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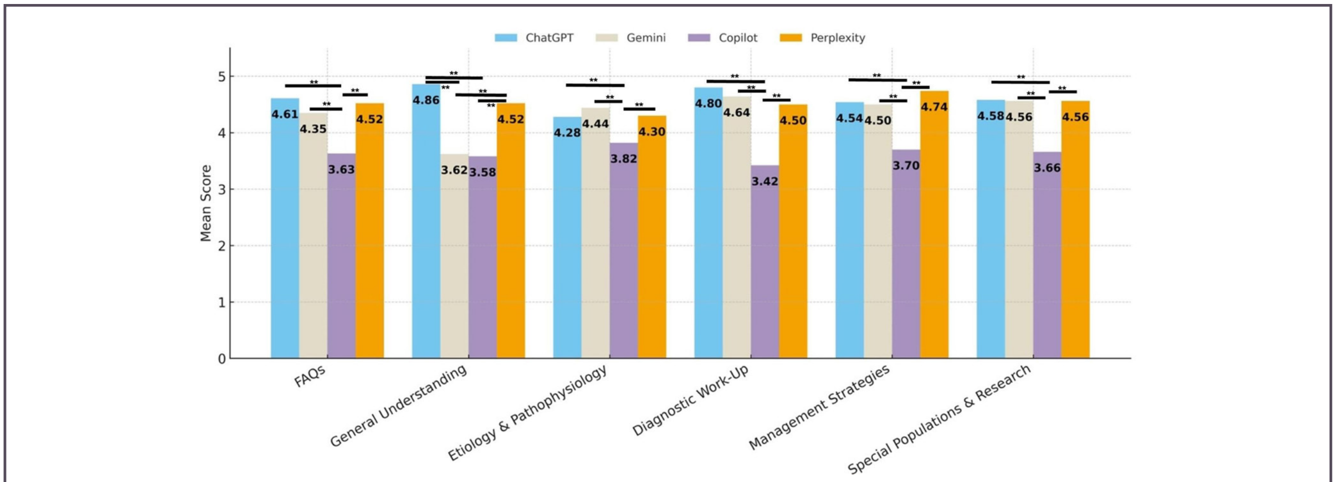

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Dear Colleagues,

We are pleased to have published the third issue of The New Journal of Urology for 2025. This issue includes ten (10) original articles and one (1) case report. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies.

The New Urology Journal is indexed in the TUBİTAK ULAKBİM TR Index since the first issue of 2011. Our journal is indexed in DOAJ, Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, Scilit, Ideal Online Database, J-GATE, and EBSCO. In addition, the New Journal of Urology is in collaboration with the Orcid and CrossRef DOI systems. The process of our journal being included in the ESCI, PubMed, and EMBASE indexes is ongoing.

We are pleased to introduce Dr. Ubeyd Sungur, our new statistical editor. I believe that he will make a great contribution to our journal with his vast experience in this field. The editorial team is very grateful to all the authors and reviewers who have contributed to this issue.

We request that you submit your articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Respectfully yours

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Original Research

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RESEARCH ARTICLE

The Importance of MTHFD2 Expression in Renal Cell Carcinoma

Onur Ceylan [1], Remzi Arslan [1]
[1] Department of Pathology. Ataturk University, Faculty of Medicine, Erzurum, Türkiye

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Corresponding Author;
Onur Ceylan, Assoc.Prof., MD

Address: Ataturk University
Faculty of Medicine Department of
Medical Pathology
Erzurum, Türkiye

E-mail: dr.onurceylan@gmail.com

ORCID
O.C. 0000-0001-7025-0521
R.A. 0000-0002-3198-4706

Abstract

Objective: Renal cell carcinoma (RCC) carries a poor prognosis at advanced stages. Identifying reliable prognostic biomarkers is essential for improved clinical management. Methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), a key mitochondrial enzyme in the folate cycle, is overexpressed in various rapidly proliferating malignancies. However, its prognostic value in RCC remains underexplored. For this reason, we purposed to search the prognostic role of MTHFD2 expression in RCC.

Materials and Methods: This study included 124 RCC patients who applied radical nephrectomy between 2015 and 2020. Immunohistochemical analysis of MTHFD2 expression was performed on paraffin-embedded tumor samples. Expression levels were classified using a histoscore-based system: low (grades 0–1) and high (grades 2–3). Correlations between MTHFD2 expression and clinical/pathological parameters were evaluated, and survival analysis was conducted.

Results: MTHFD2 overexpression was detected in 53% of tumors and was absent in adjacent non-tumor tissues. High expression was significantly associated with adverse prognostic features, including higher histological grade, sarcomatoid differentiation, advanced pT stage, and presence of distant metastases (all $p < 0.05$). Patients with high MTHFD2 expression had significantly reduced overall survival ($p < 0.001$). Remarkably, early-stage tumors (pT1–2) with high MTHFD2 expression were linked to shorter survival compared to more advanced tumors (pT3–4) with low expression.

Conclusion: Our results pointed out that high expression of MTHFD2 is associated with poor prognosis in RCC and may function as an independent prognostic biomarker. These findings underscore the potential of MTHFD2 in risk stratification and as a therapeutic target in RCC.

Keywords: MTHFD2, renal cell carcinoma, prognostic marker, immunohistochemical study

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INTRODUCTION

Renal cell carcinoma (RCC) ranks ninth among all cancers (1), with its incidence increasing by approximately 2% in recent years (2). Around one-third of RCC cases metastasize, and metastases are often already present at the time of diagnosis (3). Despite slight improvements in the five-year survival rate, the prognosis for advanced-stage RCC remains poor (1). Recently, therapies targeting vascular endothelial growth factor (VEGF) and specific immunotherapy agents have been introduced as standard treatments for RCC. However, the emergence of resistance to these targeted therapies has become an increasing concern. Therefore, novel treatment strategies are urgently needed, particularly for patients with advanced disease (4).

Folic acid metabolism controls nucleotide synthesis, methylation, and repair, and is involved in the development of many tumors. A single carbon unit is transferred from serine to tetrahydrofolate (THF) by serine hydroxymethyl transferases to form methylenetetrahydrofolate (MTHF). This single carbon unit is then transferred between different types of THF to complete the folate cycle. This cycle consists of separate parallel reactions: cytoplasmic, mitochondrial and nucleus (5). In mitochondria, these reactions take place via two different methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), consisting of MTHFD2 and MTHFD2L (6) (Figure 1). Among these, MTHFD2 is more highly expressed and plays a predominant role in supporting mitochondrial folate metabolism and in responding to growth factor stimulation (7, 8). MTHFD2 is essential for cancer cell proliferation and tumor progression. While it is minimally or not expressed in most normal adult tissues, high levels of MTHFD2 expression have been observed in various malignancies and in developing embryos (6). Previous studies have demonstrated that MTHFD2 overexpression correlates with poor prognosis in some cancers, including colorectal carcinoma (9), breast carcinoma (10), RCC (11), and hepatocellular carcinoma (HCC) (12). However, limited data exist on its specific prognostic role in RCC. Therefore, in this study, we aimed to evaluate the clinical significance of MTHFD2 expression in RCC and explore its association with established prognostic parameters.

MATERIALS AND METHODS

Patients' General Information and Features of Their Tissues

This study included 124 radical nephrectomy materials from patients diagnosed with renal cell carcinoma (RCC) at our institution between January 2015 and 2020. Of these, 86 cases were clear cell RCC, 22 were chromophobe

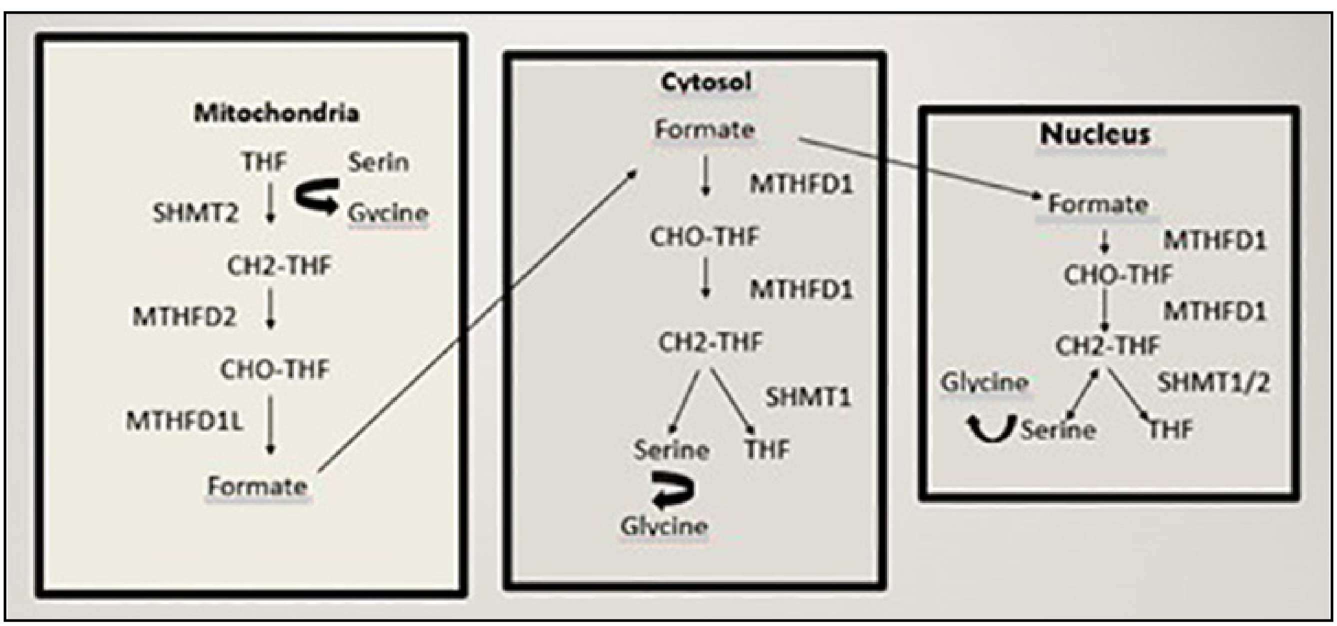

Figure 1. Schematic representation of folate one-carbon metabolism.

RCC, and 16 were papillary RCC. Prognostic parameters such as lymphovascular invasion, histological subtype, histological grade (according to the 2016 The World Health Organisation/International Society of Urological Pathology [WHO/ISUP]), macroscopic tumor diameter, presence of sarcomatoid and rhabdoid features, and pathological staging (pTNM) were recorded. Survival data were also collected. This study was approved by Ethics Committee of Atatürk University (Approval number: B.30.2.ATA.0.01.00/388, Date: 26.06.2020).

Histological grading was not applicable to chromophobe RCC cases; thus, grading evaluation was conducted on 102 cases. Tumor staging including primary tumor (pT), regional lymph nodes (pN), and distant metastases (pM) was based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual (13). For many cases, pN and pM statuses were indeterminate and recorded as pNx and pMx, respectively (Table 1, 2).

The mean follow-up period was 37 ± 17 months (1–71 months). Overall survival was calculated from the date of surgery to either death or the last follow-up. Only RCC-related mortality was included in the survival analysis; deaths due to unrelated causes were excluded. For the purpose of analysis, MTHFD2 expression was categorized as low (histoscore grades 0–1) or high (grades 2–3).

Formalin-fixed, paraffin-embedded blocks containing both tumor and non-tumor tissues were selected from each case for immunohistochemical analysis.

Immunohistochemical Study

Blocks with the highest tumor density were selected and sections of four microns were taken. These materials laid in the Ventana automated immunohistochemistry staining device after being kept on charged slides in a 70-degree drying oven for 15 minutes. Following deparaffinization, dehydration, hydrogen peroxide processes, tissues were treated with MTHFD2 antibody (Leica, United Kingdom). Cytoplasmic staining was considered positive for MTHFD2. For MTHFD2, a staining rate of 0% was classified as Grade 0, 1-10% as Grade 1, 11-49% as Grade 2, and ≥50% as Grade 3. Staining intensity was evaluated as follows: no staining: Grade 0; weak staining: Grade 1; moderate staining: Grade 2; and strong staining: Grade 3. The immunoreactivity score was calculated by multiplying staining intensity and staining rate. And it was evaluated as follows: (negative) 0: Grade 0; 1-3: Grade 1; 4-6: Grade 2; 7-9: Grade 3 (Figure 2).

Table 1. Histopathological and demographic features of the patients

Age ± SD	Patients (n = 124) (%)
	58 ± 13.7
Gender n (%)	
Male	70 (56)
Female	54 (44)
Tumor Macroscopic Diameter (cm)	
n (%)	6.3 ± 2.6
≤ 4 cm	26 (21)
4<x≤7 cm	64 (52)
7<x≤10 cm	24 (19)
>10 cm	10 (8)
Histological Type n (%)	
Clear cell	86 (69)
Papillary	16 (13)
Chromophobe	22 (18)
pT n (%)	
pT1	62 (50)
pT2	20 (16)
pT3	40 (32)
pT4	2 (2)
pN n (%)	
pN0, x	100 (81)
pN1,2, 3	24 (19)
pM n (%)	
pM0,x	104 (84)
pM1	20 (16)
Recurrence n (%)	
Absent	118 (95)
Present	6 (5)
Sarcomatoid Features n (%)	
Absent	118 (95)
Present	6 (5)
Rhabdoid Features n (%)	
Absent	116 (94)
Present	8 (6)
Outcome n (%)	
Survived	94 (76)
Died	30 (24)

pT: *Primary Tumor,* **pN:** *Lymph Node Metastasis,* **pM:** *Distant Metastasis*

Table 2. Correlation between prognostic factors and MTHFD2 expression

	Histoscore				P
	Grade 0 (n = 57)	**Grade 1 (n = 51)**	**Grade 2 (n = 6)**	**Grade 3 (n = 10)**	
Histological Type n					
Clear cell	39	35	6	6	*0.6485*
Papillary	2	12	0	2	
Chromophobe	16	4	0	2	
pT (n)					
pT1, 2	51	25	4	2	***0.0001***
pT3, 4	6	26	2	8	
pN (n)					
pN, x	55	49	6	8	*0.4102*
pN1, 2, 3	2	2	0	2	
pM (n)					
pM0,x	55	39	4	6	***0.0046***
pM1	2	12	2	4	
Recurrence n					
Absent	55	47	6	10	*0.8443*
Present	2	4	0	0	
Sarcomatoid Features n					
Absent	57	49	4	8	***0.0184***
Present	0	2	2	2	
Rhabdoid Features n					
Absent	55	49	4	8	*0.1307*
Present	2	2	2	2	
Outcome n					
Survived	53	45	**7**	6	**< *0.001***
Died	4	6	**1**	4	

pT: *Primary Tumor,* **pN:** *Lymph Node Metastasis,* **pM:** *Distant Metastasis*

Statistical Analysis

The relationship between MTHFD2 expression and prognostic factors was evaluated with the Spearman correlation test. For survival analysis Kaplan-Meier survival analysis and log-rank test were used. The Cox regression multivariate analysis was applied to determine independent prognostic factors. Descriptive information is stated as mean and deviation for continuous measurements and n as percentage for categorical variables. For the two-tailed p value, <0.05 was received as significant. Hazard rate rates obtained as a result of Cox regression analysis presented. In addition, overall survival rate and standard error values reported with 95% confidence intervals (Figure 4). MedCalc software was used for statistical analysis.

RESULTS

Patients' Demographic and Histopathological Features

A total of 124 patients were included in the study, with a mean age of 58 ± 13.7 years (range: 17–85). The male-to-female ratio was 1.3. The histological subtypes of RCC were distributed as follows: clear cell RCC in 69% of cases, papillary RCC in 13%, and chromophobe RCC in 18%. The mean tumor diameter was 6.3 ± 2.6 cm (1.3–13 cm) (Table 1). Regarding tumor grade, 12 cases were grade 4, 32 were grade 3, 42 were grade 2, and 16 were grade 1. During follow-up, 30 patients died due to RCC-related complications. Among the deceased patients, 18 had clear cell RCC, 8 had papillary RCC, and 4 had chromophobe RCC.

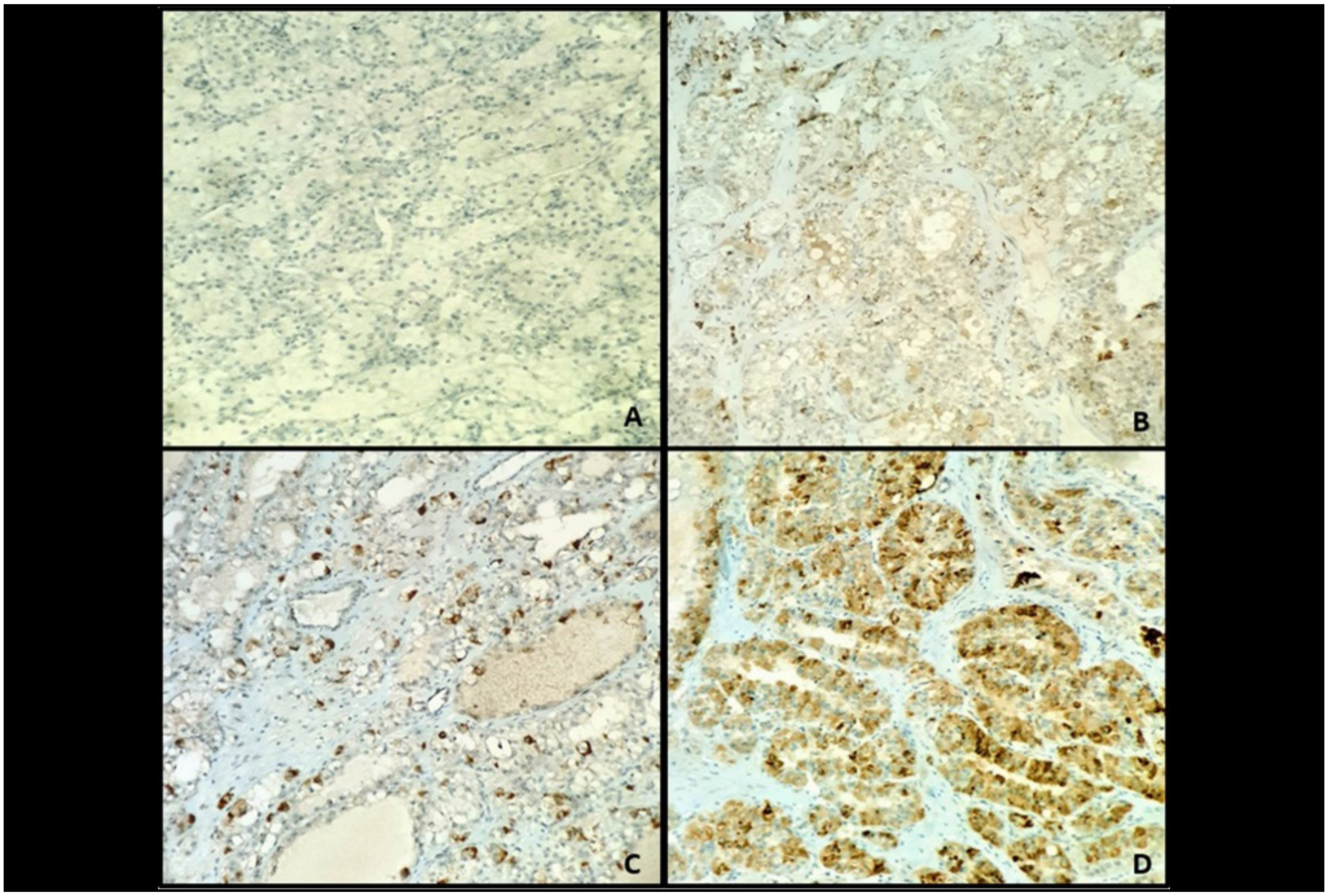

Figure 2. Histological images of MTHFD2 staining (x200) **A:** no MTHFD2 staining, **B:** weak MTHFD2 staining, **C:** moderate MTHFD2 staining, **D:** strong MTHFD2 staining

Prognostic Significance of MTHFD2 expression in RCC

MTHFD2 overexpression was observed in tumor tissues in 66 (53%) of the 124 cases. No MTHFD2 expression was detected in adjacent non-neoplastic tissues. Stronger expression was particularly noted in areas exhibiting rhabdoid and sarcomatoid morphology (Figure 3).

MTHFD2 overexpression was significantly associated with adverse pathological features including advanced pT stage, presence of distant metastasis, and sarcomatoid differentiation (all $p < 0.05$). Moreover, high MTHFD2 expression correlated significantly with key determinants of pT staging such as invasion into the renal pelvis and perirenal adipose tissue ($p < 0.05$ for all). Additionally, an important association was observed between MTHFD2 expression and histological grade in clear cell and papillary RCC ($p = 0.037$). Significant associations weren't found between MTHFD2 expression and histologic subtype, pN stage, recurrence, or rhabdoid features ($p > 0.05$) (Table 2). Likewise, no significant correlations were identified with age ($p = 0.37$), gender ($p = 0.64$), tumor size ($p = 0.98$), lymphovascular invasion ($p = 0.30$), or perineural invasion ($p = 0.31$).

Kaplan–Meier survival analysis revealed 1-, 3-, and 5-year overall survival rates of 85%, 83%, and 80%, respectively. High MTHFD2 expression was significantly associated with decreased survival compared to low expression, as confirmed by the log-rank test ($p < 0.001$) (Figure 4).

In multivariate Cox regression analysis—including MTHFD2 expression, pT stage, and presence of metastasis—MTHFD2 overexpression remained an independent prognostic factor for overall survival (Hazard Ratio = 5.25; 95% CI: 1.30–21.23; $p = 0.0019$).

To further evaluate the prognostic value of MTHFD2, subgroup survival analyses were conducted based on pT and metastasis status. pT stage was dichotomized into early (pT1–2) and advanced (pT3–4). Patients were stratified into the following subgroups:

1- low expression/ no distant metastasis, low expression/ distant metastasis, high expression/no distant metastasis, and high expression/distant metastasis

2- low expression/early pT, low expression/advanced pT, high expression/early pT, and high expression/advanced pT

Patients with high MTHFD2 expression and distant metastasis had the poorest survival outcomes (p = 0.0004), as did those with high MTHFD2 expression and advanced pT stage (p = 0.0031). Notably, patients with early-stage tumors (pT1–2) but high MTHFD2 expression had shorter survival than those with more advanced tumors (pT3–4) and low expression, highlighting its independent prognostic impact (Figures 4).

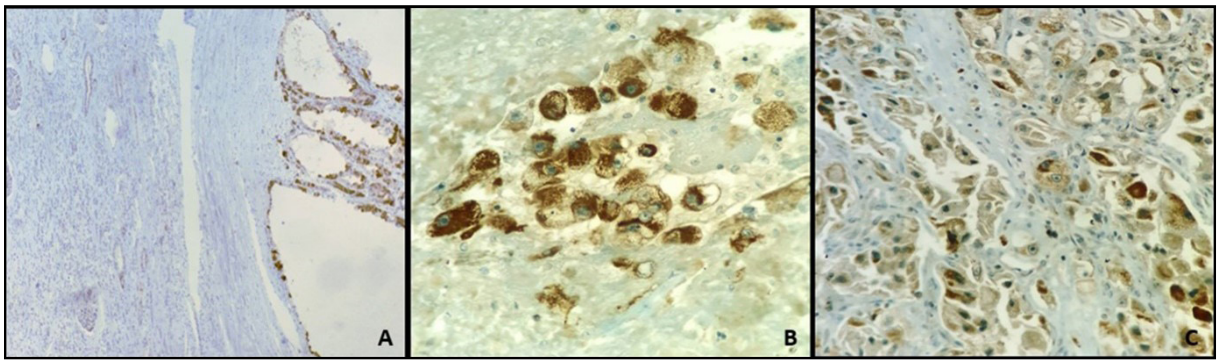

Figure 3. Histological images of MTHFD2 overexpression in different areas

A: Overexpression of MTHFD2 in tumoral areas and no staining in adjacent non-tumoral glomeruli and tubules (x200), **B:** stronger expression with MTHFD2 in areas containing rhabdoid morphology (x400), **C:** stronger expression with MTHFD2 in areas containing sarcomatoid morphology (x200)

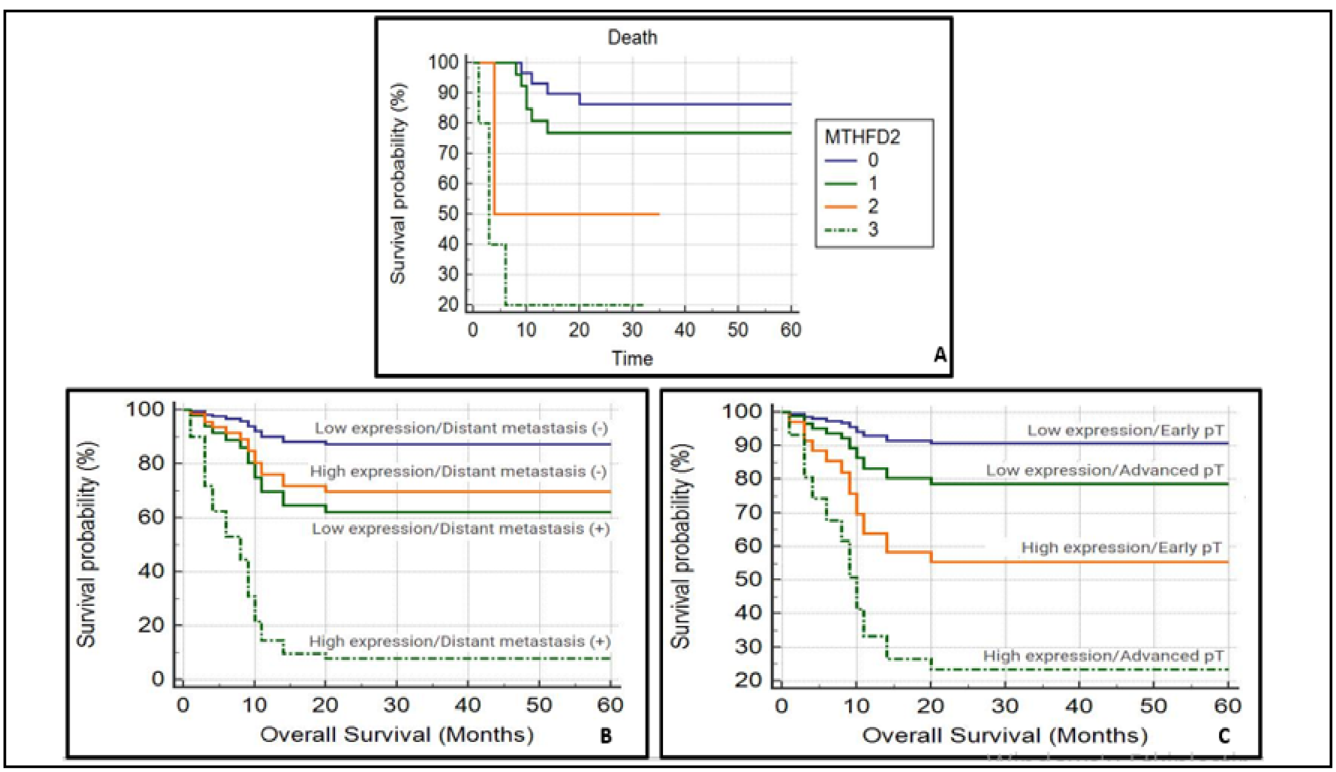

Figure 4.A: Kaplan–Meier survival curve according to MTHFD2 expression, **B:** MTHFD2 expression/distant metastasis status (Cox regression analysis), **C:** MTHFD2 expression/primary tumor (pT) status (Cox regression analysis)

DISCUSSION

In the present study, we investigated MTHFD2 expression in both tumoral and adjacent non-tumoral renal tissues to assess its prognostic value in RCC. Our results demonstrated that MTHFD2 was not expressed in normal kidney tissues but was significantly overexpressed in RCC specimens. Importantly, high MTHFD2 expression was significantly correlated with adverse prognostic factors, such as higher pT stage, distant metastasis (pM), sarcomatoid differentiation, histological grade, and reduced survival. Multivariate analysis confirmed that MTHFD2 overexpression is an independent prognostic marker in RCC. To further explore its prognostic role, subgroup survival analyses were performed based on pT stage and distant metastasis. Patients with high MTHFD2 expression combined with either distant metastasis or advanced pT stage had the shortest survival times. Remarkably, even among early-stage tumors (pT1–2), cases with MTHFD2 overexpression exhibited shorter survival compared to those with more advanced tumors (pT3–4) but low MTHFD2 expression. This finding strongly supports the role of MTHFD2 as an independent and clinically relevant prognostic biomarker.

Our findings are consistent with previous studies investigating the association of RCC and MTHFD2. In RCC, Lin et al. showed that MTHFD2 expression was significantly associated with advanced clinical stage, higher pathological grade, and reduced survival, and proposed that MTHFD2 may represent a therapeutic target (14). Silva et al. reported that MTHFD2 expression differed significantly among subtypes of RCC, and high MTHFD2 levels were associated with poor histological features and short survival (15).

In addition, recent studies in the literature have increasingly emphasized the relationship between MTHFD2 overexpression and poor prognosis in various malignancies (6, 9–12). Nilsson et al. showed that MTHFD2 is absent in normal adult tissues but is highly expressed in several cancers, particularly breast cancer, and is associated with poor prognosis, suggesting a critical role for mitochondrial one-carbon metabolism in malignancy (6). Similarly, Ju et al. reported that MTHFD2 promotes tumor growth and distant metastasis in colorectal carcinoma, and its suppression significantly reduced tumor burden (16). Miyo et al. also found that MTHFD2 overexpression correlated with lower disease-free and overall survival in colorectal cancer (17). In hepatocellular carcinoma, Liu et al. demonstrated that MTHFD2 overexpression was associated with worse outcomes, including advanced stage, recurrence, and metastasis (18).

In light of these results and the existing literature, our study further supports the hypothesis that MTHFD2 plays a pivotal role in tumor survival, progression, and metastasis. The significant associations between MTHFD2 expression and key prognostic indicators underscore its potential utility as a prognostic biomarker in RCC.

We did not find a statistically significant association between MTHFD2 expression and recurrence, which may be attributed to the low number of recurrent cases (5%) in our cohort. This limitation highlights the need for further studies with larger patient populations to explore this relationship more thoroughly.

CONCLUSION

Our findings show that MTHFD2 overexpression is associated with poor prognosis in RCC. The most notable result is that even early-stage RCC cases with high MTHFD2 expression demonstrated worse survival outcomes than those with advanced-stage disease and low expression. These results promote the potential usage of MTHFD2 as an independent prognostic biomarker in RCC. However, further validation in larger, multi-institutional cohorts is necessary to confirm its clinical utility.

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Conflict of Interest: None declared.

Ethics Approval: This study was approved by Ethics Committee of Atatürk University (Approval number: B.30.2.ATA.0.01.00/388, Date: 26.06.2020).

Author Contribution: Consept and design, data analysis, data collection, critical revision and supervision; Onur Ceylan. The draft of the manuscript, data acquisition statistical analysis; Onur Ceylan and Remzi Arslan. All

authors have read and approved the final manuscript.

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RESEARCH ARTICLE

Evaluation of Human Serum Albumin's Potential Effects on Renal Ischemia-Reperfusion Injury in a Rat Model

Ümit Yıldırım [1], Mehmet Uslu [1], Mehmet Ezer [1], İsmet Bilger Erihan [1], Ali Alper Kahraman [2], Seyit Ali Bingöl [2]

[1] Department of Urology, Kafkas University, Faculty of Medicine, Kars, Türkiye

[2] Department of Histology and Embryology, Kafkas University, Faculty of Medicine, Kars, Türkiye

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Corresponding Author;
Ümit Yıldırım, Assoc. Prof., MD

Address: Kafkas University, School of Medicine, Department of Urology, Kars, Türkiye,
E-mail: dr.umityildirim87@gmail.com

ORCID

Ü.Y. 0000-0003-3065-9001
M.U. 0000-0002-8370-3793
M.E. 0000-0003-4422-6768
İ.B.E. 0000-0003-0763-5220
A.A.K. 0000-0003-2924-2655
S.A.B. 0000-0001-6422-9582

Abstract

Objective: The purpose of this study is to examine how acute ischemia-reperfusion injury (IRI) in a rat model is affected by replacing human serum albumin (HSA).

Material and Methods: Thirty-six male Wistar albino rats were randomly divided into six groups: Control, Ischemia, Ischemia-Reperfusion (IR), Placebo, Preoperative Albumin (A1), and Intraoperative Albumin (A2). The renal artery of the kidney was blocked using 3/0 silk sutures to induce ischemia, followed by one hour of reperfusion in certain groups. The A1 group received 20% HSA (2.5 g/kg intraperitoneally) 24 hours before surgery, while the A2 group received the same dose 30 minutes before reperfusion. Samples of kidney and blood tissue were gathered for immunohistochemical, histological, and biochemical assessments. Biochemical parameters included ischemia-modified albumin (IMA), total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI). Histological assessments measured cortical and medullary damage, while immunohistochemistry evaluated oxidative stress markers such as superoxide dismutase (SOD1), glutathione reductase (GSR), and myeloperoxidase (MPO).

