univariate and multivariable analyses in our study. Preoperative DJ stent placement also remained independently associated with postoperative fever/SIRS after adjustment; however, the confidence interval approached the null value and the statistical significance was borderline. Similarly, the association observed for stone volume should be interpreted with some caution despite reaching statistical significance. Operation time was additionally evaluated as a clinically relevant perioperative covariate. However, it was not independently associated with postoperative fever/SIRS in the multivariable analysis (aOR=1.062 per 10-minute increase; 95% CI: 0.793–1.422; p = 0.687). Importantly, adjustment for operation time did not materially alter the association between MCI and postoperative fever/SIRS, with the effect estimate for MCI remaining essentially unchanged. No significant multicollinearity was observed between DJ stenting and MCI (VIF <1.3), suggesting that these variables represent distinct aspects of the underlying risk. While DJ stenting may be associated with bacterial colonization or prior obstruction, MCI appears to capture local anatomical interaction between the stone and the urothelial surface. Importantly, MCI remained independently associated with postoperative fever/SIRS when analyzed as a continuous variable, supporting a dose-response relationship between increasing mucosal contact and postoperative fever/SIRS. Although hospital stay was statistically longer in patients with postoperative fever/SIRS, the absolute difference between groups was relatively small, suggesting that this finding may reflect institutional discharge practices or early management rather than a clinically substantial prolongation of hospitalization.

Although stone burden has consistently been identified as a key determinant of postoperative fever/SIRS, our findings suggest that MCI may capture an additional anatomical dimension that is not fully reflected by conventional measures of stone size alone. While larger stones generally present a greater overall surface area, MCI specifically quantifies the extent of direct contact between the stone and the urothelial mucosa, thereby reflecting local epithelial exposure rather than absolute stone volume. In the present study, both stone volume and MCI remained independently associated with postoperative fever/SIRS in multivariable analysis, despite the inclusion of both variables in the same model. Furthermore, multicollinearity analysis demonstrated low VIF values, suggesting that substantial overlap between these parameters is unlikely. From a pathophysiological perspective, this distinction may be clinically relevant, as increased stone–mucosa contact could facilitate local inflammation, bacterial biofilm persistence, and subsequent bacterial translocation during endoscopic manipulation and periods of elevated intrarenal pressure (13,14). Therefore, MCI may provide complementary information beyond traditional stone burden metrics when assessing the risk of postoperative fever/SIRS.

The independent association between MCI and postoperative fever/SIRS suggests that local anatomical interaction between the stone and the collecting system may represent an important contributing factor to the development of postoperative fever/SIRS. While systemic inflammatory markers have been associated with infection risk in previous studies, our findings indicate that MCI may provide additional predictive information beyond these parameters. Infectious complications during RIRS are thought to be primarily related to increased intrarenal pressure, which facilitates bacterial translocation through pyelovenous and pyelolymphatic backflow (14,15). In addition, mucosal microtrauma caused by stone fragmentation and endoscopic manipulation may further promote bacterial dissemination (5,16,17). In this context, greater stone–mucosa contact may reflect not only a geometric characteristic but also a clinically relevant indicator of epithelial disruption and potential bacterial burden. The observed dose–response relationship between increasing MCI values and postoperative fever/SIRS further supports the biological plausibility of this association.

Previous studies have consistently demonstrated that systemic inflammatory markers are associated with postoperative infectious complications in endourological procedures. For instance, Sen et al. (18) reported that an elevated preoperative NLR was an independent predictor of postoperative sepsis following percutaneous nephrolithotomy. Similarly, Bai et al. (19) showed that NLR was significantly associated with the development of SIRS after flexible ureteroscopy, while Yahşi et al. (20) demonstrated that SII is a significant predictor of postoperative SIRS after ureteroscopy. However, in our cohort, although inflammatory indices such as NLR, PLR, and LMR were significantly associated with postoperative fever/SIRS in univariate analysis, their discriminative performance remained limited, and none retained independent significance in multivariable analysis. In contrast, MCI demonstrated superior discriminative performance (AUC=0.811), while the multivariable model achieved good overall discrimination with an apparent AUC of 0.874. Internal validation using Harrell-type bootstrap optimism correction yielded an optimism-corrected AUC of 0.862 and a calibration slope of 0.926, supporting the stability of the model and suggesting only modest overfitting. Pairwise ROC comparison further showed that the discriminative ability of MCI was significantly higher than that of PLR, whereas the differences between MCI and NLR and between MCI and LMR did not reach statistical significance.

Several mechanisms may potentially explain the observed association between MCI and postoperative fever/SIRS:

- increased mucosal surface contact may amplify local inflammatory response;
- larger contact areas may be associated with higher bacterial colonization and biofilm formation;
- irrigation under elevated intrarenal pressure may facilitate bacterial translocation in cases with extensive mucosal exposure
- greater contact may indicate a more complex stone configuration, requiring prolonged manipulation and increasing the likelihood of mucosal injury.

It should be noted that MCI is derived from preoperative imaging and reflects a static anatomical relationship between the stone and the urothelial surface. Intraoperative factors such as stone relocation, repositioning, and fragment migration may alter this relationship during the procedure. However, the primary objective of MCI is to provide a preoperative risk assessment based on baseline anatomical characteristics. Therefore, while intraoperative dynamics may influence infection risk, MCI is intended to capture the initial stone–mucosa interaction present before surgery. This baseline anatomical relationship may be relevant to the risk of postoperative fever/SIRS by reflecting the extent of mucosal exposure and the potential for local inflammatory and bacterial processes.

From a clinical perspective, increasing MCI values were associated with progressively higher risk of postoperative fever/SIRS. Therefore, MCI may help identify patients who could benefit from closer postoperative monitoring and more individualized perioperative management. Although a cutoff value of 0.157 demonstrated good discriminatory performance in this cohort, it was derived and evaluated within the same dataset and should therefore be considered exploratory until externally validated. The potential impact of MCI-guided management strategies on clinical outcomes requires further investigation in prospective studies.

Previous predictive models for infectious complications after RIRS have incorporated clinical variables such as operative time, stone burden, and comorbidities (21–23). However, to our knowledge, no prior study has introduced a quantitative parameter directly reflecting stone–mucosa interaction. In this regard, MCI represents a novel, anatomically grounded metric that can be objectively derived from preoperative CT imaging. The strong association between MCI and postoperative fever/SIRS, together with its superior discriminative performance compared with conventional inflammatory markers, highlights the potential clinical relevance of local anatomical factors in postoperative risk assessment. Furthermore, interobserver agreement for MCI measurements was excellent (ICC=0.993; 95% CI: 0.988–0.997), supporting the reproducibility of the measurement approach. Nevertheless, because the measurements were performed within the context of a single study cohort, further validation in independent external cohorts and by independent observers is warranted before widespread clinical implementation.

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings and introduce potential selection bias. Second, MCI was calculated using 2-dimensional measurements on axial CT images rather than 3-dimensional volumetric analysis, which may not fully capture the spatial complexity of stone-mucosa interaction. Third, microbiological data such as stone cultures or renal pelvic urine cultures were not available. Although all patients had negative preoperative bladder urine cultures, it is well established that these do not exclude bacterial colonization within the collecting system or stone matrix. Therefore, the absence of microbiological confirmation limits our ability to determine whether individual postoperative fever/SIRS events were truly infectious in origin.

Additionally, the duration of preoperative DJ stenting was not available and could not be analyzed, which may represent an unmeasured confounder. Certain intraoperative parameters, including irrigation pressure and intrarenal pressure control, were also not recorded and therefore could not be incorporated into the model, despite their known association with infectious complications. Furthermore, intraoperative factors such as stone relocation, repositioning, and fragment migration were not evaluated and may influence the dynamic interaction between the stone and the urothelium. Although external validation was not performed, internal validation using a Harrell-type bootstrap optimism-correction procedure yielded an optimism-corrected AUC of 0.862 and a calibration slope of 0.926, suggesting acceptable model stability and only modest overfitting. In addition, the optimal MCI cutoff value was derived and evaluated within the same cohort. Therefore, the performance of the dichotomized MCI should be interpreted with caution, as data-driven threshold selection may lead to optimistic estimates of discrimination and effect size. Consequently, the cutoff-based analyses should be considered exploratory until externally validated. Future prospective multicenter studies incorporating 3-dimensional imaging, standardized microbiological assessment, independent reproducibility analyses, and external validation are warranted to further refine and validate the clinical applicability of MCI.

CONCLUSION

In conclusion, the occurrence of postoperative fever/SIRS after RIRS appears to be associated not only with established clinical factors such as age, stone burden, and preoperative DJ stent placement, but also with local anatomical stone–mucosa interaction. MCI remained independently associated with postoperative fever/SIRS when analyzed as a continuous variable and demonstrated superior discriminative performance compared with conventional inflammatory markers. Internal validation supported the stability of the proposed model, although external validation remains necessary. Therefore, MCI may represent a useful imaging-based parameter for preoperative risk stratification for postoperative fever/SIRS in patients with negative preoperative urine cultures undergoing RIRS. However, further prospective multicenter studies and external validation in broader patient populations are required before routine clinical implementation.

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Competing Interests: The authors declare that they have no competing interests.

Ethics Approval: This study was approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (Decision No: 2025/10–10; Date: December 16, 2025). The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective design, informed consent was waived by the ethics committee.

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

FÇ, BK: Study conception and design, data analysis, manuscript drafting.
FÇ, BK: Data collection and interpretation.
FÇ, BK: Critical revision and supervision.
All authors read and approved the final manuscript.

Author's Statement Regarding the Use of AI-Assisted Tools: During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely to assist with language editing and translation to improve the clarity and readability of the text. No AI tool was used to generate scientific content, analyze

or interpret data, or formulate the study conclusions. The authors reviewed and edited the output as necessary, verified all content, and accept full responsibility for the accuracy and integrity of the manuscript.

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RESEARCH ARTICLE

Often Correct, Not Reliably Correct: A Blinded Audit of GPT-5.2 as Guideline-Decision Support for a Rare Cancer (Penile Squamous Cell Carcinoma)

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Abstract

Objective: Large language models (LLMs) are increasingly used as guideline-decision support in oncology, but most validation has occurred in common cancers, where clinicians can usually recognize errors. The safety-critical setting is the opposite — rare cancers, where local expertise is limited, and errors may go unrecognized. Whether common-cancer concordance reflects the reliability needed there is unclear.

Methods: We benchmarked GPT-5.2 against the EAU-ASCO 2025 Penile Cancer Guidelines using 100 guideline-derived questions across five domains and three zero-shot prompting strategies, yielding 300 responses. Two experienced urologists, blinded to prompt identity, scored concordance on a 3-point scale and classified errors as hallucination, omission, temporal, or reasoning. The primary analysis was a mixed-effects ordinal logistic regression with question as a random intercept; a cluster-robust logistic regression served as sensitivity. Reporting followed TRIPOD-LLM.

Results: GPT-5.2 was fully concordant in 236 of 300 responses (78.7%; 95% confidence interval, 73.7–82.9; weighted κ=0.914). Prompt strategy did not improve performance (role-play +3 percentage points; 95% credible interval, −2 to +9). The domain effect was not robust once between-question clustering was modeled. Among 64 non-concordant responses, omission predominated (47.7%) and reasoning errors followed (37.5%); in treatment, omission accounted for 68.0% of errors, including loss of guideline-specified detail. Four questions were uniformly discordant across all three prompts.

Conclusion: Headline concordance overstated clinical reliability. The clinically informative finding was not the overall accuracy but the structure of failure — omission of decision-critical treatment detail and stable errors. Prompt engineering did not rescue performance. Current LLM output may assist orientation in rare-cancer decision pathways but is not ready as stand-alone guideline-decision support.