Results: Biochemical analyses showed no significant differences in TOS, TAS, OSI, and IMA levels between groups. Histological evaluation revealed that the A2 group had reduced kidney damage, particularly in the medulla, compared to the ischemia and placebo groups. Immunohistochemical findings indicated minor differences in oxidative stress marker expression, though not statistically significant.

Conclusion: Intraoperative HSA replacement has the potential to reduce ischemia-induced renal injury in rats, especially in medullary tissues. These findings suggest that HSA may be a promising therapeutic agent for managing ischemic kidney damage during partial nephrectomy. Further clinical studies are needed to validate its efficacy and safety in human applications.

Keywords: human serum albumin, ischemia-reperfusion injury, oxidative stress, rat model, renal ischemia

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INTRODUCTION

Renal cell carcinoma (RCC) is the seventh most common type of cancer globally, with approximately 350,000 new cases diagnosed annually (1). The incidence of RCC has increased sharply, especially in the past 50 years. This rise can be attributed to advancements in medical imaging technologies such as magnetic resonance imaging and computed tomography. These remarkable improvements in diagnostic equipment have also enhanced the variety and success of treatment methods (2). The guidelines of the European Association of Urology recommend partial nephrectomy (PN) for tumors classified as T1 (localized) in the TNM tumor staging system (3,4). During PN, it is often necessary to temporarily clamp the vessels supplying blood flow to the kidney to delineate tumor margins better, clearly visualize the tumor base, and prevent excessive bleeding. Even though this interruption in blood flow is temporary, the ischemic damage to the kidney can result in permanent loss of function (5).

Reactive oxygen species (ROS) generated by mitochondria are temporarily increased when the kidney is reperfused or ischemic, which sets off pro-inflammatory processes. Among other pathogenic processes, excessive ROS production by mitochondria damages cellular components and activates various acute injury mechanisms that jeopardize kidney function (6). Numerous studies in the literature have been conducted to minimize ischemia-reperfusion injury (IRI) caused by warm ischemia applied to the kidney during PN (7,8). Previous studies have clearly demonstrated that human serum albumin (HSA) is one of the primary antioxidant components in the body that combats ROS (9). Superoxide dismutase-1 (SOD1), myeloperoxidase (MPO), and glutathione reductase (GSR) are significant indicators of oxidative stress. SOD1 prevents oxidative damage by converting superoxide radicals into hydrogen peroxide and oxygen, and hence plays a central role in cellular defense systems. MPO, an enzyme found primarily in neutrophils, has a function in the formation of reactive oxygen species and is regarded as a key marker in inflammatory responses. GSR helps to maintain cellular redox homeostasis by supporting the glutathione cycle. Assessment of the expression and activity levels of these proteins gives essential information in evaluating the extent of oxidative stress and damage in renal tissue (10–12). However, according to our literature review, the effects of HSA replacement on renal IRI have not yet been investigated in rat models. No human studies have been identified on this subject either.

This study aims to investigate the potential effects of HSA replacement on acute IRI in a rat model and to shed light on future human studies on this subject.

MATERIALS AND METHODS

Animals

This current research was conducted at Kafkas University Laboratory Animal Center following the "Guide for the Care and Use of Laboratory Animals." Ethical approval for the project was obtained from the Kafkas University Animal Research Local Ethics Committee (decision date/number: 01-03-2023/2023-021). This study was funded by the Kafkas University Scientific Research Projects Unit (Project number: 2023-TS-58). A total of 36 male Wistar albino rats (aged 8–12 weeks, weighing 180–260 grams) were used in the study. The rats were housed with ad libitum food access in a room maintained at 22 ± 2°C with a 12-hour light-dark cycle.

Groups

The rats were randomly divided into six equal groups:

Control group: Nephrectomy was performed on healthy kidney tissue after anesthesia.

Ischemia group: One kidney was subjected to ischemia for one hour after anesthesia, and the damaged kidney was then removed. Although a separate sham group was not used, the control group underwent both anesthesia and nephrectomy without ischemia, reflecting both healthy renal tissue and surgical stress response. Thus, it served the functional purpose of a sham group.

IR group: One kidney underwent one hour of ischemia followed by one hour of reperfusion after anesthesia. The kidney tissue was removed after completing the reperfusion phase.

Placebo group: The procedure included one hour of ischemia followed by one hour of reperfusion. The rats were administered 12.5 ml/kg saline intraperitoneally 24 hours before surgery. At the conclusion of the reperfusion phase, kidney tissue was extracted.

Preoperative albumin (A1) group: The procedure included one hour of ischemia and one hour of reperfusion. The rats were given 2.5 g/kg of 20% HSA (12.5 ml/kg) intraperitoneally 24 hours before surgery (13, 14). At the conclusion of the reperfusion phase, kidney tissue was extracted.

Intraoperative albumin (A2) group: The procedure included one hour of ischemia and one hour of reperfusion. The rats were administered 2.5 g/kg of 20% HSA (12.5 ml/kg) intraperitoneally 30 minutes before the start of reperfusion. Kidney tissue was removed after the reperfusion period.

Anesthesia

Rats were given intramuscular injections of 90 mg/kg ketamine (Keta-Control®, Doa Pharmaceuticals) and 10 mg/kg xylazine (Vetaxyl®, Vet-Agro) to induce anesthesia (15). The procedures were carried out with constant monitoring and careful management of anesthesia, ensuring the well-being of the animals throughout the process.

Surgical Procedure

Following the induction of anesthesia, all rats were positioned in the supine position, and the surgical site was shaved and disinfected. An abdominal incision measuring 2 cm was performed. The renal artery of the kidney was blocked using 3/0 silk sutures to induce ischemia, and then the abdomen was closed. To achieve reperfusion, the surgical team reopened the abdominal cavity, removed the sutures around the renal artery, and then closed the abdomen again. Following the restoration of blood flow, the abdominal cavity was surgically accessed, and samples of tissue and blood were obtained. At the end of the entire experimental phase, the animals were responsibly sacrificed via decapitation while under deep anesthesia.

Biochemical Analyses

Serum samples were assessed to determine ischemia-modified albumin (IMA), total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index (OSI). The levels of TOS and TAS were quantified using Erel's automated colorimetric method (Rel Assay Diagnostics®, Mega Tıp, Türkiye). TOS results were expressed in μmol H_2O_2 Eq/L, while TAS values were presented in mmol Trolox Eq/L. OSI, an indicator of oxidative stress, was calculated as the ratio of TOS to TAS using the formula μmol [(TOS / (TAS × 1000)) × 100]. IMA concentrations were measured with a colorimetric approach (Rel Assay Diagnostics®, Mega Tıp, Turkey) and a spectrophotometer, with outcomes reported in u/L.

Histological Analyses

Following the experimental procedures, kidney tissues were preserved in 10% formalin and embedded in paraffin blocks. Serial sections of 5 μm thickness were cut using a microtome (Leica RM2125RTS). The sections were stained with hematoxylin-eosin (H&E), and images were captured using a light microscope (Olympus BX53, Tokyo, Japan). Each kidney was evaluated using two slides, and five fields per slide were analyzed under 20x magnification for scoring. The cortex and medulla were scored separately (0: none, 1: mild, 2: moderate, 3: severe). Total tissue damage was calculated by summing the scores.

Cortical damage was assessed by evaluating cellular changes in Bowman's capsules, distal tubules, and proximal tubules. Medullary damage was assessed by examining debris and hemorrhage in descending and ascending Henle's loops and the tubules.

Immunohistochemical (IHC) evaluations were performed using avidin-biotin-peroxidase complex (ABC) staining. Polyclonal MPO primary antibody (Elabscience, E-AB-10466, 1/50), polyclonal GSR primary antibody (Elabscience, E-AB-14115, 1/50), and polyclonal SOD1 primary antibody (Cloud-Clone, PAB960Ra01, 1/50) were used for IHC staining. Images were acquired with a light microscope (Olympus BX53, Tokyo, Japan). Each animal was assessed using two slides and five fields, and the immunoreactivity intensities of kidney histological structures (glomerulus, Bowman's capsule, urinary space, vascular space, distal tubule, and proximal tubule in the cortex) were determined.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed or ordinal data. For comparisons between multiple groups, one-way ANOVA was applied for normally distributed variables; when a significant difference was detected, post hoc pairwise comparisons were performed using Tukey's Honestly Significant Difference (HSD) test. The Kruskal-Wallis test was used for multiple comparisons of non-normally distributed or ordinal data. When a significant difference was detected, post hoc pairwise comparisons were performed using the Dunn-Bonferroni test to control the Type I error rate.

A two-tailed p-value of less than 0.05 was considered statistically significant. Exact p-values (e.g., p=0.032) were reported rather than threshold values. Effect sizes (e.g., eta squared for ANOVA or Cohen's d for pairwise comparisons) were not calculated due to the unavailability of raw data.

RESULTS

Biochemical findings

Table 1 displays the outcomes of biochemical testing. No statistically significant differences were observed in TAS, TOS, OSI, and IMA levels between paired groups. Although a statistical difference in TAS values was found among multiple groups in one-way ANOVA testing, post-hoc analysis revealed no significant differences between any two groups.

Histological Findings

Histological examinations included two slides per animal and five fields per slide. Histological images of each group are shown in Figure 1.

In the renal cortex, damage to Bowman's capsules was similar across all groups. Proximal tubule damage was higher in the ischemia group than in the other groups, while distal tubular damage was similar across the groups. When overall cortical damage was assessed, the ischemia group showed the highest degree of damage. The least damage was observed in the control group, with the intraoperative albumin-treated group displaying damage levels closer to the control group (Figure 1, A1–6).

In the renal medulla, damage to descending and ascending Henle's loops and tubular debris/hemorrhage was significantly higher in the ischemia group. Damage in the IR group was close to the ischemia group, while all other groups exhibited significantly lower levels of damage (Figure 1, B1–6).

Table 2 displays the results of the histological evaluations. Cortical damage did not differ significantly between the groups. Group A2 showed significantly less medullary damage than the ischemia group (p = 0.001). While group A1 performed better than the ischemia group, the differences were not statistically significant. When all groups were evaluated together for total damage, a statistically significant difference was detected (p=0.009). However, no significant differences were found between individual group pairs in post hoc pairwise comparisons.

Immunohistochemical Findings

Immunohistological analyses included two slides per animal and five fields per slide. Immunohistochemical images for each group are shown in Figure 1 (C-D-E).

Table 1. Comparisons of biochemical findings between groups (mean ± SD).

Groups	TAS (mmol/L)	TOS (μmol/L)	OSI	IMA (u/L)
Control	2.67 ± 0.52[a]	25.33 ± 5.35[a]	0.97 ± 0.24[a]	184.47 ± 50.14[a]
Ischemia	1.04 ± 0.84[a]	22.71 ± 10.88[a]	4.24 ± 3.71[a]	209.64 ± 146.28[a]
IR	1.05 ± 1.03[a]	23.68 ± 16.03[a]	4.55 ± 3.79[a]	272.68 ± 200.50[a]
Preop Albumin (A1)	0.88 ± 0.93[a]	26.67 ± 3.01[a]	6.65 ± 4.18[a]	154.65 ± 25.10[a]
Intraop Albumin (A2)	1.15 ± 1.01[a]	13.86 ± 5.44[a]	2.76 ± 3.82[a]	104.70 ± 121.93[a]
Placebo	0.83 ± 1.13[a]	19.25 ± 9.42[a]	5.12 ± 4.02[a]	169.53 ± 107.17[a]
p-value	0.016	0.223	0.139	0.309

TAS: total antioxidant status, TOS: total oxidant status, OSI: oxidative stress index, IMA: ischemia-modified albumin, IR: ischemia-reperfusion, *p-value*: *One-way ANOVA*, SD: Standard Deviations, [a]: Different superscripts in the same column indicate statistical differences between groups (*post-hoc Tukey HSD p≤0.0033*).

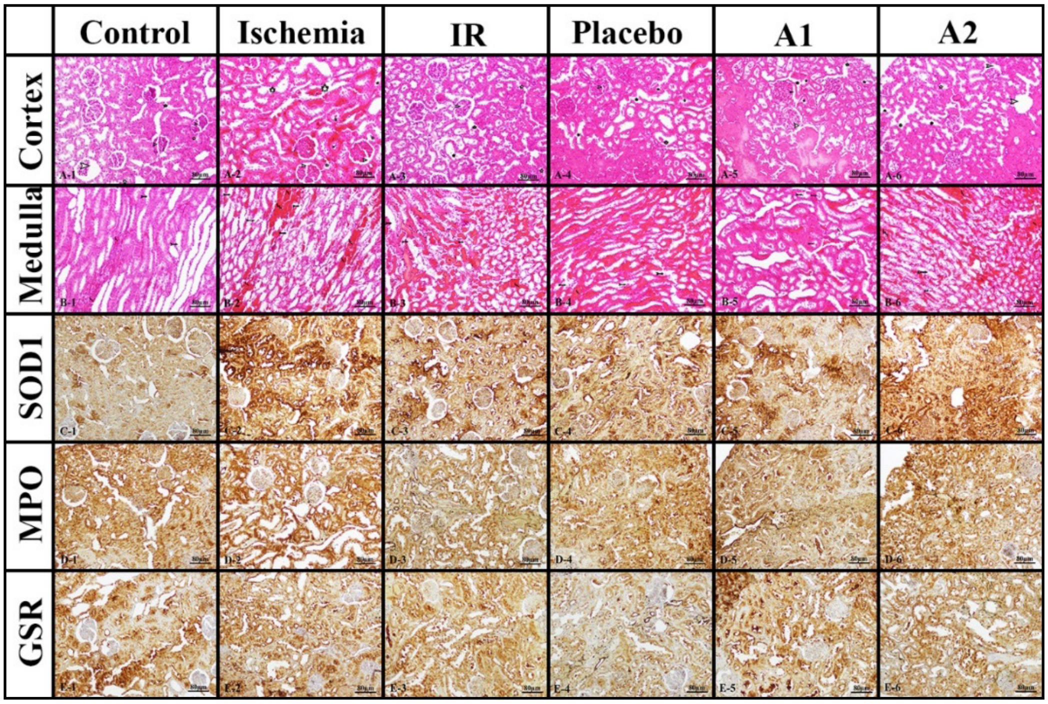

Figure 1. A. Cortex H&E staining (Arrowhead: Glomerular damage, Leaf: Tubulus Distalis damage, Star: Tubulus Proksimalis damage), A1-6, 20x (80µm). B. Medulla H&E staining (Arrow: Tubulus damage, Lightning: Hemorrhage), B1-6, 20x (80µm). C. SOD1 immunoreactivity, C1-6, 20x (80µm). D. MPO immunoreactivity, D1-6, 20x (80µm). E. GSR immunoreactivity E1-6, 20x (80µm).

The results of SOD1 immunohistochemistry are presented in Table 3. The highest cortical immunoreactivity for SOD1 was observed in the ischemia and IR groups, while other groups exhibited similar levels. Medullary immunoreactivity was comparable across all groups. When these regions were combined, no significant differences in SOD1 immunoreactivity were detected among the groups (Figure 1, C1–6).

The results of MPO immunohistochemistry are shown in Table 3. The highest cortical immunoreactivity for MPO was observed in the control group. Medullary immunoreactivity was similar across all groups. When both regions were considered together, no significant differences in MPO immunoreactivity were identified among the groups (Figure 1, D1–6).

Table 2. Comparisons of histopathological findings between groups [median (Q1-Q3)].

Groups	Cortex Damage (CD)	Medulla Damage (MD)	Total Damage (CD+MD)
Control	0.0 (0.00-1.125)^{a}	0.50 (0.375-0.625)^{ab}	0.50 (0.375-2.00)^{a}
Ischemia	0.75 (0.50-1.00)^{a}	2.00 (1.875-3.00)^{b}	3.00 (2.375-3.625)^{a}
IR	0.50 (0.375-1.50)^{a}	1.00 (0.0-1.50)^{ab}	1.50 (0.375-3.00)^{a}
Preop Albumin (A1)	0.50 (0.0-1.25)^{a}	0.50 (0.0-0.50)^{ab}	0.75 (0.50-1.625)^{a}
Intraop Albumin (A2)	0.50 (0.0-0.75)^{a}	0.0 (0.0-0.50)^{a}	0.50 (0.50-0.75)^{a}
Placebo	0.50 (0.375-1.625)^{a}	0.75 (0.375-1.00)^{ab}	1.00 (0.875-2.625)^{a}
p-value	0.703	0.002	0.009

p-value: *Kruskal wallis*. ^{a,b}: Different superscripts in the same column indicate statistical differences between groups (*post-hoc Dunn-Bonferroni test, p≤0.0033*). (MD: Ischemia-A2 p=0.001).

Table 3. Comparisons of total CAT, XDH, and GPX1 immunoreactivity between groups [median (Q1-Q3)].

Groups	SOD1	MPO	GSR
Control	0.0 (0.0-0.625)[a]	1.25 (0.375-2.00)[a]	1.00 (0.875-1.625)[a]
Ischemia	0.25 (0.0-1.125)[a]	0.75 (0.50-1.00)[a]	0.75 (0.375-1.125)[a]
IR	0.25 (0.0-1.125)[a]	0.50 (0.375-1.125)[a]	0.75 (0.0-1.50)[a]
Preop Albumin (A1)	0.25 (0.0-0.625)[a]	0.50 (0.375-1.00)[a]	0.75 (0.0-1.125)[a]
Intraop Albumin (A2)	0.25 (0.0-0.75)[a]	0.50 (0.375-1.00)[a]	0.75 (0.50-1.125)[a]
Placebo	0.50 (0.0-0.625)[a]	0.50 (0.375-1.00)[a]	0.75 (0.50-1.125)[a]
p-value	0.965	0.618	0.740

SOD1: superoxide dismutase, MPO: myeloperoxidase, GSR: glutathione reductase, IR: ischemia-reperfusion, *p-value*: *Kruskal wallis*. [a]: Different superscripts in the same column indicate statistical differences between groups (*post-hoc Dunn-Bonferroni test, $p \leq 0.0033$*).

The results of GSR immunohistochemistry are also provided in Table 3. The highest cortical immunoreactivity for GSR was found in the control group. Medullary immunoreactivity was comparable among all groups. When both regions were combined, no significant differences in GSR immunoreactivity were observed among the groups (Figure 1, E1–6).

DISCUSSION

The key finding of the presented study is that intraoperative HSA showed a potential for reducing ischemic damage in the kidney in a rat model. While this reduction was statistically significant in some groups, it was not significant in others. Although preoperative intraperitoneal administration allows more time for systemic absorption, the peak plasma concentration may occur too early, potentially declining before the critical reperfusion phase. In contrast, intraoperative administration provides a synchronized antioxidant effect exactly at the onset of reperfusion, which may explain its superior protective outcome despite lower cumulative plasma exposure (16,17).

The impact of albumin on ischemia-reperfusion injury (IRI) in different rat model tissues has been the subject of several investigations. Watts and Maiorano showed that minimal levels of albumin replacement significantly reduced myocardial damage caused by ischemia and reperfusion in rats, likely through antioxidant mechanisms (18). Sampaio de Holanda and colleagues provided direct evidence in their research that sulforaphane and albumin reduced intestinal IRI. They proposed that the antioxidant abilities of albumin may be responsible for this decrease. (19). Tang et al. studied the impact of HSA on global cerebral ischemia injury in rats and discovered that HSA therapy could mitigate early neuronal damage through Wnt/β-catenin/ROS signaling pathways (20). Last but not least, in a study conducted on ischemic rat ovaries, HSA alleviated tissue damage caused by IRI. Similar to our study, HSA was also administered intraperitoneally in this research, which is significant and supports our findings (14).

The effects of various active substances on IRI in rat kidneys have been previously studied using biochemical markers such as TAS, TOS, and IMA. Compared to the placebo group, TAS levels in the treatment groups were significantly higher in several of these studies, while TOS levels were significantly lower. Significant differences in IMA levels between groups were also reported in a number of studies (21–24). In our study, although not statistically significant, TAS levels were found to be higher in the A2 group compared to the placebo group. Similarly, we found that TOS levels in the A2 group were lower than those in the placebo group, but the difference was again not statistically significant.

Research has also examined renal IRI in a rat model utilizing albumin-enriched nanocomplexes. An albumin-enriched nanocomplex was created for the solubilization and intravascular delivery of clopidogrel bisulfate. This study documented the positive impact of the administered nanocomplex on IRI. Nonetheless, it is not possible to discuss the effects of pure albumin in this study, as albumin was primarily used as a carrier protein (25).

Maintaining kidney function after PN is crucial for patients with a single kidney, those diagnosed with chronic kidney failure before surgery, patients with multiple renal masses, and those with a history of proteinuria. Although the goal of PN is to remove the tumor while preserving the surrounding healthy parenchyma, studies have shown an approximately 10% decrease in glomerular filtration rates after surgery. This decrease is influenced by multiple factors, including the type of ischemia used (26). Albumin is among the most prevalent proteins in the mammalian body, with around 40% found in circulating blood. It is a significant constituent of various extracellular fluids, including interstitial fluid, lymph, and cerebrospinal fluid (27). Research indicates that hypoalbuminemia is identified in almost 90% of hospitalized elderly patients, attributable to various sociodemographic variables, including malnutrition (28). The scientific data indicate that the average age of patients diagnosed with kidney tumors exceeds 60, suggesting that most patients are elderly (29). When this information is interpreted, it should be considered that patients undergoing PN for kidney tumors with ischemia may be hypoalbuminemic.

The findings of our research show that HSA may reduce ischemia-induced renal ischemic damage in a rat model. The data obtained may not directly translate to humans; nevertheless, the use of HSA, which is generally an easily supplemented substance, should be evaluated in humans prior to PN. Especially in patients with hypoalbuminemia due to malnutrition or aging, preoperative HSA replacement may have potential benefits. Comprehensive clinical studies involving larger patient groups should be conducted on this subject.

Limitations

This study was conducted using a rat model, and the findings cannot be directly generalized to humans. Without clinical studies conducted on humans, the validity of the results remains limited. Additionally, the number of animals used in the study was limited (36 rats). Larger sample groups could provide stronger and more generalizable results. Although differences were observed among groups in the biochemical results (such as TAS, TOS, OSI, and IMA), these differences did not achieve statistical significance due to the small sample size, making it difficult to assess the effects of the study fully. Another limitation is related to the timing of HSA administration. Although the effects of albumin replacement administered at different time points (preoperatively and intraoperatively) were evaluated, the effects of various doses and timing protocols were not investigated.

Furthermore, the study only evaluated the acute effects of HSA on renal damage. The long-term outcomes of albumin replacement were not examined. In addition, the study's control group was limited to healthy renal tissue. To reduce animal use and maintain ethical standards, the study employed a single control group that sufficiently represented sham conditions by including anesthesia and surgical manipulation without ischemia or reperfusion. The potential effects of other possible control groups (e.g., different antioxidant treatments) were not investigated.

Although the present study has certain limitations, we believe that the results will still guide future research. This study is pioneering in its field and examines a topic with high clinical applicability.

CONCLUSION

In a rat model, human albumin has the potential to reduce renal parenchymal ischemia injury, particularly when administered intraoperatively. To verify these findings in humans, further clinical trials with a wider range of patient demographics and higher sample sizes are necessary. By expanding our understanding of the role of albumin in renal protection, future studies could pave the way for improved outcomes in kidney surgeries and enhanced postoperative recovery and nephrological health.

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Conflict of Interest: The author declares that they have no conflicts of interest.

Ethics Committee: Ethical approval for the project was obtained from the Kafkas University Animal Research Local Ethics Committee (decision date/number: 01-03-2023/2023-021).

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RESEARCH ARTICLE

Efficacy of the HALP Score in Predicting Progression in Patients Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer

Rıdvan Kayar [1], Kemal Kayar [2], İlker Artuk [2], Samet Demir [2], Emre Tokuç [3], Metin İshak Öztürk [1]

[1] Department of Urology, University of Health Science, Van Training and Research Hospital, Van, Türkiye
[2] Department of Urology, Haydarpaşa Numune SUAM, University of Health Science, İstanbul, Türkiye
[3] Department of Urology, Medical Park Göztepe Hospital Complex, Bahçeşehir University, Istanbul, Türkiye

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Corresponding Author;
Rıdvan Kayar, M.D.
Address: SBU Van Training and Research Hospital, Urology, Van, Türkiye
E-mail: dr.ridvankayar@gmail.com

ORCID
R.K. 0000-0002-1765-919X
K.K. 0000-0003-0731-9877
İ.A. 0000-0002-7889-4943
S.D. 0009-0006-5333-134X
E.T. 0000-0002-5885-9278
M.İ.Ö. 0000-0002-1868-2316

Abstract
Objective: This study investigated the prognostic value of the HALP score, comprising haemoglobin, albumin, lymphocyte, and platelet parameters, on progression and progression-free survival (PFS) in patients undergoing radical cystectomy (RC) for non-metastatic muscle-invasive bladder cancer (MIBC).
Material and Methods: A retrospective analysis was conducted on 134 MIBC patients who underwent RC between February 2014 and January 2024. The HALP score was calculated using the formula: HALP = (haemoglobin × albumin × lymphocytes) / platelets. Associations between HALP score, clinicopathological parameters, progression, and PFS were assessed via Kaplan-Meier survival analysis, ROC curve analysis, and multivariate logistic regression.
Results: The median HALP score was significantly lower in patients with disease progression (29.19 [IQR: 19.17–41.81]) compared to those without progression (37.55 [IQR: 29.61–52.25]; $p = 0.021$). Patients with a HALP score <36.38 had a mean PFS of 68.8 months (95% CI: 52.6–85.1), compared to 82.4 months (95% CI: 66.5–98.2) in patients with a HALP score ≥36.38 ($p=0.021$). ROC analysis yielded an AUC of 0.619 (95% CI: 0.518–0.721) for predicting progression, with sensitivity and specificity of 54.9% and 55.4%, respectively. Perineural invasion (PNI) emerged as an independent prognostic factor for progression (OR=2.56, 95% CI: 1.011–6.482, $p=0.047$), and low preoperative albumin levels significantly increased progression risk ($p=0.032$).
Conclusions: Although the HALP score is a statistically significant prognostic marker for predicting progression in patients with MIBC, it has limited predictive power. Our results demonstrate the potential of the HALP score as a helpful tool in individualised treatment approaches. However, the prognostic value of the HALP score needs to be confirmed in prospective and multicentre studies in larger patient populations.

Keywords: HALP score, muscle invasive bladder cancer, progression, radical cystectomy

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INTRODUCTION

Bladder cancer (BC) is the tenth most common malignancy worldwide and the thirteenth leading cause of cancer-related mortality. Exposure to environmental and occupational chemicals is an important risk factor in the aetiology of BC and the most prominent carcinogen is tobacco smoke (1). Radical cystectomy (RC) is considered the gold standard treatment for non-metastatic muscle-invasive bladder cancer (MIBC) (2).

Types of recurrence after RC include local recurrence and distant metastases (lymph nodes, lung, liver and bone). The main epidemiological factors predicting recurrence after RC are advanced age, female sex and tobacco use. In pathological evaluation, the presence of lymphovascular invasion (LVI), concomitant carcinoma in situ (CIS), positive surgical margin and lymph node involvement are considered important prognostic factors for tumour recurrence. On radiological examination cT3-T4a disease and the presence of hydroureteronephrosis are considered independent predictors of poor clinical outcome after RC (3,4).

Anemia, hypoalbuminemia (< 3.5 g/dL), low neutrophil-to-lymphocyte ratio and low lymphocyte-to-monocyte ratio have been observed as markers predicting recurrence in MIBC patients undergoing RC (5–7). The HALP score has been evaluated in several studies as an independent prognostic factor predicting survival in urologic cancers. Lower HALP scores have been significantly associated with poorer overall survival in cancers such as bladder, renal cell carcinoma and upper urinary tract urothelial carcinoma (8). There are few studies in the literature on the prognostic value of HALP score in predicting progression in MIBC patients undergoing RC. In our study, we aimed to evaluate the significance of the HALP score in determining the risk of progression.

MATERIAL AND METHODS

Our study included a total of 205 patients who underwent RC for non-metastatic MIBC between February 2014 and January 2024. A total of 71 patients were excluded from the study. Among them, 32 patients received neoadjuvant chemotherapy before surgery, which can significantly alter pathological staging and systemic inflammatory parameters, potentially confounding the prognostic value of the HALP score. Additionally, 23 patients had a secondary malignancy. Six patients with acute urinary tract infections and two patients with a history of acquired immunodeficiency were also excluded, as active infection or immunosuppressive conditions may significantly affect hematologic and nutritional biomarkers, thereby distorting the HALP score and compromising the validity of our prognostic evaluation. Furthermore, 8 patients were excluded due to incomplete follow-up at external healthcare centers. After these exclusions, the remaining 134 patients constituted the final analysis cohort.

Demographic and clinical characteristics of the patients included age, sex, comorbidities and smoking. Biochemical data including C-reactive protein (CRP, mg/L), albumin (g/L) and complete blood count parameters [haemoglobin (g/L), lymphocytes (10^9/L)] were measured and recorded two weeks prior to surgery. From these data, the HALP score was calculated using the following formula: [haemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)] / platelets (/L).

Clinicopathological data were also collected from the hospital database. These data included date of RC, tumour T and N stages, presence of concomitant CIS and prognostic factors such as LVI and perineural invasion (PNI).

Patients were systematically analysed for the presence of recurrence based on available radiological imaging and multidisciplinary uro-oncology board assessments performed during follow-up. Disease progression was specifically categorized as local recurrence, distant metastasis (lymph nodes, lung, liver, or bone), or both. Progression times (if any) and progression-free survival (PFS) times of patients with progression during follow-up were calculated in months and follow-up periods were recorded as a minimum of 8 months and a maximum of 130 months.

The analyses aimed to evaluate the prognostic effects of the HALP score on disease progression and PFS. Furthermore, the associations of HALP score with important clinicopathological factors such as tumour stage (T and N stages), LVI, PNI and the presence of concomitant CIS were extensively investigated.

Our study was approved by the Scientific Research Ethics

Committee of Haydarpaşa Numune Training and Research Hospital on December 17, 2024, with decision number HNEAH-GOAEK/KK/2024/159. Full compliance with the Declaration of Helsinki was ensured, and written informed consent was obtained from all patients enrolled in the study, who agreed to the anonymous use of their data.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 software (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median Interquartile Range (IQR), and categorical variables are presented as frequencies and percentages. Mann-Whitney U test was used for group comparisons, ROC curve analysis was used for prognostic assessment and area under the curve (AUC) was calculated. The optimal cut-off point was determined using the Youden index.

Survival analyses were performed using the Kaplan-Meier method and groups were compared using the log-rank test. PFS was evaluated in months and the significance level was accepted as $p<0.05$. Chi-squared test was used to compare categorical variables and multivariate logistic regression analysis was used to identify independent prognostic factors.

RESULTS

During the clinical follow-up of patients who underwent RC, disease progression was observed in 51 patients (38%). The median age was 66 years [IQR: 60–71] in the progression group and 65 years [IQR: 59–71] in the non-progression group, with no statistically significant difference ($p = 0.793$). The sex distribution was similar between the groups, with males comprising 86% of the progression group and 89% of the non-progression group ($p = 0.617$). A smoking history of ≥20 pack-years was present in 78% of patients with progression and in 83% of those without, which did not yield statistical significance ($p = 0.792$). Likewise, the presence of diabetes mellitus ($p = 0.238$), hypertension ($p = 0.886$), and coronary artery disease ($p = 0.963$) showed no significant differences between the groups.

Pathological evaluation revealed that advanced tumor stages (T3–T4) were significantly more frequent in the progression group (90% vs. 65.1%, $p = 0.001$). When assessed by individual T stage, T2a and T2b tumors were more prevalent among non-progressing patients, whereas T3b and T4a tumors were predominantly observed in those with progression ($p = 0.016$). PNI was significantly associated with progression and was present in 82% of the progression group compared to 54% of the non-progression group ($p = 0.001$). Conversely, lymph node involvement ($p = 0.659$), N stage distribution ($p = 0.585$), concomitant CIS ($p = 0.741$), and LVI ($p = 0.281$) did not demonstrate statistically significant associations with disease progression (Table 1). Advanced tumour stage (T3–T4) emerged as the most decisive factor associated with disease progression, highlighting its significant prognostic importance in this study.