Keywords: artificial intelligence, natural language processing, penile neoplasms, practice guidelines as topic, clinical decision-making, reproducibility of results

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INTRODUCTION

Large language models (LLMs) are increasingly used as guideline-decision support, often outside the conditions in which they were benchmarked (1). In oncology, that benchmarking has concentrated on common cancers, where the clinicians most likely to query a model are also the most likely to recognize an error (2). The deployment setting that matters most for safety is the opposite. An uncommon diagnosis, managed by clinicians with limited disease-specific experience, is precisely where decision support is most clinically valuable and where its errors are most likely to go unrecognized. Whether the concordance rates reported in common-cancer benchmarks generalize to that setting — and whether they reflect the form of reliability needed there — is unclear.

Penile squamous cell carcinoma presents a different problem. It is rare, with a global incidence of 0.80 per 100,000 males and fewer than 3,100 new cases annually across the European Union (3–5). Many urologists encounter it infrequently, particularly outside referral centers. In this setting, adherence to guideline-based management is especially important and has been associated with better outcomes (6). The same setting also creates the conditions in which a clinician may be tempted to seek rapid support from an LLM (7–8).

Previous LLM benchmarking studies in oncology, including evaluations of urological cancers, have reported concordance estimates generally ranging from 77% to 89% (9–11). A recent meta-analysis across 15 cancer types reported a pooled accuracy of 76.2% (12). Penile cancer was absent from those evaluations. As a result, it remains unclear whether performance observed in common cancers generalizes to a rare malignancy in which LLM performance may be less predictable and clinically important errors may carry greater consequences (13).

We therefore evaluated GPT-5.2 against the European Association of Urology-American Society of Clinical Oncology (EAU-ASCO) 2025 Penile Cancer Guidelines (14) using 100 guideline-derived clinical questions, three prompting strategies, and blinded expert review. In addition to concordance, we examined error structure, cross-prompt consistency, and question-level heterogeneity to assess not only whether the model was right, but also where it failed and how stable those failures were. The study was designed and reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis-Large Language Model (TRIPOD-LLM) statement (15) (Supplementary Table S1).

MATERIALS AND METHODS

Study Design and Benchmark Construction

We conducted a cross-sectional benchmarking study of GPT-5.2 (OpenAI, San Francisco, CA, USA) against the EAU-ASCO 2025 Penile Cancer Guidelines (14). The benchmark consisted of 100 clinical questions derived from the full guideline text. Questions were developed by a urologist with experience in urological oncology (A.Ş.) and were restricted to statements with objectively verifiable answers. Gold-standard responses were extracted directly from the guideline and verified by section and page number. The EAU-ASCO 2025 Penile Cancer Guidelines used as the reference standard is a reprint of the 2023 edition; potential overlap with the model's training data was not corrected for and is addressed in the Limitations.

To ensure broad clinical coverage, the number of questions per domain was allocated according to the size of the corresponding guideline section: epidemiology (n = 15), tumor, node, metastasis (TNM) classification (n = 20), diagnosis (n = 20), treatment (n = 30), and follow-up (n = 15). Questions were balanced by type, with 50 definition/classification items and 50 action-oriented items. They were also categorized by recommendation strength: 37 strong, 14 weak, and 49 not graded. Two independent urologists reviewed all questions and gold-standard responses for fidelity to the source guideline and for clinical relevance. Discrepancies were resolved by consensus. Question clarity was pilot tested before formal evaluation. The complete question set with gold-standard answers is provided in Supplementary Table S2.

Prompting Strategy and Testing Conditions

Each question was submitted to GPT-5.2 under three zero-shot prompting strategies: baseline, role-play, and chain-of-thought (Supplementary Figure S1). The baseline condition presented the question without modification. The role-play condition instructed the model to respond as a senior urologic oncologist and EAU guideline panel member. The

chain-of-thought condition instructed the model to analyze the scenario step by step (1,16). Full prompt texts are provided in Supplementary Table S3.

All 300 queries were submitted through the ChatGPT web interface between February 9, 2026, and February 19, 2026. Testing was performed under controlled conditions. A new account was used, memory was disabled, web search was turned off, no system-level or developer-level instructions were applied, and each question was submitted in a separate chat (Supplementary Figure S1). Because the web interface does not permit direct control of generation settings, default model parameters were used throughout. All 300 raw LLM responses with corresponding reviewer scores are available in Supplementary Table S4.

Blinded Evaluation Framework

Responses were assessed using a 3-tier framework (Supplementary Table S5). Tier 1 captured guideline concordance on a 3-point scale: concordant (2), partially concordant (1), or discordant (0). Tier 2 classified non-concordant responses into predefined error categories: hallucination, omission, temporal error, and reasoning error (17,18). Tier 3 assessed cross-prompt consistency.

Two experienced urologists independently scored all 300 responses. Responses were randomized separately for each reviewer, and prompt identity was masked. A 15-question calibration set was scored jointly by both reviewers to harmonize scoring criteria and resolve interpretive differences. The remaining 85 questions were scored independently. Consensus scores were obtained by rounding the mean of the two reviewers. Both reviewers independently classified error types for all responses with a consensus concordance score of 0 or 1.

Statistical Analysis

Inter-rater agreement for concordance scores was summarized with quadratic weighted Cohen's kappa (19). A 95% confidence interval was obtained by bootstrapping over questions. Each question produced three correlated responses. Concordance score (0,1,2) was therefore modeled with a mixed-effects ordinal (proportional-odds) logistic regression, with domain and prompt strategy as fixed effects and question as a random intercept. Most questions were scored identically across the three prompts. This near-uniformity produced extreme between-question separation, and maximum-likelihood estimation of the random-intercept variance became unstable at the boundary. We therefore fitted a Bayesian hierarchical ordinal model with weakly-informative priors and designated it the primary analysis. That designation was made after the data were seen. Priors were Normal (0, 2.5) for the fixed effects and half-Normal (2.5) for the random-intercept standard deviation. The model was fitted by Hamiltonian Monte Carlo with four chains and 2000 post-warmup draws each. Convergence was confirmed by R-hat and effective sample size.

Fixed effects were summarized as posterior odds ratios with 95% credible intervals. The overall contributions of domain and prompt were assessed by leave-one-out cross-validation and by likelihood-ratio tests. Both remain better calibrated than Wald tests under separation. The intraclass correlation was computed on the latent scale as $\sigma^2/(\sigma^2+\pi^2/3)$. The random-intercept variance is weakly identified under separation. We therefore examined the sensitivity of every reported quantity to the prior across five specifications (Supplementary Table S6). The proportional-odds assumption was examined by comparing coefficients across the two cumulative cut-points. Maximum-likelihood estimation of the same model, with Wald tests, was retained as a sensitivity analysis. For the binary contrast of full concordance versus not, domain odds ratios were estimated with Firth penalization, because the reference domain sat near the ceiling.

For the prompt comparison, we report the difference in full-concordance probability in percentage points, with its credible interval. We also state the improvement the data can and cannot exclude. The study was not sized to establish equivalence, and none is claimed. Supportive analyses included descriptive concordance rates with Wilson intervals, the Friedman test across prompts, the Kruskal-Wallis test across domains with Bonferroni-corrected pairwise Mann-Whitney U tests, and Spearman correlation between concordance and consistency. Because most questions were scored identically across prompts, the Friedman ranks were heavily tied, and the comparison rests on the questions that varied. Agreement on error type was summarized with Cohen's kappa, a prevalence-adjusted kappa, and category-specific agreement with bootstrap intervals. All tests were 2-sided. Analyses used

Python (SciPy, scikit-learn, statsmodels) and PyMC with ArviZ. The analysis code is available from the corresponding author on reasonable request.

No ethical approval was required because the study did not involve human participants, patient-level identifiers, or animal subjects.

RESULTS

Agreement between the two blinded reviewers was excellent. The quadratic weighted kappa for concordance scoring was 0.914 (95% CI, 0.835 to 0.967), with 94.0% exact agreement across 300 responses and no 2-point disagreements (Table 1).

Of the 300 responses, 236 (78.7%; 95% confidence interval [CI], 73.7% to 82.9%) were fully concordant with the guideline, 41 (13.7%) were partially concordant, and 23 (7.7%) were discordant (Table 1; Supplementary Table S7). Thus, roughly four of five outputs aligned fully with guideline recommendations, whereas about one in thirteen contradicted them.

The prompt strategy did not materially change performance. Full concordance was 77% with baseline prompting, 80% with role-play, and 79% with chain-of-thought. In the primary Bayesian model, the role-play and chain-of-thought odds ratios both had 95% credible intervals that included 1, and cross-validation did not favor a model with prompt. The result was unchanged in supportive analyses, including the Friedman test (χ^2=1.23, p = 0.54) and the binary cluster-robust sensitivity model (Wald χ^2=0.99, p = 0.61) (Figure 1B).

Concordance varied across domains at the descriptive level. Follow-up had the highest full concordance rate at 93.3%, whereas epidemiology had the lowest at 71.1% and also the highest discordance rate at 20.0%. This variation did not survive the structure of the data. Eighty-one of the 100 questions were scored identically across all three prompts. Most of the variance therefore lay between questions, not between domains or prompts. The intraclass correlation was high (0.87; 95% credible interval, 0.78 to 0.93). The random-intercept standard deviation was large and weakly identified (posterior median ≈4.7 on the logit scale; prior-sensitive, Supplementary Table S6). In the primary Bayesian model, every domain odds ratio had a 95% credible interval that included 1. The overall domain effect was not significant by likelihood-ratio test (χ^2=9.19, df=4, p = 0.06), and cross-validation did not distinguish the model with domain from the model without it. Domain is a between-question characteristic, and only 19 questions varied across prompts. The study had limited power to resolve a domain effect (Table 2, Panel A; Figure 1A; Supplementary Table S8; Supplementary Figure S2).

The response-level analyses pointed the other way. The Kruskal-Wallis test was nominally significant (H=13.95, df=4, p = 0.007), and a Firth-penalized logistic model placed the odds of full concordance below follow-up for epidemiology, diagnosis, and treatment (Table 2, Panel B). That model treats the 300 responses as independent. It ignores the three responses clustered within each question, and it overstates the precision of a between-question contrast. Once the clustering was restored, the domain effect did not survive. The domain gradient is suggestive, not established.

Table 1. Overall guideline concordance and inter-rater reliability by prompt strategy

	n	Concordant (score 2)	Partial (score 1)	Discordant (score 0)	Mean score	κw (95% CI)	% Agreement
Prompt A (Baseline)	100	77 (77.0%)	14 (14.0%)	9 (9.0%)	1.68	0.909 (0.823–0.967)	93.0%
Prompt B (Role-play)	100	80 (80.0%)	13 (13.0%)	7 (7.0%)	1.73	0.907 (0.812–0.972)	94.0%
Prompt C (Chain-of-thought)	100	79 (79.0%)	14 (14.0%)	7 (7.0%)	1.72	0.926 (0.836–0.984)	95.0%
Overall	300	236 (78.7%)	41 (13.7%)	23 (7.7%)	1.71	0.914 (0.835–0.967)	94.0%

Concordance scores represent consensus between two blinded reviewers. κw = quadratic weighted Cohen's kappa. Friedman test: χ^2=1.23, p = 0.54 (no significant difference between prompt strategies).

Weighted-kappa 95% confidence intervals were obtained by bootstrapping over questions. Friedman test df=2; because most questions were scored identically across prompts, the ranks were heavily tied.

Question type was not associated with concordance. Action-oriented questions did not perform differently from definition/classification items in either the descriptive comparison (Mann-Whitney p = 0.41) or the cluster-robust model (OR=1.24; 95% CI, 0.52–2.97; p = 0.62). The recommendation strength also did not explain model performance. Strong recommendations had a lower mean concordance than weak recommendations (1.61 versus 1.82), but the difference was not statistically significant in either the descriptive analysis (p = 0.20) or the cluster-robust model (OR for weak versus strong, 2.19; 95% CI, 0.50–9.52; p = 0.30; Supplementary Table S9).

Among the 64 consensus non-concordant responses, omission and reasoning failures predominated. Both reviewers identified similar error distributions. Reviewer 1 classified 46.9% as omission, 37.5% as reasoning errors, and 15.6% as hallucinations. Reviewer 2 classified 48.4% as omission, 37.5% as reasoning errors, and 14.1% as hallucinations. Averaging across reviewers, omission accounted for 47.7% of all errors, reasoning for 37.5%, and hallucination for 14.8% (Table 3; Figure 2A).

Agreement on error type was substantial overall (Cohen's kappa=0.795; prevalence-adjusted kappa=0.81), but it varied by category. It was least reliable for hallucination (category-specific kappa=0.57; 95% CI, 0.24 to 0.84). Agreement was lowest in follow-up. There, the three non-concordant responses came from one question, which one reviewer scored as omission and the other as hallucination. That single cell should not be read as a stable estimate.

Table 2. Primary and sensitivity regression analyses for guideline concordance

Panel A. Mixed-effects ordinal logistic regression*					
Fixed effect	χ^2 (LRT)	**df**	***p*-value**		
Domain (overall)	9.19	4	0.06		
Prompt strategy (overall)	1.60	2	0.45		
Random-intercept SD (σ), posterior median (95% CrI)	4.7 (3.4–6.6)				
Intraclass correlation (95% CrI)	0.87 (0.78–0.93)				
Panel B. Binary cluster-robust logistic regression (sensitivity analysis)†					
Variable	**Full concordance (%)**	**OR**	**95% CI**	***p*-value**	**Wald test‡**
Domain					χ^2=4.84, p = 0.30
Follow-up (ref.)	93.3	1.00	—	—	
Epidemiology	71.1	0.20	0.05–0.64	—	
TNM	88.3	0.59	0.14–2.11	—	
Diagnosis	73.3	0.22	0.06–0.69	—	
Treatment	72.2	0.21	0.05–0.62	—	
Prompt strategy					χ^2=0.99, p = 0.61
Baseline (ref.)	77.0	1.00	—	—	
Role-play	80.0	1.19	0.84–1.70	0.32	
Chain-of-thought	79.0	1.12	0.75–1.67	0.57	

*Mixed-effects ordinal logistic regression (proportional odds) with concordance score (0,1,2) as outcome, domain and prompt as fixed effects, question ID as random intercept. In the primary analysis the model was fitted by Bayesian estimation with weakly-informative priors; a maximum-likelihood fit with adaptive Gauss-Hermite quadrature (25 nodes) served as a sensitivity analysis. Individual domain odds ratios are not reported because the large, weakly-identified random-intercept variance renders conditional odds ratios unstable. Overall effects are assessed by likelihood-ratio χ^2 test and by leave-one-out cross-validation; Panel A gives the posterior random-intercept standard

deviation (prior-sensitive; Supplementary Table S6) and the intraclass correlation. †Binary logistic regression (fully concordant [score 2] vs not fully concordant [score 0 or 1]) with cluster-robust (sandwich) standard errors, clustered by question ID. Domain odds ratios are Firth-penalized to remain finite under the near-ceiling reference domain; this marginal model treats the 300 responses as independent, whereas every domain 95% credible interval in the primary clustered model included 1. OR <1 indicates lower odds of full concordance relative to the reference category. ‡Overall Wald chi-square test. Descriptive concordance rates by domain and prompt are provided in Supplementary Table S8.

Table 3. Error taxonomy by clinical domain — dual-reviewer classification (n = 64 consensus non-concordant responses)

			Reviewer 1			**Reviewer 2**		
Clinical domain	**n**		**Hallucination n (%)**	**Omission n (%)**	**Reasoning n (%)**	**Hallucination n (%)**	**Omission n (%)**	**Reasoning n (%)**
Epidemiology	13		3 (23.1%)	4 (30.8%)	6 (46.2%)	2 (15.4%)	4 (30.8%)	7 (53.8%)
TNM	7		1 (14.3%)	3 (42.9%)	3 (42.9%)	1 (14.3%)	3 (42.9%)	3 (42.9%)
Diagnosis	16		3 (18.8%)	5 (31.2%)	8 (50.0%)	3 (18.8%)	5 (31.2%)	8 (50.0%)
Treatment	25		3 (12.0%)	15 (60.0%)	7 (28.0%)	0 (0.0%)	19 (76.0%)	6 (24.0%)
Follow-up	3		0 (0.0%)	3 (100.0%)	0 (0.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)
Total	**64**		**10 (15.6%)**	**30 (46.9%)**	**24 (37.5%)**	**9 (14.1%)**	**31 (48.4%)**	**24 (37.5%)**

Error types based on consensus non-concordant responses (concordance score 0 or 1). Both reviewers independently classified errors. Inter-rater agreement on error type: Cohen's kappa=0.795 (87.5% agreement). Hallucination = fabricated clinical data absent from guidelines; Omission = failure to include critical guideline-specified information; Reasoning = correct facts leading to incorrect clinical conclusion. Prevalence-adjusted kappa = 0.81. Category-specific agreement (kappa): hallucination 0.57 (95% CI, 0.24–0.84), omission 0.78, reasoning 0.93. The follow-up cell reflects a single question (ID 96), scored as omission by one reviewer and hallucination by the other, and should not be over-interpreted.

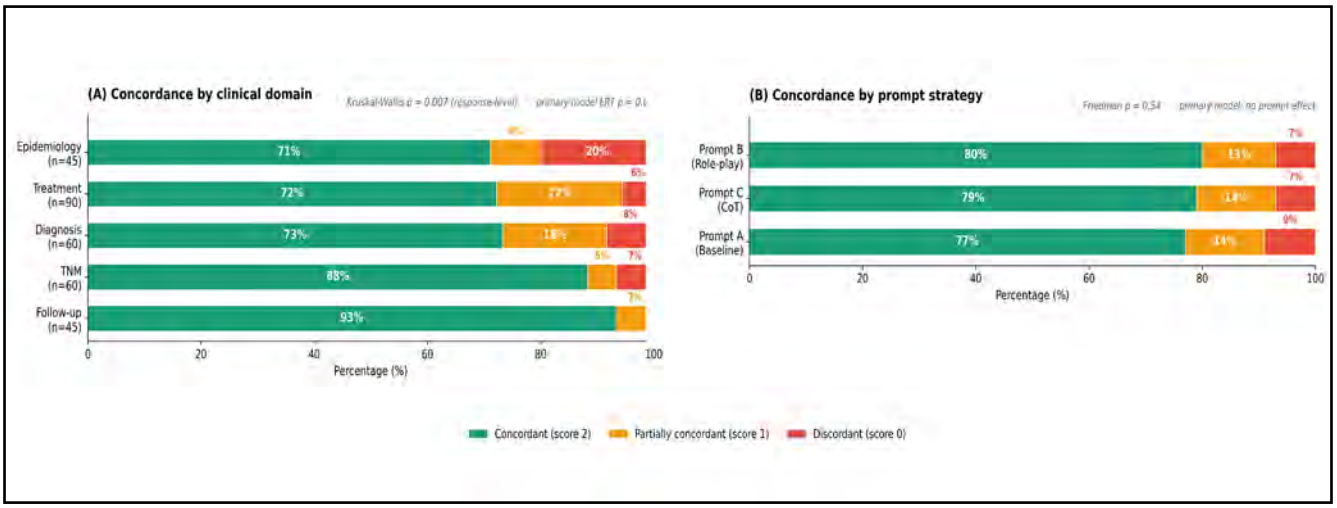

Figure 1. Distribution of guideline concordance scores. Stacked horizontal bar charts showing the proportion of concordant (score 2, green), partially concordant (score 1, amber), and discordant (score 0, red) responses. (A) By clinical domain. Follow-up achieved the highest concordance rate (93.3%, n = 45), whereas Epidemiology had the lowest (71.1%, n = 45) with the highest discordance rate (20.0%). The response-level Kruskal-Wallis test was nominally significant (H=13.95, p = 0.007); the primary Bayesian model showed no robust domain effect (likelihood-ratio χ^2=9.19, df=4, p = 0.06), and the binary cluster-robust sensitivity analysis was consistent (Wald χ^2=4.84, p = 0.30). (B) By prompt strategy. No significant difference was observed among Baseline (77%), Role-play (80%), and Chain-of-thought (79%) strategies (primary Bayesian model: no prompt effect, all 95% credible intervals including 1; Friedman χ^2=1.23, df=2, p = 0.54).

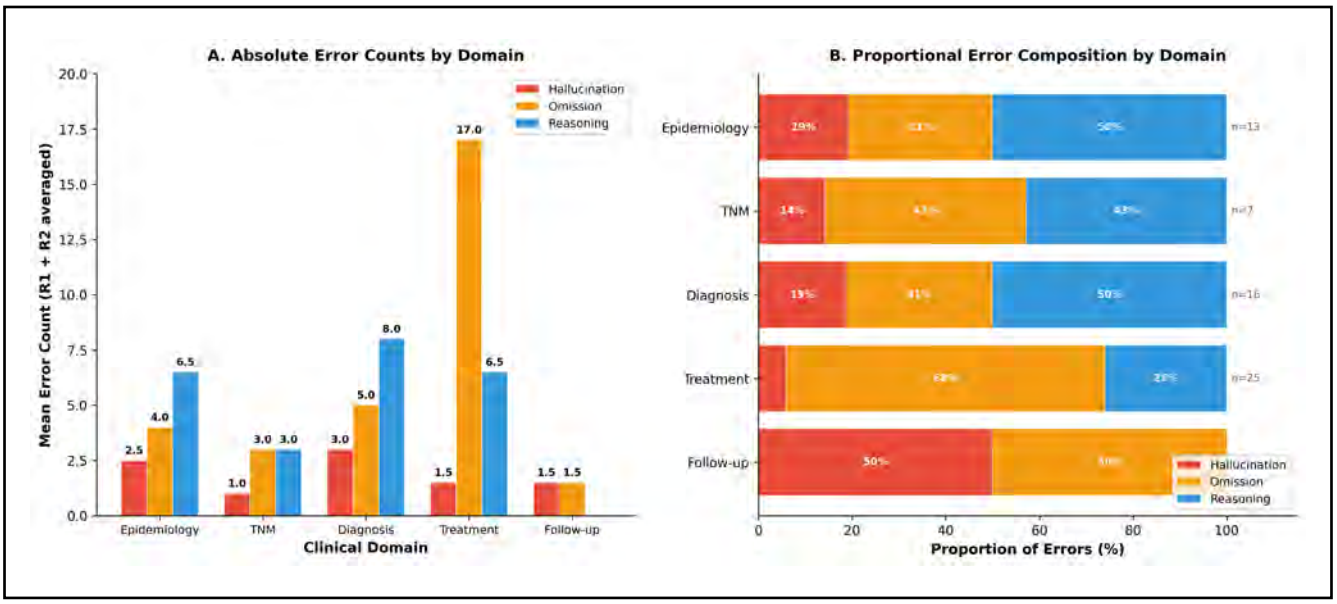

Figure 2. Error type distribution across clinical domains. Based on dual-reviewer assessment (n = 64 consensus non-concordant responses; inter-rater agreement on error type: Cohen's kappa=0.795). Values represent the mean of both reviewers' classifications. (A) Absolute error counts by domain. Treatment generated the highest absolute number of errors (n = 25), predominantly omissions. Epidemiology and diagnosis each showed a predominance of reasoning errors. (B) Proportional error composition within each domain. Reasoning errors were the dominant error type in Epidemiology (50.0%) and Diagnosis (50.0%). Omission predominated in Treatment (68.0%). Hallucination, though less frequent overall (14.8%), was present across domains; in Epidemiology, the model fabricated specific numerical risk estimates not present in the guidelines (19.2% of domain errors). Error categories: hallucination = fabricated clinical data absent from guidelines; omission = failure to include critical guideline-specified information; reasoning = correct facts leading to an incorrect clinical conclusion.

The distribution of errors differed by domain (Figure 2B; Supplementary Table S10). In treatment, omission dominated and accounted for 68.0% of errors. These responses often identified the correct therapeutic direction but omitted critical details specified in the guideline, such as saphenous vein sparing or thresholds for pelvic lymph node dissection. In epidemiology, reasoning errors were most common, accounting for 50.0% of errors, followed by omission (30.8%) and hallucination (19.2%). The hallucinations in this domain involved fabricated numerical estimates for phimosis and smoking risk. Diagnosis also showed a predominance of reasoning errors (50.0%), and TNM classification showed a similar pattern (42.9%).