Among the preoperative hematological and biochemical parameters evaluated, patients with disease progression had significantly lower HALP scores compared to those without progression (29.19 [IQR: 19.17–41.81] vs. 37.55 [IQR: 29.61–52.25], $p = 0.021$). Similarly, serum albumin levels were significantly reduced in the progression group (4.0 [IQR: 3.5–4.23] vs. 4.1 [IQR: 3.8–4.3], $p = 0.032$), suggesting a potential association between poor nutritional/inflammatory status and adverse outcomes. In contrast, no significant differences were observed in hemoglobin ($p = 0.512$) or lymphocyte counts ($p = 0.973$) between the two groups. However, platelet counts were modestly higher in patients with progression (290 [IQR: 232–358] vs. 256 [IQR: 217–316], $p = 0.048$), indicating a possible link between elevated thrombocyte levels and tumor progression (Table 2).

According to the results of the ROC curve analysis evaluating the ability of the HALP score to predict progression, the area under the curve (AUC) was calculated as 0.619 (95% CI: 0.518-0.721) and found to be statistically significant ($p=0.021$). As a result of the analysis, the optimal cut-off point was determined to be 36.38, and at this value, the sensitivity and specificity of the HALP score in predicting progression were 54.9% and 55.4% respectively. These data show that the HALP score has a limited but statistically significant predictive value in predicting the risk of progression (Table 3, Figure 1).

Table 1. Association of Clinical and Pathologic Characteristics with Progression in Patients Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer

Continuous Variables (Median [IQR])	**Progression (+) (n=51)**	**Progression (-) (n=83)**	**p**
Age	66 (60-71)	65 (59-71)	0.793**
Categorical Variables (n, %)			
Sex			0.617*
Female	7 (13.7%)	9 (10.8%)	
Male	44 (86.3%)	74 (89.2%)	
Smoking			0.792*
-	3 (5.9%)	4(4.8%)	
<20 package/years	8 (15.7%)	10 (12%)	
≥20 package/years	40 (78.4%)	69 (83.1%)	
DM			0.238*
-	42 (82.4%)	61 (73.5%)	
+	9 (14.6%)	22 (26.5%)	
HT			0.886*
-	27 (52.9%)	45 (54.2%)	
+	24 (47.1%)	38 (45.8%)	
CAD			0.963*
-	41 (80.4%)	67 (80.7%)	
+	10 (19.6%)	16 (19.3%)	
T Stage			**0.016***
T2a	2 (3.9%)	17 (20.5%)	
T2b	3 (5.9%)	14 (14.5%)	
T3a	11 (21.6%)	15 (18.1%)	
T3b	21 (41.2%)	18 (21.7%)	
T4a	14 (27.4%)	19 (22.9%)	
T4b	0 (0%)	2 (2.4%)	
T Subgroup			**0.001***
T2	5 (9.8%)	29 (34.9%)	
T3-4	46 (90.2%)	54 (65.1%)	
Lymph Node Involvement			0.659*
N-	30 (58.8%)	52 (62.7%)	
N+	21 (41.2%)	31 (37.3%)	
N Stage			0.585*
N0	30 (58.8%)	52 (62.7%)	
N1	6 (11.8%)	14 (16.9%)	
N2	14 (27.5%)	15 (18.1%)	
N3	1 (2.0%)	2 (2.4%)	
CIS			0.741*
-	34 (66.7%)	53 (63.9%)	
+	17 (33.3%)	30 (36.1%)	
PNI			**0.001***
-	9 (17.6%)	38 (45.8%)	
+	42 (82.4%)	45 (54.2%)	

LVI			
-	24 (47.1%)	47 (56.6%)	0.281*
+	27 (52.9%)	36 (43.4%)	

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Arterial Disease, CIS; carcinoma in situ, LVI: Lymphovascular Invasion, PNI: Perineural Invasion, *: Chi-square, **: Mann-Whitney U test

Table 2. Relationship of Hematologic and Biochemical Parameters with Progression in Patients Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer

	Progression (+) (n:51) (Median [IQR])	Progression (-) (n:83) (Median [IQR])	p
Halp score	29.19 (19.17-41.81)	37.55 (29.61-52.25)	**0.021****
Albumin (g/dl)	4 (3.5-4.23)	4.1 (3.8-4.3)	**0.032****
Haemoglobin (g/dl)	11.8 (10.6-13.5)	12.3 (10.9-13.5)	0.512**
Lymphocytes (10^3/µl)	1.99 (1.33-2.88)	1.98 (1.62-2.5)	0.973**
Platelets (10^3/µl)	290 (232-358)	256 (217-316)	**0.048****

**: Mann-Whitney U test

Table 3. ROC Analysis Result of HALP Score According to Progression

	Progression (+) (n:51) (Median [IQR])	Progression (-) (n:83) (Median [IQR])	p
Halp score	29.19 (19.17-41.81)	37.55 (29.61-52.25)	**0.021****
Albumin (g/dl)	4 (3.5-4.23)	4.1 (3.8-4.3)	**0.032****
Haemoglobin (g/dl)	11.8 (10.6-13.5)	12.3 (10.9-13.5)	0.512**
Lymphocytes (10^3/µl)	1.99 (1.33-2.88)	1.98 (1.62-2.5)	0.973**
Platelets (10^3/µl)	290 (232-358)	256 (217-316)	**0.048****

**: Mann-Whitney U test

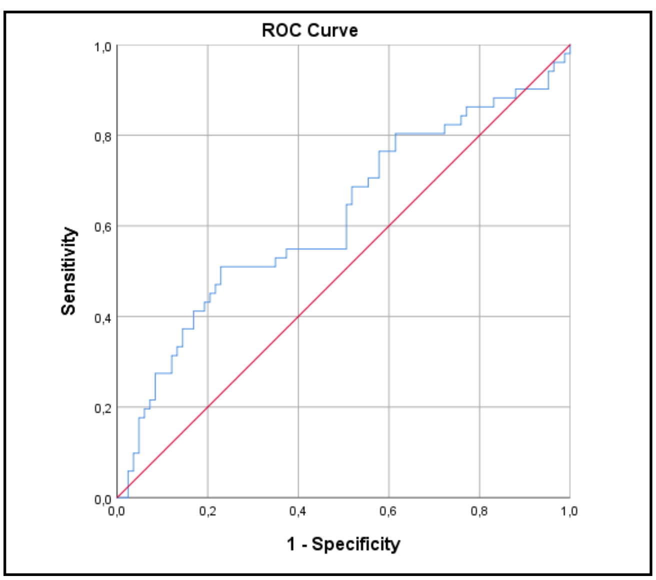

Figure 1. ROC Analysis Result of HALP Score According to Progression

Logistic regression analysis in our study group revealed that T subgroup (OR=3.09, 95% CI: 1.00-9.564, p=0.050) and perineural invasion (OR=2.56, 95% CI: 1.011-6.482, p=0.047) variables showed statistical significance as independent and strong prognostic markers in predicting muscle invasive bladder cancer progression. Although the HALP score cut-off point was not statistically significant (OR=0.65, 95% CI: 0.31-1.369, p=0.258). The overall fit of the model was supported by a -2 log-likelihood value of 160.936 and Nagelkerke R^2=0.163, which reasonably reflects the explanatory power of the model. ROC curve analysis evaluated the classification performance of the model and the AUC value was 0.705 (Table 4, Figure 2).

There was no statistically significant difference between groups for local recurrence, distant metastasis and both progression types in the distribution of progression types according to the HALP score cut-off point of 36.38 (p=0.859) (Table 5).

According to the results of the Kaplan-Meier survival analysis, when PFS times were compared according to the HALP score cut-off point of 36.38, the mean survival time was 82.4 months (95% CI: 66.5-98.2) in the group of patients with HALP score ≥36.38 and 68.8 months (95% CI: 52.6-85.1) in the group with HALP score <36.38 (Figure 3).

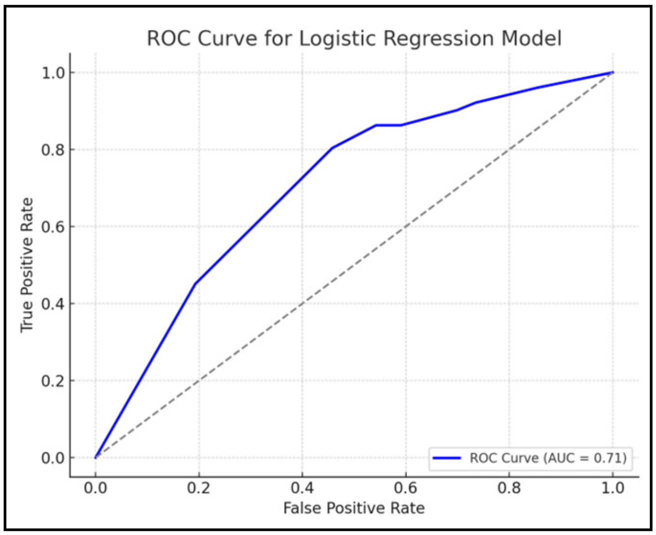

Figure 2. ROC Curve for Logistic Regression Model Predicting Muscle-Invasive Bladder Cancer Progression

DISCUSSION

MIBC is a crucial malignancy that requires a multidisciplinary approach due to its high mortality rate and aggressive clinical course. Therefore, accurate and reliable identification of prognostic markers may improve patient management by contributing to the development of individualised treatment approaches. This study aimed to add unique and clinically relevant findings to the literature by comprehensively evaluating the prognostic value of the HALP score for disease progression and survival.

Pathological factors remain integral in determining the prognosis of muscle-invasive bladder cancer. In our study, while pT stage exhibited a strong association with recurrence, LVI and pathological nodal status (pN stage) did not demonstrate statistically significant predictive value for progression. Notably, PNI emerged as the most robust independent prognostic marker for recurrence, suggesting its potential to enhance existing prognostic models for bladder cancer progression. This finding aligns partially with the work of Karakiewicz et al., who identified pathological staging and LVI as powerful predictors of recurrence but contrasts with Lotan et al., who found no significant association between LVI and recurrence. These discrepancies underscore the variability in the prognostic relevance of LVI across studies and highlight the need for further investigation (10,11).

Table 4. Logistic Regression Analysis Results in Predicting Muscle Invasive Bladder Cancer Progression

Variables	B	SE	OR	CI	Z	p
Halp Score	-0.429	0.379	0.65	0.65 (0.31-1.369)	-1.132	0.258
T Subgroup	1.129	0.576	3.09	3.09 (1.0-9.564)	1.96	**0.050**
PNI	0.940	0.474	2.56	2.56 (1.011-6.482)	1.983	**0.047**

Table 5. Statistical Distribution of Progression Types According to HALP Score

Progression Type	HALP Score < 36.38	HALP Score ≥ 36.38	p*
Local Recurrence	5 (%10)	3 (%6)	0.859
Distant Metastasis	17 (%33)	14 (%28)	
Both Local Recurrence and Distant Metastasis	6 (%12)	6 (%12)	

*: Chi-square

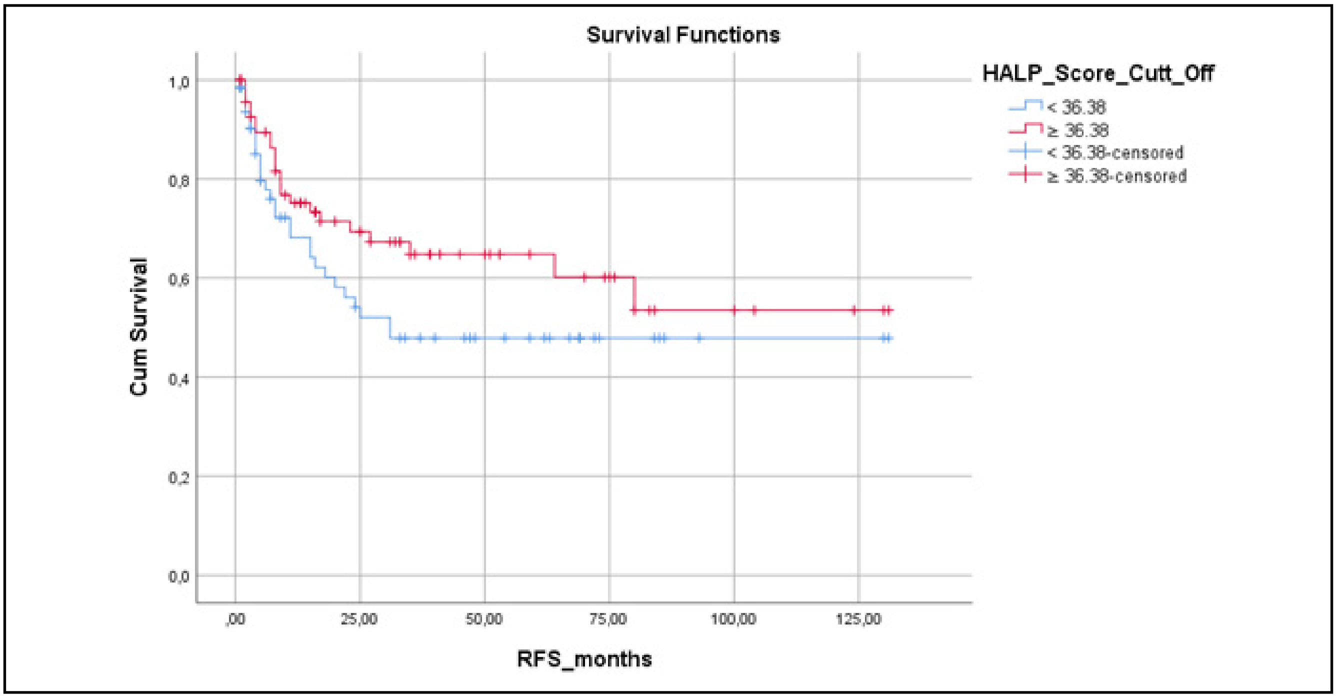

Figure 3. PFS Curve According to HALP Score (Kaplan-Meier Analysis)

Preoperative anemia is a marker of systemic health and it is a tumor burden. In this sense, it has been widely studied in the context of oncological outcomes. While our analysis did not reveal a significant relationship between preoperative anemia and recurrence, prior studies have reported conflicting results. Xia et al. identified a significant association between preoperative anemia and early recurrence in bladder and renal cancers, and Furrer et al. demonstrated increased progression risk in anemic patients requiring erythrocyte transfusions (5,12,13). These inconsistencies suggest that the impact of anemia on recurrence may be influenced by additional factors, such as treatment modalities or patient comorbidities, necessitating more nuanced exploration in future studies.

Low preoperative albumin levels, a reflection of nutritional and inflammatory status, have been consistently linked to adverse outcomes in multiple malignancies. Our findings corroborate this, as low albumin levels were significantly associated with increased postoperative recurrence risk (p=0.032). This observation is in line with previous research, such as Djalat et al.'s study in bladder cancer, Liu et al.'s work in gastric cancer and Miura et al.'s findings in non-small cell lung cancer (7,14,15). Collectively, these results highlight hypoalbuminemia as a potential universal marker of poor oncological outcomes, reinforcing its importance in preoperative risk stratification.

The prognostic utility of the HALP score, a composite index incorporating hematological and biochemical parameters, has been demonstrated across various malignancies. In our study, a low HALP score was significantly associated with advanced pT stage but not with nodal involvement, suggesting its utility may be more reflective of local tumor aggressiveness rather than systemic disease spread. This observation aligns with findings in other malignancies. For instance, Ekici et al. found that in patients with testicular cancer, a low HALP score was significantly associated with advanced T, N, and M stages, emphasizing its potential as a marker of tumor progression (16). Similarly, Zhao et al. demonstrated that low HALP scores were strongly associated with advanced TNM stage in non-small cell lung cancer (17). Additionally, Zhang et al. reported that low HALP scores were associated with advanced lymph node positivity in tongue squamous cell carcinoma, although the association with advanced T stage was not statistically significant (18). However, variability exists, as evidenced by Zhang et al.'s study on lung adenocarcinoma, where a low HALP score did not show a statistically significant association with advanced T stage or N stage (19). These discrepancies underscore the need for further disease-specific validation to clarify the prognostic implications of the HALP score across different cancer types.

The HALP score has emerged as a promising prognostic marker across various malignancies, with its association with recurrence and survival outcomes being increasingly recognized. In our study, a low HALP score was significantly associated with recurrence in patients with muscle-invasive bladder cancer, underscoring its potential as a marker of tumor aggressiveness. This finding is consistent with studies in other malignancies. For instance, in hepatocellular carcinoma, Liu et al. demonstrated that a low HALP score was a strong predictor of early recurrence following radical liver resection (20). Similarly, Zhao et al. found that a low HALP score was significantly associated with recurrence in non-small cell lung cancer while in lung adenocarcinoma, Zhang et al. reported that a low HALP score could predict recurrence risk (17,19). These results highlight the versatility of the HALP score as a prognostic indicator in different cancer types.

In gynecological malignancies, such as endometrial cancer, Wang et al. demonstrated that a low HALP score is an effective prognostic marker for recurrence (21). Additionally, reduced PFS has been reported in patients with malignancies such as gastrointestinal stromal tumors and cervical cancer, further emphasizing the significance of the HALP score in predicting oncological outcomes (22,23). Consistent with these findings, our study confirms the association of a low HALP score with recurrence and contributes to the growing body of evidence supporting its prognostic utility. Notably, this study is the first to evaluate the prognostic value of the HALP score in MIBC, marking an important contribution to literature and paving the way for its potential integration into clinical decision-making.

This study has certain limitations that should be acknowledged while also emphasizing its contributions to literature. The retrospective design, although practical for evaluating prognostic factors in a real-world setting, may limit the standardization of data collection and introduce potential selection bias. The sample size, while sufficient to demonstrate statistically significant findings, may limit the statistical power of subgroup analyses and the generalizability of results. As a single-center study, the findings may not fully capture variations across diverse populations or healthcare systems. Nevertheless, the HALP score was rigorously evaluated as an independent prognostic marker, making this study a valuable foundation for future research. While the absence of combined analyses with other established prognostic factors and the lack of long-term follow-up data may limit the development of a comprehensive prognostic model, the significant associations identified in this study provide strong evidence for the potential clinical utility of the HALP score. Moreover, the influence of adjuvant or neoadjuvant therapies on the prognostic value of the HALP score warrants further investigation in larger, multicenter studies. Despite these limitations, this study represents an important step in exploring the prognostic role of the HALP score in MIBC, contributing novel and clinically relevant insights to the field.

CONCLUSION

Our study pointed out that the HALP score is a limited yet statistically significant prognostic marker for predicting progression in patients with MIBC. While the sensitivity and specificity values of the HALP score in predicting progression, based on the optimal cut-off point, were found to be moderate, these findings highlight its limitations as a standalone prognostic marker. Nonetheless, as one of the first studies to investigate the prognostic value of the HALP score in MIBC, our work makes a valuable contribution to the literature, suggesting that the HALP score should be considered in patient management. Future prospective studies with larger sample sizes are needed to evaluate the combination of the HALP score with other prognostic factors and its impact on long-term patient outcomes, ultimately supporting its potential use in the development of individualized treatment strategies.

Conflict of Interest: The authors declare that they have nothing to disclose.

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Ethical Approval: Our study was approved by the Scientific Research Ethics Committee of Haydarpaşa Numune Training and Research Hospital on December 17, 2024, with decision number HNEAH-GOAEK/KK/2024/159.

Author Contributions: Conseption and Design; Kayar R. Data acquisition; Kayar K, Demir S. Data analysis and interpretation; Kayar K, Artuk I. Darfting the manuscript; Kayar R. Critical revision of the manuscript for scientific and favtual cotent; Kayar R, Kayar K, Tokuc E. Statistical analysis; Kayar R, Kayar K. Supervision; Ozturk MI.

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RESEARCH ARTICLE

Nephrostomy-Associated Sepsis in Cancer Patients: What Are the Risk Factors? A Retrospective Cohort Study

Ramazan Uğur [1], Emin Taha Keskin [1], Turan Özdemir [1], Ahmet Eren Sağır [1], Direnç Özbörü [1], Abdullah Zilan [1], Abdülmüttalip Şimşek [2]

[1] Department of Urology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye

[2] Department of Urology, Bahçelievler Memorial Hospital, İstanbul, Türkiye

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Corresponding Author;
Ramazan Uğur, MD

Address: Başakşehir Olympic Boulevard Road, 34480, Başakşehir /Istanbul, Turkiye
E-mail: rugur23@gmail.com

ORCID

R.U.	0000-0002-0593-8589
E.T.K.	0000-0002-1222-6424
T.Ö.	0000-0002-1131-2507
A.E.S.	0009-0004-1231-5330
D.Ö.	0009-0000-0034-4274
A.Z.	0000-0001-9429-4676
A.Ş.	0000-0001-8003-4654

Abstract

Objective: To evaluate sepsis and mortality following nephrostomy tube due to malignant etiology.

Material and Methods: Patients who underwent nephrostomy tube at our center were retrospectively evaluated. Only those with malignancy-related indications were included in the study. Patients were initially categorized into two main groups: those with urological malignancies and those with non-urological malignancies. Subsequently, they were further divided into subgroups based on the development of sepsis and survival status. Predictive factors associated with sepsis and mortality were analyzed.

Results: A total of 517 patients were identified, of whom 173 met the inclusion criteria. The mean age was 62.53 years, with a male-to-female ratio of 112:61. Among patients who developed sepsis, post-operative (post-op) platelet counts, post-op creatinine, as well as pre-operative (pre-op) and post-op neutrophil and lymphocyte counts and neutrophil-to-lymphocyte ratio (NLR) were significantly lower, whereas procalcitonin and C-reactive protein (CRP) levels were significantly higher ($p<0.05$). The presence of perirenal fat stranding and intensive care unit (ICU) admission were also significantly associated with sepsis development($p<0.05$). Regarding mortality, lower pre-op and post-op lymphocyte counts and higher procalcitonin levels were statistically significant ($p <0.05$). Postoperative NLR, creatinine and CRP were also significantly associated with mortality. Furthermore, the presence of diabetes mellitus (DM), immunosuppressive drug use (ISDU), ICU admission, and non-urological malignancies were found to be statistically significant factors associated with mortality.

Conclusion: Our findings indicate that NLR, procalcitonin, CRP, as well as pre-and post-op platelet, lymphocyte and neutrophil counts, along with the presence of perirenal fat stranding, DM, ISDU, and ICU admission and non-urological malignancies play significant roles in the development of sepsis and mortality. These findings emphasize the importance of early risk stratification and targeted management in patients undergoing nephrostomy for malignant obstruction.

Keywords: malignancy, mortality, percutaneous nephrostomy, sepsis

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INTRODUCTION

Percutaneous nephrostomy (PN) and ureteral catheterization are essential interventions commonly utilized prior to definitive management in cases of renal or supravesical urinary tract obstruction [1,2]. Although these procedures are generally effective, they are not without risks. Potential complications include bleeding, injury to adjacent organs, ureteral perforation or avulsion, and long-term sequelae such as ureteral stricture or impaired renal function. Among these, sepsis stands out as a particularly critical complication, characterized by systemic inflammation and organ dysfunction, and is associated with a high mortality rate [3,4].

Percutaneous nephrostomy is frequently effective in relieving hydroureteronephrosis (HUN) and pyelonephritis secondary to urinary tract obstruction. However, in certain patient groups—particularly those with renal failure or pre-existing septic conditions—PN may aggravate the clinical status [3–6]. In routine urological practice, it has been observed that sepsis may develop in some patients following PN, while in others with an already septic state, the clinical course may deteriorate further, often requiring admission to the intensive care unit (ICU). In rare instances, such complications can even result in mortality.

This study aims to identify clinical factors associated with the development of sepsis and mortality in patients undergoing nephrostomy due to malignancy. The findings are intended to provide valuable insights to facilitate early diagnosis, risk stratification and the development of more effective management strategies for both groups.

MATERIALS AND METHODS

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and received approval from the institutional ethics committee. Patient data were systematically utilized in strict compliance to confidentiality and privacy standards. In this study, the terms pre-operative(pre-op) and post-operative(post-op) refer to the clinical periods before and after nephrostomy tube insertion. Both pre-op and post-op clinical data were meticulously retrieved from hospital records and electronic medical systems. The study included all patients who underwent PN in our clinic, focusing exclusively on cases performed due to malignant etiologies. Patients with benign conditions—including stone-related HUN, surgical complications, ureteral strictures, or ureteropelvic junction obstructions—were excluded. The decision to perform PN was predominantly based on computed tomography (CT) evaluations. In instances where CT was not feasible, magnetic resonance imaging or ultrasound was used to guide clinical decision-making. Patients were initially categorized into two primary groups: those with urological malignancies and those with non-urological malignancies. Subsequently, they were stratified based on the presence of sepsis and survival status to comprehensively evaluate potential predictive factors. Patients diagnosed with sepsis were included only if it was considered to be nephrostomy-associated urosepsis. Sepsis was defined using the systemic inflammatory response syndrome (SIRS) criteria.

Collected data encompassed a comprehensive range of demographic and clinical parameters, including age, sex, body mass index (BMI), diabetes mellitus (DM), immunosuppressive conditions, immunosuppressive drug use (ISDU), perirenal fat stranding, solitary kidney status, urine test results (nitrite positivity, pyuria), urine culture findings, ICU admission, and both pre-op and post-op biochemical parameters (creatinine, platelet count, white blood cell count, neutrophil count, lymphocyte count, C-reactive protein [CRP], and procalcitonin). Additionally, inflammatory markers such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) were calculated and assessed (Table 1). These comprehensive data sets were utilized to identify and analyze factors associated with the development of sepsis and mortality.

Statistical Analysis

Data were analyzed using SPSS version 27.0. The normality of distribution was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed variables. Group comparisons were performed using the Student's t-test for parametric data and the Mann-Whitney U test for non-parametric data, based on the distribution characteristics. Categorical variables were analyzed using the Pearson Chi-square test. Independent factors associated with sepsis and mortality were identified through univariate and multivariable logistic regression analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 517 patients who underwent PN were initially identified, among whom 173 met the predefined inclusion and exclusion criteria. The mean age of the study population was 62.53 years, with a male-to-female ratio of 112:61. Sepsis and mortality rates were observed at 21% (37) and 26% (45), respectively. In the sepsis group, the male-to-female distribution was 22:15, while in the mortality group it was 27:18. (Table 1). No statistically significant difference was found between the groups regarding these distributions (Table 2).

Among the sepsis group, post-op platelet count and creatinine were significantly lower ($p<0.05$). Both pre-op and post-op neutrophil and lymphocyte counts, along with the neutrophil-to-lymphocyte ratio (NLR), were significantly lower, whereas procalcitonin and CRP levels were markedly higher ($p<0.05$). The presence of perirenal fat stranding on CT and ICU admission were both significantly associated ($p<0.05$) with the development of sepsis. Logistic regression analysis identified low pre-op platelet count, perirenal fat stranding, and post-op ICU admission as independent predictors of sepsis in both univariate and multivariable analyses ($p<0.05$, Table 3).

Regarding mortality, low pre-op and post-op lymphocyte counts, as well as elevated procalcitonin levels, were significantly associated with adverse outcomes ($p<0.05$). Postoperative NLR, creatinine and CRP were also significantly associated with mortality. Furthermore, the presence of DM, ISDU, ICU admission, and the presence of non-urological malignancies were significantly correlated with increased mortality (Table 2). Multivariable logistic regression analysis revealed that post-op NLR and ICU admission were independent predictors of mortality (Table 4).

Table 1. Demographic datas, Pre-operative and Post-operative Characteristics

		Mean ± SD	Min-Max
Age (Years)		62.5 ± 13. 8	25-92
BMI (kg/m²)		25.9 ± 3.9	18-34
		% (n)	
Gender	**Male**	65 (112)	
	Female	35 (61)	
DM		29 (51)	
IS		21 (36)	
ISDU		42 (72)	
Perirenal fat stranding		24 (41)	
Nephrostomy	**Unilateral**	49 (84)	
	Bilateral	51 (89)	
Solitary Kidney		6 (11)	
Nitrite (+)		9 (16)	
Pyuria		21 (37)	
Pre-op Urine Culture Growth		21 (36)	
ICU	(-)	80 (139)	
	(+)	20(34)	
Malignancy	**Urological**	52 (90)	
	Non-urological	48 (83)	
Sepsis	**Male**	20 (22)	
	Female	25 (15)	

Mortality	**Male**	24 (27)	
	Female	30 (18)	
		Mean ± SD	**Min - Max**
Fever (°C)		37.4 ± 1.1	36.1-39.2
Respiratory rate (Breaths/minute)		21 ± 4.3	12-31
Heart rate (Beats/minute)		98 ± 9.7	61-142
Pre-op Cre (mg/dL)		2.9 ± 2.5	0-15
Pre-op PLT (x10^3/μL)		290.4 ± 143.8	8-726
Pre-op WBC (x10^3/μL)		14.6 ± 51.6	1-62.8
Pre-op Neutrophil (x10^3/μL)		8.7 ± 5.2	0-35
Pre-op Lymphocyte (x10^3/μL)		1.3 ± 1.1	0-8
Pre-op CRP (x10^3/μL)		107.4 ± 88.1	1-518
Pre-op Procalcitonin (mg/L)		9.2 ± 20.7	0-103
Post-op Cre (mg/dL)		2.5 ±5.9	0-7.7
Post-op WBC (x10^3/μL)		10.3 ± 5.0	0-30
Post-op PLT (x10^3/μL)		290.3 ± 139.9	29-706
Post-op Neutrophil (x10^3/μL)		8.2 ± 4.6	0-28
Post-op Lymphocyte (x10^3/μL)		1.5 ± 2.3	0-25
Post-op CRP (x10^3/μL)		109.7 ± 126.8	1-1192
Post-op Procalcitonin (mg/L)		6.9 ± 35. 4	0-426
NLR-Pre-op (Ratio)		9.9 ± 13.2	0.2-140
PLR-Pre-op (Ratio)		301.4 ± 232. 2	1-1288.2
SII-Pre-op (Score)		2975.2 ± 4239.6	10.8-39480
NLR-Post-op (Ratio)		8.5 ± 7.5	0.03-48.4
PLR-Post-op (Ratio)		276.9 ± 192	0.05-1084.8
SII-Post-op (Score)		2519.5± 2724.7	0.4-17346.7

BMI: Body Mass Index, **Cre:** Creatinine, **CRP:** C-reactive protein, **DM**: Diabetes mellitus, **ICU**: Intensive Care Unit, **IS**: Immunosuppression, **ISDU:** Immunosuppression drug use, **NLR:** Neutrophil-to-Lymphocyte Ratio, **PLR:** Platelet-to-Lymphocyte Ratio**, PLT:** Platelets, **Post-op:** Post-operative, **Pre-op:** Pre-operative, **SII:** Systemic Immune-Inflammation Index, **WBC:** White Blood Cells

Table 2. Biomarkers and Clinical Parameters Affecting Sepsis and Mortality Risk

	Sepsis		**P value**	**Mortality**		**P value**
	(-)	(+)		(-)	(+)	
	Mean ± SD			**Mean ± SD**		
BMI	25.5 ± 4	29.2 ± 0.8	*0.216**	25.65 ± 4	28.51 ± 0.9	*0.343**
Pre-op Plt(x10^3/μL)	301.5 ± 138	249.4 ± 158	*0.051**	298 ± 144	266 ± 141	*0.194**
Post-op Plt(x10^3/μL)	304 ± 131	238 ± 158	***0.013****	299 ± 134	262 ± 154	*0.132**
Fever (°C)	36.9 ± 0.6	37.6 ± 0.9	*0.089**	36.8 ± 0.7	37.5 ± 0.8	*0.092**