The most stable feature of the dataset was not the prompt but the question. Eighty-one of 100 questions received identical consensus scores across all three prompting conditions. Seventy-two questions were uniformly concordant, five were uniformly partial, and four were uniformly discordant. The remaining 19 showed mixed performance across prompts.

The uniformly discordant questions were clinically revealing. They included fabricated biopsy specifications, incorrect claims regarding p16 and human papillomavirus (HPV) testing recommendations, and refusal to provide published diagnostic accuracy data. These failures persisted regardless of prompt strategy (Supplementary Tables S11 and S12). Cross-prompt consistency was high overall: 79% of questions received the maximum consistency score. Concordance and consistency were positively correlated (Spearman rho=0.726, $p < 0.001$). Notably, the uniformly discordant questions also received perfect consistency scores, showing that some incorrect answers were not only wrong, but stably wrong.

DISCUSSION

In this rare-cancer benchmark, GPT-5.2 showed moderate agreement with the EAU-ASCO penile cancer guideline, but prompt engineering did not improve performance. The model was often correct. It was not reliably correct. On a subset of questions, it failed reproducibly across all three prompting strategies, and some of the most stable outputs

were incorrect. That distinction matters in precisely the kind of clinical setting in which an LLM is most likely to be used: an uncommon diagnosis, limited operator familiarity, and dependence on guideline-level detail.

The overall concordance of 78.7% sits close to the pooled performance reported across oncology LLM studies and at the lower end of prior reports in urologic cancers (9–12). That result should not be read as reassuring in isolation. First, the benchmark addressed penile cancer, a domain absent from earlier evaluations. Second, the guideline tested here is a reprint of the 2023 version and may already be represented in model training data (14). The observed concordance may therefore approximate best-case performance rather than real-world generalization.

The most consistent negative finding was that prompt engineering did not help. Neither role-play nor chain-of-thought produced a credible improvement. Full concordance was 3 percentage points higher with role-play than with baseline (95% credible interval, −2 to +9), and similar with chain-of-thought. Both intervals include no change, but neither excludes an improvement of roughly eight points. Prompt variation can change wording without reliably improving clinical correctness (20–22). The data are not precise enough to prove prompting inconsequential, and we do not claim equivalence.

The clinically important result was not only whether the model failed, but how it failed. Errors in treatment were dominated by omission. The model often identified the broad treatment direction while omitting the guideline detail that determines whether care is complete. Errors in epidemiology and diagnosis were more often reasoning failures, where apparently correct facts were assembled into incorrect conclusions. Those failures may be harder for clinicians to detect than hallucinations because the output sounds plausible (23). Hallucinations were less common overall, but they were most concerning in epidemiology, where the model generated specific numerical risk estimates not present in the guideline (17,18).

The question-level analyses sharpen this picture. Most questions behaved consistently across prompts, and 81% of them received the same consensus score under all three prompting strategies. Performance, therefore, varied less by prompt phrasing than by the intrinsic content of the question. The model did not merely make isolated errors. On a subset of questions, it failed reproducibly. The high cross-prompt consistency reported in the literature should not be interpreted, on its own, as a marker of safety.

These findings also inform the memorization-versus-reasoning question. If model performance were driven mainly by the retrieval of explicit guideline text, one would expect stronger performance on strong recommendations than on weak ones. That was not observed. Strong recommendations had numerically lower concordance, and the cluster-robust comparison remained non-significant. This does not exclude partial memorization. It does suggest that simple verbatim recovery is not an adequate explanation for model behavior. The presence of fabricated numerical values in epidemiology points in the same direction, consistent with prior reports that LLM responses on epidemiological topics can contain plausible but inaccurate content (24).

This study has limitations. We evaluated one model only. The benchmark contained 100 questions and cannot exhaustively represent a 63-page guideline (14). Different question sets could yield different absolute concordance estimates, although the consistency of prompt, domain, and error patterns suggests that the qualitative findings may be more stable than the exact percentages. The domain effect did not reach statistical significance in clustered analyses, and the wide confidence intervals reflect limited precision with 15 to 30 questions per domain. We also tested zero-shot prompting without retrieval augmentation, which does not represent all deployment scenarios (25). A multi-model extension of this benchmark — incorporating closed-source models from other providers and retrieval-augmented configurations — is the natural next step and would test whether the failure structures we observed are model-specific or representative of current LLM-decision-support behavior in rare-cancer settings.

Two features limit the modeling. Most questions were answered identically across prompts, which produced extreme between-question separation. The random-intercept variance is therefore weakly identified and depends partly on the prior, although the fixed-effect conclusions held across

a range of priors. The primary analysis was also designated after the data were seen. We report it as a post-hoc primary analysis, not a pre-registered one.

CONCLUSION

Even with those limitations, the practical message is clear. Penile cancer is exactly the sort of setting in which clinicians may seek rapid algorithmic support. Our data suggest that current LLM output in this setting is not ready to function as a stand-alone clinical guide. The model was moderately concordant overall, but prompt engineering did not rescue performance; some failures were clinically consequential, and several incorrect outputs were stable across prompts. To conclude, for rare cancers, LLM responses may assist with orientation, but they should not replace direct consultation of the primary guideline.

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Ethical Approval: This study did not involve human participants, patient-level identifiers, or animal subjects; therefore, ethics committee approval was not required.

Author Contributions

Concept and design: A.Ş., H.S.G. Data collection: A.Ş., S.G. Blinded response scoring: S.G., H.S.G. Statistical analysis: H.S.G. Drafting of the manuscript: A.Ş., S.G., H.S.G. Critical revision of the manuscript: H.S.G. Supervision: H.S.G. All authors read and approved the final manuscript.

Data Availability

The data presented in this study are available from the corresponding author on reasonable request.

Supplementary Materials

The following supplementary materials are available as separate files.

Supplementary Table S1. TRIPOD-LLM reporting checklist.
Supplementary Table S2. Complete question set with gold-standard answers.
Supplementary Table S3. Full prompt texts for the three prompting strategies.
Supplementary Table S4. All 300 LLM responses with corresponding reviewer scores.
Supplementary Table S5. Three-tier scoring rubric.
Supplementary Table S6. Model estimation, prior-sensitivity, and validation diagnostics.
Supplementary Table S7. Discordant responses.
Supplementary Table S8. Concordance rates by clinical domain and prompt strategy.
Supplementary Table S9. Exploratory clustered analyses (question type and recommendation strength).
Supplementary Table S10. Domain × error-type cross-tabulation by reviewer.
Supplementary Table S11. Illustrative difficult examples.
Supplementary Table S12. Consistently non-concordant questions.
Supplementary Figure S1. Study design and workflow.
Supplementary Figure S2. Heat map of concordance rates by clinical domain and prompt strategy.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: During the preparation of this work, the authors used a generative AI tool, Claude (Anthropic), to assist with writing and language editing, formatting, and reference management. AI tools were not used for study design, data collection, statistical analysis, or figure generation. The authors reviewed and edited all content, take full responsibility for its integrity, originality, and accuracy, and confirm that no AI tool is listed as an author.

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RESEARCH ARTICLE

Association Between Postvoid Residual Urine Volume and Estimated Glomerular Filtration Rate in Men with Benign Prostatic Obstruction

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Abstract

Objective: The relationship between postvoid residual urine volume (PVR) and estimated glomerular filtration rate (eGFR) in men with benign prostatic obstruction (BPO) remains controversial. This study aimed to evaluate the association between PVR and eGFR.

Methods: This retrospective study included 172 men with lower urinary tract symptoms (LUTS) secondary to BPO. Correlations between eGFR and clinical variables were evaluated using Spearman correlation analysis. Patients were stratified into four PVR categories (<50, 50–99, 100–149, and ≥150 mL), and eGFR values were compared using the Kruskal-Wallis test. Multivariable linear regression identified variables independently associated with eGFR.

Results: Median age was 67 years, median PVR was 100 mL, and median eGFR was 84 mL/min/1.73 m^2. PVR showed a moderate negative correlation with eGFR ($\rho = -0.356$, $p < 0.001$). Median eGFR differed significantly across PVR categories (90.5, 85.0, 78.0, and 79.5 mL/min/1.73 m^2; $p < 0.001$). In multivariable analysis, only age ($\beta = -0.369$, $p < 0.001$) and PVR ($\beta = -0.288$, $p < 0.001$) remained independently associated with eGFR. International Prostate Symptom Score (IPSS), prostate volume (PV), and urinary flow parameters were not independently associated with eGFR.

Conclusion: Higher PVR was independently associated with lower eGFR in men with BPO after excluding major causes of CKD. PVR may represent a clinically useful marker of reduced eGFR and may provide additional clinical value beyond IPSS, urinary flow parameters, and PV. Prospective studies are warranted to confirm these findings.

Keywords: prostatic hyperplasia, urinary retention, glomerular filtration rate, lower urinary tract symptoms, renal insufficiency

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INTRODUCTION

Benign prostatic hyperplasia (BPH) refers to a benign increase in prostate size in elderly men. It occurs in nearly 10% of men in their 40 s and up to 90% of men older than 80 years of age (1). Aging, genetic factors, hormones, and metabolic conditions contribute to the development of BPH (2). The clinical picture of BPH includes the presence of lower urinary tract symptoms (LUTS). These symptoms include voiding problems, such as a weak or hesitant urine stream, and storage problems, such as frequent urination, urinary urgency, and nocturia (1,2). Chronic kidney disease (CKD) is another common age-related condition and one of the main public health problems around the world, affecting about 850 million people (3). CKD is characterized by evidence of kidney damage, which includes abnormal findings detected by imaging or proteinuria and/or a decline in kidney function as assessed by glomerular filtration rate (4).

Although BPH is the underlying pathological condition, LUTS and bladder outlet obstruction are more directly related to benign prostatic obstruction (BPO), which represents the functional manifestation of prostatic enlargement in affected patients. Many studies have investigated the relationship between parameters related to LUTS/BPO and kidney function. Results regarding symptom severity have been conflicting. Rule et al. (5) found that moderate-to-severe LUTS was independently associated with CKD. Nevertheless, following reports have found no evidence to support this relationship; Hong et al. (6) observed no independent association between the International Prostate Symptom Score (IPSS) and CKD, and Lee et al. (7) did not observe a significant correlation between the IPSS and estimated glomerular filtration rate (eGFR), and Hallan et al. (8), after adjusting for age and other risk factors, reported that LUTS was not independently associated with future kidney failure. Likewise, Bauer et al. (9) indicated that, after adjusting for important confounding factors, LUTS severity was not independently associated with multiple measures of kidney dysfunction.

There seems to be a more definite relation of impaired renal function with a reduced maximum urinary flow rate (Qmax), in contrast. According to the findings of Rule et al. (5) and Hong et al. (6), reduced peak flow rates are independently associated with CKD. In concordance with the previous studies, Lee et al. (7) found that Qmax was the single BPO-related parameter that was still significantly associated with eGFR after multivariable adjustment.

The current evidence related to the role of postvoid residual urine volume (PVR) in the progression of CKD appears to be both limited and inconsistent. Rule et al. (5) found a nonsignificant positive relation between chronic urinary retention and CKD, while Hong et al. (6) and Lee et al. (7) failed to show an independent association of PVR with the renal function. Contrary to this, however, Yamasaki et al. (10) found that as low as PVR ≥12 mL, are independently associated with CKD in BPH patients. These findings point out that the relationship between PVR and renal dysfunction remains unclear.

Therefore, given the conflicting evidence regarding the association between PVR and eGFR, we aimed to evaluate the association in men with LUTS due to BPO. The secondary analysis was conducted to explore the associations of IPSS and Qmax with eGFR.

MATERIALS AND METHODS

Study Design and Patient Selection

The retrospective study included male patients who were followed up at the urology outpatient clinic between November 20, 2022, and March 15, 2026, due to lower urinary tract symptoms (LUTS) and who received a clinical diagnosis of BPH/BPO. The diagnosis was based on clinical evaluation documented in medical records; urodynamic confirmation of bladder outlet obstruction was not available routinely. Patient medical files were analyzed to select eligible patients. The study was approved by the Clinical Research Ethics Committee of Ankara Etlik City Hospital (Approval No: AEŞH-BADEK2–2026–434, Date: June 30, 2026) and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who met the inclusion criteria were aged >40 years, had LUTS and had uroflowmetric studies, PVR, serum creatinine, and prostate volume (PV) available from the same examination period.

Patients with chronic kidney disease (eGFR <60 mL/min/1.73 m^2), diabetes mellitus, hypertension, neurogenic

bladder dysfunction, urethral stricture disease, urinary tract malignancy, active urinary tract infection, lower urinary tract reconstruction, hydronephrosis, obstruction of the upper urinary tract, urinary retention requiring catheterization, and incomplete clinical information were excluded.

Patients with very low Qmax (<5 mL/s) were excluded to reduce the potential inclusion of patients with unrecognized urethral stricture disease.

Data Collection

Demographic and clinical characteristics were extracted from electronic patient records. The recorded variables were as follows: age, body mass index (BMI), IPSS, Qmax, average urinary flow rate (Qavg), PVR, PV, prostate-specific antigen (PSA), serum creatinine level, and eGFR. PV and PVR were measured using transabdominal ultrasonography. Uroflowmetry was performed as part of the routine clinical assessment, and Qmax and Qavg values were recorded. Only uroflowmetry measurements with a voided volume ≥150 mL were included in the analysis, considering the influence of voided volume on uroflowmetry parameters (11). PVR was determined by bladder ultrasonography immediately after uroflowmetry. A single PVR measurement obtained during the index clinical assessment was used for the analysis. eGFR values, routinely calculated in our institution using the CKD-EPI equation and recorded in the electronic medical records, were used for analysis. To reduce the influence of biological and analytical variability, the mean of the three most recent eGFR measurements available before or during the clinical assessment period were used for analysis. The interval between these measurements was not standardized because of the retrospective study design.

Study Outcomes

The primary objective of the study was to evaluate the association between PVR and eGFR. Secondary objectives were to evaluate the associations of IPSS, Qmax, and PV with eGFR.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Data distribution was examined with the help of histograms and tests for skewness. Data were presented as mean ± standard deviation or median (interquartile range), as appropriate. The correlations of eGFR with the studied parameters were determined using the Spearman correlation test. To simplify clinical interpretation, PVR was divided into four groups (<50, 50–99, 100–149, and ≥150 mL) using PVR ranges previously described in men with LUTS, and values of ≥150 mL were grouped into one category (12) and eGFR values were compared with the Kruskal-Wallis test. Variables potentially associated with eGFR were subsequently entered into a multivariable linear regression model with eGFR as the dependent variable. A 2-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 172 patients were included in the final analysis. The median age was 67 years, median IPSS was 21, median Qmax was 9.0 mL/s, and median PVR was 100 mL. The median eGFR was 84 mL/min/1.73 m² (Table 1).

Spearman's correlation analysis showed that PVR and age had a moderate negative correlation with eGFR (both $p <$ 0.001). In addition, no significant correlation was observed between eGFR and BMI, PSA, PV, IPSS, Qmax, or Qavg (all $p > 0.05$) (Table 2).

Table 1. Baseline characteristics of the study population

Variable	Value
Age (years), median (IQR)	67 (63–72)
BMI (kg/m²), mean ± SD	27.6 ± 4.0
Total PSA (ng/mL), median (IQR)	3.0 (1.6–9.0)
PV (mL), median (IQR)	65 (50–87.5)
IPSS, median (IQR)	21 (18–24)
Qmax (mL/s), median (IQR)	9.0 (7.2–11.4)
Qavg (mL/s), median (IQR)	4.0 (3.1–5.2)
PVR (mL), median (IQR)	100 (45–150)
eGFR (mL/min/1.73 m²), median (IQR)	84 (72–91)
Serum creatinine (mg/dL), median (IQR)	0.93 (0.83–1.04)

IQR, interquartile range; SD, standard deviation; BMI, body mass index; PSA, prostate-specific antigen; PV, prostate volume; IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; Qavg, average urinary flow rate; PVR, postvoid residual urine volume; eGFR, estimated glomerular filtration rate.

Median eGFR values were generally lower in the higher PVR categories (90.5, 85.0, 78.0, and 79.5 mL/min/1.73 m² for <50, 50–99, 100–149, and ≥150 mL, respectively). Overall differences between groups were statistically significant ($p < 0.001$) (Table 3, Figure 1).

In multivariable linear regression analysis including age, BMI, PV, IPSS, Qmax, Qavg, and PVR, only age and PVR (both $p < 0.001$) remained independently associated with eGFR. Neither BMI, IPSS, PV, nor urinary flow parameters showed a significant independent association with eGFR (all $p > 0.05$). The overall model explained 27.0% of the variability in eGFR ($R^2 = 0.270$, adjusted $R^2 = 0.238$, $p < 0.001$) (Table 4).

Table 2. Correlation between eGFR and clinical parameters

Variable	Spearman rho	p value
Age	-0.453	**<0.001**
BMI	-0.096	0.209
Total PSA	0.012	0.880
PV	-0.135	0.078
IPSS	-0.079	0.304
Qmax	-0.105	0.172
Qavg	-0.052	0.501
PVR	-0.356	**<0.001**

BMI, body mass index; PSA, prostate-specific antigen; PV, prostate volume; IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; Qavg, average urinary flow rate; PVR, postvoid residual urine volume; eGFR, estimated glomerular filtration rate.

Table 3. eGFR according to postvoid residual urine volume categories

PVR category	eGFR median (IQR)
<50 mL	90.5 (83.0–96.0)
50–99 mL	85.0 (76.5–92.0)
100–149 mL	78.0 (70.0–86.0)
≥150 mL	79.5 (68.0–89.0)

Kruskal–Wallis test, $p < 0.001$.

IQR, interquartile range; PVR, postvoid residual urine volume; eGFR, estimated glomerular filtration rate.

Table 4. Multivariable linear regression analysis for factors independently associated with eGFR

Variable	β	B (95% CI)	p value
Age	-0.369	-0.651 (-0.899 to -0.403)	**<0.001**
BMI	-0.132	-0.391 (-0.790 to 0.008)	0.055
PV	0.078	0.027 (-0.022 to 0.077)	0.279
IPSS	-0.026	-0.068 (-0.424 to 0.287)	0.704
Qmax	-0.157	-0.516 (-1.165 to 0.132)	0.118
Qavg	0.114	0.760 (-0.555 to 2.076)	0.255
PVR	-0.288	-0.050 (-0.074 to -0.026)	**<0.001**

Model statistics: $R^2 = 0.270$; adjusted $R^2 = 0.238$; $F = 8.649$; $p < 0.001$.

β, standardized regression coefficient; B, unstandardized regression coefficient; CI, confidence interval; BMI, body mass index; PV, prostate volume; IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; Qavg, average urinary flow rate; PVR, postvoid residual urine volume; eGFR, estimated glomerular filtration rate.

DISCUSSION

The clinical significance of elevated PVR remains an area of ongoing investigation. According to a recent study, the pathophysiology and long-term complications of chronic urinary retention are not fully understood, and further studies are needed to understand its effect on kidney function. The authors also proposed that patients with elevated PVR should be stratified according to their risk of renal deterioration and it can be noted here high-risk patients require close monitoring of kidney function (13).

Against this background, we evaluated the association between PVR and eGFR in men with LUTS secondary to BPO after excluding major causes of chronic kidney disease. We found that higher PVR was significantly associated with lower eGFR values. PVR showed a moderate negative correlation with eGFR and remained independently associated with eGFR after adjusting for age, BMI, IPSS, urinary flow parameters, and PV. Moreover, median eGFR varied significantly among PVR groups, as in general lower eGFR values have been observed in higher PVR groups. Although all patients had an eGFR ≥60 mL/min/1.73 m² by study design, the lower eGFR values observed in the higher PVR categories suggest that the association between PVR and eGFR may also be present among patients without established CKD.

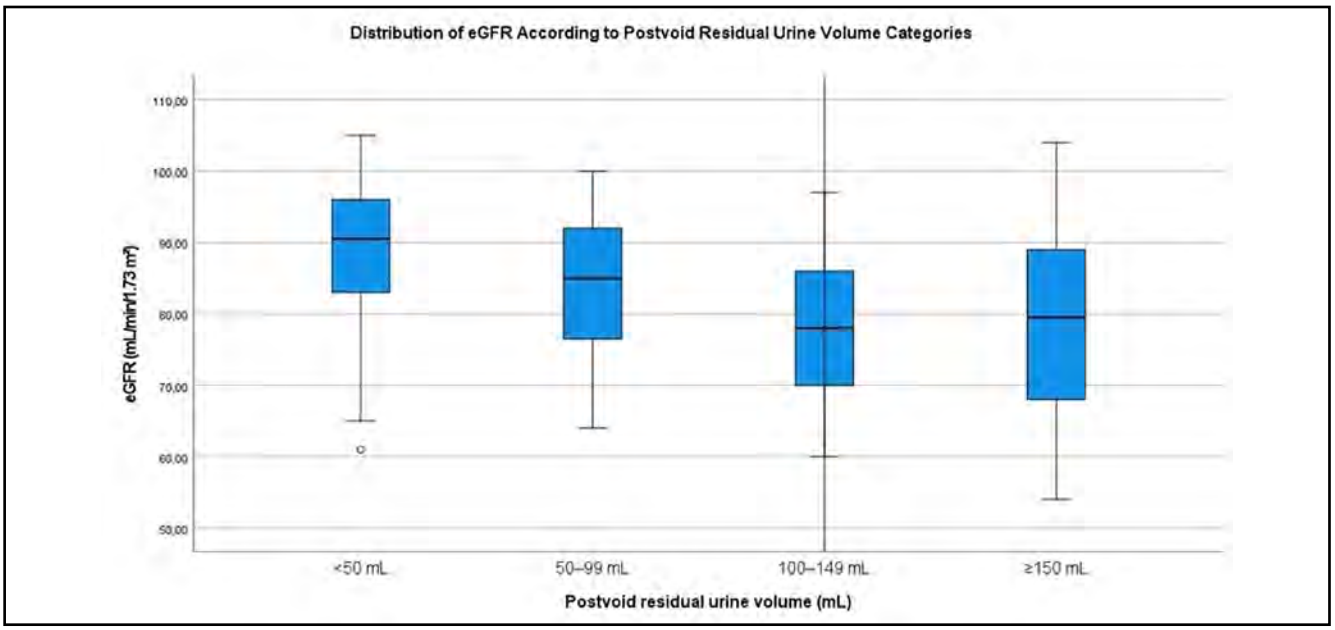

Figure 1. Distribution of eGFR According to Postvoid Residual Urine Volume Categories.

The relationship between PVR and eGFR is still unclear. A study highlighted that men with PVR >100 mL had higher odds of CKD, but this association was not statistically significant due to wide confidence intervals (5). Similar results were provided by Yamasaki et al. (10), who showed that relatively small amounts of PVR were independently associated with CKD in men suffering from BPH. In contrast, two studies demonstrated no independent association between PVR and kidney function (6,7). These findings suggest that the relationship between PVR and eGFR is potentially related to differences in study populations, definitions of CKD, and the existence of significant comorbidities. Our results contribute to the growing evidence suggesting an association between increased PVR and reduced eGFR and indicate that PVR may serve as a clinically useful marker of lower eGFR in selected patients with BPO.