Respiratory rate (Breaths/ minute)	18 ± 3.2	25 ± 4.1	0.251*	17 ± 3.5	26 ± 4.4(22-31)	0.112*
Heart rate (Beats/minute)	95 ± 7.5	112 ± 11.7	0.316*	92 ± 8.5	116 ± 11.3	0.117*
	Median (IQR)			**Median (IQR)**		
Age (Years)	67 (19)	65 (11)	0.529	67 (19)	65 (10)	0.340**
Pre-op Cre(mg/dL)	3.1 (7)	1.6 (3)	0.283 **	2.8 (7)	2.2 (3)	0.344 **
Pre-op WBC (x10^3/μL)	11.4 (7)	7.7 (5)	0.963 **	10.9 (5)	7.7 (6)	0.999 **
Pre-op Neutrophil (x10^3/μL)	9.1 (5)	5.9 (5)	0.020 **	9 (4)	5.9 (5)	0.814 **
Pre-op Lymphocyte(x10^3/μL)	1.2 (1)	0.9 (1)	0.001 **	1.2 (1)	0.9 (1)	0.031 **
Pre-op CRP(x10^3/μL)	146 (145)	164 (121)	0.001 **	146 (145)	164 (121)	0.054 **
Pre-op Procalcitonin (mg/L)	0.5 (17)	5.3 (21)	0.001 **	0.5 (3)	5.8 (23)	0.002 **
Post-op Cre(mg/dL)	2.9 (2)	1.7 (1)	0.032 **	2.3 (2)	1.9 (2)	0.004 **
Post-op WBC(x10^3/μL)	10.5 (5)	6.2 (8)	0.638 **	10 (6)	6.7 (11)	0.275 **
Post-op Neutrophil(x10^3/μL)	8.6 (3)	4.5 (7)	0.024 **	8 (4)	5.7 (10)	0.311**
Post-op Lymphocyte(x10^3/μL)	1.2 (1)	0.8 (17.8)	0.001**	1.2 (1)	0.9 (1)	0.01**
Post-op CRP(x10^3/μL)	109 (133)	152 (128)	0.001**	109 (133)	152 (128)	0.01**
Post-op Procalcitonin(mg/L)	0.2 (2)	2.9 (4)	0.018 **	0.2 (2)	2.9 (4)	0.008 **
NLR-Pre-op (Ratio)	7.5 (12)	5.8 (9.2)	0.007 **	7.5 (9)	5.8 (9.6)	0.08 **
PLR-Pre-op (Ratio)	291 (241)	117 (114)	0.681 **	260 (278)	117 (138)	0.632 **
SII-Pre-op (Score)	2226 (5848)	826 (532)	0.513 **	2165 (4406)	934 (621)	0.471**
NLR-Post-op (Ratio)	7.5 (9.7)	3.5 (11.6)	0.009 **	6.9 (7.1)	5.5 (17.2)	0.043 **
PLR-Post-op (Ratio)	294 (185)	178 (268)	0.508 **	300 (185)	178 (264)	0.854 **
SII-Post-op (Score)	2891 (3846)	621 (1216)	0.530 **	2023 (3014)	984 (1655)	0.512 **
	% (n)			**% (n)**		
Gender	**Male**	80 (90)	0.448 ***	76 (85)	24 (27)	0.402***
	Female	75 (46)		70 (43)	30 (18)	
DM	81 (41)	19 (10)	0.712 ***	63 (32)	27(19)	0.032***
IS	89 (32)	11 (4)	0.091 ***	86 (31)	14 (5)	0.06***
ISDU	72 (52)	28 (20)	0.083 ***	63 (45)	37 (27)	0.004***
Perirenal fat stranding	66 (27)	34 (14)	0.023 ***	73 (29)	27 (11)	0.826***
Nephrostomy	**Unilateral**	79 (66)	0.990 ***	70 (59)	30 (25)	0.294***
	Billateral	79 (70)		78 (68)	22 (20)	
Solitary Kidney	73 (8)	27 (3)	0.631 ***	73 (8)	27 (3)	0.941***
Nitrite (+)	81 (13)	19 (3)	0.923 ***	88 (14)	12 (2)	0.233***
Pyuria	74(35)	26 (12)	0.559 ***	74 (31)	26 (16)	0.373***
Pre-op Urine Culture Growth	75 (27)	25 (9)	0.170 ***	70 (26)	30 (11)	0.594***
ICU	(-)	91 (127)	0.001***	90 (125)	10 (14)	0.001***
	(+)	26 (9)		9 (3)	91 (31)	
Malignancy	**Urological**	82 (74)	0.228 ***	82 (73)	18(17)	
	Non-urological	75 (62)		75 (54)	25 (28)	

***: T-Test, **: Mann Whitney U, ***: Pearson Chi-Square, BMI:**Body Mass Index, **Cre:** Creatinine, **CRP:** C-reactive protein, **DM**: Diabetes mellitus, **ICU**: Intensive Care Unit, **IS**: Immunosuppression, **ISDU** Immunosuppression drug use, **NLR:** Neutrophil-to-Lymphocyte Ratio, **PLR:** Platelet-to-Lymphocyte Ratio**, PLT:** Platelets, **Post-op:** Post-operative, **Pre-op:** Pre-operative, **SII:** Systemic Immune-Inflammation Index, **WBC:** White Blood Cells,

Table 3. Univariate and multivariable logistic regression analysis to determine prognostic factors for sepsis after nephrostomy tube placement

	Univariate analysis				Multivariable analysis			
	OR	95 % CI		P value	OR	95 % CI		P value
		Lower	Upper			Lower	Upper	
Pre-op Plt(x10^3/µL)	0.981	0.966	0.996	***0.012***	0.993	0.988	0.998	***0.010***
Pre-op Lymphocyte(x10^3/µL)	1.715	0.544	5.404	*0.357*				
Pre-op CRP(x10^3/µL)	1.002	0.991	1.012	*0.783*				
Pre-op Procalcitonin (mg/L)	0.988	0.935	1.043	*0.656*				
Post-op Cre(mg/dL)	1.409	0.772	2.571	*0.264*				
Post-op CRP(x10^3/µL)	1.003	0.993	1.012	*0.607*				
Post-op procalcitonin(mg/L)	1.003	0.981	1.025	*0.807*				
Post-op Plt(x10^3/µL)	1.011	0.998	1.023	*0.102*				
Post-op: Lymphocyte (x10^3/µL)	0.382	0.056	2.591	*0.325*				
NLR-Pre-op	0.992	0.872	1.129	*0.905*				
NLR-Post-op	1.082	0.980	1.195	*0.118*				
Perirenal fat stranding	6.058	1.008	36.399	***0.049***	5.216	1.082	25.144	***0.040***
ICU	52.48	6.989	94.118	***0.001***	38.17	7.905	184.34	***0.001***

Cre: Creatinine, **CRP:** C-reactive protein, **ICU**: Intensive Care Unit, **NLR:** Neutrophil-to-Lymphocyte Ratio, **OR: Odds Ratio**, **PLT:** Platelets, **Post-op:** Post-operative, **Pre-op:** Pre-operative,

Table 4. Univariate and multivariable logistic regression analysis to determine prognostic factors for mortality after nephrostomy tube placement

	Univariate analysis				Multivariable analysis			
	OR	95 % CI		P value	OR	95 % CI		P value
		Lower	Upper			Lower	upper	
Pre-op Lymphocyte(x10^3/µL)	0.384	0.025	5.958	*0.494*				
Pre-op Procalcitonin (mg/L)	1.013	0.964	1.064	*0.606*				
Post-op Cre(mg/dL)	2.646	1.086	6.449	***0.032***	1.829	0.990	3.382	*0.54*
Post-op CRP(x10^3/µL)	0.995	0.984	1.006	*0.388*				
Post-op procalcitonin(mg/L)	1.007	0.989	1.025	*0.458*				
Post-op: Lymphocyte (x10^3/µL)	2.393	0.424	13.492	*0.323*				
NLR-Post-op	1.159	1.022	1.314	***0.021***	1.121	1.023	1.228	***0.014***
DM	4.997	0.710	35.155	*0.106*				

ISDU	9.039	0.628	130.194	*0.106*				
Post-op septic shock	13.538	0.714	256.812	*0.083*				
Malignancies (Urological/ Nonurological)	3.992	0.466	34.233	*0.207*				
ICU	185.99	9.705	3564.625	***0.001***	161.63	24.01	1087.957	***0.001***

Cre: Creatinine, **CRP:** C-reactive protein, **DM**: Diabetes mellitus, **ISDU** Immunosuppression drug use, **ICU**: Intensive Care Unit, **NLR:** Neutrophil-to-Lymphocyte Ratio, **OR: Odds Ratio**, **Post-op:** Post-operative, **Pre-op:** Pre-operative

DISCUSSION

Obstruction caused by ureteral stones, malignancies, or other benign factors can lead to HUN, acute renal failure, and, when accompanied by infection, pyelonephritis. Acute renal failure is rarely observed in healthy individuals unless there is bilateral involvement; however, in patients with comorbidities, the disease progression may be significantly accelerated [7]. Among patients with malignancies, the reactive inflammatory response may be either exaggerated or suppressed compared to that in healthy individuals [8]. This variability can be attributed to tumor-related pathophysiology or to the effects of therapeutic agents, such as chemotherapeutics, hormonal treatments, and immunotherapy.

When sepsis-related findings are analyzed, low platelet levels—along with elevated procalcitonin and CRP levels—emerge as significant markers in this patient group (Table 2). Platelets play a pivotal role in modulating the immune response during infection and maintaining vascular integrity by supporting endothelial function. In the context of sepsis, increased platelet consumption and destruction contribute to thrombocytopenia. This excessive consumption and activation of platelets may further amplify the dysregulated immune response, potentially leading to coagulopathy, multiorgan dysfunction, and increased mortality. Notably, when platelet counts fall to ≤50,000/μL, the risk of organ failure and mortality increases significantly [9–12]. Similarly, procalcitonin and CRP as essential biomarkers for assessing the severity of infection and evaluating the immune response. These markers have been consistently validated as reliable indicators across numerous studies [11]. Even though leukocytosis is commonly observed in sepsis, leukopenia may also occur, as highlighted in the SIRS criteria. In our patient cohort, neutropenia and lymphopenia were observed at statistically significant levels among those who developed sepsis (Table 2,3). The severity of neutropenia was further supported by a decrease in post-op NLR compared to pre-op values. NLR is considered a reliable marker that reflects both the intensity of the inflammatory response and the functional state of the immune system. Neutrophils constitute the first line of defense against microorganisms during infection, whereas lymphocytes reflect the activity of the adaptive immune response. An increase in neutrophil counts accompanied by a decrease in lymphocyte counts during sepsis indicates a dysregulated immune response and the uncontrolled progression of inflammation [8,9,12–14]. Interestingly, although the existing literature generally reports an elevated NLR during inflammatory conditions, our study found that NLR was lower in the sepsis group, which consisted exclusively of patients with malignancies (Table 2–3). We believe this situation is attributable to immune system dysfunction resulting from the coexistence of malignancy and sepsis [15,16]. The fact that post-op NLR emerged as an independent predictor of mortality in both univariate and multivariable analyses further highlights the prognostic value of this parameter.

In our study, ICU admission emerged as an independent predictor of sepsis in both univariate and multivariable analyses. This finding indicates that patients requiring ICU-level care are at significantly higher risk for developing sepsis, even after adjusting for other clinical factors. ICU admission likely reflects early physiological deterioration and increased disease burden. Therefore, the presence of ICU-level needs should be regarded as an early warning sign, prompting heightened clinical vigilance and timely interventions to prevent or mitigate sepsis. Another independent predictor of sepsis identified in our study was the presence of perirenal fat stranding (Table 2–3). Inflammation within the perirenal fat tissue contributes to an increased microbial burden and a heightened risk of bacterial infections. It is well known that invasive interventions under such inflammatory conditions can significantly elevate the risk of sepsis [5,17]. The Mayo Adhesive Probability (MAP) score is a valuable tool for evaluating the inflammatory burden of perirenal fat tissue and estimating the associated risks of infection and surgical complications. An elevated MAP score serves as a reliable indicator of severe perirenal inflammation and the potential progression of infection [18–20]. The integration of predictive scoring systems, such as the MAP score, into the clinical management of similar patient populations may enhance clinical decision-making and optimize treatment strategies.

When evaluating the parameters associated with mortality, it becomes evident that, despite pathophysiological similarities with sepsis, certain distinctions are observed. Notably, neutropenia and thrombocytopenia do not emerge as significant predictive factors (Table 2,4). In contrast, low pre-op and post-op lymphocyte levels, reduced post-op NLR, elevated pre-op and post-op procalcitonin and post-op CRP levels appear as key predictors of mortality, consistent with their roles in sepsis. However, among these variables, only post-op NLR was found to be an independent predictor of mortality after nephrostomy in logistic regression analysis (Table 2,4). Lymphopenia reflects a weakened immune system in the context of infection and indicates an impaired adaptive immune response [16,21,22]. Additionally, creatinine levels following nephrostomy were identified as predictors of mortality in univariate analysis; however, this association did not remain significant in multivariable analysis (Table 2,4). Although mortality rates were statistically higher among patients with non-urological malignancies, logistic regression analysis revealed no significant difference in mortality between patients with urological and non-urological malignancies (Table 2,4). Diabetes mellitus and ISDU complicate management of infections, particularly in the context of immunosuppression induced by sepsis and malignancy. These conditions exacerbate septic progression, increase the likelihood of complications, and elevate the risk of mortality [15,23,24]. Interestingly, while a statistically significant association ($p<0,05$) was found between DM and ISDU with mortality in our cohort, logistic regression analysis showed that they were not independent predictors of mortality. These results suggest that although DM and ISDU may indicate disease severity, they do not necessarily translate into increased mortality risk in all settings, highlighting the need for individualized patient assessment (Table 2,4). ICU admission emerged as a key predictor of both sepsis and mortality. ICU management strategies play a crucial role in directly influencing patient outcomes. The literature emphasizes that early ICU admission and timely implementation of supportive therapies can significantly reduce mortality rates [25]. In this context, the strong association between ICU admission and mortality observed in our study is consistent with findings in the literature. Furthermore, among the parameters variables included in multivariable logistic regression analysis, post-op ICU admission was identified as independent predictor of mortality (Table 4).

This study has several limitations, including its retrospective design, relatively small sample size, and single-center setting. Additionally, more detailed classification of malignancy types could have better illustrated the diversity of etiopathogenesis and inflammatory responses. The inclusion of data regarding chemotherapeutic agents, hormonal therapies or immunotherapies might have helped reduce heterogeneity and allowed for a more nuanced analysis. Due to the retrospective nature of our study, it was not possible to clearly differentiate between primary causes of mortality, which may have contributed to the high mortality rate observed. We believe that the actual mortality rate is likely lower, as our cohort consisted exclusively of cancer patients, and cancer-related deaths may have inflated the observed rate—constituting another important limitation of this study. Nevertheless, this study provides a foundation for future randomized prospective studies with larger cohorts, to evaluate dynamic changes in inflammatory markers. Including patients with benign causes of nephrostomy as a control group would enhance the understanding of malignancy-specific outcomes. Furthermore, assessing long-term results and quality of life would contribute the development of more comprehensive and evidence-based guidelines for the management of patients requiring nephrostomy.

CONCLUSION

In conclusion, this study has identified key predictors associated with sepsis and mortality following nephrostomy, offering important insights to inform clinical decision-making. Our findings emphasize the significance of inflammatory markers (NLR, procalcitonin, CRP), pre-op and post-op blood counts (platelet, lymphocyte, neutrophil), creatinine, and clinical factors such as perirenal fat stranding, DM, ISDU, ICU admission. The early recognition of high-risk patients, combined with timely and targeted interventions, is essential for improving clinical outcomes and minimizing adverse events in this vulnerable patient population.

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Informed Consent: Informed consent was obtained from the all patient involved in this study.

Ethical Approval: The study was approved by the Ethics Committee of Başakşehir Çam and City Hospital (Approval No: 2023-183)

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RESEARCH ARTICLE

Evidence from Hormonal and Semen Profiles Across Age Groups for Early Varicocelectomy

İsmail Ulus [1], Yusuf Şahin [2], İbrahim Hacıbey [3], Muhammet Murat Dinçer [1]

[1] Department of Urology, University of Health Sciences, Bağcılar Training and Research Hospital, İstanbul, Türkiye

[2] Department of Urology, University of Health Sciences, İstanbul Training and Research Hospital, İstanbul, Türkiye

[3] Department of Urology, Başakşehir Çam ve Sakura City Hospital, İstanbul, Türkiye

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Corresponding Author;
İsmail Ulus, MD

Address: University of Health Sciences, Bağcılar Training and Research Hospital, Department of Urology, İstanbul, Türkiye

E-mail: ismailulus06@yahoo.com

ORCID

İ.U. 0000-0002-2005-9734
Y.Ş. 0000-0001-5216-2202
İ.H. 0000-0002-2212-5504
M.M.D. 0000-0001-7110-4155

Abstract

Objective: To evaluate age-related differences in hormonal and semen parameter responses following varicocelectomy in adolescents and adults, and to explore whether early surgical intervention is justified in younger patients.

Materials and Methods: We retrospectively analyzed 82 patients who underwent subinguinal varicocelectomy and had complete pre- and postoperative hormone and semen profiles. Patients were divided into two age-based groups, group 1 (<21 years, n=30) and group 2 (>30 years, n=52). Hormonal parameters included serum FSH, LH, and total testosterone. Semen parameters included sperm concentration, motility, and morphology. Outcomes were assessed 6-12 months postoperatively.

Results: Both groups exhibited significant improvements in semen parameters postoperatively, with no significant differences in the degree of improvement between groups (p>0.05). In contrast, a significant increase in testosterone levels was observed only in group 2 (p=0.017), and this hormonal improvement was significantly greater than in group 1 (p=0.009). FSH levels were higher in group 2 preoperatively (p=0.006) and postoperatively (p=0.002), yet no significant intragroup changes in FSH or LH were detected.

Conclusion: While varicocelectomy improves semen parameters in both adolescents and adults, meaningful hormonal recovery appears to be limited to older patients. These findings suggest that early surgical intervention may not be necessary for all adolescents and highlight the importance of individualized, hormone-informed treatment strategies. Prospective studies with longer follow-up are warranted to guide age-specific clinical decision-making.

Keywords: adolescent, adult, hormone profile, semen analysis, varicocelectomy

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INTRODUCTION

Varicocele is characterized by the abnormal dilation of the pampiniform venous plexus, is the most prevalent surgically correctable cause of male infertility. Its prevalence is estimated at approximately 15% in the general male population and increases to 35-44% in men with primary infertility, and up to 81% in those with secondary infertility (1).

In adolescents and young adults, the clinical significance and management of varicocele remain subjects of debate. While varicocelectomy has been associated with improvements in semen parameters and testicular volume in this population, the overall quality of evidence is limited. Moreover, long-term data on fertility and paternity rates are lacking. As a result, current expert consensus and guidelines typically classify the presence of abnormal semen parameters in adolescents and young adults as a relative indication for surgical intervention, with conservative follow-up often recommended (2). The uncertainty surrounding the outcomes of adolescent varicocelectomy, coupled with parental concerns about potential infertility in adulthood, can create disagreement between physicians and families during the decision-making process (3).

By contrast, in adult men, particularly those over 30 years of age, there is more consistent evidence supporting varicocelectomy for improving semen quality and fertility outcomes. A comprehensive meta-analysis demonstrated that treatment of any grade varicocele in infertile men significantly enhances sperm concentration, motility, and natural conception rates (4).

Despite these findings, few studies have directly compared the outcomes of varicocelectomy across different age groups. Evaluating age-related differences in surgical efficacy is crucial for developing clear and individualized treatment strategies (5-7).

In this study, we aim to evaluate the changes in semen and also hormone levels following varicocelectomy in two distinct age groups: those under 21 years and those over 30 years. By analyzing pre- and post-operative hormone and semen parameters, we seek to determine whether our clinical outcomes are consistent with current literature and to clarify the impact of patient age on the response to varicocelectomy.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Urology Department of a tertiary care training and research hospital. Institutional review board approval was obtained prior to data collection (Approval No: 2025/07/05/050). A total of 754 patients who presented between January 2015 and December 2022 with symptoms such as scrotal pain, swelling, testicular atrophy, or infertility were screened using the hospital's electronic medical records system. Patients diagnosed with varicocele based on physical examination and/or scrotal Doppler ultrasonography were identified (n=232). Exclusion criteria included a history of inguinal or scrotal surgery (n=25), prior chemotherapy or radiotherapy due to any malignancy (n=9), absence of at least two consecutive preoperative semen analyses (n=57), and incomplete preoperative or postoperative hormonal profile (n=59). After applying the exclusion criteria, 82 patients were included in the final analysis. These patients were divided into two groups according to age at the time of surgery: group 1, patients aged <21 years (n=30), and group 2, patients aged >30 years (n=52) (Figure 1). An intentional age gap between the two groups was created to ensure a clear distinction between the younger, developing patient cohort and the established adult cohort, the latter primarily presenting with infertility.

Surgical Technique

All patients underwent standard subinguinal varicocelectomy performed under general/regional anesthesia. Through a 2-3 cm transverse incision made just below the external inguinal ring, the spermatic cord was exposed and isolated. Dilated veins were identified and ligated using 3-0 silk sutures under direct vision, without the aid of optical magnification. Care was taken to preserve the testicular artery and lymphatics, and the cremasteric and external spermatic veins were also ligated when clearly visualized. The surgical procedure was completed by repositioning the spermatic cord and closing the layers in anatomic fashion (8).

Hormonal and Semen Analysis

All patients had comprehensive semen analyses and hormonal evaluation both preoperatively and postoperatively. Semen samples were collected by masturbation following 3-4 days of sexual abstinence. Parameters assessed included sperm concentration (million/mL), progressive motility (%), and normal morphology (%). Hormonal profiles included serum levels of FSH, LH, and total testosterone. Postoperative assessment was performed within 6-12 months following surgery.

Statistical Analysis

Descriptive statistics included mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For non-normally distributed quantitative independent variables, the Mann-Whitney U test was used. The Wilcoxon signed-rank test was applied for dependent quantitative variables with a non-normal distribution. For categorical independent variables, the Chi-square test was used, and Fisher's exact test was applied when the assumptions for the Chi-square test were not met. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA).

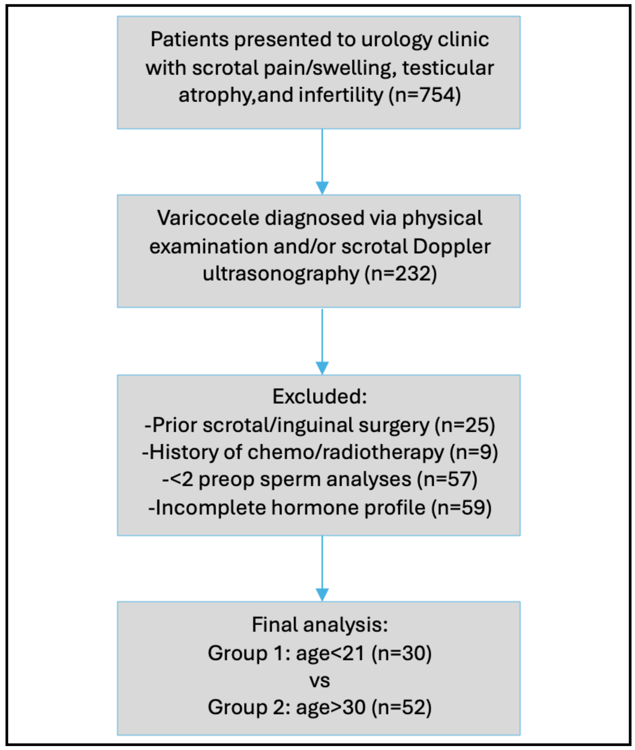

Figure 1. Study Flowchart

Table 1. Comparison of Groups in Terms of Clinical Features

		Group 1 (n=30)		Group 2 (n=52)		p value
		n	%	n	%	
Pain		20	66.7%	4	7.7%	<0.001[a]
Infertility		0	0.0%	46	88.5%	<0.001[a]
Atrophy		2	6.7%	0	0.0%	0.131[a]
Varicose appearance		8	26.7%	2	3.8%	0.002[a]
Varicocele degree right	0	27	90.0%	38	73.1%	0.069[a]
	1	1	3.3%	3	5.8%	
	2	2	6.7%	9	17.3%	
	3	0	0.0%	2	3.8%	
Varicocele degree left	0	0	0.0%	1	1.9%	1.000[a]
	1	0	0.0%	3	5.8%	
	2	13	43.3%	22	42.3%	
	3	17	56.7%	26	50.0%	
Operation side	Bilateral	3	10.0%	13	25.0%	0.099[a]
	Right	0	0.0%	1	1.9%	1.000[a]
	Left	27	90.0%	38	73.1%	0.069[a]
Postoperative complications	No	28	93.3%	49	94.2%	1.000[a]
	Yes	2	6.7%	3	5.8%	
Age at the time of operation (mean±SD)		18±1.91		35±4.83		
Postoperative analysis day (mean±SD)		143.0±46.4		143.7±52.6		0.839[b]

[a] Fisher's exact test, [b] Mann-Whitney U test.
SD: Standard Deviation

RESULTS

A total of 82 patients were included in the study, comprising 30 patients in group 1 and 52 patients in group 2. The proportion of patients presenting with scrotal pain (p<0.001) or varicose appearance (p=0.002) was significantly lower in group 2 compared to group 1. Conversely, the proportion of patients presenting with infertility was significantly higher in group 2 (p<0.001). No significant differences were observed between the groups regarding testicular atrophy complaint, laterality of varicocele, varicocele grade, surgical side, postoperative complication rates, or the timing of semen analysis (p>0.05 for all comparisons) (Table 1).

Table 2. Comparison of Groups in Terms of Pre- and Postoperative Hormone and Semen Parameters

	Group 1 (n=30)		Group 2 (n=52)		
	mean±SD	**median**	**mean±SD**	**median**	**p value**
FSH					
Preoperative	5.08±3.57	4.25	6.82±3.66	6.05	0.006 [b]
Postoperative	4.90±2.97	4.23	6.70±3.15	5.92	0.002 [b]
Pre/Postoperative Change	-0.19±1.08	0.07	-0.12±1.37	-0.17	0.870 [b]
Intragroup p-value	0.742[c]		0.662[c]		
LH					
Preoperative	5.51±2.87	4.71	6.05±2.81	5.43	0.290 [b]
Postoperative	5.25±1.78	4.94	5.75±2.37	5.15	0.476 [b]
Pre/Postoperative Change	-0.27±1.68	-0.09	-0.31±1.78	-0.29	0.665 [b]
Intragroup p-value	0.926[c]		0.389[c]		
Total testosterone					
Preoperative	4.46±1.52	4.37	4.07±1.80	3.66	0.147 [b]
Postoperative	4.22±1.49	3.93	4.38±1.72	4.06	0.762 [b]
Pre/Postoperative Change	-0.24±0.81	-0.38	0.31±1.02	0.39	0.009 [b]
Intragroup p-value	0.098[c]		0.017[c]		
Concentration					
Preoperative	16.7±22.6	8.0	9.4±10.6	7.0	0.194 [b]
Postoperative	32.2±27.8	20.5	31.7±26.3	26.5	0.862 [b]
Pre/Postoperative Change	15.5±27.5	6.5	22.3±21.9	17.5	0.076 [b]
Intragroup p-value	0.001[c]		<0.001[c]		
Motility					
Preoperative	28.8±16.0	30.0	29.3±13.8	30.0	0.735 [b]
Postoperative	39.8±10.5	38.5	35.7±15.5	34.5	0.186 [b]
Pre/Postoperative Change	11.0±13.7	12.5	6.4±15.1	5.0	0.128 [b]
Intragroup p-value	<0.001[c]		0.008[c]		
Morphology					
Preoperative	1.23±0.77	1.00	1.21±0.46	1.00	0.531 [b]
Postoperative	1.93±0.74	2.00	1.88±0.83	2.00	0.602 [b]
Pre/Postoperative Change	0.70±1.02	1.00	0.67±0.79	1.00	0.510 [b]
Intragroup p-value	0.002[c]		<0.001[c]		

[b] Mann-Whitney U test, [c] Wilcoxon signed-rank test.

SD: Standard Deviation

In hormonal analyses, preoperative (p=0.006) and postoperative (p=0.002) FSH levels were significantly higher in group 2 compared to group 1. However, within-group comparisons revealed no significant change in FSH or LH levels pre- and postoperatively in either age group (p>0.05). Similarly, there were no significant differences in the degree of FSH or LH change between the groups. Regarding testosterone levels, postoperative testosterone values increased significantly compared to preoperative values only in group 2 (p=0.017). Furthermore, the degree of testosterone increase was significantly greater in group 2 compared to group 1 (p=0.009) (Table 2).

Semen parameter analysis revealed that both groups demonstrated significant improvements in sperm concentration, progressive motility, and morphology after varicocelectomy (p<0.05 for all parameters within groups). However, the degree of improvement in these parameters did not differ significantly between the two groups (p>0.05) (Table 2).

DISCUSSION

In this retrospective cohort study, we aimed to evaluate the impact of varicocelectomy on hormonal and semen parameters in patients aged under 21 and over 30 years. Our findings revealed that postoperative testosterone levels increased significantly only in group 2, while FSH levels remained higher in this group compared to group 1. Notably, both age groups exhibited significant improvements in semen parameters postoperatively. These results suggest that early varicocelectomy in adolescents may not be necessary, as hormonal improvements are more pronounced in older patients. This study contributes to the ongoing debate regarding the optimal timing of varicocelectomy in adolescents, providing evidence that supports a more conservative approach in younger individuals.

Our findings align with previous studies indicating that varicocelectomy can lead to improvements in hormonal profiles, particularly testosterone levels, in older patients. For instance, a meta-analysis by Cannarella et al. demonstrated significant increases in serum testosterone levels post-varicocelectomy, with a mean difference of 82.45 ng/dL, especially in patients with baseline testosterone levels below 300 ng/dL (9). Similarly, a prospective cohort study reported that patients with FSH levels ≤10 mIU/mL experienced increased testosterone levels and improved semen quality after varicocelectomy (10).

While both age groups in our study demonstrated improvements in semen parameters, the lack of significant hormonal changes in the younger cohort raises questions about the necessity of early surgical intervention. This may be explained by the fact that in patients with varicocele, Sertoli cell dysfunction and decreased inhibin B levels lead to compensatory elevations in serum FSH levels. In this context, elevated FSH may be considered an indirect marker of germ cell damage. Additionally, patients with higher FSH levels have been shown to exhibit greater postoperative increases in testosterone following varicocelectomy (11). In our study, the absence of elevated FSH in the adolescent group may indicate that germ cell damage had not yet fully manifested in this population, thus potentially explaining the limited hormonal response. This observation is consistent with the notion that the hormonal benefits of varicocele repair may become more prominent once subclinical testicular damage has progressed. It also underscores the importance of hormonal assessment in the clinical decision-making process for varicocelectomy, particularly in younger patients (12).

Several studies have explored the outcomes of varicocelectomy in adolescents. A study by Van Batavia et al. found significant correlations between hormone levels and semen parameters in adolescents with varicocele, suggesting that hormonal evaluation can be a useful tool in assessing the severity of varicocele and the need for surgical intervention (13). Another study by Zhou et al. reported that adolescents with varicocele who underwent varicocelectomy showed improvements in semen parameters, including sperm count, motility, and morphology (14). However, the degree of improvement varied among individuals, highlighting the need for individualized assessment and treatment planning.

In contrast, some studies suggest that conservative management may be appropriate for certain adolescents with varicocele. A study by Bogaert et al. found that 85% of adolescents with uncorrected varicoceles managed with observation achieved paternity, a proportion similar to the 78% of men whose varicoceles were repaired (15). This finding suggests that not all adolescents with varicocele require surgical intervention, and that careful monitoring may be sufficient in some cases.

Given the variability in outcomes and the potential risks associated with surgery, it is essential to consider multiple factors when deciding on the management of varicocele in adolescents. These factors include the severity of the varicocele, the presence of symptoms, testicular volume, hormone levels, and semen parameters. A comprehensive evaluation can help identify adolescents who are most likely to benefit from surgical intervention and those who may be managed conservatively. Our findings may also highlight the importance of routinely incorporating baseline FSH and testosterone assessments in the initial evaluation of adolescents with varicocele, to enhance risk stratification and guide clinical decision-making.

It is important to note that our study has certain limitations. The retrospective design may introduce selection bias, and the relatively small sample size, especially in group 1, may limit the generalizability of our findings. Additionally, the follow-up period was limited to 6-12 months postoperatively, which may not capture long-term outcomes and even future fertility rates of each group. Another notable limitation is the absence of inhibin B level analysis, which is a major determinant of Sertoli cell dysfunction and a key regulator of the hypothalamic-pituitary-gonadal axis. Future prospective studies with larger cohorts and extended follow-up periods are warranted to validate our findings and further elucidate the age-related effects of varicocelectomy on hormonal and semen parameters.

CONCLUSION

This study demonstrates that while varicocelectomy leads to significant improvements in semen parameters in both adolescents and adults, only adults showed meaningful hormonal recovery, particularly in testosterone levels. The absence of FSH elevation and hormonal response in younger patients may indicate a lack of advanced germ cell damage, suggesting that early surgical intervention may not be necessary in all adolescent cases. These findings support a more individualized and hormone-informed approach to varicocelectomy in younger patients, rather than relying solely on varicocele degree or semen parameters. Further prospective studies are needed to optimize age-specific treatment strategies.

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Informed Consent: The written informed consent was waived due to the study's retrospective design.

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RESEARCH ARTICLE

Outcomes of BCG Therapy in Patients with High and Very High-Risk Non-Muscle-Invasive Bladder Cancer: Reassessing EAU Risk Stratification

Özgür Arıkan [1], Ayberk İplikçi [1], Hüseyin Özgür Kazan [1], Ahmet Keleş [1], Ferhat Keser [1], İlkin Hamid-zada [1], Mehmet Çağlar Çakıcı [1], Meftun Çulpan [1], Asıf Yıldırım [1]

[1] Department of Urology, Istanbul Medeniyet University, Istanbul, Türkiye

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Corresponding Author;
Ayberk Iplikci, MD, FEBU

Address: Egitim Mahallesi, Dr. Erkin Cd., 34722 Kadıköy, İstanbul, Türkiye

E-mail: ayberkiplikci@gmail.com

ORCID

O.A.	0000-0002-4647-4864
A.İ.	0000-0002-5822-7799
H.Ö.K.	0000-0003-0202-0454
A.K.	0000-0001-5436-1803
F.K.	0000-0002-2803-6481
I.H.Z.	0009-0000-0550-250X
M.Ç.Ç.	0000-0002-0176-5887
M.Ç.	0000-0001-8573-1192
A.Y.	0000-0002-3386-971X

Abstract

Objective: To evaluate the oncologic outcomes of high-risk (HR) and very high-risk (VHR) non-muscle-invasive bladder cancer (NMIBC) patients treated with Bacillus Calmette-Guérin (BCG) immunotherapy and assess the new European Association of Urology (EAU) risk stratification.