There are several possible explanations for the association between high PVR and reduced eGFR. Chronic urinary retention may lead to persistent high intravesical pressure, resulting in functional obstruction at the ureterovesical junction and poor drainage of the upper urinary tract. Persistent increases in intravesical pressure may also lead to vesicoureteral reflux, hydronephrosis, and progressive kidney damage (14,15). Prior studies have indicated that detrusor hypertrophy, bladder wall remodeling, and reduced bladder compliance may play a significant role in upper urinary tract dysfunction and may be more critical factors in determining renal dysfunction than PVR itself (14,16). Furthermore, it has been suggested that recurrent urinary tract infections and bladder stone formation are possible contributing factors to chronic urinary retention and impaired renal function (15). These pathophysiological mechanisms serve as a reasonable biological explanation for the observed association in the present study.

In this study, PV, IPSS, and urinary flow rates were not individually correlated with eGFR. In previous studies, a negative correlation between Qmax and kidney function has been identified. Hong et al. (6) reported an independent correlation between lower Qmax and CKD among male patients with LUTS due to BPH, while Lai et al. (17) revealed significant relationships between Qmax and renal function parameters in cases of CKD. Nevertheless, data on symptom severity and PV remain controversial. Kwon et al. (18) found the relationship between LUTS and kidney function to be independent of PV, implying that mere anatomical enlargement does not indicate functional severity of the disease. Similarly, the independent correlation between symptom severity and renal dysfunction was not observed by Hamm and MacDermott et al. (19) and Ponholzer et al. (20). Taken into consideration, these findings indicate that objective measures of bladder emptying dysfunction may be more useful than IPSS or PV when assessing the potential

impact of BPO on eGFR. In our cohort, PVR was the only lower urinary tract parameter that remained independently associated with eGFR, supporting its potential value as a clinically relevant marker of reduced eGFR.

This study's key strengths were its well-defined and carefully selected study population. We excluded patients with diabetes mellitus, hypertension, and previously diagnosed chronic kidney disease, which are well-established risk factors for impaired renal function and CKD progression (21, 22). Because renal function is influenced by multiple systemic factors, residual confounding may partly explain the inconsistent findings reported in previous studies evaluating the association between LUTS/BPO-related parameters and kidney function (23). By excluding these major sources of confounding, we were able to more specifically evaluate the association between BPO-related parameters and eGFR in patients with BPO. This methodological approach may partly explain why PVR remained independently associated with eGFR after multivariable adjustment.

Study limitations: This study has several limitations. Firstly, due to its retrospective and single-center design, our study cannot establish the causality between PVR and reduced eGFR. Second, although the study eGFR was defined as the mean of the three most recent eGFR measurements, the interval between these measurements was not standardized because of the retrospective design. In addition, longitudinal follow-up data were not available; therefore, changes in eGFR over time could not be evaluated. Third, PVR was based on a single measurement, and potential intra-individual variability in residual urine volume could not be assessed. Fourth, other markers of kidney damage, such as albuminuria or proteinuria, were not routinely assessed. In addition, objective assessment of bladder outlet obstruction by urodynamic studies was not available. Despite these limitations, the rigorous exclusion of patients with major causes of renal dysfunction allowed a more specific evaluation of the independent association between PVR and eGFR in patients with BPO.

CONCLUSION

Increased PVR was independently associated with reduced eGFR in men with LUTS secondary to BPO after excluding major causes of chronic kidney disease. PVR may therefore provide additional clinical value beyond IPSS, urinary flow parameters, and PV when assessing reduced eGFR. Prospective studies are required for confirmation of the results and assessment of possible association between changes in PVR and eGFR in time.

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Ethical Approval: The study was approved by the Clinical Research Ethics Committee of Ankara Etlik City Hospital (Approval No: AEŞH-BADEK2–2026–434, Date: June 30, 2026) and was conducted in accordance with the principles of the Declaration of Helsinki.

Author Contributions:
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Supervision: AED
Data Collection and/or Analysis: MYA
Analysis and/or Interpretation: AED, MYA
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CASE REPORT

Scrotal Skin Metastasis of Lung Adenocarcinoma: A Rare Case Report

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Abstract

Scrotal skin metastasis is extremely rare, predominantly originating from urogenital or gastrointestinal malignancies. Lung adenocarcinoma metastasis to the scrotum has been reported in only a limited number of cases in the literature. A 71-year-old male with a known diagnosis of lung adenocarcinoma presented with a progressively enlarging, painless 3 x 3 cm nodular mass in the right hemiscrotum. Histopathological and immunohistochemical examination confirmed metastatic pulmonary adenocarcinoma (TTF-1+, CK7+, P40-). The patient declined systemic therapy and experienced rapid disease progression, dying three months after the diagnosis of scrotal metastasis. This case highlights that metastatic disease should be considered in the differential diagnosis of scrotal lesions in patients with known malignancy, and underscores the value of immunohistochemistry in establishing the diagnosis.

Keywords: lung neoplasms, scrotal skin metastasis, cutaneous metastasis, lung adenocarcinoma

INTRODUCTION

Although cutaneous metastases may occur in advanced malignancies, scrotal skin involvement is exceptionally rare and most commonly originates from urogenital or gastrointestinal tumors. Scrotal tumors include squamous cell carcinoma, Paget's disease, basal cell carcinoma, sarcomas, malignant melanoma, and metastatic tumors (1,2). While the overall incidence of cutaneous metastasis in all cancers is approximately 10%, metastasis to the scrotal skin is exceedingly rare, with a reported incidence of approximately 0.02% (3). Scrotal skin metastases most commonly arise from urogenital and gastrointestinal malignancies, whereas lung-origin metastases have been reported in a limited number of cases in the literature (4).

Herein, we report a rare case of scrotal skin metastasis originating from lung adenocarcinoma, and discuss its clinical, histopathological, and diagnostic features.

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CASE REPORT

A 71-year-old male patient was referred to the Urology outpatient clinic by the Dermatology department for a painless scrotal skin lesion that had progressively increased in size.

Physical examination revealed a painless, mobile nodular lesion measuring approximately 3 × 3 cm in the right hemiscrotum (Figure 1). On palpation, the lesion was confined to the subcutaneous level, and the testis and epididymis were normal. The lesion surface was erythematous with signs of superficial infection, and no inguinal lymphadenopathy was detected.

His medical history included hypertension, essential thrombocytosis, lung cancer, and transurethral resection of the prostate (TURP) performed approximately 10 years prior. He had quit smoking 7 years ago, with a 45-pack-year smoking history. His oncologic history was as follows: in December 2024, a non-contrast chest CT performed for cough and dyspnea had revealed an irregularly marginated primary mass measuring 37 × 24 mm in the right upper lobe (Figure 2). F-18 FDG PET/CT performed for staging had demonstrated increased activity in the right hilar, paratracheal, and supraclavicular lymph nodes, with metastatic involvement of the skull base, C1 vertebra, right 4th rib, left iliac bone, and acetabular region. An interventional radiology-guided lung biopsy had been reported as non-small cell lung carcinoma (NSCLC); the histomorphological and immunohistochemical findings (TTF-1+, CK7+, P40−) were consistent with poorly differentiated adenocarcinoma. Systemic chemotherapy recommended by medical oncology had been declined, and a total of 15 sessions of palliative radiotherapy had been administered between December 2024 and January 2025. The scrotal skin lesion had appeared approximately 3–4 months after this lung cancer diagnosis.

Given the patient's known history of lung cancer, metastasis was strongly suspected. Scrotal ultrasonography performed to assess the depth of the lesion and testicular invasion revealed normal testicular parenchyma; the lesion was reported to be confined to the skin and subcutaneous tissues without extension to deeper structures. Magnetic resonance imaging was not deemed necessary.

Figure 1. A nodular mass measuring approximately 3 × 3 cm was observed on the right side of the scrotum during physical examination.

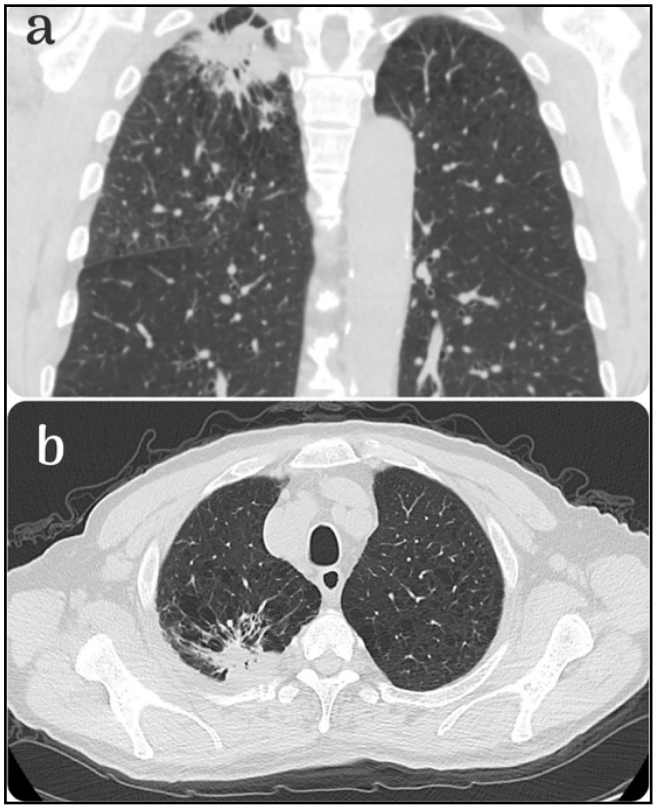

Figure 2. Chest CT demonstrates an irregular soft tissue mass measuring approximately 37 × 24 mm located in the posterior segment of the right upper lobe, showing pleural-based invasion of the 4th rib (primary lesion). *(a) Coronal section, (b) Axial section.*

Excisional biopsy was preferred over punch or incisional biopsy due to the size of the lesion (3 × 3 cm), which allowed complete removal while simultaneously providing the entire specimen for histopathological evaluation. After written informed consent was obtained, including consent for publication, the lesion was excised under local anesthesia (Figure 3).

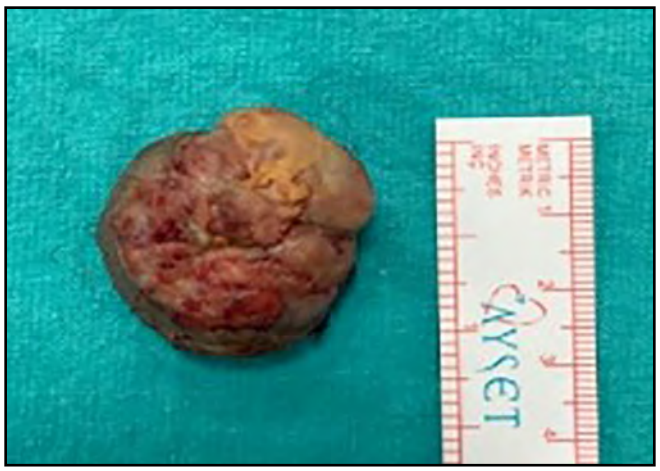

Figure 3. Appearance of the excised scrotal mass.

Following excision, the wound was closed primarily, and postoperative healing was uneventful.

Pathological examination revealed that the specimen was immunohistochemically diffusely positive for Cytokeratin-7 (CK7) and TTF-1, and negative for p40, S-100, SOX-10, and HMB-45. Microscopically, atypical epithelial cells with large hyperchromatic nuclei and prominent nucleoli were observed forming small irregular glandular structures, ulcerating the surface epidermis and infiltrating the subcutaneous adipose tissue. These morphological and immunohistochemical findings were consistent with metastatic lung adenocarcinoma, and correlated with the primary lung biopsy findings, which demonstrated the same immunophenotype (TTF-1+, CK7+, P40−) (Figure 4). The tumor base was located 1 mm from the surgical margin, while the lateral surgical margins were tumor-free. The patient was referred to the Pulmonology and Medical Oncology departments for reevaluation of oncological treatment options. Systemic therapy was again recommended; however, the patient declined for the second time. No local recurrence was observed at the excision site. The patient died approximately 3 months after the diagnosis of scrotal skin metastasis due to progression of the primary disease.