Material and Methods: This retrospective cohort study analyzed data from 211 HR and VHR NMIBC patients treated with BCG therapy between January 2015 and January 2024. Risk stratification was performed using the EAU NMIBC risk calculator. Recurrence, progression, recurrence-free survival (RFS), and progression-free survival (PFS) were assessed.

Results: The cohort comprised 144 (68.2%) HR and 67 (31.8%) VHR patients. The VHR group had significantly more adverse pathological features (larger and multiple tumors, higher pT stage, CIS, variant histology, lymphovascular invasion, tumor necrosis). While there was no significant difference in overall recurrence (33.3% vs. 37.3%, p=0.572) or progression rates (10.4% vs. 9%, p=0.741) between HR and VHR groups, the 5-year RFS was significantly lower in the VHR (56% vs. 75%, p=0.003). The 5-year PFS was similar between the groups (86% vs 91%, p=0.311).

Conclusion: In spite of the fact that the VHR group presented with more aggressive tumor characteristics, BCG therapy resulted in similar overall progression rates compared to the HR group. These findings suggest that the EAU risk stratification may overestimate the risk of progression in BCG-treated patients, particularly those classified as VHR, and that BCG remains a valuable treatment option even in this population.

Keywords: Bacillus Calmette-Guerin (BCG) therapy, EAU risk stratification, non-muscle invasive bladder cancer (NMIBC)

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INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) comprises a significant proportion of newly diagnosed bladder cancers (BC) (1). NMIBC is a heterogeneous disease with varying risks of recurrence and progression among patients (2). The presence of this inherent heterogeneity indicates the necessity of accurate risk stratification for patients. Effective risk stratification guides and optimizes the treatment and facilitates patient selection for clinical trials. Previously, the European Association of Urology (EAU) guidelines employed risk stratification for NMIBC patients. This stratification relied on risk tables developed by the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Group. These tables categorized patients into three risk groups: low, intermediate, and high-risk (HR) (3). This stratification system was refined in 2021 to incorporate an additional "very high-risk" (VHR) category (4). Risk stratification system integrates various clinical factors, including patient age, tumor stage and grade, tumor size, multiplicity, and presence of carcinoma in situ (CIS) to estimate the probability of muscle-invasive bladder cancer (MIBC) progression at one, five, and ten years. The new risk stratification system recommends early cystectomy for the VHR group due to their elevated risk of progression (4,5). However, the development of these risk groups excluded patients receiving Bacillus Calmette–Guérin (BCG) immunotherapy, a well-established treatment known to decrease NMIBC progression (4,5). Consequently, the accuracy of these updated risk groups in identifying and guiding management for patients receiving BCG remains undetermined. To address this knowledge gap, our study investigated the comparative outcomes of HR and VHR NMIBC patients who received BCG therapy.

MATERIALS AND METHODS

Study Design and Patient Population

Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee Approved by the Ethics Committee. (Approval No: 2022/0560). All patients participating in the study were informed about the study, and their informed consent was obtained. The study analyzed data from patients diagnosed with BC between January 2015 and January 2024. A total of 1535 patients were initially identified with a diagnosis of BC. Risk stratification was determined using the EAU NMIBC risk calculator, and the patient selection process is detailed in **Figure 1**.

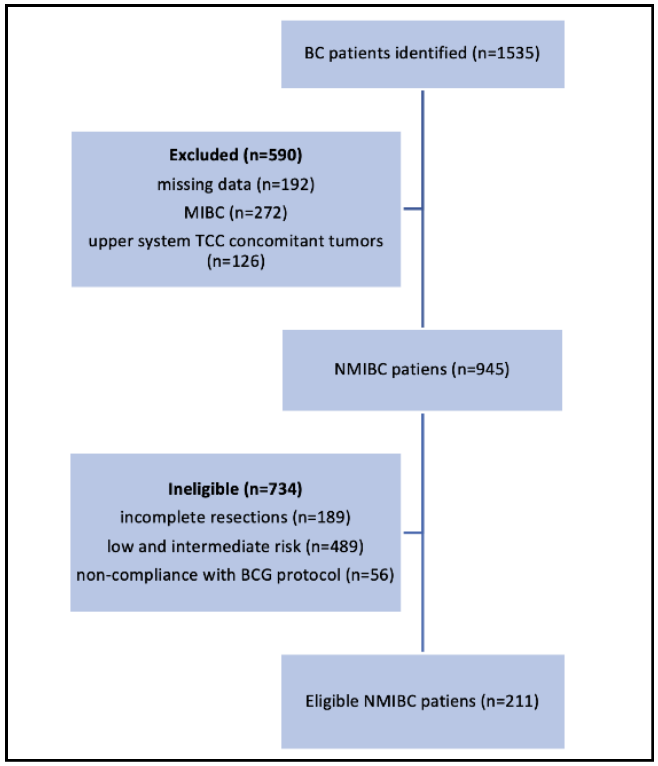


Figure 1. Study flowchart

Initial exclusions included patients with missing data (n=192), MIBC (n=272), and concomitant upper system transitional cell carcinoma (n=126), resulting in 945 patients with NMIBC. Further exclusions were applied based on the following criteria: incomplete resection at the first or second transurethral resection of bladder tumor (TURBT) (n=189), low or intermediate risk disease according to the EAU NMIBC risk calculator (n=489), and non-compliance with the established BCG protocol (n=56). The final study cohort comprised 211 eligible patients with HR or VHR NMIBC. All included patients had a minimum follow-up duration of 12 months.

Treatment Protocol

Following the initial TURBT and subsequent pathological evaluation, management decisions, including repeat TURBT, selection of intravesical therapy, and follow-up protocols, were guided by the EAU guidelines. The SWOG protocol was adopted as the BCG protocol, and adequate BCG therapy is defined as a patient receiving at least five of the six induction instillations, along with at least one maintenance cycle consisting of two of the three instillations, within 6 months (6,7).

All pathology specimens were reviewed and reported by genitourinary pathologists. Tumor grade was assigned using the 2004/2016 World Health Organization grading system.

Follow-up and Outcome Assessment

Follow-up was conducted using cystoscopy and cytology according to EAU guidelines. Recurrence was defined as the pathological confirmation of a new tumor during follow-up. Progression was defined as the detection of a pT2 or higher stage tumor on follow-up in patients with confirmed recurrent disease. The primary outcome of this study was to assess the oncologic outcomes of HR and VHR NMIBC patients receiving adequate BCG therapy.

Statistical Analysis

To examine relevant clinical characteristics and identify factors associated with disease recurrence and progression, we employed IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Data distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were analyzed with either Pearson's chi-square test for larger samples or Fisher's exact test for smaller samples. Additionally, Cox proportional hazards regression models were implemented to determine independent predictors for both disease recurrence and progression. Kaplan-Meier curves were produced to calculate survival rates for disease progression and to evaluate the differences in survival curves between groups using the log-rank test. All statistical tests were performed with a significance level set at $p < 0.05$.

RESULTS

Patient Characteristics

The study cohort consisted of 211 patients with HR or VHR NMIBC. Of these, 144 (68.2%) were classified as HR and 67 (31.8%) as VHR according to the EAU NMIBC risk calculator. The median follow-up duration was 45 months (range: 12-102 months), and Table 1 summarizes the demographic, clinical, and pathological characteristics of the two groups.

Significant differences were observed between the HR and VHR groups in several baseline characteristics. Patients in the VHR group were significantly older, with a greater proportion aged 70 years or older (61.2% vs. 27.8%; p<0.001). The VHR group also had a higher proportion of patients with multiple tumors (76.1% vs. 60.4%; p=0.026), larger tumors (≥3cm: 89.6% vs. 72.2%; p=0.005), pT1 stage tumors (92.5% vs. 74.3%; p=0.002), concomitant CIS (25.4% vs. 3.5%; p<0.001), variant histology (28.4% vs. 0.7%; p<0.001), lymphovascular invasion (11.9% vs. 0%; p<0.001), and tumor necrosis (22.4% vs. 6.9%; p=0.001). There were no statistically significant differences between the groups regarding gender (p=0.235), smoking status (p=0.751), or the need for a second transurethral resection (p=0.192).

Oncologic Outcomes

Recurrence was observed in 48 patients (33.3%) in the HR group and 25 patients (37.3%) in the VHR group (p=0.572). Progression occurred in 15 patients (10.4%) in the HR group and 6 patients (9%) in the VHR group (p=0.741). There was no statistically significant difference in recurrence or progression rates between the two risk groups.

Univariate analysis revealed factors affecting recurrence: risk group and tumor number (Table 2). On the other hand, in multivariate analysis, tumor number (multiple) (HR: 2.545, %95 CI 1.405 -4.609, p=0.002) was found to be significant. There were no statistically significant parameters in the regression analysis for factors affecting progression (Table 3).

Figure 2 shows Kaplan–Meier curve for reccurence-free survival (RFS). The p value of the log-rank method was 0.020 and the chi-square value was 5.381. The estimated RFS time was 77.7 ± 2.6 months in HR group and 64.2 ±4.7 months in VHR group. The 5-year RFS rate was 75% in the HR group and 56% in the VHR group (p=0.003). This indicates a statistically significant difference in RFS between the two risk groups, with the HR group experiencing a more favorable outcome.

Figure 3 shows the Kaplan–Meier curve for progression-free survival (PFS). The p value of the log-rank method was 0.572 and the chi-square value was 0.319. The estimated PFS time was 92.5 ± 2.2 months in HR group and 88.5 ± 3.9 months in VHR group. The 5-year PFS rate was 91% in the HR group and 86% in the VHR group (p=0.311). This indicates no statistically significant difference in PFS between the two risk groups.

Table 1. Demographic, clinical, and pathological characteristics of the groups

	High-Risk (n=144)	Very High-Risk (n=67)	p value
Age, n (%)			**<0.001**
<70	104 (72.2)	26 (38.8)	
≥70	40 (27.8)	41 (61.2)	
Gender, n (%)			0.235
Female	24 (16.7)	7 (10.4)	
Male	120 (83.3)	60 (89.6)	
Smoking status, n (%)			0.751
Never	21 (14.6)	12 (17.9)	
Exsmoker	74 (51.4)	35 (52.2)	
Smoker	49 (34)	20 (29.9)	
Number of tumors, n (%)			**0.026**
Single	57 (39.6)	16 (23.9)	
Multiple	87 (60.4)	51 (76.1)	
Maximum tumor size, n (%)			**0.005**
<3cm	40 (27.8)	7 (10.4)	
≥3cm	104 (72.2)	60 (89.6)	
Tumor stage, n (%)			**0.002**
pTa	37 (25.7)	5 (7.5)	
pT1	107 (74.3)	62 (92.5)	
Concomitant carcinoma in situ, n (%)			**<0.001**
No	139 (96.5)	50 (74.6)	
Yes	5 (3.5)	17 (25.4)	
Presence of variant histology, n (%)			**<0.001**
No	143 (99.3)	48 (71.6)	
Yes	1 (0.7)	19 (28.4)	
Presence of lymphovascular invasion, n (%)			**<0.001**
No	144 (100)	59 (88.1)	
Yes	0	8 (11.9)	
Presence of tumor necrosis, n (%)			**0.001**
No	134 (93.1)	52 (77.6)	
Yes	10 (6.9)	15 (22.4)	
Second transurethral resection, n (%)			0.192
No	40 (27.8)	13 (19.4)	
Yes	104 (72.2)	54 (80.6)	
Recurrence, n (%)			0.572
No	96 (66.7)	42 (62.7)	
Yes	48 (33.3)	25 (37.3)	
Progression, n (%)			0.741
No	129 (89.6)	61 (91)	
Yes	15 (10.4)	6 (9)	

Table 2. Univariate and multivariate analysis: Factors affecting recurrence

	Univariate Analysis		**Multivariate Analysis**	
	HR (%95 CI)	**p value**	**HR (%95 CI)**	**p value**
Risk group (Very high vs high)	1.762 (1.082 – 2.870)	**0.023**	1.476 (0.900 – 2.420)	0.123
Age (≥70 vs <70 years)	1.176 (0.725 – 1.907)	0.511		
Gender (male vs female)	0.945 (0.484 – 1.845)	0.868		
Number of tumors (multiple vs single)	2.740 (1.526 – 4.917)	**0.001**	2.545 (1.405 – 4.609)	**0.002**
Tumor size (≥3 cm vs < 3 cm)	1.591 (0.886 – 2.858)	0.120		
Tumor stage (pT1 vs pTa)	0.903 (0.445 – 1.832)	0.778		
Accompanying CIS (yes vs no)	1.260 (0.577 – 2.754)	0.562		
Variant histology (yes vs no)	1.196 (0.479 – 2.981)	0.702		
Lymphovascular invasion (yes vs no)	1.796 (0.563 – 5.731)	0.323		
Tumor necrosis (yes vs no)	1.829 (0.899 – 3.721)	0.096		

HR: High risk, **CIS:** carcinoma in situ

Table 3. Univariate analysis: Factors affecting progression

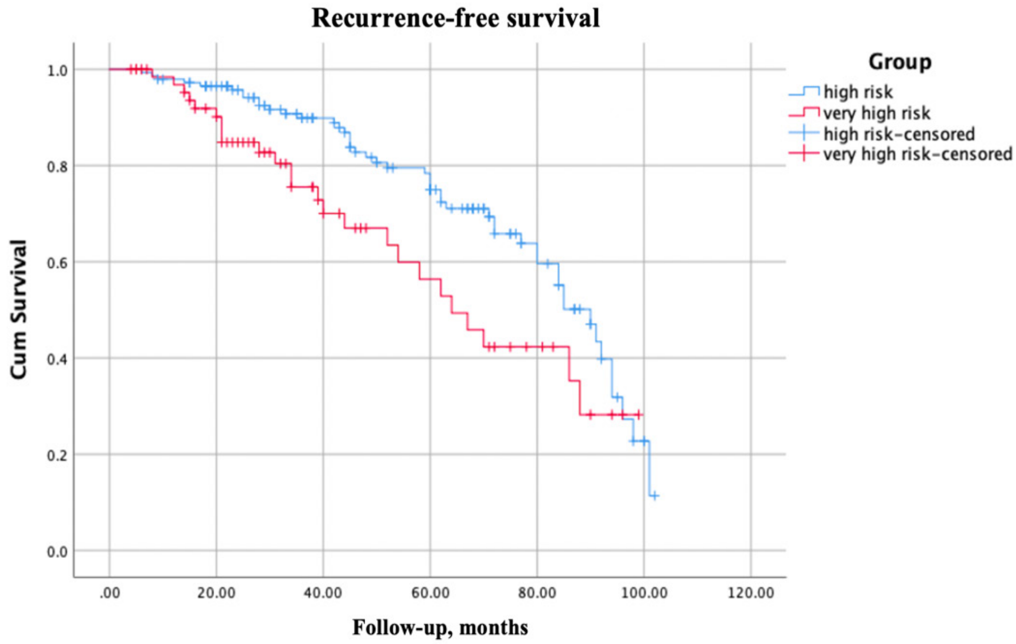
	Univariate Analysis	
	HR (%95 CI)	**p value**
Risk group (Very high vs high)	1.314 (0.507 – 3.403)	0.574
Age (≥70 vs <70 years)	1.047 (0.420 – 2.608)	0.921
Gender (male vs female)	3.125 (0.419 – 23.311)	0.266
Number of tumors (multiple vs single)	2.833 (0.952 – 8.434)	0.061
Tumor size (≥3 cm vs < 3 cm)	2.190 (0.643 – 7.461)	0.210
Accompanying CIS (yes vs no)	1.183 (0.275 – 5.090)	0.821
Variant histology (yes vs no)	0.786 (0.105 – 5.891)	0.815
Tumor necrosis (yes vs no)	1.302 (0.298 – 5.686)	0.725

HR: High risk, **CIS:** carcinoma in situ

DISCUSSION

This retrospective study evaluated the oncologic outcomes of HR and VHR NMIBC patients treated with adequate BCG therapy, aiming to address the knowledge gap regarding the applicability of the EAU risk stratification in this specific population. Our findings revealed several key observations.

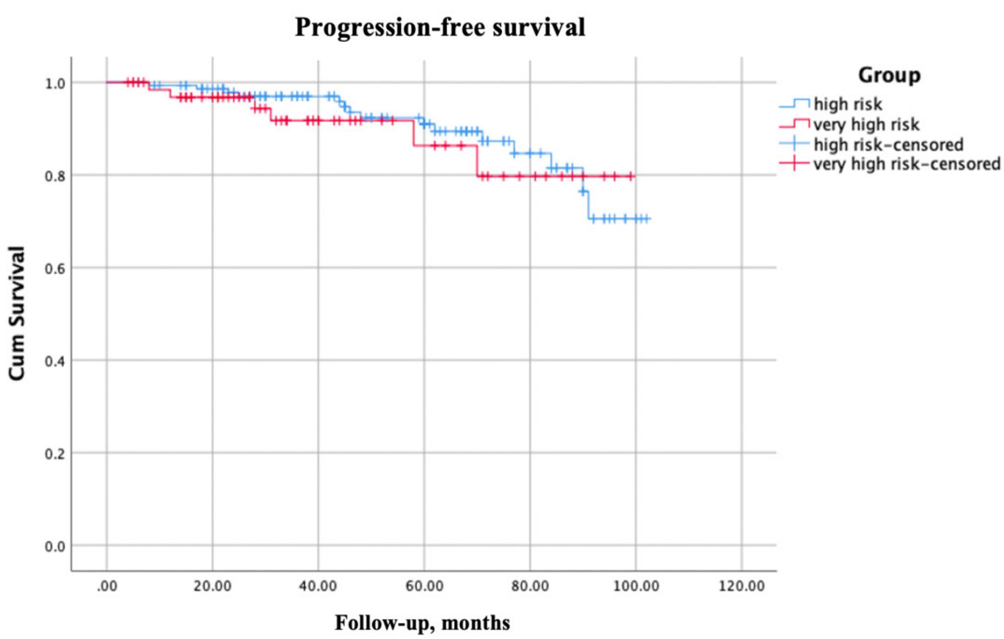
Firstly, despite the VHR group exhibiting more aggressive tumor characteristics at baseline, including older age, larger and multiple tumors, higher pT stage, presence of CIS, variant histology, lymphovascular invasion, and tumor necrosis, we did not observe a statistically significant difference in overall recurrence or progression rates between the HR and VHR groups. This suggests that BCG therapy may effectively mitigate the increased risk associated with these adverse pathological features, at least in terms of overall recurrence and progression rates. This finding is crucial, as it indicates that BCG remains a valuable treatment option even for patients classified as VHR according to the EAU criteria. Furthermore, EAU risk groups may not accurately reflect disease progression in patients classified as VHR who received immunotherapy. EAU risk stratification reports a 40% probability of progression at five years for the VHR group, potentially leading to recommendations for immediate radical cystectomy (4). However, our findings suggest that this risk estimation might be lower, particularly



Number at risk

High-Risk	144	124	92	59	28	2
Very High-Risk	67	51	24	16	8	0

Figure 2. Kaplan-Meier analysis of recurrence-free survival with BCG treatment



Number at risk

High-Risk	144	129	92	59	29	3
Very High-Risk	67	47	24	16	8	0

Figure 3. Kaplan Meier analysis of progression-free survival with BCG treatment

for patients receiving BCG therapy. This highlights the complexity of clinical decision-making for HR and VHR NMIBC patients. Studies have shown the efficacy of BCG therapy for preventing recurrence compared to intravesical chemotherapy, especially in the setting of maintenance treatment regimens (8). While some studies, such as the one by Schmidt et al., have not observed a statistically significant difference in disease progression or survival outcomes between BCG and intravesical chemotherapy (9), BCG therapy is generally recognized to delay or prevent progression (10). Lobo et al. recently reported lower disease progression rates in a study investigating the effect of BCG therapy on risk stratification. Patients in the VHR group who received induction BCG therapy (6.9%) and those who completed adequate BCG therapy (4.0%) demonstrated significantly lower progression rates at one year compared to the predicted rates of 16.0% according to the EAU risk stratification system. This trend persisted for five years, with lower progression rates observed in both the HR and VHR groups who received BCG therapy compared to the predicted EAU rates (7.4% vs. 9.6% and 16.7% vs. 40.0%, respectively) (10). Also, another recent study found a 25.8% progression risk for the VHR group at 5-year follow-up (11). Our study's findings regarding the impact of BCG therapy on disease progression align with those reported in these studies, and a lower progression rate was observed in patients receiving BCG therapy compared to the rates predicted by the EAU risk stratification system.

In line with these observations, our analysis revealed no significant difference in PFS among patients classified as HR and VHR (91% vs 86%, p=0.311, respectively) who were treated with BCG. This observation underscores the potential therapeutic role of immunotherapy in the VHR patient population. Consequently, our findings suggest re-evaluation regarding the necessity of immediate radical cystectomy for patients classified as VHR, particularly considering the significant morbidity and mortality associated with this surgical intervention. Contieri et al. also investigated the accuracy of the new EAU NMIBC risk calculator, specifically evaluating its performance in a study including patients with T1 high-grade disease who underwent a second transurethral resection followed by BCG therapy (12). Their analysis revealed a five-year PFS rate of 68.2% for the entire cohort, with a further decrease to 59.9% within the VHR group. These findings led Contieri et al. to conclude that the new risk groups might underestimate the effectiveness of BCG therapy, potentially due to the inclusion of an age threshold within the risk stratification model (12). Notably, their study did not detect a significant impact of the 70-year age limit on the outcomes within their patient population. Similarly, Krajewski et al. reported an overestimation of progression rates within a cohort of high-grade NMIBC patients, observing a five-year PFS of 82.3% (13). For patients receiving BCG therapy, the CUETO risk scoring model remains a commonly employed tool for predicting disease progression (14). However, the inherent heterogeneity of BCG treatment regimens presents a significant challenge to accurate prediction.

The present study is not without its limitations. The retrospective design introduces inherent biases, including selection bias and potential data inconsistencies. Additionally, the study was conducted at a single institution, and the relatively small sample size, particularly in the very high-risk group, may limit the study's findings.

CONCLUSION

The findings of our study suggest that BCG treatment reduced the risk of progression in VHR groups. Furthermore, the new risk classification overestimates the rate of progression in patients receiving BCG therapy. These findings underscore the necessity of incorporating BCG treatment status into treatment decision-making algorithms for this patient population. In light of these findings, further evaluation and the development of a revised classification system are imperative.

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Conflict of Interests: No potential conflict of interest relevant to this article was reported.

Ethical Approval: Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee Approved by the Ethics Committee. (Approval No: 2022/0560). All patients participating in the study were informed about the study, and their informed consent was obtained.

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RESEARCH ARTICLE

The Efficacy of Low Intensity Shock Wave Therapy (LI-SWT) in Treating Erectile Dysfunction: A Single Center Study

Emrah Özsoy [1], Musab Ali Kutluhan [2]

[1] Department of Urology, Ünye Çakırtepe Hospital, Ordu, Türkiye

[2] Department of Urology, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Türkiye

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Corresponding Author;
Emrah Ozsoy, MD
Address: Department of Urology, Unye Cakirtepe Hospital, Ordu, Türkiye
E-mail: emrahozsoy@gmail.com

ORCID
E.O. 0000-0001-7899-5202
M.A.K. 0000-0001-7117-9210

Abstract

Objective: To evaluate the effectiveness of low intensity shock wave therapy (LI-SWT) in the treatment of erectile dysfunction

Material and Methods: After ethics committee approval, male patients who applied to our clinic between March 2021 and July 2024 with the complaint of erectile dysfunction were retrospectively screened. Clinical data of 63 patients who met the inclusion criteria and underwent LI-SWT treatment were reviewed. Age, body mass index, International Index of Erectile Function (IIEF-5) and Erectile Hardness Score (EHS) score before LI-SWT treatment, previous erectile dysfunction treatment, smoking and alcohol use, benign prostatic hyperplasia (BPH) status and comorbidities were recorded. IIEF-5 and EHS scores at 3 and 6 months after LI-SWT were recorded and compared statistically. Subgroup analyses were also carried out according to comorbidities.

Results: Statistically significant improvements were observed in both IIEF-5 and EHS scores following Li-ESWT. The median IIEF-5 score increased from 13.0 at baseline to 15.0 at 3 months and 20.0 at 6 months post-treatment ($p < 0.001$). Similarly, the median EHS improved from 2.0 pre-treatment to 3.0 at 6 months ($p < 0.001$). Also significant improvements in IIEF-5 and EHS scores were observed across all subgroups at 6 months post-treatment

Conclusion: LI-SWT can be effective first line treatment option especially in mild and moderate erectile dysfunction. It can be used alternative to phosphodiesterase-5 (PDE-5) inhibitor treatment. In addition, it can be considered as single or combined with PDE-5 inhibitor treatment in severe erectile dysfunction patients with comorbid diseases.

Keywords: erectile dysfunction, EHS, IIEF-5, low intensity shock wave therapy (LI-SWT)

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INTRODUCTION

Erectile dysfunction is the inability to get or maintain an erection long enough to have sexual intercourse. The first line treatment for erectile dysfunction is phosphodiesterase-5 (PDE-5) inhibitor treatment (1). In patients unresponsive to PDE inhibitör treatment, intracavernosal injection therapy and penile prosthesis implantation can be prefered. But these treatment options are invasive and may not be applied to patient with comorbidities (2). In recent years, clinical use of regenerative treatment methods such as low intensity shock wave therapy (LI-SWT), platelet-rich plasma (PRP) and stem cells has increased with technological developments (3).

LI-SWT is a treatment modality that has been increasingly used in the treatment of erectile dysfunction. The mechanism of action of LI-SWT is endothelial cell proliferation, neoangiogenesis, reduction of smooth muscle atrophy, nerve regeneration and stem cell activation (4,5). Due to this mechanism of action, shock wave therapy has been used in musculoskeletal system diseases, diabetic ulcers and cellulitis for many years (6,7). The areas of use of LI-SWT in urology are mainly erectile dysfunction treatment, peyronie's disease and chronic prostatitis treatment (8). In current guidelines, LI-SWT treatment is recommended with a low recommendation level for patients with mild vasculogenic erectile dysfunction (9). In this study, we aimed to evaluate the efficacy of LI-SWT in patients with erectile dysfunction.

MATERIAL AND METHODS

Work Design

The ethics committee approval of the study was obtained from Ordu University Non-Interventional Scientific Research Ethics Committee (Decision No: 2025/33, Date: 2025-02-07). After ethics committee approval, male patients who applied to our clinic between March 2021 and July 2024 with the complaint of erectile dysfunction were retrospectively screened. Clinical data of 63 patients who met the inclusion criteria and underwent LI-SWT treatment were reviewed. Data were extracted from medical records and questionnaires. In our clinic, Index of Erectile Function (IIEF-5) and Erectile Hardness Score (EHS) questionnaires are routinely performed at the time of diagnosis and during follow-up period. Age, body mass index, IIEF-5 and EHS scores before LI-SWT treatment, previous erectile dysfunction treatment, smoking and alcohol use, benign prostatic hyperplasia (BPH) status and comorbidities were recorded. IIEF-5 and EHS scores were recorded at 3 and 6 months after LI-SWT.

Inclusion and Exclusion Criteria

Patients who were over 20 years of age, had regular sexual intercourse for more than 3 months, had an IIEF-5 score between 5-21 (mild, moderate, severe erectile dysfunction) and had erectile dysfunction for more than 6 months were included in our study. Testosterone replacement therapy, history of pelvic radiotherapy, history of anti-androgen hormone therapy, history of bilateral orchiectomy, use of 5-alpha reductase inhibitors, anatomical pathology in the penis or history of penile fracture, diagnosis of haemotological malignancy, spinal cord injury, polyneuropathy, stroke or neurodegenerative disease (Multiple Sclerosis, Parkinson, Multiple Atrophy), drug-induced erectile dysfunction (antipsychotics, anticonvulsives, antidepressants, thiazide diuretics, beta blockers) are exclusion criteria.

Treatment Protocol

The device used in LI-SWT treatment in our clinic is Modus ED-SWT (Inceler Medikal, Ankara, Turkiye) (Figure 1). We determined our treatment protocol as a total of 6 sessions with 3 day intervals. All sessions were done by the same clinican in outpatient clinic without anaesthesia. In order to prevent energy loss that may occur during shock wave therapy, we first applied ultrasound gel to the treatment areas. In each session, we applied 300 shock waves to 5 different regions of the penis (proximal and distal part of right corpus cavernosum, proximal and distal part of left corpus cavernosum and mid-dorsal penile region) with a total of 1500 shock waves per session (Figure 2). The frequency of the applied shock waves is 2/second and has a power of 0.15 mJ/mm^2. Focal depth and penetration of Modus ED-SWT are 28.5 mm and 68.5 mm (Figure 3). Session durations were approximately 15-20 minutes. We do not discontinue anticoagulant therapy prior to LI-SWT, as there are no contraindications.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 22 (IBM Corp. Armonk, NY, USA). Continuous variables were presented as means ± standard deviations depending on data distribution. Categorical variables were expressed as frequencies and percentages. The Wilcoxon signed-rank test was used to compare paired non-parametric data, including changes in IIEF-5 and EHS scores before and after treatment. Subgroup analyses were also performed using the Wilcoxon test to assess treatment response across clinical variables such as diabetes mellitus (DM), benign prostatic hyperplasia (BPH), cardiovascular disease (CVD) history and PDE-5 inhibitor use. A two-tailed p-value of <0.05 was considered statistically significant.

Figure 1. Modus ED-SWT device

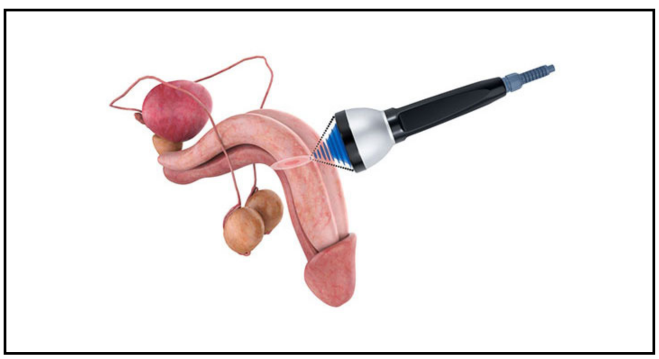

Figure 2. Application of LI-SWT

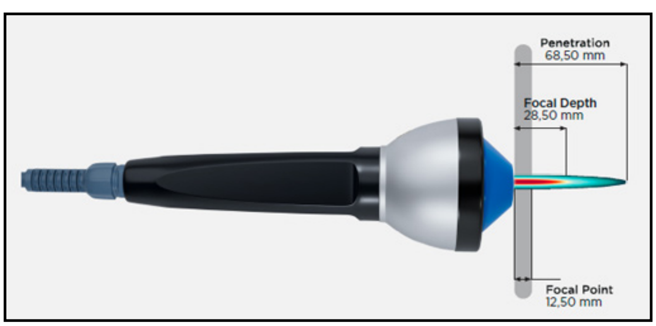

Figure 3. Penetration and depth of Modus ED-SWT

RESULTS

The mean age of the participants was 51.90 ± 13.06 years. Regarding body mass index, the majority were classified as normal weight (42.9%) and overweight (25.4%). The most common comorbidities included DM (33.3%), BPH (36.5%), hypertension (HT) (28.6%), CVD (22.2%), and hyperlipidaemia (20.6%). 30 (47.6%) patients had unresponsive treatment history to PDE-5 inhibitors. All demographic features of patients were summarised in table 1.

Table 1. Baseline characteristics and erectile function scores of the study population (n = 63)

	Value
Age (years) (Mean±Sd)	51.90 ± 13.06
BMI, n (%)	
– Underweight	12 (19.0%)
– Normal weight	27 (42.9%)
– Overweight	16 (25.4%)
– Obese	8 (12.7%)
Comorbidities, n (%)	
– Diabetes Mellitus	21 (33.3%)
– Hypertension	18 (28.6%)
– Hyperlipidemia	13 (20.6%)
– Cardiovascular Disease History	14 (22.2%)
– History of BPH	23 (36.5%)
Lifestyle factors, n (%)	
– Smoking	33 (52.4%)
– Alcohol Consumption	27 (42.9%)
Previous treatment	
– Unresponsive to PDE-5 inh treatment	30 (47.6%)
– No previous treatment	33 (52.4%)

BMI: Body Mass Index, BPH: Benign Prostatic Hyperplasia, PDE-5 inh: Phosphodiesterase 5 inhibitor

Statistically significant improvements were observed in both IIEF-5 and EHS scores following Li-ESWT. Pre-treatment median IIEF-5 score was 13.0. Post-treatment 3th and 6th month IIEF-5 scores was 15 and 20 respectively There was statistically significant difference between pre-treatment, post-treatmant 3th and 6th months IIEF-5 scores ($p < 0.001$). In addition, pre-treatment median EHS score was

2.0. Post-treatment 6th month EHS score was 3.0. There was statistically significant difference between pre-treatment and post-treatmant 6th months EHS scores ($p < 0.001$). (Table 2). Before treatment, 30 (%48) patients have severe, 23 (%36) patients have modarete and 10 (%16) patitens have mild erectile dysfunction. 6 months after LI-SWT treatment 4 (%6) patients have severe, 28 (%45) patients have modarete, 13 (%20) patients have mild and 18 (%29) patients have no erectile dysfunction. 4 patients from severe and 5 patients from modarete erectile disfunction group have no benefit after LI-SWT.

Significant difference in IIEF-5 and EHS scores were observed across all subgroups at 6 months post-treatment. There was statistically significant difference between pre-treatment and post-treatment 6th month IIEF-5 scores in patients with DM and without DM ($p = 0.001$ and $p < 0.001$ respectively). Also, significant diffrence between pre-treatment and post-treatment IIEF-5 scores was detected in patients with BPH and without BPH ($p < 0.001$ respectively). In addition, both PDE-5 inhibitor users and non-users had statistically significant increase between pre-treatment and post-treatment 6th month IIEF-5 scores ($p < 0.001$ respectively). There was statistically significant increase in post-treatment 6th month IIEF-5 scores in patients with CVD ($p = 0.008$). In terms of erection hardness, There was statistically significant increase in post-treatment 6th month EHS scores in patients with DM, BPH or CVD ($p < 0.001$ respectively). (Table 3). 6 out of 9 patients who did not benefit from LI-SWT treatment have DM, CVD and BPH diseases. One patient has uncontrolled DM while the other 2 patients have CVD.

Table 2. Comparison of IIEF-5 and EHS scores before and after Li-ESWT treatment

	Pre-treatment Median	Post-treatment Median	Wilcoxon Z Value	p*
IIEF-5 (Pre vs 3rd months)	13.0	15.0	0.0	< 0.001
IIEF-5 (Pre vs 6th months)	13.0	20.0	1.5	< 0.001
EHS (Pre vs 3rd months)	2.0	2.0	0.0	< 0.001
EHS (Pre vs 6th months)	2.0	3.0	0.0	< 0.001

*: Wilcoxon Test. EHS: Erection Hardness Score, IIEF-5: International Index of Erectile Function-5

Table 3. Subgroup analyses of IIEF-5 and EHS scores before and after LI-SWT treatment

	DM (+)	DM (-)	BPH (+)	BPH (-)	PDE-5i (+)	PDE-5i (-)	CVD (+)	CVD (-)
IIEF-5 (Preop)	11.0	14.0	12.0	14.0	13.5	12.0	9.0	14.0
IIEF-5 (Postop 6th months)	17.0	20.5	16.0	21.0	19.0	21.0	15.0	21.0
Z (IIEF-5)	0.0	1.5	0.0	1.5	1.5	0.0	0.0	1.5
p* (IIEF-5)	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.008	<0.001
EHS (Preop)	1.0	2.0	1.0	2.0	2.0	2.0	1.0	2.0
EHS (Postop 6th months)	3.0	3.0	3.0	3.0	3.0	3.0	2.0	3.0
Z (EHS)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
p* (EHS)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

*: Wilcoxon Test, EHS: Erection Hardness Score, IIEF-5: International Index of Erectile Function-5, DM: Diabetes Mellitus, BPH: Benign Prostatic Hyperplasia, CVD: Cardiovascular Disease, PDE-5i: Phosphodiesterase type 5 inhibitors

DISCUSSION

In our study, a significant response to treatment was observed at the 3rd month after the procedure in patients who underwent LI-SWT for erectile dysfunction. Treatment response continued to increase when the 6th month results were evaluated. The results of this study show that treatment efficacy was significantly higher in patients with DM, CVD and BPH. Another important result of our study is that LI-SWT treatment is effective in patients with PDE-5 inhibitor refractory erectile dysfunction. On the other hand, none of patient had treatment related complications.

The mechanism of action of LI-SWT has been studied in preclinical studies. In one of these studies demonstrated that endothelial cell regeneration and angiogenesis was increased as a result of nNOS, eNOS and VEGF activation (9). In another study, Ling G et al. found that schwann cell proliferation was increased via increased angiogenesis and activation of tissue regeneration in the penis of rats treated with LI-SWT in an age-induced erectile dysfunction model (10). The increase in angiogenesis has made LI-SWT valuable treatment option in vasculogenic type erectile dysfunction. In a systematic review of 11 studies by Brunchorst O et al, they found an average IIEF increase of 5.3 points in the 6th month after LI-SWT treatment in 799 vasculogenic erectile dysfunction patients (11). In a prospective study published in 2021 involving 66 patients, a significant increase was found in the 3rd and 6th month IIEF evaluations after LI-SWT treatment compared to the placebo group and it was stated that LI-SWT may be a useful treatment option especially in younger patients with mild vasculogenic erectile dysfunction (12). In our study the IIEF-5 values increased from 13.09 ± 4.04 before LI-SWT to 14.77 ± 3.96 in the 3rd month and 18.53 ± 5.03 in the 6th month after the procedure, showing a statistically significant increase. In addition, the mean EHS score, which was 1.47 ± 0.83 before LI-SWT, increased to 2.25 ± 0.94 at 3 months and 3.07 ± 0.92 at 6 months after the procedure.

The patient groups in which LI-SWT treatment is most frequently used in daily clinical practice are those who are unresponsive to PDE-5 inhibitor treatment, who cannot continue PDE-5 inhibitor treatment. Up to 50 per cent of those with severe erectile dysfunction due to comorbid diseases especially DM and CVD, do not benefit from PDE-5 inhibitor treatment (13) LI-SWT is one of the treatment modalities to be used in this patient group. In a prospective multicentric study, significant differences were found in IIEF-5, EHS and SQOL (Sexual Qualiy of Life-Male) indexes and penile doppler ultrasound results after LI-SWT applied to patients unresponsive to PDE-5 inhibitor treatment (14). According to our study results, the mean IIEF-5 score increased from 13.5 to 19, while the EHS score increased from 2 to 3 on average after LI-SWT treatment in the PDE-5 inhibitor unresponsive patient group. LI-SWT treatment is an alternative treatment for PDE-5 inhibitor refractory patients and has been shown to increase the efficacy of PDE-5 inhibitor treatment. Ibis MA et al. obtained higher IIEF-5 and EHS scores in patients who received PDE-5 inhibitor treatment combined with LI-SWT compared to those who received only LI-SWT treatment (15). These results further support that LI-SWT can be used as an alternative treatment method for patients who can not use PDE-5 inhibitor.

Intracavernosal injection therapy and vacuum erection devices, which are alternative treatment methods used in the treatment of erectile dysfunction, cause treatment non-compliance in patients because these are invasive treatment options. The last-line treatment method of erectile dysfunction is penile prosthesis implantation. This is a high cost treatment option and has some crucial complications such as prosthesis infection and mechanical problems (16).

In addition to treatment efficacy, LI-SWT also has different advantages in clinical use. Low side effect profile, non-invasiveness, reapplication, painless procedure and easy application are the most important advantages. Also Its relatively low cost compared to alternative treatment methods in patients with long-term effect is another advantage. Because of these advantages, it has started to be used in patients with non-vasculogenic type erectile dysfunction. In a systematic review of 9 clinical and 10 animal studies, Mason MM et al. stated that LI-SWT treatment is a safe and effective treatment method in patients with moderate erectile dysfunction with controlled DM (17). In another systematic review involving patients with erectile dysfunction after radical prostatectomy, the potential therapeutic effect of SWT treatment has been emphasised (18). Apart from erectile dysfunction, recent studies showed that LI-SWT is also effective in patients with chronic prostatitis and peyronie's disease (19,20).

One of the most important clinical problems related to LI-SWT treatment is the lack of standardisation. In clinical practice, there are different devices. Also, number of sessions, session intervals, frequency, number of pulses and power applications are not certain yet. On the other hand there is still not certain indications of LI-SWT. Although the European Society of Urology recommends LI-SWT treatment in patients with mild vasculogenic erectile dysfunction, we think that the current recommendations may change as preclinical and clinical studies increase. Ghahhari J et al. (21) reported in their multicentric study that LI-SWT treatment is an effective and safe treatment method independent of device type, power, frequency, treatment protocol and erectile dysfunction type.

The first limitation of our study is its retrospective design, which is inherently prone to selection bias and unmeasured confounding. In addition, the relatively small sample size may have reduced the statistical power, particularly in subgroup analyses. Another limitation is the lack of long-term follow-up data, which prevented us from evaluating the sustained efficacy of LI-SWT. Moreover, if penile doppler ultrasonography findings available, they could have contributed to the evaluation of LI-SWT success. Finally, many patients had comorbidities requiring various medications, which may have influenced treatment outcomes and complication rates.

CONCLUSIONS

According to our retrospective short-term results, LI-SWT can be effective first line treatment option especially in mild and moderate erectile dysfunction. It can be used alternative to PDE-5 inhibitor treatment. In addition, it may be considered as single or combined with PDE-5 inhibitor treatment in severe erectile dysfunction patients with comorbid diseases. Surely, prospective larger scaled randomized controlled studies with a long follow-up period will contribute to the establishment of ideal protocols regarding the indication and application method of LI-SWT treatment.

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Informed Consent: Informed consent was obtained from all participants included in the study

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Author Contributions: Concept and Design: EO, MK. Supervision: MK. Data Collection and/or Analysis: EO. Analysis and/or Interpretation: EO, MK. Literature Search: EO. Writing: EO, MK. Critical Review: MK.

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RESEARCH ARTICLE

Benchmarking Artificial Intelligence Models for Clinical Guidance in Nocturia and Nocturnal Polyuria: A Comparative Evaluation of ChatGPT, Gemini, Copilot, and Perplexity

Gökhan Çeker [1], İsmail Ulus [2], İbrahim Hacıbey [1]

[1] Department of Urology, Başaksehir Çam and Sakura City Hospital, Istanbul, Türkiye

[2] Department of Urology, Bağcılar Training and Research Hospital, Istanbul, Türkiye

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Corresponding Author;
Gökhan Çeker, MD

Address: Başakşehir Mahallesi G-434 Caddesi No: 2L, Başakşehir, Istanbul 34480, Türkiye

E-mail: drgokhanceker@gmail.com

ORCID

G.Ç. 0000-0002-7891-9450
İ.U. 0000-0002-2005-9734
İ.H. 0000-0002-2212-5504

Abstract

Objective: This study aimed to evaluate and compare the performance of four artificial intelligence (AI) models—ChatGPT-4.0, Gemini 1.5 Pro, Copilot, and Perplexity Pro—in answering clinical questions about nocturia and nocturnal polyuria.

Material and Methods: A total of 25 standardized clinical questions were developed across five thematic domains: general understanding, etiology and pathophysiology, diagnostic work-up, management strategies, and special populations. Responses from each AI model were scored by two blinded expert urologists using a five-point Likert scale across five quality domains: relevance, clarity, structure, utility, and factual accuracy. Mean scores were compared using repeated measures ANOVA or Friedman tests depending on data distribution. Inter-rater reliability was measured via the intraclass correlation coefficient (ICC).

Results: ChatGPT-4.0 and Perplexity Pro achieved the highest overall mean scores (4.61/5 and 4.52/5), significantly outperforming Gemini (4.35/5) and Copilot (3.63/5) ($p = 0.032$). ChatGPT scored highest in "general understanding" (4.86/5, $p = 0.018$), while Perplexity led in "management strategies" (4.74/5, $p = 0.021$). Copilot consistently scored lowest, particularly in "diagnostic work-up" (3.42/5, $p = 0.008$). In quality domain analysis, ChatGPT and Perplexity again outperformed others, especially in "factual accuracy" (4.48/5 and 4.44/5), with Copilot trailing (3.54/5, $p = 0.001$). Inter-rater reliability was excellent (ICC = 0.91).

Conclusion: ChatGPT and Perplexity Pro demonstrated strong performance in delivering clinically relevant and accurate information on nocturia and nocturnal polyuria. These findings suggest their potential as supportive tools for education and decision-making. Copilot's lower performance underscores the need for continued model refinement. AI integration in clinical contexts should remain guided by expert validation and alignment with current urological guidelines.

Keywords: artificial intelligence, large language models, nocturia, nocturnal polyuria

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INTRODUCTION

Nocturia and nocturnal polyuria are two of the most common and burdensome lower urinary tract symptoms, particularly in aging populations (1). Their clinical relevance extends beyond sleep disruption, with studies linking them to falls, depression, and cardiovascular morbidity (2,3). While nocturia is easily recognized as a symptom, identifying nocturnal polyuria as an underlying cause often requires quantitative assessment, and this distinction may not always receive adequate attention in routine clinical practice (4).

In parallel with advances in digital health technologies, artificial intelligence (AI)—particularly through large language models (LLMs) such as ChatGPT (5), Gemini (6), Perplexity (7), and Copilot (8) is gaining traction for its potential use in clinical education, patient interaction, and medical decision support. While these AI-powered models demonstrate linguistic fluency and contextual adaptability in general medical domains, their clinical reliability in specialty fields such as urology remains insufficiently evaluated.

Evidence suggests that although LLMs can produce grammatically coherent and context-aware responses, their outputs often vary in factual accuracy and alignment with clinical guidelines. In a comprehensive review, Abd-alrazaq et al. highlighted that current LLMs, despite their pedagogical potential, may propagate misinformation or provide inconsistent recommendations—especially when used without professional oversight in educational or clinical contexts (9). These findings emphasize the importance of careful model evaluation and contextual validation when implementing LLMs in specialty-specific healthcare environments. Given the high prevalence, diagnostic challenges, and clinical significance of nocturia and nocturnal polyuria, these conditions are ideal targets for assessing the performance and practical value of large language models in clinical urology.

While previous benchmarking studies have evaluated LLMs in other urological and medical domains, to our knowledge (10-13), this is the first study to systematically benchmark multiple state-of-the-art LLMs specifically on the clinical topics of nocturia and nocturnal polyuria. Our methodological approach is distinguished by the use of a guideline-driven, thematically structured question set, as well as blinded, domain-expert evaluation, providing new insights into the strengths and limitations of AI models within this under-explored area of urological practice.

The present study aims to systematically evaluate and compare the performance of four state-of-the-art LLMs—ChatGPT-4.0, Gemini 1.5 Pro, Copilot, and Perplexity Pro—on a structured set of questions related to nocturia and nocturnal polyuria. By doing so, we seek to assess their accuracy, consistency, and potential role in clinical urology.

MATERIALS AND METHODS

Study Design

This study was designed as a cross-sectional evaluation of the performance of four LLMs—ChatGPT-4.0 (OpenAI), Gemini 1.5 Pro (Google), Copilot based on GPT-4 (Microsoft), and Perplexity Pro (Perplexity AI)—in providing medical information about nocturia and nocturnal polyuria.

Questionnaire Development

A set of 25 standardized clinical questions was developed based on established international guidelines, including those from the European Association of Urology (EAU) and the International Continence Society (ICS), as well as expert input from urologists and commonly encountered patient queries. For instance, the first two questions were: (1) What is the standard International Continence Society (ICS) definition of nocturia? In addition, (2) How is nocturnal polyuria defined according to the International Continence Society (ICS)? The full list of questions is provided in the Supplementary Material. This approach ensured that the questions comprehensively and accurately reflect current evidence-based practices in the diagnosis and management of nocturia and nocturnal polyuria. The sample size of 25 questions was selected to comprehensively cover all major clinical domains relevant to nocturia and nocturnal polyuria while ensuring the evaluation process remained feasible and manageable for expert reviewers. Although no formal power calculation was performed, this number is consistent with similar benchmarking studies in the literature (14, 15). Two independent urologists were chosen as evaluators to maximize inter-rater reliability. We acknowledge that the sample size and number of raters may limit the statistical power and generalizability of the findings. The questions were systematically divided into five thematic categories:

1. General Understanding
2. Etiology and Pathophysiology
3. Diagnostic Work-Up
4. Management Strategies
5. Special Populations and Research

These categories were selected to encompass both foundational and advanced aspects of the topic, ensuring a broad and structured evaluation of LLMs' performance.

Prompting Methodology

Each of the 25 questions was submitted to the four LLMs (ChatGPT-4.0, Gemini 1.5 Pro, Copilot, and Perplexity Pro) using a standardized prompt format. All questions were entered in English, exactly as worded in the Supplementary Material, with no additional context or preamble. For each model, default settings were used (e.g., temperature, maximum tokens, and model-specific parameters were left at their platform defaults; browsing or enhanced real-time data retrieval was not enabled). Each response was generated in a single turn, and no follow-up clarifications or edits were made to the model output. This approach ensured consistent, unbiased, and reproducible input conditions across all AI platforms.

All large language models were accessed via their official platforms in April 2025, using the latest versions available at that time. For each model, default settings were applied, and features such as web browsing or real-time data retrieval were turned off to ensure standardization across all platforms. Nevertheless, we acknowledge that inherent differences in the models' functionalities and potential platform updates may serve as confounding factors in comparative performance analyses.

Data Collection

Each question was individually submitted to the four selected LLMs during April 2025. For consistency, default settings were used for each model without enabling additional features such as browsing or enhanced real-time data retrieval. All responses were collected in their original form without any modifications.

Evaluation Process

Two independent expert urologists, each with at least five years of clinical experience in managing lower urinary tract symptoms, served as evaluators. For structured evaluation, each LLM-generated response was assessed using a standardized 5-point Likert scale (16) adapted to clinical quality assessment across five quality domains:

- **Relevance:** The extent to which the answer directly addressed the question.
- **Clarity:** The readability and ease of understanding of the response.
- **Structure:** The logical organization and coherence of the information.
- **Utility:** The practical usefulness of the information for clinical or educational purposes.
- **Factual Accuracy:** The accuracy of the information is based on current evidence and clinical guidelines.

The Likert scale was defined as follows:
1 = Poor (inaccurate or irrelevant),
2 = Fair (partially correct but lacking key information),
3 = Satisfactory (generally correct but not well-supported by evidence),
4 = Good (mostly accurate with minor omissions),
5 = Excellent (fully accurate, comprehensive, and aligned with scientific literature).

Scores from both evaluators were averaged to calculate a final domain score per response. To reduce potential bias, evaluators were blinded to each other's ratings and to the identity of the LLM that generated the response.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, standard deviation, and range) were calculated to summarize the Likert scale scores for each evaluation domain across the four LLMs. The normality of data distribution was assessed using the Shapiro–Wilk test. The assumption of normality was met for the General Understanding and Special Populations and Research categories ($p > 0.05$). In contrast, the data for Etiology & Pathophysiology, Diagnostic Work-Up, and Management Strategies significantly deviated from a normal distribution ($p < 0.05$). Accordingly, repeated measures ANOVA was applied to normally distributed data, while the Friedman test was used as a non-parametric alternative for domains that violated the normality assumption. Post-hoc pairwise comparisons were performed using the Bonferroni correction to control for multiple testing where applicable. Inter-rater reliability between the two expert evaluators was assessed using the intraclass correlation coefficient (ICC). An ICC above 0.75 was interpreted as indicating good agreement, while values above 0.90 were considered excellent (17). All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Ethical Considerations

This study did not involve human participants, animal subjects and patient data. Therefore, ethical approval was not required in accordance with institutional and national research committee standards. All AI models were accessed through publicly available platforms under their respective terms of use.

RESULTS

Inter-rater reliability between the two expert urologists was excellent, with an ICC of 0.91, indicating strong agreement in scoring.

Overall Performance Across All Questions

Among the four LLMs, ChatGPT achieved the highest overall mean score (4.61 ± 0.32), followed by Perplexity Pro (4.52 ± 0.30) and Gemini (4.35 ± 0.28), while Copilot scored the lowest (3.63 ± 0.45). These differences were statistically significant (p = 0.032) (Table 1, Fig. 1). As an example, in response to the question "At what age-related thresholds is nocturnal urine output considered excessive?", ChatGPT provided a guideline-concordant answer:

"For individuals over 65 years, nocturnal urine output is considered excessive when it exceeds 33% of the total 24-hour urine output. For younger adults, the threshold is 20%." This response received high scores in relevance, clarity, and factual accuracy. In contrast, Copilot answered: *"For adults over 65 years, nocturnal urine output exceeding 20-33% of the total 24-hour output is considered excessive."* This response was assigned lower scores, as it reflects guideline ambiguity and lacks precise cut-off values.

Performance Across Thematic Categories

LLM performance was further analyzed across five thematic subcategories:

- General Understanding: ChatGPT (4.86 ± 0.21) and Perplexity (4.52 ± 0.29) significantly outperformed Gemini (3.62 ± 0.38) and Copilot (3.58 ± 0.36) (p = 0.018).
- Etiology & Pathophysiology: All models except Copilot performed comparably (ChatGPT: 4.28, Gemini: 4.44, Perplexity: 4.30), while Copilot lagged behind (3.82 ± 0.41) (p = 0.047).
- Diagnostic Work-Up: ChatGPT (4.80 ± 0.27) had the highest performance, followed by Gemini and Perplexity, with Copilot again trailing (3.42 ± 0.48) (p = 0.008).
- Management Strategies: Perplexity (4.74 ± 0.22) slightly outperformed ChatGPT and Gemini, whereas Copilot remained significantly lower (3.70 ± 0.42) (p = 0.021).
- Special Populations & Research: ChatGPT, Gemini, and Perplexity each scored similarly high (~4.56–4.58), while Copilot was significantly lower (3.66 ± 0.43) (p = 0.025).
- Gemini's performance was more variable—comparable to

Table 1. Comparative performance of four AI models across thematic categories related to nocturia and nocturnal polyuria

Topic	ChatGPT	Gemini	Copilot	Perplexity	p-value
FAQs (n=25)	4.61 ± 0.32[a]	4.35 ± 0.28[a]	3.63 ± 0.45[b]	4.52 ± 0.30[a]	0.032
General Understanding	4.86 ± 0.21[a]	3.62 ± 0.38[b]	3.58 ± 0.36[b]	4.52 ± 0.29[a]	0.018
Etiology & Pathophysiology	4.28 ± 0.30[a]	4.44 ± 0.38[a]	3.82 ± 0.41[b]	4.30 ± 0.31[a]	0.047
Diagnostic Work-Up	4.80 ± 0.27[a]	4.64 ± 0.24[a]	3.42 ± 0.48[b]	4.50 ± 0.29[a]	0.008
Management Strategies	4.54 ± 0.33[a]	4.50 ± 0.25[a]	3.70 ± 0.42[b]	4.74 ± 0.22[a]	0.021
Special Populations & Research	4.58 ± 0.29[a]	4.56 ± 0.27[a]	3.66 ± 0.43[b]	4.56 ± 0.26[a]	0.025

Superscript lower-case letters are used to identify statistically significant differences between groups. The same letters (e.g., a-a) indicate no significant difference, while different letters (e.g., a-b) indicate a significant difference (p<0.05).

FAQs: frequently asked questions.

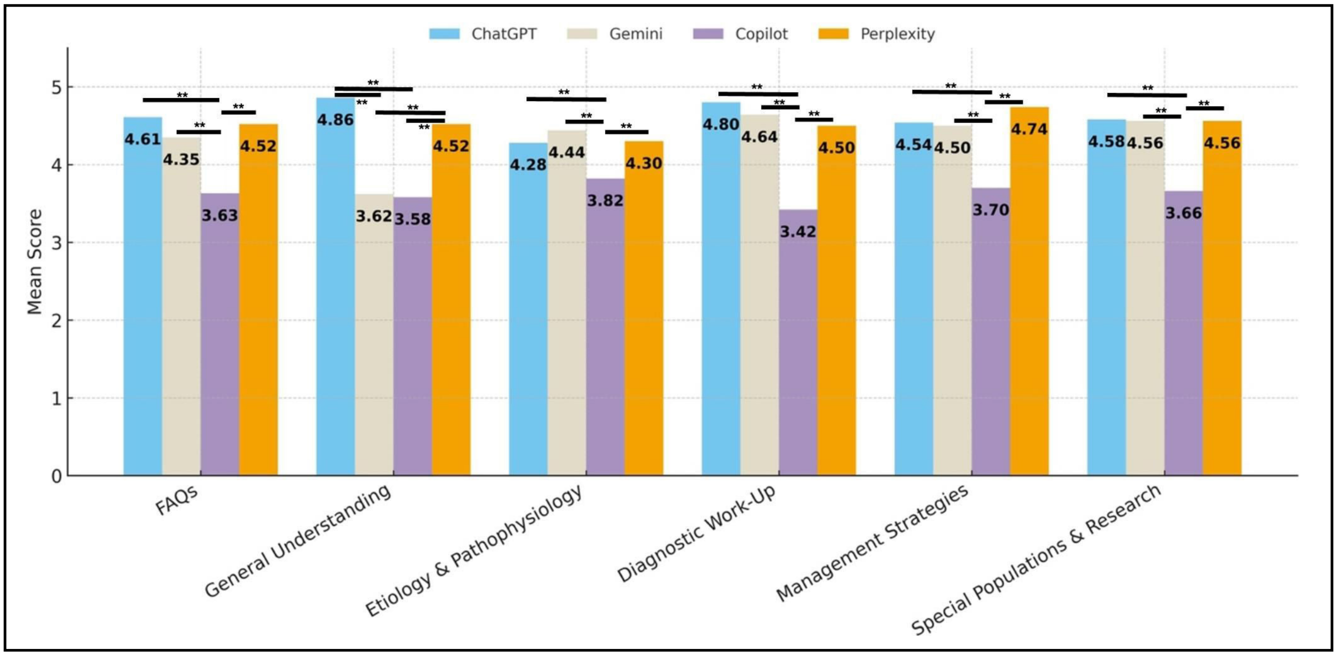

Figure 1. Mean performance scores of four artificial intelligence models across five thematic domains related to nocturia and nocturnal polyuria. FAQs, frequently asked questions. Asterisks indicate statistically significant differences between models ($p < 0.05$).

Table 2. Comparative quality domain scores of AI models in answering clinical questions on nocturia and nocturnal polyuria

Topic	ChatGPT	Gemini	Copilot	Perplexity	p-value
Relevance	4.80 ± 0.26^a	4.64 ± 0.31^a	4.08 ± 0.42^b	4.78 ± 0.24^a	0.015
Clarity	4.64 ± 0.23^a	4.38 ± 0.30^a	3.64 ± 0.39^b	4.60 ± 0.27^a	0.012
Structure	4.66 ± 0.25^a	4.40 ± 0.28^a	3.60 ± 0.43^b	4.44 ± 0.26^a	0.010
Utility	4.48 ± 0.30^a	4.20 ± 0.29^a	3.32 ± 0.40^b	4.36 ± 0.25^a	0.005
Factual Accuracy	4.48 ± 0.27^a	4.14 ± 0.32^b	3.54 ± 0.38^c	4.44 ± 0.23^a	0.001

Superscript lower-case letters in the tables (e.g., *a, b, c*) denote statistically distinct groups; values sharing the same letter are not significantly different ($p < 0.05$).

ChatGPT and Perplexity in some categories (e.g., *Etiology & Pathophysiology*), yet significantly lower in others (e.g., *General Understanding* and *Special Populations*). This variability suggests that while Gemini can produce high-quality responses in certain contexts, its consistency remains limited.

Performance Across Quality Domains

Evaluation across the five quality domains revealed consistent patterns of performance superiority by ChatGPT and Perplexity Pro (Table 2, Fig. 2):

- Relevance: ChatGPT (4.80 ± 0.26), Perplexity (4.78 ± 0.24), and Gemini (4.64 ± 0.31) all scored significantly higher than Copilot (4.08 ± 0.42) ($p = 0.015$).
- Clarity: ChatGPT (4.64 ± 0.23) and Perplexity (4.60 ± 0.27) demonstrated excellent clarity, outperforming Gemini and Copilot, the latter scoring significantly lower (3.64 ± 0.39) ($p = 0.012$).
- Structure: Similar trends were observed, with ChatGPT and Perplexity again leading, while Copilot had the lowest structure score (3.60 ± 0.43) ($p = 0.010$).
- Utility: ChatGPT (4.48 ± 0.30) and Perplexity (4.36 ± 0.25) offered the most clinically useful responses, whereas Copilot was substantially weaker (3.32 ± 0.40) ($p = 0.005$).

- Factual Accuracy: The most notable disparities were observed in the factual accuracy domain, where Copilot scored the lowest (3.54 ± 0.38) and each model was assigned a different statistical grouping (a, b, c in Table 2), indicating highly significant differences between all AI models (p = 0.001). Similarly, Copilot's clarity and structure scores were significantly lower, reflecting limitations in presenting responses in a logically organized and easy-to-understand manner.

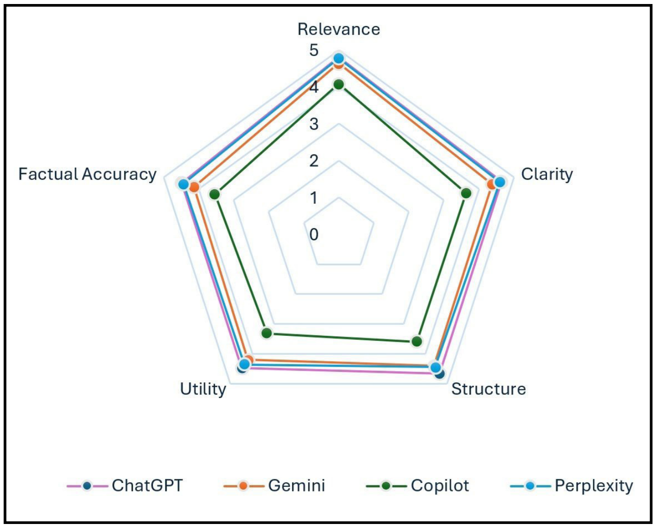

Figure 2. Radar chart illustrating the comparative quality performance of four AI models in answering clinical questions on nocturia and nocturnal polyuria. Higher values reflect better domain-specific performance on a 5-point Likert scale.

DISCUSSION

As generative AI becomes increasingly embedded in clinical informatics, evaluating its reliability in domain-specific contexts such as urology is essential. This study provides a systematic evaluation of four widely used LLMs—ChatGPT-4.0, Gemini 1.5 Pro, Copilot (GPT-4-based), and Perplexity Pro—in the context of nocturia and nocturnal polyuria, two highly prevalent and distressing lower urinary tract conditions frequently encountered in urological practice. While all four models successfully produced responses to expert-formulated clinical questions, their overall performance varied substantially across thematic domains and quality criteria. To the best of our knowledge, this is the first study to systematically evaluate the performance of LLMs in addressing clinical content specifically related to nocturia and nocturnal polyuria.

Consistent with prior research evaluating LLMs in urology-related topics such as urolithiasis management (18), our findings revealed that ChatGPT-4.0 and Perplexity Pro consistently outperformed Gemini and Copilot in key areas such as diagnostic clarity, clinical accuracy, and procedural explanation. In particular, ChatGPT achieved the highest average score across all five evaluation domains—relevance, clarity, structure, utility, and factual accuracy—while Copilot scored the lowest, often failing to provide guideline-based or adequately detailed responses. Gemini performed comparably to ChatGPT and Perplexity Pro in all thematic domains except 'General Understanding', where it scored significantly lower. This suggests that while Gemini's content accuracy is largely consistent, its introductory clarity or foundational summarization may require improvement. This domain-specific inconsistency is critical, given that nocturnal polyuria and nocturia often require nuanced diagnostic differentiation and personalized treatment planning.

These findings reinforce earlier reports in the literature demonstrating ChatGPT's high accuracy in specialty-specific medical contexts. For example, Zhu et al. compared five large language models by posing 22 questions on prostate cancer, and ChatGPT achieved the highest accuracy rate among them (19). Similarly, Caglar et al. found that ChatGPT maintained a guideline adherence rate exceeding 90% in pediatric urology, highlighting its potential in medical education and patient counseling (20). Hacıbey and Halis further supported these results by showing that ChatGPT outperformed other LLMs in addressing clinically relevant questions regarding onabotulinum toxin and sacral neuromodulation (SNM) in the treatment of overactive bladder (15). Consistent with these studies, our evaluation showed that ChatGPT achieved near-perfect scores in the "General Understanding" and "Diagnostic Work-Up" domains.