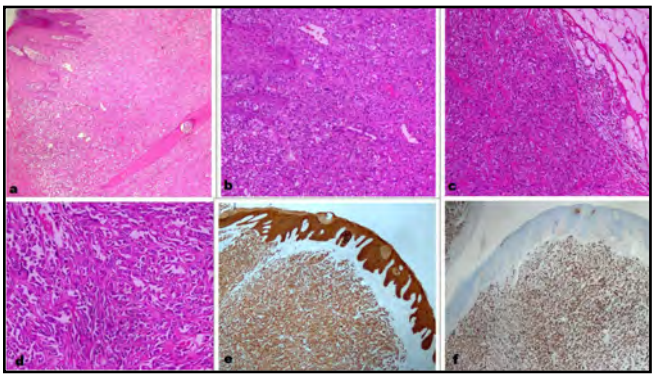

Figure 4. (a,b) Tumor infiltration was observed under the skin (H&E ×40, H&E ×100), (c) The tumor spreads to the subcutaneous fat tissue (H&E ×100), (d) The tumor consists of atypical epithelial cells that form small irregular glandular structures with large hyperchromatic nuclei and prominent nucleoli (H&E ×100), (e) Diffuse positive staining with CK7 was observed in the tumor, (f) Diffuse positive staining with TTF-1 was observed in the tumor.

DISCUSSION

Although most lesions of the scrotal skin are benign, primary malignancies and metastatic foci should be considered in the differential diagnosis. In the study by Hoyt et al. (4), one of the most comprehensive reviews in the literature, 29 patients with scrotal cutaneous metastasis were evaluated; it was reported that primary foci most commonly originated from the urogenital system (44%), gastrointestinal system (37%), and lung (13%).

Lung cancer is one of the leading causes of cancer-related deaths worldwide and frequently metastasizes to the brain, bone, liver, and adrenal glands (5). Cutaneous metastases are rarer, being reported in approximately 1–12% of patients with lung cancer (6,7). While they typically occur in the chest, neck, head, and abdominal regions, scrotal skin involvement is uncommonly reported (8).

In the literature, a case reported by Coussa-Koniski et al. (8), described metastatic involvement of the scrotal wall in a patient with primary lung adenocarcinoma, emphasizing that most such cases indicate advanced systemic disease. Similarly, the study by Molina Garrido et al. (7), highlighted that cutaneous metastasis as the initial finding of lung cancer is rare (0.8%), typically indicating advanced disease and associated with short survival. Given the limited number of reported

cases, this report contributes additional clinicopathological evidence regarding atypical cutaneous dissemination patterns of lung adenocarcinoma.

In this case, the development of a scrotal lesion approximately 3–4 months after the diagnosis of lung adenocarcinoma suggests a relatively early onset of metastasis. This may be an important indicator of the aggressive course of the disease.

Cutaneous metastases typically present as painless, elevated, erythematous, or nodular lesions and may occasionally exhibit ulceration. Similarly, in this case, there was a painless, elevated nodular lesion on the right side of the scrotum. The differential diagnosis of scrotal skin lesions includes hidradenoma, poroma, basal cell carcinoma, squamous cell carcinoma, and pilomatricoma; however, in patients with a known history of malignancy, metastatic involvement should always be considered. Given the patient's known history of lung adenocarcinoma, an excisional biopsy was performed with suspicion of metastasis.

Histopathological and immunohistochemical evaluations are of great importance in the diagnosis of cutaneous metastases. In particular, TTF-1 (Thyroid Transcription Factor-1) positivity is a sensitive and relatively specific marker for lung-origin adenocarcinomas, although it should be interpreted within the full clinical and immunohistochemical context. CK7 positivity can also be observed in lung, breast, and gynecological adenocarcinomas, while p40 negativity helps exclude squamous cell carcinoma. In this case, the diffuse positivity of TTF-1 and CK7, and the negativity of p40, S-100, SOX-10, and HMB-45 confirmed that the lesion was metastatic adenocarcinoma of pulmonary origin.

Several mechanisms have been proposed for the pathogenesis of cutaneous metastases. The most commonly accepted include hematogenous dissemination, lymphatic dissemination, and direct invasion (4). The rich lymphatic network of the scrotum, particularly its close association with inguinal lymph nodes, may facilitate this process. In this case, the confinement of the lesion to the subcutaneous level without invasion of deeper structures, combined with the widespread bone and lymph node metastases already present at initial staging, may suggest hematogenous dissemination as a possible metastatic pathway. Additionally, it is thought that retrograde venous flow and valveless venous systems such as Batson's plexus may play a role in transporting cells to atypical metastatic sites, particularly in lung and gastrointestinal tumors (9).

In this case, no local recurrence was observed despite the close deep surgical margin (1 mm), and palliative follow-up was maintained. Cutaneous metastases are generally associated with poor prognosis. The mean survival time in cutaneous metastases originating from lung cancer is reported to range between 3–6 months (10). Similarly, in this case, consistent with the survival time reported in the literature, the patient died 3 months after the diagnosis of scrotal skin metastasis. Therefore, early recognition of such lesions is important for planning palliative approaches and preserving quality of life.

CONCLUSION

To conclude, scrotal skin metastasis is extremely rare and usually indicates advanced systemic disease. In patients with lung adenocarcinoma, any newly developing scrotal lesion should raise suspicion for metastatic involvement.

Conflict of Interest: The authors, declare that there are no conflicts of interest regarding this case report.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

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CASE REPORT

Rare Paratesticular Tumor of the Scrotum: A Case of Well-Differentiated Liposarcoma

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Abstract

Paratesticular liposarcoma is an exceedingly rare malignant neoplasm accounting for less than 12% of all liposarcoma. We present a 69-year-old male with a progressively enlarging, painless left scrotal mass over three months. Physical examination revealed an 18 cm firm mass, and imaging demonstrated a heterogeneous lesion with mixed signal intensity. The patient underwent radical orchidectomy with wide local excision. Histopathological examination confirmed well-differentiated liposarcoma measuring 22 × 19 cm, with immunohistochemical analysis showing positive MDM2 and CDK4 staining. The patient remained disease-free at 24-month follow-up without adjuvant therapy, emphasizing the curative potential of complete surgical excision for this rare entity.

Keywords: paratesticular liposarcoma, well-differentiated liposarcoma, orchidectomy, scrotal mass, rare case report

INTRODUCTION

Paratesticular liposarcoma represents an exceedingly rare malignant neoplasm arising from mesenchymal tissues surrounding the testis, accounting for less than 12% of all liposarcomas (1,2). Well-differentiated liposarcoma constitutes the most common histological subtype according to the 2020 WHO classification, characterized by mature adipose tissue with scattered atypical stromal cells (3). Fewer than 200 cases have been documented worldwide, predominantly affecting patients in the fifth to seventh decades of life (2).

Clinical presentation typically involves a painless, slowly enlarging scrotal mass that may be misdiagnosed as benign conditions due to its indolent nature (3,4). Standardized diagnostic and therapeutic guidelines remain elusive due

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to the condition's rarity, creating significant management challenges (2). Comprehensive magnetic resonance imaging characteristics are rarely documented, limiting radiological diagnostic criteria (5).

Prognosis varies considerably by histological subtype, with well-differentiated variants showing excellent outcomes following complete excision, contrasting sharply with aggressive dedifferentiated forms (6). Radical orchidectomy with wide local excision represents the cornerstone of curative treatment (1,7).

We present a rare case of giant well-differentiated paratesticular liposarcoma with detailed clinical, radiological, pathological, and follow-up findings, highlighting the diagnostic challenges and favorable outcome after complete surgical excision, thereby contributing to the limited literature on this uncommon entity.

CASE PRESENTATION

A 69-year-old male patient presented to our urology department with a 3-month history of a progressively enlarging, painless left scrotal mass. The patient reported no associated symptoms such as pain, urinary complaints, or systemic symptoms. His medical history was unremarkable, with no previous history of testicular trauma, cryptorchidism, or family history of testicular malignancies. The patient denied any previous radiation exposure or use of immunosuppressive medications.

Physical examination revealed significant left hemiscrotal asymmetry with a large, firm, non-tender, and fixed mass measuring approximately 18 cm in its greatest dimension. The mass caused visible distension of the scrotal skin, while the contralateral right testis appeared normal in size, consistency, and position (Figure1a). Palpation confirmed the mass to be separate from the testicular parenchyma, suggesting a paratesticular origin. No inguinal lymphadenopathy was detected bilaterally, and abdominal examination was unremarkable. Informed consent was obtained from the patient for publication of this case report and accompanying images.

Laboratory investigations included serum tumor markers, which demonstrated normal levels of alpha-fetoprotein, beta-human chorionic gonadotropin, and Lactate Dehydrogenase (LDH). Complete blood count, liver function tests, and renal function parameters were within normal limits.

Scrotal ultrasonography revealed a large, heterogeneous, hyperechoic solid mass measuring 7.5 × 18.5 cm, adjacent to the left testis with preserved testicular parenchyma. Color Doppler examination showed minimal internal vascularity within the mass. Based on the imaging characteristics, an initial radiological diagnosis of liposarcoma was suspected. Pelvic magnetic resonance imaging confirmed a large heterogeneous mass with mixed signal intensity components on both T1 and T2-weighted sequences. Although no significant pathological enhancement was observed after gadolinium administration, the imaging features raised strong suspicion for malignancy (Figure1b).

Figure 1a. Marked left hemiscrotal asymmetry with a large mass, **1b.** Pelvic magnetic resonance imaging shows a large mass lesion (red arrow) with heterogeneous signal intensity located in the left scrotum, the testicle (blue arrow).

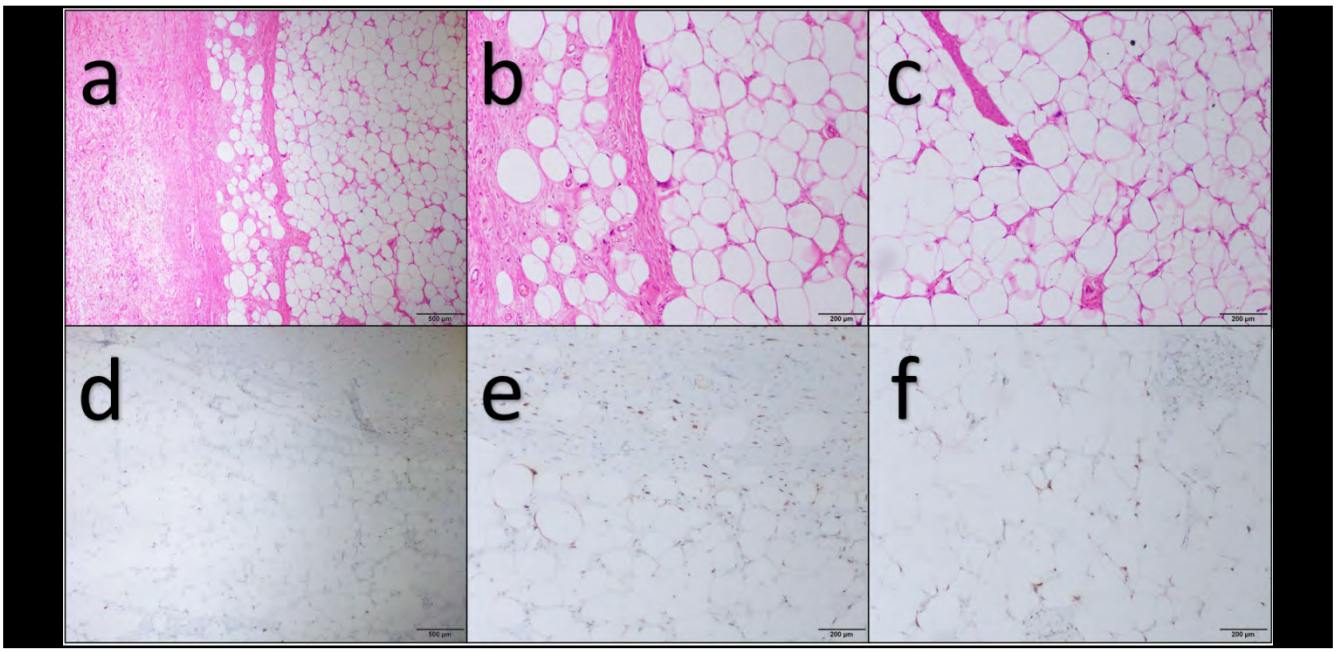

Figure 2a,b,c. Neoplastic proliferation composed predominantly of mature adipocytes of variable size, 2 d S100 positivity within adipocytic cells, **2e.** Nuclear MDM2 and 2f. CDK4 positive tumor cells.