Interestingly, Gemini exhibited high scores in the "Etiology and Pathophysiology" category, suggesting a potential strength in conceptual reasoning. However, both Gemini and Copilot showed limitations in domains requiring the synthesis of clinical guidelines and nuanced patient-centered reasoning. Copilot consistently scored the lowest across all evaluated domains, with particularly poor performance in factual accuracy and utility. While some of these shortcomings may stem from inherent architectural limitations or reliance on a general-purpose training corpus, other contributing factors likely include insufficient exposure to domain-specific medical content, lack of clinical fine-tuning, and potential dataset bias. These deficits are particularly critical in clinical communication contexts, where precision, guideline adherence, and applicability are essential. The findings underscore the necessity for future LLMs to be trained on structured, peer-reviewed clinical corpora and to undergo post-hoc validation aligned with specialty-specific standards. Supporting this, a recent evaluation of the Me-LLaMA model demonstrated that LLMs with access to curated clinical datasets significantly outperformed those trained primarily on unfiltered web-based content (21).

From a clinical utility standpoint, these findings carry significant implications. Nocturia and nocturnal polyuria are associated with sleep disturbances, falls, cardiovascular morbidity, and reduced quality of life—especially in older adults (2,3). Providing patients and clinicians with accurate, easily digestible information is essential for safe and effective management.

While LLMs generally demonstrated strong linguistic fluency, our results highlight that this does not always ensure clinical reliability. Copilot and, to a lesser extent, Gemini frequently produced responses lacking clinical precision, especially in diagnostic and management-related areas. Similar concerns have been echoed in recent literature, including studies evaluating AI in radiology (22), oncology (23), and urology (24), where model outputs sometimes conflicted with current standards of care.

Recent studies have demonstrated both the potential and the limitations of AI in clinical urology and broader healthcare. For example, Shah et al. reported that AI models have achieved promising results in the detection and grading of prostate cancer and the prediction of kidney stone composition. However, they cautioned that clinical integration requires large-scale validation and careful management of ethical concerns (25). Similarly, de Hond et al. reviewed the development and validation of AI-based prediction models, emphasizing that many published models lack sufficient external validation and are often built on data that do not fully represent real-world clinical diversity, thereby limiting their generalizability (26). Saraswat et al. further highlighted that the lack of explainability in "black-box" AI models creates barriers to clinical trust, citing specific cases where clinicians were reluctant to accept algorithmic recommendations without clear, interpretable reasoning (27). Our findings resonate with these prior observations: while advanced LLMs such as ChatGPT and Perplexity performed well on structured, guideline-based questions, they were less reliable in nuanced, case-based scenarios—underscoring the continued need for explainable, validated, and context-aware AI tools in clinical practice.

The implications of these findings are particularly relevant in the context of increasing reliance on generative AI for patient counseling, academic learning, and even clinical triage. Although advanced LLMs show promising performance and may serve as supportive tools in clinical education and communication, their use in diagnostic or therapeutic decision-making should be approached with caution (28). Importantly, none of the models evaluated in this study disclosed uncertainty levels or cited peer-reviewed sources—features that are essential for safe clinical integration. Based on these findings, several practical pathways exist for integrating LLMs into clinical and educational workflows in urology. Beyond educational and supportive roles, LLMs could be integrated into real-world urological practice through their deployment in clinical decision support systems, patient-facing triage tools, and automated guideline consultation platforms. For example, AI-powered chatbots could provide initial guidance for patients reporting nocturia symptoms, assist clinicians in reviewing complex cases, or streamline documentation by generating summaries and templated clinical notes. In training programs, LLMs may serve as interactive educational companions, simulating patient scenarios and reinforcing guideline-based reasoning. Successful integration will require rigorous validation, clear scope definition, and ongoing human oversight to ensure patient safety and high-quality care.

In the context of growing clinical reliance on AI, the ethical and regulatory landscape for LLMs remains underdeveloped. Notably, none of the evaluated models provided explicit uncertainty estimates or confidence scores alongside their responses. This lack of "uncertainty calibration" poses a significant risk: users may assume an AI-generated answer is fully reliable, even when the underlying model is uncertain or operating outside its domain of expertise. Furthermore, the absence of source attribution—meaning the models do not cite peer-reviewed guidelines, original studies, or medical authorities—makes it difficult for clinicians and patients to verify the validity of the information provided. These limitations heighten the risk of misinformation, misinterpretation, and over-reliance on AI in clinical settings. For LLMs to be safely integrated into healthcare, robust frameworks for uncertainty communication, mandatory source citation, and continuous safety oversight by human experts will be essential. Developers and regulatory bodies must prioritize the inclusion of these features to ensure transparency, accountability, and the ethical use of generative AI in medicine.

This study has several strengths. The use of a standardized, thematically organized question set enabled structured comparisons across five clinically relevant domains. Scoring by two blinded expert evaluators ensured high inter-rater reliability (ICC = 0.91), and the multidimensional evaluation system provided a robust and nuanced performance profile for each AI model.

Future research should explore the integration of LLMs into real-time clinical scenarios, comparing AI-assisted versus physician-led decision-making. Additionally, incorporating patient perspectives and evaluating user trust will be essential to determining the acceptability of these technologies in clinical environments. Developers of LLMs should also prioritize embedding up-to-date clinical guidelines, integrating source attribution, and designing models that can flag uncertain or lower-confidence responses.

Study Limitations

This study has several limitations. First, the use of static, one-shot prompting does not reflect dynamic clinical questioning. Second, the models were evaluated without real-world patient interactions and without access to browsing-enabled features, which may limit the depth and currentness of responses. Third, in the context of increasing regulatory scrutiny over generative AI in healthcare (e.g., the EU AI Act), the absence of transparent traceability and confidence calibration mechanisms in LLM outputs remains a critical barrier to clinical adoption (29). In addition, none of the evaluated models provided explicit uncertainty estimates or cited peer-reviewed sources to support their answers. This lack of "uncertainty calibration" and "source attribution" may increase the risk of misinformation and over-reliance on AI-generated content. Until future LLMs can reliably communicate their confidence and directly attribute recommendations to established clinical guidelines, their use in unsupervised clinical decision-making should be approached with extreme caution and subject to ongoing human oversight. Fourth, the relatively limited sample size (25 questions) and the use of only two expert evaluators, although consistent with similar benchmarking studies, may restrict the generalizability of our results and reduce the ability to detect smaller differences between models. Future research involving larger and more diverse question sets, as well as additional expert reviewers, will be important to validate and extend these findings. Although mean scores and standard deviations were reported for ease of interpretation and comparison with previous studies, it should be acknowledged that Likert-type scale data are ordinal in nature. Therefore, medians and interquartile ranges may be more appropriate statistical measures for these data, as they better represent the central tendency and variability without assuming equal intervals between response categories. Future implementations in clinical decision support should include metadata layers that communicate uncertainty and cite sources to align with ethical standards of medical practice.

CONCLUSION

This study highlights that ChatGPT and Perplexity Pro currently represent the most reliable LLMs for generating clinically relevant information about nocturia and nocturnal polyuria. While they may assist in medical education and patient engagement, none of the evaluated models are ready for unsupervised clinical deployment. Their future integration must be supported by rigorous validation, expert oversight, and continuous alignment with updated medical guidelines.

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Ethical Approval: This study did not involve human participants, animal subjects, or patient data. Therefore, ethical approval was not required in accordance with institutional and national research committee standards. All AI models were accessed through publicly available platforms under their respective terms of use.

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RESEARCH ARTICLE

Incidental Extraprostatic Findings in Multiparametric Prostate MRI: A Retrospective Evaluation from a Tertiary Care Center

Ferhat Yakup Suçeken [1], Aydan Arslan [2], Deniz Çeliker [2], Timuçin Şipal [3], İsmail Evren [4], Eyüp Veli Küçük [1]

[1] Department of Urology, İstanbul Ümraniye Training and Research Hospital, İstanbul, Türkiye
[2] Department of Radiology, İstanbul Ümraniye Training and Research Hospital, İstanbul, Türkiye
[3] Department of Urology, University of Kırıkkale, Kırıkkale, Türkiye
[4] Department of Urology, İstanbul Bakırköy Sadi Konuk Training and Research Hospital, İstanbul, Türkiye

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Corresponding Author;
Ferhat Yakup Suçeken, MD
Address: Medical doctor, Urologist Department of Urology, İstanbul Ümraniye Training and Research Hospital, İstanbul, Turkiye
E-mail: ykpsckn@gmail.com

ORCID
A.A. 0000-0002-6073-1927
D.Ç. 0000-0001-9152-5600
T.S. 0000-0003-3992-2013
İ.E. 0000-0003-4008-8038
E.V.K. 0000-0003-1744-8242

Abstract

Objective: Prostate cancer is a significant health problem in men worldwide. Multiparametric magnetic resonance imaging of the prostate (mpMRI) is a diagnostic tool used in the management of men with suspected prostate cancer. This modality provides valuable information regarding extraprostatic tissues and the prostate gland. This study aimed to identify incidental extraprostatic findings (IEPFs) in patients who underwent mpMRI.

Methods: Data from patients who underwent mpMRI at our institution between October 2021 and September 2022 were retrospectively reviewed. Two experienced radiologists assessed the mpMRI scan images and reported using the Prostate Imaging Reporting and Data System (PI-RADS) categories. The findings were categorized as either related or unrelated to the genitourinary system. The findings were categorized into three groups: mild, moderate, and severe. A comparative analysis was performed to determine the clinical relationship between the PI-RADS score and age.

Results: A total of 1000 scans were reviewed. A total of 29.4 % (n=294) of the patients had IEPFs. Fifty-one (5.1%) of these findings were related to the genitourinary system of the patient. Categorization based on the severity of the findings revealed that 333 patients had mild, 20 had moderate, and 13 had severe IEPFs. Analysis revealed a statistically significant difference in the distribution of genitourinary and non-genitourinary findings across groups ($p < 0.001$).

Conclusion: As a diagnostic adjunct tool, mpMRI is not only valuable for aiding in the diagnosis of prostate cancer but also for the detection of IEPFs, the distribution of these findings differs significantly between genitourinary and non-genitourinary system, which may have important clinical implications.

Keywords: extraprostatic findings, MRI, PI-RADS score, prostate

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INTRODUCTION

Prostate cancer is the second most common cause of cancer-related deaths among men. Prostate-specific antigen (PSA) and digital rectal examination (DRE) are considered the initial steps in the diagnosis of prostate cancer (1). Multiparametric prostate magnetic resonance imaging (mpMRI) is performed before prostate biopsy (2).

mpMRI is more sensitive in detecting lesions defined as International Society of Urological Pathology (ISUP) grade 2 or higher (2). The current European Association of Urology (EAU) guidelines recommend performing mpMRI before biopsy, especially in patients with normal DRE findings and PSA values in the range of 2-10 ng/mL, who are suspected to have prostate cancer.

MpMRI can also effectively detect clinically significant prostate cancer and reveal extracapsular extension, lymph node metastasis, and metastases in the pelvic bones within the target area (2-5) Another advantage of mpMRI is that it can detect incidental findings unrelated to the genitourinary system. Although this is not uncommon, there are only a few studies on this subject (9,12,13).

This study aimed to present our data on incidental extraprostatic findings (IEPFs) in patients who underwent mpMRI and to increase awareness among clinicians interpreting mpMRI images.

MATERIALS AND METHODS

Study Design and Setting

This retrospective observational study included patients who underwent mpMRI at our institution between October 2021 and September 2022 following suspicion of prostate cancer based on elevated serum PSA levels and/or DRE. A retrospective analysis allows the assessment of incidental findings without altering patient care or imaging parameters. However, the design is inherently subject to certain limitations, including selection bias (e.g., patients referred to a tertiary center may differ from the general population) and observer bias (despite a dual-reader review). To minimize these biases, two radiologists with different experience levels independently reviewed the images and reached a consensus on all findings.

Exclusion Criteria: Patients with lymph node metastasis, seminal vesicle invasion, and bladder invasion, technically inadequate mpMRI scans (e.g., incomplete sequences or excessive motion artifacts), and missing or incomplete patient records.

Imaging Protocol: MpMRI scans were performed using a 1.5 Tesla system (Optima MR450, GE Healthcare). The scan consisted of T1-T2 weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced sequences. Hyoscine-N-butylbromide (20 mg) was administered to reduce bowel motion. Image Evaluation: Two radiologists (8 and 3years of experience) jointly reviewed the images. Findings consistent with direct prostate cancer involvement were excluded from the IEPFs classification. All other findings were categorized as genitourinary (GU) or non-genitourinary (non-GU) and graded as follows:

Group 1: Mild (clinically insignificant)
Group 2: Moderate (requires follow-up)
Group 3: Severe (urgent management)

Statistical Analysis

Statistical analyses were performed using SPSS v25.0. Normality was assessed using the Shapiro-Wilk test. One-way ANOVA was used to compare age; Kruskal-Wallis test for Prostate Imaging Reporting and Data System (PI-RADS) score; Chi-square test for GU/Non-GU across groups. Descriptive statistics are presented as mean ± SD or median (IQR) and frequencies with percentages. Confidence intervals (CIs) were calculated for the prevalence data.

Power Analysis: A post hoc power analysis was conducted using the observed proportions between Groups 1 (75.4%) and 2+3 (24.6%). The power to detect this difference with 294 patients exceeded 99% ($\alpha = 0.05$), confirming the adequacy of the sample size.

Ethics and Confidentiality: This study has been approved by the Institutional Ethical Review Committee of Istanbul Umraniye Training and Research Hospital (No:106).

Data were anonymized and managed according to institutional privacy policies to ensure confidentiality in compliance with the ethical standards for retrospective studies.

RESULTS

During the study period, mpMRI was performed in 1058 cases. Among these patients, five could not undergo mpMRI because of claustrophobia, contrast allergy, and the presence of an MRI-incompatible cardiac pacemaker. Therefore, the target population consisted of 1053 patients who underwent mpMRI. However, 53 patients were excluded due to lymph node metastasis (n=45), seminal vesicle invasion (n=7), and urinary bladder invasion (n=1). Thus, 1000 patients were included in the study. A retrospective review of these scans revealed IEPFs in 294 cases (29.4 %). Multiple extraprostatic findings were detected in 74 patients. A total of 51 findings were related to the genitourinary system (Table 1).

Bladder diverticulum (n=9), diffuse bladder wall thickening compatible with cystitis (n=8), epididymal cysts (n=8), hydrocele (n=6), bladder stones (n=5), bladder trabeculation (n=4), herniation of the bladder into the inguinal canal (n=3), utricle cyst (n=1), seminal vesicle calcification (n=1), cystic dilation of the ureter (n=1), and undescended testicle (n=1) were detected as IEPFs (Figure 1). In four cases, irregular thickening of the bladder wall was observed, and in three of these cases, biopsy and subsequent histopathological evaluation revealed bladder cancer.

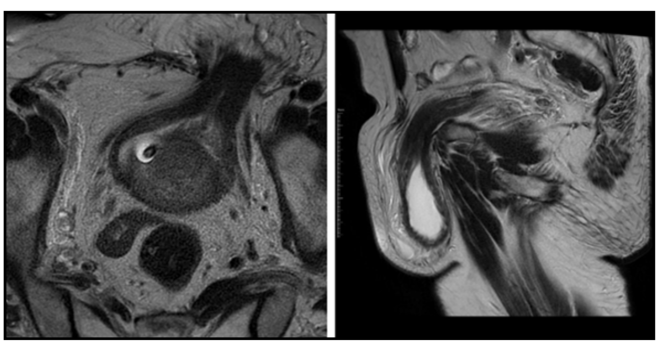

Figure 1. Axial and coronal T2-weighted MR images of bladder herniation into the inguinal canal

In a case with a PI-RADS score of 5, histopathological examination led to a diagnosis of urothelial carcinoma. On this mpMRI image, a diffusion-restricting lesion was identified at the distal end of the right ureter, accompanied by thickening of the bladder wall.

In our series, 315 IEPFs were unrelated to the genitourinary system (Table2, Figure 4). Inguinal hernia was detected in 187 cases. Of these patients, five had both bowel and fatty tissue herniation, whereas 182 had only fatty tissue herniation. Other findings included T1-T2 hypointense sclerotic bone lesions initially considered as enostosis (n=85), free fluid in the pelvis (n=13), trochanteric bursitis (n=3), metastatic lesions in the pelvic bones (n=2), trauma-related fracture in the coccygeal bone (n=2), aneurysmal bone cyst in the pubic bone (n=1), lymphocele (n=1), lumbosacral transitional vertebral anomaly (n=12), Tarlov cyst (n=5), and avascular necrosis (n=1) (Figure 2). In one case with a PI-RADS score of 2, suspicious multiple obturator and pararectal lymphadenopathies were detected. Sampling of these adenopathies led to the diagnosis of chronic lymphocytic leukemia.In another case, rectum invasion was observed. In another case with a PI-RADS score of 2, the sonographic examination performed due to a centrally vascularized inguinal lymphadenopathy without a fatty hilum and with asymmetrical cortical thickening led to the diagnosis of tuberculosis (Figure 3).

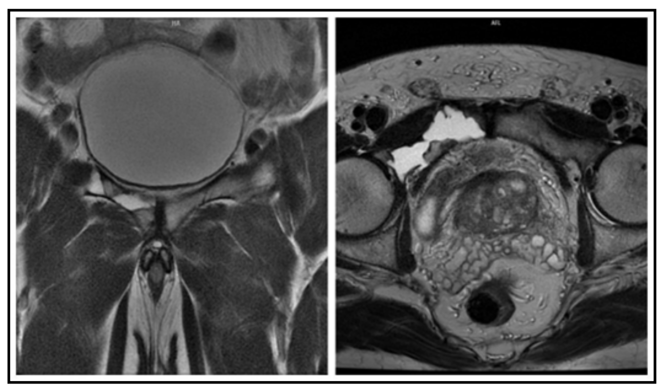

Figure 2. Cystic lesion with thin septations in the right pubic ramus adjacent to the right symphysis pubis (aneurysmal bone cyst due to biopsy).

Based on the clinical significance of the IEPFs, 333 (91%) patients were classified as Group 1 (mild), 20 (5.5%) patients were classified as Group 2 (moderate), and 13 (3.5%) as Group 3 (severe).

Table 2 presents the comparative demographic and imaging metrics across the groups. Group 1 had a slightly higher mean age (62.4 ± 5.6); however, this difference was not statistically significant ($p = 0.9782$). GU findings were significantly more common in group 1. Chi-square analysis showed a significant difference in the distribution of genitourinary and non-genitourinary findings among the groups ($p < 0.001$).

Table 1. Extraprostatic Findings by Clinical Significance Group (Sorted by Frequency)

Extraprostatic findings	Group 1	Group 2	Group 3
İnguinal hernia	182	0	0
Enostosis	85	0	0
Pelvic free fluid	13	0	0
Lumbosacral transitional anomaly	12	0	0
Bladder diverticulum	9	0	0
Bladder wall thickening	0	8	0
Epididymal Cyst	8	0	0
Hydrocele	6	0	0
Tarlov cyst	5	0	0
Bowel hernia	0	5	0
Bladder stone	0	5	0
Bladder trabeculation	4	0	0
Trochanteric bursitis	3	0	0
Bladder carcinoma	0	0	3
Bladder hernia	0	0	3
Pelvic bone metastasis	0	0	2
Coccyx fracture	2	0	0
Tuberculosis	0	0	1
Rectal invasion	0	0	1
Undescended testicle	0	1	0
Transitional cell carcinoma of the genitourinary system	0	0	1
Aneurysmal bone cyst	0	0	1
Prostatic utricle cyst	1	0	0
Lymphocele	1	0	0
Cystic dilatation of the ureter	1	0	0
Chronic lymphocytic leukemia	0	0	1
Calcification of the seminal vesicle	1	0	0
Femoral head avascular necrosis	0	1	0

Table 2. Variable Comparison Across Clinical Significance Groups

Variable	Group 1	Group 2	Group 3	p
Mean Age ± SD	62.4 ± 5.6	62.5 ± 6.0	62.1 ± 6.2	0.9782 γ
Median PI-RADS category	2.0	2.0	2.0	-
Genitourinary Findings	30	14	7	<0.001 ^{X}
Non-genitourinary Findings	303	6	6	

Statistical tests used: γ= One-way ANOVA was used for age, °= Kruskal-Wallis test was used for PI-RADS, X= Chi-square test was used to compare genitourinary vs. non-genitourinary distribution across groups.

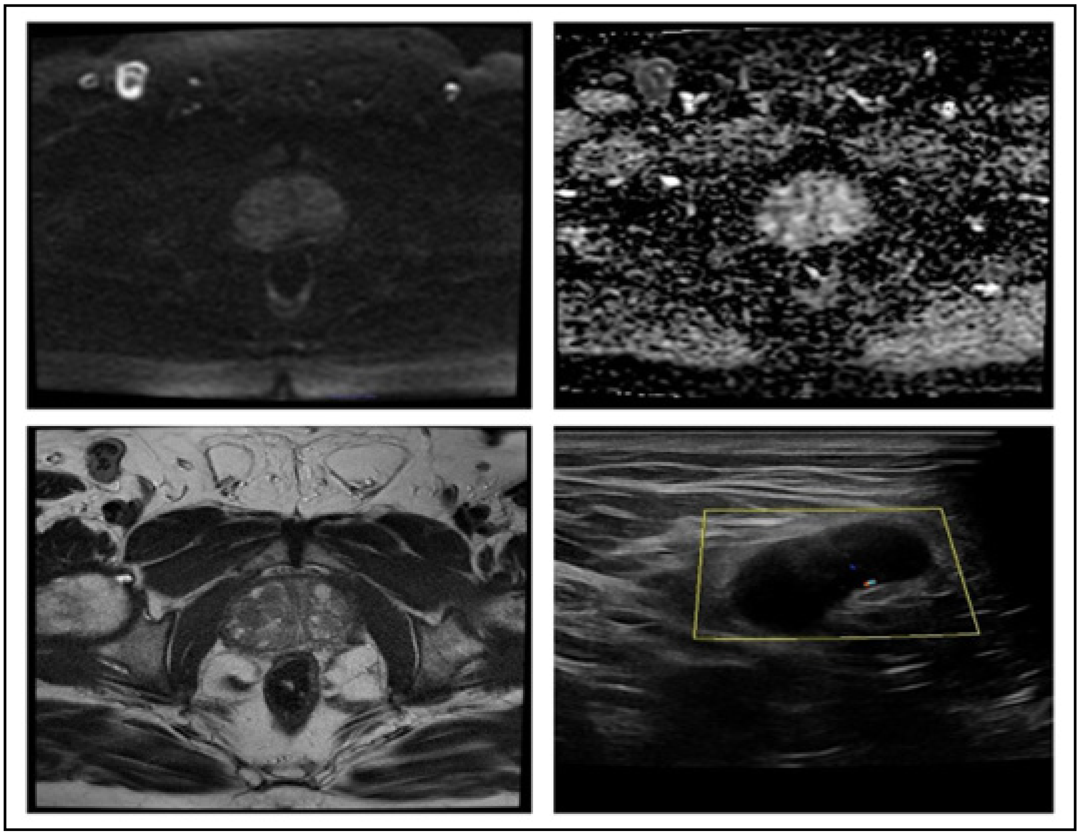

Figure 3. Multiparametric Prostate MR examination and ultrasound images of tuberculosis-associated inguinal lymphadenopathy

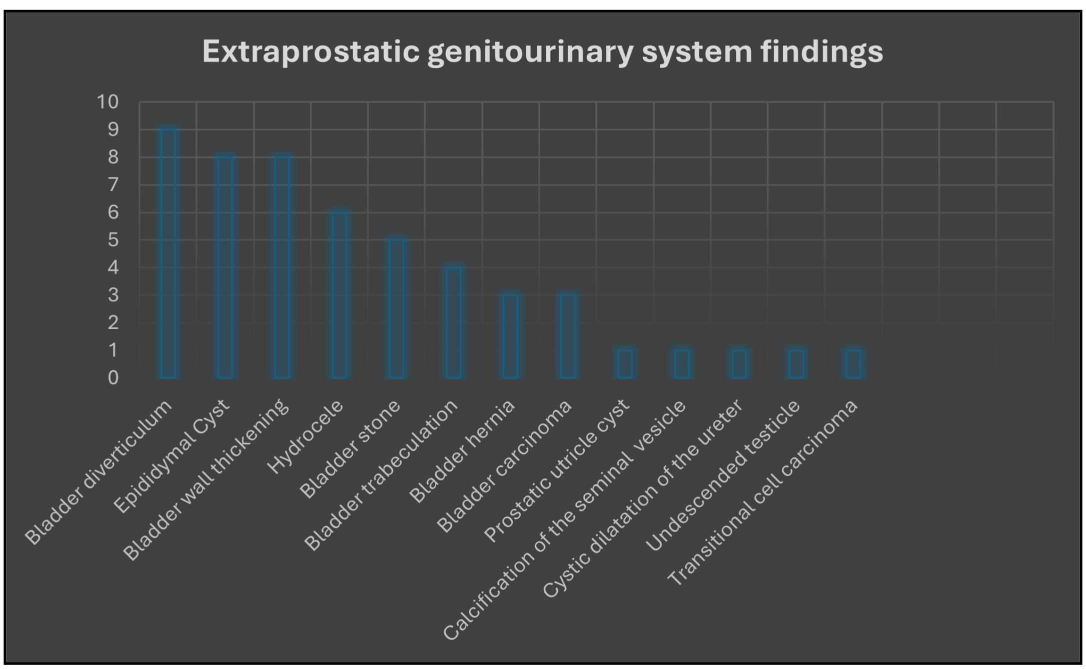

Figure 4. Incidentally detected extraprostatic genitourinary system findings

DISCUSSION

The use of mpMRI before biopsy in patients with suspected prostate cancer is recommended by current guidelines. Therefore, mpMRI has become an essential milestone in prostate biopsy decisions. It is more sensitive in patients with tumors larger than 6 mm and those with a high Gleason score (2,6-8).

Considering the high imaging quality provided by this method, mpMRI not only assists in decision-making regarding prostate biopsy but can also reveal IEPFs, which can lead to the diagnosis and treatment of these findings. In addition to IEPFs, MRI can also detect the invasion of prostate tumors into adjacent organs and lymphadenopathies (2).

Our study included 1000 patients, and IEPFs were detected in 294 (29.4%) of them. Of these, 51 (14%) were related to the genitourinary system, whereas 312 (86%) were unrelated. In a study conducted by Cutaia et al., which included 647 patients, IEPFs were detected in 52.7% of the cohort (9). In another study by Emekli et al. (10), 426 patients were included, and 49.8% had IEPFs. Similarly, Sherrer et al. (11) worked on the same subject and found that 40% of their 580 participants had IEPFs.

The lower percentage of patients with incidental findings in our study can be ascribed to the fact that our institution is a tertiary referral center and some potential IEPFs might have been treated before undergoing mpMRI at our institution. Additional factors, such as patient demographics, referral patterns, and imaging protocol variations, may also influence the observed rate. These factors should be considered when interpreting the lower detection rate.

Cutaia et al. showed that 322 (69.8%) patients with IEPFs had findings unrelated to the genitourinary system, while 139 (30.2%) had genitourinary system findings (9). In the study by Emekli et al., genitourinary system findings constituted 41.1% (n=132) of all IEPFs detected (10). In a study by Sherrer et al., 51% (n=179) of the 349 IEPFs were unrelated to the genitourinary system, while the remaining were genitourinary system-related (9-11). Our study aligns with the literature, as genitourinary system-unrelated findings were more common than genitourinary system findings.

In line with our analysis, Cutaia et al. categorized IEPFs according to their clinical significance (9). In this study, 355 patients were included in group 1, 94 patients were classified as group 2, and 12 (2.6%) patients were classified as group 3. In contrast, Emekli et al. classified patients into clinically significant and clinically insignificant IEPFs groups (10). The authors reported that 6.9% (n=22) of patients had clinically significant findings.

Since T2 coronal imaging focuses on the prostate in mpMRI performed in accordance with the PI-RADS score, liver and spleen lesions were not detected in our study. Fat-suppressed coronal T2-weighted images can be acquired to detect other organ pathologies. However, these approaches are time-consuming and expensive. Notably, artificial intelligence is a hot topic in mpMRI practice; however, its sensitivity in detecting IEPFs needs to be clarified (12).

In a study by Ediz et al. (13), the PI-RADS scoring system did not contribute to the diagnosis of incidental mp-MRI. This finding aligns with our results, as shown in **Table 2**, where no relationship was found between the PIRAD scores and IEPFs.

The recent review by Ponsiglione et al. (14) reported a substantially higher overall prevalence of incidental non-prostatic findings on mpMRI in different studies, compared to 29, 4 % in our cohort. This discrepancy may be attributed to differences in institutional imaging protocols, classification criteria, and patient selection criteria. Unlike their pictorial review, which broadly illustrated hepatic, renal, and gastrointestinal findings, our study applied a structured three-tier classification (mild, moderate, severe) and specifically quantified genitourinary IEPFs. Genitourinary lesions were emphasized in our dataset, comprising 13.9% of all incidental findings. Additionally, our exclusion of patients with known metastatic or locally advanced disease may explain the relatively lower detection rate for some non-prostatic findings compared with the broader inclusion criteria in their analysis.

Our study had some strengths and limitations. The main limitations of this study are its retrospective design, single-center data, and relatively limited number of patients included. However, our study is the most extensive series to date, which represents its strength.

CONCLUSION

Despite the abovementioned limitations, we conclude that mpMRI plays a vital role in detecting prostate cancer and identifying incidental extraprostatic findings, which can be clinically significant and life-saving in some cases. A standardized approach to interpret and classify IEPFs may enhance clinical decision-making.

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Conflicts of interest: The authors declare that they have no competing interests.

Ethics Statement: This study has been approved by the Institutional Ethical Review Committee of Istanbul Umraniye Training and Research Hospital (No:106).

Author Contributions: Conceptualization: Ferhat Yakup Suçeken and Aydan Arslan Data curation: Deniz Çeliker, Ferhta Yakup Suçeken and Aydan Arslan. Investigation: Ferhat Yakup Suçeken Methodology: Aydan Arslan Supervision: Eyup Veli Kucuk Writing–original draft: Ferhat Yakup Suçeken Writing–critical revision of the manuscript for important intellectual content: Deniz Celiker,İsmail Evren, Timuçin Şipal and Eyup Veli Kucuk.

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RESEARCH ARTICLE

Comparing ChatGPT and MSKCC Nomogram for Prostate Cancer Risk Predictions: A Correlation Study

Serkan Gönültaş [1], Mustafa Gökhan Köse [2], Sina Kardaş [2], Serhat Yentür [1], Filip Paslanmaz [1], Engin Kandirali [1]

[1] Department of Urology, Bağcılar Training and Research Hospital, İstanbul, Türkiye

[2] Department of Urology, Gaziosmanpaşa Training and Research Hospital, İstanbul, Türkiye

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Corresponding Author;
Serkan Gönültaş, M.D.
Address: Department of Urology, Bagcilar Training and Research Hospital, İstanbul, Türkiye
E-mail: dr.serkangonultas@hotmail.com

ORCID

S.G.	0000-0001-6556-7751
M.G.K.	0000-0002-2491-0178
S.K.	0000-0002-0759-5284
S.Y.	0000-0003-4196-2145
F.P.	0000-0003-4556-5518
E.K.	0000-0003-0580-2144

Abstract

Objectives: Accurate prediction of risks such as extracapsular spread, seminal vesicle invasion and lymph node involvement is critical for treatment planning and patient prognosis in prostate cancer. Traditional nomograms are widely used for this risk stratification. In recent years, artificial intelligence (AI)-based Chabot's have shown potential in this field. The aim of this study was to evaluate the correlation between AI chatbot (ChatGPT-4o) predictions and Memorial Sloan Kettering Cancer Center (MSKCC) nomogram predictions in prostate cancer patients according to risk groups.

Materials and Methods: 40 synthetic patient scenarios representing low, intermediate, high and locally advanced risk groups were created. These scenarios were entered into both ChatGPT-4o and MSKCC nomogram and predictions of "Organ-Confined Disease", "Extracapsular Extension", "Seminal Vesicle Invasion" and "Lymph Node Involvement" were obtained. The obtained data were analyzed using Spearman Correlation Coefficient.

Results: In general, there was a significant positive correlation between ChatGPT-4o and MSKCC nomogram in all prediction topics ($p < 0.001$). However, no significant correlation was found between the predictions of "Organ-Confined Disease" ($r = 0.521$, $p = 0.123$), "Seminal Vesicle Invasion" ($r = 0.382$, $p = 0.276$) and "Lymph Node Involvement" ($r = 0.218$, $p = 0.546$) in the high-risk patient group. Similarly, no significant correlation was found between the estimates of "Organ-Confined Disease" ($r = 0.522$, $p = 0.122$) and "Extracapsular Extension" ($r = 0.524$, $p = 0.120$) in the locally advanced patient group.