Preoperative staging with contrast-enhanced computed tomography of the chest, abdomen, and pelvis revealed no evidence of metastatic disease. The patient underwent left inguinal exploration with radical excision of the paratesticular mass and left orchidectomy.

Gross examination revealed a well-circumscribed but non-encapsulated, lobulated mass with a yellowish-white cut surface and soft to partially firm consistency, adjacent to the orchidectomy specimen. The cut surface demonstrated a heterogeneous appearance with focal fibrous areas.

Microscopic examination showed a neoplastic proliferation composed predominantly of mature adipocytes of variable size, separated by thick fibrous septa. These septa contained scattered atypical stromal cells characterized by enlarged, hyperchromatic, irregular nuclei. Occasional multinucleated atypical cells and focal lipoblastic differentiation were identified. Mitotic activity was low, and no areas of tumor necrosis were observed. The tumor did not invade the testicular parenchyma or epididymis but demonstrated limited extension into the surrounding soft tissues. Surgical resection margins were free of tumor (Figure2a-c).

Immunohistochemical analysis demonstrated nuclear positivity for MDM2 and CDK4 in tumor cells. S-100 protein showed focal positivity within adipocytic components, while desmin and smooth muscle actin were negative (Figure2 d-f). Based on the histomorphological features and immunohistochemical profile, the findings were consistent with a diagnosis of well-differentiated liposarcoma.

Postoperative recovery was uneventful, and the patient was discharged on the third postoperative day. Given the complete excision with negative margins and the well-differentiated histological subtype, adjuvant therapy was not indicated. During a 24-month follow-up period, serial clinical examinations and computed tomography scans showed no evidence of local recurrence or distant metastases, with the patient remaining in complete remission.

DISCUSSION

Our 69-year-old patient falls within the typical age range for paratesticular liposarcoma, which predominantly affects patients in the fifth to seventh decades of life. This demographic pattern is consistent with similar cases, including a 75-year-old patient described (1) and a 73-year-old patient reported (2). Well-differentiated histological subtypes appear to have a predilection for older patients, whereas dedifferentiated variants may present at younger ages (7), as illustrated by the 62-year-old patient with giant dedifferentiated liposarcoma reported (8).

The left-sided presentation aligns with several documented cases (8,9). Radical left inguinal orchidectomy with wide local excision proved optimal, evidenced by our patient's excellent 24-month disease-free survival. This surgical strategy is strongly supported by literature, with reports indicating that "radical orchidectomy with wide local excision comprises the cornerstone of treatment" (1,7). The importance of complete excision cannot be overstated, given the potential for local recurrence in cases with inadequate surgical margins.

The role of adjuvant therapy in paratesticular liposarcoma remains controversial due to the rarity of the disease. Broadly speaking, complete surgical excision with negative margins is considered sufficient treatment for well-differentiated tumors, whereas adjuvant radiotherapy may be considered in selected patients with positive surgical margins, recurrent disease, or high-grade histological subtypes (2,9). The benefit of chemotherapy is not clearly established and is generally reserved for advanced or metastatic disease (2,6). Since our patient had a well-differentiated tumor with negative surgical margins and no evidence of metastasis, adjuvant treatment was not indicated, contrasting sharply with aggressive dedifferentiated forms, as illustrated by a reported case of pulmonary metastasis resulting in death within 22 months (6).

The comprehensive MRI documentation contributes valuable information to limited literature on radiological characteristics. While this study demonstrated MRI as "the more sensitive and accurate imaging modality" for paratesticular masses (5), detailed MRI features specific to liposarcoma remain rarely documented. Our case indicates that characteristic mixed signal intensity without significant enhancement, correlating with well-differentiated histological subtype. Molecular pathogenesis remains poorly understood, as Prakash et al. (2) noted that "due to the rarity of this disease, there are no standardized guidelines". Positive CDK4 nuclear staining supports current WHO 2020 classification criteria (3), providing molecular confirmation of our diagnosis.

CONCLUSION

Well-differentiated paratesticular liposarcoma is a rare malignancy that should be considered in the differential diagnosis of painless scrotal masses. Radical inguinal orchidectomy with complete surgical excision remains the primary treatment and is associated with favorable outcomes in patients with negative surgical margins. Reporting additional cases will help improve the understanding and management of this uncommon tumor.

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Ethical Approval: This article does not contain any studies with human participants or animals performed by any of the authors Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The procedures were in accordance with ethical standards and the Declaration of Helsinki.

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THE
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AUTHOR INDEX

YENTÜR S,	2026;(21)1:01-11.
CANITEZ İO,	2026;(21)1:01-11.
SABUNCU A,	2026;(21)1:01-11.
DEMİRTAŞ T,	2026;(21)1:01-11.
ŞAHİN S,	2026;(21)1:01-11.
KARABEY AKGÜL Ö,	2026;(21)1:01-11.
ÇİL G,	2026;(21)1:01-11.
GÖNÜLTAŞ S,	2026;(21)1:01-11.
ÇOLAKEROL A,	2026;(21)1:01-11.
DİNÇER MM,	2026;(21)1:01-11.
SAVUN M,	2026;(21)1:12-21.
MEMMİ Aİ,	2026;(21)1:12-21.
FİLTEKİN YC,	2026;(21)1:12-21.
ÇOLAKOĞLU Y,	2026;(21)1:12-21.
TOPALOĞLU K,	2026;(21)1:12-21.
CANAT HL,	2026;(21)1:12-21. 2026;(21)2:96-99.
GEZMİŞ CT,	2026;(21)1:22-29.
ÇİLESİ NC,	2026;(21)1:22-29.
ÇETİN B,	2026;(21)1:22-29.
ÇAKIROĞLU B,	2026;(21)1:22-29.
EROĞLU A,	2026;(21)1:22-29.
BALCI MBC,	2026;(21)1:22-29.
ŞAMBEL M,	2026;(21)1:30-38.
ERDOĞAN A,	2026;(21)1:30-38.
ÖZSOY Ç,	2026;(21)1:30-38.
KILIÇ Ş,	2026;(21)1:30-38.
ARSLAN B,	2026;(21)1:30-38.
İNAL MR,	2026;(21)1:30-38.
TAŞ S,	2026;(21)1:30-38.
UZUN E,	2026;(21)1:39-48.
ŞENEL S,	2026;(21)1:39-48.
KOUDONAS A,	2026;(21)1:39-48.
ÖZEN S,	2026;(21)1:39-48.
ARABACI HB,	2026;(21)1:39-48.
KIZILKAN Y,	2026;(21)1:39-48.
EFİL SC,	2026;(21)1:39-48.
CEYLAN C,	2026;(21)1:39-48.
ÖZDEN C,	2026;(21)1:39-48.
MATSUSHITA LY,	2026;(21)1:49-52.
GUIZZO WA,	2026;(21)1:49-52.
VOGEL J,	2026;(21)1:49-52.
CHIARAMELLI P,	2026;(21)1:49-52.
CUNHA JRG,	2026;(21)1:49-52.
FERNANDES RDC,	2026;(21)1:49-52.
TOLEDO LGMD,	2026;(21)1:49-52.
ERTAŞ K,	2026;(21)2:53-59.
BEDİR N,	2026;(21)2:53-59.
KELEŞ MF,	2026;(21)2:53-59. 2026;(21)3:124-130.
İLTER S,	2026;(21)2:53-59.
ERYILMAZ R,	2026;(21)2:53-59. 2026;(21)3:124-130.
KAYALI Y,	2026;(21)2:60-71.
GÖKMEN E,	2026;(21)2:72-80.
ALTUNTAŞ T,	2026;(21)2:72-80.
AKAY HB,	2026;(21)2:72-80.
ÖZGÜR G,	2026;(21)2:72-80.

eISSN 3023-6940

THE
NEW JOURNAL
OF UROLOGY

AUTHOR INDEX

ŞENOĞLU Y,	2026;(21)2:72-80.
ŞEKERCİ ÇA,	2026;(21)2:72-80.
ŞENER TE,	2026;(21)2:72-80.
BETİGÜL MERAL H,	2026;(21)2:81-89.
REZVANİ A,	2026;(21)2:81-89.
KETENCİ İ,	2026;(21)2:81-89.
ALBAYRAK İH,	2026;(21)2:90-95.
DEMİR M,	2026;(21)2:90-95.
YAĞMUR İ,	2026;(21)2:90-95.
ŞENGEL E,	2026;(21)2:90-95.
KAVUKÇU A,	2026;(21)2:90-95.
KATI B,	2026;(21)2:90-95.
PELİT ES,	2026;(21)2:90-95.
ŞEVİK Ç,	2026;(21)2:96-99.
NİŞLİ O,	2026;(21)2:96-99.
ÖZDEMİR H,	2026;(21)2:96-99.
BAYRAKTAR Z,	2026;(21)2:100-104.
TURAN Ş,	2026;(21)2:100-104.
BAKIRLI DC,	2026;(21)2:105-112.
HOROZ E,	2026;(21)2:105-112.
YILMAZ İ,	2026;(21)2:105-112.
İLBEY YÖ,	2026;(21)2:105-112.
IKADINOVIĆ J,	2026;(21)3:113-123.
ĆORIĆ A,	2026;(21)3:113-123.
POZNAN V,	2026;(21)3:113-123.
POPOV M,	2026;(21)3:113-123.
DEMİR M,	2026;(21)3:124-130.
DUMAN V,	2026;(21)3:124-130.
DEMİR H,	2026;(21)3:124-130.
DEMİR C,	2026;(21)3:124-130.
KESKİN S,	2026;(21)3:124-130.
ASLAN R,	2026;(21)3:124-130.
TAKEN K,	2026;(21)3:124-130.
ZENGİN S,	2026;(21)3:131-137.
BOYACI C,	2026;(21)3:131-137.
OLGUN A,	2026;(21)3:131-137.
KUTLUAY O,	2026;(21)3:131-137.
GUL A,	2026;(21)3:131-137.
ÇOBAN F,	2026;(21)3:138-150.
KALYENCİ B,	2026;(21)3:138-150.
ŞANLI A,	2026;(21)3:151-161.
GÖÇER S,	2026;(21)3:151-161.
GÜNGÖR HS,	2026;(21)3:151-161.
DOGAN AE,	2026;(21)3:162-169.
AYDIN MY,	2026;(21)3:162-169.
ORMAN E,	2026;(21)3:170-174.
AKÇA G,	2026;(21)3:170-174.
UZUN H,	2026;(21)3:170-174.
BEDİR R,	2026;(21)3:170-174.
YAZAR S,	2026;(21)3:170-174.
SÖNMEZ C,	2026;(21)3:175-179.
TURHAN A,	2026;(21)3:175-179.
CİN C,	2026;(21)3:175-179.
AYTEKİN C,	2026;(21)3:175-179.
YUYUCU KARABULUT Y,	2026;(21)3:175-179.
TEK M,	2026;(21)3:175-179.

eISSN 3023-6940

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OF UROLOGY

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The purpose of the New Journal of Urology is to contribute to the literature by publishing urological manuscripts such as scientific articles, reviews, letters to the editor, case reports, reports of surgical techniques, surgical history, ethics, surgical education and articles of forensic medicine.

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THE
NEW JOURNAL
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THE
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PREPARATION OF MANUSCRIPT

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THE
NEW JOURNAL
OF UROLOGY

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- Main text
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- Experimental animal studies: ARRIVE guidelines and Guide for the Care and Use of Laboratory Animals, 8th edition
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OF UROLOGY

PREPARATION OF MANUSCRIPT

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- Abstract (unstructured)
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