Conclusion: An overall high correlation between an AI-based chatbot (ChatGPT-4o) and the MSKCC nomogram was demonstrated for prostate cancer risk prediction. However, no significant correlation was observed especially in high-risk and locally advanced patient groups. These findings suggest that while AI chatbots are a potential tool for prostate cancer risk stratification, they require extensive validation and development studies before they can be put into clinical use, especially in more complex and advanced cases.

Keywords: artificial intelligence, chatbots, nomogram, prostate cancer, risk prediction

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INTRODUCTION

Prostate cancer (PCa) is the third most commonly diagnosed malignancy worldwide and it represents the most prevalent tumor of the male genitourinary system (1,2). The prognosis of the disease varies greatly depending on the stage and biologic characteristics at the time of diagnosis (3-6). Accurate prediction of the risks of extracapsular extension (ECE), seminal vesicle invasion (SVI) and lymph node involvement (LNI) is crucial for treatment planning and patient prognosis (5,6). Various nomograms are developed for preoperative risk stratification in prostate cancer using easily accessible parameters such as age, serum prostate specific antigen (PSA) level, Gleason score, clinical stage and number of biopsy positive cores (7-10). Among these nomograms, the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram is one that has been validated on large patient cohorts and is widely used in clinical practice. The MSKCC is used as an important clinical guide for the prediction of ECE, SVI and LNI risks in prostate cancer patients (8).

In recent years, artificial intelligence (AI) and large language models (LLMs) have become increasingly widespread in the medical field and have attracted interest as potential support tools in the diagnosis and treatment of diseases (11). One of these models, ChatGPT-4o, can answer complex medical questions based on user inputs and produce outputs similar to clinical decision support systems (12,13). However, there is limited data in the literature on the extent to which such chatbots provide predictions that are compatible with traditional nomograms.

In this study, we aimed to compare the ECE, SVI, LNI and organ-confined disease (OCD) predictions of ChatGPT-4o and MSKCC nomograms over scenarios created according to De Amico risk classification in patients with prostate cancer and evaluate the correlation between them.

MATERIAL AND METHODS

Study Design

This study is a comparative analysis designed using prospectively generated synthetic patient scenarios to compare the results provided by ChatGPT-4o and the traditional MSKCC nomogram in preoperative risk prediction in prostate cancer patients. The study was structured to represent low, intermediate, high and locally advanced risk groups according to the De Amico risk classification.

Creating Patient Scenarios

A total of 40 synthetic patient scenarios were created for the study, reflecting clinical practice and representing different risk groups in accordance with De Amico risk criteria. Each scenario was meticulously designed to include the essential preoperative data required for prostate cancer risk prediction. These data include the following:

- Patient Age: Indicated in years
- Serum PSA Level: expressed in ng/mL.
- Biopsy Gleason Score: Indicated as [for example, 3+4=7] with primary and secondary patterns.
- Clinical Stage: According to TNM staging system [for example, cT2a, cT3b].
- Number of Positive Biopsy Cores: The number of cores containing cancer among the total number of cores taken.

These scenarios were created by considering typical patient profiles from clinical databases and existing literature, thus providing a diversity similar to real-world cases at different risk levels (Table 1).

Data Collection and Analysis Tools

The following prediction data were obtained for each synthetic patient scenario:

<u>MSKCC Nomogram:</u> Preoperative data from each patient scenario were entered into the publicly available MSKCC nomogram web-based calculator (https://www.mskcc.org/nomograms/prostate/pre_op) to obtain the following risk estimates

- Probability of OCD: In percent (%).
- ECE Probability: In percent (%).
- SVI Probability: In percent (%).
- LNI Probability: In percent (%).

Artificial Intelligence Chatbot (ChatGPT-4o)

The same patient scenarios were entered into the ChatGPT4o (OpenAI, San Francisco, CA, USA) model to request risk estimates. Data entry was done using a specific and standardized prompt for each scenario. An example prompt structure is as follows:

Table 1. Demographic and Clinical Characteristics of Patient Scenarios

Risk Groups	Age	PSA	Gleason Score	ISUP_Group	Clinical Stage	Positive Cores / Total
Low Risk Group	58	4	3+3	1	T1c	1/12(8.33%)
	62	6.8	3+3	1	T2a	2/10(20%)
	65	5.5	3+3	1	T2a	3/12(25%)
	70	7.9	3+3	1	T1c	2/12(16.66%)
	68	9.5	3+3	1	T2a	4/12(33.33%)
	60	5.1	3+3	1	T1c	1/10(10%)
	59	3.9	3+3	1	T2a	1/12(8.33%)
	73	6	3+3	1	T1c	3/12(25%)
	66	7	3+3	1	T2a	2/12(16.66%)
	61	4,8	3+3	1	T2a	3/12(25%)
Intermediate Risk Group	60	10.1	3+4	2	T1c	3/12(25%)
	64	15	3+4	2	T2a	4/12(33.33%)
	67	9.8	4+3	3	T2b	5/12(41.66%)
	70	18	4+3	3	T2b	6/12(50%)
	66	12	3+4	2	T1c	4/12(33.33%)
	62	14	4+3	3	T2b	6/12(50%)
	74	11	3+4	2	T2a	2/10(20%)
	68	10	3+4	2	T2b	3/12(25%)
	65	17.5	4+3	3	T2b	5/12(41.66%)
	70	9.5	4+3	3	T2b	6/12(50%)
High Risk Group	72	22	4+3	3	T2c	7/12(58.33%)
	66	16.5	4+4	4	T2b	8/12(66.66%)
	65	10	5+3	4	T2c	9/12(75%)
	70	25	3+4	2	T2c	10/12(83.33%)
	74	12	4+4	4	T2c	8/12(66.66%)
	68	30	3+4	2	T2c	9/12(75%)
	64	20	4+3	3	T2c	10/12(83.33%)
	69	21	3+4	2	T2c	6/12(50%)
	67	19.5	4+4	4	T2b	8/12(66.66%)
	71	23	4+3	3	T2c	11/12(91.66%)
Locally Advance Group	66	35	4+5	5	T3b	10/12(83.33%)
	69	40	5+5	5	T4	11/12(91.66%)
	71	28	5+4	5	T3a	9/12(75%)
	64	24	4+5	5	T3b	12/12(100%)
	70	50	5+5	5	T4	12/12(100%)
	68	45	4+5	5	T3b	11/12(91.66%)
	67	30	5+4	5	T3b	12/12(100%)
	70	22.5	5+4	5	T3b	10/12(83.33%)
	65	38	4+5	5	T4	12/12(100%)
	73	60	5+5	5	T4	12/12(100%)

Patient Age (years), Serum Prostate Specific Antigen (PSA) level (ng/mL), Biopsy Gleason Score, International Society of Urologic Pathology (ISUP) Group, Clinical Stage (according to TNM classification) and Number of Positive Biopsy Cores / Total Number of Cores Taken (as percentage).

"Given the following clinical information for a prostate cancer patient, would you estimate the risks of organ-confined disease, extracapsular spread, seminal vesicle invasion, and lymph node involvement as a percentage?
- *Age: [Patient Age] years*
- *PSA [PSA Value] ng/mL*
- *Gleason Score: [Gleason Score]*
- *Clinical Stage: [Clinical Stage]*
- *Number of Positive Biopsy Cores: [Number of Positive Cores]"*

The estimates generated by ChatGPT-4o (probabilities of OCD, ECE, SVI, LNI) were recorded.

Statistical Analysis

Statistical analysis of the data obtained was performed using SPSS Statistics Version 28.0 (IBM Corp., Armonk, NY, USA). Quantitative data are presented as median and interquartile range. The Kolmogorov-Smirnov test was used to determine the normal distribution of the data. The strength and direction of the relationship between ChatGPT-4o estimates and MSKCC nomogram estimates were assessed using the Spearman Correlation Coefficient (r). Correlation analyses were performed separately in each risk group (low, intermediate, high and locally advanced risk) as well as in the overall patient group. Statistical significance level was accepted as $p \leq 0.05$ in all analyses.

Ethical Statement

Since this study used synthetically generated patient scenarios instead of real patient data, ethics committee approval was not required. The study was conducted in accordance with general research ethical principles.

RESULTS

Considering all 40 patient scenarios, overall significant positive correlation was found between the predictions provided by ChatGPT-4o and the MSKCC nomogram. In particular, a strong correlation ($r=0.971$, $p<0.001$) was found between the OCD predictions. Similarly, ECE ($r=0.979$, $p<0.001$), SVI ($r=0.976$, $p<0.001$) and LNI ($r=0.972$, $p<0.001$) predictions also exhibited generally high and significant positive correlations (Table 2).

Risk group-specific differences were observed in the analyses conducted by risk groups. In the low-risk patient group, significant positive correlations were found between OCD ($r=0.780$, $p=0.008$), ECE ($r=0.872$, $p=0.001$) and SVI ($r=0.504$, $p=0.137$) predictions. However, no significant correlation was observed in the LNI prediction ($r=0.272$, $p=0.447$). In the intermediate-risk patient group, significant positive correlations were found between ChatGPT-4o and MSKCC nomogram in all prediction topics. OCD ($r=0.851$, $p=0.002$), ECE ($r=0.851$, $p=0.002$), SVI ($r=0.936$, $p<0.001$) and LNI ($r=0.873$, $p<0.001$) predictions showed a high degree of agreement. No statistically significant correlation was found between the predictions of OCD ($r=0.521$, $p=0.123$), SVI ($r=0.382$, $p=0.276$) and LNI ($r=0.218$, $p=0.546$) in the high-risk patient group ($p>0.05$). However, a significant correlation was found in the ECE prediction ($r=0.737$, $p=0.015$). In the locally advanced patient group, no significant correlation was detected between OCD ($r=0.522$, $p=0.122$) and ECE ($r=0.524$, $p=0.120$) estimates ($p>0.05$). However, strong and significant correlations were observed between the MSKCC nomogram and ChatGPT-4o for SVI ($r=0.888$, $p<0.001$) and LNI ($r=0.899$, $p<0.001$).

DISCUSSION

The use of AI models in medicine is rapidly increasing, and various studies have been conducted in prostate cancer prognostic predictions (11). In the existing literature, AI is reported to show promising results in prostate cancer diagnosis and staging by combining imaging, pathology and clinical data (11,14). However, studies directly comparing AI chatbots with clinical risk nomograms and examining performance differences, especially in complex patient groups, are limited. Our study is an important step towards filling the knowledge gap in this field and emphasizes the need for a careful validation process before clinical use of AI. Considering that traditional nomograms have undergone years of validation based on specific clinical parameters, AI needs to be tested with similar rigor.

This study focused on the comparison of the predictions provided by ChatGPT-4o, an AI-based chatbot, and the MSKCC nomogram commonly used in clinical practice for preoperative risk prediction in prostate cancer. Our findings revealed that ChatGPT-4o were highly correlated with nomograms in general, but exhibited significant inconsistencies in certain prediction topics, especially in

Table 2. Correlation Analysis between MSKCC Nomogram and ChatGPT-4o Predictions by Risk Group

		MSKCC	ChatGPT-4o	r	p
OCD (%)	Low Risk Group	75.5(63-89)	87.5(82-93)	0.780	0.008
	Intermediate risk Group	28.5(12-61)	65.5(55-76)	0.851	0.002
	High Risk Group	7(2-16)	40.5(30-48)	0.521	**0.123**
	Locally Advance Group	1(1-2)	19(10-32)	0.522	**0.122**
	Total	13.5(1-89)	51.5(10-93)	0.971	<0.001
ECE (%)	Low Risk Group	24(11-36)	9.5(5-14)	0.872	0.001
	Intermediate risk Group	70(37-87)	27(17-37)	0.851	0.002
	High Risk Group	91.5(82-98)	50(42-58)	0.737	0.015
	Locally Advance Group	99(98-99)	66.5(55-78)	0.524	**0.120**
	Total	84.5(11-99)	39.5(5-78)	0.979	<0.001
SVI (%)	Low Risk Group	1(1-2)	2(1-3)	0.504	**0.137**
	Intermediate risk Group	12.5(3-39)	11(6-19)	0.936	<0.001
	High Risk Group	45.5(23-69)	28(22-35)	0.382	**0.276**
	Locally Advance Group	92(84-97)	41(30-52)	.0888	<0.001
	Total	35(1-97)	20.5(1-52)	0.976	<0.001
LNI (%)	Low Risk Group	1(1-2)	1(1-2)	0.272	**0.447**
	Intermediate risk Group	15.5(4-36)	5(2-8)	0.873	<0.001
	High Risk Group	45(19-71)	14(10-18)	0.218	**0.546**
	Locally Advance Group	89(81-94)	26.5(18-38)	0.899	<0.001
	Total	32.5(1-94)	9(1-38)	0.972	<0.001

This table presents the results of the correlation analysis between the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram and ChatGPT-4o predictions of Organ-Confined Disease (OCD), Extracapsular Extension (ECE), Seminal Vesicle Invasion (SVI) and Lymph Node Involvement (LNI) in each De Amico risk group and overall. Mean prediction values and minimum-maximum ranges are given in parentheses. The correlation coefficient (r) and statistical significance level (p value) are also shown. p<0.05 was considered statistically significant.

high-risk and locally advanced patient groups. These results are critical to understanding the potential and current limitations of AI-based tools in clinical practice.

The overall analysis of our study showed high and significant positive correlations between ChatGPT-4o and the MSKCC nomogram for OCD, ECE, SVI and LNI. In particular, a strong correlation was found between OCD predictions; similarly, ECE, SVI and LNI predictions also exhibited overall high and significant positive correlations. This finding suggests that ChatGPT-4o can produce similar outputs to traditional methods in complex clinical decision support processes such as prostate cancer risk prediction, thanks to their capacity to learn from large data sets. The strong correlations observed in the low- and intermediate-risk patient groups also support this potential, as in these groups, except for the LNI prediction in the low-risk group, all other predictions showed significant correlations. However, the most striking findings of our study are the discrepancies in the high-risk and locally advanced patient groups. In the high-risk group, there was no statistically significant correlation between the estimates of OCD, SVI and LNI. Similarly, no significant correlation was found in the predictions of OCD and ECE in the locally advanced patient group. Similarly, no significant correlation was found in the predictions of OCD and ECE in the locally advanced patient group. This suggests that ChatGPT-4o may not produce as reliable predictions as traditional nomograms, especially when the disease is more advanced and complex. The discrepancies observed in the high-risk and locally advanced groups may be explained by several factors. Large language models such as ChatGPT-4o are primarily trained on general internet-based sources rather than curated, domain-specific medical datasets. As a result, their ability to accurately represent rare or complex clinical scenarios remains limited. Nomograms, in contrast, are derived from large patient cohorts with detailed clinical and pathological annotations, allowing them to more precisely model the heterogeneity of advanced disease. In these groups, tumor biology is often more aggressive and unpredictable, with greater variability in features such as extracapsular spread patterns, seminal vesicle involvement, and nodal dissemination. Subtle distinctions in staging parameters (e.g., between cT3a and cT3b disease) may translate into markedly different risk profiles, but such nuances are difficult for a language-based model to capture without access to structured radiological, pathological, or molecular data. Furthermore, while ChatGPT-4o generates probability estimates by identifying linguistic patterns, it lacks true comprehension of the underlying pathophysiological mechanisms. These limitations collectively help to explain the reduced concordance with nomogram predictions in the most clinically complex patient groups.

The fact that our study provides a controlled comparison using synthetic patient scenarios representing risk groups eliminates the variability in real patient data and allows direct comparison of ChatGPT-4o and nomogram outputs. Furthermore, the reference to MSKCC, a validated nomogram widely used in clinical practice, increases the clinical validity of the results. On the other hand, the study has some limitations. The use of synthetic patient scenarios may not fully reflect the heterogeneity and clinical nuances of real-world patient populations. The use of only a single AI chatbot (ChatGPT-4o) and a single nomogram (MSKCC) may limit the generalizability of the results. Furthermore, although 40 patient scenarios were sufficient for statistical analyses, the smaller number of cases, especially in subgroups (10 scenarios in each risk group), may have led to smaller correlations not being statistically significant.

In conclusion, our findings suggest that ChatGPT-4o may be a promising tool in the field of prostate cancer risk prediction, but exhibit significant inconsistencies compared to existing nomograms, especially in complex scenarios such as high-risk and locally advanced disease. These findings emphasize the need for extensive validation and development studies on larger and real patient cohorts before AI can be widely used in clinical practice. Future research should focus on the specific training of AI models with medical data and their integration as a decision support tool for physicians.

CONCLUSION

Overall high correlation between ChatGPT-4o and the MSKCC nomogram was demonstrated for prostate cancer risk prediction. However, no significant correlation was observed especially in high-risk and locally advanced patient groups. These findings suggest that while AI chatbots are a potential tool for prostate cancer risk stratification, they require extensive validation and development studies before they can be put into clinical use, especially in more complex and advanced cases.

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EthicalApproval: Since this study used synthetically generated patient scenarios instead of real patient data, ethics committee approval was not required. The study was conducted in accordance with general research ethical principles.

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CASE REPORT

Bilateral Synchronous Renal Cell Carcinoma and Single-Stage Nephrectomy: A Case Report

İbrahim Halil Albayrak[1], Mehmet Demir[2], Eyyüp Sabri Pelit[2], İsmail Yağmur[2]

[1] Department of Urology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Türkiye

[2] Department of Urology, Harran University, Şanlıurfa, Türkiye

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Corresponding Author;
İbrahim Halil Albayrak, MD
Address: Department of Urology, Şanlıurfa Training and Research Hospital, Şanlıurfa, Türkiye
E-mail: i.halil.albayrak@gmail.com

ORCID

İ.H.A.	0000-0002-6448-2243
M.D.	0000-0002-3618-0547
E.S.P.	0000-0001-8550-5072
İ.Y.	0000-0002-4208-5095

Abstract

Bilateral renal cell carcinoma (RCC) is a rare condition, accounting for approximately 0.3% of all kidney cancer cases. There is no consensus on the surgical approach for treating bilateral synchronous renal masses. In this article, we present a single-stage surgical approach for a 76-year-old male patient with large bilateral synchronous RCC. Surgical intervention involved performing a right-sided partial nephrectomy concurrently with a total nephrectomy on the left kidney. No metastasis or local recurrence was observed in the postoperative 30-month follow-up. In selected cases, single-stage bilateral nephrectomy/partial nephrectomy can be safely performed in experienced centers.

Keywords: synchronous renal cell carcinoma, single-stage nephrectomy, partial nephrectomy, complication

INTRODUCTION

Bilateral renal cell carcinoma occurs in less than 5% of kidney cancer cases (2). Multiple tumors detected within six months are defined as synchronous (1). Bilateral synchronous renal cell carcinoma accounts for a small fraction of cases, with an estimated prevalence of 0.3% (2). There is no consensus on the surgical approach for treating bilateral synchronous renal masses. Evaluating the surgical strategies used in managing these patients in light of existing literature is crucial in shaping treatment protocols and guiding clinical practice. In light of these considerations, we found it valuable to report this particular case.

CASE REPORT

A 76-year-old white male patient was referred to our clinic after bilateral renal masses were detected during an evaluation for flank pain. His medical history included coronary artery disease and a 50 pack-year smoking history. There was no family history of genitourinary cancer. Physical examination revealed a palpable mass in the right flank region. Laboratory tests, including complete blood count, basic metabolic profile, and liver function tests, were within normal limits. Preoperative creatinine level was 1.2 mg/dL. Contrast-enhanced computed tomography (CT) of the entire abdomen showed a mass measuring 94x81 mm in the

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posterolateral region of the right kidney and another mass measuring 79x75 mm extending from the lower pole to the renal hilum of the left kidney (RCC?) (Figure 1). Contrast-enhanced abdominal and thoracic computed tomography (CT) scans were performed to evaluate for metastasis. No metastatic lesions were detected on imaging.

A simultaneous bilateral nephron-sparing surgery was planned. A Chevron incision was made in the supine position to access the left kidney first (Figure 2). The tumor was found to have invaded the renal pedicle, making partial nephrectomy unsuitable, so left radical nephrectomy was performed (Figure 3B). The right kidney was then accessed, revealing a 9 cm mass extending throughout the entire kidney posteriorly. Right partial nephrectomy was performed by clamping the renal artery and vein (ischemia time: 19 minutes) (Figure 3A). The operation lasted 185 minutes. In the postoperative period, the patient received one unit of erythrocyte suspension. No complications other than hemorrhage were observed. Postoperatively, the patient was discharged with a creatinine level of 3.2 mg/dL on day six.

Pathological examination confirmed papillary renal cell carcinoma on both sides, with no tumor detected at the surgical margins. During follow-ups, a gradual decrease in urine output and a progressive increase in serum creatinine and BUN levels were observed. As a result, the patient was included in a routine dialysis program in the first postoperative month. At the 30-month follow-up, no local recurrence or metastasis was detected.

Figure 1. Contrast-enhanced CT images of tumors in both kidneys

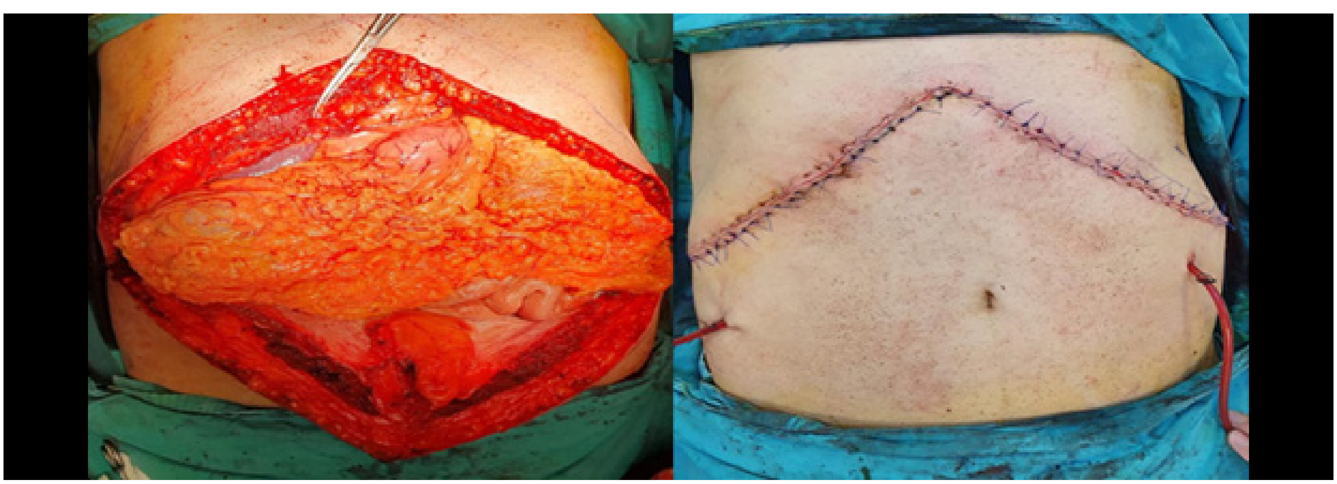

Figure 2. Chevron incision

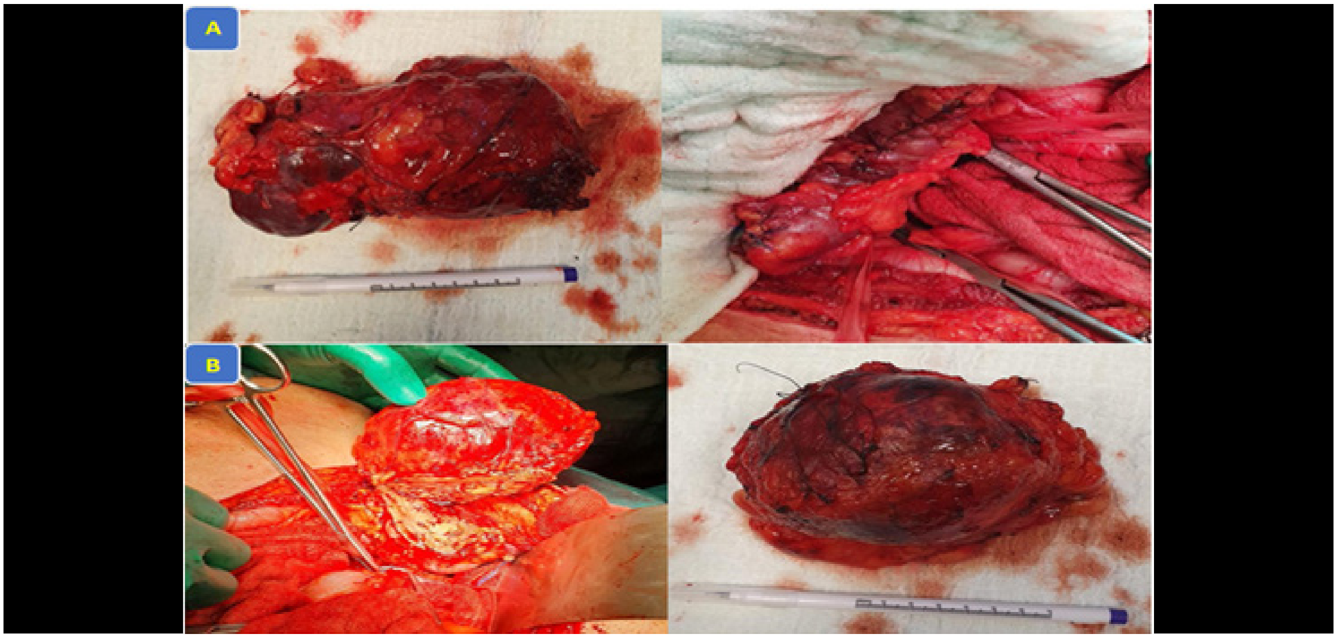

Figure 3.A. Right kidney mass and remaining renal tissue, B. Left kidney

DISCUSSION

Bilateral synchronous RCC is a rare condition (2). The etiology remains uncertain, whether it results from contralateral RCC metastasis or multiple de novo primary tumors (3). The optimal surgical strategy for managing such cases remains a topic of ongoing debate among clinicians. The choice between staged bilateral surgery and single-stage surgery remains controversial, and the decision should be made based on the physician's judgment and the patient's condition (4). Our patient was a refugee affected by the war in Syria and had to return to his country after treatment. Since long-term follow-up and treatment could not be performed, we obtained informed consent and preferred a single-stage surgery.

The literature points out that single-stage bilateral surgery provides oncological and functional outcomes comparable to unilateral surgery (5). Single-stage bilateral kidney surgery offers advantages such as reduced morbidity and mortality associated with anesthesia (6). Additionally, compared to staged nephrectomy, it leads to faster recovery and a shorter surgical process, allowing patients to return to their normal lives more quickly and improving their quality of life (7).

However, single-stage bilateral nephrectomy also has disadvantages. The complexity of the surgical procedure and the increased risk of postoperative complications must be considered. Factors such as the surgical team's experience, the patient's overall health status, and tumor characteristics should be taken into account (5,8). In a study by Mason et al. involving 76 patients who underwent single-stage bilateral partial nephrectomy, the procedure was shown to be safe, with a complication rate of 20% (6). In a study published by vignesh et al. in 2020, consisting of 107 patients, they found similar results between single-stage bilateral partial nephrectomy and staged bilateral partial nephrectomy (9). Kotb et al. reported that kidney function was preserved in a case series of three patients undergoing single-stage bilateral partial nephrectomy, with no Clavien-3 or higher complications observed (7). However, in this series, tumor sizes were <3 cm. On the other hand, Wang et al. found that in four patients who underwent single-stage bilateral surgery for renal tumors, renal failure developed within six years of follow-up, and they recommended staged surgeries instead (8).

Rather than hemorrhage, no early postoperative complications were observed in our case. Nevertheless, renal failure developed during follow-ups. We believe this was not due to simultaneous bilateral surgery. Given the tumor location and size, we had to perform total nephrectomy on the left side and remove more than 50% of the kidney tissue on the right side. Therefore, even if a staged nephrectomy had been performed, renal failure might have developed due to the small amount of remaining renal tissue.

In conclusion, the surgical approach for bilateral synchronous RCC remains controversial, and individualized evaluation is crucial. In our case, considering the tumor characteristics and the patient's overall condition, single-stage surgery was preferred and successfully performed. A review of similar cases in the literature suggests that single-stage surgery provides oncological and functional outcomes comparable to staged surgery while offering significant advantages by eliminating the need for additional surgical procedures. In our patient, combining radical and partial nephrectomy accelerated postoperative recovery and protected the patient from additional surgical and anesthesia risks. This case demonstrates that single-stage surgery can be a safe and effective option when careful patient selection is made.

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

Author's Contributions: IHA: writing of the case report. MD: operated the case and manuscript review. ESP: operated the case. IY: manuscript review.

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CORRECTION

Correction to: A Rare Case of Bladder Tumor: Squamous Cell Papilloma

Görkem Akça [1], Hakkı Uzun [1], Hasan Güçer [2], Eyüp Dil [1], Selim Yazar [1], Erdem Orman [1]

[1] Department of Urology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Türkiye
[2] Department of Pathology, Recep Tayyip Erdoğan University Training and Research Hospital, Rize, Türkiye

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Corresponding Author;
Görkem Akça, MD
Address: Recep Tayyip Erdoğan University Training and Research Hospital, Department of Urology, Rize, Türkiye
E-mail: gakca7@hotmail.com

ORCID

G.A. 0000-0002-7019-4264
H.U. 0000-0002-5189-3166
H.G. 0000-0002-9122-379X
E.D. 0000-0001-7739-4253
S.Y. 0000-0002-9843-9008
E.O. 0000-0003-1422-7137

In the published PDF version of the A Rare Case of Bladder Tumor: Squamous Cell Papilloma, Figures 1, 2, and 3 were inadvertently omitted due to a publisher error.

We apologize to our readers and the research community for this oversight. A corrected and complete version of the article, which includes the missing visuals, has been re-published with this erratum notice.

The purpose of this correction is to maintain an accurate scientific record.

Corrected version can be accessed via the following link: https://doi.org/10.33719/nju1630050

REFERENCE

Akca G, Uzun H, Gucer H, Dil E, Yazar S, Orman E. A Rare Case of Bladder Tumor: Squamous Cell Papilloma. New J Urol. 2025;20(2):117-120. **doi:** https://doi.org/10.33719/nju1630050

Cite; Akca G, Uzun H, Gucer H, Dil E, Yazar S, Orman E. A Rare Case of Bladder Tumor: Squamous Cell Papilloma. New J Urol. 2025;20(3):212-213. **doi:** https://doi.org/10.33719/nju1804400

Figure 1. CT image depicting a lesion in the anterior wall of the bladder.

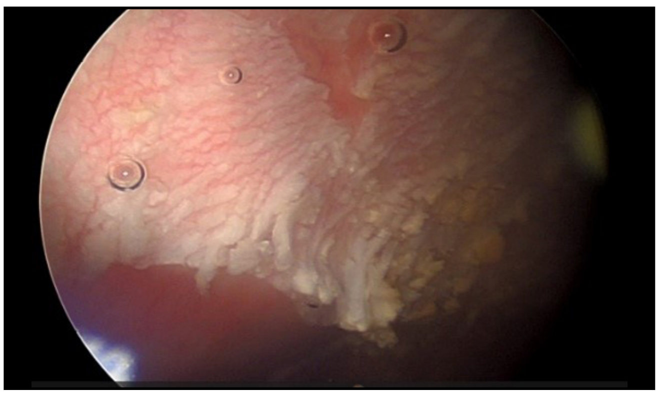

Figure 2. Cystoscopic image of the lesion

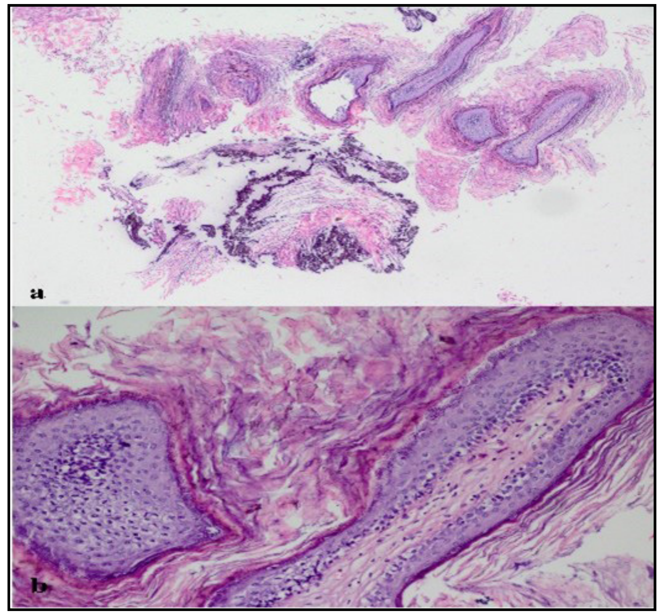

Figure 3. Papillary structures lined with squamous epithelium composed of benign appearing squamous cells and thick calcified keratin layers.

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